AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON MARCH 28, 2000

REGISTRATION NO. 333-96127

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 4
TO
FORM S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

RIGEL PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

<TABLE>
<S> <C> <C>
DELAWARE 8731 94-3248524
(State or other jurisdiction of incorporation or organization) (Primary Standard Industrial Classification Code Number) (I.R.S. Employer Identification No.)
</TABLE>

240 EAST GRAND AVENUE
SOUTH SAN FRANCISCO, CALIFORNIA 94080
(650) 624-1100
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

JAMES M. GOWER
PRESIDENT AND CHIEF EXECUTIVE OFFICER
RIGEL PHARMACEUTICALS, INC.
240 EAST GRAND AVENUE
SOUTH SAN FRANCISCO, CALIFORNIA 94080
(650) 624-1100

(Name, address, including zip code, and telephone number, including area code, of agent for service)

COPIES TO:

<TABLE>
<S> <C>
PATRICK A. POHLEN, ESQ.
COOLEY GODWARD LLP
FIVE PALO ALTO SQUARE
3000 EL CAMINO REAL
PALO ALTO, CA 94306-2155
(650) 843-5000

RICHARD R. PLUMRIDGE, ESQ.
JEFF T. HARRIS, ESQ.
ARUN JHA, ESQ.
BROBECK, PHLEGER & HARRISON LLP
370 INTERLOCKEN BLVD., SUITE 500
BROOMFIELD, CO 80021
(303) 410-2000
</TABLE>

APPROXIMATE DATE OF PROPOSED SALE TO THE PUBLIC:
AS SOON AS PRACTICABLE AFTER THE REGISTRATION STATEMENT BECOMES EFFECTIVE.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended (the "Securities Act"), check the following box. / /

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. / /

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement

number for the same offering. / /

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering. / /

If delivery of the prospectus is expected to be made pursuant to Rule 434, check the following box. / /

THE REGISTRANT HEREBY AMENDS THIS REGISTRATION STATEMENT ON SUCH DATE OR DATES AS MAY BE NECESSARY TO DELAY ITS EFFECTIVE DATE UNTIL THE REGISTRANT SHALL FILE A FURTHER AMENDMENT WHICH SPECIFICALLY STATES THAT THIS REGISTRATION STATEMENT SHALL THEREAFTER BECOME EFFECTIVE IN ACCORDANCE WITH SECTION 8(a) OF THE SECURITIES ACT OF 1933, AS AMENDED, OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(a), MAY DETERMINE.

EXPLANATORY NOTE

This Amendment No. 4 to Form S-1 Registration Statement is being filed for the sole purpose of filing additional exhibits as per Item 16(a) of Part II.

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 13. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth the costs and expenses, other than the underwriting discounts payable by us, in connection with the sale of common stock being registered. All amounts are estimates except the SEC registration fee, the NASD filing fee and the Nasdaq National Market listing fee.

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SEC registration fee	$ 32,789
NASD filing fee	$ 1,000
Nasdaq National Market listing fee	$ 95,000
Blue Sky Fees and Expenses	$ 18,000
Transfer Agent and Registrar fees	$ 3,500
Accounting fees and expenses	$ 215,000
Legal fees and expenses	$ 450,000
Printing and engraving costs	$ 180,000
Miscellaneous expenses	$ 4,711
Total	$1,000,000

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ITEM 14. INDEMNIFICATION OF DIRECTORS AND OFFICERS

As permitted by Delaware law, our amended and restated certificate of incorporation provides that no director of ours will be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director, except for liability:

- - for any breach of duty of loyalty to us or to our stockholders;

- - for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;

- - for unlawful payment of dividends or unlawful stock repurchases or redemptions under Section 174 of the Delaware General Corporation Law; or

- - for any transaction from which the director derived an improper personal benefit.

Our amended and restated certificate of incorporation further provides that we must indemnify our directors and executive officers and may indemnify our other officers and employees and agents to the fullest extent permitted by Delaware law. We believe that indemnification under our amended and restated certificate of incorporation covers negligence and gross negligence on the part of indemnified parties.

We have entered into indemnification agreements with each of our directors and certain officers. These agreements, among other things, require us to indemnify each director and officer for certain expenses including attorneys' fees, judgments, fines and settlement amounts incurred by any such person in any action or proceeding, including any action by or in the right of Rigel, arising out of the person's services as our director or officer, any subsidiary of ours

or any other company or enterprise to which the person provides services at our request.

The underwriting agreement (Exhibit 1.1) will provide for indemnification by the underwriters of Rigel, our directors, our officers who sign the registration statement, and our controlling persons for some liabilities, including liabilities arising under the Securities Act.

ITEM 15. RECENT SALES OF UNREGISTERED SECURITIES

Since July 15, 1996, Rigel has sold and issued unregistered securities to a limited number of persons, as described below. None of these transactions involved any underwriters, underwriting discounts or commissions, or any public offering, and Rigel believes that each transaction was exempt from the registration requirements of the Securities Act by virtue of Section 4(2) thereof, Regulation D promulgated thereunder or Rule 701 pursuant to compensatory benefit plans and contracts relating to compensation as provided under Rule 701. The recipients of securities in each such transaction represented their intention to acquire the securities for investment only and not with a view to or for sale in connection with any distribution thereof, and appropriate legends were affixed to the share certificates and instruments issued in such transactions. We believe that all recipients had adequate access to information about Rigel, through their relationships with Rigel.

Since July 15, 1996, Rigel has sold and issued the following unregistered securities:

(1) From July 15, 1996 to January 31, 2000, we granted incentive stock options and nonstatutory stock options to purchase an aggregate of 7,597,099 shares of Rigel's common stock at exercise prices ranging from $0.10 to $4.50 per share to employees, directors and consultants under the Plan. Of these stock options 655,162 shares have been canceled without being exercised, 588,334 shares have been exercised, 2,500 shares have been repurchased and 6,108,603 shares remain outstanding.

(2) In July 1996 and January 1997, we sold an aggregate of 2,860,000 shares of our common stock to five purchasers at a purchase price of $0.001 per share, 350,000 shares of which we repurchased.

(3) From July 1996 to January 1997, we sold an aggregate of 665,000 shares of our Series A preferred stock to four purchasers at a purchase price of $0.10 per share.

(4) In January 1997, we sold an aggregate of 7,500,000 shares of our Series B preferred stock to nine purchasers at a purchase price of $0.80 per share.

(5) In May 1997, we issued a warrant to purchase 175,000 shares of our Series B preferred stock at a purchase price of $0.80 per share.

(6) From November 1997 to January 1998, we sold an aggregate of 7,406,843 shares of our Series C preferred stock to twelve purchasers at a purchase price of $1.14 per share.

(7) In June 1998, we issued a warrant to purchase 131,578 shares of Series C preferred stock at an exercise price of $1.14 per share.

(8) From December 1998 to May 1999, we sold an aggregate of 6,481,864 shares of our Series D preferred stock to ten purchasers at a purchase price of $2.00 per share.

(9) In December 1998, we issued five warrants to purchase an aggregate of 191,100 shares of Series D preferred stock at an exercise price of $2.00 per share, of which 180 shares have been exercised.

(10) On February 3, 2000, we sold an aggregate of 2,508,330 shares of our Series E preferred stock to thirteen purchasers at a purchase price of $6.00 per share, and issued 50,000 shares of Series E preferred stock to one entity for a license for technology.

ITEM 16. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

<TABLE>
<C> <S>
1.1 Form of Underwriting Agreement.

3.1*		Amended and Restated Certificate of Incorporation of Rigel to be filed upon the closing of the offering made pursuant to this Registration Statement.
3.2*		Amended and Restated Bylaws of Rigel to be filed upon the closing of the offering made pursuant to this Registration Statement.
4.1*		Specimen Common Stock Certificate.
4.2*		Amended and Restated Investor Rights Agreement, dated February 3, 2000, between Rigel and holders of Rigel's Series B, Series C, Series D and Series E preferred stock.
4.3*		Form of warrant to purchase shares of common stock.
4.4*		Warrant issued to Lighthouse Capital Partners II, L.P. for purchase of shares of Series B preferred stock.
4.5*		Warrant issued to Lighthouse Capital Partners II, L.P. for purchase of shares of Series C preferred stock.
4.6*		Form of warrant to purchase shares of Series D preferred stock.
5.1*		Opinion of Cooley Godward LLP.
10.1*		Form of Indemnity Agreement.
10.2*		2000 Equity Incentive Plan.
10.3*		Form of Stock Option Agreement pursuant to 2000 Equity Incentive Plan.
10.4*		2000 Employee Stock Purchase Plan.
10.5*		2000 Non-Employee Directors' Stock Option Plan.
10.6		Collaboration Agreement between Rigel and Janssen Pharmaceutica N.V., dated December 4, 1998.
10.7		Collaborative Research and License Agreement between Rigel and Pfizer Inc., dated January 31, 1999.
10.8		Collaboration Agreement between Rigel and Novartis Pharma AG, dated May 26, 1999.
10.9	++	License and Research Agreement between Rigel and Cell Genesys, Inc., dated September 2, 1999.
10.10*		Collaborative Research and Development Agreement between Rigel and Neurocrine Biosciences, Inc., dated December 1997.
10.11*		Employment agreement between Rigel and Donald Payan, dated January 16, 1997.
10.12*		Lease between Rigel and Britannia Pointe Grand Limited Partnership, dated June 2, 1998.
23.1*		Consent of Ernst & Young LLP, Independent Auditors.
23.2*		Consent of Cooley Godward LLP (included in Exhibit 5.1).
24.1*		Power of Attorney
27.1*		Financial Data Schedule.

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* Previously filed.

++ Confidential treatment requested as to specific portions, which portions are omitted and filed separately with the Securities and Exchange Commission.

ITEM 17. UNDERTAKINGS

The registrant hereby undertakes to provide to the Underwriters at the closing specified in the Underwriting Agreement certificates in such denominations and registered in such names as required by the Underwriters to permit prompt delivery to each purchaser.

Insofar as indemnification by the registrant for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the provisions referenced in Item 14 of this Registration Statement or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act, and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered hereunder, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act, the information omitted from the form of Prospectus filed as part of this Registration Statement in reliance upon Rule 430A and contained in a form of Prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this Registration Statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of Prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant has duly caused this Amendment No. 4 to the Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of South San Francisco, State of California, on the 28th day of March, 2000.

<TABLE>
<S> <C>
RIGEL PHARMACEUTICALS, INC.

By: /s/ JAMES M. GOWER
James M. Gower
CHIEF EXECUTIVE OFFICER
</TABLE>

<TABLE>
<CAPTION>

SIGNATURE	TITLE	DATE
<S>	<C>	<C>
/s/ JAMES M. GOWER James M. Gower	President, Chief Executive Officer and Director (Principal Executive Officer)	March 28, 2000
/s/ BRIAN C. CUNNINGHAM Brian C. Cunningham	Senior Vice President, Chief Financial Officer, Chief Operating Officer and Secretary (Principal Finance and Accounting Officer)	March 28, 2000
/s/ DONALD G. PAYAN Donald G. Payan	Executive Vice President, Chief Scientific Officer and Director	March 28, 2000
/s/ JEAN DELEAGE Jean Deleage	Director	March 28, 2000
/s/ ALAN D. FRAZIER Alan D. Frazier	Director	March 28, 2000
/s/ WALTER H. MOOS Walter H. Moos	Director	March 28, 2000
/s/ STEPHEN A. SHERWIN Stephen A. Sherwin	Director	March 28, 2000

</TABLE>

EXHIBIT INDEX

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EXHIBIT
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NUMBER	DESCRIPTION
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24.1*	Power of Attorney
27.1*	Financial Data Schedule.
</TABLE>	

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* Previously filed.

++ Confidential treatment requested as to specific portions, which portions are omitted and filed separately with the Securities and Exchange Commission.

Exhibit 1.1

UNDERWRITING AGREEMENT

March __, 2000

Warburg Dillon Read LLC
Robertson Stephens
Prudential Vector Healthcare
as Managing Underwriters
c/o Warburg Dillon Read LLC
299 Park Avenue
New York, New York 10171-0026

Ladies and Gentlemen:

Rigel Pharmaceuticals, Inc. a Delaware corporation (the "Company"), proposes to issue and sell to the underwriters named in Schedule A annexed hereto (the "Underwriters") an aggregate of 9,000,000 shares (the "Firm Shares") of Common Stock, $0.001 par value (the "Common Stock"), of the Company. In addition, solely for the purpose of covering over-allotments, the Company proposes to grant to the Underwriters the option to purchase from the Company up to an additional 1,350,000 shares of Common Stock (the "Additional Shares"). The Firm Shares and the Addtional Shares are hereinafter collectively sometimes referred to as the "Shares." The Shares are described in the Prospectus which is referred to below.

The Company has filed, in accordance with the provisions of the Securities Act of 1933, as amended, and the rules and regulations thereunder (collectively called the "Act"), with the Securities and Exchange Commission (the "Commission") a registration statement on Form S-1 (Registration No. 333-96127) including a prospectus, relating to the Shares. The Company has furnished to you, for use by the Underwriters and by dealers, copies of one or more preliminary prospectuses (each thereof being herein called a "Preliminary Prospectus") relating to the Shares. Except where the context otherwise requires, the registration statement, as amended when it becomes effective, including all documents filed as a part thereof, and including any information contained in a prospectus subsequently filed with the Commission pursuant to Rule 424(b) under the Act and deemed to be part of the registration statement at the time of effectiveness pursuant to Rule 430(A) under the Act and also including any registration statement filed pursuant to Rule 462(b) under the Act, is herein called the "Registration Statement," and the prospectus, in the form filed by the Company with the Commission pursuant to Rule 424(b) under the Act on or before the second business day after the date hereof (or such earlier time as may be required under the Act) or, if no such filing is required, the form of final prospectus included in the Registration Statement at the time it became effective, is herein called the "Prospectus."

The Company and the Underwriters agree as follows:

1. SALE AND PURCHASE. Upon the basis of the warranties and representations and subject to the terms and conditions herein set forth, the Company agrees to sell to the respective Underwriters and each of the Underwriters, severally and not jointly, agrees to purchase from the Company the aggregate number of Firm Shares set forth opposite the name of such Underwriter in Schedule A attached hereto in each case at a purchase price of $ per Share. The Company is advised by you that the Underwriters intend (i) to make a public offering of their respective portions of the Firm Shares as soon after the effective date of the Registration Statement as in your judgment is advisable and (ii) initially to offer the Firm Shares upon the terms set forth in the Prospectus. You may from time to time increase or decrease the public offering price after the initial public offering to such extent as you may determine.

In addition, the Company hereby grants to the several Underwriters the option to purchase, and upon the basis of the warranties and representations and subject to the terms and conditions herein set forth, the Underwriters shall have the right to purchase, severally and not jointly, from the Company, ratably in accordance with the number of Firm Shares to be purchased by each of them, all or a portion of the Additional Shares as may be necessary to cover over-allotments made in connection with the offering of the Firm Shares, at the same purchase price per share to be paid by the Underwriters to the Company for the Firm Shares. This option may be exercised by you on behalf of the several Underwriters at any time (but not more than once) on or before the thirtieth (30th) day following the date hereof, by written notice to the Company. Such notice shall set forth the aggregate number of Additional Shares as to which the option is being exercised, and the date and time when the Additional Shares are to be delivered (such date

and time being herein referred to as the "Additional Time of Purchase"); PROVIDED, HOWEVER, that the Additional Time of Purchase shall not be earlier than the Time of Purchase (as defined below) nor earlier than the second business day1 after the date on which the option shall have been exercised nor later than the tenth (10th) business day after the date on which the option shall have been exercised. The number of Additional Shares to be sold to each Underwriter shall be the number which bears the same proportion to the aggregate number of Additional Shares being purchased as the number of Firm Shares set forth opposite the name of such Underwriter on Schedule A hereto bears to the total number of Firm Shares (subject, in each case, to such adjustment as you may determine to eliminate fractional shares).

2. PAYMENT AND DELIVERY. Payment of the purchase price for the Firm Shares shall be made to the Company by Federal Funds wire transfer, against delivery of the certificates for the Firm Shares to you through the facilities of the Depository Trust Company (DTC) for the respective accounts of the Underwriters. Such payment and delivery shall be made at 10:00 A.M., New York City time, on April __, 2000 (unless another time shall be agreed to by you and the Company or unless postponed in accordance with the provisions of Section 8 hereof). The time at which such payment and delivery are actually made is hereinafter sometimes called the "Time of Purchase." Certificates for the Firm Shares shall be delivered to

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1 As used herein "business day" shall mean a day on which the New York Stock Exchange is open for trading.

you in definitive form in such names and in such denominations as you shall specify on the second business day preceding the Time of Purchase. For the purpose of expediting the checking of the certificates for the Firm Shares by you, the Company agrees to make such certificates available to you for such purpose at least one full business day preceding the Time of Purchase.

Payment of the purchase price for the Additional Shares shall be made at the Additional Time of Purchase in the same manner and at the same office as the payment for the Firm Shares. Certificates for the Additional Shares shall be delivered to you in definitive form in such names and in such denominations as you shall specify no later than the second business day preceding the Additional Time of Purchase. For the purpose of expediting the checking of the certificates for the Additional Shares by you, the Company agrees to make such certificates available to you for such purpose at least one full business day preceding the Additional Time of Purchase.

3. REPRESENTATIONS AND WARRANTIES OF THE COMPANY. The Company represents and warrants to each of the Underwriters that:

(a) the Company has not received, and has no notice of, any order of the Commission preventing or suspending the use of any Preliminary Prospectus, or instituting proceedings for that purpose, and each Preliminary Prospectus, at the time of filing thereof, conformed in all material respects to the requirements of the Act; and when the Registration Statement became effective, the Registration Statement and the Prospectus fully complied in all material respects with the provisions of the Act, and the Registration Statement did not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading, and the Prospectus did not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; any statutes, regulations, contracts or other documents that are required to be described in the Registration Statement or the Prospectus or to be filed as exhibits to the Registration Statement have been so described or filed; provided, however, that the Company makes no warranty or representation with respect to any statement contained in the Registration Statement or the Prospectus in reliance upon and in conformity with information concerning the Underwriters and furnished in writing by or on behalf of any Underwriter through you to the Company expressly for use in the Registration Statement or the Prospectus; the documents incorporated by reference in the Prospectus, at the time they were filed with the Commission, complied in all material respects with the requirements of the Act and the Exchange Act, and do not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; and when the Registration Statement becomes effective, the documents incorporated by reference in the Prospectus, will comply in all material respects with the requirements of the Act and the Exchange Act, and will not contain an untrue statement of a material fact or omit to state a material

fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; and the Company has not distributed any offering material in connection

with the offering or sale of the Shares other than the Registration Statement, the Preliminary Prospectus, the Prospectus or any other materials, if any, permitted by the Act;

(b) as of the date of this Agreement, the Company has an authorized capitalization as set forth under the heading entitled "Actual" in the section of the Registration Statement and the Prospectus entitled "Capitalization" and, as of the Time of Purchase and the Additional Time of Purchase, as the case may be, the Company shall have an authorized capitalization as set forth under the heading entitled "As Adjusted" in the section of the Registration Statement and the Prospectus entitled "Capitalization"; all of the issued and outstanding shares of capital stock including Common Stock of the Company have been duly and validly authorized and issued and are fully paid and non-assessable, have been issued in compliance with all federal and state securities laws and were not issued in violation of any preemptive right, resale right, right of first refusal or similar right;

(c) the Company has been duly incorporated and is validly existing as a corporation in good standing under the laws of the State of Delaware, with full corporate power and authority to own, lease and operate its properties and conduct its business as described in the Registration Statement;

(d) the Company is qualified to do business as a foreign corporation in good standing in each jurisdiction where the ownership or leasing of its properties or the conduct of its business requires such qualification, except where the failure to so qualify would not have a material adverse effect on the business, properties, financial condition or results of operation of the Company taken as a whole (a "Material Adverse Effect"). The Company has no subsidiaries (as defined in the Rules and Regulations); the Company does not own, directly or indirectly, any shares of stock or any other equity or long-term debt securities of any corporation or have any equity interest in any firm, partnership, joint venture, association or other entity; complete and correct copies of the certificates of incorporation and of the bylaws of the Company and all amendments thereto have been delivered to you, and except as set forth in the exhibits to the Registration Statement no changes therein will be made subsequent to the date hereof and prior to the Closing Date or, if later, the Option Closing Date;

(e) the Company is duly qualified or licensed by and is in good standing in each jurisdiction in which it conducts its business and in which the failure, individually or in the aggregate, to be so licensed or qualified could have a Material Adverse Effect; and the Company is in compliance in all material respects with the laws, orders, rules, regulations and directives issued or administered by such jurisdictions;

(f) The Company is not in breach of, or in default under (nor has any event occurred which with notice, lapse of time, or both would result in any breach of, or constitute a default under), its charter or by-laws or in the performance or observance of any obligation, agreement, covenant or condition contained in any indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company is a party or by which it or its properties is bound, and the execution, delivery and performance of this Agreement, the issuance and sale of the Shares and the consummation of the transactions contemplated hereby will not conflict with, or result in any breach of or constitute a default under (nor constitute any event which with notice, lapse of time, or both would result in any breach of, or constitute a default under), any provisions of the charter or by-laws of the Company or under any provision of any license, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company is a party or by which it or its properties may be bound or affected, or under any federal, state, local or foreign law, regulation or rule or any decree, judgment or order applicable to the Company;

(g) this Agreement has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company enforceable in accordance with its terms;

(h) the capital stock of the Company, including the Shares, conforms in all material respects to the description thereof contained in the Registration Statement and Prospectus and the certificates for the Shares are in due and proper form and the holders of the Shares will not be subject to personal liability by reason of being such holders;

(i) the Shares have been duly and validly authorized and, when issued and delivered against payment therefor as provided herein, will be duly and validly issued and fully paid and non-assessable;

(j) no approval, authorization, consent or order of or filing with any national, state or local governmental or regulatory commission, board, body, authority or agency is required in connection with the issuance and sale of the Shares or the consummation by the Company of the transactions as contemplated hereby other than registration of the Shares under the Act and any necessary qualification under the securities or blue sky laws of the various jurisdictions in which the Shares are being offered by the Underwriters or under the rules and regulations of the National Association of Securities Dealers, Inc. (NASD);

(k) no person has the right, contractual or otherwise, to cause the Company to issue to it, or register pursuant to the Act, any shares of capital stock of the Company upon the issue and sale of the Shares to the Underwriters hereunder, nor does any person have preemptive rights, co-sale rights, rights of first refusal or other rights to purchase any of the Shares other than those that have been expressly waived prior to the date hereof;

(l) Ernst & Young LLP, whose report on the financial statements of the Company is filed with the Commission as part of the Registration Statement and Prospectus, are independent public accountants as required by the Act;

(m) The Company has all necessary licenses, authorizations, consents and approvals and has made all necessary filings required under any federal, state, local or foreign law, regulation or rule, and has obtained all necessary authorizations, consents and approvals from other persons, in order to conduct its business; the Company is not in violation of, or in default under, any such license, authorization, consent or approval or any federal, state, local or foreign law, regulation or rule or any decree, order or judgment applicable to the Company the effect of which could have a Material Adverse Effect;

(n) all legal or governmental proceedings, contracts, leases or documents of a character required to be described in the Registration Statement or the Prospectus or to be filed as an exhibit to the Registration Statement have been so described or filed as required;

(o) there are no actions, suits, claims, investigations or proceedings pending or threatened to which the Company or any of its officers is a party or of which any of their respective properties is subject at law or in equity, or before or by any federal, state, local or foreign governmental or regulatory commission, board, body, authority or agency which could result in a judgment, decree or order having a Material Adverse Effect or prevent consummation of the transactions contemplated hereby;

(p) the audited financial statements included in the Registration Statement and the Prospectus present fairly the financial position of the Company

as of the dates indicated and the results of operations and cash flows of the Company for the periods specified; such financial statements have been prepared in conformity with generally accepted accounting principles applied on consistent basis during the periods involved;

(q) subsequent to the respective dates as of which information is given in the Registration Statement and the Prospectus, there has not been (i) any material adverse change, or any development which, in the Company's reasonable judgment, is likely to cause a material adverse change, in the business, properties or assets described or referred to in the Registration

Statement, or the results of operations, condition (financial or otherwise), business or operations of the Company taken as a whole, (ii) any transaction which is material to the Company, except transactions in the ordinary course of business, (iii) any obligation, direct or contingent, which is material to the Company and its Subsidiaries taken as a whole, incurred by the Company, except obligations incurred in the ordinary course of business, (iv) any change in the capital stock or outstanding indebtedness of the Company or (v) any dividend or distribution of any kind declared, paid or made on the capital stock of the Company. The Company does not have any material contingent obligation which is not disclosed in the Registration Statement;

(r) the Company has obtained the agreement of (i) each of its directors and officers, (ii) the holders of at least 98.0% of the outstanding common stock and preferred stock, and (iii) the holders of other securities convertible into or exercisable or exchangeable for common stock or warrants or other rights to purchase common stock (such that the aggregate of such securities which are not subject to such agreement does not represent more than 1% of the outstanding common stock), and stockholders not to sell, offer to sell, contract to sell, hypothecate, grant any option to sell or otherwise dispose of, directly or indirectly, any shares of Common Stock or securities convertible into or exercisable or exchangeable for Common Stock or warrants or other rights to purchase Common Stock for a period of 180 days after the date of the Prospectus;

(s) the Company is not and, after giving effect to the offering and sale of the Shares, will not be an "investment company" or an entity "controlled" by an "investment company," as such terms are defined in the Investment Company Act of 1940, as amended (the "Investment Company Act"); and

(t) except as described in the Registration Statement and Prospectus, the Company owns, or has obtained valid and enforceable licenses for, or other rights to use, the inventions, patent applications, patents, trademarks (both registered and unregistered), tradenames, copyrights and trade secrets described in the Registration Statement and Prospectus as being owned or licensed by it, which the Company reasonably believes are necessary for the conduct of its business (collectively, "Intellectual Property") and which the failure to own, license or have such rights could have a Material Adverse Effect. Except as described in the Registration Statement and Prospectus, (i) the Company believes that there are no third parties who have or will be able to establish their rights to any Intellectual Property, except for the ownership rights of the owners of the Intellectual Property which is licensed to the Company; (ii) to the Company's knowledge there is no infringement by third parties of any Intellectual Property; (iii) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others challenging the Company's rights in or to any Intellectual Property, and

the Company is unaware of any facts which would form a reasonable basis for any such claim; (iv) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others challenging the validity or scope of any Intellectual Property, and the Company is unaware of any facts which would form a reasonable basis for any such claim; (v) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others that the Company infringes or otherwise violates any patent, trademark, copyright, trade secret or other proprietary rights of others, and the Company is unaware of any facts which would form a reasonable basis for any such claim; (vi) to the Company's knowledge there is no patent or patent application which contains claims that interfere with the issued or pending claims of any of the patents and patent applications owned by the Company which could have a Material Adverse Effect; and (vii) there is no prior art of which the Company is aware that may render any patent application owned by the Company unpatentable which has not been disclosed to the U.S. Patent and Trademark Office and which could have a Material Adverse Effect.

4. CERTAIN COVENANTS OF THE COMPANY. The Company hereby agrees:

(a) to furnish such information as may be required and otherwise to cooperate in qualifying the Shares for offering and sale under the securities or blue sky laws of such states as you may

designate and to maintain such qualifications in effect so long as required for the distribution of the Shares; PROVIDED that the Company shall not be required to qualify as a foreign corporation or to consent to the service of process under the laws of any such state (except service of process with respect to the offering and sale of the Shares); and to promptly advise you of the receipt by the Company of any notification with respect to the suspension of the qualification of the Shares for sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose;

(b) to make available to the Underwriters in New York City, as soon as practicable after the Registration Statement becomes effective, and thereafter from time to time to furnish to the Underwriters, as many copies of the Prospectus (or of the Prospectus as amended or supplemented if the Company shall have made any amendments or supplements thereto after the effective date of the Registration Statement) as the Underwriters may request for the purposes contemplated by the Act; in case any Underwriter is required to deliver a prospectus within the nine-month period referred to in Section 10(a)(3) of the Act in connection with the sale of the Shares, the Company will prepare promptly upon request, but at the expense of such Underwriter, such amendment or amendments to the Registration Statement and such prospectuses as may be necessary to permit compliance with the requirements of Section 10(a)(3) of the Act;

(c) to advise you promptly and (if requested by you) to confirm such advice in writing, (i) when the Registration Statement has become effective and when any post-effective amendment thereto becomes effective and (ii) if Rule 430A under the Act is used, when the Prospectus is filed with the Commission pursuant to Rule 424(b) under the Act (which the Company agrees to file in a timely manner under such Rules);

(d) to advise you promptly, confirming such advice in writing, of any request by the Commission for amendments or supplements to the Registration Statement or Prospectus or for additional information with respect thereto, or of notice of institution of proceedings for, or the entry of a stop order suspending the effectiveness of the Registration Statement and, if the Commission should enter a stop order suspending the effectiveness of the Registration Statement, to make every reasonable effort to obtain the lifting or removal of such order as soon as possible; to advise you promptly of any

proposal to amend or supplement the Registration Statement or Prospectus and to file no such amendment or supplement to which you shall object in writing;

(e) to file promptly all reports and any definitive proxy or information statement required to be filed by the Company with the Commission in order to comply with the Exchange Act subsequent to the date of the Prospectus and for so long as the delivery of a prospectus is required in connection with the offering or sale of the shares, and to promptly notify you of such filing;

(f) if necessary or appropriate, to file a registration statement pursuant to Rule 462(b) under the Act;

(g) to furnish to you and, upon request, to each of the other Underwriters for a period of five years from the date of this Agreement (i) copies of any reports or other communications which the Company shall send to its stockholders or shall from time to time publish or publicly disseminate, (ii) copies of all annual, quarterly and current reports filed with the Commission on Forms 10-K, 10-Q and 8-K, or such other similar form as may be designated by the Commission, (iii) copies of documents or reports filed with any national securities exchange on which any class of securities of the Company is listed, and (iv) such other information as you may reasonably request regarding the Company, in each case as soon as such communications, documents or information becomes available;

(h) to advise the Underwriters promptly of the happening of any event known to the Company within the time during which a Prospectus relating to the Shares is required to be delivered under the Act which, in the judgment of the Company, would require the making of any change in the Prospectus then being used, so that the Prospectus would not include an untrue statement of material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they are made, not misleading, and, during such time, to prepare and furnish, at the Company's expense, to the Underwriters promptly such

amendments or supplements to such Prospectus as may be necessary to reflect any such change and to furnish you a copy of such proposed amendment or supplement before filing any such amendment or supplement with the Commission;

(i) to make generally available to its stockholders, and to deliver to you, an earnings statement of the Company (which will satisfy the provisions of Section 11(a) of the Act) covering a period of twelve months beginning after the effective date of the Registration Statement (as defined in Rule 158(c) of the Act) as soon as is reasonably practicable after the termination of such twelve-month period;

(j) to furnish to its stockholders as soon as practicable after the end of each fiscal year an annual report (including a balance sheet and statements of income, stockholders' equity and of cash flow of the Company for such fiscal year, accompanied

by a copy of the certificate or report thereon of nationally recognized independent certified public accountants;

(k) to furnish to you signed copies of the Registration Statement, as initially filed with the Commission, and of all amendments thereto (including all exhibits thereto) and sufficient conformed copies of the foregoing (other than exhibits) for distribution of a copy to each of the other Underwriters;

(l) to apply the net proceeds from the sale of the Shares in the manner set forth under the caption "Use of Proceeds" in the Prospectus;

(m) to pay all costs, expenses, fees and taxes (other than any transfer taxes and fees and disbursements of counsel for the Underwriters except as set forth under Section 5 hereof) in connection with (i) the preparation and filing of the Registration Statement, each Preliminary Prospectus, the Prospectus, and any amendments or supplements thereto, and the printing and furnishing of copies of each thereof to the Underwriters and to dealers (including costs of mailing and shipment), (ii) the registration, issue, sale and delivery of the Shares, (iii) the producing, word processing and/or printing of this Agreement, any Agreement Among Underwriters, any dealer agreements, any Powers of Attorney and any closing documents (including compilations thereof) and the reproduction and/or printing and furnishing of copies of each thereof to the Underwriters and (except closing documents) to dealers (including costs of mailing and shipment), (iv) the qualification of the Shares for offering and sale under state laws and the determination of their eligibility for investment under state law as aforesaid (including the legal fees and filing fees and other disbursements of counsel for the Underwriters) and the printing and furnishing of copies of any blue sky surveys or legal investment surveys to the Underwriters and to dealers, (v) any listing of the Shares on any securities exchange or qualification of the Shares for quotation on NASDAQ and any registration thereof under the Exchange Act, (vi) any filing for review of the public offering of the Shares by the NASD and (vii) the performance of the Company's other obligations hereunder;

(n) to furnish to you, before filing with the Commission subsequent to the effective date of the Registration Statement and during the period referred to in paragraph (f) above, a copy of any document proposed to be filed pursuant to Section 13, 14 or 15(d) of the Exchange Act;

(o) not to sell, offer or agree to sell, contract to sell, grant any option to sell or otherwise dispose of, directly or indirectly, any shares of Common Stock or securities convertible into or exchangeable or exercisable for Common Stock or warrants or other

rights to purchase Common Stock or any other securities of the Company that are substantially similar to Common Stock or permit the registration under the Act of any shares of Common Stock, except for (i) issuances of Common Stock upon the exercise of outstanding options, warrants and debentures, (ii) the registration of the Shares and the sales to the Underwriters pursuant to this Agreement, and (iii) the granting of stock options under the Company's 2000 Equity Incentive Plan and Non-Employee Directors' Plan for a period

of 180 days after the date hereof, without the prior written consent of Warburg Dillon Read LLC ("WDR"); and

(p) to use its best efforts to cause the Common Stock to be listed for quotation on the National Association of Securities Dealers Automated Quotation National Market System ("NASDAQ").

5. REIMBURSEMENT OF UNDERWRITERS' EXPENSES. If the Shares are not delivered for any reason other than the termination of this Agreement pursuant to the second paragraph of Section 7 hereof or the default by one or more of the Underwriters in its or their respective obligations hereunder, the Company shall, in addition to paying the amounts described in Section 4(n) hereof, reimburse the Underwriters for all of their reasonable out-of-pocket expenses, including the fees and disbursements of their counsel.

6. CONDITIONS OF UNDERWRITERS' OBLIGATIONS. The several obligations of the Underwriters hereunder are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the Time of Purchase (and the several obligations of the Underwriters at the Additional Time of Purchase are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the Time of Purchase (unless previously waived) and at the Additional Time of Purchase, as the case may be), the performance by the Company of its obligations hereunder and to the following additional conditions precedent:

(a) The Company shall furnish to you at the Time of Purchase and at the Additional Time of Purchase, as the case may be, an opinion of Cooley Godward LLP, counsel for the Company, addressed to the Underwriters, and dated the Time of Purchase or the Additional Time of Purchase, as the case may be, with reproduced copies for each of the other Underwriters and in form satisfactory to Brobeck, Phleger & Harrison LLP, counsel for the Underwriters, stating that:

(i) the Company has been duly incorporated and is validly existing as a corporation in good standing under the laws of the State of Delaware, with full corporate power and authority to own, lease and operate its properties and conduct its business as described in the Registration Statement and the Prospectus, to execute and deliver this Agreement and to issue, sell and deliver the Shares as herein contemplated;

(ii) the Company is duly qualified or licensed by each jurisdiction in which it conducts its business and in which the failure, individually or in the aggregate, to be so licensed or qualified could have a Material Adverse Effect and the Company is duly qualified, and in good standing, in each jurisdiction in which it owns or leases real property or maintain an office and in which such qualification is necessary and except where failure to be so qualified would not have a Material Adverse Effect;

(iii) this Agreement has been duly authorized, executed and delivered by the Company;

(iv) the Shares have been duly authorized and, when issued and delivered to and paid for by the Underwriters, will be validly issued and will be fully paid and non-assessable;

(v) the Company has an authorized capitalization as set forth in the Registration Statement and the Prospectus; the outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid, nonassessable and free of any preemptive rights arising under the Company's certificate of incorporation, as amended and restated, or the Delaware General Corporate Law and, to such counsel's knowledge, any contractual preemptive rights, resale rights, rights of first refusal and similar rights; the Shares when issued will be free of statutory and contractual preemptive rights; the certificates for the Shares are in due and proper form and the holders of the Shares will not be subject to personal liability by reason of being such holders;

(vi) the capital stock of the Company, including the Shares, conforms to the description thereof contained in the Registration Statement and Prospectus;

(vii) the Registration Statement and the Prospectus (except as to the financial statements and schedules and other financial and statistical data contained

or incorporated by reference therein, as to which such counsel need express no opinion) comply as to form in all material respects with the requirements of the Act;

(viii) the Registration Statement has become effective under the Act and, to the best of such counsel's knowledge, no stop order proceedings with respect thereto are pending or threatened under the Act and any required filing of the Prospectus and any supplement thereto pursuant to Rule 424 under the Act has been made in the manner and within the time period required by such Rule 424;

(ix) no approval, authorization, consent or order of or filing with any national, state or local governmental or regulatory commission, board, body, authority or agency is required in connection with the issuance and sale of the Shares and consummation by the Company of the transactions as contemplated hereby other than registration of the Shares under the Act (except such counsel need express no opinion as to any necessary qualification under the state securities or blue sky laws of the various jurisdictions in which the Shares are being offered by the Underwriters);

(x) the execution, delivery and performance of this Agreement by the Company and the consummation by the Company of the transactions contemplated hereby do not and will not conflict with, or result in any breach of, or constitute a default under (nor constitute any event which with notice, lapse of time, or both, would result in any breach of, or constitute a default under), any provisions of the charter or by-laws of the Company or under any provision of any license, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company is a party or by which any of them or their respective properties may be bound or affected and which are listed on Schedule A attached to the opinion being provided pursuant to this Section 6(a), or under any federal, state, local or foreign law, regulation or rule or any decree, judgment or order applicable to the Company;

(xi) to the best of such counsel's knowledge, the Company is not in violation of its charter or by-laws or is in breach of, or in default under (nor has any event occurred which with notice, lapse of time, or both would result in any breach of, or constitute a default under), any license, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company is a party or by which it or its properties may be bound or affected and which are listed on Schedule A attached to the opinion being provided pursuant to this Section 6(a), or under any federal, state, local or foreign law, regulation or rule or any decree, judgment or order applicable to the Company;

(xii) to the best of such counsel's knowledge, there are no contracts, licenses, agreements, leases or documents of a character which are required to be

filed as exhibits to the Registration Statement or to be summarized or described in the Prospectus which have not been so filed, summarized or described;

(xiii) to the best of such counsel's knowledge, there are no actions, suits, claims, investigations or proceedings pending, threatened or contemplated to which the Company is subject or of which any of its properties is subject at law or in equity or before or by any federal, state, local or foreign governmental or regulatory commission, board, body, authority or agency which are required to be described in the Prospectus but are not so described;

(xiv) the Company will not, upon consummation of the transactions contemplated by this Agreement, be an "investment company," or a "promoter" or "principal underwriter" for, a "registered investment company," as such

terms are defined in the Investment Company Act of 1940, as amended; and

(xv) such counsel have participated in conferences with officers and other representatives of the Company, representatives of the independent public accountants of the Company and representatives of the Underwriters at which the contents of the Registration Statement and Prospectus were discussed and, although such counsel is not passing upon and does not assume responsibility for the accuracy, completeness or fairness of the statements contained in the Registration Statement or Prospectus (except as and to the extent stated in subparagraphs (vi) and (viii) above), on the basis of the foregoing nothing has come to the attention of such counsel that causes them to believe that the Registration Statement or any amendment thereto at the time such Registration Statement or amendment became effective contained an untrue statement of a material fact or omitted to state a material fact required to be stated therein or necessary to make the statements therein not misleading, or that the Prospectus or any supplement thereto at the date of such Prospectus or such supplement, and at all times up to and including the Time of Purchase or Additional Time of Purchase, as the case may be, of a material fact or omitted to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading (it being understood that such counsel need express no opinion with respect to the financial statements and schedules and other financial and statistical data included in the Registration Statement or Prospectus).

(b) The Company shall furnish to you at the Time of Purchase and at the Additional Time of Purchase, as the case may be, an opinion of Flehr Hohbach Test Albritton & Herbert LLP, patent counsel for the Company, addressed to the Underwriters, and dated the Time of Purchase or the Additional Time of Purchase, as the case may be, with reproduced copies for each of the other Underwriters, substantially in the form attached hereto as EXHIBIT A and satisfactory to Brobeck, Phleger & Harrison LLP, counsel for the Underwriters.

(c) You shall have received from Ernst & Young LLP, letters dated, respectively, the date of this Agreement and the Time of Purchase and Additional Time of Purchase, as the case may be, and addressed to the Underwriters (with reproduced copies for each of the Underwriters) in the forms heretofore approved by WDR.

(d) You shall have received at the Time of Purchase and at the Additional Time of Purchase, as the case may be, the opinion of Brobeck, Phleger & Harrison LLP, counsel for the Underwriters, dated the Time of Purchase or the Additional Time of Purchase, as the case may be, as to the matters referred to in subparagraphs (viii) (with respect to the Shares only), (ix) and (x) of paragraph (a) of this Section 6.

In addition, such counsel shall state that such counsel have participated in conferences with officers and other representatives of the Company, counsel for the Company, representatives of the independent public accountants of the Company and representatives of the Underwriters at which the contents of the Registration Statement and Prospectus and related matters were discussed and, although such counsel is not passing upon and does not assume any responsibility for the accuracy, completeness or fairness of the statements contained in the Registration Statement and Prospectus (except as to matters referred to with respect to the Shares under subparagraph (viii) of paragraph (a) of this Section 6), on the basis of the foregoing (relying as to materiality to a large extent upon the opinions of officers and other representatives of the Company), no facts have come to the attention of such counsel which lead them to believe that the Registration Statement or any amendment thereto at the time such Registration Statement or amendment became effective contained an untrue statement of a material fact or omitted to state a material fact required to be stated therein or necessary to make the statements therein not misleading or that the Prospectus as of its date or any supplement thereto as of its date contained an untrue statement of a material fact or omitted to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading (it being understood that such counsel need express no comment with respect to the financial statements and schedules and other financial and statistical data included in the Registration Statement or Prospectus).

(e) No amendment or supplement to the Registration Statement or Prospectus shall be filed prior to the time the Registration Statement becomes effective to which you object in writing.

(f) The Registration Statement shall become effective, or if Rule 430A under the Act is used, the Prospectus shall have been filed with the Commission pursuant to

Rule 424(b) under the Act, at or before 5:00 P.M., New York City time, on the date of this Agreement, unless a later time (but not later than 5:00 P.M., New York City time, on the second full business day after the date of this Agreement) shall be agreed to by the Company and you in writing or by telephone, confirmed in writing; PROVIDED, HOWEVER, that the Company and you and any group of Underwriters, including you, who have agreed hereunder to purchase in the aggregate at least 50% of the Firm Shares may from time to time agree on a later date.

(g) Prior to the Time of Purchase or the Additional Time of Purchase, as the case may be, (i) no stop order with respect to the effectiveness of the Registration Statement shall have been issued under the Act or proceedings initiated under Section 8(d) or 8(e) of the Act; (ii) the Registration Statement and all amendments thereto, or modifications thereof, if any, shall not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading; and (iii) the Prospectus and all amendments or supplements thereto, or modifications thereof, if any, shall not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they are made, not misleading.

(h) Between the time of execution of this Agreement and the Time of Purchase or the Additional Time of Purchase, as the case may be, (i) no material and unfavorable change, financial or otherwise (other than as referred to in the Registration Statement and Prospectus), in the business, condition or prospects of the Company and its Subsidiaries taken as a whole shall occur or become known and (ii) no transaction which is material and unfavorable to the Company shall have been entered into by the Company.

(i) The Company will, at the Time of Purchase or Additional Time of Purchase, as the case may be, deliver to you a certificate of two of its executive officers to the effect that the representations and warranties of the Company as set forth in this Agreement are true and correct as of each such date, that the Company shall perform such of its obligations under this Agreement as are to be performed at or before the Time of Purchase and at or before the Additional Time of Purchase, as the case may be and the conditions set forth in paragraphs (g) and (h) of this Section 6 have been met.

(j) You shall have received signed letters, dated the date of this Agreement, from each of the directors and officers of the Company and each stockholder of the Company designated by you to the effect that such persons shall not sell, offer or agree to sell, contract to sell, grant any option to sell or otherwise dispose of, directly or indirectly, any shares of Common Stock of the Company or securities convertible into or exchangeable or exercisable for Common Stock or warrants or other rights to purchase Common Stock or any other securities of the Company that are substantially similar to the Common Stock for a period of 180 days after the date of the Prospectus without WDR's prior written consent.

(k) The Company shall have furnished to you such other documents and certificates as to the accuracy and completeness of any statement in the Registration Statement and the Prospectus as of the Time of Purchase and the Additional Time of Purchase, as the case may be, as you may reasonably request.

(l) The Shares shall have been approved for listing for quotation on NASDAQ, subject only to notice of issuance at or prior to the Time of Purchase or the Additional Time of Purchase, as the case may be.

(m) Between the time of execution of this Agreement and the Time of Purchase or Additional Time of Purchase, as the case may

be, there shall not have occurred any downgrading, nor shall any notice or announcement have been given or made of (i) any intended or potential downgrading or (ii) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization," as that term is defined in Rule 436(g)(2) under the Act.

7. EFFECTIVE DATE OF AGREEMENT; TERMINATION. This Agreement shall become effective (i) if Rule 430A under the Act is not used, when you shall have received notification of the effectiveness of the Registration Statement, or (ii) if Rule 430A under the Act is used, when the parties hereto have executed and delivered this Agreement.

The obligations of the several Underwriters hereunder shall be subject to termination in the absolute discretion of you or any group of Underwriters (which may include you) which has agreed to purchase in the aggregate at least 50% of the Firm Shares, if, since the time of execution of this Agreement or the respective dates as of which information is given in the Registration Statement and Prospectus, (y) there has been any material adverse and unfavorable change, financial or otherwise (other than as referred to in the Registration Statement and Prospectus), in the operations, business, or condition of the Company which would, in your judgment or in the judgment of such group of Underwriters, make it impracticable to market the Shares, or (z) there shall have occurred any downgrading, or any notice shall have been given of (i) any intended or potential downgrading or (ii) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization", as that term is defined in Rule 436(g)(2) under the Act or, if, at any time prior to the Time of Purchase or, with respect to the purchase of any Additional Shares, the Additional Time of Purchase, as the case may be, trading in securities on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market shall have been suspended or limitations or minimum prices shall have been established on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market, or if a banking moratorium shall have been declared either by the United States or New York State authorities, or if the United States shall have declared war in accordance with its constitutional processes or there shall have occurred any material outbreak or escalation of hostilities or other national or international calamity or crisis of such magnitude in its effect on the financial markets of the United States as, in your judgment or in the judgment of such group of Underwriters, to make it impracticable to market the Shares.

If you or any group of Underwriters elects to terminate this Agreement as provided in this Section 7, the Company and each other Underwriter shall be notified promptly by letter or telegram.

If the sale to the Underwriters of the Shares, as contemplated by this Agreement, is not carried out by the Underwriters for any reason permitted under this Agreement or if such sale is not carried out because the Company shall be unable to comply with any of the terms of this Agreement, the Company shall not be under any obligation or liability under this Agreement (except to the extent provided in Sections 4(n), 5 and 9 hereof), and the Underwriters shall be under no obligation or liability to the Company under this Agreement (except to the extent provided in Section 9 hereof) or to one another hereunder.

8. INCREASE IN UNDERWRITERS' COMMITMENTS. Subject to Sections 6 and 7, if any Underwriter shall default in its obligation to take up and pay for the Firm Shares to be purchased by it hereunder (otherwise than for a reason sufficient to justify the termination of this Agreement under the provisions of Section 7 hereof) and if the number of Firm Shares which all Underwriters so defaulting shall have agreed but failed to take up and pay for does not exceed 10% of the total number of Firm Shares, the non-defaulting Underwriters shall take up and pay for (in addition to the aggregate number of Firm Shares they are obligated to purchase pursuant to Section 1 hereof) the number of Firm Shares agreed to be purchased by all such defaulting Underwriters, as hereinafter provided. Such Shares shall be taken up and paid for by such non-defaulting Underwriter or Underwriters in such amount or amounts as you may designate with the consent of each Underwriter so designated or, in the event no such designation is made, such Shares shall be taken up and paid for by all non-defaulting Underwriters pro rata in proportion to the aggregate number of Firm Shares set opposite the names of such non-defaulting Underwriters in Schedule A.

Without relieving any defaulting Underwriter from its obligations hereunder, the Company agrees with the non-defaulting Underwriters that it will not sell any Firm Shares hereunder unless all of the Firm Shares are purchased by the Underwriters (or by substituted Underwriters selected by you with the approval of the Company or selected by the Company with your

approval).

If a new Underwriter or Underwriters are substituted by the Underwriters or by the Company for a defaulting Underwriter or Underwriters in accordance with the foregoing provision, the Company or you shall have the right to postpone the Time of Purchase for a period not exceeding five business days in order that any necessary changes in the Registration Statement and Prospectus and other documents may be effected.

The term Underwriter as used in this Agreement shall refer to and include any Underwriter substituted under this Section 8 with like effect as if such substituted Underwriter had originally been named in Schedule A.

If the aggregate number of Shares which the defaulting Underwriter or Underwriters agreed to purchase exceeds 10% of the total number of Shares which all Underwriters agreed to purchase hereunder, and if neither the non-defaulting Underwriters nor

the Company shall make arrangements within the five business day period stated above for the purchase of all the Shares which the defaulting Underwriter or Underwriters agreed to purchase hereunder, this Agreement shall be terminated without further act or deed and without any liability on the part of the Company to any non-defaulting Underwriter and without any liability on the part of any non-defaulting Underwriter to the Company. Nothing in this paragraph, and no action taken hereunder, shall relieve any defaulting Underwriter from liability in respect of any default of such Underwriter under this Agreement.

9. INDEMNITY AND CONTRIBUTION.

(a) The Company agrees to indemnify, defend and hold harmless each Underwriter, its partners, directors and officers, and any person who controls any Underwriter within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which, jointly or severally, any such Underwriter or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in the Registration Statement (or in the Registration Statement as amended by any post-effective amendment thereof by the Company) or in a Prospectus (the term Prospectus for the purpose of this Section 9 being deemed to include any Preliminary Prospectus, the Prospectus and the Prospectus as amended or supplemented by the Company), or arises out of or is based upon any omission or alleged omission to state a material fact required to be stated in either such Registration Statement or Prospectus or necessary to make the statements made therein not misleading, except insofar as any such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of any Underwriter through you to the Company expressly for use with reference to such Underwriter in such Registration Statement or such Prospectus or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Registration Statement or such Prospectus or necessary to make such information not misleading.

If any action, suit or proceeding (together, a "Proceeding") is brought against an Underwriter or any such person in respect of which indemnity may be sought against the Company pursuant to the foregoing paragraph, such Underwriter or such person shall promptly notify the Company in writing of the institution of such Proceeding and the Company shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all reasonable fees and expenses; provided, however, that the omission to so notify the Company shall not relieve the Company from any liability which the Company may have to any Underwriter or any such person or otherwise, except to the extent such ommission is determined by a court of competent jurisdiction to materially affect the Company's ability to defend such proceeding. Such Underwriter or such person shall have the right to employ its or their own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of such Underwriter or of such person unless the employment of such counsel shall have been authorized in writing by the Company in connection with the defense of such Proceeding or the Company shall not have, within a reasonable period of time in light of the circumstances, employed counsel to have charge of the defense of such Proceeding or

such indemnified party or parties shall have reasonably

concluded that there may be defenses available to it or them which are different from, additional to or in conflict with those available to the Company (in which case the Company shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties), in any of which events such reasonable fees and expenses shall be borne by the Company and paid as incurred (it being understood, however, that the Company shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). The Company shall not be liable for any settlement of any Proceeding effected without its written consent but if settled with the written consent of the Company, the Company agrees to indemnify and hold harmless any Underwriter and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without its written consent if (i) such settlement is entered into more than 60 business days after receipt by such indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior written notice of its intention to settle. No indemnifying party shall, without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are the subject matter of such Proceeding and does not include an admission of fault, cupability or a failure to act, by or on behalf of such indemnified party.

(b) Each Underwriter severally agrees to indemnify, defend and hold harmless the Company, its directors and officers, and any person who controls the Company within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which, jointly or severally, the Company or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of such Underwriter through you to the Company expressly for use with reference to such Underwriter in the Registration Statement (or in the Registration Statement as amended by any post-effective amendment thereof by the Company) or in a Prospectus, or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Registration Statement or such Prospectus or necessary to make such information not misleading.

If any Proceeding is brought against the Company or any such person in respect of which indemnity may be sought against any Underwriter pursuant to the foregoing paragraph, the Company or such person shall promptly notify such Underwriter in writing of the institution of such Proceeding and such Underwriter shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all

reasonable fees and expenses; provided, however, that the omission to so notify such Underwriter shall not relieve such Underwriter from any liability which such Underwriter may have to the Company or any such person or otherwise, except to the extent such omission is determined by a court of competent jurisdiction to materially affect such Underwriter's ability to defend such Proceeding. The Company or such person shall have the right to employ its own counsel in any such case, but the fees and expenses of such counsel shall be at the

expense of the Company or such person unless the employment of such counsel shall have been authorized in writing by such Underwriter in connection with the defense of such Proceeding or such Underwriter shall not have, within a reasonable period of time in light of the circumstances, employed counsel to have charge of the defense of such Proceeding or such indemnified party or parties shall have reasonably concluded that there may be defenses available to it or them which are different from or additional to or in conflict with those available to such Underwriter (in which case such Underwriter shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties, but such Underwriter may employ counsel and participate in the defense thereof but the fees and expenses of such counsel shall be at the expense of such Underwriter), in any of which events such reasonable fees and expenses shall be borne by such Underwriter and paid as incurred (it being understood, however, that such Underwriter shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). No Underwriter shall be liable for any settlement of any such Proceeding effected without the written consent of such Underwriter but if settled with the written consent of such Underwriter, such Underwriter agrees to indemnify and hold harmless the Company and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without its written consent if (i) such settlement is entered into more than 60 business days after receipt by such indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior written notice of its intention to settle. No indemnifying party shall, without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are the subject matter of such Proceeding.

(c) If the indemnification provided for in this Section 9 is unavailable to an indemnified party under subsections (a) and (b) of this Section 9 in respect of any losses, damages, expenses, liabilities or claims referred to therein, then each applicable indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, damages, expenses, liabilities or claims (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Underwriters on the other hand from the offering of the Shares or (ii) if the allocation provided by clause (i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) above

but also the relative fault of the Company on the one hand and of the Underwriters on the other in connection with the statements or omissions which resulted in such losses, damages, expenses, liabilities or claims, as well as any other relevant equitable considerations. The relative benefits received by the Company on the one hand and the Underwriters on the other shall be deemed to be in the same respective proportions as the total proceeds from the offering (net of underwriting discounts and commissions but before deducting expenses) received by the Company and the total underwriting discounts and commissions received by the Underwriters, bear to the aggregate public offering price of the Shares. The relative fault of the Company on the one hand and of the Underwriters on the other shall be determined by reference to, among other things, whether the untrue statement or alleged untrue statement of a material fact or omission or alleged omission relates to information supplied by the Company or by the Underwriters and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The amount paid or payable by a party as a result of the losses, damages, expenses, liabilities and claims referred to in this subsection shall be deemed to include any legal or other fees or expenses reasonably incurred by such party in connection with

investigating, preparing to defend or defending any Proceeding.

(d) The Company and the Underwriters agree that it would not be just and equitable if contribution pursuant to this Section 9 were determined by pro rata allocation (even if the Underwriters were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in subsection (c) above. Notwithstanding the provisions of this Section 9, no Underwriter shall be required to contribute any amount in excess of the amount by which the total price at which the Shares underwritten by such Underwriter and distributed to the public were offered to the public exceeds the amount of any damage which such Underwriter has otherwise been required to pay by reason of such untrue statement or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Underwriters' obligations to contribute pursuant to this Section 9 are several in proportion to their respective underwriting commitments and not joint.

(e) The indemnity and contribution agreements contained in this Section 9 and the covenants, warranties and representations of the Company contained in this Agreement shall remain in full force and effect regardless of any investigation made by or on behalf of any Underwriter, its partners, directors or officers or any person (including each partner, officer or director of such person) who controls any Underwriter within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, or by or on behalf of the Company, its directors or officers or any person who controls the Company within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and shall survive any termination of this Agreement or the issuance and delivery of the Shares. The Company and each Underwriter agree promptly to notify each other of the commencement of any Proceeding against it and, in the case of the Company, against any of the Company's officers or directors in connection with the issuance and sale of the Shares, or in connection with the Registration Statement or Prospectus.

10. NOTICES. Except as otherwise herein provided, all statements, requests, notices and agreements shall be in writing or by telegram and, if to the Underwriters, shall be

sufficient in all respects if delivered or sent to Warburg Dillon Read LLC, 299 Park Avenue, New York, N.Y. 10171-0026, Attention: Syndicate Department and, if to the Company, shall be sufficient in all respects if delivered or sent to the Company at the offices of the Company at _____, Attention: _____.

11. GOVERNING LAW; CONSTRUCTION. This Agreement and any claim, counterclaim or dispute of any kind or nature whatsoever arising out of or in any way relating to this Agreement ("Claim"), directly or indirectly, shall be governed by, and construed in accordance with, the laws of the State of New York. The Section headings in this Agreement have been inserted as a matter of convenience of reference and are not a part of this Agreement.

12. SUBMISSION TO JURISDICTION. Except as set forth below, no Claim may be commenced, prosecuted or continued in any court other than the courts of the State of New York located in the City and County of New York or in the United States District Court for the Southern District of New York, which courts shall have jurisdiction over the adjudication of such matters, and the Company consents to the jurisdiction of such courts and personal service with respect thereto. The Company hereby consents to personal jurisdiction, service and venue in any court in which any Claim arising out of or in any way relating to this Agreement is brought by any third party against Warburg Dillon Read LLC or any indemnified party. Each of Warburg Dillon Read LLC and the Company (on its behalf and, to the extent permitted by applicable law, on behalf of its stockholders and affiliates) waives all right to trial by jury in any action, proceeding or counterclaim (whether based upon contract, tort or otherwise) in any way arising out of or relating to this Agreement. The Company agrees that a final judgment in any such action, proceeding or counterclaim brought in any such court shall be conclusive and binding upon the Company and may be enforced in any other courts in the jurisdiction of which the Company is or may be subject, by suit upon such judgment.

13. PARTIES AT INTEREST. The Agreement herein set forth has been and is made solely for the benefit of the Underwriters and the Company and to the extent provided in Section 9 hereof the controlling persons, directors and officers referred to in such section, and their respective successors, assigns, heirs, personal representatives and executors and administrators. No

other person, partnership, association or corporation (including a purchaser, as such purchaser, from any of the Underwriters) shall acquire or have any right under or by virtue of this Agreement.

14. COUNTERPARTS. This Agreement may be signed by the parties in one or more counterparts which together shall constitute one and the same agreement among the parties.

15. SUCCESSORS AND ASSIGNS. This Agreement shall be binding upon the Underwriters and the Company and their successors and assigns and any successor or assign of any substantial portion of the Company's and any of the Underwriters' respective businesses and/or assets.

16. MISCELLANEOUS. Warburg Dillon Read LLC, an indirect, wholly owned subsidiary of UBS AG, is not a bank and is separate from any affiliated bank, including any U.S. branch or agency of Warburg Dillon Read LLC. Because Warburg Dillon Read LLC is a

separately incorporated entity, it is solely responsible for its own contractual obligations and commitments, including obligations with respect to sales and purchases of securities. Securities sold, offered or recommended by Warburg Dillon Read LLC are not deposits, are not insured by the Federal Deposit Insurance Corporation, are not guaranteed by a branch or agency, and are not otherwise an obligation or responsibility of a branch or agency.

17. A lending affiliate of Warburg Dillon Read LLC may have lending relationships with issuers of securities underwritten or privately placed by Warburg Dillon Read LLC. To the extent required under the securities laws, prospectuses and other disclosure documents for securities underwritten or privately placed by Warburg Dillon Read LLC will disclose the existence of any such lending relationships and whether the proceeds of the issue will be used to repay debts owed to affiliates of Warburg Dillon Read LLC.

If the foregoing correctly sets forth the understanding among the Company and the Underwriters, please so indicate in the space provided below for the purpose, whereupon this letter and your acceptance shall constitute a binding agreement among the Company and the Underwriters, severally.

Very truly yours,

RIGEL PHARMACEUTICALS, INC.

By: _____
Title:

Accepted and agreed to as of the
date first above written, on
behalf of themselves and the
other several Underwriters
named in Schedule A

WARBURG DILLON READ LLC
ROBERTSON STEPHENS
PRUDENTIAL VECTOR HEALTHCARE

By: WARBURG DILLON READ LLC

By: _____
Title:

By: _____
Title:

SCHEDULE A

UNDERWRITER	Number of FIRM SHARES

WARBURG DILLON READ LLC
ROBERTSON STEPHENS
PRUDENTIAL VECTOR HEALTHCARE

Total..... ==========

EXHIBIT A

[LETTERHEAD OF FLEHR HOHBACK TEST ALBRITTON & HERBERT LLP]

WARBURG DILLON READ LLC
ROBERTSON STEPHENS
PRUDENTIAL VECTOR HEALTHCARE
AS MANAGING UNDERWRITERS
C/O WARBURG DILLON READ LLC
299 PARK AVENUE
NEW YOR, NEW YORK 10171-0026

Ladies and Gentlemen:

We have acted as special patent counsel to Rigel Pharmaceuticals, Inc., a Delaware corporation (the "Company"), in connection with the entering into by the Company of that certain Underwriting Agreement by and among Warburg Dillon Read LLC, Robertson Stephens and Prudential Vector Healthcare as representatives of the several Underwriters named therein (collectively the "Underwriters"), and the Company, dated March __, 2000 (the "Underwriting Agreement"). This opinion is provided to you pursuant to Section 6(b) of the Underwriting Agreement.

For the purposes of rendering the opinions set forth below, we have reviewed or are otherwise familiar with the following (collectively the "Documents"):

1. the Underwriting Agreement;

2. that certain Registration Statement on Form S-1, as filed by the Company with the Securities and Exchange Commission on February __, 2000, together with any and all exhibits; Amendment No. 1 as filed by the Company with the Securities and Exchange Commission (the "SEC") on March __, 2000, Amendment No. 2 as filed with the SEC on March __, 2000, Amendment No. 3 as filed with the SEC on March __, 2000, Amendment No. 4 as filed with the SEC on March __, 2000, and the amendment filed pursuant to Rule 462(b) of the Securities Act of 1933, as amended (collectively, the "Registration Statement");

3. the Company's Prospectus dated March 8, 2000;

4. the patent applications which we are prosecuting listed on Schedule A attached hereto, which Schedule includes all of the patent applications referred to in the Prospectus (the "Patent Applications");

5. The results of a patent litigation search of the LitAlert database conducted on, or about March 24, 2000, with respect to the Company;

6. copies of assignments relevant to ownership of the Patent Applications being prosecuted by us;

7. our internal files pertaining to Company.

Whenever our opinions herein are qualified by the phrase "to the best of our knowledge," except as may be further qualified below, such language means that based upon the actual knowledge of attorneys presently within our firm (I.E., not including matters as to which such attorneys could be deemed

to have constructive knowledge and not including knowledge of attorneys or patent agents outside of Patent Counsel who, at any time, may have had

responsibility for the Company matters, including responsibility for the prosecution of the any of the Patent Applications) after reviewing of the Documents or based on being otherwise familiar with the Documents, and such review of or our familiarity with our files, including the prosecution file histories for the Patent Applications being prosecuted by us, we believe that such opinions are factually correct.

Based upon, and subject to the foregoing, and upon a review of such matters of law as we have deemed appropriate, it is our opinion and judgment that:

1. The statements in the Prospectus relating to U.S. patent matters, under the captions "RISK FACTORS -- Our success is dependent on intellectual property rights held by us and third parties and such rights are difficult and costly to protect; Our success will depend partly on our ability to operate without infringing on or misappropriating the proprietary rights of others" and "BUSINESS -- Corporate Collaborations; Intellectual Property", insofar as such statements constitute matters of law, legal conclusions, or summaries of legal matters or proceedings, are correct in all material respects and present fairly the facts and information purported to be shown.

2. To the best of our knowledge, with respect to the Patent Applications which we are prosecuting, referred to in the Registration Statement, referred to in the Registration Statement which are listed in Schedule A, the sections of the Registration Statement entitled "RISK FACTORS - -- Our success is dependent on intellectual property rights held by us and third parties and such rights are difficult and costly to protect; Our success will depend partly on our ability to operate without infringing on or misappropriating the proprietary rights of others" and "BUSINESS -- Corporate Collaborations; Intellectual Property", at the time the Registration Statement became effective, did not contain any untrue statement of material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances in which they were made, not misleading.

3. To the best of our knowledge, with respect to the Patent Applications which we are prosecuting, referred to in the Prospectus which are listed in Schedule A, the sections of the Prospectus entitled "RISK FACTORS -- Our success is dependent on intellectual property rights held by us and third parties and such rights are difficult and costly to protect; Our success will depend partly on our ability to operate without infringing on or misappropriating the proprietary rights of others" and "BUSINESS -- Corporate Collaborations; Intellectual Property", as of its date and as of the Closing Date (as defined in the Underwriting Agreement), do not contain any untrue statement of material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances in which they were made, not misleading.

4. To the best of our knowledge, except as described in the Prospectus, and with the exception of proceedings before the PTO, there are no pending, or threatened, legal or governmental proceedings relating to any of the Patent Applications which we are prosecuting.

5. To the best of our knowledge, the Company owns each of the Patent Applications which we are prosecuting, with the exception of certain patent applications exclusively licensed to the Company with respect to which Stanford University may have ownership rights. To the best of our knowledge, Stanford University has not assigned any rights to the Patent Applications to any third party.

6. To the best of our knowledge, no security interests have been recorded in the PTO with respect to any of the Patent Applications which we are prosecuting.

7. To the best of our knowledge, no liens have been recorded against the Company with respect to any of the Patent Applications which we are prosecuting.

8. To the best of our knowledge, except as described in the Prospectus, and except for any rights reserved to the United States Government, no third party other than Stanford University has any rights to any of the Patent Applications which we are prosecuting that are referred to in the Prospectus and listed in Schedule A.

9. To the best of our knowledge, except as described in the Prospectus, no interference has been declared or provoked with respect to any of the Patent Applications which we are prosecuting.

10. To the best of our knowledge, the Company has not received any

notice challenging the validity or enforceability of any of the Patent Applications.

11. While there can be no guarantee that any particular patent application will issue as a patent, each of the U.S. Patent Applications that are referred to in the Prospectus which we are prosecuting and listed in Schedule A, was property filed, and is being properly and diligently prosecuted, in the PTO.

12. For each U.S. patent application listed in Schedule A which we are prosecuting, to the best of our knowledge all information known, to date, to be "material to patentability", as defined in 37 C.F.R. Section 1.56(b), has been disclosed, or will be disclosed pursuant to 37 C.F.R. Section 1.97, to the PTO.

13. Without any searches specifically having been conducted, or having been required to have been conducted, for the purpose of rendering this opinion, and while there can be no guarantee that any particular patent application will issue as a patent, each of the U.S. patent applications that are referred to in the Prospectus and listed in Schedule A, discloses what we believe to be patentable subject matter.

14. To the best of our knowledge, without any searches having been conducted for the purpose of rendering this opinion, no third party is infringing any of the Patent Applications.

15. To the best of our knowledge, except as described in the Prospectus regarding M&E, no claim, which is presently pending, has been asserted against the Company relating to the potential infringement of, or conflict with, any patents, trademarks, copyrights, trade secrets, or proprietary rights, of others.

Furthermore, we call to your attention that our opinion is limited to such facts as they existed on March __, 2000, and does not take into account any changes of circumstances, fact, or law, subsequent thereto.

This opinion is for Underwriters' information only, is to be relied upon only by Underwriters, and is to be used only in connection with the transaction reflected in the Underwriting Agreement. This opinion is not to be quoted, or referred to, in whole or in part, in the Registration Statement or Prospectus, or in any literature or oral presentations used in connection with the sale of securities.

Very truly yours,

Fleh Hohbach Test
Albritton & Herbert LLP

cc:

Schedule A

EXHIBIT 10.6

COLLABORATION AGREEMENT

THIS COLLABORATION AGREEMENT (the "Agreement") is entered into as of December 4, 1998 (the "Effective Date") by and between RIGEL PHARMACEUTICALS, INC., a Delaware corporation ("Rigel") with its offices at 772 Lucerne Drive, Sunnyvale, California 94086, and JANSSEN PHARMACEUTICA N.V., a Belgian corporation ("Janssen") with offices at Turnhoutseweg 30, 2340 Beerse, Belgium (Rigel and Janssen individually referred to as "Party", and collectively as "Parties").

RECITALS

WHEREAS, Rigel is a leader in the discovery and validation of functional peptide-target interactions regulating the cell cycle in specific tumor cells; and

WHEREAS, Janssen is engaged in the research, development, marketing, manufacture and distribution of pharmaceutical compounds useful in treating or preventing human diseases and conditions; and

WHEREAS, Rigel and Janssen desire to enter into a collaborative relationship to conduct research to identify novel targets for drug discovery, as generally described in the Research Plan, with Janssen developing and commercializing any compounds resulting therefrom; and

WHEREAS, Rigel and Janssen agree that they will conduct the research under this Agreement on a collaborative basis with a goal of discovering and identifying products that are suitable for commercialization; and

WHEREAS, Johnson & Johnson Development Corporation has agreed to purchase and Rigel has agreed to sell one million five hundred thousand (1,500,000) shares of Rigel Series D Preferred Stock with a total value of US$3 million pursuant to a stock purchase agreement between the Parties of even date herewith (the "Stock Purchase Agreement"); and

WHEREAS, if the research collaboration is successful, the resulting compounds may have a broad range of applications, particularly in the diagnosis, therapeutic treatment and/or prevention of certain tumors and other diseases;

NOW, THEREFORE, in consideration of the foregoing and the covenants and promises contained in this Agreement, the Parties agree as follows:

1. DEFINITIONS

As used herein, the following terms shall have the following meanings:

1.1 "ACTIVE PEPTIDE" shall mean a molecule which changes cellular function in an assay specified by the RMC.

1.2 "AFFILIATE" shall mean any company or entity controlled by, controlling, or under common control with a Party hereto and shall include without limitation any company fifty percent (50%) or more of whose voting stock or participating profit interest is owned or controlled, directly or indirectly, by a Party, and any company which owns or controls, directly or indirectly, fifty percent (50%) or more of the voting stock of a Party.

1.3 "CONFIDENTIAL INFORMATION" shall mean all information (generally not known to the public), inventions, know-how or data disclosed by a Party to the other pursuant to this Agreement including, without limitation, Rigel Know-How, Janssen Know-How, manufacturing, marketing, financial, personnel, scientific and other business information and plans, and the material terms of this Agreement, whether in oral, written, graphic or electronic form.

1.4 "CONTROL" shall mean the possession of the ability to grant a license or sublicense to know-how and patents without violating the terms of any agreement or other arrangement with, or the rights of, any Third Party.

1.5 "DATE OF FIRST SALE" means the day on which Janssen, its Affiliate or its sublicensee first sells a Product to a Third Party in an arm's length transaction.

1.6 "DEVELOPMENT CANDIDATE" shall mean a compound selected for pre-phase I studies, including, but not limited to, GLP toxicological and pharmacological studies using GMP material.

1.7 "DIAGNOSTIC PRODUCT" shall mean any composition of matter used for the diagnosis of a disease or condition, including but not limited to, the diagnosis of disease susceptibility, or a choice of treatment or monitoring of a disease or condition, or the determination of genetic traits where such composition of matter is a component of a Validated Target-Peptide Pair or was identified by or on behalf of Rigel or Janssen in a Janssen Collaboration Assay and/or a Janssen Non-Collaboration Assay.

1.8 "EXCLUSIVITY TERM" shall have the meaning assigned to it in Section 3.6.

1.9 "FDA" means the United States Food and Drug Administration.

1.10 "FIELD OF RESEARCH" shall mean the identification of Molecular Targets and the related Active Peptides which cause alterations in the cell cycle of human tumor cells, including changes in the capacity to transit through various cell cycle stages, and restoration of normal cell cycle progression which would result in the inhibition of proliferation or the induction of apoptosis in these human tumor cells.

1.11 "FTE" shall mean the equivalent of a full-time scientist based on at least of 47 (forty-seven) weeks per year of scientific work carried out by one or more employees or consultants of Rigel, each of whom devotes a portion of his or her time to scientific work on or directly related to the Research Program; PROVIDED, HOWEVER, that Janssen understands and agrees that Rigel retains complete discretion to change the identity, the frequency and time which any individual employee devotes to the Research Program. Scientific work on or directly related to the Research Program to be performed by Rigel employees or consultants can include, but is not limited to, experimental laboratory work, recording and writing up results, reviewing literature and references, attending selected and appropriate seminars and symposia, managing and leading scientific staff, and carrying out Research Program management duties (including service on the Research Management Committee).

1.12 "HOMOLOGUE" shall mean a modification to one of the components of a VTPP which is functionally equivalent to such VTPP component.

1.13 "INTERNAL JANSSEN RESEARCH" shall mean the internal research conducted by Janssen and its permitted sublicensees using Rigel Technology or with Rigel Technology Assays, to assess the alteration or normalization of uncontrolled cell growth, cell division, dissemination or differentiation status of cancer cells.

1.14 "JANSSEN COLLABORATION ASSAY" shall mean a drug discovery assay incorporating a Janssen Collaboration Target.

1.15 "Janssen Know-How" shall mean any and all tangible or intangible know-how, trade secrets, inventions (whether or not patentable), data, preclinical and clinical results, physical, chemical or biological material, and other information that is necessary and useful in the Field of Research and that Janssen owns or Controls on the Effective Date and any replication or any part of such information or material. Janssen Know-How shall exclude Janssen Patents.

1.16 "JANSSEN PATENTS" shall mean all foreign and domestic patents (including, without limitation, extensions, reissues, reexaminations, renewals and inventors certificates) issued as of, and patents issuing from patent applications (including substitutions, provisionals, divisionals, continuations and continuations-in-part) that are pending as of, the Effective Date which claim inventions or discoveries necessary and useful in the Field of Research and are owned or Controlled by Janssen. The RMC shall compile a list of Janssen Patents from time to time.

1.17 "JANSSEN COLLABORATION TARGET" means a Validated Target-Peptide Pair delivered by Rigel as provided in Section 3.5.

1.18 "JANSSEN TECHNOLOGY" shall mean Janssen Patents and Janssen Know-How.

1.19 "MAJOR MARKET" shall mean the U.S.A., France, Germany, United Kingdom or any country in the EU pursuant to an NDA approval by the EMEA, or Japan.

1.20 "MOLECULAR TARGET" shall mean a molecule shown in an assay specified by the RMC to play a role in a research pathway in human tumor cells.

1.21 "NDA" shall mean a New Drug Application or its equivalent for biological products as more fully defined in 21 C.F.R. Section 314.5 et seq., and any equivalent filing in any regulatory jurisdiction.

1.22 "NET SALES" means the gross sales price billed by Janssen or an Affiliate thereof or a sub-licensee thereof for sales of Products hereunder to a Third Party less (in each case as may be applicable thereto and consistent with such Party's then existing standard business practices): (a) standard trade discounts, including cash discounts or rebates, actually allowed or granted from the billed amount, (b) credits or allowances actually granted upon claims, rejections or returns of Products, including recalls, regardless of the party requesting such recall, (c) charges included as part of the gross sales price for freight, postage, shipping and insurance charges, to the extent specifically billed, (d) taxes (other than income taxes), duties or other governmental charges levied on or measured by the billing amount when included in billing, as adjusted for rebates and refunds, and (e) accounts that are uncollectible and written off Janssen's books as uncollectible, provided that any uncollectible accounts excluded pursuant to this clause (e) which are subsequently collected by Janssen shall be included in Net Sales for the royalty period in which such amounts are collected. In the event any Product is sold in the form of a combination containing one or more active ingredients in addition to a Product, Net Sales for such combination will be calculated by multiplying actual Net Sales of such combination by the fraction A/(A+B), where A is the invoice price of the applicable Product, if sold separately, and B is the total invoice price of any other active component or components, or non-consumable devices (such as, for example, implantable pumps or electronic stimulators; however, items such as, for example, disposable transdermal patches or prefilled syringes shall constitute consumable devices) in the combination, if sold separately. If, on a country-by-country basis, the other active component or components in the combination are not sold separately in said country, Net Sales for the purpose of determining royalties of the combination shall be calculated by multiplying actual Net Sales of such combination by the fraction A/C, where A is the invoice price of the applicable Product, if sold separately, and C is the invoice price of the combination. If, on a country-by-country basis, neither the Product nor the other active component or components of the combination is sold separately in said country, Net Sales for the purposes of determining royalties of the combination shall be determined by the Parties in good faith.

1.23 "NON-COLLABORATION PHARMACEUTICAL PRODUCT" shall mean a composition of matter, including, but not limited to a chemical entity, a pro-drug, an isomer, a non-peptide, and a protein or nucleic acid or any fragment thereof, that was identified by or on behalf of Janssen or its permitted sublicensees in the Internal Janssen Research, that is useful for treating and/or preventing human diseases.

1.24 "PHARMACEUTICAL COLLABORATION PRODUCT" shall mean a composition of matter, including, but not limited to, a chemical entity, a pro drug, an isomer, a non-peptide, and a protein or nucleic acid or any fragment thereof, that was identified by or on behalf of Rigel or Janssen in a Janssen Collaboration Assay, that is useful for treating and/or preventing human

diseases; PROVIDED, HOWEVER, that the term "Pharmaceutical Collaboration Product" specifically excludes any composition of matter marketed or being developed by Janssen as of the Effective Date.

1.25 "PHASE III CLINICAL TRIAL" shall mean that clinical trial of a Product designed to be on a sufficient number of patients to establish the safety and efficacy of a Product and generate pharmacoeconomic data to support regulatory approval in a therapeutic indication as more fully defined in 21 C.F.R. 312.21(c), or any equivalent clinical trial in a non-U.S. regulatory jurisdiction.

1.26 "PRELIMINARY TARGET-PEPTIDE PAIRS" shall mean a Molecular Target together with an Active Peptide that binds thereto, which pair has been identified or discovered in the course of the Research Program, and which has been Validated Preliminarily.

1.27 "PRODUCTS" shall mean the Pharmaceutical Collaboration Products, the Target-Peptide Therapeutic Products, the Diagnostic Products and the Non-Collaboration Pharmaceutical Products.

1.28 "REGULATORY APPROVAL" shall mean any approval (including price and reimbursement approvals), licenses, registrations, or authorizations of any federal, state or local regulatory agency, department, bureau or other government entity, necessary for the manufacture, use, storage, import,

transport or sale of a Product in a regulatory jurisdiction.

1.29 "RESEARCH MANAGEMENT COMMITTEE" OR "RMC" shall mean the committee formed pursuant to Section 2.1.

1.30 "RESEARCH PERIOD" shall have the meaning assigned to it in Section 3.3.

1.31 "RESEARCH PLAN" shall mean the research plan attached as Exhibit A to this Agreement, as it may be modified or amended from time to time as permitted herein.

1.32 "RESEARCH PROGRAM" shall mean the program of the collaborative research as described in Article 3.

1.33 "RESEARCH PROGRAM KNOW-HOW" shall mean any tangible or intangible know-how, trade secrets, inventions (whether or not patentable), data, preclinical and clinical results, physical, chemical or biological material, and other information, including information concerning target-peptide interaction developed in the Research Program (including, without limitation, the functional role of the Molecular Target involved) that is within the Field of Research, and any replication or any part of such information or material; PROVIDED, HOWEVER, that the term "Research Program Know-How" as defined specifically excludes Research Program Patents and any compounds identified in Internal Janssen Research.

1.34 "RESEARCH PROGRAM PATENTS" shall mean all foreign and domestic patents (including extensions, reissues, reexaminations, renewals and inventors certificates) issuing from applications (including substitutions, provisionals, divisionals, continuations and continuations-

in-part) that claim inventions that are made in the Research Program and that are filed by or on behalf of one or both of the Parties hereto.

1.35 "RESEARCH PROGRAM TECHNOLOGY" shall mean the Research Program Patents and Research Program Know-How.

1.36 "RIGEL TECHNOLOGY ASSAYS" shall mean the assays transferred to Janssen or its permitted sublicensees for use in the Internal Janssen Research which assess the alteration or normalization of uncontrolled cell growth, cell division, dissemination or differentiation status of cancer cells, which are more specifically listed in Exhibit B.

1.37 "RIGEL KNOW-HOW" shall mean any and all tangible or intangible know-how, trade secrets, inventions (whether or not patentable), data, preclinical and clinical results, physical, chemical or biological material, and other information that is necessary and useful in the Field of Research and that Rigel owns or Controls on the Effective Date and any replication or any part of such information or material, but subject to any limitations contained in any license agreements.

1.38 "RIGEL PATENTS" shall mean all foreign and domestic patents (including, without limitation, extensions, reissues, reexaminations, renewals and inventors certificates) issued as of, and patents issuing from applications (including substitutions, provisionals, divisionals, continuations and continuations-in-part) pending as of, the Effective Date which claim inventions or discoveries necessary and useful in the Field of Research and are owned or Controlled by Rigel, but subject to any limitations contained in any license agreements.

1.39 "RIGEL TECHNOLOGY" shall mean the Rigel Patents and Rigel Know-How.

1.40 "STANFORD AGREEMENTS" shall mean the agreements by and between Rigel and The Board of Trustees of Leland Stanford Junior University dated October 7, 1996 (the "1996 Agreement"), August 18, 1997 (the "1997 Agreement"), and March 27, 1998 (the "1998 Agreement"), which have been provided to Janssen with commercial terms redacted, and attached hereto as Exhibit D.

1.41 "STANFORD REQUIRED PROVISIONS" shall mean the provisions relating to (a) royalty reports, payments and accounting, (b) warranties or negation thereof, and (c) indemnity, contained respectively in Articles 8, 9 and 10 of the 1996 Agreement, Articles 7, 9 and 10 of the 1997 Agreement, and Articles 7, 8, and 9 of the 1998 Agreement.

1.42 "TARGET-PEPTIDE THERAPEUTIC PRODUCT" shall mean a product that contains a component of a VTPP or a Homologue thereof.

1.43 "TERM OF THE AGREEMENT" shall have the meaning assigned to it in Article 10.

1.44 "TERRITORY" shall mean the entire world.

1.45 "THIRD PARTY" shall mean any person or entity other than Janssen, Rigel and Affiliates of either.

1.46 "VALIDATED PRELIMINARILY" shall mean demonstration of a functional phenotype change in a primary assay and such other criteria as determined by the RMC prior to the commencement of target evaluation by Rigel.

1.47 "VALIDATED TARGET-PEPTIDE PAIR" OR "VTPP" shall mean a Molecular Target together with an Active Peptide that binds thereto, which pair has been identified or discovered during the course of the Research Program in the Field of Research, that meets the criteria for full validation established by the RMC at the time that the respective Preliminary Target Peptide Pair is selected for further validation.

2. RESEARCH PROGRAM GOVERNANCE

2.1 FORMATION OF RESEARCH MANAGEMENT COMMITTEE. The Research Program established by this Agreement shall be overseen by a Research Management Committee composed of an equal number of representatives from each Party (the "Research Management Committee") drawn from the ranks of senior scientists and senior research management of each Party. The total number of RMC members shall be agreed upon by the RMC from time to time. The Parties shall designate their representatives on the RMC within ten (10) days after the Effective Date. The Parties shall notify one another in writing of any change in the membership of the RMC as appropriate to allow for the participation of different research groups within Janssen and Rigel. The Parties shall agree upon the appropriate qualifications for members of the RMC and mechanisms for making substitutions for RMC members. An alternate member designated by a Party may serve temporarily in the absence of a permanent member of the RMC for such Party. Each Party shall designate one of its representatives as a co-chair of the RMC. Each co-chair of the RMC will be responsible for the agenda and the minutes of alternating RMC meetings.

2.2 RESEARCH PLAN DEVELOPMENT AND MODIFICATION. The RMC shall develop and periodically modify the Research Plan, commencing with the initial Research Plan attached hereto as Exhibit A.

2.3 RMC ACTIONS. In taking actions by the RMC, each Party shall have one vote. If the RMC fails to reach unanimity on a matter before it for decision, the matter shall be referred for resolution to the CEO of Rigel and the V.P. of Biological Research of Janssen for their consideration and agreement. If they are unable to agree after negotiation in good faith, the matter shall be resolved consistent with Janssen's position; PROVIDED, HOWEVER, that solely in connection with technical issues involving Rigel Technology such as, for example, how to carry out a certain experiment or which technique to be applied to obtain a certain result, such issues shall be resolved consistent with Rigel's position. Strategic decisions such as, for example, selection of Preliminary Target Peptide Pairs for further validation and the criteria for such validation, shall be resolved consistent with Janssen's position.

2.4 MEETINGS OF THE RMC. The RMC:

(a) shall hold meetings at such times and places as shall be determined by the RMC (it being expected that meetings will alternate between the U.S. and European offices of each party) but in no event shall such meetings be held in person less frequently than once every three (3) months during the first two (2) years after the Effective Date;

(b) may conduct meetings in person or by telephone conference, provided that meetings by telephone conference shall not reduce the number of meetings in person specified in paragraph (a) above;

(c) by mutual consent of the representatives of each Party, may invite other senior personnel of their organization to attend meetings of the RMC, as appropriate however such other senior personnel shall not have any duties of an RMC member.

(d) may act without a meeting if prior to such action a written

consent thereto is signed by all members of the RMC;

(e) may form and subsequently disband subcommittees with appropriate representation from each party; and

(f) may amend or expand upon the foregoing procedures for its internal operation by unanimous written consent.

2.5 MINUTES. At each meeting, the RMC shall elect a secretary who will prepare, within ten (10) days after each meeting (whether held in person or be telecommunication), the minutes reporting in reasonable detail the actions taken by the RMC, the status of the Research Program, issues requiring resolution and resolutions of previously reported issues, which minutes are to be signed by the RMC co-chair persons from each of the Parties.

2.6 SUBCOMMITTEES. Any subcommittee established by the RMC shall have appropriate representation of each Party and may include representatives who are not members of the RMC. Any such subcommittee shall be given assignments from the RMC, shall be subject to the authority of the RMC and shall report its actions to the RMC. At the request of either Party at any time, any such subcommittee shall be dissolved and its powers and functions returned to the RMC. The RMC shall not delegate any of its RMC Functions and Powers as described in Article 2.7, without retaining the final approval before implementing the subcommittee assignments.

2.7 RMC FUNCTIONS AND POWERS. The activities of the Parties under this Agreement shall be managed by the RMC only to the extent set forth herein (unless otherwise mutually agreed by the Parties). During the Research Period the RMC shall:

(a) determine the goals for the Research Program and establish and review the Research Plan for accomplishing such goals;

(b) encourage and facilitate ongoing cooperation and information exchange between the parties;

(c) monitor the progress of the Research Plan and the parties' diligence in carrying out their responsibilities thereunder;

(d) allocate tasks and coordinate activities required to perform the Research Plan;

(e) schedule routine visits by Rigel and Janssen personnel to Janssen and Rigel, respectively, and oversee secondment of Janssen and Rigel personnel pursuant to Section 3.9;

(f) establish prospective criteria to determine when a Molecular Target and Active Peptide is a Preliminary Target-Peptide Pair or a Validated Target-Peptide Pair, and to amend the Research Plan accordingly;

(g) identify and select Preliminary Target-Peptide Pairs and Validated Target-Peptide Pairs pursuant to Section 3.4 and 3.5;

(h) perform such other functions as expressly provided herein, as appropriate to further the purposes of this Agreement, as mutually agreed by the Parties.

2.8 OBLIGATIONS OF PARTIES DURING THE RESEARCH PERIOD. Janssen and Rigel shall provide the RMC with reasonable access during regular business hours to all Janssen Know-How, Rigel Know-How and Research Program Know-How specific to the Research Program that the RMC determines that is reasonably required in order to perform its obligations hereunder, subject to any bona fide obligations of confidentiality to a Third Party.

2.9 LIMITATIONS OF POWERS OF THE RMC. The RMC shall have no power to amend this Agreement and shall have only such powers as are specifically delegated to it hereunder.

3. CONDUCT OF RESEARCH PROGRAM

3.1 SCOPE OF THE RESEARCH PROGRAM. The Parties hereby agree to establish and conduct, during the Research Period, a collaborative research program pursuant to the Research Plan in the Field of Research, as described in this Article 3. The Parties will collaborate in producing Validated Target-Peptide Pairs in order to discover, develop and manufacture products useful in diagnosing, treating or preventing diseases in humans.

3.2 RESEARCH ACTIVITIES; REVISIONS.

(a) The Parties will perform research in the Field of Research as directed by the RMC and pursuant to the Research Plan. Modifications of the Research Plan shall be made in writing and only as directed and approved by the RMC. In the event of any such modification, Exhibit A, the obligations of the parties including, but not limited to, Rigel's resource obligations

under this Section 3.2 and Janssen's research support obligations under Section 6.2, shall be revised as necessary and appropriate, subject to written approval of the Parties.

(b) Rigel agrees to commit the resources set forth in this subsection (b), to exert the efforts necessary and reasonable and consistent with its normal business practices to execute and perform the Research Plan (including extensions for the balance of the Research Period), to maintain and utilize the scientific staff, laboratories, offices and other facilities consistent with such undertaking. Rigel and Janssen agree to reasonably cooperate with each other in the conduct of the Research Plan. The Parties hereby agree that Rigel's current laboratories; offices and other facilities are satisfactory for purposes of this Section 3.2. During the first three (3) years of the Research Period, Rigel shall commit 10 FTEs to the Research Program. The purchase of any item including, but not limited to, cell lines reasonably required by Rigel to conduct the Research Plan shall be Rigel's obligation and responsibility and all cost associated therewith shall be to Rigel's account.

3.3 RESEARCH PERIOD; EXTENSIONS. The Research Program will commence on the Effective Date and terminate three (3) years thereafter, unless extended by mutual agreement or unless this Agreement is terminated earlier as provided in Article 10 (the "Research Period"). Janssen shall have an option to extend the Research Period beyond the initial Research Period of three (3) years for additional one year periods for a total of two (2) years by giving notice to Rigel at least one hundred twenty (120) days prior to the anniversary of the end of the Research Period that it intends to exercise its option. The compensation per FTE will be at the payment level as set forth herein.

3.4 IDENTIFICATION OF PRELIMINARY TARGET-PEPTIDE PAIRS. During the Research Period, the RMC shall identify Preliminary Target-Peptide Pairs and shall issue a list thereof not less often than quarterly.

3.5 IDENTIFICATION OF VALIDATED TARGET-PEPTIDE PAIRS.

(a) During the Research Period, the RMC shall select Preliminary Target-Peptide Pairs to be further evaluated to determine whether they are suitable to be selected by the RMC as Validated Target-Peptide Pairs for the purpose of compound screening as provided in Section 3.6. Prior to commencing such evaluation, the RMC shall establish the criteria ("Validation Criteria") pursuant to Section 2.7(f) required for such Preliminary Target-Peptide Pairs to qualify as Validated Target-Peptide Pairs.

(b) Preliminary Target-Peptide Pairs for which it has not been established by the end of the Research Period whether or not they meet the Validation Criteria, shall revert to Rigel; PROVIDED, HOWEVER, that the Parties may determine that any Preliminary Target-Peptide Pair not fully validated may be transferred to Janssen for further validation as Internal Janssen Research.

(c) During the Research Period, the RMC shall issue a list of Validated Target-Peptide Pairs within thirty (30) days after each RMC meeting, and a final list thereof

within thirty (30) days after the end of the Research Period. Promptly after a Validated Target Peptide Pair has been listed, Rigel shall transfer all Research Program Technology necessary for Janssen to initiate screening with respect to that Validated Target Peptide Pair. Rigel shall not transfer any component of a Validated Target Peptide Pair to any Third Party without prior written approval of the Janssen.

3.6 COMPOUND SCREENING; DILIGENCE.

(a) Janssen may initiate compound screening with each Validated Target-Peptide Pair at any time during the first three (3) years following its determination by the RMC as a Validated Target-Peptide Pair (the "Exclusivity Term"). Janssen shall notify Rigel promptly upon the initiation of screening with each Validated Target-Peptide Pair.

(b) If Janssen does not initiate compound screening with a Validated Target-Peptide Pair during the Exclusivity Term pertaining to such

Validated Target-Peptide Pair, or, having timely initiated compound screening, Janssen fails to pursue such screening in a manner consistent with Janssen's normal research practices, then, in either case, the licenses granted herein by Rigel to Janssen for such Validated Target-Peptide Pair shall terminate and Janssen shall grant Rigel an exclusive, worldwide, royalty-free license, with the right to sublicense, under its interest in the Research Program Technology with respect to such Validated Target-Peptide Pair.

(c) If, according to Rigel, Janssen has failed to comply with the diligence requirements as set forth in subsection (b) above, Rigel shall notify Janssen thereof in writing. Within thirty (30) days of such notice, the Parties shall meet to discuss the matter. If no agreement is reached, the dispute shall be resolved as provided in Section 12.3. Effective upon such resolution, the licenses granted by Rigel hereunder shall terminate as provided in subsection (b) above, or shall continue, depending on whether or not Janssen is found to have breached the diligence obligations as described in subsection (b).

3.7 ADDITIONAL JANSSEN RIGHT TO VALIDATED TARGET-PEPTIDE PAIR. With respect to each Validated Target-Peptide Pair which reverts to Rigel as provided in Section 3.6, Rigel will, upon identifying a compound during the term of this Agreement which modulates the activity of such Validated Target-Peptide Pair or its constituents provide written notice to Janssen of such compound and provide the information reasonably necessary for Janssen to determine whether Janssen wishes to discuss licensing such compound. If Janssen notifies Rigel within ninety (90) days of Rigel's notice, of its desire to license such compound, the Parties will conduct good faith negotiations of terms upon which Rigel will license such compound to Janssen; PROVIDED, HOWEVER, if the Parties are unable to reach agreement within a further period of ninety (90) days (or such further period as the Parties may mutually agree) after Janssen's notice, then Janssen will have no rights with respect to such compound and Rigel will be free to exploit such compound alone or with others without obligation or liability to Janssen; PROVIDED, HOWEVER, that Rigel shall not enter into any agreement with a Third Party on terms which are substantially the same or less favorable to Rigel, than the terms last offered by Janssen.

3.8 RIGEL SCREENING. Rigel may initiate compound screening with a Validated Target-Peptide Pair upon the explicit written request of Janssen and acceptance by Rigel. However, Janssen shall have the exclusive right and license to develop and exploit any compound so identified or discovered by Rigel upon the terms provided in Sections 5.2 and 5.3.

3.9 SECONDMENT. In order to further a close working relationship, the Parties will provide offices and support to each other at each other's facilities for the visiting personnel of the other Party, as provided herein. During the Research Period, each Party shall provide employees at the other Party's facilities, on an as-needed basis to be determined by the RMC. In addition, the RMC shall arrange for routine visits by other Rigel personnel to Janssen facilities to facilitate information exchange between the Parties.

4. INTERNAL JANSSEN RESEARCH

4.1 TECHNOLOGY TRANSFER. During the Research Period, Janssen will periodically notify Rigel of the Rigel Technology Assays and other assays that are part of the Janssen Internal Research which Janssen or its permitted sublicensees choose to pursue. Promptly thereafter, Rigel and Janssen shall meet to determine whether the Rigel Technology Assays and such other assays described in such notice are within the scope of Internal Janssen Research. If the Parties determine that such assays are within the scope of the Internal Janssen Research, Rigel shall transfer the Rigel Technology Assays to Janssen or its permitted sublicensees, and shall provide such reasonable assistance as is necessary to establish functioning assays, such assistance to be included in the 10 FTE's that Rigel is required to allocate to the Research Program. For the avoidance of any doubt, any Rigel Technology Assays transferred, and any information shared with Janssen or its permitted sublicensees in connection with the Internal Janssen Research shall be used by Janssen or its permitted sublicensees only to the extent of the licenses granted to Janssen under Section 5.4.

4.2 USE OF RIGEL ASSAYS. Janssen shall use the Rigel Technology Assays for the Internal Janssen Research only, and shall not transfer or otherwise grant access to such assays to any Affiliate or Third Party, other than to permitted sublicensees pursuant to Section 5.4.

4.3 REPORTING. Janssen shall provide Rigel with written reports on the Internal Janssen Research and the use of the Rigel Technology Assays not less than once every calendar year.

5. LICENSE GRANTS; CONFLICTING PROGRAMS; DILIGENCE

5.1 LICENSE GRANTS FOR COLLABORATIVE RESEARCH.

(a) GRANT BY RIGEL. Rigel hereby grants to Janssen and its Affiliates a nonexclusive, non-transferable, royalty-free license in the Field of Research during the Research Period under the Rigel Technology, and Rigel's interest in the Research Program Technology in the Territory, subject to the terms of this Agreement, solely for the purpose of carrying out Janssen's responsibilities under the Research Program.

(b) GRANT BY JANSSEN. Janssen hereby grants to Rigel and its Affiliates a nonexclusive, non-transferable, royalty-free license in the Field of Research during the Research Period under the Janssen Technology and Janssen's interest in the Research Program Technology in the Territory, subject to the terms of this Agreement, solely for the purpose of carrying out Rigel's responsibilities under the Research Program.

5.2 COMMERCIAL LICENSE GRANT. Subject to the terms and conditions of this Agreement, Rigel hereby grants to Janssen and its Affiliates an exclusive, royalty-bearing license, with the right to grant sublicenses, under the Rigel Technology and Rigel's interest in the Research Program Technology, to discover, develop, identify, make, have made, use, sell, have sold, offer for sale, export, and import Products in the Territory.

5.3 COMMERCIAL DUE DILIGENCE. The rights granted under Section 5.2 shall be subject to Janssen's obligation to discover, develop and commercially exploit Products using the level of effort commensurate with other Janssen products at a similar stage of development and of similar importance (based on criteria such as patient population, price per treatment and competitive position). If Janssen fails to use such diligence, Rigel may notify Janssen of such failure and, if not cured within six (6) months of such notice, terminate the license under Section 5.2 with respect to such Product.

5.4 LICENSE FOR INTERNAL JANSSEN RESEARCH. Rigel hereby grants Janssen a non-exclusive, worldwide, royalty bearing license, during the Term of Agreement under the Rigel Technology and Rigel's interest in the Research Program Technology to the extent necessary to use the Rigel Technology Assays for the Internal Janssen Research. Janssen shall have the right to grant sublicenses under the license granted under this Section 5.4 to The R.W. Johnson Pharmaceutical Research Institute, a Division of Ortho-McNeil Pharmaceutical, Inc., and subject to Rigel's prior approval (which approval shall not be unreasonably withheld) to other named Affiliates; PROVIDED, HOWEVER, that any such sublicense shall provide for a license to Rigel corresponding to the license granted by Janssen to Rigel under Section 5.5, and shall be subject and subordinate to the terms of this Agreement. Janssen shall provide Rigel with a copy of each sublicense agreement.

5.5 LICENSE TO RIGEL OF IMPROVEMENTS TO RIGEL TECHNOLOGY. Janssen hereby grants to Rigel a nonexclusive, royalty-free, paid-up, worldwide license (i) under Janssen's interest in all Research Program Technology, and (ii) under Janssen's interest in any know-how, inventions or discoveries generated or made in the course of the Internal Janssen Research, only to the extent it constitutes an improvement of Rigel Technology.

5.6 EXCLUSIVITY PERIOD. During the first 18 months after the Effective Date, Rigel will not enter into a research collaboration with a Third Party ("Third Party Collaboration") in the Field of Research (the "Exclusive Research Period").

5.7 CONFLICTING PROGRAMS.

(a) After the Exclusive Research Period and during the Research Period, Rigel will notify Janssen if it has decided to pursue a research project in human oncology described in such notice ("Additional Program"). Within sixty (60) days after receipt of Rigel's notice, the Parties shall determine whether or not the Additional Program conflicts with the Research Program. An Additional Program will be considered to conflict with the Research Program if, after consultation with the RMC, the VP Biological Research of Janssen and the CEO of Rigel agree that there is significant overlap between the molecular targets or pathways of the Additional Program and the Field of Research.

(b) If such a conflict is determined to exist then (i) Rigel shall not proceed with the Additional Program, and (ii) Janssen may notify Rigel within sixty (60) days of such determination of its interest in such Additional Program. If Janssen so notifies Rigel, then the Parties will enter

into good faith discussions to determine whether there are mutually agreeable terms upon which they wish to collaborate with respect to the Additional Program. If Janssen does not so notify Rigel or if the Parties do not enter into an agreement with respect to the Additional Program within ninety (90) days (or such further period as the Parties may agree) after Janssen's notice, then such Additional Program shall not be added to the Research Program.

(c) If such a conflict is determined not to exist, Janssen may notify Rigel within sixty (60) days of such determination of its interest in such Additional Program. If Janssen so notifies Rigel, then the Parties will enter into good faith discussions to determine whether there are mutually agreeable terms upon which they wish to collaborate with respect to the Additional Program. If Janssen does not so notify Rigel or if the Parties do not enter into an agreement with respect to the Additional Program within ninety (90) days (or such further period as the Parties may agree) after Janssen's notice, then Rigel shall be free to pursue the Additional Program alone or with a Third Party; PROVIDED, HOWEVER, that Rigel shall not enter into any agreement with a Third Party on terms which are substantially the same or less favorable to Rigel, than the terms last offered by Janssen to Rigel in writing.

5.8 SUBLICENSES UNDER STANFORD AGREEMENTS. Subject to Section 6.15 (Third Party Payments by Rigel), the Parties hereby acknowledge that the Stanford Required Provisions are included in this Agreement for the benefit of Stanford University. The sublicenses granted hereunder shall remain in effect after termination of the Stanford Agreements, provided that any obligations of Janssen under the sublicenses granted herein shall be owed to Stanford.

6. FINANCIAL SUPPORT

6.1 SIGNING PAYMENT. Within ten (10) days of the Effective Date of this Agreement, Janssen will pay Rigel One Million US Dollars (US$1,000,000).

6.2 RESEARCH SUPPORT. Janssen will provide funding to support Rigel's efforts under the Research Program and 10 FTE'S of Rigel at a rate of US$2,500,000 per year. Such amount shall be paid quarterly in advance.

6.3 PAYMENTS FOR PHARMACEUTICAL COLLABORATION PRODUCTS.

(a) MILESTONE PAYMENTS. For Pharmaceutical Collaboration Products, the following payments will be due to Rigel upon the occurrence of the following events:

<TABLE>
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MILESTONE EVENT	AMOUNT OF PAYMENT
<S>	<C>
1) First to occur of either (a) Janssen initiating compound screening with the second Validated Target-Peptide Pair delivered by Rigel or (b) six (6) months after Rigel delivers the second Validated Target-Peptide Pair.	$500,000
2) Demonstration by Janssen of IN VIVO efficacy in at least one animal model of the first Pharmaceutical Collaboration Product identified in a screening assay using a Janssen Collaboration Target.	$500,000
3) Selection by Janssen of the first Development Candidate.	$1 million
4) Enrollment of the fifth patient in a Phase III Clinical Trial for the first Pharmaceutical Collaboration Product	$2 million
5) Approval of the first NDA for each Pharmaceutical Collaboration Product in the first Major Market.	$5 million

</TABLE>

(b) ROYALTIES. Janssen shall pay Rigel royalties on Net Sales of Pharmaceutical Collaboration Products at a rate of four percent (4%)

when the Pharmaceutical Collaboration Product contains a compound originating from Janssen's compound collection and six percent (6%) when the Pharmaceutical Collaboration Product contains a compound originating from Rigel's compound collection.

6.4 PAYMENTS FOR TARGET-PEPTIDE THERAPEUTIC PRODUCTS.

(a) MILESTONE PAYMENTS. For Target-Peptide Therapeutic Products, the following payments will be due to Rigel upon the occurrence of the following events:

MILESTONE EVENT	AMOUNT OF PAYMENT
1) Demonstration by Janssen of in vivo efficacy in at least one animal model of the first Target-Peptide Therapeutic Product.	$500,000
2) Selection by Janssen of the first Development Candidate.	$1 million

3) Enrollment of the fifth patient in a Phase III Clinical Trial for the first Target-Peptide Therapeutic Product	$2 million
4) Approval of the first NDA for each Target-Peptide Therapeutic Product in the first Major Market.	$5 million

(b) ROYALTIES. Janssen shall pay Rigel royalties on Net Sales of Target-Peptide Therapeutic Products at a rate of six percent (6%).

6.5 PAYMENTS FOR DIAGNOSTIC PRODUCTS.

(a) MILESTONE PAYMENTS. For Diagnostic Products, the following payment will be due to Rigel upon the occurrence of the following event:

MILESTONE EVENT	AMOUNT OF PAYMENT
1) Regulatory Approval of the first Diagnostic Product derived from each VTPP	$500,000.00

(b) ROYALTIES. Janssen shall pay Rigel royalties on Net Sales of Diagnostic Products at a rate of two percent (2%) when the Diagnostic Product is patented, and one percent (1%) when the Diagnostic Product is not patented.

6.6 PAYMENTS FOR NON-COLLABORATION PHARMACEUTICAL PRODUCTS.

(a) MILESTONE PAYMENTS. For Non-Collaboration Pharmaceutical Products, the following payments will be due to Rigel upon the occurrence of the following events:

MILESTONE EVENT	AMOUNT OF PAYMENT
1) Enrollment of the fifth patient in a Phase III Clinical Trial for the first Non-Collaboration Pharmaceutical Product	$1 million
2) Approval of the first NDA for the first Non-Collaboration Pharmaceutical Product in the first Major Market.	$2.5 million

</TABLE>

(b) ROYALTIES. Janssen shall pay Rigel royalties on Net Sales of Non-Collaboration Pharmaceutical Products at a rate of two percent (2%).

6.7 ROYALTY PERIOD.

(a) In respect of Products for which a royalty is due, Janssen's obligation to pay royalties to Rigel shall be for a period of ten (10) years, on a Product-by-Product basis, from the Date of First Sale of each such Product.

(b) For the purposes of determining whether royalties are due hereunder, different dosage forms of a Product shall not be considered different Products provided that different dosage forms contain the same active ingredient.

(c) Upon termination of the royalty payment obligation, Janssen shall thereafter have in perpetuity a royalty-free, non-exclusive license to make, have made, use, sell, have sold, and import such Products hereunder, without any accounting to Rigel.

6.8 MANNER OF PAYMENT. Remittance of payments under this Article 6 shall be made by means of wire transfer or other telegraphic transfer in U.S. Dollars to Rigel's account in a bank in the United States to be designated from time to time by Rigel.

6.9 REPORTS. Janssen shall provide written notice of the occurrence of all milestone events in this Article. Within forty-five (45) days following each quarterly period of a calendar year after the Date of First Sale of the first Product, Janssen shall render to Rigel a written report setting forth the Net Sales of such Products sold and the royalty due and payable on a Product-by-Product and country-by-country basis (including all deductions taken from the gross sales price in determining Net Sales).

6.10 INVOICING. All payments to be made by Janssen under this Agreement shall be made based upon an invoice to be submitted by Rigel to Janssen. The invoice shall be in the form attached hereto as Exhibit C. Except as otherwise provided in Section 6.1, all payments shall be due within fifteen (15) days of the receipt of such invoice by Janssen.

6.11 RECORDS AND AUDIT.

(a) During the term of this Agreement and for a period of at least two (2) years thereafter, Janssen shall keep complete and accurate records pertaining to the sale or other disposition of the Products commercialized by it, in sufficient detail to permit Rigel to confirm the accuracy of all payments due hereunder.

(b) Rigel shall have the right to cause an independent, certified public accountant acceptable to Janssen to audit such records to confirm Janssen's Net Sales of Products and royalty payments made under this Agreement; PROVIDED, HOWEVER, that such auditor shall not disclose Janssen's confidential information to Rigel, except to the extent such disclosure is necessary to verify the amount of royalties due under this Agreement. Such audits may be exercised once a year, within two (2) years after the royalty period to which such records relate, upon prior written notice to Janssen and during normal business hours. Rigel shall bear the full cost of such audit unless such audit discloses an understatement of more than five percent (5%) from the amount of the Net Sales or royalties previously paid. In such case, Janssen shall bear

the full cost of such audit. In case that such audit discloses an overpayment of royalties by Janssen, such overpayment shall be refunded to Janssen. The terms of this Section 6.11 shall survive any termination or expiration of this Agreement for a period of two (2) years.

6.12 FOREIGN EXCHANGE. The remittance of royalties payable on Net Sales will be payable in U.S. dollars to Rigel at a bank and to an account designated by Rigel using a rate of exchange of the currency of the country from which the royalties are payable in accordance with the currency exchange

rates as published in the Wall Street Journal at the end of the calendar quarter in which the Net Sales were made. All references to dollars herein are references to U.S. dollar.

6.13 BLOCKED CURRENCY. Where royalties are due for Net Sales in a country where by reason of currency regulations of any kind it is impossible to make royalty payments for that country's Net Sales said royalties shall be deposited in whatever currency is allowable for the benefit or credit of Rigel in any accredited bank in that country as shall be acceptable to Rigel. Moreover, when necessary to facilitate payments from countries other than the United States, when requested by Janssen, Rigel shall enter into direct license agreements with Janssen Affiliates designated by Janssen, whereby such Affiliate will be obligated to remit royalty payments due for Net Sales in such country directly to Rigel. Each such license agreement shall contain substantially the same terms as this Agreement insofar as such terms are lawful under applicable laws and regulations of the particular country; and Janssen shall be responsible for the performance of all obligations of Janssen Affiliates under such license agreements.

6.14 TAXES. All payments under this Agreement will be made without any deduction or withholding for or on account of any tax unless such deduction or withholding on behalf of Rigel is required by any applicable law. If Janssen is so required to deduct or withhold, Janssen will:

(a) promptly notify Rigel of such requirement;

(b) pay to the relevant authorities the full amount required to be deducted or withheld promptly upon the earlier of determining that such deduction or withholding is required or receiving notice that such amount has been assessed against Rigel;

(c) promptly forward to Rigel an official receipt (or certified copy), or other documentation reasonably acceptable to Rigel, evidencing such payment to such authorities.

6.15 THIRD PARTY PAYMENTS BY RIGEL. All payments due to Third Parties pursuant to agreement between Rigel and a Third Party that relate to Rigel Technology shall be made by and or the account of Rigel. Janssen assumes no responsibility for any payment due to Stanford University, the State University of New York at Stony Brook, BASF, any other Third Party pursuant to an agreement between Rigel and such Third Party.

7. INTELLECTUAL PROPERTY

7.1 INFORMATION AND REPORTS. The Parties will provide to the RMC promptly and at least quarterly the results of the research activities conducted in the Research Program, such reports to be in such form as specified by the RMC. The Parties shall keep complete and accurate records pertaining to the results of work conducted pursuant to the Research Program. Such records shall be maintained for a period of at least five (5) years following the year in which any such efforts were made hereunder; PROVIDED, HOWEVER, that all laboratory notebooks pertaining to the result of the work conducted pursuant to the Research Program shall be maintained for at least twenty (20) years.

7.2 DISCLOSURE OF PATENTABLE INVENTIONS. In addition to the disclosures required, each Party shall provide the other any invention disclosure related to the Research Program which has been submitted to it in the normal course of disclosing an invention. Such invention disclosures shall be provided promptly after submission and in no event later than 10 business days after the end of the calendar quarter in which the disclosure was submitted.

7.3 OWNERSHIP OF RESEARCH PROGRAM KNOW-HOW; INVENTIONS. Except as otherwise set forth herein, Research Program Know-How (including, without limitation, any patentable invention or discovery) acquired, developed or made solely by employees of one Party during the course of the Research Program ("Sole Inventions") shall be the property of such Party. Research Program Know-How (including, without limitation, any patentable invention or discovery) acquired, developed or made jointly by employees of Janssen and Rigel as determined in accordance with United States rules of inventorship, shall be owned jointly by Janssen and Rigel, each to own an undivided one-half (1/2) interest in such Research Program Know-How ("Joint Invention") except as provided and subject to the licenses granted herein. Each Party shall cooperate with the other in completing any patent applications relating to Joint Inventions, and in executing and delivering any instrument required to assign, convey or transfer to such other Party its undivided one-half (1/2) interest.

7.4 PATENT PROSECUTION. Each Party will prepare, file, prosecute and maintain patent applications for its Sole Inventions and shall be responsible for related interference proceedings. The Parties will endeavor to ensure that such patent applications are filed before any public disclosure by either Party to maintain the validity of patent applications to be filed outside of the United States and to comply with the provisions of Article 9. Janssen shall be responsible for filing and prosecuting applications for, and maintaining, Joint Inventions not related to Rigel Technology, using counsel of its choice, throughout the world. Janssen shall pay all expenses for filing applications for, and maintenance of, such Joint Inventions. In the event that a Party decides not to proceed with filing or prosecuting an application for, or maintaining, a Research Program Patent for which it is responsible under this Section 7.3, it shall give the other Party ninety (90) days written notice before any public disclosure or any relevant prosecution or maintenance deadline and transmit all information reasonable and appropriate relating to such Research Program Patent, and such other Party shall have the right to pursue, at its own expense, prosecution of such application for, or maintenance of, such patent.

7.5 INFRINGEMENT BY THIRD PARTIES.

(a) NOTICE. Each Party shall promptly notify the other in writing of any alleged or threatened infringement of the Research Program Patents, which may adversely impact the rights of the Parties hereunder, of which it becomes aware.

(b) ENFORCEMENT ACTION. In the event that the Parties become aware of any alleged or threatened infringement of the Research Program Patents, other than Research Program Patents relating to Rigel Technology, Janssen shall have the right, but not the obligation, to take appropriate action against any person or entity directly or contributorily infringing such Research Program Patent. In the event Janssen fails to institute an infringement suit or take other reasonable action in response to such infringement within sixty (60) days, Rigel shall have the right, but not the obligation upon thirty (30) days written notice to Janssen, to institute such suit or take other appropriate action in its own name, the joint owner's name, or both. Rigel shall have the right, but not the obligation, to take appropriate action against any person or entity directly or contributorily infringing a Research Program Patent relating to Rigel Technology. In the event Rigel fails to institute an infringement suit or take other reasonable action in response to such infringement within sixty (60) days, Janssen shall have the right, but not the obligation upon thirty (30) days notice to Rigel, to institute such suit or take other appropriate action in its own name, the joint owner's name, or both. Regardless of which Party brings an enforcement action, the other Party hereby agrees to cooperate reasonably in any such effort, including, if required, furnishing a power of attorney. The Party not bringing the action shall have the right to participate in such action at its own expense with its own counsel and in such case any recovery obtained by settlement or otherwise shall be shared by the Parties in accordance with their economic interests in such Research Program Patent.

7.6 INFRINGEMENT OF THIRD PARTY PATENT RIGHTS.

(a) JOINT STRATEGY. In the event that the use or sale of a Product becomes the subject of a claim of infringement of a patent, copyright or other proprietary right anywhere in the world, and without regard to which Party is charged with said infringement, and the venue of such claim, the Parties shall promptly confer to discuss the claim.

(b) DEFENSE. Unless the Parties otherwise agree, Janssen shall assume the primary responsibility for the conduct of the defense of any such claim. Rigel shall have the right, but not the obligation, to participate in any such suit at its sole option and at its own expense. Each Party shall reasonably cooperate with the Party conducting the defense of the claim. Neither Party shall enter into any settlement that affects the other party's rights or interests without such other party's written consent, not to be unreasonably withheld.

8. REPRESENTATIONS AND WARRANTIES

8.1 REPRESENTATIONS AND WARRANTIES. Each Party represents and warrants to the other that:

(a) CORPORATE POWER. It is duly organized and validly existing under the laws of its state or country of incorporation, and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof.

(b) DUE AUTHORIZATION. It is duly authorized to execute and deliver this Agreement and to perform its obligations hereunder, and the person or persons executing this Agreement on its behalf has been duly authorized to do so by all requisite corporate action.

(c) BINDING AGREEMENT. This Agreement is legally binding upon it and enforceable in accordance with its terms. The execution, delivery and performance of this Agreement by it does not conflict with any agreement, instrument or understanding, oral or written, to which it is a Party or by which it may be bound, nor violate any material law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.

(d) GRANT OF RIGHTS; MAINTENANCE OF AGREEMENTS. It has not, and will not during the term of this Agreement, grant any right to any Third Party which would conflict with the rights granted to the other Party hereunder. It has (or will have at the time performance is due) maintained and will maintain and keep in full force and effect all agreements necessary to perform its obligations hereunder.

(e) VALIDITY. It is aware of no action, suit or inquiry or investigation instituted by any governmental agency, which questions or threatens the validity of this Agreement.

(f) EMPLOYEE OBLIGATIONS. All of its employees, officers and consultants have executed agreements requiring in the case of employees and officers, assignment to the Party of all inventions made during the course of and as a result of their association with such Party and obligating the individual to maintain as confidential the confidential information of the Party, as well as the confidential information of a Third Party which such Party may receive.

(g) PERFORMANCE BY AFFILIATES. The Parties recognize that each may perform some or all of its obligations under this Agreement through Affiliates, provided, however, that each Party shall remain responsible and be guarantor of the performance by its Affiliates and shall cause its Affiliates to comply with the provisions of this Agreement in connection with such performance.

8.2 WARRANTY AND DISCLAIMER CONCERNING TECHNOLOGY. As of the Effective Date of this Agreement, it is not aware of any Third Party patents that would prevent the other Party from exercising the licenses granted herein, or would prevent a Party from carrying out the Research Program. NOTWITHSTANDING THE FOREGOING, THE TECHNOLOGY PROVIDED BY EACH PARTY HEREUNDER IS PROVIDED "AS IS" AND EACH PARTY EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, NONINFRINGEMENT

OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES OR ARISING FROM A COURSE OF DEALING, USAGE OR TRADE PRACTICES, IN ALL CASES WITH RESPECT THERETO. Without limiting the generality of the foregoing, each Party expressly does not warrant (i) the success of any research commenced under the Research Program or (ii) the safety or usefulness for any purpose of the technology it provides hereunder.

9. CONFIDENTIALITY; PUBLICATION

9.1 CONFIDENTIALITY. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing by the Parties, the Parties agree that, for the term of this Agreement and for five (5) years thereafter, the receiving Party (the "Receiving Party") shall keep confidential and shall not publish or otherwise disclose and shall not use for any purpose other than as provided for in this Agreement any Confidential Information furnished to it by the other Party (the "Disclosing Party") pursuant to this Agreement unless the Receiving Party can demonstrate by contemporaneous, competent written proof that such Confidential Information:

(a) was already known to the Receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the Disclosing Party;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party in breach of the Agreement;

(d) was disclosed to the Receiving Party, other than under an obligation of confidentiality to a Third Party, by a Third Party who had no obligation to the Disclosing Party or any Third Party not to disclose such information to others; or

(e) was independently discovered or developed by the Receiving Party without the use of Confidential Information belonging to the Disclosing Party.

9.2 AUTHORIZED DISCLOSURE. Each Party may disclose Confidential Information belonging to the other Party to the extent such disclosure is reasonably necessary in the following instances:

(a) filing or prosecuting patents relating to Research Program Technology;

(b) regulatory filings;

(c) prosecuting or defending litigation;

(d) complying with applicable governmental regulations;

(e) conducting pre-clinical or clinical trials of Products; and

(f) disclosure to Affiliates, sublicensees, employees, consultants or agents who agree to be bound by similar terms of confidentiality and non-use at least equivalent in scope to those set forth in this Article 9.

Notwithstanding the foregoing, in the event a Party is authorized to make a disclosure of the other party's Confidential Information pursuant to this Section 9.2 it will, except where impracticable, give reasonable advance notice to the other Party of such disclosure and use reasonable efforts to secure confidential treatment of such information. In any event, the Parties agree to take all reasonable action to avoid disclosure of Confidential Information hereunder. The Parties will consult with each other concerning the provisions of this Agreement to be redacted in any filings made by the Parties with the Securities and Exchange Commission or as otherwise required by law.

9.3 PUBLICATIONS.

(a) REVIEW AND APPROVAL. Each Party to this Agreement recognizes that the publication of papers, including oral presentations and abstracts, regarding the Research Program Know-How and the Research Program Patents, subject to reasonable controls to protect Confidential Information, will be beneficial to both Parties. However, each Party shall have the right to review and approve any paper proposed for publication by the other Party or its permitted sublicensees, including oral presentations and abstracts, which utilizes data generated from the Research Program and/or includes Research Program Know-How or Confidential Information of the reviewing Party.

(b) REVIEW AND APPROVAL PROCESS. At least thirty (30) days before any such paper is presented or submitted for publication, the Party or its permitted sublicensee proposing publication shall deliver a complete copy to the other Party. The receiving Party shall review any such paper and give its comments to the publishing Party or its permitted sublicensee within thirty (30) days of the delivery of such paper to the receiving Party. With respect to oral presentation materials and abstracts, the Parties shall make reasonable efforts to expedite review of such materials and abstracts, and shall return such items as soon as practicable to the publishing Party with appropriate comments, if any, but in no event later than thirty (30) days from the delivery date thereof to the receiving Party. The publishing Party or its permitted sublicensee shall comply with the other Party's request to delete references to such other Party's Confidential Information in any such paper and agrees to withhold publication of same an additional ninety (90) days in order to permit the Parties to file patent application, if either of the Parties deem it necessary, in accordance with the terms of this Agreement.

9.4 PUBLICITY. Neither Party shall, without the prior written consent of the other Party (which consent shall not be unreasonably withheld or delayed), originate any publicity, news release or public announcement, written or oral, whether to the public or press, relating to this Agreement, including its existence, the subject matter to which it relates, performance under it or any of its terms or to any amendment hereto, excepting only such announcements as in the opinion of counsel for the Party making such announcement is required by law to be made. Any such announcements shall be factual and as brief as

possible. If a Party decides to make an

announcement required by law, it will give the other Party 10 business days' advance written notice, where possible, of the text of the announcement so that the other Party will have an opportunity to comment upon the announcement. To the extent that the receiving Party requests that any information in the materials proposed to be disclosed be deleted, the disclosing Party shall request confidential treatment of such information pursuant to any applicable rules or regulations (including those of the Securities and Exchange Commission) relating to the confidential treatment of such information so that there be omitted from the materials that are proposed to be disclosed any information that the receiving Party reasonably requests to be deleted. The Parties shall mutually agree upon a press release to be made on or promptly after the Effective Date. Any information which has been disclosed to Third Parties pursuant to this Section 9.4 may be repeated in whole or in part in any subsequent disclosures or statements to Third Parties without the restrictions contained herein.

10. TERM AND TERMINATION

10.1 TERM OF THE AGREEMENT. This Agreement shall become effective upon the Effective Date and continue, unless earlier terminated pursuant to Section 10.2 or 10.3, until the expiration of the last to expire patent claiming a Product (the "Term of Agreement").

10.2 EARLY TERMINATION. This Agreement shall terminate upon thirty (30) days prior notice by Rigel (a) if Janssen has not selected a Preliminary Target-Peptide Pair for further evaluation pursuant to Section 3.4 prior to the expiration of the Research Period or, (b) if Janssen does not initiate compound screening as provided in Section 3.6 prior to the expiration of the latest to expire Exclusivity Term.

10.3 TERMINATION FOR BREACH. In the event that (a) either Party shall commit a material breach at any time and (b) such defaulting Party shall fail to remedy such material breach within sixty (60) days after the date of notice thereof by the non-defaulting Party to the defaulting Party (or, if such material breach cannot be remedied within sixty (60) days, such longer period of time as may be reasonably necessary provided the defaulting Party commences to remedy such material breach within such sixty (60) day period and thereafter proceeds promptly and diligently to complete such remedy) (with respect to the defaulting Party, an "Event of Default"), then the non-defaulting Party may at any time thereafter terminate this Agreement.

10.4 JANSSEN REMEDIES UPON TERMINATION. If this Agreement is terminated as a result of an Event of Default by Rigel, the licenses granted in Article 5 herein shall survive such termination. In such event, Janssen's obligations in Article 6 shall survive, except that all royalty rates shall be reduced by fifty percent.

10.5 RIGEL CHANGE OF CONTROL.

(a) If a Rigel Change of Control (as defined below) occurs during the Research Period, then Janssen shall have the right, in its sole discretion, to terminate the Research Program and the Research Period by giving thirty (30) days' prior written notice thereof

to Rigel at any time during the sixty (60) day period following the occurrence of the Rigel Change of Control. Upon such termination by Janssen pursuant to this subsection (a), then:

(i) all unspent research funds paid to Rigel pursuant to Section 6.2 shall be returned promptly to Janssen; and

(ii) Rigel shall have no further obligation to transfer VTPPs or Rigel Technology Assays, or provide other assistance to Janssen for Internal Janssen Research;

(iii) Section 2, 3 (except for Sections 3.6 (Compound Screening; Diligence) and 3.7 (Additional Janssen Right to Validated Target-Peptide Pair), 5.1, 5.6, 5.7, and 7.2 shall terminate;

(iv) all other terms and conditions of this Agreement shall continue in full force and effect.

(b) For the purpose of this Section 10.5, a "Rigel Change of

Control" shall have occurred only at such time as a Third Party with (i) annual sales of pharmaceutical and diagnostic products of more than one billion dollars, and (ii) a market capitalization of more than fifteen billion dollars acquires, in one transaction or a series of transactions, either (y) all or substantially all of the assets of Rigel, or (z) more than 50% of the outstanding voting securities of Rigel (whether by stock acquisition, merger or otherwise).

10.6 TERMINATION NOT SOLE REMEDY. Termination is not the sole remedy under this Agreement, and, whether or not termination is effected, all other remedies will remain available except as agreed to otherwise herein (including, without limitation, any remedies in favor of Janssen referred to in Paragraph 10.5).

11. INDEMNITY

11.1 RESEARCH AND DEVELOPMENT INDEMNIFICATION. Each Party (the "Indemnifying Party") shall indemnify, defend and hold the other Party (the "Indemnified Party") harmless from and against any and all liabilities, claims, damages, costs, expenses or money judgments incurred by or rendered against the Indemnified Party and its Affiliates and sub-licensees incurred in the defense or settlement of a Third Party lawsuit or in a satisfaction of a Third Party judgment arising out of any injuries to person and/or damage to property resulting from (a) negligence of the Indemnifying Party performed in carrying out the development program hereunder, and (b) personal injury to the Indemnified Party's employees or agents or damage to the Indemnified Party's property resulting from acts in carrying out activities contemplated by this Agreement.

11.2 PRODUCT LIABILITY. Janssen hereby agrees to indemnify, hold harmless and defend Rigel and its directors, officers, employees, and agents against any claim or claims, including, but not limited to liability, suits, actions, demands, expenses and/or loss including reasonable legal expenses and attorneys fees, arising from bodily injury and death, resulting from or arising out of the manufacture, use or sale of Products by Janssen, its Affiliates and sub-licensees.

11.3 CONTROL OF DEFENSE. Any entity entitled to indemnification under this Article shall give notice to the indemnifying Party of any Claims that may be subject to indemnification, promptly after learning of such Claim, and the indemnifying Party shall assume the defense of such Claims with counsel reasonably satisfactory to the indemnified Party. If such defense is assumed by the indemnifying Party with counsel so selected, the indemnifying Party will not be subject to any liability for any settlement of such Claims made by the indemnified Party without its consent (but such consent will not be unreasonably withheld or delayed), and will not be obligated to pay the fees and expenses of any separate counsel retained by the indemnified Party with respect to such Claims.

12. GOVERNING LAW; DISPUTE RESOLUTION

12.1 GOVERNING LAW. This Agreement shall be governed by Delaware law, as such law applies to contracts entered into in Delaware by residents of Delaware.

12.2 COMPLIANCE WITH LAWS. The Parties shall comply with all applicable laws, rules, regulations and orders of the United States and all jurisdictions and any agency or court thereof in connection with this Agreement and the transactions contemplated thereby.

12.3 DISPUTE RESOLUTION. Except as provided in Section 2.3 above, in the event of a dispute, the Parties shall refer such dispute to a designated executive of Rigel and a designated executive of Janssen for attempted resolution by good faith negotiations within thirty (30) days after such referral is made. In the event such executives are unable to resolve such dispute within such thirty (30) day period, either Party may invoke the provisions of Section 12.4 below.

12.4 JURISDICTION AND VENUE. Except as provided in Section 2.3 and 12.3 above, any claim or controversy arising out of or related to this Agreement or any breach hereof shall be adjudicated in the state and federal courts having jurisdiction over disputes arising in the State of Delaware, and the Parties hereby consent to the jurisdiction and venue of such court.

13. PRODUCT DEVELOPMENT AND COMMERCIALIZATION

13.1 JANSSEN'S DEVELOPMENT RESPONSIBILITIES. Janssen shall be solely responsible for and have the sole right to select a compound for development into a Product. Once such a compound is selected for development, Janssen shall

be solely responsible for and shall have the sole right to develop such compound throughout Pre-phase I and Phases I, II and III including making all Drug Approval Applications and obtaining all Regulatory Approvals on a worldwide basis. In this regard, Janssen agrees to carry out development of such compound consistent with its normal business practices. This development effort shall include the right to slow or terminate development and all other actions deemed by Janssen to be reasonable in the development of the compound. Moreover, Janssen shall be responsible for all cost and expenses in connection with such development efforts.

13.2 MARKETING OBLIGATIONS. All business decisions, including, but not limited to, the design, sale, price and promotion of Products under this Agreement and the decision whether to market any particular Product shall be within the sole discretion of Janssen. Any marketing of a

Product in one market or country shall not obligate Janssen to market said Product in any other market or country. Furthermore Janssen makes no representation or warranty that the market of a Product shall be the exclusive means by which Janssen will participate in any therapeutic field.

14. GENERAL PROVISIONS

14.1 NOTICES. All notices required or permitted to be given under this Agreement shall be in writing and shall be mailed by registered or certified mail addressed to the signatory to whom such notice is required or permitted to be given and transmitted by facsimile to the number indicated below. All notices shall be deemed to have been given when mailed, as evidenced by the postmark at the point of mailing, or faxed; provided that such fax is confirmed by electronic confirmation of transmission.

All notices to Janssen shall be addressed as follows:

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
2340 Beerse, BELGIUM
Attention: Executive Vice President
Fax: (32+14) 60-28-41

with a copy to:

Office of General Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933 U.S.A.,
Telephone (732) 524-2485,
Telecopy (732) 524-2788

All notices to Rigel shall be addressed as follows:

Rigel Pharmaceuticals, Inc.
772 Lucerne Drive
Sunnyvale, California 94086
Attn: President
Fax: (408) 736-1588

with a copy to:

Cooley Godward LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, California 94306
Attn: Robert L. Jones, Esq.
Fax: (650) 857-0663

Any Party may, by written notice to the other, designate a new address or fax number to which notices to the Party giving the notice shall thereafter be mailed or faxed.

14.2 FORCE MAJEURE. No Party shall be liable for any delay or failure of performance to the extent such delay or failure is caused by circumstances beyond its reasonable control and that by the exercise of due diligence it is unable to prevent, provided that the Party claiming excuse uses its best efforts

to overcome the same.

14.3 ENTIRETY OF AGREEMENT. This Agreement embodies the entire, final and complete agreement and understanding between the Parties and replaces and supersedes all prior discussions and agreements between them with respect to its subject matter. No modification or waiver of any terms or conditions hereof shall be effective unless made in writing and signed by a duly authorized officer of each Party.

14.4 NON-WAIVER. The failure of a Party in any one or more instances to insist upon strict performance of any of the terms and conditions of this Agreement shall not constitute a waiver or relinquishment, to any extent, of the right to assert or rely upon any such terms or conditions on any future occasion.

14.5 DISCLAIMER OF AGENCY. Neither Party is, or will be deemed to be, the legal representative or agent of the other, nor shall either Party have the right or authority to assume, create, or incur any Third Party liability or obligation of any kind, express or implied, against or in the name of or on behalf of another except as expressly set forth in this Agreement.

14.6 SEVERABILITY. If a court of competent jurisdiction declares any provision of this Agreement invalid or unenforceable, or if any government or other agency having jurisdiction over either Rigel or Janssen deems any provision to be contrary to any laws, then that provision shall be severed and the remainder of the Agreement shall continue in full force and effect. To the extent possible, the Parties shall revise such invalidated provision in a manner that will closely approximate the parties' original intent.

14.7 AFFILIATES; ASSIGNMENT. Except as otherwise provided herein, neither Party may assign its rights or delegate its duties under this Agreement without the prior written consent of the other Party, not to be unreasonably withheld; PROVIDED, HOWEVER, that either Party may assign this Agreement to any of its Affiliates or to any successor by merger or sale of substantially all of its business unit to which this Agreement relates in a manner such that the assignor will remain liable and responsible for the performance and observance of all its duties and obligations hereunder. This Agreement shall be binding upon the successors and permitted assigns of the Parties. Any attempted delegation or assignment not in accordance with this Section 14.7 shall be of no force or effect

14.8 HEADINGS. The headings contained in this Agreement have been added for convenience only and shall not be construed as limiting.

14.9 COUNTERPARTS. This Agreement may be executed in one or more counterparts, each of which shall be an original and all of which shall constitute together the same document.

14.10 ENGLISH LANGUAGE. This Agreement has been prepared in the English language and shall be construed in the English language.

14.11 LICENSOR BANKRUPTCY. All rights and licenses granted under or pursuant to this Agreement by Rigel to Janssen are, and shall otherwise be deemed to be, for purposes of Section 365(n) of Title 11, U.S. Code (the "Bankruptcy Code"), licenses of rights to "intellectual property" as defined under section 101(60) of the Bankruptcy Code. The Parties agree that Janssen, as a licensee of such rights under this Agreement, shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code. Rigel agrees during the term of this Agreement to create and maintain current copies or, if not amenable to copying, detailed descriptions or other appropriate embodiments, of all such intellectual property. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against Rigel under the Bankruptcy Code, Janssen shall be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and the same, if not already in its possession, shall be promptly delivered to Janssen, upon written request therefor by Janssen, (a) upon any such commencement of a bankruptcy proceeding, unless Rigel elects to continue to perform all of its obligations under this Agreement, or (b) if not delivered under clause (a) above, upon the rejection of this Agreement by or on behalf of Rigel.

14.12 NO OTHER REPRESENTATIONS. Each of the Parties hereto acknowledges and agrees (a) that no representation or promise not expressly contained in this Agreement has been made by the other Party hereto or by any of its agents, employees, representatives or attorneys; (b) that this Agreement is not being entered into on the basis of, of in reliance on, any promise or representation, expressed or implied, covering the subject matter hereof, other than those which are set forth expressly in this Agreement; and (c) that each Party has had the opportunity to be represented by counsel of its own choice in this matter, including the negotiations which preceded the execution of this Agreement.

IN WITNESS WHEREOF, the Parties hereto have duly executed this Agreement.

RIGEL PHARMACEUTICALS, INC.	JANSSEN PHARMACEUTICA, N.V.
By: /s/ James Gower	By: /s/ Gustav van Reet
Name: Jim Gower	Name: Dr. Gustav van Reet
Title: President and CEO	Title: Managing Director
	By: /s/ Didier de Chaffoy de Courcelles
	Name: Didier de Chaffoy de Courcelles
	Title: Vice President Biological Research

EXHIBIT A

RESEARCH PLAN

SYNOPSIS

RIGEL-JANSSEN COLLABORATION PROPOSAL

APPROACH: To identify targets that regulate cell cycle checkpoint control mechanisms. This will be accomplished by introducing into selected tumor cells using proprietary retroviral delivery-vectors cDNA libraries and constrained 18mer random peptide libraries in order to alter the cellular phenotype of specific tumor cells. Using this approach in tumor cells, which exhibit uncontrolled proliferation, target-peptide pairs will be identified which restore normal cell-cycle progression and sensitivity to chemotherapeutic agents.

cDNA LIBRARIES: Human fetal liver and brain. The reason for choosing these tissues is that cells in these organs have a high degree on "differentiation control mechanisms" and hence should contain targets that are important in regulating the cell cycle.

PEPTIDE LIBRARIES: The first library to be tested will be a constrained 18mer random peptide library. Other libraries will be screened as necessary.

CELL LINES FOR PRIMARY SCREENS: Cell lines derived from Colon, Lung and Breast tumors will be studied. From Colon, the line HT-29; Lung, the cell lines A549 (p53 wt) and H-1299; and Breast, the line MDA-MB-231. For each cell line the p53, Rb, p16 and p21 status will be evaluated using antibodies and sequencing of the gene to determine the presence and absence of specific mutations. These will be compared to control levels from normal tissues.

PRIMARY SCREENS: For each of the above tumor cell lines, retrovirally delivered libraries (cDNA and random constrained peptide) will be introduced into cells. The cells will be stained with the Cell Tracker dye and monitored for cell division by high through put FACS. Cells that don't divide will be sorted and stained with a DNA labeling dye in order to identify those cells in G0/G1, S or G2M. After several rounds of enrichment, library members that block/arrest cell division in a particular phase of the cell cycle, will be identified.

SECONDARY SCREENS: Individual cDNA and peptide hits from the primary screens will be evaluated in the same FACS assay as above, and in proliferation and apoptosis assays in a "panel" of cell lines to be determined by the RMC.

PATHWAY MAPPING. Using the Yeast Two-Hybrid (YTH) technology cDNA hits (those found by Rigel in their functional screens, or by Janssen, such as Hrad17, Hrad1, etc.) will be used in YTH to find their interacting protein partners, and these will be evaluated in the above assays for function. Proteins that are demonstrated to significantly alter cell cycle in tumor cells, will be subjected to a YTH screen with a constrained peptide library

to find an enriched "peptide binding" library that can identify functional sites on these proteins in the above assays. The goal is to identify peptide-protein pairs that restore proteins in normal cell cycle responses in a significant number of tumor cell lines.

RESOURCES: 10 Rigel FTEs for 36 months.

IDENTIFICATION OF FUNCTIONAL PEPTIDE-TARGET INTERACTIONS REGULATING CELL CYCLE IN SPECIFIC TUMOR CELLS

JANSSEN PROJECT OUTLINE

INTRODUCTION

The hallmark of a malignant cell is uncontrolled proliferation. This phenotype is acquired through the accumulation of gene mutations, the majority of which promote passage through the cell cycle. Cancer cells ignore growth regulatory signals and remain committed to cell division. Classic oncogenes, such as RAS, lead to inappropriate transition from G1 to S phase of the cell cycle, mimicking proliferative extracellular signals. Cell cycle checkpoint controls ensure faithful replication and segregation of the genome. The loss of cell cycle checkpoint control results in genomic: instability, greatly accelerating the accumulation of mutations which drive malignant transformation. Hence, checkpoint regulators, such as p53 and ATM (ataxia telangiectasia mutated), also function as tumor suppressors. Thus, modulating cell cycle checkpoint pathways with therapeutic agents could exploit the differences between normal and tumor cells, both improving the selectivity of radio- and chemotherapy, and leading to novel cancer treatments. THE GOAL OF THIS PROPOSAL IS TO IDENTIFY PEPTIDE/PROTEIN INTERACTIONS THAT INHIBIT THE ABILITY OF SPECIFIC TUMOR CELLS TO PROLIFERATE, BY ALTERING THEIR CAPACITY TO TRANSIT THROUGH VARIOUS STAGES OF THE CELL CYCLE. This will be accomplished by identifying intracellular targets, and their cognate regulating peptides, capable of inhibiting tumor cell progression through the cell cycle, either by activating cell cycle checkpoint pathways or ameliorating checkpoint defects (see Table I for summary). The identification of these targets will allow for low molecular weight compound screening to isolate activators or inhibitors of cell cycle checkpoint pathways.

Table 1 Summary of screens to identify functional peptide-target interactions regulating cell cycle in specific tumor cells.

SCREENING APPROACH	READOUT	LIBRARY STRUCTURE + TARGETING MOTIF
1. Functional screening with peptide libraries for inhibitors of tumor cell progression through various phases of the cell cycle	Identify tumor cells arrested in specific cell cycle phase using four-parameter cell-based high throughput FACS assay	- Linear 20 mer +/- NLS* - Constrained 18-mer stem loop +/- NLS - 4 helix bundle +/- NLS
2. Functional analysis of proteins (Hrad17, Hrad1, Hrad9, etc.) isolated by Janssen implicated in cell-cycle control.	Examine effect of protein, antisense, mutated protein or peptide binding library on tumor cells in assays under Specific Aim 1	
2.1 Retroviral-mediated functional analysis of cell cycle control proteins		- N/A
2.2 Large scale randon-mutagenesis analysis of cell cycle control proteins: Generation of libraries of mutant proteins		- Library of mutated proteins
2.3 Cell cycle control protein-binding peptide library screen (see 3.2)		- "enriched by binding" library: constrained 18 mer stem-loop +/- NLS
3. Elucidation of the signaling pathways that mediate the control of cell cycle checkpoints in specific tumor cells		-
3.1 Two hybrid screening of peptide hits from 1 to identify functional peptide-target protein pairs	LacZ+, His+	- cDNA library: - a specific tumor cells - a human fetal liver/brain

3.2 Isolation of peptides that bind to specific proteins implicated in cell cycle regulation and determination of their ability to specially inhibit tumor replication and progression through various phases of the cell cycle.	LacZ+, His+	- enriched by binding" peptide library: constrained 18 mer stem-loop +/- NLS
3.3 Cell cycle checkpoint pathway mapping	LacZ+, His+	- cDNA libraries - "enriched by binding" peptide library: constrained 18mer stem-loop +/- NLS

</TABLE>
* NLS = nuclear localization sequence

A. SPECIFIC AIMS

The outline of the Specific Aims below, is followed by a more detailed discussion of the Experimental Methods and the Design of the Project.

SPECIFIC AIM 1:

FUNCTIONAL SCREENING WITH PEPTIDE LIBRARIES FOR INHIBITORS OF TUMOR CELL PROGRESSION THROUGH VARIOUS PHASES OF THE CELL CYCLE.

Screens in specific aim 1 will be conducted on a panel of tumor cell lines to be chosen by Janssen. These cell lines will be selected based on their representation of important oncology markets, biological significance, and clinical relevance. The characteristics of the tumor cell lines are detailed in an addendum to be provided by Janssen. A Rigel-Janssen joint research committee will review this information to ensure that it includes information relating to culture conditions and molecular defects in key intracellular targets that could influence the assay conditions (e.g. p53, Rb status, etc.).

Tumor cells selected by Janssen will each be infected with three structurally different retroviral peptide libraries with and without sub-cellular localization sequences (Appendix A). These peptide libraries will consist of a linear 20mer with and without a nuclear localization signal (NLS), a stem loop constrained 18mer with and without an NLS, and a third constrained library containing a different scaffolding, such as a 4-helix bundle with and without an NLS Library infected tumor cells which are inhibited in their progression through specific phases of the cell cycle will be selected using a high throughput fluorescent activated cell sorter (FACS) (Appendix B). After several rounds of enrichment, individual peptide sequences will be tested for inhibitory function. Validated peptide hits will be subjected to secondary assays in a broader panel of representative tumor cell lines to be chosen by Janssen in order to determine their physiologic characteristics and specificity. Peptides that demonstrate desirable characteristics will be used as bait in a yeast two-hybrid screen to locate their intracellular binding partners (see specific aim 3.1 for details). The right-hand side of Figure 1 illustrates this identification cycle for functional peptide-target protein interactions (the left-hand side will be discussed in section 2.3 and 3.3 below).

[Diagram]
(Figure 1)

SPECIFIC AIM 2:

FUNCTIONAL ANALYSIS OF PROTEINS IMPLICATED IN CELL CYCLE CHECKPOINT CONTROL.

Cell cycle checkpoint control proteins, selected by Janssen scientists, will be subjected to a detailed functional analysis to establish their potential as targets for further pharmaceutical development. Initial examples will include, but are not limited to, Hrad1 and Hrad17, two human homologues of S. POMBE proteins implicated in DNA damage-dependent and DNA replication-dependent cell cycle checkpoints. The genes encoding these proteins will be transduced into selected cell lines and analyzed for cell cycle perturbances. Mutagenesis studies will be conducted on each gene to identify mutants with dominant-negative effects on cell cycle

progression and checkpoint responses to anticancer agents. Together this information will provide insight into the role these proteins play in mammalian checkpoint control and how mutations in these genes may contribute to tumorigenesis and chemotherapic sensitivity. These cell cycle control proteins will be screened for interacting peptides in a yeast two-hybrid system. The binding peptides will be assayed for their ability to influence tumor cell growth and sensitivity to chemotherapic treatments.

2.1 Retroviral-Mediated Functional Analysis Of Cell Cycle Control Proteins.

Cell cycle control genes selected by Janssen will be cloned into Rigel's proprietary retroviral expression system for stable transduction into selected tumor lines. Optimized infection protocols will be developed for each cell line. Transduced cells will be analyzed for cell cycle effects and changes in apoptotic responses (by FACS-based ways described in Appendix B). The radiation and chemotherapeutic sensitivity of cells expressing these cell cycle control genes will be assayed in collaboration with Janssen scientists. Anti-sense versions of each gene will be assessed for loss-of-function phenotype and/or dominant negative effects in cell cycle assays.

2.2 LARGE-SCALE RANDOM-MUTAGENESIS ANALYSIS OF CELL CYCLE CONTROL PROTEINS: GENERATION OF LIBRARIES OF MUTANT PROTEINS.

Selected cell cycle control proteins will be randomly mutagenized to create libraries of mutated proteins (Appendix C) and screened for dominant negative cell cycle effects in different cell lines as described in Specific Aim 2.1.

2.3 CELL CYCLE CONTROL PROTEIN-BINDING PEPTIDE LIBRARY SCREEN.

The cell cycle control proteins defined above will be screened in a yeast two-hybrid assay for interacting binding peptides (as described in Specific Aim 3.2). These interacting peptides will be introduced into selected tumor cell lines to assess effects on cell cycle and sensitivity to chemotherapeutic treatments as described in Specific Aim 1.

SPECIFIC AIM 3:

ELUCIDATION OF THE SIGNALING PATHWAYS THAT MEDIATE THE CONTROL OF CELL CYCLE CHECKPOINTS IN SPECIFIC TUMOR CELLS

Specific aim 3 represents the final phase in the derivation of functional-based peptide-protein pairs that are members of a pathway(s) that regulate cell cycle in specific tumor cells.

3.1 TWO-HYBRID SCREENING OF PEPTIDE HITS TO IDENTIFY FUNCTIONAL PEPTIDE-TARGET PROTEIN PAIRS.

The peptide hits identified in Specific will be used as bait in a two-hybrid screen to identify their intracellular binding partners (Appendix D). This will identify peptide-target pairs that can be further assessed in secondary and orthogonal assays to be determined by the Rigel

Janssen joint research committee for their potential to specifically inhibit tumor cells progression through various phases of the cell cycle. These protein targets will also be subjected to additional two-hybrid screening to identify neighboring interacting proteins that may also regulate the cell cycle and proliferation of tumor cells (see 3.3 below).

3.2 ISOLATION OF PEPTIDES THAT BIND TO SPECIFIC PROTEINS IMPLICATED IN CELL CYCLE REGULATION AND DETERMINATION OF THEIR ABILITY TO SPECIFICALLY INHIBIT TUMOR REPLICATION AND PROGRESSION THROUGH VARIOUS PHASES OF THE CELL CYCLE.

The cell cycle control proteins selected by Janssen (see Specific Aim 2.1) will be subjected to a two-hybrid screen using a combinatorial peptide library to identify specific binding peptides (Appendix E). The two-hybrid peptide libraries contain the same peptide structures and sub-cellular localization sequences as described in Specific Aim 1 and Appendix A. The isolated target-binding peptides will be assessed for their ability to inhibit cell cycle progression in tumor cells. Validated peptide hits will be subjected to secondary assays to confirm their function and specificity.

3.3 CELL CYCLE CHECKPOINT PATHWAY MAPPING.

The protein targets identified above (Specific Aim 2 and 3.1) will be screened for additional interactions with other proteins by yeast two-hybrid technology (Appendix D). These binding proteins will be assayed for their ability to halt tumor cell progression through various cell cycle phases. Those that have function in this basic assay will be subjected to a two-hybrid screen using a combinatorial peptide library to identify specific binding peptides (Appendix F). The two-hybrid peptide libraries contain the same peptide structures and sub-cellular localization sequences as described in Specific Aim 1 and Appendix A. The isolated target-binding peptides. will be assessed for their ability to inhibit cell cycle progression in tumor cells. Validated peptide hits will be subjected to secondary assays to confirm their function and specificity. This process represents a reverse of what was described earlier in Specific Aim 1 and is illustrated in the left-hand side of Figure 1.

B. EXPERIMENTAL DESIGN AND METHODS

SPECIFIC AIM 1:

FUNCTIONAL SCREENING WITH PEPTIDE LIBRARIES FOR INHIBITORS OF TUMOR CELL PROGRESSION THROUGH VARIOUS PHASES OF THE CELL CYCLE.

RATIONALE:

Altered regulation of proteins that control cell cycle checkpoints may result in chromosomal instability which underlies the transformed state of many tumor cells. Using Rigel's high throughput genetic screens, it is expected that novel tumor-specific targets will be identified, which when bound to a peptide, will result in the cell being blocked from exiting a specific phase of the cell cycle.

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Rigel has demonstrated that it can identify and express cell cycle regulating proteins, and specific peptides derived from them, which arrest cells in a specific phase of the cell cycle (Appendix F). Consequently, it is expected that the use of combinatorial constrained peptide libraries delivered using a retroviral-based system will identify peptide families which interact with novel cell-cycle checkpoint regulating targets.

1.1 PEPTIDE LIBRARY SCREENING AND TARGET IDENTIFICATION USING A CELL CYCLE CHECKPOINT ASSAY.

Tumor cells selected by Janssen will be infected with each Rigel peptide library (Appendix A). The screening protocol and timeline for identification of the peptide inhibitors and their target proteins is shown diagrammatically in Figure 2 for each of the three structurally different peptide libraries.

(Figure 2)

Each of these peptide libraries will be packaged into infectious viral particles (for protocol, see Appendix G). Each library will be a mixture of random peptide sequences with and without a nuclear localization sequence (NLS) upstream of a reporter gene to identify infected cells and relative peptide expression (Appendix H). In fact, we have developed several retroviral constructs to control all aspects of peptide expression and localization. This gives us great flexibility when designing retroviral libraries within any cell, line and with whichever characteristics are deemed necessary for intracellular peptide expression (Appendix I). The three structurally different peptide libraries will consist of a linear 20-mer (first year), a constrained stem-loop 18-mer (first to second year) and a third structure such as a 4-helix bundle to be determined by year three (Appendix A).

Each screen will start with production of the primary retrovirus peptide library. This primary library will be used to infect at least 109 tumor cells. After infection, the tumor cells will be loaded with a fluorescent dye (celltracker) that is uniformly partitioned into dividing cells. As cell division progresses, the fluorescence is diminished proportionately to the number of cell divisions. Hence, cells that fail to divide remain maximally bright (Appendix B). The screen is conducted over a time period such that, in tumor cells where no library is expressed, greater than 99% of the tumor cells undergo a sufficient number of cell divisions resulting in less than 1% of cells with the maximal celltracker fluorescence in the FACS. Prior to the high throughput FACS sort, cultures of cells are labeled with a DNA staining dye, such as Hoechst 33342, which enables the identification of viable cells in different phases of the cell cycle. Cells which are maximally bright with the celltracker dye (i.e. cells where the expressed peptide inhibits division) will be sorted according to the specific phase of the cell cycle in which they have been arrested (Appendix B). A positive control construct encoding the cyclin-CDK-inhibitor (CKD-family member, p21, will be used to optimize the may conditions in selected target cell lines. Enriched non-dividing tumor cell populations will be subjected to RT-PCR to amplify the integrated peptide sequences. The PCR material will be used to construct a now "enriched" retrovirus peptide library to initiate the next screening round.

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It will take approximately 5-7 rounds of enrichment to identify individual peptide sequences capable of inhibiting tumor cell cycle progression. For a discussion of the statistics associated with enrichment, see Appendix J. The most important factor that influences the number of enrichment rounds necessary to identify individual peptide hits is the ratio between real positive peptide hits in the original library and heritable false positives. The frequency of real positive peptide hits is dependent upon the qualitative ability of the peptide to access and, in the correct conformation, bind to the regulatory domains on proteins in the pathway of interest. This is why we use multiple scaffolding structures for presentation of random peptide surfaces and also different localization sequences fused to those peptide structures (Appendix A). Enrichment of real positive peptides becomes less efficient with false positive rates above 2%. Consequently, great effort is placed in developing robust assays with multiple parameters being analyzed for a given biologic process.

Uneven RT-PCR amplification may decrease overall amplification of real peptides hits from one round to another. This is overcome by additional rounds of library enrichment and is why RT-PCR amplification is carefully monitored after each round of screening. We are also developing a direct biological rescue to expedite enrichment and to overcome any decrease in amplification of peptide hits due to uneven RT-PCR. Biological rescue involves direct transfer of recombinant retroviral inserts from positively identified cell clones into naive cells for retesting. By supplying retrovirus proteins GAG-POL-ENV to cells, integrated proviral transcripts encoding putative peptide hits are selectively re-packaged and secreted as new virions capable of infecting new cells. Positive cells can be converted to retroviral producers by superinfection of gagGAG-POL-ENV genes or alternatively, tetracycline-inducible packaging functions can be preengineered into target cell lines. By either strategy, peptides from enriched cells can be selectively transferred to new cells and re-tested for phenotypic effects, eliminating the time-intensive and potentially biased intermediary molecular cloning steps.

A separate strategy to enhance enrichment will involve a retroviral system with inducible expression (e.g. tetracycline dependent). Inducible transcription units can be placed within the retroviral vector, alternatively, inducible promoter elements may be inserted into the retroviral promoter within the LTR (see Appendix H). In this scheme, peptide expression is repressed following sorting to alleviate the peptide-specific cell cycle arrest and to allow a post-sort growout: Cells arrested due to non-peptide specific causes, such as mutation or aneuploidy, would remain arrested. Re-induction of the peptide expression will reinstate the arrested phenotype in true peptide hits. which can subsequently be enriched in another round of sorting.

Once enrichment is achieved and individual peptide sequences are shown to effect inhibition in an Independent assay, the peptides will. be introduced into a panel of tumor cells (to be obtained from the NCI) for secondary and orthogonal assays as determined by the Rigel Janssen joint research committee. Validated peptides will then be used as bait to isolate their interacting protein targets by two-hybrid approaches (see section 3 for details).

SPECIFIC AIM 2:

FUNCTIONAL ANALYSIS OF PROTEINS IMPLICATED IN CELL CYCLE CHECKPOINT CONTROL.

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RATIONALE:

Cell cycle control genes identified by Janssen, including (but not limited to) human homologues of S. POMBE RADL+ and RAD17+ checkpoint genes, will be expressed in selected cell lines for detailed functional analysis to establish their potential as targets for further pharmaceutical development. Expression of dominant-negative mutants of cell cycle checkpoint regulators, such as p53 and hBUB 1. account for some inappropriate tumor cell responses to DNA damaging and spindle-disrupting agents, respectively. Hence, mutagenesis studies will be conducted on each cell cycle control gene to identify dominant-negative mutants of these proteins. This will serve to map functional domains important in the regulation of cell cycle checkpoint function and chemotherapeutic sensitivity. Selected cell cycle control proteins will be screened for interacting peptides in a yeast two-hybrid system. These binding peptides will be assayed for their ability to influence tumor cell growth and for their sensitivity to chemotherapeutic treatments.

2.1 RETROVIRAL-MEDIATED FUNCTIONAL ANALYSIS OF CELL CYCLE CONTROL PROTEINS.

Cell cycle control genes selected by Janssen will be transferred into Rigel's retroviral system for stable expression and functional analysis in selected tumor cell lines. Encoding sequences will be cloned into the multiple cloning region of the basic retroviral vector construct (Appendix H). An internal ribosome entry site placed immediately 3' of the multiple cloning site, drives cap-independent translation of downstream encoding sequences. This allows co-translational selection with a downstream FACS-selectable marker (e.g. GFP). Infectious retroviral particles are produced by transient transfection of retroviral vector, constructs into high efficiency packaging cell lines (Appendix G), harvested, and used to infect target cell lines for stable integration into the target cell genome. Optimal infection protocols will be developed for each cell line using- a GFP control vector. A generic protocol is detailed in Appendix G. Examples of infection rate for various tumor cell lines is shown in Table 2.

TABLE 2. INFECTION RATES WITH RIGEL RETROVIRAL CONSTRUCTS FOR VARIOUS TUMOR CELL LINES.

<TABLE>
<CAPTION>
- ---------- ----- CELL LINE INFECTION EFFICIENCY (%)

A549 (non-small cell lung cancer)	>80
HeLa (cervical carcinoma)	>70
T47D (breast cancer)	>70
SW480 (colorectal cancer)	>70
CEM (T-lymphoblastoid leukemia)	>30

</TABLE>

In most cases, transduction rates of >70% are achievable with limited optimization of the standard protocol. Occasionally, cells express low levels of the retroviral receptor recognized by the retroviral envelope protein. This may be compensated by engineering the target cell lines to express higher receptor levels by introducing die ecotropic envelope protein receptor (EcoR), a basic amino acid transporter. For example, infection efficiency of Jurkat T-lymphoblastoid

leukemia cells was enhanced from ~15% to >90% in EcoR-expressing lines. Alternatively, retroviral vector particles may be pseudotyped with the Vesticular Stomatitis Virus G-protein (VSV-G), which interacts with membrane lipids, (phosphatidylserine) to promote fusion.

The infection efficiency of individual constructs is monitored via IRES-driven GFP coexpression by FACS and/or microscopy. Cells expressing cell cycle control genes will be analyzed for direct cell cycle effects and induction of apoptosis, (Annexin-V binding) by FACS-assay. Furthermore, the transduced cells will be assayed for chemotherapeutic (e.g. DNA replication inhibitors, anti-metabolites, microtubule-disrupting agents) and radiation (UV and gamma) sensitivity alterations in collaboration with Janssen scientists.

Anti-sense versions of each cell cycle control gene will be constructed by inserting the cDNA sequence in reverse orientation into the basic vector. The insert length will be varied, creating small libraries of specific anti-sense effectors for each gene. These constructs will be used to generate infectious retroviral vector particles and transduced into selected cell lines as described above. The transduced cells will be assayed for loss-of-function and/or dominant negative effects on cell cycle checkpoint control as described above.

2.2 LARGE SCALE RANDOM-MUTAGENESIS ANALYSIS OF CELL CYCLE CONTROL PROTEINS: GENERATION OF LIBRARIES OF MUTANT PROTEINS.

The polymerase chain reaction (PCR) can be used to generate comprehensive, unbiased single-point mutation libraries. Essentially, the mutagenesis strategy takes advantage of the ability of Taq DNA polymerase to alter the fidelity of replication by doping the PCR reaction with divalent cations. The use of magnesium to stabilize non-complementary base-pairs and manganese to impair recognition of complementary base-pairs allows mutation of up to 2% of all nucleotides per gene. The mutation frequency can be controlled by dusting levels of the divalent cations to produce an average of one mutation per gene. The use of altered dNTP ratios can eliminate the inherent bias for transition-mutations in PCR mutagenesis. This controlled PCR mutagenesis procedure can create complex, representative, mutant cDNA libraries for genes of any length which can then be used to probe for critical functional domains of the encoded protein. Then libraries are screened in the functional assay detailed in Appendix B. The Janssen-Rigel joint research committee will determine treatment regimes with relevant DNA damaging agents, radiation or chemotherapeutics for the tumor cells expressing different cell cycle control gene mutant libraries.

2.3 CELL CYCLE CONTROL PROTEIN-BINDING PEPTIDE LIBRARY SCREEN.

The cell cycle control proteins defined above will be screened in a yeast two-hybrid assay for interacting peptides as described in Specific Aim 3.2. Interacting peptide encoding sequences will be transferred into a shuttle vector for transfer into tumor cell lines. Peptide effects on cell cycle checkpoint function will be assayed as described in Specific Aim 2.1.

SPECIFIC AIM 3:

ELUCIDATION OF THE SIGNALING PATHWAYS THAT MEDIATE THE CONTROL OF CELL CYCLE CHECKPOINTS IN SPECIFIC TUMOR CELLS

RATIONALE:

Peptides that inhibit the ability of tumor cells to transit through specific phases of the cell cycle do so by binding to intracellular proteins

that am members of pathways which control cell replication. Identification of functional Peptide-target Protein Pairs which significantly alter these responses will enable screening for low molecular weight inhibitory compounds.

3.1 TWO-HYBRID SCREENING OF PEPTIDE HITS TO IDENTIFY FUNCTIONAL PEPTIDE-TARGET PROTEIN PAIRS.

The peptide hits identified in specific aim 1 will be used as bait in a two-hybrid screen to identify their intracellular binding partners. This will identify peptide-target pairs that can be assessed in secondary and orthogonal assays for their potential to specifically inhibit tumor cell transition through the cell cycle and proliferation. The cDNA libraries to be used are derived from the specific tumor cells used in the screen, and from a control library derived from human fetal liver and brain.

The identified peptide/protein pairs will be assessed for their ability to regulate tumor cell growth and cell cycle progression in a panel of tumor cell lines derived from a variety of sources (e.g. National Cancer Institute tissue bank) in order to determine specificity, in addition to being examined for their effect on normal cells, such as human epithelial and endothelial cells and murine primary bone marrow cells. These protein targets will also be subjected to additional two-hybrid screening to identify neighboring interacting proteins (pathway mapping) involved in cell cycle pathways in tumor cells (see section 3-3).

The screening protocol for identification of peptide binding proteins is summarized in Appendix E. The methods are as follows: oligo sequences encoding the peptide hits will be cloned into pAS2- 1K to fuse to the C-terminal of GAL4 DNA binding domain. The oligos can also be cloned into pAS2N to fuse to the N-terminal of GAL4 DNA binding domain. Both bait plasmids can be used for subsequent screenings.

The bait plasmids will be transformed into the Y 190 yeast strain. This yeast strain has the highest sensitivity for yeast two-hybrid screening. Optimal 3AT concentration needed to suppress any HIS background expression will be determined on SD-WH+3AT plates.

cDNA libraries from both tumor cells and fetal and human brain will be used to transform the yeast already containing the bait plasmid. At least 20 million transformants from each library will be screened on SD-LWH+3AT plates. HIS+ and LacZ+ clones will be grown up in SD-L liquid medium to retrieve plasmid and for retransformation into Y190 to verify the binding specificity.

3.2 ISOLATION OF PEPTIDES THAT BIND TO SPECIFIC PROTEINS IMPLICATED IN CELL CYCLE REGULATION AND DETERMINATION OF THEIR ABILITY TO SPECIFICALLY INHIBIT TUMOR REPLICATION AND PROGRESSION THROUGH VARIOUS PHASES OF THE CELL CYCLE.

Hrad1, Hrad17, and other proteins implicated in regulating the cell cycle identified by Janssen (see Specific Aim 2), will be subjected to a yeast two-hybrid screen using a peptide library to identify binding peptides as described in Appendix F. The identified binding peptides will then be assessed for their ability to inhibit specific tumor cells in their progression through the call cycle. Validated peptide hits will be subjected to secondary assays to confirm their function and specificity. This will identify functional peptides that bind to the cell cycle control proteins and inhibit tumor growth (left side of Figure 1).

3.3 CELL CYCLE CHECKPOINT PATHWAY MAPPING.

The second-level two-hybrid screening of protein targets that bind to peptide hits (from Specific Aim 3.1), or cell cycle control proteins selected by Janssen (Specific Aim 2-1). is referred to as functional-based pathway mapping. This will elucidate interacting members within the cell cycle checkpoint control pathway. These interacting proteins will be assayed for their ability to modulate growth and progression through the cell cycle in "normal" and tumor cell lines. Those with function will be subjected to a, two-hybrid screen using a peptide library to identify binding peptides (Appendix F). The protocol is the same as described in Appendix E, except that peptide libraries are used instead of cDNA libraries. These binding peptides will then be assessed for their ability to inhibit growth and cell cycle progression in tumor cells. Individual peptide hits will be subjected to secondary assays to confirm their function and specificity. This will produce additional peptide/protein pairs capable of regulating tumor growth.

C. INITIAL STEPS FOR TARGET IDENTIFICATION/VALIDATION (SEE FLOWCHART IN APPENDIX K)

It is important to recognize that once a protein target has been identified that binds to a confirmed peptide hit, by virtue of the functional screen that produced the peptide hit the functional relationship of the target protein to the pathway of interest is defined for that particular cell type. False positives only arise if the peptide hit binds to additional proteins not related

to the functional pathway altered by the peptide hit. Below is a protocol to discriminate false positives from pathway specific peptide/protein target pairs.

Once the desired change in the phenotype of the library-infected cells is achieved, the peptides responsible will be sequenced. Individual peptide sequences derived from the libraries will be tested for their ability to inhibit tumor cell progression through various phases of the cell cycle in the original screening assay under Section 1.0. Individual peptides, with inhibitory effects will be subjected to two-hybrid screening using cDNA libraries. derived from human tumor cell lines. cDNAs that are isolated from the two-hybrid screen and retested for binding to the peptide will be defined as initial targets. In parallel with the two-hybrid screening, peptide hits will be subjected to secondary screens to test their specificity in several tumor cell lines (see

Appendix K). Orthogonal assays will include evaluating peptide effects on the cell cycle and proliferative characteristics of normal and primary cells.

Once protein targets that bind to the functional peptides have been isolated and confirmed by two-hybrid screening, their ability to interact in mammalian cells will be assessed. This will be accomplished by uniquely tagging both the target protein and peptide and then immunoprecipitating in either direction to determine if its partner can be co-immunoprecipitated. After this test, the resulting peptide/protein pairs can be subjected to numerous secondary and orthogonal assays to confirm their role in cell cycle regulation. The type of peptide/protein pairs identified will dicate the exact assays performed. These assays include over-expression of the target protein and dominant negative mutants, anti-sense expression of the target protein sequence, complementation by over-expressing the target protein in cells expressing the inhibitory binding peptide, and knockout somatic cell lines of the target protein. These assays will assist in the determination of targets to be introduced into Janssen small molecule compound screens. Below is a brief description of the rationale and approach for each of the assays described above.

Over-expression of the target protein may modulate cell cycle progression or modify checkpoint responses in tumor cells, thereby implicating a regulatory role. This can be accomplished very simply with Rigel's retroviral vector system. By using reporter genes downstream of the cDNA encoding the target protein we can track infected cells and determine the relative concentration of the target protein. This will allow us to titrate its biological effect as a means to confirm the target protein's role in inhibiting tumor cell progression through the cell cycle. If overexpression of the protein target influences the cell cycle, mutant libraries of the protein can be screened for loss-of-function as described below.

Target proteins will be randomly mutated (see Appendix C) and screened in FACS assay (Appendix B) for mutant proteins that inhibit tumor cell cycle function. Two variations of this approach allow us to narrow our screen of mutant target proteins. One variation is to perform mutagenesis on the target cDNA and then subject than to a 2-hybrid screw with the cognate peptide as bait to identify mutants that no longer bind the peptide. These mutant proteins can be tested for loss-of-function in mammalian cells. Alternatively, the peptide is chemically crosslinked to the target protein to identify the region bound by. the peptide using mass then the peptide-binding region of the target protein is randomly mutated and the screened for their ability to inhibit tumor cell growth. The advantage of this variation is that the regulatory domain of the target protein is identified.

A third approach to confirming the role of the target protein in tumor cell cycle regulation is complementation. The screening cell lines are infected with this peptide and its target protein that is under the control of an inducible promoter such as tetracycline or metallothionein. The target protein is induced and tested for its ability to overcome the inhibition of the peptide.

Finally, somatic and germline knockout call lines of the target protein con be generated to assess tumor cell growth in the absence of the target protein. Although this approach takes

longer, in the case of the germline knockout mice they allow for in vivo experiments to assess the function of the target protein.

Some or all of the above methods can be employed to confirm that a Peptide/protein pair, identified in the initial screen functions. It will be the task of the joint scientific board from Rigel and Janssen to determine which assays am necessary to sufficiently define a functional peptide/protein pair for the next phase of development, specifically small molecular weight compound screening.

D. HEADCOUNT

To run optimally, the project will take 10 Rigel FTEs:

XIANG XU: Dr. Xu is the Project leader for the Cell Cycle Regulation Project She will coordinate all scientific and administrative aspects of the project. In addition, she will carry out functional analysis of specific targets identified in the screens and in the secondary two-hybrid analyses. She is full time on this project.

JIM LORENS: Dr. Lorens is Head of Technology Development at Rigel. He will work directly on retroviral vector design and library resew techniques, in addition to carrying out many of the experiments detail under Specific Aim 2, which is the analysis of proteins identified by Janssen that regulate can cycle checkpoint controls. He is full time on this project.

YNGJU JANG: Y. Long is a Senior Research Associate who is responsible for conducting the cell based high throughput screens on the different tumor call lines. She will carry out the primary infections with the libraries an the different turn cells and do the different labeling steps to prepare the cell lines for HTS. She will also help in the library rescue and re-infection steps. She is full time on this project.

YASUMICHI HITOSHI: Dr. Hitoshi is a Senior Scientist responsible for carrying out functional analysis of specific targets identified in the HTS assays. In addition, he will carry out the generation of the "protein mutant libraries" of specific proteins identified by Janssen and characterize the functionally important mutants. He is full time on this project.

DAVID PADILLA: D. Padilla is a cell biology Research Associate responsible for all the tissue culture work for the project. He maintains all the different tumor cell lines, the Phoenix packaging cell line, and the sorted cell populations. He is full time on the project.

RANDY ARMSTRONG: R. Armstrong is the Senior Research Associate in charge of retroviral library design and production. He is responsible for the generation of all peptide libraries with their various scaffolds and localization sequences. He will perform the library rescue for the peptide screens, the subsequent subcloning of both the peptide hits and the targets into shuttle vectors for post two-hybrid functional analysis. He is full time on this project.

BETTY HUANG: B. Huang is the Senior Research Associate in charge of two-hybrid screening. She is responsible for setting up and carrying out all, the two-hybrid assays, analyzing and isolating full-length clones, and generating the cDNA libraries. She is full time on this project.

YING LUO: Dr. Luo is Head of Target Identification and the two-hybrid technology group at Rigel. He is responsible for developing and constructing the vectors, as well as analyzing the results of the screens. He will develop and maintain the database of genes derived from two hybrid technology and the supporting bioinformatics. He will also establish and implement mammalian two-hybrid screening. He is full time on this project.

JOHN PATTON: J. Patton is the Research Associate in charge of an the DNA sequencing. This includes sequencing of all rescued libraries (to check for enrichment and contamination), all verified peptide hits, and all two-hybrid hits. He is also responsible for managing the sequence database and all related DNA bioinformatics of the project. He will coordinate the data entry into the Cell Cycle database. He is full time on this project.

DENIM PEARSALL: D. Pearsall is a Senior Research Associate in charge of analyzing all the peptide hits in different tumor cell lines, determining peptide hit specificity, and conducting secondary proliferation assays in normal and transformed cell lines. She is also responsible for coordinating all the initial steps in the cell based high throughput screens. She is full time on this project.

BILL THRONDSET. Throndset is the Senior Research Associate in charge of the high-speed flow cytometry and is responsible for setting-up and implementing all the FACS-based assays. He win perform these assays and sort the library hits for the Cell Cycle project. He will also supervise the FACS-associated bioinformatics for all the screens. He is full time on this project.

JEFF QUAST: J. Quast is a molecular biology Research Associate in the target identification group. He is responsible for all the support work on the two-hybrid analyses, including media prep, plate pouring, minipreps, colony picking, gel analysis, and subcloning. He is full time on this project.

APPENDIX A

[diagram]

APPENDIX B

FUNCTIONAL SCREEN FOR PEPTIDE INHIBITORS OF TUMOR CELL PROGRESSION

[diagram]

APPENDIX C

MUTAGENIC PCR GENERATES A LIBRARY OF RANDOM TARGET CDNA VARIANTS

[diagram]

APPENDIX D

YEAST TWO-HYBRID SCREENING

[diagram]

1. GROW UP YEAST REPORTER STRAINS ON YPD PLATES FROM FROZEN STOCK.

Since no antibiotics are added into the yeast medium, very stringent sterilization procedures are required during inoculation.

There are many reporter strains available from different resources. In general, Y190 consistently showed higher sensitivity than other yeast strains such as HF7c. Yeast reporter strains with both a lacZ reporter gene and a HIS3 reporter gene are strongly recommended. HIS selection will ensure that only interacting clones will grow, which makes colony picking much easier later.

2. DETERMINE OPTIMAL 3AT CONCENTRATION.

3AT can be used to suppress background expression from the HIS reporter gene of Y190. 3AT concentration varies among different reporter strains and ranges from 0 mM (HF7c) to 15 mM (Y190). To test the optimal concentration of 3AT, one yeast colony should be re-suspended in 10 ml of TE. 100 uI of the re-suspended yeast is spread on SD-H+0mM3AT, SD-H+5mM3AT, SD-H+10mM3AT, SD-H+15mM3AT, SD-H+25mM3AT, and SD-H+40mM3AT plates. Although 15 mM 3AT is sufficient to suppress background HIS expression of Y190, higher concentrations of 3AT (30-40 mM) are routinely used in our cDNA library screening.

3. CONSTRUCT BAIT PLASMID.

pAS2/pACT2 series plasmids showed higher level of sensitivity than pGAD424 /pGBT9 series plasmids (Estojak et al 1995; Legrain et al. 1994). The disadvantage of using pAS2 is the large size of this plasmid (8 kb), which may present a challenge to cloning large cDNA fragments into the plasmid. Peptide fragments should fused to the C-terminal and/or N-terminal of GaL4 binding domain in frame (Figure 4A). The junction sequence between GAL4 and cDNA should have a GGG amino acid sequence to avoid any interruption of domain structure. Alternatively, a constrained peptide presentation structure may be used. Either full-length cDNA or partial fragments can be used to generate bait plasmid.

4. TRANSFORM BAIT INTO YEAST: 1ST ROUND.

1 ug of bait plasmid is transformed into Y190 with small-scale yeast transformation protocol. Transformants should be plated on SD-W, SD-WH, and SD-WH+3AT(5-40mM) plates. A LacZ color assay can also be done after colonies grow to a diameter of 1mm. If colonies grow up on SD-WH+40mM3AT plates, after 3 days incubation and/or LacZ color assay of these colonies show a positive result after only 30 minutes incubation with X-Gal, the bait gem is not suitable for two-hybrid screening without further modification. The bait gene itself may be able to activate transcription of reporter genes HIS/lacZ

Although co-transformation of the bait plasmid and cDNA library can be done in a single step, co-transformation efficiency is at least 10 fold lower than single plasmid transformation. A mating approach may also be used to introduce cDNA library into yeast cells containing the bait vector. Please refer to the protocol published by Finley and Brent (Finley and Brent, 1994).

5. TRANSFORM CDNA LIBRARY 2ND ROUND

Y 190 containing bait plasmid is grown up for second round of transformation by cDNA library plasmid. Incubation time after transformation varies significantly from 4 days to 11 days.

6. IDENTIFY POSITIVE CLONES

Identification of positive clones needs experience. It should also be pointed out that background colonies at lightly populated areas of the plates tend to grow bigger, occasionally reaching the size of a positive colony in a dense area on the same plate. The size of the positive colony should be at least 4 times bigger than the neighboring background colonies. Positive colonies may also turn red faster.

7. PERFORM LACZ COLOR ASSAY.

Positive colonies should be re-streaked to another SD-LVM+3AT plate to isolate single colonies for color assay and plasmid retrieval. If a colony does not turn blue after a 4-hour incubation, strong protein-protein interaction is highly unlikely. It is not recommended to pick positive clones after 12 hours incubation, except when the protein-protein interaction being studied is very weak.

8. RETRIEVE PLASMIDS.

There are several methods to retrieve plasmids from yeast, ranging from lyticase lysis to glass beads. Electroporation is by far the most efficient method to transform plasmids from yeast miniprep into E. COLI. Bait and cDNA plasmid may carry different antibiotic selection markers to facilitate separation in E. COLI. For example, Rigel's bait plasmid carries a Kanr gene and the cDNA plasmid carries an Ampr gene.

9. VERITY POSITIVE CLONES.

cDNA clones recovered from positive HIS/lacZ double colonies should be re-transformed into yeast with other non-specific bait controls to rule out non-specific binding. IN VITRO protein binding assays and function assays should also be done to rule out false positive clones.

2

Yeast Two-Hybrid Screening

[diagram]

1

From Identified Gene to Peptide Hits

[diagram]

Appendix E

3

Appendix F

Retrovirally expressed cell cycle control proteins and peptides induce cell cycle arrest

DIAGRAM

DIAGRAM

DIAGRAM

4

Appendix G

Protocol for Transfection of Phoenix Cells and Infection of Nonadherent Target Cells

DIAGRAM

Day 1:

Seed Phoenix cells (Es or As) in 10cm plates at 5 x 10x6 cells in 6 ml (DMEM + 10% FBS + Pen/Strep) per plate the day before transfection.

Day 2:

Allow all reagents to reach room temperature 30 min. before starting. Add 50 microM chloroquine at 8 microliter/plate (50 microM final) before preparing the transfection solution.

Mix CaPO4 reagents in 15 ml polypropylene tube:

Per plate: 10 micrograms DNA
122 microliters 2M CaCl2
876 microliters H2O
1.0 ml 2X HBS

Add 2X HBS and depress the expulsion button completely to bubble air through the mix for 10 secs. Immediately add mixture gently dropwise to plate. Incubate 3-8 hours. Remove medium and replace with 6.0 ml DMEM-medium.

Day 3:

Change medium again to 6.0 mls of medium optimal for the cells to be infected. Move to 32 degree C either in the morning or afternoon depending on the Phoenix cell confluency and whether you will infect at 48 or 72 hrs after transfection.

Day 4 or 5:

Collect virus supernatant from transfected plates (6.0 ml) into 50 ml tubes and add protamine sulfate to a final concentration of 5 micrograms/ml. Pass through a 0.45 microm filter. Count target cells and distribute 10x7 cells per 10 cm plate transfected to 50 ml tubes and pellet 5 min. Resuspend each pellet of target cells in virus supernatant and transfer to a 6 well plate at 1.0-1.2 ml per well. Seal plate with parafilm and centrifuge at RT for 30-90 min. at 2500 RPM. Remove parafilm and incubate plate over night at 37 degrees C.

Day 5:

Collect and pellet each well of target cells. Resuspend in 3 ml medium and transfer back to the same 6 well plate. Infection can be repeated by refeeding the Phoenix cells with 6ml fresh medium and reinfecting the same cells again up to 3 times to increase % of cells infected (for instance at 48, 56, and 72 hours)

Day 7 or 8:

At 48 to 72 hrs. post infection, target cells are ready to analyze for expression.

APPENDIX H

[diagram]

APPENDIX I

RETROVIRAL LIBRARY DESIGN FEATURES

[diagram]

APPENDIX J

[chart]

APPENDIX K

FLOW CHART FOR FUNCTIONAL SCREENS

(IDENTIFICATION OF FUNCTIONAL PEPTIDE/PROTEIN PAIRS)

[diagram]

RIGEL - JANSSEN COLLABORATION

[chart]

TIMELINES FOR RIGEL SCREENS

[diagram]

RIGEL - JANSSEN COLLABORATION

IDENTIFICATION OF NOVEL DRUG DISCOVERY TARGETS

[diagram]

[diagram]

[diagram]

RIGEL - JANSSEN COLLABORATION

IDENTIFICATION OF NOVEL DRUG DISCOVERY TARGETS

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

RIGEL - JANSSEN COLLABORATION

IDENTIFICATION OF NOVEL DRUG DISCOVERY TARGETS

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

15

RIGEL - JANSSEN COLLABORATION

IDENTIFICATION OF NOVEL DRUG DISCOVERY TARGETS

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

16

RIGEL - JANSSEN COLLABORATION

[diagram]

[diagram]

17

RIGEL - JANSSEN COLLABORATION

[diagram]

[diagram]

[diagram]

[diagram]

[diagram]

18

RIGEL - JANSSEN COLLABORATION

[diagram]

[diagram]

[diagram]

EXHIBIT B

RIGEL TECHNOLOGY ASSAYS

EXHIBIT C

FORM OF INVOICE

[Rigel Letterhead]

INVOICE NO. [__]

[Invoice Date]
Janssen Pharmaceutica NV
F.A.O. Lidi Van Gool
Turnhoutseweg 30
2340 Beerse
Belgium
VAT number 403834160

COLLABORATION AGREEMENT BETWEEN RIGEL, INC. AND JANSSEN PHARMACEUTICA, N.V.
DATED DECEMBER 4, 1998

Dear Ms. Van Gool:

Pursuant to Section [ ] of the above agreement, please pay to Rigel the following amount for [description of services for research funding or a milestone event for milestone payments, or make reference to net sales report from Janssen for royalty payments]:

US$ [ ]

Please remit the above amount within fifteen (15) days from the date this invoice by wire transfer to the following account:

[account information]

Sincerely,

Rigel, Inc.

- ----------

EXHIBIT D

STANFORD AGREEMENTS

AGREEMENT

Effective as of October 7, 1996 ("Effective Date"), THE BOARD OF TRUSTEES OF

THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California ("STANFORD") and RIGEL PHARMACEUTICALS, INC., a Delaware corporation having a principle place of business at 24 Windsor Drive, Hillsborough, CA 94010 ("RIGEL"), agree as follows:

1. BACKGROUND.

1.1 STANFORD has an assignment of U.S. Patent Application No. 08/589,109, entitled "Methods for Screening for Transdominant Effector Peptides and RNA Molecules" (the "NOLAN/ROTHENBERG PATENT APPLICATION") claiming an invention developed in the laboratory of Dr. Garry Nolan (the "Invention"), and any Licensed Patent(s), as hereinafter defined, which may claim such Invention.

1.2 STANFORD has certain biological materials and other know-how ("Know-How"), as herein defined, pertaining to the Invention.

1.3 STANFORD desires to have the Know-How and Invention perfected and marketed at the earliest possible time in order that products resulting therefrom may be available for public use and benefit.

1.4 RIGEL desires a license under said Know-How, Invention, and Licensed Patent(s) in the field of use of gene transfer technologies, including retrovirally mediated nucleic acid libraries, for drug development, drug delivery, drug screening, and target analysis and discovery associated with the development, manufacture, use and sale of Licensed product(s), as defined below.

1.5 RIGEL acknowledges that certain of the Cell Lines (as defined below) were made in the course of research supported by Progenesys.

1.6 The patent application entitled "Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules," which claims technology useful in the field and which was developed in the laboratory of Dr. Garry Nolan (the "Nolan Patent Application"), has previously been assigned to RIGEL.

2. DEFINITIONS.

2.1 "LICENSED BIOLOGICAL MATERIALS" means the materials listed on Exhibit A, including certain vector libraries ("Vector Libraries") and cell lines ("Cell Lines") set forth therein, as amended from time to time upon the parties' mutual written consent.

2.2 "LICENSED KNOW-HOW" means all know-how necessary or useful for the commercial exploitation of the Licensed Patents in the Licensed Field of Use, including without limitation all know-how, trade secrets, protocols, information, processes or other subject matter

which is either disclosed in the Nolan/Rothenberg Patent Application, or necessary or useful to practice the licenses granted to RIGEL in this Agreement with respect to the Invention. Licensed Know-How excludes the Licensed Patents and includes the Licensed Biological Materials.

2.3 "LICENSED PATENT(S)" means any Letters Patent, both foreign (subject to Section 7) and domestic, issued upon (i) the Nolan/Rothenberg Patent Application (STANFORD's U.S. Patent Application, Serial Number 08/589,109 filed January 23, 1996), (ii) any substitutions, divisionals, continuations, and continuations-in-part (to the extent such continuations-in-part claim subject matter disclosed or claimed in the Nolan/Rothenberg Patent Application as filed on January 23, 1996 and to the extent that the practice of an invention claimed in a Licensed Patent issuing from a patent application other than such continuation-in-part would infringe a claim of Licensed Patent issuing from such continuation-in-part), and (iii) any foreign counterparts of (i) or (ii).

2.4 "LICENSED TECHNOLOGY" means the Licensed Patent(s) and the Licensed Know-How.

2.5 "LICENSED PRODUCT(S)" means:

(a) any product, the manufacture, use, sale, offer for sale or import of which:

(1) is covered by a valid claim of an issued, unexpired Licensed Patent(s) directed to the Invention (claim of an issued, unexpired Licensed Patent(s) shall be presumed to be valid unless and until it has been held to be invalid by a final judgment of a court of competent jurisdiction from which no appeal can be or is taken), or

(2) is covered by any claim being prosecuted in a pending application directed to the Invention, which claim has not been pending

for more than three (3) years from first filing of such claim;

(b) any product which directly incorporates any of the Licensed Biological Materials; or

(c) any product which would not, but for the use of the Licensed Biological Materials, have been identified, discovered, or developed.

2.6 "NET SALES" means the gross revenue derived by RIGEL and/or RIGEL's sublicensee(s) from the sales of Licensed Product(s), less the following items but only insofar as they actually pertain to the disposition of such Licensed Product(s) by RIGEL or RIGEL's sublicensee(s), are included in such gross revenue, and are separately billed:

(a) Import, export, excise and sales taxes, and custom duties;

(b) Credit for returns, allowances, trades, or retroactive price adjustments;

(c) Transportation charges, issuances and allowances;

(d) Discounts actually allowed; or

(E) Royalties payable to third parties on the manufacture, use, sale, offer for sale or import of Licensed Products.

2.7 "LICENSED FIELD OF USE" means the use of gene transfer technologies, including retrovirally mediated nucleic acid libraries, for drug development, drug delivery, and target analysis and discovery. Solely with respect to the phiNX Cell Lines set forth on Exhibit A, the Licensed Field of Use excludes the use of such Cell Lines, derivatives or vectors thereof or other tangible products that are a direct lineal descendent from such Cell Lines (although obtained in any manner therefrom), wherein cells treated with any one or more of the aforementioned materials are contained within a human subject or are subsequently transplanted into a human subject.

2.8 "EXCLUSIVE" means that, subject to Article 4, STANFORD shall not grant further licenses in the Licensed Field of Use.

3. GRANT.

3.1 STANFORD hereby grants and RIGEL hereby accepts a worldwide license in the Licensed Field of Use under STANFORD's right, title and interest in the Licensed Patents and the Vector Libraries to make, use, sell, offer for sale and import Licensed Product(s).

3.2 The license granted in Section 3.1 is Exclusive, including the right to sublicense pursuant to Article 13, in the Licensed Field of Use for a term (the "Exclusivity Term") commencing as of the Effective Date and ending on the first to occur of the following:

(a) twenty (20) years from the Effective Date; or

(b) ten (10) years from the date of first commercial sale of a Licensed Product(s) by RIGEL or RIGEL's sublicensee(s). RIGEL agrees to promptly inform STANFORD in writing of the date of first commercial sale of Licensed Products. After expiration of the Exclusivity Term, said license shall become nonexclusive and continue indefinitely.

3.3 STANFORD additionally grants, and RIGEL hereby accepts, a worldwide, nonexclusive license in the Licensed Field of Use under STANFORD's right, title and interest in the Licensed Know-How other than the Vector Libraries to make, use, sell, offer for sale and import Licensed Product(s). The term of such nonexclusive license shall commence upon the Effective Date and, continiue indefinitely.

3.4 Notwithstanding the Exclusive license granted to RIGEL, pursuant to Sections 3.1 and 3.2, STANFORD shall have the right to practice the Licensed Patents and to use the Vector Libraries for non-commercial, academic research purposes.

4. GOVERNMENT RIGHTS.

This Agreement is subject to all of the terms and conditions of Title 35 United States Code Sections 200 through 204, including an obligation that

Licensed Product(s) sold or produced in the United States be "manufactured substantially in the United States," and RIGEL agrees to take all reasonable action necessary on its part as licensee to enable STANFORD to satisfy its obligation thereunder, relating to the Invention. STANFORD agrees to provide reasonable assistance to RIGEL in the event RIGEL decides to seek a waiver under such domestic manufacture equipment.

5. DILIGENCE.

5.1 As an inducement to STANFORD to enter into this Agreement, RIGEL agrees to use all reasonable efforts and diligence to proceed with the development, manufacture, and sale of Licensed Product(s) and to diligently develop markets for the Licensed Product(s). RIGEL shall demonstrate such diligence to STANFORD by achieving proof of principle through written documentation of the following within eighteen (18) months after the Effective Date:

(a) Construction of a retroviral vector library;

(b) Infection of cells with such vector library;

(c) Detection of a physiological response to such infection in an infected cell; and

(d) Isolation and analysis of the peptide eliciting such physiological response from the cell.

5.2 If RIGEL is unable to demonstrate the foregoing proof of principle within eighteen (18) months after the Effective Date, STANFORD may elect to narrow the definition of the Licensed Field of Use to include only the use of retrovirally mediated nucleic acid libraries for drug development, drug delivery, drug screening, and target analysis and discovery, by providing written notice to RIGEL thereof. Additionally, RIGEL shall provide to STANFORD within eighteen (18) months after the Effective Date a plan for the development and commercialization of Licensed Products (a "Development Plan"). STANFORD shall comment upon and approve such plan, which approval shall not be unreasonably withheld. After the Development Plan is approved by STANFORD, RIGEL shall use reasonable efforts to diligently perform its obligations under such Development Plan. If Stanford reasonably believes that RIGEL is not using reasonable efforts to perform the Development Plan, STANFORD may so notify RIGEL. The parties shall promptly thereafter meet to discuss RIGEL's progress under the Development Plan, and shall develop a mutually agreeable plan for remedying any such lack of diligence (the "Proposed Remedy"). If RIGEL fails to perform the Proposed Remedy within one hundred and eighty (180) days after the Proposed Remedy is agreed upon, STANFORD may elect to narrow the definition of the Licensed Field of Use to include only the use of retrovirally mediated nucleic acid libraries for drug development, drug delivery, and target analysis and discovery by providing written notice to RIGEL. If RIGEL then fails to perform the Proposed Remedy within ninety (90) days after receiving STANFORD's notice that it has elected to so narrow the

Licensed Field of Use definition, then STANFORD may elect to convert the Exclusive License granted to RIGEL pursuant to Sections 3.1 and 3.2 to a nonexclusive license for the remaining term of this Agreement.

5.3 PROGRESS REPORT. On or before each anniversary of the Effective Date until RIGEL markets a Licensed Product(s), RIGEL shall make a written annual report to STANFORD covering RIGEL's progress during the preceding year toward commercial use of Licensed Product(s). Such report shall include, as a minimum, information sufficient to enable STANFORD to satisfy relevant reporting requirements of the U.S. Government and to ascertain RIGEL's progress toward meeting the diligence requirements of this Article 5.

6. ROYALTIES.

6.1 RIGEL agrees to pay to STANFORD a noncreditable, nonrefundable license issue royalty of _____ half of which shall be paid within forty-five (45) days after the Effective Date and the balance of which shall be on the first anniversary of the Effective Date.

6.2 Upon each anniversary of the Effective Date, RIGEL shall also pay to STANFORD a Minimum Annual Royalty as follows:

Anniversary of Effective Date	Minimum Annual Royalty Due
First and Second	_____
Third through Seventh	_____
Eighth and Thereafter	_____

Said Minimum Annual Royalty payments are nonrefundable but they are creditable against earned royalties to the extent provided in Paragraph 6.5. The foregoing Minimum Annual Royalty payment shall be decreased by fifty percent (50%) if either:

(i) Stanford abandons all patent applications from which Licensed Patent(s) could issue prior to the time that any Licensed Patent(s) issue; or

(ii) Stanford elects to narrow the definition of the Licensed Field of Use pursuant to Section 5.2.

6.3 If Rigel grants to a third party a sublicense under the Licensed Technology solely for research, and not commercialization purposes (a "Research Sublicense"), Rigel shall also pay to STANFORD a milestone payment equal to _____ of any research milestone payment that RIGEL receives as consideration for the grant of such Research Sublicense. RIGEL shall pay such amount to STANFORD within sixty (60) days after RIGEL receives such research milestone payment.

If RIGEL grants to a third party a sublicense under the Licensed Technology which includes the right to sell and offer for sale Licensed Products (a "Commercialization Sublicense"), RIGEL shall pay to STANFORD a sublicense fee as follows:

First Sublicense Granted	_____
Second Sublicensed Granted	_____
Each Additional Sublicense Granted	_____

RIGEL shall pay such sublicense fees to STANFORD within sixty (60) days after the effective date of each Commercialization Sublicense.

6.4 In addition, RIGEL shall pay STANFORD earned royalties equal to _____ of Net Sales of Licensed Products set forth in Sections 2.5(a) and 2.5(b), or _____of Net Sales of Licensed Products which can only be categorized under Section 2.5(c). If a Licensed product can be included in more than one of Sections 2.5(a), 2.5(b) or 2.5(c), the royalty rate due to STANFORD on Net Sales of such Licensed Product shall be _____.

6.5 As further consideration for the license granted to RIGEL under this Agreement, RIGEL shall issue to STANFORD _____shares of Preferred Stock of RIGEL, pursuant to a Stock Purchase Agreement. If such number of shares shall equal less than _____of the total outstanding shares of RIGEL's stock at any time during the period from the date of issuance of such stock until one (1) year thereafter, STANFORD and RIGEL shall discuss whether RIGEL shall adjust the number of shares issued to Stanford under this Section 6.5.

6.6 Creditable payments under this Agreement shall be an offset to RIGEL against up to fifty percent (50%) of each earned royalty payment which RIGEL would be required to pay pursuant to Paragraph 6.4 until the entire credit is exhausted.

6.7 If this Agreement is not terminated in accordance with other provisions hereof, RIGEL's obligation to pay royalties hereunder shall continue until ten (10) years after first commercial sale of Licensed Products.

6.8 The royalty on sales in currencies other than U.S. Dollars shall be calculated using the appropriate foreign exchange rate for such currency quoted by the Bank of America (San Francisco) foreign exchange desk, on the close of business on the last banking day of each calendar quarter. Royalty payments to STANFORD shall be in U.S. Dollars. All non-U.S. taxes related to royalty payments shall be paid by RIGEL and are not deductible from the payments due STANFORD.

6.9 Within thirty (30) days after receipt of a statement from STANFORD, RIGEL shall reimburse STANFORD for all costs incurred by STANFORD, including those costs incurred prior to the Effective Date, in connection with the preparation, filing and prosecution of all patent applications and maintenance of patents claiming the Invention.

7. PATENT RIGHTS.

STANFORD shall have the obligation to file, prosecute and maintain all patent applications and patents included in the Licensed Patents. STANFORD will provide RIGEL

with an opportunity to review and comment upon the prosecution strategy and to consult with STANFORD on the content of patent filings, and will provide copies of any correspondence relating to patent applications and patents included in the Licensed Patents to RIGEL or a designee of RIGEL. RIGEL shall have the right to designate, in its sole discretion, those foreign countries in which STANFORD will file, prosecute and maintain patents and patent applications included in the Licensed Patents. STANFORD may propose to file, prosecute and maintain a Licensed Patent in a country which RIGEL has not designated pursuant to this Section 7. If RIGEL agrees to such designation, it shall reimburse STANFORD costs of such filing, prosecution of maintenance of such patent or patent applications pursuant to Section 6.9 and such patent or patent applications shall be included in the Licensed Patents. If RIGEL does not agree to such proposal, STANFORD may elect to proceed with such filing, prosecution or maintenance at its own expense, and such patent or patent application shall not be included in the Licensed Patents.

8. ROYALTY REPORTS, PAYMENTS, AND ACCOUNTING.

8.1 QUARTERLY EARNED ROYALTY PAYMENT AND REPORT. Beginning with the first sale of a Licensed Product, RIGEL shall make written reports (even if there are no sales) and earned royalty payments to STANFORD within thirty (30) days after the end of each calendar quarter. This report shall be in the form of the report of Exhibit B and shall state the number, description, and aggregate Net Sales of Licensed Product(s) during such completed calendar quarter, and resulting calculation pursuant to Paragraph 6.4 of earned royalty payment due STANFORD for such completed calendar quarter. Concurrent with the making of each such report, RIGEL shall include payment due STANFORD of royalties for the calendar quarter covered by such report.

8.2 ACCOUNTING. RIGEL agrees to keep and maintain records for a period of three (3) years showing the manufacture, sale, use, and other disposition of products sold or otherwise disposed of under the license herein granted. Such records will include general ledger records showing cash receipts and expenses, and records which include production records, customers serial numbers and related information in sufficient detail to enable the royalties payable hereunder by RIGEL to be determined. RIGEL further agrees to permit its books and records to be examined by STANFORD from time to time to the extent necessary to verify reports provided for in Paragraph 8.1. Such examination is to be made by STANFORD or its designee, at the expense of STANFORD, except in the event that the results of the audit reveal an underreporting of royalties due STANFORD of five percent (5%) or more, then the audit costs shall be paid by RIGEL.

9. NEGATION OF WARRANTIES.

9.1 Nothing in this Agreement is or shall be construed as:

(a) A warranty or representation by STANFORD as to the validity or scope of any Licensed Patent(s);

(b) A warranty or representation that anything made, used, sold, or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights, and other rights of third parties;

(c) An obligation to bring or prosecute actions or suits against third parties for infringement, except to the extent and in the circumstances described in Article 13;

(d) Granting by implication, estoppel, or otherwise any licenses or rights under patents or other rights of STANFORD or other persons other than Licensed Patent(s), regardless of whether such patents or other rights are dominant or subordinate to any Licensed Patent(s); or

(e) An obligation to furnish any technology or technological information other than the Licensed Technology.

9.2 Except as expressly set forth in the Agreement STANFORD MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE LICENSED PRODUCT(S) WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER RIGHTS, OR ANY OTHER EXPRESS OR IMPLIED WARRANTIES.

9.3 RIGEL agrees that nothing in this Agreement grants RIGEL any express or implied license or right under or to:

(a) U.S. Patent No. 4,237,224, "Process for Producing Biologically Functional Molecular Chimeras"; U.S. Patent No. 4,468,464 and U.S. Patent No. 4,740470, both entitled, "Biologically Functional Molecular Chimeras" (collectively known as the Cohen/Boyer patents), or reissues thereof; or

(b) U.S. Patent 4,656,134 "Amplification of Eucaryotic Genes" or any patent application corresponding thereto.

9.4 STANFORD represents and warrants that it has all right, power and authority necessary to grant the licenses set forth in Article 3 to RIGEL, and that it has not, and will not during the term of this Agreement, grant any right to any third party which would conflict with the rights granted to RIGEL hereunder.

10. INDEMNITY.

10.1 RIGEL agrees to indemnify, hold harmless, and defend STANFORD and Stanford Health Services and their respective trustees, officers, employees, students, and agents against any and all claims by third parties for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale, or other disposition of

the Invention, Licensed Technology, or Licensed Product(s) by RIGEL or RIGEL's sublicensee(s) or customers.

10.2 STANFORD shall not be liable for any indirect, special, consequential or other damages whatsoever, whether grounded in tort (including negligence), strict liability, contract or otherwise. STANFORD shall not have any responsibilities or liabilities whosoever with respect to Licensed Product(s).

10.3 RIGEL shall at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering any and all employees with respect to activities performed under this Agreement.

10.4 In addition to the foregoing, RIGEL shall maintain Comprehensive General Liability Insurance including Products Liability Insurance, with reputable and financially secure insurance carrier(s) to cover the activities of RIGEL and its sublicensee(s) in the amounts and during the periods specified herein. Such insurance shall provide minimum limits of liability of One Million Dollars ($1,000,000) as of the first anniversary of the date upon which RIGEL first leases a facility in which it will conduct research and development activities, and of Five Million Dollars ($5,000,000) as of the commencement of human clinical trials of Licensed Products. Such insurance shall include STANFORD, Stanford Health Services, their trustees, directors, officers, employees, students, and agents as additional insureds. Such insurance shall be written to cover claims incurred, discovered, manifested, or made during or after the expiration of this Agreement. At STANFORD's request, RIGEL shall furnish a Certificate of Insurance evidencing primary coverage and requiring thirty (30) days prior written notice of cancellation or material change to STANFORD. RIGEL shall advise STANFORD, in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All such insurance of RIGEL shall be primary coverage; insurance of STANFORD or Stanford Health Services shall be excess and noncontributory.

11. MARKING.

Prior to the issuance of patents on the Invention, RIGEL agrees to mark Licensed Product(s) (or their containers or labels) made, sold, or otherwise disposed of by it under the licenses granted in this Agreement with the words "Patent Pending," and following the issuance of one or more patents, with the numbers of the Licensed Patent(s).

12. STANFORD NAMES AND MARKS.

RIGEL agrees not to identify STANFORD in any promotional advertising or other promotional materials to be disseminated to the pubic or any portion thereof or to use the name of any STANFORD faculty member, employee, or student or any trademark, service mark, trade name, or symbol of STANFORD or the Stanford University Hospital, or that is associated with either of them, without STANFORD's prior written consent, except as required by law. STANFORD shall not unreasonably hold consent under this Section 12.

13. INFRINGEMENT BY OTHERS: PROTECTION OF PATENTS.

13.1 RIGEL shall promptly inform STANFORD of any suspected infringement of any Licensed Patent(s) by a third party. During the Exclusive period of this Agreement, STANFORD and RIGEL each shall have the right to institute an action for infringement of the Licensed Patent(s) against such third party in accordance with the following:

(a) If STANFORD and RIGEL agree to institute suit jointly, the suit shall be brought in both their names, the out-of-pocket costs thereof shall be borne equally, and any recovery or settlement shall be shared equally. RIGEL and STANFORD shall agree to the manner in which they shall exercise control over such action. STANFORD may, if it so desires, also be represented by separate counsel of its own selection, the fees for which counsel shall be paid by STANFORD;

(b) In the absence of agreement to institute a suit jointly, STANFORD may institute suit, and, at its option, join RIGEL as a plaintiff. If STANFORD decides to institute suit, then it shall notify RIGEL in writing. STANFORD shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement; and

(c) In the absence of agreement to institute a suit jointly and if STANFORD notifies RIGEL that it has decided not to join in or institute a suit, as provided in (a) or (b) above, RIGEL may institute suit and, at its option, join STANFORD as a plaintiff. RIGEL shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement, provided, however, that any recovery in excess of litigation costs shall be deemed to be Net Sales, and RIGEL shall pay STANFORD royalties thereon at the rates specified herein.

13.2 Should either STANFORD or RIGEL commence a suit under the provisions of Paragraph 13.1 and thereafter elect to abandon the same, it shall give timely notice to the other party who may, if it so desires, continue prosecution of such suit, provided, however, that the sharing of expenses and any recovery in such suit shall be as agreed upon between STANFORD and RIGEL.

14. SUBLICENSE(S).

14.1 RIGEL may grant sublicense(s) under its Exclusive license rights during the Exclusivity Term. RIGEL may grant sublicense(s) under nonexclusive license rights, if such sublicense is in conjunction with a sublicense of other RIGEL proprietary technology.

14.2 If RIGEL is unable or unwilling to serve or develop a potential market or market territory for which there is a willing sublicense(s), RIGEL will, at STANFORD's request negotiate in good faith a sublicense(s) hereunder on commercially reasonable terms.

14.3 Any sublicense(s) granted by RIGEL under this Agreement shall be subject and subordinate to terms and conditions of this Agreement, except:

(a) Sublicense terms and conditions shall reflect that any sublicensee(s) shall not grant a sublicense to a third party; and

(b) The earned royalty rate specified in the sublicense(s) may be at higher rates than the rates in this Agreement.

Any such sublicense(s) also shall expressly include the provisions of Articles 8, 9, and 10 for the benefit of STANFORD and provide for the transfer of all obligations including the payment of royalties specified in such sublicense(s), to STANFORD or its designee, in the event that this Agreement is terminated.

14.4 RIGEL agrees to provide STANFORD a copy of any sublicense(s) granted pursuant to this Article 14.

15. TERMINATION.

15.1 RIGEL may terminate this Agreement by giving STANFORD notice in writing at least thirty (30) days in advance of the Effective Date of termination selected by RIGEL.

15.2 STANFORD may terminate this Agreement if RIGEL:

(a) Is in default in payment of royalty or providing of reports;

(b) Is in material breach of any provision hereof; or

(c) Intentionally provides any false report;

and RIGEL fails to remedy any such default, breach, or false report within thirty (30) days after written notice thereof by STANFORD.

15.3 SURVIVING ANY TERMINATION ARE:

(a) RIGEL's obligation to pay royalties accrued or accruable;

(b) Any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party; and

(c) The provisions of Articles 8, 9, and 10.

16. ASSIGNMENT.

This Agreement may not be assigned by either party without the express written consent of the other party, except that RIGEL may assign the Agreement in connection with a merger, consolidation or sale of all or substantially all of RIGEL's assets.

17. DOUBLE PATENTING CONTINGENCY.

If the PTO rejects either the Nolan/Rothenberg Patent Application for double patenting in view of the claims of the Nolan Patent Application, or the claims of the Nolan Patent Application for double patenting in view of the claims of the Nolan/Rothenberg Patent Application, then RIGEL may elect to assign its right, title and interest in the Nolan Patent Application to STANFORD, in which case STANFORD shall grant to RIGEL an irrevocable, exclusive, worldwide, royalty-free license under STANFORD's right, title and interest in the Nolan Patent Application for all purposes.

18. ARBITRATION.

18.1 Any controversy arising under or related to this Agreement, and any disputed claim by either party against the other under this Agreement excluding any dispute relating to patent validity or infringement arising under this Agreement, shall be settled by arbitration in accordance with the Licensing Agreement Arbitration Rules of the American Arbitration Association.

18.2 Upon request by either party, arbitration will be by a third party arbitrator mutually agreed upon in writing by RIGEL and STANFORD within thirty (30) days of such arbitration request. Judgement upon the award rendered by the arbitrator shall be final and nonappealable and may be entered in any court having jurisdiction thereof.

18.3 The parties shall be entitled to discovery in like manner as if the arbitration were a civil suit in the California Superior Court.

18.4 Any arbitration shall be held at Stanford, California, unless the parties hereto mutually agree in writing to another place.

19. NOTICES.

All notices under this Agreement shall be deemed to have been fully given when done in writing and deposited in the United States mail registered or certified, and addressed as follows:

To STANFORD: Office of Technology Licensing
Stanford University
900 Welch Road, Suite 350
Palo Alto, CA 94304-1850

Attention: Director

To RIGEL: 24 Windsor Drive
Hillsborough, CA 94010

Attention: Dr. Donald G. Payan

Either party may change its address upon written notice to the other party.

20. WAIVER

None of the terms of this Agreement can be waived except by the written

consent of the party waiving compliance.

21. APPLICABLE LAW.

This Agreement shall be governed by the laws of the State of California applicable to agreements negotiated, executed and performed wholly within California.

22. SEVERABILITY.

If any provision or provisions of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby.

23. ENTIRE AGREEMENT.

This Agreement, together with the Exhibits attached hereto, embodies the entire understanding of the parties and shall supercede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof. No amendment or modification hereof shall be valid or binding upon the parties unless made in writing and signed by duly authorized representatives of both parties.

24. COUNTERPARTS.

This Agreement may be executed in counterparts, with the same force and effect as if the parties had executed the same instrument.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement in duplicate originals by their duly authorized officers or representatives.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

Signature /s/ Katherine Ku

Name Katherine Ku

Title Director, Technology Licensing

Date October 7, 1996

RIGEL

Signature /s/ Donald G. Payan

Name Donald G. Payan

Title President & CEO

Date 10/9/96

EXHIBIT A

MATERIALS FROM NOLAN LAB TO BE LICENSED TO RIGEL

VECTOR LIBRARIES

1. Random peptide library in pMSCU & Bst X1
2. SH-3 first generation library
3. CPP32 inhibitor peptide library
4. SH-3 second generation library
5. Coiled-coil library

PLASMIDS

1. pMSCU SD & Bst X1
2. pBabc Pur
3. pMSCU SD - IRES neo Bst X1
4. p5 & MD

CELL LINES

1. phiNX cell lines - gp, eco, ampho
2. 293 T

EXHIBIT B

SAMPLE REPORTING FORM

Stanford Docket No. S_____-_____

This report is provided pursuant to the license agreement between Stanford University and _____.

License Agreement Effective Date: _____

Report Covering Period	_____
Fixed Fees (Annual Minimum Payment)	$_____
Number of Sublicense Executed	_____
Net Sales	$_____
Royalty Calculation	_____
Royalty Subtotal	$_____
Credit	$_____
Royalty Due	$_____

Comments:

AMENDMENT

The Board of Trustees of the Leland Stanford Junior University ("Stanford") and Rigel Pharmaceuticals, Inc. ("Rigel") agree to extend the time period within which Rigel must pay the license issue royalty due to Stanford pursuant to the License Agreement between Stanford and Rigel dated October 7, 1996 (the "Agreement"). Section 6.1 of the Agreement is hereby amended to provide that Rigel will pay the license issue royalty to Stanford within ninety (90) days after the Effective Date of the Agreement.

Accepted and agreed by:

/s/ Katherine Ku	/s/ Donald G. Payan
- ----------	----------
Ms. Katherine Ku; Director, Technology Licensing Stanford University	Dr. Donald G. Payan Rigel Pharmaceuticals, Inc.
December 6, 1996	November 25, 1996
- ----------	----------
Date	Date

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LICENSE AGREEMENT

Effective as of August 18, 1997 (the "Effective Date"), THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California ("STANFORD") and RIGEL PHARMACEUTICALS, INC., a Delaware corporation having a principle place of business at 772 Lucerne Drive, Sunnyvale, CA 94086 ("RIGEL"), agree as follows:

1. BACKGROUND.

1.1 STANFORD owns certain Phoenix and 293T cell lines and derivatives thereof developed in the laboratories of Dr. Garry Nolan and Dr. Michele Calos at STANFORD.

1.2 STANFORD has previously granted to RIGEL a nonexclusive license to such materials pursuant to the License Agreement between RIGEL and STANFORD dated October 7, 1996 (the "1996 License Agreement").

1.3 RIGEL now desires to obtain an exclusive worldwide license to such materials for all uses in the RIGEL Field (as defined below), which exclusive license shall be in addition to the nonexclusive license provided in the 1996 License Agreement.

2. DEFINITIONS.

2.1 "EXCLUSIVE" means that, subject to Article 3, STANFORD shall not grant further licenses in the RIGEL Field.

2.2 "GENE THERAPY" means the treatment of cells which are contained within a human subject or which are subsequently transplanted into a human subject with the Materials.

2.3 "LICENSED PRODUCT(S)" means any product in the RIGEL Field which: (i) directly incorporates any of the Materials; or (ii) would not, but for the use of the Materials, have been identified, discovered or developed. Licensed Products shall include without limitation both diagnostic and therapeutic pharmaceutical products.

2.4 "MATERIALS" means the PhiNX helper-free retrovirus producer lines, PhiNX ampho and PhiNX eco (collectively, the "Phoenix cell lines") and the 293T cell lines developed in the laboratories of Dr. Garry Nolan and Dr. Michele Calos at STANFORD.

2.5 "RIGEL FIELD" means the creation and use of retrovirally produced peptide and protein libraries of random sequence for the screening of transdominant effector peptides and RNA molecules as claimed in U.S. Patent Application Serial No. 589911/PCT No. 9701019 (entitled "Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules") as such claims were filed on January 23, 1997, and U.S. Patent Application Serial No. 589109/PCT No. 9701048 (entitled "Methods for Screening for Transdominant Effector Peptides and RNA Molecules"), as such claims were filed on January 23, 1997, as well as any

processes, techniques and applications disclosed in the foregoing patent applications, for drug discovery and therapeutic target identification.

2.6 "NET SALES" means the gross revenue derived by RIGEL and/or RIGEL's sublicensees from the sales of Licensed Product(s), less the following items insofar as they actually pertain to the disposition of such Licensed Product(s) by RIGEL or RIGEL's sublicensees, are included in such gross revenue, and are separately billed.

(a) Import, export, excise and sales taxes, and custom duties;

(b) Credit for returns, allowances, trades or retroactive price adjustments;

(c) Transportation charges, issuance and allowances;

(d) Discounts actually allowed; or

(e) Royalties payable to third parties on the manufacture, use, sale offer for sale or import of Licensed Products.

3. GRANT; TRANSFER OF MATERIALS.

3.1 STANFORD hereby grants, and RIGEL hereby accepts, a worldwide, royalty-bearing, sublicensable license in the RIGEL Field under STANFORD's right, title and interest in the Materials to make, use, sell, offer for sale and import Licensed Products.

3.2 The license granted in Section 3.1 is Exclusive, including the right to sublicense pursuant to Article 12, in the RIGEL Field for a term (the "Exclusivity Term") commencing as of the Effective Date and ending three (3) years thereafter with respect to both the 293T and Phoenix cell lines; provided, however, that RIGEL may extend such Exclusivity Term with respect to either or both of such cell lines as follows: If RIGEL elects to extend the Exclusivity Term with respect to the 293T cell line for an additional year, RIGEL shall pay to STANFORD an exclusivity extension fee of _____ (the "293T Exclusivity Extension Fee"). If RIGEL elects to extend the Exclusivity Term with respect to the Phoenix cell line for an additional year, RIGEL shall pay to STANFORD an exclusivity extension fee of _____ (the "Phoenix Exclusivity Extension Fee"). Such exclusivity extension fees shall be due any time prior to the third anniversary of the Effective Date, and shall operate to extend the Exclusivity Term until the fourth anniversary of the Effective Date with respect to the 293T cell line, if RIGEL pays the 293T Exclusivity Extension Fee, and/or the Phoenix cell line, if RIGEL pays the Phoenix Exclusivity Extension Fee. RIGEL may elect to extend the Exclusivity Term for additional one year periods of time with respect to the 293T cell line and/or the Phoenix cell line, as applicable, by so notifying STANFORD of its intent to extend the Exclusivity Term with respect to the 293T cell line and/or the Phoenix cell line at least thirty (30) days prior to the following anniversary of the Effective Date and paying to STANFORD either or both of the 293T Exclusivity Extension Fee and the Phoenix Extension Fee, as applicable, prior to the following anniversary of the Effective Date. Any exclusivity extension fees paid by RIGEL pursuant to this Section 3.2 shall be nonrefundable but creditable against

earned royalties as provided in Section 6.4. If RIGEL extends the Exclusivity Term, RIGEL and STANFORD shall discuss in good faith additional appropriate diligence milestones.

3.3 After expiration of the Exclusivity Term with respect to the 293T cell line and/or the Phoenix cell line, the license granted to RIGEL pursuant to Section 3.1 with respect to such cell line(s), shall terminate. Such termination shall not affect the term of the nonexclusive license granted to RIGEL under the 1996 License Agreement.

3.4 Notwithstanding the Exclusive license granted to RIGEL pursuant to Section 3.1, STANFORD shall have the right to use and to distribute the Materials to other nonprofit and academic institutions for non-commercial, academic research purposes in the RIGEL Field. Any transfer of the Materials by STANFORD pursuant to this Section 3.4 shall be governed by a material transfer agreement which (i) restricts the recipient's use of the Materials to the performance of specified academic research projects, (ii) does not allow the recipient to transfer the Materials to any other entity, and (iii) contains other terms and conditions typically included in agreements governing the transfer and use of biological materials for noncommercial academic research purposes.

3.5 Promptly after the Effective Date, STANFORD shall transfer to RIGEL such quantities of the Materials as RIGEL shall reasonably request. Thereafter, STANFORD shall transfer to RIGEL such additional quantities of Materials as RIGEL shall reasonably request in the event that RIGEL's stock of the Materials is destroyed or contaminated.

4. GOVERNMENT RIGHTS.

This Agreement is subject to all of the terms and conditions of Title 35 United States Code Sections 200 through 204, including an obligation that Licensed Product(s) sold or produced in the United States be "manufactured substantially in the United States," and RIGEL agrees to take all reasonable action necessary on its part as licensee to enable STANFORD to satisfy its obligation thereunder. STANFORD agrees to provide reasonable assistance to RIGEL in the event RIGEL decides to seek a waiver under such domestic manufacture requirement.

5. DILIGENCE.

5.1 As an inducement to STANFORD to enter into this Agreement, RIGEL agrees to use all reasonable efforts and diligence to proceed with the development, manufacture and sale of Licensed Product(s) and to develop diligently markets for the Licensed Product(s). RIGEL shall demonstrate such diligence to STANFORD by achieving proof of principle though written documentation of the following achievements:

(a) Construction of a retroviral vector library;

(b) Infection of cells with such vector library;

(c) Detection of a physiological response to such infection in an infected cell;

(d) Isolation and analysis of the peptide eliciting such physiological response from the cell; and

(e) Identification of two novel targets for drug design, or demonstration that two previously known targets have a novel activity suitable for drug design.

5.2 If RIGEL is unable to demonstrate items 5.1(a) through (d) within eighteen (18) months after the Effective Date, and item 5.1(e) within thirty six (36) months after the Effective Date, STANFORD may request that RIGEL meet with STANFORD to discuss RIGEL's lack of diligence. The parties shall meet within thirty (30) days after RIGEL receives any such notice to develop a mutually agreeable plan for remedying any such lack of diligence (the "Proposed Remedy"). If RIGEL fails to perform the Proposed Remedy within one hundred eighty (180) days after the Proposed Remedy is agreed upon, STANFORD may elect to terminate this Agreement, which termination shall not have any effect upon the rights granted to RIGEL pursuant to the 1996 License Agreement.

5.3 On or before each anniversary of the Effective Date during the Exclusivity Term, RIGEL shall make a written annual report to STANFORD covering RIGEL's progress during the preceding year toward commercial use of the Licensed Product(s). Such report shall include as a minimum information sufficient to enable STANFORD to satisfy relevant reporting requirements of the U.S. Government and to ascertain RIGEL's progress toward meeting the diligence requirements of this Article 5.

6. LICENSE FEE AND ROYALTIES.

6.1 In partial consideration for the Exclusive License granted by STANFORD to RIGEL with respect to the Phoenix cell lines included in the Materials, RIGEL agrees to pay to STANFORD the following:

(a) A noncreditable, nonrefundable license issue royalty of _____, which amount shall be paid within thirty (30) days after the Effective Date.

(b) An exclusivity fee equal to _____ for each of the three (3) years following the first anniversary of the Effective Date, which amounts shall be paid to STANFORD within thirty (30) days after each of the first, second and third anniversaries of the Effective Date. Such payments shall be nonrefundable but creditable against earned royalties to the extent provided in Section 6.4.

(c) RIGEL shall issue to STANFORD _____ Stock of RIGEL, pursuant to a stock purchase agreement to be entered into between RIGEL and STANFORD within ninety (90) days after the Effective Date.

(d) If RIGEL grants to a third party a sublicense to the Materials solely for research, and not commercialization purposes (a "Research Sublicense"), RIGEL shall also pay to STANFORD a milestone payment equal to _____ payment that

RIGEL receives as consideration for the grant of such Research Sublicense. RIGEL shall pay such amount to STANFORD within sixty (60) days after RIGEL receives such research milestone payment. If RIGEL grants to a third party a sublicense under the Materials which includes the right to sell and offer for sale Licensed Products (a "Commercialization Sublicense"), RIGEL shall pay to STANFORD a sublicense fee as follows:

First Commercialization Sublicense Granted	_____
Second Commercialization Sublicense Granted	_____
Each Additional Commercialization Sublicense Granted	_____

If RIGEL owes amounts to STANFORD pursuant to this Section 6.1(d) and also pursuant to Section 6.3 of the 1996 License Agreement with respect to a particular Research Sublicense or Commercialization Sublicense, the amounts due to STANFORD pursuant to this Section 6.1(d) shall be reduced by any amounts due to STANFORD pursuant to Section 6.3 of the 1996 License Agreement with respect to such Research Sublicense or Commercialization Sublicense. RIGEL shall pay such sublicense fees to STANFORD within sixty (60) days after the effective date of each Commercialization Sublicense.

6.2 In partial consideration for the Exclusive License granted by STANFORD to RIGEL for the 293T cell lines included in the Materials, RIGEL agrees to pay to STANFORD an exclusivity fee equal to _____ for each of the three (3) years following the first anniversary of the Effective Date, which amounts shall be paid to STANFORD within thirty (30) days after each of the first, second and third anniversaries of the Effective Date. Such payments shall be nonrefundable but creditable against earned royalties to the extent provided in Section 6.4.

6.3 As further consideration for the license granted to RIGEL pursuant to Section 3.1, RIGEL shall pay to STANFORD earned royalties equal to _____ of Net Sales of Licensed Products by RIGEL and its sublicensees; provided, however, that if royalties on Net Sales of a particular Licensed Product by RIGEL and its sublicensees would be due to STANFORD pursuant to both this Section 6.3 and Section 6.4 of the 1996 License Agreement, RIGEL shall be obligated to pay only the royalties due to STANFORD pursuant to Section 6.4 of the 1996 License Agreement on Net Sales of such Licensed Products.

6.4 Creditable payments under this Agreement shall be an offset to RIGEL against up to fifty percent (50%) of each earned royalty payment which RIGEL would be required to pay pursuant to Section 6.4 until the entire creditable amount is exhausted.

6.5 If this Agreement is not terminated in accordance with other provisions hereof, RIGEL's obligation to pay royalties pursuant to Section 6.3 shall continue until ten (10) years after first commercial sale of Licensed Products.

6.6 The royalties on sales in currencies other than U.S. Dollars shall be calculated using the appropriate foreign exchange rate for such currency quoted by the Bank of America (San Francisco) foreign exchange desk, on the close of business on the last banking day of each calendar quarter. Royalty payments to STANFORD shall be in U.S. Dollars. All non-U.S. taxes related to royalty payments shall be paid by RIGEL and are not deductible from the payments due STANFORD.

7. Royalty Reports, Payments, and Accounting.

7.1 QUARTERLY EARNED ROYALTY PAYMENT AND REPORT. Beginning with the first sale of a Licensed Product, RIGEL shall make written reports (even if there are no sales in a particular quarter) and earned royalty payments to STANFORD within thirty (30) days after the end of each calendar quarter. This report shall be in the form of the report of Exhibit A and shall state the number, description, and aggregate Net Sales of Licensed Product(s) during such completed calendar quarter, and resulting calculation pursuant to Section 6.3 of earned royalty payments due STANFORD for such completed calendar quarter. Concurrent with the making of each such report, RIGEL shall include payment due STANFORD of earned royalties for the calendar quarter covered by such report.

7.2 ACCOUNTING. RIGEL agrees to keep and maintain records for a period of three (3) years showing the manufacture, sale, use, and other disposition of products sold or otherwise disposed of under the license herein

granted. Such records will include general ledger records showing cash receipts and expenses, and records which include production records, customers serial numbers and related information in sufficient detail to enable the royalties payable hereunder by RIGEL to be determined. RIGEL further agrees to permit its books and records to be examined by STANFORD from time to time to the extent necessary to verify reports provided for in Section 7.1. Such examination is to be made by STANFORD or its designee, at the expense of STANFORD, except in the event that the results of the audit reveal an underreporting of royalties due STANFORD of five percent (5%) or more, then the audit costs shall be paid by RIGEL.

8. PATENTS; NEW INVENTIONS.

8.1 STANFORD's Office of Technology Licensing represents and warrants that to the best of its knowledge as of the Effective Date, STANFORD has not sought or obtained patent protection of the Materials or any use thereof in the Rigel Field. STANFORD agrees that future inventions and discoveries using or relating to the Materials may be useful to RIGEL in the development and/or commercialization of Licensed Products. Subject to STANFORD's obligations with respect to sponsored research, STANFORD will, as soon as practicable, bring any such new invention or discovery to RIGEL's attention and provide RIGEL a reasonable opportunity to negotiate a license therefor.

9. WARRANTIES.

9.1 STANFORD's Office of Technology Licensing represents and warrants that as of the Effective Date, it has received no claims by third parties that the use of the Materials infringes any patents, copyrights, and other rights of third parties.

9.2 STANFORD represents and warrants that it has all right, power and authority necessary to grant the License set forth in Article 3 to RIGEL, and that it has not, and will not during the term of this Agreement, grant any right or interest in the Materials to any third party which would conflict with the rights granted to RIGEL hereunder.

9.3 RIGEL agrees that nothing in this Agreement grants RIGEL any express or implied license or right under or to:

(a) U.S. Patent No. 4,237,224, "Process for Producing Biologically Functional Molecular Chimeras"; U.S. Patent No. 4,468,464 and U.S. Patent No. 4,740,470, both entitled, "Biologically Functional Molecular Chimeras" (collectively known as the Cohen/Boyer patents), or reissues thereof; or

(b) U.S. Patent 4,656,134, entitled "Amplification of Eucaryotic Genes" or any patent application corresponding thereto.

9.4 Except as provided in Section 9.1 and as otherwise expressly set forth in this Agreement, nothing in this Agreement will be construed as a warranty or representation that anything made, used, sold, or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights, and trademarks of third parties; conferring rights to use in advertising, publicity, or otherwise any trademark or the name of "STANFORD"; or granting by implication, estoppel, or otherwise any licenses or rights under patents of STANFORD.

9.5 EXCEPT AS EXPRESSLY SET FORTH IN THE AGREEMENT, STANFORD MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE LICENSED PRODUCT(S) WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER RIGHTS, OR ANY OTHER EXPRESS OR IMPLIED WARRANTIES.

10. INDEMNITY.

10.1 RIGEL agrees to indemnify, hold harmless, and defend STANFORD and STANFORD Health Services (or any successor thereto) and their respective trustees, officers, employees, students, and agents against any and all claims by third parties for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale, or other disposition of the Materials or Licensed Product(s) by RIGEL or RIGEL's sublicensee(s) or customers.

10.2 STANFORD shall not be liable for any indirect, special,

consequential or other damages whatsoever, whether grounded in tort (including negligence), strict liability, contract or otherwise. STANFORD shall not have any responsibilities or liabilities whatsoever with respect to Licensed Product(s).

10.3 RIGEL shall at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering any and all employees with respect to activities performed under this Agreement.

10.4 In addition to the foregoing, RIGEL shall maintain Comprehensive General Liability Insurance, including Products Liability Insurance, with reputable and financially secure insurance carrier(s) to cover the activities of RIGEL and its sublicensee(s) in the amounts and during the periods specified herein. Such insurance shall provide minimum limits of liability of One Million Dollars ($1,000,000) as of the first anniversary of the date upon which RIGEL first leases a facility in which it will conduct research and development activities, and of Five Million Dollars ($5,000,000) as of the commencement of human clinical trials of Licensed Products. Such insurance shall include STANFORD, Stanford Health Services (or any successor thereto), their trustees, directors, officers, employees, students, and agents as additional insureds. Such insurance shall be written to cover claims incurred, discovered, manifested, or made during or after the expiration of this Agreement. At STANFORD's request, RIGEL shall furnish a Certificate of Insurance evidencing primary coverage and requiring thirty (30) days prior written notice of cancellation or material change to STANFORD. RIGEL shall advise STANFORD, in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All such insurance of RIGEL shall be primary coverage; insurance of STANFORD or Stanford Health Services (or any successor thereto) shall be excess and noncontributory.

11. STANFORD NAMES AND MARKS

11.1 RIGEL agrees not to identify STANFORD in any promotional advertising or other promotional materials to be disseminated to the public or any portion thereof or to use the name of any STANFORD faculty member, employee, or student or any trademark, service mark, trade name, or symbol of STANFORD or the STANFORD Health Services (or any successor thereto), or that is associated with either of them, without STANFORD's prior written consent, except as required by law. STANFORD shall not unreasonably hold consent under this Section 11.

12. SUBLICENSE(S).

12.1 RIGEL may, solely in conjunction with a sublicense under the rights licensed to RIGEL pursuant to Section 3.1 of the 1996 License Agreement, grant sublicense(s) under its Exclusive license rights during the Exclusivity Term.

12.2 Any sublicense(s) granted by RIGEL under this Agreement shall be subject and subordinate to terms and conditions of this Agreement, except:

(a) Sublicense terms and conditions shall reflect that any sublicensee(s) shall not grant a sublicense to a third party; and

(b) The earned royalty rate specified in the sublicense(s) may be at higher rates than the rates in this Agreement.

Any such sublicense(s) also shall expressly include the provisions of Articles 7, 9, and 10 for the benefit of STANFORD and provide for the transfer of all obligations including the payment of royalties specified in such sublicense(s), to STANFORD or its designee, in the event that this Agreement is terminated, if such sublicenses remain in effect after termination of this Agreement.

12.3 RIGEL agrees to provide STANFORD a copy of any sublicense(s) granted pursuant to this Article 12.

13. TERM AND TERMINATION.

13.1 The term of this Agreement shall commence upon the Effective Date and shall continue until expiration of both the Phoenix cell Exclusivity Term and the 293T cell line Exclusivity Term. Additionally, RIGEL may terminate this Agreement prior to such expiration date by giving STANFORD notice in writing at least thirty (30) days in advance of the effective date of termination selected by RIGEL. If RIGEL terminates this Agreement prior to the third anniversary of the Effective Date, RIGEL's obligations to make the payments due to STANFORD pursuant to Sections 6.1(b), and 6.2 and shall survive such termination until expiration of RIGEL's obligations thereunder. Any termination or expiration of this Agreement shall have no effect upon the Rights granted to RIGEL pursuant to the 1996 License Agreement.

13.2 STANFORD may terminate this Agreement if RIGEL:

(a) Is in default in payment of royalty or providing of reports;

(b) Is in material breach of any provision hereof; or

(c) Intentionally provides any false report;

and RIGEL fails to remedy any such default, breach, or false report within thirty (30) days after written notice thereof to RIGEL by STANFORD.

13.3 SURVIVING ANY TERMINATION ARE:

(a) RIGEL's obligation to pay exclusivity fees pursuant to Sections 6.1(b) and 6.2, royalties accrued or accruable pursuant to Section 6.3, and Sections 6.4, 6.5 and 6.6;

(b) Any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party; and

(c) The provisions of Articles 7, 9 and 10.

14. ASSIGNMENT.

This Agreement may not be assigned by either party without the express written consent of the other party, except that RIGEL may assign the Agreement in connection with a merger, consolidation or sale of all or substantially all of RIGEL's assets.

15. ARBITRATION.

15.1 Any controversy arising under or related to this Agreement, and any disputed claim by either party against the other under this Agreement excluding any dispute relating to patent validity or infringement arising under this Agreement, shall be settled by arbitration in accordance with the Licensing Agreement Arbitration Rules of the American Arbitration Association.

15.2 Upon request by either party, arbitration will be by a third party arbitrator mutually agreed upon in writing by RIGEL and STANFORD within thirty (30) days of such arbitration request. Judgment upon the award rendered by the arbitrator shall be final and nonappealable and may be entered in any court having jurisdiction thereof.

15.3 The parties shall be entitled to discovery in like manner as if the arbitration were a civil suit in the California Superior Court.

15.4 Any arbitration shall be held at Stanford, California, unless the parties hereto mutually agree in writing to another place.

16. NOTICES.

All notices under this Agreement shall be deemed to have been fully given when done in writing and deposited in the United States mail registered or certified, and addressed as follows:

To STANFORD: Office of Technology Licensing
Stanford University
900 Welch Road, Suite 350
Palo Alto, CA 94304-1850

Attention: Director

To RIGEL: 772 Lucerne Drive
Sunnyvale, CA 94086

Attention: Dr. Donald G. Payan

Either party may change its address upon written notice to the other party.

17. WAIVER.

None of the terms of this Agreement can be waived except by the written consent of the party waiving compliance.

18. APPLICABLE LAW.

This Agreement shall be governed by the laws of the State of California applicable to agreements negotiated, executed and performed wholly within California. Any claim or controversy arising out of or related to this Agreement or any breach hereof shall be submitted to a court of applicable jurisdiction in the State of California, and each party hereby consents to the jurisdiction and venue of such court.

19. SEVERABILITY.

If any provision or provisions of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby.

20. ENTIRE AGREEMENT.

This Agreement, together with the Exhibit attached hereto, embodies the entire understanding of the parties and shall supersede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof. No amendment or modification hereof shall be valid or binding upon the parties unless made in writing and signed by duly authorized representatives of both parties.

21. COUNTERPARTS.

This Agreement may be executed in counterparts, with the same force and effect as if the parties had executed the same instrument.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement in duplicate originals by their duly authorized officers or representatives.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

Signature /s/ Jon Sandelin

Name Jon Sandelin

Title Acting Director

Date August 18, 1997

RIGEL PHARMACEUTICALS , INC.

Signature /s/ Donald G. Payan

Name Donald G. Payan

Title VP R&D and COO

Date 8/18/97

EXHIBIT A

SAMPLE REPORTING FORM

Stanford Docket No. S____-_____

This report is provided pursuant to the license agreement between Stanford University and _____.

License Agreement Effective Date: _____

<TABLE>
<S> <C>

Report Covering Period	
Fixed Fees (Annual Minimum Payment)	$
Number of Sublicenses Executed	
Net Sales	$

Royalty Calculation	
Royalty Subtotal	$
Credit	$
Royalty Due	$

</TABLE>

<TABLE>

<S> <C>

</TABLE>

LICENSE AGREEMENT

Effective as of March 27, 1998 ("Effective Date"), THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California ("STANFORD"), and RIGEL PHARMACEUTICALS, INC., a Delaware corporation doing business as RIGEL, INC. in California, having a principal place of business at 772 Lucerne Drive, Sunnyvale, California 94086 ("RIGEL"), agree as follows:

1. BACKGROUND

1.1 STANFORD has an assignment of U.S Provisional Applications (the "Provisionals"), Serial No. 042576, filed April 2, 1997, and Serial No. 054623, filed August 4, 1997 entitled, "Detection of Molecular Interactions by Reporter Subunit Complementation" from the laboratory of Helen M. Blau Ph.D. (the "Invention"), and as described in Stanford Docket S96-125, and any Licensed Patents, as hereinafter defined, which may claim such Invention.

1.2 STANFORD has certain biological materials ("Licensed BIOLOGICAL Materials") and other know-how ("Know-How"), as defined below, pertaining to the Inventions.

1.3 STANFORD desires to have the Know-How and Inventions perfected and

marketed at the earliest possible time in order that products resulting therefrom may be available for public use and benefit.

1.4 RIGEL desires a license under said Know-How, Invention and Licensed Patents to develop, manufacture, use and sell Licensed Products in the Licensed Field of Use, as defined below.

1.5 The Know-How and Invention were made in the course of research supported by the National Institutes of Health.

2. DEFINITIONS

2.1 "EXCLUSIVE" means that STANFORD shall not grant further licenses in the Licensed Territory in the Licensed Field of Use.

2.2 "LICENSED BIOLOGICAL MATERIALS" means the materials listed on Exhibit A, as amended from time to time upon the parties' mutual written consent.

2.3 "LICENSED FIELD OF USE" means, subject to Section 14:

(a) the development of reporter systems useful for the analysis of protein-protein interactions;

(b) the development of methods for analyzing molecular interactions by reporter subunit complementation; and

(c) applications of the systems and methods set forth in (a) and (b) to functional genomics, target analysis and drug discovery.

2.4 "LICENSED KNOW-HOW" means know-how useful for the commercial exploitation of the Licensed Patents in the Licensed Field of Use and is provided to RIGEL by STANFORD, including know-how, trade secrets, protocols, information, processes or other subject matter which is either disclosed in the Licensed Patents, or useful to practice the Invention in the Licensed Field of Use. Licensed Know-How excludes the Licensed Patents and includes the Licensed Biological Materials. STANFORD has no obligation to provide such know-how.

2.5 "LICENSED PATENTS" means any Letters Patent issued upon (i) patent applications claiming priority from or based upon the Provisionals; (ii) any patents issuing from any divisional, continuations, substitute, or continuation-in-part (to the extent provided in this Section 2.5) application relating to the patent applications described in (i); and (iii) any foreign counterparts of the patent applications described in (i) or (ii). Continuation-in-part applications are included in the Licensed Patents to the extent that such continuation-in-part claims subject matter disclosed in the applications set forth in (i) and to the extent that the practice of an invention claimed in a Licensed Patent issuing from a patent application other than such continuation-in-part would infringe a claim of a Licensed Patent issuing from such continuation-in-part.

2.6 "LICENSED PRODUCTS" means

(a) any product, the manufacture, use, sale, offer for sale and import of which:

(i) is covered by one or more valid claims of an issued, unexpired Licensed Patent directed to the Invention. Claims of issued, unexpired Licensed Patent shall be presumed to be valid unless and until they have been held to be invalid by a final judgment of a court of competent jurisdiction from which no appeal can be or is taken; or

(ii) is covered by any claim being prosecuted in a pending application directed to the Invention, which claim has not been pending for more than three (3) years from the first filing of such claim; and

(b) any product which directly incorporates any of the Licensed Biological Materials; and

(c) any product which would not, but for the use of the Licensed Technology, have been identified, discovered or developed.

2.7 "LICENSED TECHNOLOGY" means the Licensed Patents and the Licensed Know-How.

2.8 "LICENSED TERRITORY" means all the countries in the world.

2.9 "NET SALES" means the gross revenue derived by RIGEL and/or its sublicensee(s) from the sales of Licensed Products to end users thereof, less the following items but only insofar as they actually pertain to the disposition

of such Licensed Products by RIGEL or RIGEL's sublicensee(s), are included in such gross revenue, and are separately billed:

(a) import, export, excise and sales taxes, and custom duties;

(b) transportation charges, issuances and allowances;

(c) credit for returns, allowances, trades or retroactive price adjustments;

(d) discounts actually allowed; or

(e) royalties payable to third parties on the manufacture, use, sale, offer for sale or import of Licensed Products.

2.10 "SERVICE PROVIDER" means a third party contract research or similar organization that performs assay services (i) for other entities on a fee-for-service basis and (ii) not in connection with such organization's own drug development programs (whether such programs are conducted solely by such entity or jointly by such entity and one or more third parties).

3. GRANT

3.1 STANFORD hereby grants, and RIGEL hereby accepts, a license in the Licensed Field of Use to make, use, sell, offer for sale and import Licensed Products in the Licensed Territory.

3.2 RIGEL hereby grants, and STANFORD hereby accepts, a non-exclusive, royalty free license under its interest in any inventions conceived by RIGEL during the term of this Agreement that solely relate to the technology claimed in the Licensed Patents and any intellectual property rights related thereto (collectively, "Improvements"), to practice and grant licenses under such Improvements solely for noncommercial, academic research purposes.

3.3 The license granted to RIGEL pursuant to Section 3.1 under the Licensed Know-How shall be nonexclusive for the term of this Agreement. The license granted in Section 3.1 under the Licensed Patents is Exclusive for a term (the "Exclusivity Term") commencing as of the Effective Date and ending (except as otherwise provided in this Agreement) on the first to occur of the following:

(a) the fifth anniversary of the Effective Date if STANFORD does not grant a license under the Licensed Patents outside the Licensed Field of Use to a third party prior to or on such date; or

(b) the eighth anniversary of the Effective Date, if STANFORD grants a license under the Licensed Patents outside the Licensed Field of Use to a third party prior to or on the fifth anniversary of the Effective Date.

After expiration of the Exclusivity Term, the license granted to RIGEL pursuant to Section 3.1 under the Licensed Patents shall be nonexclusive for the remainder of the term of the Agreement.

3.4 Notwithstanding the Exclusive license under the Licensed Patents granted to RIGEL pursuant to Section 3.1, STANFORD shall have the right to practice the Licensed Technology in the Licensed Field of Use for noncommercial, academic research purposes. STANFORD shall have the right to publish any information included in the Licensed Technology.

3.5 STANFORD may grant sublicenses under Improvements to third parties solely for noncommercial, academic research purposes, provided that each such sublicense is granted in conjunction with a license under the Licensed Technology. After the expiration of the Exclusivity Term, STANFORD may grant sublicenses under Improvements to third parties for purposes other than conducting noncommercial academic research, provided that each such sublicense is granted solely in conjunction with the grant of a license under the Licensed Technology. STANFORD's license under Section 3.2 and its ability to grant sublicenses thereunder as provided in this Section 3.5 shall survive termination of this Agreement.

4. GOVERNMENT RIGHTS

This Agreement is subject to all of the terms and conditions of Title 35 United States Code Sections 200 through 204, including an obligation that Licensed Products sold or produced in the United States be "manufactured substantially in the United States," and RIGEL agrees to take all reasonable

action necessary on its part as licensee to enable STANFORD to satisfy its obligation thereunder relating to Inventions.

5. DILIGENCE; PROGRESS REPORTS

5.1 As an inducement to STANFORD to enter into this Agreement, RIGEL agrees to use all commercially reasonable efforts and diligence to proceed with the development, manufacture and sale of Licensed Products and to diligently develop markets for the Licensed Products. RIGEL shall demonstrate such diligence to STANFORD by achieving the following goals:

(a) before the first anniversary of the Effective Date, RIGEL shall identify and characterize beta gal mutants with improved properties (e.g., mutants which have lower affinities than those disclosed in the Provisional and yet still provide adequate complementary binding characteristics such that the assay's signal to noise ratio is adequate for high throughput commercial use.)

(b) before the second anniversary of the Effective Date, RIGEL shall establish two (2) new high throughput screening assays that utilize the Licensed Technology, one (1) of which is primarily useful for target identification and one (1) of which is primarily useful for screening to identify small molecules that bind to drug targets; and

(c) before the fourth anniversary of the Effective Date, use the assays described in (b) to identify one new drug target and one small molecule that competes with the binding of molecules to a drug target.

5.2 If RIGEL is unable to demonstrate its diligence by achieving the goals provided in Section 5.1 within the time frames set forth therein, the parties shall meet no later than thirty (30) days after the relevant date set forth in Section 5.1 to discuss in good faith the reasons for such

failure, and mutually acceptable mechanisms for remedying such failure. If the parties do not agree upon modifications to the diligence requirements set forth in Section 5.1 during such discussion, then STANFORD may thereafter convert RIGEL's exclusive license under the Licensed Patents to non-exclusive upon thirty (30) days written notice to RIGEL.

5.3 If RIGEL succeeds in meeting the goals provided in Section 5.1, RIGEL and STANFORD agree to meet within ninety (90) days prior to the fourth anniversary of the Effective Date to establish further mutually acceptable diligence requirements applicable to the next two (2) year period during the term of the Agreement. If the parties, after good faith effort, cannot agree on such additional requirements, STANFORD may in its sole discretion elect to convert RIGEL's exclusive license under the Licensed Patents to non-exclusive as of the fourth anniversary of the Effective Date by written notice to RIGEL.

5.4 On or before August 1, 1998 and each anniversary thereof until RIGEL markets Licensed Products, RIGEL shall make a written annual report to STANFORD covering RIGEL's progress during the preceding year toward commercial use of Licensed Products. Such report shall include, as a minimum, information sufficient to enable STANFORD to satisfy reporting requirements of the U.S. Government and for STANFORD to ascertain progress by RIGEL toward meeting the diligence requirements of this Article 5.

6. PAYMENTS AND ROYALTIES

6.1 RIGEL shall upon the Effective Date:

(a) pay to STANFORD a noncreditable, nonrefundable license issue royalty of _____; and

(b) issue to STANFORD _____ Stock pursuant to a stock purchase agreement to be separately executed by the parties.

6.2 Subject to Section 6.6, RIGEL also agrees to pay the following minimum annual royalties to STANFORD within thirty (30) days after the occurrence of each date below:

<TABLE>
<CAPTION>

Anniversary of Effective Date	Minimum Annual Royalty Due
<S>	<C>
First and Second	_____
Third through Fifth	_____
Sixth and Thereafter	_____

</TABLE>

These minimum annual royalty payments are nonrefundable, but they are creditable against earned royalties due to Stanford pursuant to Section 6.4. In addition, the minimum annual royalties set forth in this Section 6.2 shall be reduced by fifty percent (50%) if STANFORD abandons all patent applications from which Licensed Patents could issue prior to the time that any Licensed Patents issue.

6.3 RIGEL also agrees to pay to STANFORD upon the occurrence of the following events, the following amounts:

<TABLE>
<CAPTION>

Event	Milestones
<S>	<C>
Earlier of the execution of the first sublicense by Rigel under the Licensed Technology or 18 months after the Effective Date	_____
Earlier of the execution of the second sublicense by Rigel under the Licensed Technology or 48 months after the Effective Date	_____
Earlier of the execution of the third sublicense by Rigel under the Licensed Technology or 78 months after the Effective Date	_____
Execution of any additional sublicenses by Rigel after payment of all of the foregoing milestones	_____

</TABLE>

6.4 RIGEL shall pay to STANFORD earned royalties of _____ of Net Sales during the Exclusivity Term. Should total earned royalties due on Licensed Products to STANFORD under this Agreement and any other agreement between STANFORD and RIGEL (the "Other Agreements") equal or exceed _____ of Net Sales, STANFORD shall, upon request by RIGEL, meet with RIGEL to discuss an appropriate mechanism, if RIGEL's royalty obligations under this Agreement and the Other Agreements render further development and commercialization of License Products uneconomic. The parties will discuss in good faith appropriate adjustments to RIGEL's obligations under this Agreement..

6.5 RIGEL shall also pay to STANFORD _____ upon the issuance of the first patent included in the Licensed Patents.

6.6 Within thirty (30) days after the license granted under the Licensed Patents pursuant to Section 3.1 becomes non-exclusive pursuant to Sections 3.3, 5.2 or 5.3, STANFORD shall provide to RIGEL a written summary of all non-confidential material terms of any other license agreements with third parties relating to the Licensed Technology. STANFORD shall use reasonable efforts to obtain consent of any such third parties to disclose such material terms or at least a general description of the economic terms of such other license agreements to RIGEL. Within thirty (30) days after receiving such summary, RIGEL shall elect one of the following options by written notice to STANFORD:

(a) to allow this Agreement to continue in full force and effect, except that the minimum annual royalties due to STANFORD pursuant to Section 6.2 shall be reduced by fifty percent (50%); or

(b) to modify the terms of this Agreement to include terms no less favorable to RIGEL than those STANFORD then provides to third party licensees of the Licensed Technology.

If no such license agreement between STANFORD and any such third party exists at the time RIGEL must elect either (a) or (b), then (a) shall automatically apply. If RIGEL elects the option set forth in Section 6.6(a), such a reduction shall be in addition to any reduction resulting from the application of Section 6.2. If RIGEL elects the option set forth in Section 6.6(b), RIGEL and STANFORD shall modify the Agreement to contain all rights and obligations contained in licenses available to such other licensees.

6.7 Creditable payments under this Agreement shall be offset against up to fifty percent (50%) of each earned royalty payment which RIGEL would be

required to pay pursuant to Section 6.4, until the entire creditable amount is exhausted.

6.8 If this Agreement is not terminated in accordance with other provisions hereof, RIGEL's obligation to pay royalties hereunder shall continue until ten (10) years after first commercial sale of Licensed Products.

6.9 The royalty on sales in currencies other than U.S. Dollars shall be calculated using the appropriate foreign exchange rate for such currency quoted by the Bank of America (San Francisco) foreign exchange desk, on the close of business on the last banking day of each calendar quarter. Royalty payments to STANFORD shall be in U.S. Dollars. All non-U.S. taxes related to royalty payments shall be paid by RIGEL and are not deductible from the payments due STANFORD.

7. ROYALTY REPORTS, PAYMENTS, AND ACCOUNTING

7.1 QUARTERLY EARNED ROYALTY PAYMENT AND REPORT - Beginning with the first sale of Licensed Products, RIGEL shall make written reports (even if there are no sales) and earned royalty payments to STANFORD within thirty (30) days after the end of each calendar quarter. This report shall be in the form of the report of Appendix B and shall state the number, description and aggregate Net Sales of Licensed Products during such completed calendar quarter, and shall state the resulting calculation pursuant to Section 6.4 of earned royalty payments due STANFORD for such completed calendar quarter. Concurrent with the making of each such report, RIGEL shall include payment due STANFORD of royalties for the calendar quarter covered by such report.

7.2 ACCOUNTING - RIGEL agrees to keep and maintain records for a period of three (3) years showing the manufacture, sale, use and other disposition of products sold or otherwise disposed of under the licenses herein granted. Such records will include general ledger records showing cash receipts and expenses and records which include production records, customers, serial numbers and related information in sufficient detail to enable the royalties payable hereunder by RIGEL to be determined. RIGEL further agrees to permit its books and records to be examined by STANFORD from time to time to the extent necessary to verify reports provided

for in Section 7.1. Such examination is to be made by STANFORD or its designee, at the expense of STANFORD, except in the event that the results of the audit reveal an underreporting of royalties due STANFORD of five percent (5%) or more, then the audit costs shall be paid by RIGEL.

8. NEGATION OF WARRANTIES

8.1 Nothing in this Agreement is or shall be construed as:

(a) a warranty or representation by STANFORD as to the validity or scope of any Licensed Patents;

(b) a warranty or representation that anything made, used, sold or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights and other rights of third parties;

(c) an obligation to bring or prosecute actions or suits against third parties for infringement, except to the extent and in the circumstances described in Article 13;

(d) granting by implication, estoppel or otherwise any licenses or rights under patents or other rights of STANFORD or other persons other than Licensed Technology, regardless of whether such patents or other rights are dominant or subordinate to any Licensed Technology; or

(e) an obligation to furnish any technology or technological information other than the Licensed Technology.

8.2 Except as expressly set forth in this Agreement, STANFORD MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE LICENSED PRODUCT(S) WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER RIGHTS OR ANY OTHER EXPRESS OR IMPLIED WARRANTIES.

8.3 RIGEL agrees that nothing in this Agreement grants RIGEL any express or implied license or right under or to U.S. Patent 4,656,134 "Amplification of Eucaryotic Genes" or any patent application corresponding thereto.

9. INDEMNITY

9.1 LICENSEE agrees to indemnify, hold harmless, and defend STANFORD, UCSF-Stanford Health Care and Stanford Health Services and their respective trustees, officers, employees, students and agents against any and all claims for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale or

other disposition of Inventions, Licensed Products or Licensed Technology by RIGEL or RIGEL's sublicensee(s), or their customers.

9.2 STANFORD shall not be liable for any indirect, special, consequential or other damages whatsoever, whether grounded in tort (including negligence), strict liability, contract or otherwise. STANFORD shall not have any responsibilities or liabilities whatsoever with respect to Licensed Product(s).

9.3 LICENSEE shall at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering any and all employees with respect to activities performed under this Agreement.

9.4 In addition to the foregoing, LICENSEE shall maintain, during the term of this Agreement, Comprehensive General Liability Insurance, including Products Liability Insurance, with reputable and financially secure insurance carrier(s) to cover the activities of LICENSEE and its sublicensee(s). Such insurance shall provide minimum limits of liability of $5 Million and shall include STANFORD, UCSF-Stanford Health Care, Stanford Health Services, their trustees, directors, officers, employees, students and agents as additional insureds. Such insurance shall be written to cover claims incurred, discovered, manifested, or made during or after the expiration of this Agreement. At STANFORD's request, LICENSEE shall furnish a Certificate of Insurance evidencing primary coverage and requiring thirty (30) days prior written notice of cancellation or material change to STANFORD. LICENSEE shall advise STANFORD, in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All such insurance of LICENSEE shall be primary coverage; insurance of STANFORD, USCF-Stanford Health Care, and Stanford Health Services shall be excess and noncontributory.

10. MARKING

Prior to the issuance of patents on the Inventions, RIGEL agrees to mark Licensed Products (or their containers or labels) made, sold, or otherwise disposed of by it under the license granted in this Agreement with the words "Patent Pending," and following the issuance of one or more patents, with the numbers of the Licensed Patents.

11. STANFORD NAMES AND MARKS

RIGEL agrees not to identify STANFORD in any promotional advertising or other promotional materials to be disseminated to the public or any portion thereof or to use the name of any STANFORD faculty member, employee, or student or any trademark, service mark, trade name, or symbol of STANFORD, STANFORD Health Services or UC-Stanford Health Care, or that is associated with any of them, without STANFORD's prior written consent.

12. PATENT RIGHTS

12.1 STANFORD shall have the obligation to file, prosecute and maintain all patent applications and patents included in the Licensed Patents.

12.2 STANFORD will provide RIGEL with an opportunity to review and comment upon the prosecution strategy and to consult with STANFORD on the content of patent filings. In addition, STANFORD will provide RIGEL or a designee of RIGEL with copies of any correspondence relating to patent applications and patents included in the Licensed Patents.

12.3 RIGEL shall have the right to designate, in its sole discretion, those foreign countries in which STANFORD will file, prosecute and maintain patents and patent applications included in the Licensed Patents. STANFORD may propose to file, prosecute and maintain Licensed Patents in a country which RIGEL has not designated pursuant to this Section 12.3. If RIGEL agrees to such designation, it shall reimburse STANFORD for the costs of such filing, prosecution and maintenance of such patents or patent applications pursuant to Section 12.4 and such patents or patent applications shall be included in the Licensed Patents. If RIGEL does not agree to such proposal, STANFORD may elect to proceed with such filing, prosecution or maintenance at its own expense, and

such patents or patent applications in such country shall not be included in the Licensed Patents.

12.4 Within thirty (30) days after the Effective Date, RIGEL shall reimburse STANFORD for all costs incurred by STANFORD prior to the Effective Date in connection with the filing and prosecution of the patent applications described in Section 2.5 ("Prior Patent Costs"). RIGEL shall also reimburse STANFORD for all costs incurred by STANFORD after the Effective Date with respect to the filing, prosecution, issuance and maintenance of patent applications described in Section 2.5 and the Licensed Patents ("Future Patent Costs"); PROVIDED, HOWEVER, that:

(a) if STANFORD grants a license under the Licensed Patents to any third party (an "Other Licensee"), RIGEL's obligation to reimburse STANFORD under this Section 12.4(a) shall be reduced such that RIGEL and such Other Licensee(s) shall pay a pro-rata share of all Future Patent Costs incurred after the date STANFORD executes such license agreement with such Other Licensee (such pro-rata share shall be equal to the total Future Patent Costs incurred divided by the number of licensees under the Licensed Patents at the time such costs are incurred); and

(b) in addition to any reimbursement due RIGEL pursuant to Section 12.4(a), if STANFORD grants a license under the Licensed Patents to an Other Licensee prior to the second anniversary of the Effective Date, STANFORD shall reimburse RIGEL for fifty percent (50%) of the Prior Patent Costs.

13. INFRINGEMENT BY OTHERS: PROTECTION OF PATENTS

13.1 RIGEL shall promptly inform STANFORD of any suspected infringement of any Licensed Patents by a third party. During the Exclusivity Term, STANFORD and RIGEL each shall have the right to institute an action for infringement of the Licensed Patents against such third party in accordance with the following:

(a) if STANFORD and RIGEL agree to institute suit jointly, the suit shall be brought in both their names, the out-of-pocket costs thereof shall be borne equally, and any recovery or settlement shall be shared equally. RIGEL and STANFORD shall agree to the manner in which they shall exercise control over such action. STANFORD may, if it so desires, also be represented by separate counsel of its own selection, the fees for which counsel shall be paid by STANFORD;

(b) in the absence of agreement to institute a suit jointly, STANFORD may institute suit, and, at its option, join RIGEL as a plaintiff. If STANFORD decides to institute suit, then it shall notify RIGEL in writing. STANFORD shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement; and

(c) in the absence of agreement to institute a suit jointly and if STANFORD notifies RIGEL that it has decided not to join in or institute a suit, as provided in (a) or (b) above, RIGEL may institute suit and, at its option, join STANFORD as a plaintiff. RIGEL shall bear the entire cost of such litigation. Any recovery in excess of litigation costs will be shared with STANFORD as follows:

(i) Any payment for past sales will be deemed to be Net Sales and RIGEL will pay STANFORD royalties thereon at the rates specified in Paragraph 6.4; and

(ii) any payment which covers future sales will be deemed a sublicense and royalties will be shared as specified in Paragraph 6.3 and Article 15.

LICENSEE and STANFORD agree to negotiate in good faith an appropriate compensation to STANFORD for any non-cash amounts or awards received in any settlement or cross-license resulting from a suit brought by RIGEL pursuant to this Section 13.1(c). STANFORD will not share in the portion of the recovery, if any, that is payment for "willful infringement."

13.2 Should either STANFORD or RIGEL commence a suit under the provisions of Section 13.1 and thereafter elect to abandon the same, it shall give timely notice to the other party who may, if it so desires, continue prosecution of such suit; PROVIDED, HOWEVER, that the sharing of expenses and any recovery in such suit shall be as agreed upon between STANFORD and RIGEL.

14. OTHER LICENSEE(S) OF STANFORD

14.1 If during the Exclusivity Term STANFORD discusses with, or has received an offer from, a third party (a "Potential Licensee") with respect to an opportunity for such Potential Licensee to obtain a license under the

Licensed Technology within the Licensed Field of Use, STANFORD may so notify RIGEL. Such notice shall specify the field within which such Potential Licensee desires to obtain a license under the Licensed Technology (the "Field of Interest"). Within thirty (30) days after RIGEL receives a notice from STANFORD pursuant to this Section 14.1, the parties will meet to discuss RIGEL's current activities directed toward, or

plans for, developing Licensed Products useful within the Field of Interest. If RIGEL does not demonstrate that it is then diligently conducting such activities or provide plans for diligently developing Licensed Products within the Field of Interest that are reasonably acceptable to STANFORD, then RIGEL and STANFORD shall discuss in good faith reasonable modifications to the Agreement that exclude the Field of Interest from the definition of the Licensed Field of Use. STANFORD may thereafter license to such Potential Licensee the Licensed Technology in the Field of Interest.

14.2 If STANFORD has not entered into an agreement with a Service Provider outside the Licensed Field of Use during the Exclusivity Term, then after the expiration of the Exclusivity Term STANFORD and RIGEL agree to discuss in good faith how to modify appropriately the definition of the Licensed Field of Use to enable STANFORD to increase the interest of Service Providers in obtaining a license under the Licensed Technology outside any modified Licensed Field of Use.

15. SUBLICENSE(S)

15.1 RIGEL may grant sublicense(s) to its corporate partners in conjunction with a sublicense of RIGEL's proprietary technology other than the Licensed Technology and Improvements; provided that the Licensed Technology is applicable to the field within which RIGEL and such corporate partner are collaborating.

15.2 Any sublicense(s) granted by RIGEL under this Agreement shall be subject and subordinate to terms and conditions of this Agreement, except:

(a) Sublicense terms and conditions shall reflect that any sublicensee(s) shall not grant sublicenses to a third parties (subject to Section 15.4); and

(b) The earned royalty rate specified in the sublicense(s) may be at higher rates than the rates in this Agreement.

Any such sublicense(s) also shall expressly include the provisions of Articles 7, 8, and 9 for the benefit of STANFORD and provide for the transfer of all obligations, including the payment of royalties specified in such sublicense(s), to STANFORD or its designee, in the event that this Agreement is terminated if such sublicenses remain in effect after termination of this Agreement.

15.3 RIGEL agrees to provide STANFORD with a copy of any sublicense granted pursuant to this Article 15.

15.4 STANFORD agrees that RIGEL and/or its permitted sublicensee(s) may (i) distribute Licensed Products through their normal channels, and (ii) contract for the manufacture of Licensed Products with one or more third parties.

16. TERMINATION

16.1 RIGEL may terminate this Agreement by giving STANFORD notice in writing at least thirty (30) days in advance of the effective date of termination selected by RIGEL.

16.2 STANFORD may terminate this Agreement if RIGEL:

(a) is in default in payment of royalties or providing of reports;

(b) is in breach of any provision hereof (subject to Section 5.2); or

(c) intentionally provides any false report;

and fails to remedy any such default, breach, or false report within thirty (30) days after written notice thereof by STANFORD.

16.3 Surviving any termination are:

(a) RIGEL's obligation to pay royalties accrued or accruable;

(b) any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party; and

(c) the provisions of Sections 3.2, 3.5 and Articles 7, 8 and 9.

17. ASSIGNMENT

This Agreement may not be assigned by either party without the express written consent of the other party, except that RIGEL may assign the Agreement in connection with a merger, consolidation or sale of all or substantially all of RIGEL's assets.

18. ARBITRATION

18.1 Any controversy arising under or related to this Agreement, and any disputed claim by either party against the other under this Agreement excluding any dispute relating to patent validity or infringement arising under this Agreement, shall be settled by arbitration in accordance with the Licensing Agreement Arbitration Rules of the American Arbitration Association.

18.2 Upon request by either party, arbitration will be by a third party arbitrator mutually agreed upon in writing by RIGEL and STANFORD within thirty (30) days of such arbitration request. Judgement upon the award rendered by the arbitrator shall be final and nonappealable and may be entered in any court having jurisdiction thereof.

18.3 The parties shall be entitled to discovery in like manner as if the arbitration were a civil suit in the California Superior Court.

18.4 Any arbitration shall be held at Stanford, California, unless the parties hereto mutually agree in writing to another place.

19. NOTICES

All notices under this Agreement shall be deemed to have been fully given when done in writing and deposited in the United States mail, registered or certified, and addressed as follows:

To STANFORD: Office of Technology Licensing

STANFORD University
900 Welch Road, Suite 350
Palo Alto, CA 94304-1850

Attention: Director

To RIGEL: Rigel, Inc.
772 Lucerne Drive
Sunnyvale, CA 94086

Attention: President

Either party may change its address upon written notice to the other party.

20. WAIVER

None of the terms of this Agreement can be waived except by the written consent of the party waiving compliance.

21. APPLICABLE LAW

This Agreement shall be governed by the laws of the State of California applicable to agreements negotiated, executed and performed wholly within California.

22. SEVERABILITY; ENTIRE AGREEMENT

If any provision of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby. This Agreement embodies the entire understanding of the parties and shall supersede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof. No amendment or modification hereof shall be valid or binding upon the parties

unless made in writing and signed by duly authorized representatives of both parties.

23. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original and all of which together shall constitute one legal instrument.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement in duplicate originals by their duly authorized officers or representatives.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

Signature /s/ Katherine Ku

Name Katherine Ku

Title Director

Date April 15, 1998

RIGEL

Signature /s/ James M. Gower

Name James M. Gower

Title President & CEO

Date 3/27/98

EXHIBIT A
LICENSED BIOLOGICAL MATERIALS

EXHIBIT 10.7

COLLABORATIVE RESEARCH AND LICENSE AGREEMENT

THIS COLLABORATIVE RESEARCH AND LICENSE AGREEMENT ("the Agreement") is entered into as of January 31, 1999 ("Effective Date") by and between PFIZER INC, a Delaware corporation, having an office at 235 East 42nd Street, New York, New York 10017-5755 ("Pfizer") and RIGEL PHARMACEUTICALS, INC., a Delaware corporation, having an address at 772 Lucerne Drive, Sunnyvale, California 94086 ("Rigel"). Pfizer and Rigel and their Affiliates may be referred to herein individually as a "Party" or collectively as the "Parties."

WHEREAS, Rigel has the capability and expertise to undertake research for the discovery of novel and selective elements of the IL-4 signaling pathway involved in the modulation of IgE synthesis that are suitable targets for an IgE synthesis-inhibitor, lead identification program;

WHEREAS, Rigel owns the patents, patent applications and licenses with third parties set forth in Exhibit A attached to and made a part of this Agreement with respect to retroviral expression technology and cell lines engineered for identifying components of the IL-4 pathway; and

WHEREAS, Pfizer has the capability to undertake research for the discovery and evaluation of biosynthetic, biochemical and organic matter for treatment of disease and also the capability for clinical analysis, manufacturing and marketing with respect to a wide variety of drugs for medicinal use in human and animal health; and

WHEREAS, the Parties plan to seek patent protection for biological elements that regulate IgE synthesis which will serve as molecular targets for compounds from Pfizer's chemical library and patent protection for Licensed Products which make up the subject matter of this Agreement;

NOW, THEREFORE, the Parties agree as follows:

1. DEFINITIONS

Whenever used in this Agreement, the terms defined in this Section 1 shall have the meanings specified.

1.1 "AFFILIATE" means (a) any corporation or other legal entity owning, directly or indirectly, fifty percent (50%) or more of the voting capital shares or similar voting securities of a Party; (b) any corporation or other legal entity fifty percent (50%) or more of the voting capital shares or similar voting rights of which is owned, directly or indirectly, by a Party; or (c) any corporation or other legal entity fifty percent (50%) or more of the voting capital shares or similar voting rights of which is owned, directly or indirectly, by a corporation or other legal entity which owns, directly or indirectly, fifty percent (50%) or more of the voting capital shares or similar voting securities of such Party.

1.2 "ANIMAL HEALTH PRODUCT" shall mean any Licensed Product intended for animal patients.

1.3 "AREA" means research directed to the discovery of cDNA, peptides or proteins within the IL-4 signaling pathway that selectively regulate IgE synthesis further described in the Research Plan.

1.4 "DISCOVERY MILESTONE" shall have the meaning given to that term in Section 3.3.

1.5 "EFFECTIVE DATE" is January 31, 1999.

1.6 "HIGH THROUGHPUT SCREEN" or "HTS" means a primary assay performed by or under the direction of Pfizer that incorporates a Molecular Target for the purpose of identifying potential Licensed Products.

1.7 "HUMAN HEALTH PRODUCT" shall mean any Licensed Product intended for human patients.

1.8 "LICENSED PRODUCT" means any chemical or biological entity that (a) directly, selectively and specifically modulates the activity of a Molecular Target; (b) was identified by Pfizer in HTS; (c) is to be used for the management of any disease or any therapeutic indication in human or animal patients; and (d) the manufacture, use or sale of which would infringe Valid Claims.

1.9 "MOLECULAR TARGET" shall mean any cDNA, peptide or protein

identified in the Research Program.

1.10 "NET SALES" means the gross amount invoiced by Pfizer, its Affiliates, or any sublicensee of Pfizer for sales to a third party or third parties of Licensed Products, less normal and customary trade discounts actually allowed, rebates, returns, credits, taxes the legal incidence of which is on the purchaser and separately shown on Pfizer's or any sublicensee of Pfizer's invoices and transportation, insurance and postage charges, if prepaid by Pfizer or any sublicensee of Pfizer and billed on Pfizer's or any sublicensee of Pfizer's invoices as a separate item.

1.11 "PRODUCT PATENT RIGHTS" shall mean all the Valid Claims covering Licensed Products, whether domestic or foreign, including all continuations, continuations-in-part, divisions, and renewals, all letters patent granted thereon, and all reissues, re-examinations and extensions thereof.

1.12 "PFIZER COMPOUND LIBRARY" means those Pfizer compounds which it may use for HTS.

1.13 "PFIZER CONFIDENTIAL INFORMATION" means all information about any element of Pfizer Technology or Program Technology, except for Program Technology assigned to Rigel pursuant to Section 5.1, which is disclosed by Pfizer to Rigel and designated "Confidential" in writing by Pfizer at the time of disclosure or within thirty (30) days following disclosure to Rigel to the extent that such information as of the date of disclosure to Rigel is not (i) demonstrably known to Rigel other than by virtue of a prior confidential disclosure to Rigel by Pfizer; (ii) disclosed in published literature, or otherwise generally known to the public through no fault or omission of Rigel; or (iii) obtained from a third party free from any obligation of confidentiality to Pfizer prior to disclosure to Rigel by Pfizer.

1.14 "PFIZER TECHNOLOGY" means Technology that is or was developed by employees of or consultants to Pfizer alone or jointly with third parties prior to the Effective Date, but, in the case of consultants or third parties, only to the extent Pfizer has the right to grant rights to such Technology.

1.15 "PROGRAM INVENTIONS" shall have the meaning given to it in Section 5.1.

1.16 "PROGRAM TECHNOLOGY" means Technology within the Area that is or was developed by employees of or consultants to Pfizer or Rigel solely or jointly with each other in the course of performing the Research Program; PROVIDED, HOWEVER, that Rigel's peptide library, Phoenix cell line and Felix cell line shall not be Program Technology and are owned by or exclusively licensed to Rigel and deemed to be Rigel Technology and that the Pfizer Compound Library shall not be Program Technology and is owned by or exclusively licensed and deemed to be Pfizer Technology.

1.17 "RECOMMENDED FOR DEVELOPMENT NOTICE" or "RFD" shall have the meaning provided in the Research Plan.

1.18 "RESEARCH COMMITTEE" shall have the meaning given to that term in Section 2.5.1.

1.19 "RESEARCH PERIOD" means the period beginning on the Effective Date and ending on the date the Research Program terminates as provided in Section 8.1.

1.20 "RESEARCH PLAN" means the written plan describing the research and development to be carried out by Rigel and Pfizer pursuant to this Agreement, as amended from time to time. The initial Research Plan is appended to this Agreement as Exhibit B.

1.21 "RESEARCH PROGRAM" is the collaborative research program in the Area conducted by Pfizer and Rigel pursuant to the Research Plan.

1.22 "RIGEL CONFIDENTIAL INFORMATION" means all information about any element of the Rigel Technology or Program Technology, except for Program Technology assigned to Pfizer pursuant to Section 5.1, which is disclosed by Rigel to Pfizer and designated "Confidential" in writing by Rigel at the time of disclosure or within thirty (30) days following disclosure to Pfizer to the extent that such information as of the date of disclosure to Pfizer is not (i) demonstrably known to Pfizer other than by virtue of a prior confidential disclosure to Pfizer

by Rigel; (ii) disclosed in published literature, or otherwise generally known to the public through no fault or omission of Pfizer; or (iii) obtained from a third party free from any obligation of confidentiality to Rigel prior to disclosure to Pfizer by Rigel.

1.23 "RIGEL PATENT RIGHTS" shall mean the Valid Claims in Rigel's patents and patent applications, listed in Exhibit A, any patents granted thereon, including any divisions, continuations, continuations-in-part, renewals, extensions, reexaminations, reissues or foreign counterparts thereof.

1.24 "RIGEL TECHNOLOGY" means Technology that is or was developed by employees of or consultants to Rigel alone or jointly with, or licensed to Rigel from, third parties prior to the Effective Date, but, in the case of consultants or third parties, only to the extent Rigel has the right to grant rights to such Technology.

1.25 "TARGET PATENT RIGHTS" shall have the meaning given to it in Section 6.1.1.

1.26 "TECHNOLOGY" means and includes all unpatented materials, technology, technical information, know-how, expertise and trade secrets.

1.27 "VALID CLAIM" means a claim within a patent or patent application so long as such claim shall not have been disclaimed by the Parties or shall not have been held invalid in a final decision rendered by a tribunal of competent jurisdiction from which no appeal has been or can be taken.

2. COLLABORATIVE RESEARCH PROGRAM

2.1 PURPOSE. Rigel and Pfizer shall conduct the Research Program throughout the Research Period. The objective of the Research Program is to discover Molecular Targets and to discover and develop Licensed Products.

2.2 AMENDMENT TO RESEARCH PLAN. The Research Plan may be amended from time to time by unanimous agreement of the Research Committee. Exhibit B shall be revised as necessary to reflect each such amendment.

2.3 CONTINGENT LICENSE. If during the Research Period Rigel ceases to do business or is unable to perform its duties and obligations as set forth in the Research Plan, whether due to insolvency, bankruptcy or any other reason, Pfizer shall have a non-exclusive license in the Area under the Rigel Technology and under Rigel Patent Rights to carry out and complete the Research Plan.

2.4 EXCLUSIVITY. Rigel agrees, during the Research Period, not to conduct research itself or sponsor any other research, or engage in any research sponsored with any third party in the Area except pursuant to the Research Program.

2.5 RESEARCH COMMITTEE.

2.5.1 PURPOSE. Pfizer and Rigel shall establish a Research Committee (the "Research Committee"):

(a) to review and evaluate progress of the Research Program throughout the Research Period under the Research Plan;

(b) to prepare any amendments to the Research Plans;

(c) to coordinate and monitor publication of research results obtained from and the exchange of information and materials that relate to the Research Program (This function will survive the termination of Research Period for a period of three (3) years).

2.5.2 Membership. Within ten (10) days of the Effective Date each Party shall appoint, in its sole discretion, four (4) members to the Research Committee. Substitutes may be appointed at any time. The members initially shall be:

Pfizer Appointees:	Rigel Appointees:
1. Dr. Scott Kennedy	1. Dr. Donald Payan
2. Dr. Edward D. Pagani	2. Dr. David Ferrick
3. Dr. Phil Vickers	3. Dr. Jeremy Caldwell
4. Dr. John Watson	4. To be determined.

2.5.3 Co-Chairs. The Research Committee shall be chaired by two (2) chairpersons, one appointed by Rigel and the other by Pfizer. The Co-Chairs will have the responsibility to ensure that a Research Committee meeting agenda is distributed to the Research Committee prior to the meeting.

2.5.4 Meetings. The Research Committee shall meet in person at least quarterly, at places and on dates suggested by Pfizer and by Rigel in turn. The location of the first meeting of the Research Committee shall be at Pfizer's election. Representatives of Pfizer or Rigel or both, in addition to members of the Research Committee, may attend such meetings at the invitation of either Party.

2.5.5 Minutes. The Research Committee shall keep accurate minutes of its deliberations which record all proposed decisions and all actions recommended or taken. Drafts of the minutes shall be delivered to all Research Committee members within fifteen (15) business days after each meeting. The Party choosing the location of the meeting shall be responsible for the preparation and circulation of the draft minutes. Draft minutes shall be edited by the co-chairpersons and shall be issued in final form only with their approval and agreement.

2.5.6 Decisions. All decisions of the Research Committee shall be by the unanimous vote of its members.

2.5.7 Expenses. Pfizer and Rigel shall each bear all expenses, including reasonable travel, related to the participation of their designated members of the Research Committee, respectively.

2.6 REPORTS AND MATERIALS.

2.6.1 Reports. Pfizer and Rigel each shall furnish to the Research Committee:

(a) summary written reports within fifteen (15) days after the end of each three (3) month period during the Research Period, describing its progress under the Research Plan; and

(b) a comprehensive written report within thirty (30) days after the end of the Research Period, describing in detail the work accomplished by it under the Research Plan during and discussing and evaluating the results of such work.

2.6.2 Materials. Rigel shall provide the following Program Technology to Pfizer:

(a) all Molecular Targets identified in the course of the Research Program;

(b) all other Program Technology, including biological materials, which is: specific to a Molecular Target which has been delivered to Pfizer by Rigel pursuant to Section 2.6.2(a); necessary for Pfizer to perform its obligations under the Research Program; or necessary for Pfizer to perform HTS with delivered Molecular Targets;

PROVIDED, HOWEVER, that such Program Technology will not include the transfer of any portion of Rigel's peptide libraries or Rigel Technology to Pfizer or the transfer of the Pfizer compound library or any portion of it to Rigel. Rigel agrees to supply reasonable quantities of Molecular Targets and biological materials specific to such Molecular Targets to Pfizer for the performance of the Research Program; and Pfizer agrees to supply reasonable quantities of Molecular Targets to perform HTS; PROVIDED, HOWEVER, that if either Party needs quantities of such materials which quantities are larger than would otherwise be anticipated by the supplying Party, the Parties will meet and discuss in good faith appropriate compensation to the supplying Party for such supply.

2.6.3 Pfizer's Selection of Molecular Targets. Pfizer may, in its sole, unfettered discretion, select for HTS during the Research Program and the three (3) year period immediately following the Research Period, any Molecular Target identified in the Research Program. To prevent the reversion of a Molecular Target to Rigel pursuant to Section 2.6.5, Pfizer

must commence HTS on a Molecular Target within a period of two (2) years after its selection of such Molecular Target for HTS.

2.6.4 Exclusivity of Molecular Targets. Molecular Targets for which Pfizer has initiated HTS shall be exclusive to Pfizer and shall not be conveyed to a third party in any manner by Rigel.

2.6.5 Reversion to Rigel. The following shall become Rigel Technology, and Rigel shall have no obligations to Pfizer with respect to: Molecular Targets which are not selected pursuant to Section 2.6.3; and any Molecular Target for which Pfizer has failed to satisfy the due diligence obligations set forth in Section 2.6.3; PROVIDED, HOWEVER, that no Molecular Target for which Pfizer has initiated HTS shall revert to Rigel.

2.7 LABORATORY FACILITIES AND PERSONNEL. Pfizer and Rigel shall provide suitable laboratory facilities, equipment and personnel for the work to be done under the Research Program.

2.8 DILIGENT EFFORTS. Rigel and Pfizer each shall use reasonably diligent efforts to achieve the objectives of the Research Program.

2.9 KEY INVESTIGATOR. If during the Research Period Dr. Donald Payan's association with Rigel, in the capacity as chief scientific officer or a similar role ends for any reason and the Parties are unable to agree on a successor acceptable to Pfizer, in its sole and unfettered discretion, within one hundred eighty (180) days of his dissociation, Pfizer may terminate this Agreement pursuant to Section 8.3.1.

3. PAYMENTS.

3.1 RESEARCH PROGRAM FUNDING.

3.1.1 Pfizer will fund the research to be performed by Rigel, pursuant to the Agreement, according to the following schedule:

COMMITMENT YEAR	ANNUAL COMMITMENT
1	$2,350,000.00
2	$2,350,000.00

The funding payments of two million three hundred and fifty thousand dollars ($2,350,000.00) shall support the work of the equivalent of ten (10) full time employees ("FTEs") of Rigel.

3.1.2 All funding payments shall be made quarterly in advance for work scheduled to be performed by Rigel during any three (3) month period, against Rigel's invoice for the FTEs allocated to the Research Program for such three (3) month period. Adjustments as necessary to reflect the work actually performed by Rigel shall be made at the end of each three (3) month period and shall be reflected in Rigel's invoice for the next three (3) month period. It is understood that all payments pursuant to this Section are non-creditable and non-refundable. Rigel shall also furnish to Pfizer the name and percent effort of each Rigel employee assigned to perform the Research Plan during each three (3) month period.

3.1.3 The amount of the funding payment for each quarter shall be based on the work in progress pursuant to the applicable Research Plan and the associated annual budget for Research Program personnel (FTEs); provided, however, that the aggregate amount of funding payments made in any commitment year shall not exceed the annual commitment for such commitment year.

3.1.4 Rigel shall keep for three (3) years from the conclusion of the Research Period complete and accurate records of its expenditures of payments received by it pursuant to

this Research Agreement. The records shall conform to generally accepted accounting practices (GAAP) as applied to similar companies similarly situated. Pfizer shall have the right at its own expense during the Research Period and during the subsequent three-year period to appoint an independent

certified public accountant reasonably acceptable to Rigel to inspect said records to verify the accuracy of the FTE allocation, pursuant to the Research Plan. Upon reasonable notice by Pfizer, Rigel shall make its records available for inspection by the independent certified public accountant during regular business hours at the place or places where such records are customarily kept, to verify the accuracy of the FTE allocation. This right of inspection shall not be exercised more than once in any calendar year and not more than once with respect to records covering any specific period of time. All information concerning such expenditures, and all information learned in the course of any audit or inspection, shall be deemed to be Rigel's Confidential Information. The failure of Pfizer to request verification of any expenditures before or during the three-year period shall be considered acceptance by Pfizer of the accuracy of such FTE allocation, and Rigel shall have no obligation to maintain any records pertaining to such report or statement beyond such three year period. The results of such inspection, if any, shall be binding on the parties.

3.1.5 If Pfizer, in its sole, unfettered discretion, extends the Research Program for a third year as set forth in Section 8.4, Pfizer shall pay Rigel two million five hundred thousand dollars ($2,500,000.00) with respect to the extension period on the same terms and conditions set forth in this Section 3. The funding payments shall support the work of ten (10) Rigel FTEs.

3.2 INITIAL PAYMENT. Within fifteen (15) days of the execution of this Agreement, Pfizer will pay to Rigel a one time, non refundable, noncreditable payment of two million dollars ($2,000,000.00).

3.3 DISCOVERY MILESTONE PAYMENTS. Within sixty (60) days after Rigel's delivery to Pfizer of Molecular Targets meeting the D3/D4 criteria set forth in Exhibit B and within thirty (30) days after Pfizer's selection, in its sole, unfettered discretion, of a Molecular Target for HTS ("Discovery Milestones"), as the case may be, Pfizer shall pay Rigel according to the following schedule:

DISCOVERY STAGE	DELIVERABLE	MILESTONE PAYMENT
D3	Molecular Targets No. 1-3	$75,000.00 each
D3	Molecular Targets No. 4-6	$100,000.00 each
D3	Molecular Targets No. 7+	$150,000.00 each
D4a/D4b	Molecular Targets No.1-3	$150,000.00 each
D4a/D4b	Molecular Targets No.4-6	$200,000.00 each
D4a/D4b	Molecular Targets No.7+	$250,000.00 each
HTS	Molecular Target No.1	$200,000.00

HTS	Molecular Target No.2	$250,000.00
HTS	Molecular Target No.3	$300,000.00
HTS	Molecular Target No.4	$350,000.00
HTS	Molecular Target No.5	$400,000.00
HTS	Molecular Target No.6	$450,000.00
HTS	Molecular Target No.7+	No Additional Payments

3.4 DISCOVERY MILESTONE PAYMENT CHARACTERISTICS. Discovery Milestone payments are in addition to the other payments in this Section 3 and are noncreditable and non-refundable. If Pfizer in its sole, unfettered discretion, selects a Molecular Target for HTS which does not meet the criteria for D3 or D4, such Molecular Target shall be deemed to have met both D3 and D4 criteria for the purposes of the payment for Discovery Milestones to Rigel under Section 3.3.

3.5 LIMITATION OF DISCOVERY MILESTONE PAYMENTS. Irrespective of the number of Molecular Targets meeting the criteria or the number of Molecular Targets selected by Pfizer for HTS, the aggregate amount which Pfizer shall pay to Rigel for Discovery Milestones shall not exceed (a) one million three hundred fifty thousand dollars ($1,350,000.00) in the case of Molecular Targets meeting the D3 criteria; (b) one million eight hundred thousand dollars ($1,800,000.00) in the case of Molecular Targets which meet the

D4a/D4b criteria; and (c) one million nine hundred fifty thousand dollars ($1,950,000.00) in the case of Molecular Targets selected for HTS in Pfizer's sole, unfettered discretion.

3.6 RECOMMENDED FOR DEVELOPMENT. Pfizer will pay to Rigel the sum of five hundred thousand dollars ($500,000.00) each time Pfizer issues a Recommended for Development Notice for a Human Health Product and a sum of two hundred fifty thousand dollars ($250,000.00) each time Pfizer issues a RFD notice for a Animal Health Product; PROVIDED, HOWEVER, that such payment will be made only once for each compound identified in a specific Pfizer HTS for a specific indication and will not include back-up compounds identified in the same HTS for the same indication. These payments are noncreditable and non-refundable, and shall be paid to Rigel within thirty (30) days of Pfizer's issuance of the applicable RFD notice.

3.7 ROYALTIES ON NET SALES OF LICENSED PRODUCTS.

3.7.1 Pfizer shall pay Rigel a royalty based on the Net Sales of each Licensed Product. Such royalty shall be paid with respect to each country of the world from the date of the first commercial sale (the date of the invoice of Pfizer or any sublicensee of Pfizer with respect to such sale) of such Licensed Product in each such country until the expiration of the last Product Patent Right to expire with respect to each such country and each such Licensed Product. If the manufacture and sale of a Licensed Product takes place in countries where there are no Product Patent Rights, Pfizer will pay to Rigel a royalty based on the Net Sales of each Licensed Product in each such country for ten (10) years after the first commercial sale of such Licensed Product in such country.

3.7.2 Unpatented Products. Pfizer will commercialize only those products derived or resulting from HTS which are covered by Product Patent Rights. If, in the unlikely

event, Pfizer determines in its absolute, unfettered discretion to commercialize an unpatented product, it will meet with Rigel to discuss additional compensation, if any, to Rigel, for use of the Molecular Target on the basis of which Pfizer conducted HTS to identify such product given Pfizer's advancement and commercialization of an unpatented product will have involved extraordinary development costs to Pfizer.

3.8 ROYALTY RATES. The royalty paid each year shall be based on increments of world-wide Net Sales with respect to each of the Licensed Products according to the following schedule:

<TABLE>
<CAPTION>

	HUMAN HEALTH PRODUCT	ANIMAL HEALTH PRODUCT
Annual Net Sales (Dollars)	Royalty Rate	Royalty Rate
<S>	<C>	<C>
$0-$500MM	2%	1%
> $500MM < $750MM	--	2%
> $500MM < 1B	3%	--
> = $750MM	--	3%
> = $1B	4%	--

</TABLE>

3.9 PAYMENT DATES FOR ROYALTIES. Royalties shall be paid by Pfizer on Net Sales within sixty (60) days after the end of each calendar quarter in which such Net Sales are made. Such payments shall be accompanied by a statement showing the Net Sales of each Licensed Product by Pfizer or any sublicensee of Pfizer in each country, the applicable royalty rate for such Licensed Product, and a calculation of the amount of royalty due, including any offsets.

3.10 ACCOUNTING FOR ROYALTIES. The Net Sales used for computing the royalties payable to Rigel by Pfizer shall be computed in U.S. dollars, and royalties shall be paid in U.S. dollars by wire transfer in immediately available funds to a U.S. account designated by Rigel, or by other mutually acceptable means. For purposes of determining the amount of royalties due, the

amount of Net Sales in any foreign currency shall be computed by (a) converting such amount into U.S. dollars at the prevailing commercial rate of exchange for purchasing dollars with such foreign currency as published in the Wall Street Journal for the close of the last business day of the calendar quarter for which the relevant royalty payment is to be made by Pfizer; and (b) deducting the amount of any governmental tax, duty, charge, or other fee actually paid in respect of such conversion into, and remittance of U.S. dollars.

3.11 RECORDS FOR ROYALTIES. Pfizer shall keep for three (3) years from the date of each payment of royalties complete and accurate records of sales by Pfizer, its Affiliates or sublicensees of each Licensed Product in sufficient detail to allow the accruing royalties to be determined accurately. Rigel shall have the right for a period of three (3) years after receiving any report or statement with respect to royalties due and payable to appoint at its expense (except as otherwise provided in this Section 3.11), an independent certified public accountant reasonably acceptable to Pfizer to inspect the relevant records of Pfizer, its Affiliates or

sublicensees to verify such report or statement. Pfizer, its Affiliates or sublicensees shall make its records available for inspection by such independent certified public accountant during regular business hours at such place or places where such records are customarily kept, upon reasonable notice from Rigel, to verify the accuracy of the reports and payments. Such inspection right shall not be exercised more than once in any calendar year nor more than once with respect to sales in any given period. Rigel agrees to hold in strict confidence all information concerning royalty payments and reports, and all information learned in the course of any audit or inspection, except to the extent necessary for Rigel to reveal such information in order to enforce its rights under this Agreement or if disclosure is required by law. The failure of Rigel to request verification of any report or statement during said three (3) year period shall be considered acceptance of the accuracy of such report, and Pfizer shall have no obligation to maintain records pertaining to such report or statement beyond said three (3) year period. The findings of each inspection, if any, shall be binding on both Parties.

3.12 MILESTONE PAYMENTS FOR LICENSED PRODUCTS. Pfizer shall pay Rigel, within sixty (60) days of the completion of each event set forth below ("Event"), the payment listed opposite that Event. Payments shall be made in U.S. dollars by wire transfer in immediately available funds to a U.S. bank account designated by Rigel, or other mutually acceptable means. Pfizer shall be obligated to make each payment only once with respect to each Licensed Product affected by an Event and such payment for such Event shall not be due with respect to any subsequent Licensed Product directed to a Molecular Target and indication which has previously been the subject of the same Event. With the exception of any such milestone paid to Rigel for the occurrence of the earlier of Submission of IND or initiation of human (Section 3.12.1(i)) or animal (Section 3.12.2(i)) clinical trials, payments made by Pfizer pursuant to this Section 3.12 with respect to a Licensed Product shall be credited against sums due to Rigel pursuant to Section 3.8 of this Agreement with respect to Net Sales of such Licensed Product. Fifty percent (50%) of the milestone payment paid to Rigel for commencement of Phase III human clinical trials (Section 3.12.1(ii)) and submission of NADA for animal use (Section 3.12.2 (ii)) shall be credited against royalty payments and one hundred percent (100%) of milestone payments paid to Rigel for NDA/PLA filing for human use (Section 3.12.1 (iii)) and for NADA/PLA approval in any country for animal use (Section 3.12.2 (iii)); PROVIDED, HOWEVER, that the sums due pursuant to Section 3.8 in any calendar year with respect to such Licensed Product shall not be reduced by virtue of this credit by more than fifty percent (50%):

3.12.1 HUMAN HEALTH PRODUCT

<TABLE>
<CAPTION>

EVENT	AMOUNT (DOLLARS)
<S>	<C>
(i) Submission of INDA or initiation of human clinical testing in any country (whichever occurs first)	$1,000,000.00
(ii) Commencement of Phase III human clinical trials in any country	$2,000,000.00
(iii) NDA/PLA Filing in any country for human use	$4,000,000.00

</TABLE>

3.12.2 ANIMAL HEALTH PRODUCT

<TABLE>
<CAPTION>

EVENT	AMOUNT (DOLLARS)
<S>	<C>
(i) Submission of INAD or initiation of animal clinical testing in any country (whichever occurs first)	$ 500,000.00
(ii) Submission of NADA in any country for animal use	$1,000,000.00
(iii) NADA/PLA Approval in any country for animal use	$2,000,000.00

</TABLE>

For the purposes of the foregoing, "IND" "INAD" or "INDA" shall mean an Investigational New Drug Application filed with the U.S. Food and Drug Administration (FDA), or a similar filing made with a counterpart health regulatory authority in another country; "NDA/PLA" or "NADA/PLA" shall mean a New Drug Application, Product License Application, or other application for authority to market a Licensed Product filed with the U.S. FDA or a counterpart health regulatory agency in another country.

3.13 U.S. FUNDS. Each payment pursuant to this Agreement shall be paid by Pfizer in U.S. currency by wire transfer in immediately available funds to an account designated by Rigel, or by other mutually acceptable means. If a payment due date is not otherwise specified in this Agreement, payment shall be made within thirty (30) days after receipt and acceptance by Pfizer of the invoice from Rigel.

4. TREATMENT OF CONFIDENTIAL INFORMATION

4.1 CONFIDENTIALITY

4.1.1 Pfizer and Rigel each recognize that the other's Confidential Information constitutes highly valuable, confidential information. Subject to the terms and conditions of the Agreement, Pfizer and Rigel each agree that during the Research Period and for five (5) years thereafter, it will keep confidential, and will cause its Affiliates to keep confidential, all Rigel Confidential Information or Pfizer Confidential Information, as the case may be, that is disclosed to it, or to any of its Affiliates pursuant to this Agreement. Neither Pfizer nor Rigel nor any of their respective Affiliates shall use such Confidential Information except as expressly permitted in this Agreement.

4.1.2 Pfizer and Rigel each agree that any disclosure of the other's Confidential Information to any officer, employee or agent of the other Party or of any of its Affiliates shall be made only if and to the extent necessary to carry out its responsibilities under this Agreement and shall be limited to the maximum extent possible consistent with such responsibilities. Pfizer and Rigel each agree not to disclose the other's Confidential Information to any third parties under any circumstance without written permission from the other Party. Each Party shall take such action, and shall cause its Affiliates to take such action, to preserve the confidentiality of each other's Confidential Information as it would customarily take to preserve the confidentiality of its own similar Confidential Information. Each Party, upon the other's request, will return all

the Confidential Information disclosed to the other Party pursuant to this Agreement, including all copies and extracts of documents, within sixty (60) days of the request upon the termination of this Agreement except for one (1) copy which may be kept for the purpose of complying with continuing obligations under this Agreement.

4.1.3 Rigel and Pfizer each represent that all of its employees, Affiliates and any consultants to such Party, participating in the Research Program who shall have access to Pfizer Technology, Rigel Technology or Program Technology and Pfizer Confidential Information and Rigel Confidential Information are bound by agreement to maintain such information in confidence with the same degree of care each Party holds it own confidential information.

4.2 PUBLICATION. Notwithstanding any matter set forth with particularity in this Agreement to the contrary, results obtained in the course of the Research Program may be submitted for publication following scientific review by the Research Committee and subsequent approval by Rigel's and Pfizer's

managements, which approval shall not be unreasonably withheld. After receipt of the proposed publication by both Pfizer's and Rigel's managements, written approval or disapproval shall be provided within thirty (30) days for a manuscript, within fourteen (14) days for an abstract for presentation at, or inclusion in the proceedings of a scientific meeting, and within fourteen (14) days for a transcript of an oral presentation to be given at a scientific meeting.

4.3 PUBLICITY. Except as required by law, and except for approved press releases which may be issued by each Party upon the signing of this Agreement, neither Party may disclose the terms of this Agreement without the prior written consent of the other Party; PROVIDED, HOWEVER, that Rigel may disclose the terms, or provide copies, of this Agreement as necessary in the normal course of business to bankers, investors and others bound by obligations of confidentiality not to disclose such information to other third parties in order to obtain financing.

4.4 PERMITTED DISCLOSURE.

4.4.1 If either Party is requested to disclose the Confidential Information in connection with a legal or administrative proceeding or is otherwise required by law to disclose the Confidential Information, such Party will give the other Party prompt notice of such request. The disclosing Party may seek an appropriate protective order or other remedy or waive compliance with the provisions of this Agreement. If such Party seeks a protective order or other remedy, the other Party will cooperate. If such Party fails to obtain a protective order or waive compliance with the relevant provisions of this Agreement, the other Party will disclose only that portion of Confidential Information which its legal counsel determines it is required to disclose.

4.4.2 Disclosure of Inventions. Each Party shall promptly inform the other about all inventions in the Area that are conceived, made or developed in the course of carrying out the Research Program by employees of, or consultants to, either of them solely, or jointly with employees of, or consultants to the other.

5. INTELLECTUAL PROPERTY RIGHTS.

5.1 OWNERSHIP. All Rigel Confidential Information, Rigel Technology and Rigel Patent Rights shall be owned by Rigel. All Pfizer Confidential Information, Pfizer Technology and Pfizer Patent Rights shall be owned by Pfizer. Program Technology (including, without limitation, any patentable invention or discovery) acquired, developed or made solely or jointly by employees or agents of either Party during the course of the Research Program ("Program Inventions") shall be the property of Pfizer and deemed to be Pfizer Confidential Information if it pertains to or is an improvement upon its HTS compound library or a Licensed Product and shall be the property of Rigel and deemed to be Rigel Confidential Information if it pertains to or is an improvement upon Rigel Patents, Rigel Technology or pertains to or is an improvement upon Molecular Targets which are not selected for HTS by Pfizer. Each Party shall cooperate with the other in completing any patent applications relating to Program Inventions, and in executing and delivering any instrument required to assign, convey or transfer to such other Party its interest, as provided in the preceding sentence.

5.2 GRANTS OF RESEARCH LICENSES.

5.2.1 Program License. Rigel and Pfizer each grants to the other a nonexclusive, worldwide, royalty-free license during the Research Period, including the right to grant sublicenses to Affiliates, to make and use Confidential Information, Program Technology and Product Patent Rights for the purpose of performing the Research Program; provided, however, that the other Party shall not acquire, by virtue of this Section or any other Section, any rights in the following:

(a) Rigel's peptide libraries;

(b) the Pfizer Compound Library; or

(c) any compounds active in the HTS which Pfizer chooses, in its sole, unfettered discretion, not to develop or otherwise include in Program Technology.

5.2.2 Research License.

(a) Rigel grants Pfizer an irrevocable, nonexclusive, worldwide license under its interest in Program Technology, except Rigel Core Technology, and under all intangible technology, technical information, know-how, expertise and trade secrets within Rigel Technology disclosed to Pfizer during the course of the Research Program, solely for the purpose of conducting research.

(b) Pfizer grants Rigel an irrevocable, nonexclusive, worldwide license under Pfizer's interest in all intangible technology, technical information, know-how, expertise and trade secrets within Program Technology, and under all intangible technology, technical information, know-how, expertise and trade secrets within Pfizer Technology disclosed to Rigel during the course of the Research Program, solely for the purpose of conducting research.

(c) For purposes of this Section 5.2.2, Rigel Core Technology shall mean:

(i) Rigel's peptide libraries

(ii) Rigel's Phoenix cell lines

(iii) Felix cell lines

5.3 GRANT OF COMMERCIALIZATION LICENSE, TERM, RIGHTS AND OBLIGATIONS.

5.3.1 Grant to Pfizer. Rigel hereby grants to Pfizer an exclusive, world-wide license, including the right to grant sublicenses, to research, manufacture, use, sell, offer for sale and import Licensed Products under Rigel's interest in the Product Patent Rights and the Molecular Targets.

5.3.2 Term of License. The term of the grant to Pfizer set forth in Section 5.3.1 shall begin on the Effective Date. The duration of the term of the grant shall be determined on a country-by-country basis. For any country in which there are Product Patent Rights, the term shall end on the date of the last to expire of the Product Patent Rights in such country. For all other countries, the term shall expire on the tenth (10th) anniversary of the first commercial sale of such Licensed Product in such country.

5.3.3 Paid-Up License. Upon the expiration of Pfizer's obligation to pay royalties on Net Sales of Licensed Products as provided in Section 3.7.1, the license granted in Section 5.3.1 shall become an irrevocable, nonexclusive paid-up license.

5.3.4 Pfizer Obligations.

(a) Pfizer shall use reasonably diligent efforts to exploit Licensed Products commercially employing similar effort to that applied to other products similarly situated; provided, however, Pfizer may, in its sole, unfettered judgement, discontinue the development or sale of any Licensed Product in any country in the world or all of them.

(b) If Pfizer grants a sublicense pursuant to this Section 5, Pfizer shall guarantee that any sublicensee fulfills all of Pfizer's obligations under this Agreement; PROVIDED, HOWEVER, that Pfizer shall not be relieved of its obligations pursuant to this Agreement.

5.3.5 Technical Assistance. Rigel shall provide to Pfizer or any sublicensee of Pfizer, at Pfizer's request and expense, any agreed technical assistance reasonably necessary to enable Pfizer or such sublicensee to manufacture, use, sell, offer for sale or import each Licensed Product and to enjoy fully all the rights granted to Pfizer pursuant to this License Agreement; provided, however, that Rigel is reasonably capable of providing that assistance. Pfizer shall reimburse Rigel's costs of providing such assistance.

6. PROVISIONS CONCERNING THE FILING, PROSECUTION AND MAINTENANCE OF PATENT RIGHTS.

The following provisions relate to the filing, prosecution and maintenance of patents and patent applications during the term of this Agreement:

6.1 FILING, PROSECUTION AND MAINTENANCE BY RIGEL.

6.1.1 With respect to any Rigel interest in patents and patent applications which claim a Molecular Target ("Target Patent Rights"), Rigel shall have the obligation:

(a) to file applications for letters patent on any invention included in Target Patent Rights; PROVIDED, HOWEVER, that Rigel shall consult with Pfizer regarding countries in which such patent applications should be filed and shall file patent applications in those countries where Pfizer requests that Rigel file such applications; and, further provided, that Rigel, at its option and expense, may file in countries where Pfizer does not request

that Rigel file such applications;

(b) to take all reasonable steps to prosecute all pending and new patent applications included within Target Patent Rights;

(c) to respond to oppositions, nullity actions, re-examinations, revocation actions and similar proceedings filed by third parties against the grant of letters patent for such applications;

(d) to maintain in force any letters patent included in Target Patent Rights by duly filing all necessary papers and paying any fees required by the patent laws of the particular country in which such letters patent were granted; and

(e) to cooperate fully with, and take all reasonable and necessary actions requested by, Pfizer in connection with the preparation, prosecution and maintenance of any letters patent included in Target Patent Rights.

Rigel shall notify Pfizer in a timely manner of any decision to abandon a pending patent application or an issued patent included in Target Patent Rights. Thereafter, Pfizer shall have the option, at its expense, of continuing to prosecute any such pending patent application or of keeping the issued patent in force.

6.1.2 Copies of Documents. Rigel shall provide to Pfizer copies of all patent applications that are part of Target Patent Rights prior to filing, for the purpose of obtaining substantive comment of Pfizer patent counsel. Rigel shall also provide to Pfizer copies of all documents relating to prosecution of all such patent applications in a timely manner and shall provide to Pfizer every six (6) months a report detailing their status.

6.1.3 Reimbursement of Costs for Filing Prosecuting and Maintaining Target Patent Rights. Within ninety (90) days of rendered patent services and thirty (30) days of receipt of invoices from Rigel, Pfizer shall reimburse Rigel for all the costs of writing, filing, prosecuting, responding to opposition and maintaining patent applications and patents in countries where Pfizer requests that patent applications be filed, prosecuted and maintained. Such reimbursement shall be in addition to payments described in Section 3. However, Pfizer may, upon sixty (60) days notice, request that Rigel discontinue filing or prosecution of patent applications in any country and discontinue reimbursing Rigel for the costs of filing, prosecuting, responding to opposition or maintaining such patent application or patent in any country. Rigel shall pay all costs in those countries in which Pfizer does not request that Rigel file, prosecute or maintain patent applications and patents, but in which Rigel, at its option, elects to do so.

6.1.4 Pfizer shall have the right to file on behalf of and as an agent for Rigel all applications and take all actions necessary to obtain patent extensions pursuant to 35 USC Section 156 and foreign counterparts for Target Patent Rights described in Section 6.1 licensed to Pfizer. Rigel agrees, to sign, at Pfizer's expense, such further documents and take such further actions as may be requested by Pfizer in this regard.

6.2 FILING, PROSECUTION AND MAINTENANCE BY PFIZER. With respect to Product Patent Rights claiming compounds in the Pfizer Compound Library or Licensed Products, Pfizer shall have those rights and duties ascribed to Rigel in Section 6.1, except that Pfizer will bear all related expenses.

6.3 DISCLAIMING A VALID CLAIM. Neither Party may disclaim a Valid Claim within Target Patent Rights or Product Patent Rights without the consent of the other.

6.4 ACTUAL OR THREATENED DISCLOSURE OR INFRINGEMENT. When information comes to the attention of Pfizer to the effect that any Target Patent Rights or Product Patent Rights relating to a Licensed Product have been or are threatened to be unlawfully infringed, Pfizer shall have the right at its expense to take such action as it may deem necessary to prosecute or prevent such unlawful infringement, including the right to bring or defend any suit, action or proceeding involving any such infringement. Pfizer shall notify Rigel promptly of the receipt of any such information and of the commencement of any such suit, action or proceeding. If Pfizer determines that it is necessary or desirable for Rigel to join any such suit, action or proceeding, Rigel shall, at Pfizer's expense, execute all papers and perform such other acts as may be reasonably required to permit Pfizer to commence such action, suit or proceeding in which case Pfizer shall hold Rigel free, clear and harmless from any and all costs and expenses of litigation, including attorneys fees. If Pfizer brings a suit, it shall have the right first to reimburse itself out of any sums recovered in such suit or in its settlement for all costs and expenses, including attorney's fees, related to such suit or settlement, and twenty percent (20%) of any funds that shall remain from said recovery shall be paid to Rigel and the balance of such

funds shall be retained by Pfizer. Each Party shall always have the right to be represented by counsel of its own selection and at its own expense in any suit instituted by the other for infringement under the terms of this Section. If Pfizer lacks standing and Rigel has standing to bring any such suit, action or proceeding, then Rigel shall do so at the request of Pfizer and at Pfizer's expense.

6.5 DEFENSE OF INFRINGEMENT CLAIMS. Rigel will cooperate with Pfizer at Pfizer's expense in the defense of any suit, action or proceeding against Pfizer or any sublicensee of Pfizer alleging the infringement of the intellectual property rights of a third party by reason of the use of Target Patent Rights or Product Patent Rights in the manufacture, use or sale of the Licensed Product. Pfizer shall give Rigel prompt written notice of the commencement of any such suit, action or proceeding or claim of infringement and will furnish Rigel a copy of each communication relating to the alleged infringement. Rigel shall give to Pfizer all authority (including the right to exclusive control of the defense of any such suit, action or proceeding and the exclusive right after consultation with Rigel, to compromise, litigate, settle or otherwise dispose of any such suit, action or proceeding), at Pfizer's expense, including by providing information and assistance necessary to defend or settle any such suit, action or proceeding; PROVIDED, HOWEVER, Pfizer shall obtain Rigel's prior consent to such part of any settlement which contemplates payment or other action by Rigel or has a material adverse effect on Rigel's

business. If the Parties agree that Rigel should institute or join any suit, action or proceeding pursuant to this Section, Pfizer may, at Pfizer's expense, join Rigel as a defendant if necessary or desirable, and Rigel shall execute all documents and take all other actions, including giving testimony, which may reasonably be required in connection with the prosecution of such suit, action or proceeding.

7. ACQUISITION OF RIGHTS FROM THIRD PARTIES. During the Research Period, each Party which acquires technology, patents or information in the Area from third parties during the course of the Research Program and wants to use such technology, patents or information in its performance of the Research Program shall obtain the prior written consent of the other Party, such consent not to be unreasonably withheld, prior to using such technology, patents or information in its performance of the Research Program. If the other Party gives the acquiring Party consent to use such third party technology, patents or information in the performance of the Research Program, such technology, patents or information shall be deemed either the Confidential Information or the Technology of the acquiring Party, as appropriate.

8. TERM, TERMINATION AND RENEWAL.

8.1 TERM. Unless sooner terminated or extended, the Research Period shall expire two (2) calendar years from the Effective Date. Unless sooner terminated or extended, the Agreement shall expire upon the expiration of Pfizer's financial obligations under this Agreement.

8.2 EVENTS OF TERMINATION. The following events shall constitute an event of termination ("Events of Termination"):

8.2.1 Rigel or Pfizer shall fail in any material respect to perform or observe any term, covenant or understanding contained in this Agreement, and any such failure shall remain unremedied for sixty (60) days after written notice to the failing Party; or

8.2.2 If any written representation or warranty by Rigel or Pfizer, or any of its officers, made under or in connection with this Agreement or any other contemporaneous written agreement between the Parties shall prove to have been incorrect in any material respect when made.

8.3 TERMINATION.

8.3.1 Upon the occurrence of any Event of Termination, the Party not responsible may, by written notice to the other Party, terminate this Agreement.

8.3.2 If Pfizer terminates this Agreement pursuant to Section 8.3.1, the terms and conditions of the Agreement, shall not terminate, but instead shall terminate or expire according to its terms. If Rigel terminates this Agreement pursuant to Section 8.3.1, the terms and conditions of the Agreement shall terminate immediately.

8.3.3 Termination of this Agreement for any reason, with or without cause, will not terminate the license granted pursuant to Section 5.2.2.

8.3.4 Termination of this Agreement for any reason shall be without prejudice to:

(a) the rights and obligations of the Parties in any Section which provide by its terms for performance by either Party subsequent to termination;

(b) Rigel's right to receive all royalty, milestone or other payments accrued hereunder; or

(c) any other remedies which either Party may otherwise have.

8.4 RENEWAL. Pfizer shall have the option, in its sole, unfettered discretion, of renewing the Research Program for a one (1) year extension period on the same terms and conditions set forth in this Agreement by written notice to Rigel. This option shall expire if not exercised by Pfizer at least three (3) months prior to the termination date described in Section 8.1. If Pfizer exercises this option, the Parties shall adopt an annual Research Plan during the ensuing ninety (90) day period, including a budget. All other terms and conditions of this Agreement shall otherwise remain in full force and effect except as set forth in Section 3.1.5.

9. REPRESENTATIONS AND WARRANTIES.

9.1 REPRESENTATIONS AND WARRANTIES OF BOTH PARTIES. Rigel and Pfizer each represents and warrants as follows:

9.1.1 It is a corporation duly organized, validly existing and is in good standing under the laws of the State of Delaware, is qualified to do business and is in good standing as a foreign corporation in each jurisdiction in which the conduct of its business or the ownership of its properties requires such qualification and has all requisite power and authority, corporate or otherwise, to conduct its business as now being conducted, to own, lease and operate its properties and to execute, deliver and perform this Agreement.

9.1.2 The execution, delivery and performance by it of this Agreement have been duly authorized by all necessary corporate action and do not and will not (i) require any additional consent or approval of its stockholders beyond the approvals already obtained; (ii) violate any provision of any law, rule, regulations, order, writ, judgment, injunctions, decree, determination award presently in effect having applicability to it or any provision of its certificate of incorporation or by-laws; or (iii) result in a breach of or constitute a default under any material agreement, mortgage, lease, license, permit or other instrument or obligation to which it is a Party or by which it or its properties may be bound or affected.

9.1.3 This Agreement is a legal, valid and binding obligation of it enforceable against it in accordance with its terms and conditions, except as such enforceability may be limited by applicable bankruptcy, insolvency, moratorium, reorganization or similar laws, from time to time in effect, affecting creditor's rights generally.

9.1.4 It is not under any obligation to any person, or entity, contractual or otherwise, that is conflicting or inconsistent in any respect with the terms of this Agreement or that would impede the diligent and complete fulfillment of its obligations.

9.1.5 It has good and marketable title to or valid leases or licenses for, all of its properties, rights and assets necessary for the fulfillment of its responsibilities under the Research Program, subject to no claim of any third party other than the relevant lessors or licensors.

9.2 REPRESENTATIONS AND WARRANTIES OF RIGEL.

9.2.1 LICENSES GRANTED. Rigel represents and warrants to Pfizer that it has the right to grant the licenses granted pursuant to this Agreement, and that the licenses so granted do not conflict with or violate the terms of any agreement between Rigel and any third party.

9.2.2 FINANCIAL STABILITY. Rigel represents and warrants as of the Effective Date that it has received subsequent to October 31, 1998 cash aggregating at least $7 million from equity investment and at least $3 million from license fees and research support which, together with other cash on hand and projected cash receipts, is sufficient to meet its projected cash expenses during the next following 18 months exclusive, in each case, respectively, of cash received or to be received from Pfizer and of cash Rigel is required to

expend to perform fully its obligations under the Research Program. Rigel further represents and warrants that during the Research Period it will continue to maintain sufficient financial resources to perform fully its obligations under the Research Program and will furnish to Pfizer, not earlier than January 31, 1999 or more often than annually thereafter, within sixty (60) days after receipt of Pfizer's written request therefor, reasonable evidence of sufficient financial resources to perform fully its remaining obligations under the Research Program; provided, however, the information contained in, and any information furnished pursuant to Pfizer's request under, this Section 9.2.2 is Confidential Information of Rigel and is subject to the requirements of Article 4 of this Agreement.

9.2.3 GOVERNMENTAL CONSENTS. No consent, approval, qualification, order or authorization of, or filing with, any local, state, or federal governmental authority is required on the part of Rigel in connection with Rigel's valid execution, delivery, or performance of this Agreement.

9.2.4 CAPITALIZATION AND VOTING RIGHTS. The authorized capital of Rigel consists, or will consist immediately prior to the Effective Date, of:

(a) Preferred Stock. 22,000,000 shares of Preferred Stock, par value $.001, of which 665,000 shares have been designated Series A Preferred Stock, all of which are issued and outstanding; 7,675,000 shares have been designated Series B Preferred Stock, of which 7,500,000 are issued and outstanding; 8,000,000 shares have been designated Series C Preferred Stock, of which 7,386,843 are issued and outstanding; and 5,660,000 shares of Series D Preferred Stock, of which 3,481,864 are issued and outstanding (before giving effect to any transactions with Pfizer). The rights, privileges and preferences of the Series A, Series B, Series C and Series D Preferred Stock are as stated in the restated certificate of incorporation.

(b) Common Stock. 35,000,000 shares of common stock, par value $.001 ("Common Stock"), of which 2,675,333 shares are issued and outstanding.

(c) The outstanding shares of Series A Preferred Stock, Series B Preferred Stock, Series C Preferred Stock, and Common Stock have been duly authorized and validly issued, are fully paid and nonassessable, and were issued in accordance with the registration or qualification provisions of the Securities Act and any relevant state securities laws or pursuant to valid exemptions therefrom.

(d) Except for (i) the conversion privileges of the Series A, Series B, Series C, and Series D Preferred Stock, (ii) the rights provided in paragraph 2.3 of a certain Investor Rights Agreement separately furnished to Pfizer, (iii) a warrant to purchase 175,000 shares of Series B Preferred Stock, (iv) a warrant to purchase 131,578 shares of Series C Preferred Stock, and (v) shares to be issued to Pfizer under a certain stock purchase agreement executed on even date herewith, there are not outstanding any options, warrants, rights (including conversion or preemptive rights and rights of first refusal), proxy or stockholder agreements or agreements of any kind for the purchase or acquisition from Rigel of any of its securities. In addition, Rigel has reserved 5,325,000 shares of its Common Stock for purchase upon exercise of options to be granted in the future under Rigel's 1997 Stock Option Plan (the "Option Plan"). Rigel is not a party or subject to any agreement or understanding, and, to the best of Rigel's knowledge, there is no agreement or understanding between any persons that affects or relates to the voting or giving of written consents with respect to any security or the voting by a director of Rigel.

9.2.5 SUBSIDIARIES. As of the Effective Date, Rigel does not own or control, directly or indirectly, any interest in any other corporation, partnership, limited liability company, association, or other business entity. Rigel is not a participant in any joint venture, partnership, or similar arrangement.

9.2.6 PERMITS. Rigel has all franchises, permits, licenses, and any similar authority necessary for the conduct of its business as now being conducted by it, the lack of which could materially and adversely affect the business, properties, prospects, or financial condition of Rigel, and believes it can obtain, without undue burden or expense, any similar authority for the conduct of its business as presently planned to be conducted. Rigel is not in default in any material respect under any of such franchises, permits, licenses or other similar authority.

9.2.7 COMPLIANCE WITH OTHER INSTRUMENTS. Rigel is not in violation or default in any material respect of any provision of its restated certificate of incorporation or bylaws or in any material respect of any provision of any mortgage, indenture, agreement, instrument, or contract to which it is a party or by which it is bound or, to the best of its knowledge, of any federal or

state judgment, order, writ, decree, statute, rule, regulation or restriction applicable to Rigel. The execution, delivery, and performance by Rigel of this Agreement and the consummation of the transactions contemplated hereby and thereby, will not result in any such violation or be in material conflict with or constitute, with or without the passage of time or giving of notice, either a material default under any such provision or an event that results in the creation of any material lien, charge, or encumbrance upon any assets of Rigel

or the suspension, revocation, impairment, forfeiture, or nonrenewal of any material permit, license, authorization, or approval applicable to Rigel, its business or operations, or any of its assets or properties.

9.2.8 LITIGATION. There is no action, suit, proceeding, or investigation pending or currently threatened against Rigel that questions the validity of this Agreement or the right of Rigel to enter into this Agreement, or to consummate the transactions contemplated hereby, or that might result, either individually or in the aggregate, in any material adverse change in the assets, business, properties, prospects, or financial condition of Rigel, or in any material change in the current equity ownership of Rigel. The foregoing includes, without limitation, any action, suit, proceeding, or investigation pending or currently threatened involving the prior employment of any of Rigel's employees, their use in connection with Rigel's business of any information or techniques allegedly proprietary to any of their former employers, their obligations under any agreements with prior employers, or negotiations by Rigel with potential backers of, or investors in, Rigel or its proposed business. Rigel is not a party to or, to the best of its knowledge, named in or subject to any order, writ, injunction, judgment, or decree of any court, government agency, or instrumentality. There is no action, suit, proceeding or investigation by Rigel currently pending or that Rigel currently intends to initiate.

9.2.9 DISCLOSURE. Rigel has provided Pfizer with all the information reasonably available to it without undue expense that Pfizer has requested for deciding whether to enter into this Agreement. This Agreement does not contain any untrue statement of a material fact or, to the best of Rigel's knowledge, omits to state a material fact necessary to make the statements made by Rigel herein not misleading.

9.2.10 FINANCIAL STATEMENTS. Rigel has delivered to Pfizer its unaudited balance sheet as at August 31, 1998 and unaudited statement of income and cash flows for the eight months ending August 31, 1998 (collectively, the "Financial Statements"). The Financial Statements, have been prepared in accordance with generally accepted accounting principles applied on a consistent basis throughout the periods indicated, except as disclosed therein, and present fairly the financial condition and position of Rigel as of August 31, 1998; provided, however, that the unaudited financial statements are subject to normal recurring year-end audit adjustments (which are not expected to be material), and do not contain all footnotes required under generally accepted accounting principles.

9.2.11 CHANGES. Since August 31, 1998 there has not been:

(a) any damage, destruction or loss, whether or not covered by insurance, materially and adversely affecting the business, properties, prospects, assets, liabilities or financial condition of Rigel (as such business is presently conducted and as it is presently proposed to be conducted);

(b) any waiver or compromise by Rigel of a valuable right or of a material debt owed to it;

(c) any satisfaction or discharge of any lien, claim, or encumbrance or payment of any obligation by Rigel, except in the ordinary course of business and that is not

material to the business, properties, prospects, or financial condition of Rigel (as such business is presently conducted and as it is presently proposed to be conducted);

(d) any sale, assignment, or transfer of any patents, trademarks, copyrights, trade secrets, or other intangible assets;

(e) any resignation or termination of employment of any key officer of Rigel and Rigel, to the best of its knowledge, does not know of the impending resignation or termination of employment of any such officer;

(f) any mortgage, pledge, transfer of a security interest in, or lien, created by Rigel, with respect to any of its material properties or assets, except liens for taxes not yet due or payable;

(g) any loans or guarantees made by Rigel to or for the benefit of its employees, stockholders, officers, or directors, or any members of their immediate families, other than travel advances and other advances made in the ordinary course of its business;

(h) any declaration, setting aside, or payment of any dividend or other distribution of Rigel's assets in respect of any of Rigel's capital stock, or any direct or indirect redemption, purchase, or other acquisition of any of such stock by Rigel;

(i) any material adverse change in the business, property, assets, liabilities, financial condition or results of operations of Rigel;

(j) any change (individually or in the aggregate), except in the ordinary course of business, in the contingent obligations of Rigel by way of guarantee, endorsement, indemnity, warranty or otherwise;

(k) except in the ordinary course of business, any material change in the compensation arrangement of any of Rigel's employees, officers or directors; or

(l) to the best of Rigel's knowledge, any other event or condition of any character that might materially and adversely affect the business, properties, prospects, or financial condition of Rigel (as such business is presently conducted and as it is presently proposed to be conducted).

9.2.12 PATENTS AND TRADEMARKS. To the best of its knowledge (but without having conducted any special investigation), Rigel owns or possesses sufficient legal rights to all patents, trademarks, service marks, trade names, copyrights, trade secrets, licenses, information, and proprietary rights and processes (including technology currently licensed from Stanford University) necessary for its business as now conducted and as proposed to be conducted without any conflict with, or infringement of the rights of, others. Rigel currently licenses certain technology from Stanford University (the "Licensed Technology") on an "as is" basis, with no representation or warranty from Stanford University that such technology does not infringe the proprietary rights of others. To Rigel's knowledge, Rigel has not, as of the date hereof, received any claims from any third party alleging that the use of the Licensed Technology infringes the

proprietary rights of such party. Except for agreements with its own employees or consultants and standard end-user license agreements, there are no outstanding options, licenses, or agreements of any kind relating to the foregoing, nor is Rigel bound by or a party to any options, licenses, or agreements of any kind with respect to the patents, trademarks, service marks, trade names, copyrights, trade secrets, licenses, information, and proprietary rights and processes of any other person or entity, other than the license agreements with Janssen Pharmaceutica N.V., Stanford University, SUNY, and BASF. Rigel has not received any communications alleging that Rigel has violated or, by conducting its business as proposed, would violate any of the patents, trademarks, service marks, trade names, copyrights, trade secrets, or other proprietary rights or processes of any other person or entity. Rigel is not aware that any of its employees is obligated under any contract (including licenses, covenants, or commitments of any nature) or other agreement, or subject to any judgment, decree, or order of any court or administrative agency, that would interfere with the use of such employee's best efforts to promote the interests of Rigel or that would conflict with Rigel's business as proposed to be conducted. Neither the execution nor delivery of this Agreement, nor the carrying on of Rigel's business by the employees of Rigel, nor the conduct of Rigel's business as proposed, will, to the best of Rigel's knowledge, conflict with or result in a breach of the terms, conditions, or provisions of, or constitute a default under, any contract, covenant, or instrument under which any of such employees is now obligated. Rigel is not aware of any violation by a third party of any of Rigel's patents, licenses, trademarks, service marks, tradenames, copyrights, trade secrets or other proprietary rights.

9.2.13 EMPLOYEES; EMPLOYEE COMPENSATION. There is no strike, labor dispute or union organization activities pending or, to the best of Rigel's knowledge, threatened between it and its employees. None of Rigel's employees belongs to any union or collective bargaining unit. To the best of its knowledge, Rigel has complied in all material respects with all applicable state and federal equal opportunity and other laws related to employment. To the best of Rigel's knowledge, no employee of Rigel is or will be in violation of any judgment, decree, or order, or any term of any employment contract, patent disclosure agreement, or other contract or agreement relating to the

relationship of any such employee with Rigel, or any other party because of the nature of the business conducted or presently proposed to be conducted by Rigel or to the use by the employee of his or her best efforts with respect to such business. Rigel is not a party to or bound by any currently effective employment contract, deferred compensation agreement, bonus plan, incentive plan, profit sharing plan, retirement agreement, or other employee compensation agreement, except as entered into in the ordinary course of business. Rigel is not aware that any officer or key employee, or that any group of key employees, intends to terminate their employment with Rigel, nor does Rigel have a present intention to terminate the employment of any of the foregoing. Subject to general principles related to wrongful termination of employees, the employment of each officer and employee of Rigel is terminable at the will of Rigel.

9.2.14 PROPRIETARY INFORMATION AND INVENTIONS AGREEMENTS. Each employee and officer of Rigel has executed a Proprietary Information and Inventions Agreement. Each consultant to Rigel has executed a Consulting Agreement containing confidentiality and assignment of inventions provisions similar to those included in the Proprietary Information and Inventions Agreement.

9.2.15 TAX RETURNS, PAYMENTS, AND ELECTIONS. Rigel has timely filed all tax returns and reports (federal, state and local) as required by law. These returns and reports are true and correct in all material respects. Rigel has paid all taxes and other assessments due, except those contested by it in good faith. Rigel has not elected pursuant to the Internal Revenue Code of 1986, as amended ("Code"), to be treated as an S corporation or a collapsible corporation pursuant to Section 1362(a) or Section 341(f) of the Code, nor has it made any other elections pursuant to the Code (other than elections that relate solely to methods of accounting, depreciation, or amortization) that would have a material effect on the business, properties, prospects, or financial condition of Rigel. Rigel has never had any tax deficiency proposed or assessed against it and has not executed any waiver of any statute of limitations on the assessment or collection of any tax or governmental charge. None of Rigel's federal income tax returns and none of its state income or franchise tax or sales or use tax returns has ever been audited by governmental authorities.

9.2.16 INSURANCE. Rigel has in full force and effect fire and casualty insurance policies, with extended coverage, in amounts customary for companies similarly situated to Rigel.

9.2.17 ENVIRONMENTAL AND SAFETY LAWS. Rigel is not in violation of any applicable statute, law, or regulation relating to the environment or occupational health and safety, and to the best of its knowledge, no material expenditures are or will be required in order to comply with any such existing statute, law, or regulation.

9.2.18 REAL PROPERTY HOLDING CORPORATION. Rigel is not a real property holding corporation within the meaning of Code section 897(c)(2) and any regulations promulgated thereunder.

9.2.19 FDA APPROVAL. The U.S. Food and Drug Administration has not delivered a letter of nonapproval, nor threatened to deliver such a letter, with respect to any product manufactured, marketed, licensed or developed by Rigel, or any product which Rigel intends to manufacture, market, license or develop.

9.2.20 INVESTMENT COMPANY ACT. Rigel is not an "investment company", or a company "controlled" by an "investment company", within the meaning of the Investment Company Act of 1940, as amended.

10. COVENANTS OF RIGEL AND PFIZER OTHER THAN REPORTING REQUIREMENTS.

Throughout the term of the Agreement, Rigel and Pfizer each shall:

10.1 maintain and preserve its corporate existence, rights, franchises and privileges in the jurisdiction of its incorporation, and qualify and remain qualified as a foreign corporation in good standing in each jurisdiction in which such qualification is from time to time necessary or desirable in view of their business and operations or the ownership of their properties.

10.2 comply in all material respects with the requirements of all applicable laws, rules, regulations and orders of any government authority to the extent necessary to conduct the

Research Program, except for those laws, rules, regulations, and orders it may be contesting in good faith.

11. INDEMNIFICATION.

Pfizer will indemnify Rigel for damages, settlements, costs, legal fees and other expenses incurred in connection with a claim against Rigel based on a Licensed Product or any action or omission of Pfizer, its agents or employees whether such claims allege negligence, willful misconduct or strict liability, related to the obligations of Pfizer under this Agreement. Pfizer, in its sole discretion, shall choose legal counsel, shall control the defense of such claim or action and shall have the right to settle same on such terms and conditions it deems advisable.

12. NOTICES.

All notices and invoices shall be in writing mailed via certified mail, return receipt requested, courier, or facsimile transmission with transmission confirmed addressed as follow, or to such other address as may be designated from time to time:

IF TO PFIZER: To Pfizer at its address as set forth at the beginning of this Agreement.
Attention: President, Central Research
with copy to: Office of the General Counsel
Fax:

IF TO RIGEL: Rigel at its address as set forth at the beginning of this Agreement.
Attention: President
Fax: (408) 736-1588

Notices shall be deemed given as of the date received or five (5) days after dispatch.

13. GOVERNING LAW.

This Agreement shall be governed by and construed in accordance with the laws of the State of New York.

14. MISCELLANEOUS.

14.1 BINDING EFFECT. This Agreement shall be binding upon and inure to the benefit of the Parties and their respective legal representatives, successors and permitted assigns.

14.2 HEADINGS. Paragraph headings are inserted for convenience of reference only and do not form a part of this Agreement.

14.3 COUNTERPARTS. This Agreement may be executed simultaneously in two or more counterparts, each of which shall be deemed an original. Signatures may be transmitted via facsimile, thereby constituting the valid signature and delivery of this Agreement.

14.4 AMENDMENT, WAIVER. This Agreement may be amended, modified, superseded or canceled, and any of the terms may be waived, only by a written instrument executed by each Party or, in the case of waiver, by the Party or Parties waiving compliance. The delay or failure of any Party at any time or times to require performance of any provisions shall in no manner affect the rights at a later time to enforce the same. No waiver by any Party of any condition or of the breach of any term contained in this Agreement, whether by conduct, or otherwise, in any one or more instances, shall be deemed to be, or considered as, a further or continuing waiver of any such condition or of the breach of such term or any other term of this Agreement.

14.5 NO THIRD PARTY BENEFICIARIES. No third party including any employee of any Party to this Agreement, shall have or acquire any rights by reason of this Agreement. Nothing contained in this Agreement shall be deemed to constitute the Parties partners with each other or any third party.

14.6 ASSIGNMENT AND SUCCESSORS. This Agreement may not be assigned by either Party, except that each Party may assign this Agreement and the rights and interests of such Party, in whole or in part, to any of its Affiliates, any purchaser of all or substantially all of its assets or to any successor corporation resulting from any merger or consolidation of such Party with or into such corporations.

14.7 FORCE MAJEURE. Neither Pfizer nor Rigel shall be liable for failure of or delay in performing obligations set forth in this Agreement, and neither shall be deemed in breach of its obligations, if such failure or delay is due to natural disasters or any causes reasonably beyond the control of Pfizer or Rigel.

14.8 SEVERABILITY. If any provision of this Agreement is or becomes invalid or is ruled invalid by any court of competent jurisdiction or is deemed unenforceable, it is the intention of the Parties that the remainder of the Agreement shall not be affected so long as the essential benefits of this Agreement remain enforceable and obtainable.

14.9 INTEGRATION. This Agreement supersedes all other agreements and understandings between the parties with respect to the subject matter discussed herein.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives.

Agreed: Pfizer Inc and Affiliates	Agreed: Rigel Pharmaceuticals, Inc. and Affiliates
By: /s/ George M. Milne Jr.	By: /s/ James M. Gower
George M. Milne, Jr.	James M. Gower
President	Chief Executive Officer
Pfizer Central Research	Rigel Pharmaceuticals, Inc.
Date: 1/29/99	Date 1/26/99

EXHIBIT A

RIGEL PATENT RIGHTS

<TABLE>
<CAPTION>

LICENSED TECHNOLOGIES	TITLE/MATERIAL	INVENTOR	PATENT FILING DATE	
<S>	<C>	<C>	<C>	<C>
1.	Phoenix and 293T cells lines	Garry Nolan, Stanford University	-	Non-Exclusive license 10/7/96
2.	Phoenix and 293T cells lines	Garry Nolan, Stanford University	-	Exclusive license 8/18/97
3A. USSN 08,589,109	Methods for Screening for Transdominant Effector Peptides and RNA Molecules	Garry Nolan & Michael Rothenberg, assigned to Stanford University	1/23/96	Technology licensed by Rigel 10/7/96
3B. USSN 08,787,738	Methods for Screening for Transdominant Effector Peptides and RNA Molecules	Garry Nolan & Michael Rothenberg, assigned to Stanford University	1/23/97	CIP
3C. PCT US97/01048	Methods for Screening for Transdominant Effector Peptides and RNA Molecules	Garry Nolan & Michael Rothenberg, assigned to Stanford University	1/23/97	PCT
4. US patents # 5,283,173 5,468,614 5,667,973	A Genetic System to Detect Protein-Protein Interactions	Stanley Fields & Ok-Kyu Song, assigned to the Research Foundation of SUNY (Stonybrook)	1/24/90; continued 2/1/94; continued 9/16/97	Technology licensed 1/12/98

5. Provisional application # 60,042,576, and 60,054,623; (replaced by application 09,053,614)	Detection of Molecular Interactions by Reporter Subunit Complementation	Helen Blau, assigned to Stanford University	4/2/97 8/4/97 4/1/98	Technology licensed by Rigel 3/27/98
6. (TET system includes 16 patents)	Tetracycline Regulated Expression Technology: The TET System	BASF Bioresearch Corp.		Technology licensed 5/1/98

</TABLE>

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PATENTS	TITLE	AUTHOR	PATENT FILING DATE	
<S>	<C>	<C>	<C>	<C>
1A. USSN 08,589,911	Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules	Garry Nolan	1/23/96	Assigned to Rigel 10/20/97
1B. USSN 08,789,333	Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules	Garry Nolan	1/23/97	CIP
1C. USSN 08,963,368	Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules	Garry Nolan	11/3/97	divisional
1D. PCT US97/01019	Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules	Garry Nolan	1/23/97	PCT
2. USSN 08,873,601	Combinatorial Enzymatic Complexes	Garry Nolan & Donald Payan	6/12/97	Assigned to Rigel 9/9/97
3. USSN 09,047,119	Small Molecule Library Screening Using FACS	Donald Payan	3/24/98	
4. 09,050,863	Mammalian Protein Interaction Cloning System	Ying Luo, Betty Huang, & Donald Payan	3/30/98	
5. 60,080,444	Peptides Causing Formation of Compact Structures	Dave Anderson	4/2/98	
6. 09,076,624	Methods and Compositions for Screening for Modulators of IgE Synthesis, Secretion and Switch Rearrangement	Dave Ferrick, Susan Swift, Randy Armstrong, Bryan Fox	5/12/98	
7A. 09,133,944	Shuttle Vectors	Ying Luo, Peiwen Yu, Jim Lorens	8/14/98	
7B.	Shuttle Vectors	Ying Luo, Peiwen Yu, Jim Lorens	In process	CIP
8.	Green Fluorescent Protein Fusions with Random Peptides	David Anderson	10/9/98	

</TABLE>

EXHIBIT B

RESEARCH PLAN

1. GOALS

The goal of this collaboration between Rigel and Pfizer is to identify novel and selective elements of the IL-4 signaling pathway that are suitable targets for an IgE synthesis inhibitor, lead identification program.

2. RESEARCH PLAN

The research strategy for the first two years of the Pfizer-Rigel collaboration is shown in FIGURE 1. During this time, research activities will take place primarily at Rigel towards the goal of discovering novel Molecular Targets in the IL-4 signaling pathway that can be further developed by Pfizer into high throughput screens (HTS) at Pfizer to find agents to inhibit IL-4 signaling and IgE synthesis for the treatment of allergic disease and asthma. In brief, Rigel uses intracellular retrovirus expression of peptide libraries in an IL-4 responsive reporter cell line to discover peptide inhibitors of the IL-4 signaling pathway. The peptide inhibitors are validated by showing their selectivity in inhibiting IL-4 directed IgE synthesis over IL-10 directed IgG synthesis. The peptide inhibitors are used to isolate their protein ligands using Yeast Two Hybrid (YTH) technology, and then these ligands will be valided for their effect on IgE synthesis at Rigel using a combination of IN VITRO mutagenesis and further YTH pathway mapping.

2.1 DELIVERABLES AND TIMELINE

2.1.1 RESEARCH ACTIVITIES, 0-12 MONTHS:

DELIVERABLE 1 (D1)--ISOLATION AND CONFIRMATION OF INHIBITORY PEPTIDES:

(a) (8 MONTHS) Rigel will endeavor to isolate specific peptide inhibitors of IL-4-induced, B cell germline E transcription, from stem loop peptide libraries (2x10(9) component complexity) using a Fas-mediated apoptosis cell survival assay. The greater the number of peptides actually expressed in the reporter cell line, the greater the chances of finding novel Molecular Targets, so every reasonable effort will be made to maximize the representation of the peptide library in the reporter cell line. However, taking transfection efficiency into account, no less than 10(8) components will be have been expressed in the B-cell reporter cell line. The iterative enrichment of inhibitory peptides and their characterization will be carried out by Rigel as shown in Figure 2.

(b) (12 MONTHS) As noted in Figure 2, Rigel will endeavor to confirm that individual peptide inhibitors confer the IL-4 resistant phenotype in a Fas-mediated apoptosis cell survival assay. The capacity of this assay would allow 100+ peptide inhibitors to be taken forward through this assay for confirmation.

2.1.2 RESEARCH ACTIVITIES, 12-18 MONTHS:

DELIVERABLE 2 (D2)--IgE SYNTHESIS INHIBITION AND SPECIFICITY OF INDIVIDUAL PEPTIDE HITS:

Rigel will endeavor to demonstrate that recovered single peptide hits inhibit IgE synthesis SELECTIVELY over IgG synthesis as follows:

(a) Measure IgE versus IgG secretion/switching inhibition in a cytokine stimulated BL16 B-cell line. The goal is that the inhibitory peptide will inhibit IgE levels in the media produced by the IgM+ BL16 cell line stimulated with IL-4 by 20 fold over an irrelevant peptide control. If the peptide also inhibits IL-10 driven IgG levels from the IgM+ BL16 cell line, the goal will be that the peptide will inhibit IgE levels by 20 fold more than IgG. Secreted antibody levels will be measured in the media by ELISA. Because of the higher throughput of the BL16 assay (capacity = 100+ peptides) versus the primary PBL assay (capacity = 10 peptides), it is expected that the BL16 assay will be used to rapidly select peptides that will serve as baits in YTH screening, while the PBL assay will only be performed on those peptides whose ligands are not known components of the IL-4 signaling pathway.

(b) Confirm that the peptide inhibitor meets the same criteria as in D2a in primary cells by performing similar experiments to those in D2a in cytokine stimulated IgM+ enriched human peripheral blood lymphocytes or IgM+ enriched human tonsillar B-cells. Because of the low throughput and variability of this assay, those peptides that are the binding partners of known members of the IL-4 signaling pathway will not be tested in this assay.

D2 CRITERIA: Section 2.1.2(a) shall be known as D2a criteria, and Section 2.1.2(b) above shall be known as D2b criteria.

DELIVERABLE 3 (D3)--CLONING OF FULL LENGTH CDNAS OF PROTEINS BINDING OF INHIBITORY PEPTIDES:

Rigel will deliver full length sequences of protein binding partners of inhibitory peptides. Up to 20 functionally active single peptide hits will be used as bait in a YTH system (YTH level 1) to identify cDNAs encoding the target protein partners of the active peptides. Rigel will perform bioinformatic analysis to identify the isolated clones. Pfizer will also contribute bioinformatic analysis in order to attempt to identify some of these clones based on homology to sequences in public databases and private databases available to Pfizer. Bioinformatics, RACE (Rapid Amplification of CDNA Ends), or cDNA cloning will be used by Rigel to obtain full length cDNA sequences encoding up to 12 independent target proteins from the cDNA sequences isolated using YTH.

D3 MILESTONE CRITERIA: D3 criteria comprise meeting each of the following: (1) the cDNA is the ligand of an inhibitory peptide that met the criteria in D2a and D2b. (2) The cDNA contains the full length coding region, and is either the only ligand for a given peptide inhibitor or can be conclusively shown to be the ligand responsible for the IL-4 inhibition. (3) At the time of its discovery, the cDNA did not encode a protein already known in the literature or to Pfizer to be a component of the IL-4 signaling pathway whose inhibition would be expected to have a specific effect on the germline epsilon promoter. These proteins must include the following: IL-4R alpha chain, IL-4R gamma chain, Jak kinases, STAT6, as well as two other proteins (a transcription factor and an enzyme) whose role is unpublished and identity is known to Pfizer through confidential sources. The identity of these proteins are as follows: The transcription factor Bc16, and the Pim family of Ser/Thr Kinases, particularly Pim-2.
[to be added at the time of the execution of the Agreement.] (4) The cDNA is not identical or overlapping with another cDNA for which a D3 milestone has already been triggered.

At Pfizer's sole, unfettered discretion, a D3 milestone may be paid to Rigel by Pfizer in the absence of one or more of the first three criteria being met.

2.1.3 RESEARCH ACTIVITIES, 18-24 MONTHS

DELIVERABLE 4 (D4)--VALIDATION OF CDNAS IDENTIFIED IN DELIVERABLE 3 (D3):

(a) Rigel will endeavor to complete mutagenesis target validation data for two proteins identified in Deliverable 3. Greater than one hundred mutants will be generated for each target by error prone PCR and delivered via retrovirus constructs to the Fas-mediated apoptosis survival assay to select for dominant negative mutants that confer the IL-4 resistant phenotype. If dominant negatives are found, selective inhibition of IgE synthesis over IgG synthesis will be measured as in Deliverable 2a and 2b above, with the same throughput for the BL16 and PBL assays.

(b) Rigel will endeavor to deliver additional protein targets and pathway mapping in the IL-4/germline E pathway. Up to five full length cloned protein targets identified in Deliverable 3 will be used as bait in YTH experiments (YTH level 2) to identify further protein binding partners which interact with each clone in order to map the IL-4 signaling pathway and validate the role of these proteins in IL-4 signaling. If the protein binding partner of an inhibitory peptide were to be found to bind to a known member of the IL-4 signaling pathway, this would represent partial validation of this D3 protein in the IL-4 signaling pathway. Full length clones for up to 8 of the binding partners will be sought in preparation for possible future YTH level 3 screening during an optional 3rd year of the Pfizer-Rigel collaboration.

D4 MILESTONE CRITERIA: D4 criteria comprise meeting either one of the following two criteria for a D3 cDNA clone or its encoded protein. (a) Successful selection of one or more dominant negative mutants of a cDNA whose effect after intracellular retroviral expression satisfies the criteria applied to inhibitory peptides in D2a and D2b. (b) Demonstration in YTH level 2 that the protein encoded by a given cDNA binds to a known member of the IL-4 signal transduction pathway. Specific qualifying components would be all those noted in the D3 Milestone Criteria.

At Pfizer's sole, unfettered discretion, a D4 milestone may be paid to Rigel by Pfizer in the absence of one or more of the criteria being met.

2.2 PROGRAM TECHNOLOGIES

Certain reagents will be enabling to Pfizer's efforts to validate Molecular Targets, to progress Molecular Targets to the HTS phase, and to engage in research in the IgE synthesis inhibition area. Since they are not explicitly stated elsewhere, the following reagents will be considered Program Technologies: the IL-4 driven Fas reporter cell line, an IL-4 driven GFP reporter cell line, the BL16 cell line derivative used in this collaboration, any useful derivatives of these that may be used in the course of the collaboration, other enabling cell lines specifically made for this collaboration, and the PBL assay.

2.3 PROGRESSION OF MOLECULAR TARGETS AT PFIZER

Once potential Molecular Targets are available, Pfizer will have the sole unfettered discretion of which to select for progression to HTS and beyond. Pfizer will perform target validation experiments and will adapt the Molecular Target for HTS. From this point, a Pfizer project team will follow a standard drug discovery progression from lead discovery, candidate optimization, and candidate validation using IN VITRO and IN VIVO models. Compounds satisfying candidate criteria will follow the usual Pfizer preclinical development program (i.e. General Pharmacology, Genetic Toxicology, and Exploratory Toxicology studies) to the recommendation for development (RFD) stage.

Genetic Toxicology, and Exploratory Toxicology studies) to the recommendation for development (RFD) stage.

After a Candidate Alert Notice ("CAN") is issued, General Pharmacology and exploratory Toxicology studies in two species will be conducted. A RFD (or CANTOX) document will issue by approval of Pfizer's Early Development Management Team after a satisfactory completion of General Pharmacology and the 14-day rat and dog (or monkey) Exploratory Toxicology, including histopathology, evaluations. For studies in man, Pfizer policy is that a clinical candidate should have a safety margin of 10x between a predicted human efficacious dose (plasma concentration and/or exposure taken into account) and a non-observable-adverse-effect-level (NOAEL).

FIGURE 1

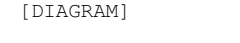

FIGURE 2

RIGEL: SELECTION OF PEPTIDE INHIBITORS OF IL-4 SIGNALING (0-12 months)

EXHIBIT 10.8

COLLABORATION AGREEMENT

THIS COLLABORATION AGREEMENT ("Agreement") is entered into as of May 26th, 1999 ("Effective Date") by and between RIGEL PHARMACEUTICALS, INC., a Delaware corporation ("Rigel") with its offices at 240 East Grand Avenue, South San Francisco, CA 94080, and NOVARTIS PHARMA AG, a Swiss corporation ("Novartis") with offices at Lichtstrasse 35, CH-4058, Basel, Switzerland (collectively, "Parties"; individually, a "Party").

RECITALS

WHEREAS, Rigel is a leader in the discovery and validation of intracellular target molecules involved in the modulation of human disease; and

WHEREAS, Novartis is engaged in the research, development, marketing, manufacture and distribution of pharmaceutical compounds useful in treating or preventing human diseases and conditions; and

WHEREAS, Rigel and Novartis desire to enter into a collaborative relationship to conduct research on intracellular target molecules and to discover, develop and manufacture pharmaceutical products useful for treating or preventing diseases associated with human disease; and

WHEREAS, Novartis is purchasing two million (2,000,000) shares of Rigel Series D Preferred Stock with a total value of US$4 million pursuant to a stock purchase agreement between the Parties of even date herewith (the "Stock Purchase Agreement"), and the Parties are further entering into an Equity Option Agreement pursuant to which Novartis may purchase up to an additional US$10 million in value of Rigel equity;

NOW, THEREFORE, in consideration of the foregoing and the covenants and promises contained in this Agreement, the Parties agree as follows:

1. DEFINITIONS

As used herein, the following terms (whether used in their singular or plural form) shall have the following meanings:

"AFFILIATE" shall mean, with respect to a Party to this Agreement, any other entity, whether de jure or de facto, which directly or indirectly controls, is controlled by, or is under common control with, such Party. A business entity or Party shall be regarded as in control of another business entity if it owns, or directly or indirectly controls, at least fifty percent (50%) (or such lesser percentage which is the maximum allowed to be owned by a foreign entity in a particular jurisdiction) of the voting stock or other ownership interest of the other entity, or if it directly or indirectly possesses the power to direct or cause the direction of the management and policies of the other entity by any lawful means whatsoever.

"AT-NOVARTIS PROJECT" shall mean a Program of Research performed by Novartis as provided in Section 4.2 hereof.

"B-CELL PROJECT" shall mean the Program of Research directed to the identification of Novel Validated Targets involved in the process of B-Cell activation, as the Program of Research is more fully described in Exhibit A-2 hereto.

"COLLABORATION PROJECT" shall mean a Joint Project or an At-Novartis Project.

"COMMENCEMENT DATE" shall mean the date upon which a Collaboration Project shall commence as set forth in Exhibit B or as determined pursuant to the provisions of Section 2.2 hereof.

"COMPOUND SCREENING" shall mean the use of a primary assay for testing biological or chemical materials, including chemical materials coming out of high-throughput screening, to determine whether they show pharmaceutically relevant activity.

"CONFIDENTIAL INFORMATION" shall mean any invention, discovery, patent application or claim, trade secret, idea, improvement or other work of authorship, any process, formula, data, program, drawing, information, price, technique, sample, compound, extract, media, vector and/or cell line and procedures and formulations for producing any such sample, compound, extract, media, vector and/or cell line, any process, formula or data relating to any research project, work in process, future development, engineering, manufacturing, marketing, servicing, financing or personnel matter relating to a Party, its present or future products, sales, suppliers, clients, customers,

employees, investors, or business, whether in oral, written, graphic or electronic form.

"CONTROL" shall mean the possession of the ability to grant a license or sublicense to know-how or patents without violating the terms of any agreement or other arrangement with, or the rights of, any Third Party.

"COOPERATION MANAGEMENT COMMITTEE" or "CMC" shall mean the committee formed pursuant to Section 3.1.

"EXCLUSIVITY TERM" shall have the meaning assigned to it in Section 5.2.

"EXTENSION FEE" shall have the meaning assigned to it in Section 7.5.

"FSC-STATUS" or "Final Selected Compound Status" shall mean the point at which a Product is declared, following Novartis' standard compound development procedures, an 'FSC Compound' or equivalent status by Novartis' Research Management Board or some other similar body, which declaration authorizes the initiation of preclinical development programs aimed, INTER ALIA, at the detailed investigation of those toxicological, bioavailability, pharmacokinetic and formulation parameters whose successful completion will allow progression of the Product to Phase I Clinical Trials.

"FTE" shall mean the equivalent of a full-time twelve (12) months (including normal vacations, sick days and holidays) work of a person, carried out by one or more employees or consultants of a Party, each of whom devotes all or a portion of his or her time to a Collaboration Project; provided, however, that each Party understands and agrees that the other Party retains complete discretion to change the identity, the frequency and time which

any individual employee devotes to a Collaboration Project. Scientific work on or directly related to a Collaboration Project to be performed by a Party's employees or consultants can include, but is not limited to, experimental laboratory work, recording and writing up results, reviewing literature and references, holding scientific discussions, managing and leading scientific staff, and carrying out Research Cooperation management duties (including service on the Cooperation Management Committee).

"JOINT INVENTION" shall have the meaning assigned to it in Section 8.1.

"JOINT PROJECT" shall mean a Program of Research which Novartis and Rigel agree will be conducted collaboratively as provided in Section 4.1 hereof.

"JOINT TECHNOLOGY" shall mean Know-How and Patents conceived or reduced to practice by at least one employee of Novartis and at least one employee of Rigel during the course of a Program of Research.

"KNOW-HOW" shall mean any and all tangible or intangible know-how, trade secret, invention (whether or not patentable), data, pre-clinical and clinical result, physical, chemical or biological material, and other information.

"LEAD COMPOUND" shall mean an active compound identified by Rigel in the course of Compound Screening on the basis of a Novel Validated Target pursuant to Section 5.6.

"MILESTONE EVENT" shall have the meaning assigned to it in Section 7.2.

"MILESTONE PAYMENT" shall have the meaning assigned to it in Section 7.2.

"NOTICE DATE" shall have the meaning assigned to it in Section 4.1.4 and 4.2.4.

"NOVARTIS KNOW-HOW" shall mean any Know-How that is necessary and useful in a Program of Research and that Novartis owns or Controls on the Effective Date, and any replication or any part of such information or material.

"NOVARTIS PATENTS" shall mean all Patents which claim inventions or discoveries necessary and useful in a Program of Research and that that Novartis owns or Controls on the Effective Date.

"NOVARTIS TECHNOLOGY" shall mean Novartis Know-How and Novartis Patents, subject to any limitation contained in the agreements under which Novartis' rights to the use of such Novartis Technology are derived.

"NOVEL VALIDATED TARGET" shall mean a specific molecule in an intracellular signaling pathway which, when bound by a specific peptide, changes in a predetermined way the phenotype of a target cell with a degree of specificity and in a manner meeting the predetermined validation criteria set by

the CMC for Joint Projects and by Novartis for At-Novartis Projects.

"PATENTS" shall mean all foreign and domestic patents (including, without limitation, extensions, reexaminations, reissues, renewals and inventors certificates) and patents issuing from patent applications (including substitutions, provisionals, divisionals, continuations and continuations-in-part).

"PHASE I CLINICAL TRIALS" shall mean first clinical trial where the Product is applied in healthy human volunteers to test safety of such Product.

"PRODUCT" shall mean a molecule in the various stages of development from identification in Compound Screening to and including commercialization, which is useful to diagnose, treat or prevent human diseases or conditions and whose principal mechanism of action by which it exerts its pharmacological activity is based upon, derived from or discovered with the use of, a Novel Validated Target.

"PROGRAM OF RESEARCH" shall mean research utilizing Rigel Technology to identify specific target molecules and peptides which bind thereto that alter a selected phenotype of a target cell population, including the use of retroviral vector and expression systems which express libraries of molecules in target cells, high-speed fluorescent cell sorting systems to identify the cells in which the selected phenotype change has occurred and two-hybrid screening assays to elaborate the intracellular interactions of the specific target molecules and other means and methods, whether or not utilizing Rigel Technology, appropriate in a particular program.

"PROGRAM PROPOSAL" shall mean a written description of a Program of Research specifying in reasonable detail the specific goals of the project including clinical objectives, target cells to be utilized, desired biologic endpoints of assays of the target cells, project time frames and resource requirements.

"PROJECT CONTACT PERSON" shall have the meaning assigned to it in Section 3.8.

"PROJECT KNOW-HOW" shall mean Know-How developed, conceived or reduced to practice by a Party in the course of a Collaboration Project.

"PROJECT PATENT" shall mean a Patent claiming Project Know-How.

"PROJECT TECHNOLOGY" shall mean Project Know-How and Project Patents.

"RESEARCH COOPERATION" shall mean the Joint Projects and the At-Novartis Projects.

"RESEARCH PERIOD" shall mean, for each Joint Project and each At-Novartis Project, five (5) years commencing as of the corresponding Commencement Date, subject to earlier termination as permitted hereby.

"RIGEL CORE TECHNOLOGY" shall mean Rigel's proprietary packaging cell lines (e.g., without limitation, that designated as Phoenix), high-speed functional genomic screening technology, two-hybrid screening assays, retroviral vector systems and expression systems that utilize these vectors to express libraries of molecules in target cells and high speed fluorescent cell sorting systems and any improvements thereon, and any Patents and Know-How relating thereto owned or Controlled by Rigel, subject to any limitation contained in the agreements under which Rigel's rights to the use of such Rigel Core Technology are derived.

"RIGEL KNOW-HOW" shall mean any Know-How other than Rigel Core Technology that is useful in a Collaboration Project and that Rigel owns or Controls on the Effective Date and any replication or any part of such information or material.

"RIGEL PATENTS" shall mean all Patents other than Rigel Core Technology which claim inventions or discoveries useful in a Collaboration Project and that are owned or Controlled by Rigel on the Effective Date.

"RIGEL TECHNOLOGY" shall mean the Rigel Patents and Rigel Know-How, subject to any limitation contained in the agreements under which Rigel's rights to the use of such Rigel Technology are derived.

"SOLE INVENTIONS" shall have the meaning assigned to it in Section 8.1.

"T-CELL PROJECT" shall mean the Program of Research directed to the identification of Novel Validated Targets involved in the process of T-Cell

activation, as the Program of Research is more fully described in Exhibit A-1 hereto.

"TERM OF AGREEMENT" shall have the meaning assigned to it in Section 11.1.

"TERRITORY" shall mean the entire world.

"THIRD PARTY" shall mean any person or entity other than Novartis, Rigel and Affiliates of either.

2. SELECTION OF PROJECTS

2.1 NOVARTIS ACCESS TO FIVE PROJECTS. Novartis may have access to up to five (5) Programs of Research of which at least two (2) will be Joint Projects and no more than three (3) will be At-Novartis Projects.

2.2 PROPOSAL FOR A PROGRAM OF RESEARCH.

2.2.1 JOINT PROJECTS. A Program of Research for a Joint Project may be proposed by Novartis or Rigel submitting to the other a Program Proposal. Within thirty (30) days of receipt of a Program Proposal the receiving party shall determine whether it has any agreement with a Third Party which would prevent it from agreeing to conduct pursuant to this Agreement the Program of Research identified in the Program Proposal and notify the proposing party accordingly. If the receiving party is free to conduct the Program of Research pursuant to this Agreement, the Parties shall meet to determine whether they will agree to conduct such Program of Research pursuant to this Agreement. If so, the CMC shall meet promptly to prepare a mutually agreeable description of the Program of Research to be attached as an exhibit to this Agreement, to specify the number of FTEs which will be utilized, the Commencement Date and the number of FTEs as well as the resources to be allocated at Novartis. If the receiving party is not free to conduct the Program of Research pursuant to this Agreement, neither Party shall have any obligation or liability to the other with respect to such Program of Research.

2.2.2 AT-NOVARTIS PROJECTS.

(a) Novartis may propose a Program of Research for an At- Novartis Project by submitting to Rigel a corresponding Program Proposal.

(b) Novartis shall have the right to proceed with such Program of Research, unless Rigel notifies Novartis in writing within thirty (30) days of receipt of a

Program Proposal (i) that in Rigel's opinion, the Program of Research as proposed by Novartis is scientifically not feasible, or (ii) that Rigel is engaged in advanced negotiations with a Third Party regarding a collaboration on a Program of Research which would conflict with the Program of Research proposed by Novartis under this Agreement, or (iii) that Rigel has initiated an internal Program of Research, as evidenced by written records, which would conflict with the Program of Research proposed by Novartis.

(c) If Rigel provides to Novartis a notice pursuant to subsection (b)(i) above, the Parties shall meet to discuss and revise the proposed Program Proposal as appropriate to address Rigel's comments and suggestions, whereafter Novartis shall have the right to proceed with such Program of Research based on the revised Program Proposal. If Rigel provides to Novartis a notice pursuant to subsection (b)(ii) or (b)(iii) above, such Program of Research may not be pursued by Novartis, and neither Party shall have any obligation or liability to the other with respect to such Program of Research.

(d) If Novartis has the right to proceed with a Program of Research as provided in this Section 2.2.2, Novartis will provide to Rigel a mutually agreeable description of the Program of Research, including the validation criteria to be applied for determining whether a molecule is a Novel Validated Target, to be attached as an exhibit to this Agreement which description shall specify the Commencement Date of the At-Novartis Project. Thereafter, the Parties will meet promptly to specify the Rigel Technology and Rigel Core Technology to be transferred and the time of the transfer thereof to Novartis pursuant to Section 4.2.5 hereof.

2.3 NUMBER AND KIND OF ADDITIONAL PROGRAMS OF RESEARCH. The parties hereby agree that the Commencement Date of the T-Cell Project shall be the Effective Date of this Agreement. Subject to Section 2.2, Novartis and Rigel will add to this Agreement two (2) additional Programs of Research prior to the first (1st) anniversary of the Effective Date and two(2) Programs of Research prior to the second (2nd) anniversary of the Effective Date.

2.4 T-CELL PROJECT. Novartis and Rigel hereby agree that the T-Cell Project is to be conducted as a Joint Project as provided in Section 4.1 and is

one of the Programs of Research referred to in Section 2.1. A mutually agreeable description of the Program of Research is set forth in Exhibit A-1. The number of FTEs and the Commencement Date for the T-Cell Project are set forth in Exhibit B-1.

2.5 B-CELL PROJECT. Novartis hereby acknowledges that Rigel has proposed the B-Cell Project as the second Joint Project in compliance with Section 2.2, and that Novartis has no agreement with a Third Party which would prevent it from agreeing to engage in the B-Cell Project pursuant to this Agreement. A mutually agreeable description of the Program of Research for the B-Cell Project is set forth in Exhibit A-2. The number of FTEs and the Commencement Date for the B-Cell Project are set forth in Exhibit B-2. Novartis will notify Rigel within ninety (90) days after the Effective Date whether it agrees that the B-Cell Project shall be conducted as the second Joint Project. If Novartis does not so agree, Rigel's proposal of the B-Cell Project shall be considered withdrawn as of the ninety-first (91st) day after the Effective Date and neither Novartis nor Rigel shall thereafter have any obligation or liability to the other with respect to the B-Cell Project.

3. RESEARCH COOPERATION GOVERNANCE

3.1 JOINT COOPERATION COMMITTEE FORMATION. The Research Cooperation established by this Agreement shall be overseen or monitored, pursuant to the provisions of Section 3.7 hereof, by a Cooperation Management Committee composed of an equal number of representatives from each Party (the "Cooperation Management Committee"). Each Party shall initially designate three (3) representatives on the CMC within ten (10) business days after the Effective Date. The addition of further representatives to the CMC, if any, shall occur pursuant to the provisions of Section 3.3.6 hereof. Each Party may, upon notice to the other Party, change its representatives to the CMC to allow for the participation of different research groups within Novartis or Rigel, as the case may be. The Parties shall agree upon the appropriate qualifications for members of the CMC. An alternate member designated by a Party may serve temporarily in the absence of a permanent member of the CMC for such Party. Each Party shall designate one of its representatives as a Co-Chair of the CMC. Each Co-Chair of the CMC will be responsible for the agenda and the minutes of alternating CMC meetings.

3.2 CMC ACTIONS. Actions by the CMC pursuant to this Agreement shall be taken only with unanimous approval of all of the representatives of the CMC. If the CMC fails to reach unanimity on a matter before it for decision, the matter shall be referred for resolution to the designated executives of the Parties identified in Section 13.2.

3.3 MEETINGS OF THE CMC. The CMC:

3.3.1 shall hold meetings at such times and places as shall be determined by the CMC (it being expected that meetings will alternate between one of Novartis' research sites on the one hand and Rigel's head offices on the other hand) but in no event shall such meetings be held in person less frequently than once every three (3) months during the entire period during which the Research Period of at least one Collaboration Project is not yet expired or terminated;

3.3.2 may conduct meetings in person or by telephone or video conference;

3.3.3 by mutual consent of the representatives of each Party, may invite other personnel of either Party to attend meetings of the CMC;

3.3.4 may act without a meeting if prior to such action a written consent thereto is signed by all members of the CMC;

3.3.5 may form and subsequently disband subcommittees with appropriate representation from each Party;

3.3.6 may increase or decrease the equal number of CMC representatives each Party can designate; and

3.3.7 may amend or expand upon the foregoing procedures for its internal operation by unanimous written consent.

3.4 MINUTES. Subject to the provisions of Section 3.1 hereof, one of the Co-chairs of the CMC will prepare, within ten (10) business days after each meeting (whether held in person or by telephone or video conference), the minutes reporting in reasonable detail the actions taken by the CMC, the status of each Collaboration Project, the then current list of Novel Validated Targets, issues requiring resolution and resolutions of previously reported

issues, which minutes are to be approved by the signature of the CMC Co-Chair of the other Party.

3.5 SUBCOMMITTEES. Any subcommittee established by the CMC shall have appropriate representation of each Party and may include representatives of a Party who are not members of the CMC. Any such subcommittee shall be subject to the CMC and shall report its activities and actions to the CMC. At the request of either Party at any time, any such committee shall be dissolved and its powers and functions returned to the CMC.

3.6 REPORTS. Novartis and Rigel shall each provide written reports at or before each CMC meeting describing its activities and results under the Research Cooperation. Such reports shall be in such form and contain such detail as the CMC shall determine.

3.7 CMC FUNCTIONS AND POWERS. The activities of the Parties under this Agreement shall be managed by the CMC only to the extent set forth herein (unless otherwise mutually agreed by the Parties). The CMC shall:

3.7.1 foster the collaborative relationship between the Parties;

3.7.2 facilitate and monitor the technology transfer under the Collaboration Projects;

3.7.3 approve the validation criteria for a Novel Validated Target within sixty (60) days of each Commencement Date;

3.7.4 pursuant to Section 5.4 and provided Novartis has requested Rigel screening thereunder, approve in advance the criteria for a Lead Compound identified by Rigel and to be reported to Novartis;

3.7.5 monitor the progress of the research in the Joint Projects;

3.7.6 monitor the status of At-Novartis Projects to allow assessment of whether or when a Milestone Payment is due;

3.7.7 review and allocate annual FTEs in the Joint Projects, within the framework of the contractually agreed funding level;

3.7.8 clear scientific publications relating to the Joint Projects, and, insofar as containing work from both Parties, relating to At-Novartis Projects, subject to the review and approval of both Parties pursuant to Section 10.3;

3.7.9 perform such other functions as elsewhere explicitly provided in this Agreement and as appropriate to further the purposes of this Agreement as mutually determined by the Parties.

3.8 PROJECT CONTACT PERSONS. Subject to the CMC, the day-to-day communication between the Parties and project coordination of each Joint Project will be performed by two (2) "Project Contact Persons", one to be appointed by each Party.

3.9 OBLIGATIONS OF PARTIES. Each one of the Parties shall have the right to inspect the other Party's records through a qualified independent Third Party, reasonably acceptable to the other Party, to determine whether the other Party's performance complies with the

terms of this Agreement, but not more frequently than once in any year during the Research Period and subject to (1) the confidentiality obligations of Article 10 and (2) any BONA FIDE obligations of confidentiality to a Third Party.

3.10 LIMITATIONS OF POWERS OF THE CMC. The CMC shall have no power to amend this Agreement and shall have only such powers as are specifically delegated to it hereunder.

4. CONDUCT OF JOINT AND AT-NOVARTIS

4.1 CONDUCT OF JOINT PROJECTS.

4.1.1 SCOPE OF JOINT PROJECTS. Each Joint Project will be conducted as a collaborative research program during its Research Period to identify and validate Novel Validated Targets. The Parties intend that these Novel Validated Targets will be suitable to enable Compound Screening to identify molecules useful for the development and manufacture of Products.

4.1.2 REVISIONS OF JOINT PROJECTS. By mutual agreement in writing the Parties may revise the scope of a Joint Project.

4.1.3 PERFORMANCE OF RESEARCH ACTIVITIES. Each Party will perform the activities assigned to it in the Program of Research for each Joint Project, or as directed by the CMC, in good scientific manner, and in compliance with all applicable good laboratory practices and applicable legal requirements to attempt to achieve efficiently and expeditiously its objectives described in the Program of Research attached to this Agreement pursuant to Section 2.2.1.

4.1.4 IDENTIFICATION OF NOVEL VALIDATED TARGETS. Rigel shall notify the CMC in writing of each Novel Validated Target identified by Rigel during the Research Period of each Joint Project promptly after its identification. Such notice shall be accompanied with a report and sufficient data which establish that the validation criteria predetermined by the CMC pursuant to Section 3.7.3 have been met. The CMC shall issue a list of the Novel Validated Targets identified in the course of such Joint Project as a part of the minutes of each CMC meeting and a final list within thirty (30) days after the end of such Research Period. The date on which Rigel has delivered the notice described in this Section 4.1.4, provided Novartis has not within ten (10) business days of receipt of said notice informed Rigel that in Novartis' opinion, the CMC-predetermined validation cirteria have not been met, shall be considered the "Notice Date" of such Novel Validated Target. If Novartis informs Rigel that in Novartis' opinion, the CMC-predetermined validation criteria have not yet been met, the matter will be discussed and brought to a decision at the next meeting of the CMC.

4.1.5 TECHNOLOGY TRANSFER. Rigel, as from time to time it may be directed by the CMC, shall transfer to Novartis at no additional cost to Novartis such Rigel Technology and Rigel Core Technology as shall be necessary for the purpose of enabling Novartis to perform its responsibilities under the applicable Program of Research of Joint Projects to identify Novel Validated Targets. Novartis may use such Rigel Technology and Rigel Core Technology pursuant to the licenses granted under this Agreement.

4.1.6 SECONDMENT. In order to further a close working relationship, the Parties may agree to provide offices and support at its facilities for the personnel of the other Party.

4.2 CONDUCT OF AT-NOVARTIS PROJECTS.

4.2.1 SCOPE OF AT-NOVARTIS PROJECTS. Each At-Novartis Project shall be performed by Novartis fully in-house to identify and validate Novel Validated Targets. It is intended that these Novel Validated Targets will be suitable to enable Compound Screening to identify molecules useful for the development and manufacture of Products.

4.2.2 REVISIONS OF AT-NOVARTIS PROJECTS. By mutual agreement in writing the Parties may revise the scope of an At-Novartis Project.

4.2.3 PERFORMANCE OF RESEARCH ACTIVITIES. Novartis will perform research in accordance with the Program of Research for each At-Novartis Project in good scientific manner, and in compliance with all applicable good laboratory practices and applicable legal requirements to attempt to achieve efficiently and expeditiously its objectives described in the Program of Research attached to this Agreement pursuant to Section 2.2.2.

4.2.4 IDENTIFICATION OF NOVEL VALIDATED TARGETS. Novartis shall notify the CMC in writing of any Novel Validated Targets identified by Novartis during the Research Period of each At-Novartis Project promptly after its identification. Such notice shall be accompanied with a report and sufficient data which establish that the validation criteria predetermined pursuant to Section 2.2.2(d) have been met. CMC shall issue a list of the Novel Validated Targets identified in the course of such At-Novartis Project as a part of the minutes of each CMC meeting and a final list within thirty (30) days after the end of such Research Period. The date on which Novartis has provided the notice described in this Section 4.2.4 shall be considered the "Notice Date" of such Novel Validated Target.

4.2.5 TECHNOLOGY TRANSFER. Rigel will transfer to Novartis such Rigel Technology and Rigel Core Technology, including without limitation the Phoenix packaging cell line, as reasonably necessary to enable the target identification activities Novartis is to perform in each At-Novartis Project as proposed by Novartis and reasonably acceptable to Rigel; provided, however, that Novartis shall reimburse Rigel its reasonable costs and expenses therefor. Novartis may use such Rigel Technology and Rigel Core Technology pursuant to the licenses granted under this Agreement.

4.3 ADDITIONAL PROJECTS. If Novartis expresses an interest in cooperating with Rigel with respect to any Programs of Research in addition to the two Joint Projects and three At-Novartis Projects, Rigel and Novartis will meet promptly to discuss in good faith whether and under what terms they could agree to cooperate with respect to such further research projects.

4.4 DISCLOSURE. Rigel and Novartis will disclose to the CMC promptly and at least quarterly the results of the research activities conducted in each Collaboration Project, such reports to be in such form as specified by the CMC. The Parties shall keep complete and accurate records pertaining to the results of work conducted pursuant to each Collaboration Project. Such records shall be maintained by each Party for a period of at least three (3) years following the year in which any such efforts were made hereunder.

4.5 DISCRETIONARY TERMINATION OF RESEARCH PERIOD.

4.5.1 DISCRETIONARY TERMINATION DATE FOR JOINT PROJECTS. Novartis may at its discretion terminate each Joint Project, individually, upon at least six (6) months prior written notice as hereinafter provided. If Novartis gives notice of termination for a given Joint Project no later than eighteen (18) months from the applicable Commencement Date, termination of such Joint Project will take effect at twenty-four (24) months from its Commencement Date. If Novartis gives notice of termination for a given Joint Project after eighteen (18) months but no later than thirty-six (36) months from the applicable Commencement Date, termination of such Joint Project will take effect at forty-two (42) months from its Commencement Date.

4.5.2 DISCRETIONARY TERMINATION OF AT-NOVARTIS PROJECTS. Novartis may, at its discretion, terminate each At-Novartis Project, individually, at any time with immediate effect.

4.5.3 EFFECT OF DISCRETIONARY TERMINATION.

(a) If Novartis terminates the T-Cell Project effective twenty-four (24) months after the applicable Commencement Date or forty-two (42) months after the applicable Commencement Date, Novartis will keep all rights and licenses granted under Section 6.2 with respect to those Novel Validated Targets identified prior to the termination of the Research Period, subject to the applicable milestone and/or royalty payment obligations of Article 7 and Exhibit C.

(b) If Novartis terminates any Joint Project other than the T-Cell Project

(i) effective twenty-four (24) months after the applicable Commencement Date, all licenses granted to Novartis relating to such Joint Project shall terminate upon the termination such Joint Project, and the rights to all Novel Validated Targets identified as of the date of termination shall revert to Rigel;

(ii) effective forty-two (42) months from the applicable Commencement Date, Novartis will keep all rights and licenses granted under Section 6.2 with respect to those Novel Validated Targets identified prior to the termination of the Research Period, subject to the applicable milestone and/or royalty payment obligations of Article 7 and Exhibit C.

(c) If Novartis terminates any At-Novartis Project at or effective prior to forty-two (42) months after the applicable Commencement Date, all licenses granted to Novartis relating to such At-Novartis Project shall terminate upon termination of such At-Novartis Project, and the rights to all Novel Validated Targets identified as of the date of termination shall revert to Rigel. If Novartis terminates an At-Novartis Project after forty-two (42) months, Novartis shall keep the rights to the Novel Validated Targets identified in the course of such At-Novartis Project as licensed under Section 6.2.

4.6 TERMINATION OF COLLABORATION PROJECT FOR BREACH.

4.6.1 Either Party may terminate a Collaboration Project after sixty (60) days prior notice to the other that the other Party has committed a material breach of its obligations

in the performance of such Collaboration Project unless the other Party cures (to the extent practicable) the breach within such period of time.

4.6.2 If Novartis terminates a Collaboration Project under Section 4.6.1 above, Novartis will keep all rights and licenses granted under Section 6.2 with respect to those Novel Validated Targets identified prior to the termination of the Research Period, subject to the applicable milestone and/or royalty payment obligations of Article 7 and Exhibit C.

4.6.3 If Rigel terminates a Collaboration Project under Section 4.6.1 above, all licenses granted to Novartis for such Collaboration Project shall terminate and the rights to all Novel Validated Targets identified

in the course of such Collaboration Project shall revert to Rigel.

4.7 TERMINATION OF JOINT PROJECT FOR SCIENTIFIC REASONS. If it is determined by both Parties before the end of the 12th month of a Joint Project already underway that it is no longer scientifically feasible, the Parties shall meet for good faith discussions to determine if an alternate project may be substituted on substantially similar terms. If after the 12th month of a Joint Project the CMC determines that for scientific reasons, a Joint Project cannot yield any Novel Validated Targets, or that such Novel Validated Targets will not be suitable for Compound Screening in high-throughput format, Novartis shall have to right to terminate such Joint Project with written notice effective upon receipt by Rigel. Upon such termination, Novartis shall make to Rigel, upon receipt of a corresponding invoice, a termination payment for non-cancelable commitments and other costs incurred by Rigel due to such termination corresponding to three (3) months of the research support payable pursuant to Section 7.1. Upon termination pursuant to this Section 4.7, all licenses granted to Novartis for such Joint Project shall terminate, and the rights to all Novel Validated Targets identified in the course of such Joint Project (if any) shall revert to Rigel.

4.8 EXISTING OBLIGATIONS. The termination of any Research Period shall not relieve the Parties of any obligation that accrued prior to such expiration or termination.

5. COMPOUND SCREENING AND DEVELOPMENT

5.1 NOVARTIS COMPOUND SCREENING. Novartis shall have the right to initiate Compound Screening with each Novel Validated Target upon notice to Rigel any time during the Exclusivity Term with respect to such Novel Validated Target.

5.2 EXCLUSIVITY TERM. Novartis' screening right under Section 5.1 shall be exclusive ('exclusive', as used in this Section 5.2 and subject to the provisions of Section 5.5, shall mean 'to the exclusion also of Rigel') during the first two (2) years ("Exclusivity Term") after the Notice Date. Subject to Section 5.3, Novartis may, after the first two years, extend the Exclusivity Term with respect to a Novel Validated Target for up to five (5) additional one (1) year periods upon payment to Rigel of the appropriate Extension Fee provided in Section 7.5 on or before (i) the day which is thirty (30) days prior to the end of such Exclusivity Term or (ii) if Novartis has informed Rigel in writing on or before a date with is sixty (60) days prior to the end of such Exclusivity Term, thirty (30) days after receipt of a corresponding invoice from Rigel, whichever is the later. Upon expiration of the Exclusivity Term, Novartis' right to conduct Compound Screening with a Novel Validated Target, subject to the payments required by Section 7.2 and 7.4, shall become nonexclusive

and Rigel shall also have the nonexclusive right, including the right to sublicense, to conduct Compound Screening with such Novel Validated Target.

5.3 NOVARTIS DILIGENCE.

5.3.1 In addition to the payment of the Extension Fee and as a further condition for Novartis to extend the Exclusivity Term, Novartis shall be obligated to maintain itself or through its Affiliates or sublicensees a diligent, continuous program of utilizing the Novel Validated Target to identify molecules useful for the development and manufacture of Products.

5.3.2 Novartis shall be deemed to be maintaining a diligent continuous program with respect to a Novel Validated Target if Novartis (i) is actively using the Novel Validated Target in Novartis' screening systems for Compound Screening or, (ii) is actively undertaking diligent, commercially reasonable efforts, similar to those used for products of comparable commercial potential originating in Novartis for the continuing development of a Product and the commercialization of a Product including, without limitation, the performance of an active derivatisation and lead optimization program, the designation of FSC Status, initiation of clinical trials, submission of regulatory filings and commercial launch of a Product.

5.4 REPORTING. During each applicable Exclusivity Term, Novartis shall provide information on its activities under Section 5.3.1 or 5.3.2 above to the CMC on a quarterly basis. At any time during the Exclusivity Term with respect to a Novel Validated Target, Novartis shall on a not less than quarterly basis provide documentation to the reasonable satisfaction of Rigel that Novartis is maintaining a diligent, continuous program with respect to the Novel Validated Target.

5.5 CONVERSION OF EXCLUSIVE RIGHT. If Novartis does not pay the Extension Fee or does not maintain a diligent continuous program with respect to a Novel Validated Target as provided in Section 5.3 above, then the Exclusivity Term shall be deemed expired and Novartis' screening right under Section 5.1, subject to the payments required by Section 7.2 and 7.4, shall become non-exclusive, perpetual, and fully paid-up, and Rigel shall have the

nonexclusive right, including the right to sublicense, to conduct Compound Screening with such Novel Validated Target.

5.6 RIGEL SCREENING. At any time during the Exclusivity Term with respect to a Novel Validated Target, Novartis, at its sole discretion, may request in writing that Rigel conduct Compound Screening of Rigel's small-molecule compound library against such Novel Validated Target. If Rigel agrees to conduct such screening, the CMC shall establish criteria for an active compound to qualify as a Lead Compound. Thereafter, Rigel will conduct such screening pursuant to a workplan to be agreed to by the Parties. If Rigel identifies a Lead Compound, it shall so notify Novartis, and Section 6.4 hereof shall then apply.

6. LICENSE GRANTS; NONCOMPETITION

6.1 RESEARCH LICENSE GRANTS.

6.1.1 GRANT BY RIGEL. Rigel hereby grants to Novartis and its Affiliates a nonexclusive, non-transferable, royalty-free license during the Research Period for each

Collaboration Project under the Rigel Technology, Rigel Core Technology and Rigel's interest in Project Technology in the Territory, subject to the terms of this Agreement, solely for the purpose of carrying out Novartis' responsibilities under the applicable Collaboration Project.

6.1.2 GRANT BY NOVARTIS. Novartis hereby grants to Rigel and its Affiliates a nonexclusive, non-transferable, royalty-free license during the Research Period for each Collaboration Project under the Novartis Technology and Novartis' interest in the Project Technology, subject to the terms of this Agreement, solely for the purpose of carrying out Rigel's responsibilities under the applicable Collaboration Project.

6.2 COMMERCIAL LICENSE GRANTS.

6.2.1 Subject to Section 5.3 and the other terms and conditions of this Agreement, Rigel hereby grants to Novartis and its Affiliates an exclusive license, with the right to grant sublicenses, under the Rigel Technology and Rigel's interest in the Project Technology to make, have made, use, import, offer for sale and sell Products.

6.2.2 Subject to the terms and conditions of this Agreement, Rigel hereby grants to Novartis and its Affiliates a nonexclusive, non-transferable, royalty-free license under Rigel Core Technology only for confirmational screening and similar uses relating to Novel Validated Targets identified in the course of a Collaboration Project, it being understood that Novartis has the right to use such Technology for the purposes of further development, registration and commercialisation of Products.

6.3 LICENSE TO RIGEL OF IMPROVEMENTS TO RIGEL CORE TECHNOLOGY. Novartis hereby grants to Rigel a nonexclusive, royalty-free, worldwide license, with the right to sublicense, under Novartis' interest in the Project Technology only to the extent it constitutes an improvement of the Rigel Core Technology licensed to Novartis hereunder. For the avoidance of any doubt, the license granted by Novartis under this Section 6.3 shall not include, without limitation, any Patents or Know-How claiming the composition of matter, method of making or use of Products.

6.4 OPTION FOR LICENSE FOR RIGEL LEAD COMPOUND. Novartis shall have an option during the ninety (90) days following receipt of Rigel's notice of identification of a Lead Compound as provided in Section 5.6 to negotiate with Rigel a worldwide, exclusive license to such Lead Compound and compounds derived therefrom under terms to be agreed but including those shown on Exhibit C hereto. If Novartis does not execute such a license within such period, Rigel shall have no further obligation or liability to Novartis for such Lead Compound.

7. FINANCIAL SUPPORT

7.1 RESEARCH SUPPORT. Novartis will provide funding to support Rigel's efforts during the Research Period of each Joint Project, on an FTE basis at a rate of $250,000 per year multiplied by the number of FTEs as shown in Exhibit B for such Joint Project. The amounts payable shall be paid in advance by certified or bank check or wire transfer in United States dollars in four equal payments to be paid quarterly upon presentation of a corresponding invoice by Rigel. Payments shall be made no later than (a) by the first (1st) business day of each applicable Research Period quarter or (b) thirty (30) days after receipt of the

corresponding invoice, whichever is the later. Research support under this Section 7.1 shall not be credited against any equity, milestone or royalty payments due Rigel hereunder.

7.2 MILESTONE PAYMENTS TO RIGEL. Novartis will pay to Rigel the following amounts ("Milestone Payments") in respect of the achievements with respect to each Joint Project and each At-Novartis Project:

<TABLE>
<CAPTION>

MILESTONE EVENT		AMOUNT OF PAYMENT
<S>		<C>
1)	NOTICE DATE OF THE FIRST NOVEL VALIDATED TARGET	$500,000
2)	NOTICE DATE OF EACH SUBSEQUENT NOVEL VALIDATED TARGET - PER NOVEL VALIDATED TARGET	$250,000
3)	INITIATION OF COMPOUND SCREENING WITH EACH NOVEL VALIDATED TARGET:	
	PER NOVEL VALIDATED TARGET:	
	FIRST FOUR (4) NOVEL VALIDATED TARGETS, CUMULATED OVER ALL COLLABORATION PROJECTS	$1.25 million
	EACH SUBSEQUENT NOVEL VALIDATED TARGET	$1 million
4)	FSC STATUS DECLARATION OF THE FIRST PRODUCT IDENTIFIED IN COMPOUND SCREENING CONDUCTED AGAINST EACH NOVEL VALIDATED TARGET PURSUANT TO SECTION 5.3 - PER NOVEL VALIDATED TARGET	$1.5 million
5)	FIRST PRODUCT IDENTIFIED ON THE BASIS OF A NOVEL VALIDATED TARGET ENTERS PHASE I CLINICAL TRIALS - PER NOVEL VALIDATED TARGET	$2.5 million

</TABLE>

All Milestone Payments to be made by Novartis to Rigel pursuant to this Section 7.2 shall be made within thirty (30) days of receipt of an invoice from Rigel. Novartis shall promptly report to Rigel the occurrence of the Milestone Events 3), 4), and 5).

7.3 PROJECT ACCESS PAYMENTS. No later than (a) by the Commencement Date of each Joint Project and each At-Novartis Project or (b) thirty (30) days after receipt of the corresponding invoice from Rigel, whichever is the later, Novartis will pay Rigel a project access fee of $400,000.

7.4 ROYALTIES. Novartis shall pay to Rigel all royalties due to Third Party licenses listed on Exhibit D hereto in the event Novartis shall practice the inventions of the Patents licensed thereunder. Further, if applicable pursuant to Articles 5.6 and 6.4, Novartis shall pay to Rigel the royalties as provided in Exhibit C. For the avoidance of any doubt, Novartis shall pay to Rigel no other royalties under this Agreement.

7.5 EXTENSION FEE. As provided in Section 5.2, the amount payable by Novartis to extend the Exclusivity Term for each year after the initial two (2) year Exclusivity Term

for a Novel Validated Target ("Extension Fee") shall be $50,000 for the third (3rd) year, $100,000 for the fourth (4th) year and, $200,000 for each of the fifth (5th), sixth (6th) and seventh (7th) year.

8. INTELLECTUAL PROPERTY

8.1 OWNERSHIP OF PROJECT KNOW-HOW; INVENTIONS. Project Know-How invented (as determined in accordance with United States rules of inventorship) solely by employees of one Party during the course of a Collaboration Project ("Sole Inventions") shall be the property of such Party. In the event that employees of Novartis and Rigel jointly invent any Project Know-How (again as determined in accordance with United States rules of inventorship), such Project Know-How shall be owned jointly by Novartis and Rigel, each to own an undivided one-half (1/2) interest in such Project Know-How ("Joint Invention") except as provided herein. Each Party shall cooperate with the other in completing any patent applications relating to Joint Inventions, and in executing and delivering any instrument required to assign, convey or transfer to such other Party its undivided one-half (1/2) interest.

8.2 PATENT PROSECUTION.

8.2.1 Novartis Patents and Rigel Patents licensed hereunder

shall be prosecuted and maintained by Novartis and Rigel, respectively, at such Party's option and its own expense; provided, however, that the Parties shall consult with and consider the comments of the CMC with respect to the prosecution of applications for such patents.

8.2.2 Each Party will prepare, file, prosecute and maintain patent applications for its Sole Inventions and shall be responsible for related interference proceedings.

8.2.3 In case of Joint Inventions, the Parties will mutually agree on the responsibility for filing and prosecuting applications or patent applications relating thereto, and the defense against Third Parties who infringe on Patents issuing thereon.

8.3 INFRINGEMENT OF THIRD-PARTY RIGHTS.

8.3.1 If a Third Party claims that the practice of the Rigel Technology or Rigel Core Technology under this Agreement infringes on its Patents, each Party shall notify the other Party promptly upon learning of such claim.

8.3.2 Promptly upon such notification, the Parties shall meet to discuss the strategy and appropriate steps to be taken to deal with such claim, including, without limitation, by working around the Patents of the Third Party, by practicing the Rigel Technology or Rigel Core Technology in countries where the Third Party has no applicable Patents, by seeking to invalidate the Third Party Patents or by entering into negotiations with such Third Party regarding a license under its Patents. The Parties shall further agree on an equitable and fair distribution of the costs resulting from any such course of action.

9. REPRESENTATIONS AND WARRANTIES

9.1 REPRESENTATIONS AND WARRANTIES. Each Party represents and warrants to the other that:

9.1.1 CORPORATE POWER. It is duly organized and validly existing under the laws of its state or country of incorporation, and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof.

9.1.2 DUE AUTHORIZATION. It is duly authorized to execute and deliver this Agreement and to perform its obligations hereunder, and the person or persons executing this Agreement on its behalf has been duly authorized to do so by all requisite corporate action.

9.1.3 BINDING AGREEMENT. This Agreement is legally binding upon it and enforceable in accordance with its terms. The execution, delivery and performance of this Agreement by it does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it may be bound, nor violate any material law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.

9.1.4 GRANT OF RIGHTS; MAINTENANCE OF AGREEMENTS. It has not, and will not during the Term of the Agreement, grant any right to any Third Party which would conflict with the rights granted to the other Party hereunder. It has (or will have at the time performance is due) maintained and will maintain and keep in full force and effect all agreements necessary to perform its obligations hereunder.

9.1.5 VALIDITY. It is aware of no action, suit or inquiry or investigation instituted by any governmental agency which questions or threatens the validity of this Agreement.

9.1.6 EMPLOYEE OBLIGATIONS. All of its employees, officers and consultants have executed agreements requiring in the case of employees and officers, assignment to the Party of all inventions made during the course of and as a result of their association with such Party and obligating the individual to maintain as confidential the confidential information of the Party, as well as the confidential information of a Third Party which such Party may receive.

9.2 DISCLAIMER CONCERNING TECHNOLOGY. THE TECHNOLOGY PROVIDED BY EACH PARTY HEREUNDER IS PROVIDED "AS IS" AND EACH PARTY EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, NONINFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES OR ARISING FROM A COURSE OF DEALING, USAGE OR TRADE PRACTICES, IN ALL CASES WITH RESPECT THERETO. Without limiting the generality of the foregoing, each Party expressly does not warrant (i) the success of any Program of Research or (ii) the safety or usefulness for any purpose of the technology it provides

hereunder.

10. CONFIDENTIALITY; PUBLICATION

10.1 CONFIDENTIALITY. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing by the Parties, the Parties agree that, for the Term of the Agreement and for five (5) years thereafter, the receiving Party (the "Receiving Party") shall keep confidential and shall not publish or otherwise disclose and shall not use for any purpose other than as provided in this Agreement any Confidential Information furnished to it

by the other Party (the "Disclosing Party") pursuant to this Agreement unless the Receiving Party can demonstrate by contemporaneous, competent written proof that such Confidential Information:

(a) was already known to the Receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the Disclosing Party;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party in breach of the Agreement;

(d) was disclosed to the Receiving Party, other than under an obligation of confidentiality to a Third Party, by a Third Party who had no obligation to the Disclosing Party or any Third Party not to disclose such information to others; or

(e) was independently discovered or developed by the Receiving Party without the use of Confidential Information belonging to the Disclosing Party.

10.2 AUTHORIZED DISCLOSURE.

10.2.1 Each Party may disclose Confidential Information belonging to the other Party to the extent such disclosure is reasonably necessary in the following instances:

(a) filing or prosecuting Patents relating to Project Know-How;

(b) regulatory filings;

(c) prosecuting or defending litigation;

(d) complying with applicable governmental regulations;

(e) conducting pre-clinical or clinical trials of Products; and

(f) disclosure to Affiliates, sublicensees, employees, consultants or agents who agree to be bound by similar terms of confidentiality and non-use at least equivalent in scope to those set forth in this Article 10.

10.2.2 Notwithstanding the foregoing, in the event a Party is required to make a disclosure of the other Party's Confidential Information pursuant to this Section 10.2 it will, except where impracticable, give reasonable advance notice to the other Party of such disclosure and use commercially reasonable efforts to secure confidential treatment of such information. In any event, the Parties agree to take all reasonable action to avoid disclosure of Confidential Information hereunder. The Parties will consult with each other and agree on the provisions of this Agreement to be redacted in any filings made by the Parties with the Securities and Exchange Commission or as otherwise required by law.

10.3 PUBLICATIONS.

10.3.1 REVIEW AND APPROVAL. Each Party to this Agreement recognizes that the publication of papers, including oral presentations and abstracts, regarding the Research Cooperation, subject to reasonable controls to protect Confidential Information, can be beneficial to both Parties. However, each Party shall have the right to review and approve any paper proposed for publication by the other Party, including oral presentations and abstracts,

which utilizes data generated from the Research Cooperation or includes Confidential Information of the reviewing Party.

10.3.2 REVIEW AND APPROVAL PROCESS. At least forty-five (45) days before any such paper is presented or submitted for publication, the Party proposing publication shall deliver a complete copy to the other Party. The receiving Party shall review any such paper and give its comments to the publishing Party within thirty (30) days of the delivery of such paper to the receiving Party. With respect to oral presentation materials and abstracts, the Parties shall make reasonable efforts to expedite review of such materials and abstracts, and shall return such items as soon as practicable to the publishing Party with appropriate comments, if any, but in no event later than thirty (30) days from the delivery date thereof to the receiving Party. The publishing Party shall comply with the other Party's request to delete references to such other Party's Confidential Information in any such paper and agrees to withhold publication of same an additional ninety (90) days in order to permit the Parties to obtain patent protection, if either of the Parties deem it necessary, in accordance with the terms of this Agreement.

10.4 SAMPLES. Samples of compounds provided by one Party (the "Supplying Party") to the other Party (the "Receiving Party") during the Research Program shall not be supplied or sent by the Receiving Party to any Third Party without the written consent of the Supplying Party. The Receiving Party shall return to the Supplying Party any samples not used upon expiration or termination of the applicable Research Period, except that Novartis may retain such samples to the extent necessary to exercise the licenses granted in Section 6.2.

11. TERM AND TERMINATION

11.1 TERM OF THE AGREEMENT. This Agreement shall become effective upon the Effective Date and continue until the later of (i) the expiration of the obligation of Novartis to pay royalties as provided in Section 7.4, and (ii) the expiration of the last Patent licensed to Novartis under this Agreement, whereupon the licenses granted under Sections 6.2 and 6.3 shall be deemed non-exclusive, perpetual and fully paid-up.

11.2 TERMINATION FOR MATERIAL BREACH. Each Party shall have the right to terminate this Agreement after ninety (90) days prior notice to the other that the other Party has committed a material breach of the Agreement other than performance of obligations under a Collaboration Project, unless the other Party cures (to the extent practicable) the breach within such period of time. Licenses granted to the non-breaching Party under Section 6 of this Agreement shall not be affected by termination for material breach. All licenses granted to the breaching Party under Section 6 of this Agreement shall automatically terminate upon such termination.

11.3 ACCRUED RIGHTS, SURVIVING OBLIGATIONS. Expiration or termination of this Agreement shall not affect any accrued rights or obligations of either Party. Sections 9, 10, 11 (and Section 6 to the extent referenced therein), 12, 13, 14.1, and 14.3 through 14.10, and any

definitions of terms used therein shall survive any expiration or termination of this Agreement.

12. INDEMNITY

12.1 INDEMNIFICATION. Each Party hereby agrees to save, defend and hold the other Party and its directors, officers, employees, and agents harmless from and against any and all claims, suits, actions, demands, liabilities, expenses and/or loss, including reasonable legal expense and attorneys' fees (collectively, "Claims") for damage to persons or property resulting directly or indirectly from actions in connection with a Collaboration Project by the indemnifying Party, its Affiliates, agents or sublicensees, but only to the extent such Claims result from the gross negligence or willful misconduct of the indemnifying Party or its Affiliates, agents or sublicensees and do not result from the negligence of the Party seeking indemnification.

12.2 PRODUCT LIABILITY. Novartis hereby agrees to indemnify, hold harmless and defend Rigel and its directors, officers, employees, and agents against any Claim or Claims, including, but not limited to claims for bodily injury and death, resulting from or arising out of the manufacture, use or sale of Products by Novartis, its Affiliates and sublicensees.

12.3 CONTROL OF DEFENSE. Any entity entitled to indemnification under this Article 12 shall give notice to the indemnifying Party of any Claims that may be subject to indemnification and, promptly after learning of such Claim, the indemnifying Party shall assume the defense of such Claims with counsel reasonably satisfactory to the indemnified Party. If such defense is assumed by the indemnifying Party with counsel so selected, the indemnifying Party will not be subject to any liability for any settlement of such Claims made by the indemnified Party without its consent (but such consent will not be unreasonably

withheld or delayed), and will not be obligated to pay the fees and expenses of any separate counsel retained by the indemnified Party with respect to such Claims.

13. GOVERNING LAW; DISPUTE RESOLUTION

13.1 GOVERNING LAW. This Agreement shall be governed by laws of the state of Delaware, as such law applies to contracts entered into in Delaware by residents of Delaware, without reference to its choice of law provisions.

13.2 DISPUTE RESOLUTION. In the event of any dispute, the Parties shall refer such dispute to a designated executive of Rigel and a designated executive of Novartis for attempted resolution by good faith negotiations within thirty (30) days after such referral is made. In the event such executives are unable to resolve such dispute within such thirty (30) day period, either Party may invoke the provisions of Section 13.3 below.

13.3 JURISDICTION AND VENUE. Except as provided in Section 13.2 above, any claim or controversy arising out of or related to this Agreement or any breach hereof shall be adjudicated in the federal district court of Dover, Delaware, and the Parties hereby consent to the jurisdiction and venue of such court.

14. GENERAL PROVISIONS

14.1 NOTICES. All notices required or permitted to be given under this Agreement shall be in writing and shall be mailed by registered or certified mail addressed to

the signatory to whom such notice is required or permitted to be given and transmitted by facsimile to the number indicated below. All notices shall be deemed to have been given when mailed, as evidenced by the postmark at the point of mailing, or faxed; provided that such fax is confirmed by electronic confirmation of transmission.

All notices to Novartis shall be addressed as follows:

Novartis Pharma AG
Lichtstrasse 35
P.O. Box
CH-4002 Basel
Switzerland
Attn: Legal Department
Fax: +41-61-324-6859

All notices to Rigel shall be addressed as follows:

Rigel Pharmaceuticals, Inc.
240 East Grand Avenue
South San Francisco, CA 94080
Attn: President
Fax: +1-650-624-1101

with a copy to:

Cooley Godward LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, California 94306
Attn: Patrick A. Pohlen, Esq.
Fax: (650) 857-0663

Any Party may, by written notice to the other, designate a new address or fax number to which notices to the Party giving the notice shall thereafter be mailed or faxed.

14.2 FORCE MAJEURE. No Party shall be liable for any delay or failure of performance to the extent such delay or failure is caused by circumstances beyond its reasonable control and that by the exercise of due diligence it is unable to prevent, provided that the Party claiming excuse uses commercially reasonable efforts to overcome the same.

14.3 ENTIRETY OF AGREEMENT. This Agreement embodies the entire, final and complete agreement and understanding between the Parties and replaces and supersedes all prior discussions and agreements between them with respect to its subject matter. No modification or waiver of any terms or conditions hereof shall be effective unless made in writing and signed by a duly authorized officer of each Party.

14.4 NON-WAIVER. The failure of a Party in any one or more instances to insist upon strict performance of any of the terms and conditions of this Agreement shall not constitute a waiver or relinquishment, to any extent, of the

right to assert or rely upon any such terms or conditions on any future occasion.

14.5 DISCLAIMER OF AGENCY. Neither Party is, or will be deemed to be, the legal representative or agent of the other, nor shall either Party have the right or authority to assume, create, or incur any third Party liability or obligation of any kind, express or implied, against or in the name of or on behalf of another except as expressly set forth in this Agreement.

14.6 SEVERABILITY. If a court of competent jurisdiction declares any provision of this Agreement invalid or unenforceable, or if any government or other agency having jurisdiction over either Rigel or Novartis deems any provision to be contrary to any laws, then that provision shall be severed and the remainder of the Agreement shall continue in full force and effect. To the extent possible, the Parties shall revise such invalidated provision in a manner that will closely approximate the Parties' original intent.

14.7 AMBIGUITIES. The Parties hereby acknowledge that they have drafted this Agreement jointly. Thus, any presumption that ambiguous provisions shall be construed against the party drafting an agreement is inapplicable, and each Party expressly agrees not to invoke said presumption in the event of a dispute between the Parties relating to this Agreement.

14.8 AFFILIATES; ASSIGNMENT. Except as otherwise provided herein, neither Party may assign its rights or delegate its duties under this Agreement without the prior written consent of the other Party, not to be unreasonably withheld; provided, however, that either Party may assign this Agreement to any of its Affiliates or to any successor by merger or sale of substantially all of the assets or business unit to which this Agreement relates; provided further, however, that any such assignment shall be made in a manner such that the assignee expressly undertakes in writing to be liable and responsible for the performance and observance of all its duties and obligations hereunder. This Agreement shall be binding upon the successors and permitted assigns of the Parties. Any attempted delegation or assignment not in accordance with this Section 14.7 shall be of no force or effect.

14.9 HEADINGS. The headings contained in this Agreement have been added for convenience only and shall not be construed as limiting.

14.10 COUNTERPARTS. This Agreement may be executed in one or more counterparts, each of which shall be an original and all of which shall constitute together the same document.

IN WITNESS WHEREOF, the Parties hereto have duly executed this Agreement.

RIGEL PHARMACEUTICALS, INC.	NOVARTIS PHARMA AG
By: /s/ James M. Gower	By: /s/ Paul Herring
Name: James M. Gower	Name: Dr. Paul Herring
Title: President & CEO	Title: Head of Research

EXHIBIT A-1

T-CELL PROGRAM OF RESEARCH

NOVEL REGULATORY PATHWAYS IN T AND B LYMPHOCYTES

NOVARTIS PROJECT OUTLINE

PROJECT I: IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT T CELL ACTIVATION

INTRODUCTION

Activation of specific signaling pathways in lymphocytes determines the quality, magnitude and duration of immune responses. In transplantation, acute and chronic inflammatory diseases, and autoimmunity, it is these pathways that are responsible for the induction, maintenance and exacerbation of' disuse lymphocyte responses. Of the many activation pathways that have been elucidated, most are ubiquitous and not unique to a particular cell lineage. The goal of this proposal is to identify and validate novel signaling molecules specific for T cell activation and effector function. From these molecules, T cell-specific targets will be identified that axe effective in modulating immune-mediated processes. A combination of high throughput functional and yeast two-hybrid genetic screens will be employed to isolate and map novel signaling molecules in lymphocyte activation. Engagement of the B cell receptor (BCR) in conjunction with T cell assistance stimulates humoral immunity characterized by immunoglobulin production and antigen presentation by B cells. Likewise, T cell signaling through the T cell receptor (TCR) and other molecules such as CD28 leads to specific cellular immunity. Summarized below, in Table 1, is our strategy for identifying and validating novel T cell intracellular signaling molecules. Each approach, its readout, and the libraries to be used are detailed in the remaining sections of the proposal.

TABLE 1. SUMMARY OF SCREENS TO IDENTIFY INTRACELLULAR REGULATORS OF LYMPHOCYTE ACTIVATION AND/OR EFFECTOR FUNCTION.

<TABLE>
<CAPTION>

APPROACH	READOUT	INTRACELLULAR TARGETING STRUCTURES AND MOTIFS
<S> PROJECT I IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT T CELL ACTIVATION	<C>	<C>
1. PRIMARY SCREENS		
1.1 Primary peptide screen for inhibition of CD25 (IL-2R(alpha) chain) in a cell line (to be determined by the RMC) stimulated through CD3 +/-CD28	Enrichment by FACS for absent or decreased CD25 expression (measured by (alpha) -CD25 monoclonal antibody) Enrichment by FACS for absent or decreased reporter activity (fluorescence-based screen) or isolation of survivors (survival-based screen)	GFP/BFP scaffold peptide libraries (12 mer and 18 mer) Potential additional library scaffolds (constrained 18 mer (beta)- lactamase, DHFR) to be determined by the RMC
1.2 Primary peptide screen for inhibition of IL-2 promoter activity in a cell line stimulated through CD3 +/-CD28		
2. SECONDARY ASSAYS		
2.1 Secondary assays measuring expression of cell surface T cell co-stimulatory molecules in T cell lines (to be determined by the RMC) and primary human PBL T cells stimulated through CD3 +/-CD28	Analytical flow cytometry measuring expression of CD28, CTLA-4, ICOS, CDw150 and CD40L (additional markers to be determined by the RMC) Analytical flow cytometry measuring expression of Th1/Th2 differentiation markers to be determined by the RMC (e.g., (beta) subunits of IL-12 and IFN(gamma) receptors, ESTE-2, IL-12R(alpha), CD45RA, CD45RO and CD148)	
2.2 Secondary assays measuring T cell differentiation into Th1 and Th2 cells in T cell lines (to be determined by the RMC) and primary human PBL T cells; stimulus to be determined by the RMC		
3. PATHWAY MAPPING		
3.1 Yeast two-hybrid screens on cDNA and peptide hits to identify intracellular binding	Lac Z+, His	cDNA: -Anti-CD3 activated T cells from human spleen

partners; functional
analysis of interacting
proteins

3.2 Yeast-Two Hybrid isolation of peptides that bind to functional cDNAs;	Lac Z+, His+	Constrained 18 mer and other scaffolds (GFP/BFP, (beta)-lactamase, DHFR) to be

</TABLE>

<TABLE>

functional analysis of these peptides		determined by the RMC

</TABLE>

PROJECT I.

IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT T CELL ACTIVATION.

1 Primary Screens

Screens in Project I will isolate inhibitors/modulators of TCR-induced T cell activation (Appendix A). CD25 and IL-2 are such fundamental markers of activated T cells that their upstream regulators may also be biased toward T cell co-stimulation and/or Thl/2 development. Blockade of the above markers will negatively affect T cell function and B-T cell interactions leading to T cell' activation. Modulating T cell activation and function has clinical relevance for transplantation, autoimmunity and inflammatory diseases.

1.1 Primary peptide screen for inhibition of CD25 in T cells stimulated through CD3 +/-CD28

CD3 positive T cell lines will be selected for their ability to upregulate CD25 and produce IL-2 in response to crosslinking of their TCR. The cell lines selected for primary screening will possess kinetics and levels of expression of' the above markers that are most similar to primary human peripheral blood and splenic T cells. In primary screens, CD25 will be measured by flow cytometry and enriched for desired phenotypes following peptide library expression. The T cell lines will each be infected with 4 peptide libraries: two loop-3 BFP scaffold peptide libraries (12 mer and 18 mer) and two loop-4 BFP scaffold peptide libraries (12 mer and 18 mer. Other library scaffolds may be utilized as deemed necessary by the RMC (constrained 18 mer, (beta)-lactamase, DHFR). After several rounds of enrichment, individual peptide sequences will be tested for function in the original screening assay.

1.2 Functional screening for inhibitors of TCR-induced transcription of the IL-2 promoter in cell lines carrying the IL-2 promoter upstream of a reporter fused to death genes.

An alternative method for the flow-based screen described in section 1.1 is to generate cell lines that monitor IL-2 promoter activity by survival. A CD3-responsive fragment of the IL-2 promoter will be cloned into a retroviral vector in the reverse orientation. This will be upstream of a splice site followed by a reporter (GFP) and then an IRES ending with a fusion of two death genes, thymidine kinase (TK) and cytosine deaminase (CD) (Appendix B). This construct will be packaged and used to infect the CD3-responsive T cell lines. In response to activation of the IL-2 promoter, the infected cells will become fluorescent or, after addition of the death ligand (ganciclovir for TK and 5-FC (fluorocytosine) for CD), will die. These reporter/survival T cell lines will be infected with 4 libraries: two loop-3 BFP scaffold peptide libraries (12 mer and 18 mer) and two loop-4 BFP scaffold peptide libraries (12 mer and 18 mer). Other library scaffolds may be utilized as deemed necessary by the RMC (constrained 18 mer, (beta) lactamase, DHFR). Peptides capable of inhibiting promoter activity will decrease GFP expression. Peptides capable of shutting off the promoter will rescue the cells from death in the presence of the death gene inducers. After sufficient rounds of enrichment, individual peptide sequences will be tested for function in the original screening assay. This reporter/survival strategy is adaptable to any promoter that is inducible by an extracellular signal. As proof of principle, we have generated cell lines expressing TK,

CD8/CD95 and TK/GFP fusion that are efficiently killed in the presence of ganciclovir or anti-CD8 monoclonal antibody, respectively (Appendix C).

2. SECONDARY ASSAYS

2.1 Secondary assays measuring expression of cell surface T cell co- stimulatory molecules in T cell lines and primary human PBL T cells stimulated through CD3 +/-CD28

Confirmed peptide hits from the primary functional screens will be subjected to secondary assays in T cell lines and primary peripheral blood and splenic T cells. In these assays, the effects of the hits on CD3-induced co-stimulation will be tested. Markers associated with T cell co-stimulation will be assessed by analytical flow cytometry for their modulation by the primary peptide hits. The markers that will be analyzed are CD28, ICOS, CTLA-4, CDwl50 and CD40L (other markers may be added as deemed appropriate by the RMC). Peptides that demonstrate desirable characteristics will be used as bait in a genetic yeast two-hybrid screen to isolate their intracellular binding partner. These cDNAs will be validated by a number of assays to test whether they directly regulate T cell co-stimulation or not. Figure I summarizes the interrelationship of the various methods described above to map functional targets in T cell activation.

FIGURE 1

DIAGRAM

2.2 Secondary assays measuring T cell differentiation into Th1 and Th2 cells in T cell lines and primary human PBL T cells

Confirmed peptide hits from the primary functional screens will be subjected to secondary assays in T cell lines and primary peripheral blood and splenic T cells. In these assays, the effects of the hits on Th1/2 development will be tested. Markers associated with Th1/2 development will be assessed by analytical flow cytometry for their modulation by the primary peptide hits. The markers that will be analyzed are IL-12R-alpha and beta-2 chains, IFN-gamma-R-beta chain, ESTE-2, CD45RA, CD45RO and CD148 (other markers may be added as deemed appropriate by the RMC). Peptides that demonstrate desirable characteristics will be used as bait in a gneetic yeast two-hybrid screen to isiolate their intracellular binding partner. These cDNAs will be validated by a number of assays to test whether they directly regulate Th1/2 development or not. Figure 1 summarizes the interrelationship of the various methods described above to map functional targets in T cell activation.

EXPERIMENTAL DESIGN AND METHODS

PROJECT I.

IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT T CELL ACTIVATION.

RATIONALE:

T cells are pivotal in determining the type of immune response and its duration. Alterations in T cell activation and regulation are implicated in numerous diseases such as acute and chronic inflammation, autoimmunity and graft rejection. The screens in this approach will identify T cell activation-specific signaling molecules and assess their bias towards co-stimulation and/or Thl/2 development. This will permit specific intervention into T cell-mediated processes that contribute to or are the basis of disease.

1. PRIMARY SCREENS.

1.1 Primary peptide screen for inhibition of CD25 in T cells stimulated through CD3 +/-CD28

Several T cell lines, including MOLT, Jurkat, Hut-102, Hut-78 and those to be determined by the Novartis - Rigel Joint Research Committee, will be tested for the presence of surface CD3. Those that express CD3 will be cultured with anti-CD3 to crosslink the TCR and test for the upregulation of CD25 and production of IL-2 (Appendix A). It is important that the kinetics and levels of expression of these markers overlap those observed in anti-CD3 stimulated primary human T cells.

PEPTIDE LIBRARY SCREENING AND PROTEIN TARGET IDENTIFICATION.

Cell lines selected as described above will be infected with one of 4 peptide libraries containing random 12 or 18 mer peptides on loop 3 or 4 of a BFP scaffold. Each of the peptide libraries will be packaged into infectious viral particles (for protocol, see Appendix E). Each library sequence will be upstream of a reporter gene to identify and/or select for infected cells and relative peptide expression (Appendix F). Likewise, for hit confirmation, each individual peptide sequence will be engineered into the same retroviral vectors upstream of a reporter gene.

We have developed several retroviral constructs to control all aspects of

peptide expression and localization. This gives us great flexibility when designing retroviral libraries within any cell line and with whatever characteristics are deemed necessary for intracellular peptide expression (see Appendix G). Constrained peptides have many valuable features compared to linear peptides, including enhanced resistance to proteolysis and a restricted conformation space that can result in a higher binding affinity for cognate binding proteins.

Each screen will start with production of the primary retrovirus peptide library. The primary library will be used to infect 10(8) to 10(9) T cells. After infection, the cells will be stimulated with anti-CD3 and, two days later, those cells containing a library member (positive for the fluorescent reporter) and inhibited for surface expression of CD25 will be enriched by FACS. This enriched population will be subjected to biological rescue to amplify and transfer the integrated peptide sequences to naive cells. The process will be repeated

until significant alteration in the expression of CD25 is observed by FACS. At this point, individual peptide sequences will be cloned and tested in the original screening assay for their ability to alter phenotype.

It will take approximately 4-6 rounds of enrichment to identify individual sequences capable of inhibiting TCR induction of CD25. For a discussion of the statistics associated with enrichment, see Appendix H. The most important factor that influences the number of enrichment rounds necessary to identify individual peptide hits is the ratio between real positive hits in the original library and heritable false positives. The frequency of real positive hits is dependent upon the qualitative ability of the over-expressed library member to alter the pathway of interest. Enrichment of real positive peptides becomes less efficient with false positive rates above 2%. For this reason, great effort is placed in developing robust cell lines.

To obtain phenotypic enrichment in the primary screens, the desired phenotype must be transferred from the enriched library-infected population to a naive population repetitively. Historically, we have used RT-PCR to rescue library members from the phenotypically desirable cells of one round, generate a new retroviral library and infect naive cells to enrich once again for the desired altered cell phenotype. Although RT-PCR works, uneven amplification will decrease overall amplification of real peptide hits from one round to another. Additional rounds of library enrichment can overcome this overall decrease of real hit amplification. However, to overcome the potential problems of RT-PCR and for more efficient transfer of phenotype from one round to the next, we are replacing RT-PCR amplification with a direct biological rescue (`Appendix I). Biological rescue involves direct transfer of recombinant retroviral inserts from positively identified cell clones into naive cells for re-testing. By supplying retrovirus proteins GAG-POL-ENV to library-enriched cells, integrated proviral transcripts encoding putative peptide hits are selectively re-packaged and secreted as new virions capable of infecting new cells. Positive cells can be converted to retroviral producers by superinfection of GAG-POL-ENV genes or alternatively, tetracycline-inducible packaging functions can be pre-engineered into target cell lines. By either strategy, peptides from enriched cells can be selectively transferred to new cells and re-tested for phenotypic effects, eliminating the time-intensive and potentially biased intermediary molecular cloning steps. Proof of principle demonstrating the feasibility of this approach is shown in Appendix J.

1.2 Functional screening for inhibitors of TCR-induced transcription of the IL-2 promoter in cell lines carrying the IL-2 promoter upstream of n reporter fused to death genes

An alternative to the flow-based screens outlined above is to generate cell lines that survive when promoters critical to T cell activation are inhibited. This is a very stringent assay with very low background. This is accomplished by infecting CD3-inducible T cell lines with the following construct: A retroviral vector containing a TCR-responsive fragment of the IL-2 promoter in the reverse orientation followed by a splice site, a reporter gene such as GFP, an IRES and finally a fusion of two death genes, TK and CD (Appendix B). The determination of the appropriate death genes to use will be dependent on which is most robust in the particular T cell line chosen. Briefly, cells will be infected with the reporter/death gene construct and induced with anti-CD3. Cells expressing higher levels of GFP will then be enriched by FACS. The anti-CD3 will be removed and the cells will be enriched for absent or decreased reporter fluorescence. Alternatively, pools of infected cells are divided and grown in parallel so that one set can be induced and tested for GFP/death

gene induction without having to subject its sibling to TCR engagement. This will control for any lasting effect TCR engagement may have on the GYP reporter and the fused death genes.

The method will be as follows: The survival cell lines from above are infected with the desired library (Appendix E). Leaky cells (constitutive expression of the IL-2 promoter) are not a concern since the addition of the second signal is required to kill cells. The second signal will be withheld until the library has had time to express allowing all possible promoter inhibitors to manifest. Two days after library infection, the cells are induced with anti-CD3 in the presence of the appropriate death signal (ganciclovir for TK and 5-FC for CD). Cells carrying peptides that inhibit induction of the engineered IL-2 promoter fragment will not produce the death genes and will survive. After the survivors grow out (approximately I week), they will again be subjected to anti-CD3 and the death signals. The genes encoding the peptides responsible for the survivors will be transferred to naive cells by biological rescue as previously described (section 1.1). The identification of individual inhibitory peptides should occur in only 3-4 rounds since the false positive background for survival screens is lower than for FACS-based screening. Once enrichment is achieved and individual sequences are independently shown to inhibit IL-2 promoter activation, these sequences will be introduced into a standard set of secondary and orthogonal assays as described below in section 2. As well, the proteins they interact with will be identified as discussed in section 3 below.

2 SECONDARY ASSAYS TO ASSESS PHYSIOLOGIC CHARACTERISTICS AND SPECIFICITY OF PRIMARY FUNCTIONAL PEPTIDE HITS.

2.1 Secondary assays measuring expression of cell surface T cell co-stimulatory molecules in T cell lines and primary human PBL T cells stimulated through CD3 +/-CD28

After library enrichment, individual sequences shown to modulate CD25 expression or IL-2 promoter activation will be introduced into a standard set of secondary assays. The overall aim of these assays is to test the specificity and physiologic characteristics of the functional peptide hits. This will be a critical step in determining priority of hits for more intensive investigation. Many of these assays will be performed in T cell lines and primary peripheral blood or splenic T cells. The ability of the hits to alter anti-CD3 induced expression of co-stimulatory molecules will be measured. These include but are not limited to CD28, ICOS, CTLA-4 CDwl50 and CD40L. Functionally validated peptide hits will then be used as bait to isolate their interacting protein targets by genetic (yeast two-hybrid) screening technologies (see section 3 for yeast two-hybrid details). These new interacting partners can be cycled into the functional assays to assess their specific role in T cell signaling. In this manner, activation pathways that mediate multiple functions in T cells can be deconvoluted in a step-wise manner.

2.2 Secondary assays measuring T cell differentiation into Th1 and Th2 cells in T cell lines and primary human PBL T cells

Just as described above in section 2.1, peptide hits from the primary screens will be tested for their ability to influence Thl/2 development. CD3 activation combined with the presence of the appropriate cytokines will bias T cells towards Thl or Th2 development. Cell surface markers such as IL-12R (alpha) and (beta)2 chains, IFN-(gamma)R (beta) chain, ESTE-2, CD45RA, CD45RO and CD148 have been shown to be associated Thl/2 development. The peptide hits will be assessed for their ability to modulate these markers. They will also be tested for their

ability to alter the secretion of cytokines associated with Thl (IFN-(gamma)) and Th2 responses (IL-4).

Functionally validated peptide hits will then be used as bait to isolate their interacting protein targets by genetic (yeast two-hybrid) screening technologies (see section 3 for yeast two-hybrid details). These new interacting partners can be cycled into the functional assays to assess their specific role in T cell signaling. In this manner, activation pathways that mediate multiple functions in T cells can be deconvoluted in a step-wise manner.

PROJECT I - PATHWAY MAPPING.

FUNCTIONAL MAPPING OF NOVEL T CELL SIGNALING PROTEINS.

3.1 Yeast two-hybrid screening, to identify and map proteins that interact with functional peptide hits.

Peptides that modulate lymphocyte activation do so by binding to intracellular proteins that are members of signal transduction pathways which ultimately lead to diverse phenotypic endpoints in T cells. Identification of functional peptide-target protein pairs in these pathways will enable subsequent screening for low molecular weight compounds that alter T cell function.

Priority peptide hits from the library screens that alter lymphocyte activation will be subjected to yeast two-hybrid screening to identify their intracellular binding partners. The libraries to be screened are described in

section 1 above. The screening protocol for identification of interacting proteins is summarized in Appendix D. Briefly, sequences encoding the target peptides will be cloned into pAS2-1K to fuse to the C-terminal of GAL4 DNA binding domain. The oligos can also be cloned into pAS2N to fuse to the N-terminal of GAL4 DNA binding domain. Both bait plasmids can be used for subsequent screenings. The bait plasmids will be transformed into the Y190 yeast strain. This yeast strain has the highest sensitivity for yeast two-hybrid screening. Optimal 3AT concentration needed to suppress any HIS background expression will be determined on SD-WH+3AT plates. The cDNA libraries will be fused with the GAL4 activation domain and transformed into the yeast already containing the bait plasmid. At least 20 million transformants from each library will be screened on SD-LWH+3AT plates. HIS+ and LacZ+ clones will be grown up in SD-L liquid medium to retrieve plasmid and for retransformation into Y190 to verify the binding specificity.

Isolated proteins that are determined to interact with the functional sequence baits will be tested for their ability to affect T cell activation in the previously discussed secondary assays. The various ways to determine function in the secondary assays is by simple overexpression of the putative target protein and any potential dominant-negative domains, and random mutagenesis to destroy functioning domains (Appendix K).

INITIAL STEPS FOR TARGET IDENTIFICATION/VALIDATION (SEE FLOWCHART IN APPENDIX L).

It is important to recognize that once a target protein/peptide pair has been identified, the relationship between that target protein and the pathway of interest for that particular cell type is defined by virtue of the functional screen that produced it. False positives arise only if the hit binds to additional proteins not related to the functional pathway of interest. The

binding peptide minimizes this possibility as it binds to only a portion of the cDNA in a manner that regulates the pathway of interest. Below is a protocol to discriminate false positives from pathway-specific protein/peptide target pairs.

Once the desired change in the phenotype of the library-infected cells is achieved, the cDNAs/peptides responsible will be sequenced. Individual sequences derived from the libraries, and subsequently two-hybrid approaches will be tested for their ability to alter T or B cell activation as described earlier. Targets are defined as functional cDNAs whose binding peptide can alter its influence on lymphocyte activation in a desired way.

The protein/peptide pairs can be subjected to numerous secondary assays to confirm their role and specificity in lymphocyte activation/regulation. The type of protein/peptide pairs identified will dictate the exact assays performed. These assays include over-expression in lymphocytes of the target protein, their individual functional domains, dominant negative mutants (large-scale mutagenesis of specific cDNAs to generate libraries of "mutant targets," see Appendix L) and anti-sense mRNA of the target protein sequence. The readouts will include changes in the expression of activation-upregulated surface proteins, cytokine production and proliferation as described in Section 1 and 2. In addition, the ability to revert the phenotype of activated lymphocytes by over-expressing the target protein in cells expressing the inhibitory binding peptide will be tested. These assays will assist the Joint Novartis-Rigel Research Committee in their determination of targets to be introduced into Novartis small molecule compound screens. Below is a brief description of the rationale and approach for each of the assays described above.

Over-expression of the target protein or individual functional domains may modulate lymphocyte activation, thereby implicating the specific protein in one of the activation-coupled intracellular regulatory pathways. This can be accomplished very simply with Rigel's retroviral vector system. By using reporter genes downstream of the cDNA-encoding the target protein or domain, we can track infected cells and determine the relative production of the target protein/domain. This will allow us to titrate its biological effect as a means to confirm the target protein's role in lymphocyte activation. If overexpression of the protein target influences T cell activation, mutant libraries of the protein can then be screened for loss-of-function as described below.

Target proteins will be randomly mutated (see Appendix L) and screened in the FACS assays described in Section 1 for mutant proteins that alter lymphocyte activation. Two variations of this approach allow us to narrow our screen of mutant target proteins. One variation is to perform mutagenesis on the target cDNA and then subject the mutagenized target to a two-hybrid screen with the cognate peptide as bait to identify mutants that no longer bind the peptide. These mutant proteins can be tested for loss-of-function in mammalian cells. Alternatively, the peptide can be chemically crosslinked to the target protein to identify the region bound by the peptide using mass spectrometry. Subsequently, the peptide-binding region of the target protein is randomly mutated and the clones screened for their ability to inhibit lymphocyte activation. The advantage of this variation is that the regulatory domain of the target protein is identified.

A third approach to confirm the role of the target protein in lymphocyte activation is to overcome peptide inhibition by overexpressing the target protein. The screening cell lines are infected with the peptide and its target protein where the target protein under the control

of an inducible promoter such as tetracycline or metallothionein. When the target protein is induced, its ability to outcompete inhibition by the peptide can be tested.

Some or all of the above methods can be employed to confirm that a protein/peptide pair, identified in the initial screen is functionally relevant. Because of our retroviral technology virtually any strategy of intracellular expression can be approached to verify protein/peptide target pairs in living cells. It will be the task of the Joint Novartis-Rigel Research Committee to determine which assays are necessary to sufficiently define a functional protein/peptide pair for the next phase of development, specifically small molecular weight compound screening.

HEADCOUNT

To run optimally, the T cell project (Project I) and the B cell project (Project II) will each take 12 full-time Rigel FTEs. Listed here are the scientists who would begin working on the T cell project:

DAVID FERRICK: Dr. Ferrick is the project director and is the primary supervisor responsible for ensuring the project hits milestones and objectives in a timely mariner. In addition, he is the head of Molecular and Cell Biology and will supervise all aspects of the various constructs, library generation, library enrichment steps, target validation, and target analysis. Also, he is responsible for the supervision and data analysis resulting from the HTS FACS analysis/sorting.

CHARLENE LIAO: Dr. Liao is the project leader and will coordinate all communication between Rigel and Novartis. She will be responsible for the development of all primary and secondary assays for the screens. She will generate the IL-2 promoter survival cell lines and oversee their screening. She is responsible for analyzing the function of individual peptide and protein hits in cell lines and primary cells.

PEIWEN YU: Dr. Yu is a Scientist who is investigating functional T cell targets and two-hybrid hits. She is involved in developing many of the functional assays related to T cell function.

TBH: A Scientist is required to be in charge of retroviral library design and production. He will be responsible for the generation of all peptide libraries with their scaffold and localization sequences. He will perform library rescue and the subsequent subcloning of the individual peptide hits. He will also shuttle hits from the yeast two-hybrid screen to mammalian vectors for post two-hybrid functional analysis.

S. SWIFT: S. Swift is the Senior Research Associate in charge of retroviral production and tissue culture. She is responsible for conducting the library screens, which involves the generation of the infectious library for each round of enrichment screening and all aspects of tissue culture associated with the screening effort. She is also coordinating and performing biological rescue to transfer enriched peptide clones from one round to the next, as well as RT-PCR isolation of individual peptide sequences.

G. MINTIER: G. Mintier is the Research Associate responsible for retroviral vector design and testing. He will generate the retroviral constructs to be used in all the screens. He will be responsible for performing the peptide screens and conducting the rescue of the hits from those screens. He will be involved in the screening for proteins that bind the peptide hits.

H. KHOSHNEVISAN: H. Khoshnevisan is a cell biology Research Associate responsible for all the tissue culture work for the project. She maintains all the different lymphocyte cell lines, the Phoenix packaging cell line, and the sorted cell populations.

M. AUJAY: M. Aujay is the Research Assistant in charge of the sequencing core. She will be responsible for all DNA sequencing on this project. This includes sequencing of all rescued libraries to check for enrichment and contamination, all verified peptide hits, and two-hybrid hits. She is also responsible for managing the sequence database and all related

DNA bioinformatics of the project. She will coordinate the data entry into the appropriate databases.

P. FALLON: P. Fallon is the Senior Research Associate in charge of' the high-speed flow cytometry core. He is responsible for setting-up and implementing all the FACS-based assays. He will be responsible for adapting all assays for FACS-based sorting. He will perform these assays and sort the library hits. He will also supervise the FACS-associated bioinformatics for all the screens.

B. HUANG: B. Huang is an Intracellular Pathway Mapping Manager in charge of' two-hybrid screening. She is responsible for setting up and carrying out all the two-hybrid assays, analyzing and isolating full-length clones, and generating the cDNA libraries.

D. HATRAN: D. Hatran is a molecular biology Research Associate in the target identification group. He is responsible for all the support work on the one- and two-hybrid analyses, including media prep, plate pouring, minipreps, colony picking, gel analysis, and subcloning.

C. LAU: C. Lau is a Research Associate responsible for all the subcloning of hits into expression vectors and execution of secondary assays to verify function in primary cells. She will also perform various labor-intensive tasks associated with the screening effort such as peptide rescue, library sequencing and tissue culture.

12.

APPENDIX A

[DIAGRAM]

13.

APPENDIX B

[DIAGRAM]

14.

APPENDIX C

[DIAGRAM]

15.

APPENDIX D(1)

[DIAGRAM]

16.

APPENDIX D (2)

[DIAGRAM]

17.

APPENDIX E

PROTOCOL FOR TRANSFECTION OF PHOENIX CELLS AND INFECTION OF NONADHERENT TARGET CELLS

[DIAGRAM]

DAY 1:

Seed Phoenix cells (Es or As) in 10cm plates at 5 x 10(6) cells in 6 ml (DMEM + 10% FBS + Pen/Strep) per plate the day before transfection.

DAY 2:

Allow all reagents to reach room temperature 30 min. before starting. Add 50 mM chloroquine at 8 microl/plate (50 microM final) before preparing the transfection solution.

Mix CaPO4 reagents in 15ml polypropylene tube:

per plate: 10 microg. DNA
122 microliter 2M CaCl(2)
876 microliter H20
1.0ml 2X HBS

Add 2X HBS and depress the expulsion button completely to bubble air through the mix for 10 secs. Immediately add mixture gently dropwise to plate.

Incubate 3-8 hours.

Remove medium and replace with 6.0 ml DMEM-medium.

DAY 3:

Change medium again to 6.0 mls of medium optimal for the cells to be infected.

Move to 32(degree) C either in the morning or afternoon depending on the Phoenix cell confluency and whether you will infect at 48 or 72 hrs after transfection.

DAY 4 OR 5:

Collect virus supernatant from transfected plates (6.0 ml) into 50 ml tubes and add protamine sulfate to a final concentration of 5 microg./ml.

Pass through a 0.45 micrometer filter.

Count target cells and distribute 10(7) cells per 10 cm plate transfected to 50 ml tubes and pellet 5 min.

Resuspend each pellet of target cells in virus supernatant and transfer to a 6 well plate at 1.0-1.2 ml per well.

Seal plate with parafilm and centrifuge at RT for 30-90 min. at 2500 RPM.

Remove parafilm and incubate plate over night at 37(degree)C.

DAY 5:

Collect and pellet each well of target cells. Resuspend in 3 ml medium and transfer back to the same 6well plate.

Infection can be repeated by refeeding the Phoenix cells with 6ml fresh medium and reinfecting the same cells again up to 3 times to increase % of cells infected (for instance at 48, 56, and 72 hours)

DAY 7 OR DAY 8:

At 48 to 72 hrs. post infection, target cells are ready to analyze for expression.

APPENDIX F

[DIAGRAM]

APPENDIX G

[DIAGRAM]

APPENDIX H

[DIAGRAM]

APPENDIX J

[DIAGRAM]

23.

APPENDIX K

[DIAGRAM]

24.

APPENDIX L (1)

[DIAGRAM]

25.

APPENDIX L(2)

[DIAGRAM]

26.

Rigel-Novartis Collaboration

[DIAGRAM]

27.

EXHIBIT A-2

B-CELL PROGRAM OF RESEARCH

Provisional Draft

NOVEL REGULATORY PATHWAYS IN T AND B LYMPHOCYTES

NOVARTIS PROJECT OUTLINE

PROJECT II: IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT BCR-INDUCED IG PRODUCTION

INTRODUCTION

Activation of specific signaling pathways in lymphocytes determines the quality, magnitude and duration of immune responses. In transplantation, acute and chronic inflammatory diseases, and autoimmunity, it is these pathways that are responsible for the induction, maintenance and exacerbation of disease lymphocyte responses. Of the many activation pathways that have been elucidated, most are ubiquitous and not unique to a particular cell lineage. The goal of this proposal is to identify and validate novel (signaling) molecules specific for B cell activation and effector function as potential pharmacological targets for B cell inhibition. From these molecules, B ce!l-specific targets will be identified that are effective in modulating immune-mediated processes. A combination of high throughput functional and yeast two-hybrid genetic screens will be employed to isolate and map novel (signaling) molecules essential for lymphocyte activation. Engagement of the B cell receptor (BCR) together with additional activation principals stimulates humoral immunity characterized by immunoglobulin production and antigen presentation by B cells. Summarized below, in Table 1, are four strategies for identifying and validating novel B cell intracellular signaling molecules. Each approach, its readout, and the libraries to be used are detailed in the remaining sections of the proposal. Two of these approaches (to be chosen by the Joint Novartis-Rigel Research Management Committee) will be pursued initially.

PREFINAL DRAFT -- ELEMENTS YET TO BE FINALIZED

1.

TABLE 1. SUMMARY OF SCREENS TO IDENTIFY INTRACELLULAR REGULATORS OF LYMPHOCYTE ACTIVATION AND/OR EFFECTOR FUNCTION.

PROJECT II IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT BCR-INDUCED IG PRODUCTION

APPROACH	READOUT	LIBRARY
1. PRIMARY SCREENS		
*	*	
2. SECONDARY ASSAYS		
*	*	

EXPERIMENTAL DESIGN AND METHODS

IDENTIFICATION OF REGULATORY PROTEINS THAT AFFECT B CELL ACTIVATION

1. Primary Screens

During xeno-transplantation, the initial hyperacute rejection is predominantly mediated by complement and secretory Ig. Inhibition of secretory Ig production may result in suppression of the rejection. Therefore, the primary goal of our screen is to identify protein targets that are involved in the pathways that lead to the production and secretion of Ig. Three different primary screening' strategies and a backup screen are proposed which have distinctive advantages and disadvantages (Appendix A). The knowledge obtained from these screens provides a comprehensive perspective on this complex and intractable area in a manner not possible with any single approach.

1.1 Screen 1: Primary peptide screen looking for signaling molecules involved in BCR activation as measured by inhibition of B cell activation marker up-regulation.

RATIONALE:

The first approach involves screening peptides that directly inhibit the up-regulation of multiple cell surface markers related to B cell signaling that are upstream or connected to the Ig secretion pathway. This approach is based on multiple marker sorting and can lead to the discovery of proliferative signaling molecules in the BCR pathway:

CELL LINES, CONSTRUCTS, AND ACTIVATION MARKERS:

Four activation markers will initially be evaluated for their up-regulation upon anti-Ig activation (e.g. CD69, IL-5R, surface Ig, MHC Class II, and Ca2t mobilization). Expression of the activation markers will be optimized to ensure the lowest background, a critical factor in our inhibitory peptide screens. It will also be important to ensure that the signaling event triggered by FACS sorting is reversible so that multiple rounds of screening are possible.

A panel of Ig+ mature B cell lines will be tested for their ability to upregulate several key activation markers in response to BCR engagement. Those with the greatest dynamic range of primary B cell activation will be employed in the primary screens. The selected cell lines will then be infected with the Tet-off transactivator tTA and TRE-LYT2 producing viruses (Appendix B). The integration of the tTA plasmid will be selected by hygromycin; background of TRE promoter and the expression of tTA will be selected according to LYT2 expression. High level of induction and low background of tTA activity will determine the feasibility of the Tet-regulated system in the appropriate cell line.

PEPTIDE LIBRARY SCREENING AND PROTEIN TARGET IDENTIFICATION:

Cell lines selected as described above will be infected with one of Rigel's peptide libraries. We have developed several retroviral constructs to control all aspects of peptide expression and localization. This gives us great flexibility when designing retroviral libraries within any cell line and with whatever characteristics are deemed necessary for intracellular peptide expression (Appendix C). Constrained peptides have many valuable features compared to linear peptides, including enhanced resistance to proteolysis and a restricted

conformation space that can result in a higher binding affinity for cognate binding proteins. In order to screen for as great a range of targets as possible, three different libraries driven by the Tel..off, TRE promoter will be used initially: two constrained libraries (a 12 mer and an 18 mer library inserted at loop 3 ora BFP scaffold) and a linear library fused directly to a puromycin resistance gene (18 mer). Dependent upon the results of the screens using these libraries, the RMC may determine other library scaffolds should also be utilized (e.g. constrained 18 mer, (beta)-1actamase based, enzyme based).

These primary libraries will be used to infect 108 to 109 B cells (Appendix D) and the cells will be grown without Dox to allow peptide expression (Appendix E). The cells will be stimulated with anti-Ig and selected for loss of up-regulation of the cell surface markers. This population of cells contains either inhibitory peptides or somatic mutations. To remove somatic mutations, the cells will be grown out in the presence of Dox (peptide expression turned off), followed by sorting for up-regulation of surface markers after stimulation with anti-Ig. The GFP positive cells can then be funneled into multiple rounds of selection, carried out by turning the peptides on and off until a definitive peptide-dependent phenotype is obtained. After the final round of enrichment, the GFP positive cells (peptide off) will be sorted into individual wells of duplicate 96-well plates and treated +/- Dox. Peptide sequences from those cells exhibiting the appropriate phenotype will then be isolated and transferred to a naive population of cells. Their phenotype will be verified as being peptide-dependent on an individual sequence basis.

This screen may have significantly higher background than the other screens and, therefore, may take longer to identify hits. However, there is an advantage in that inhibitors with complex phenotype can be isolated using this approach.

1.2 Screen 2: Primary peptide screen for inhibitors of IgH promoter activity in a mature B cell line stimulated through the BCR.

RATIONALE:

The effect of BCR activation on IgH production is two fold the IgH promoter activity is enhanced and there is an immediate increased production of the secretory form of Ig. Inhibitors that block Ig(mu) promoter activity inhibit an upstream event of all Ig production, which may or may not inhibit the translational control of the pre-existing mRNA of Ig. However, in either case, therapeutic targets identified which block Ig production will be relevant for hyperacute rejection (minutes-hours). In addition, since antibody production is considered to be important during chronic rejection (months-years), the targets found in this screen may also be particularly useful in later sages of rejection.

CONSTRUCTS AND CELL LINES:

In order to carry out the screen, an Ig+ mature B cell line that has robustly enhanced activity of IgH promoter upon BCE signaling will be obtained. A construct with a GFP/TK fusion driven by an IgH promoter will be used (Appendix F). Regions of the IgH promoter that confer the lowest background and the highest inducibility will be determined in the selected cell line. The Tet-off transactivator will then be integrated into the chosen cell line as described in Screen 1 (Section 1.1).

PEPTIDE LIBRARY SCREENING AND PROTEIN TARGET IDENTIFICATION:

Cell lines selected as described above will be infected with one of Rigel's peptide libraries as described in screen 1.

These primary libraries will be used to infect 10s to 109 B cells. The cells will be grown out in media without Dox, which allows for peptide library expression (Appendix G). Cells will be stimulated with anti-Ig antibodies, and selected in ganciclovir. Cells containing the TK reporter will be killed by the ganciclovir unless a peptide inhibitor is present which inhibits the gene's expression (Appendix H). The peptide-containing survivors will be enriched by FACS for GFP negative cells (containing an inhibitor of the GFP reporter). This will remove residual GFP-expressing cells that were not eliminated by the ganciclovir. The cells that do not fluoresce will contain either peptides or somatic mutations that inhibit alternative splicing or protein synthesis. To remove the background caused by somatic mutations, the cells will be grown in the presence of Dox (to turn off peptides) and (alpha) Ig allowing GFP/TK to express. The GFP positive cells will be sorted into individual wells of a 96-well plate. Triplicate plates will be grown in different combinations of Dox and ganciclovir to confirm that the phenotypic change is due to the peptide. The peptides will then be isolated from those cells and transferred to a naive population of cells where their phenotypes will be verified as being peptide-dependent on an individual sequence basis.

1.3 Screen 3: Primary peptide screen for inhibitors of secretory Ig expression as measured by TK/GFP transgene in a mature B cell line.

RATIONALE:

This strategy searches for inhibitors of Ig secretion and is the most direct measure of the goal as defined in this proposal. This approach will directly target the splicing step and translation of the IgH chain that is responsible for generating the secretory form of Ig.

Increased promoter activity after BCR ligation and/or increased stability

of Ig(mu) mRNA in B cells are thought to be critical for the enhanced level of RNA message. The understanding of the contributions of these two phenomena during B cell development and immune responses has been elusive. However, this approach should allow for the discovery of drug targets in either case.

CELL LINES AND CONSTRUCT:

Ig+ mature B cell lines will be tested for their ability to produce secretory Ig. The most inducible cell line will be infected with a retroviral construct containing a TK/GFP fusion gene inserted after (mu)4, the secretory segment (S) and the puromycin resistance gene following the cytoplasmic exon (Appendix I). Cells will be selected in puromycin to obtain a population that contains stably integrated transgenes. Upon anti-Ig stimulation, GFP and TK activity will reflect the expression of the secretory forms of Ig. Before screening, the physiological nature of the BCR-induced splicing event in both the endogenous and the transgene will be confirmed using PCR analysis. The tTA expressing cell line will be generated as described in Screen 1.

PEPTIDE LIBRARY SCREENING AND PROTEIN TARGET IDENTIFICATION:

The screening protocol will be identical to that described in Screen 2 (Appendix G).

1.4 Back-up Screen: Primary peptide screen for inhibition of BCR signaling measured by apoptosis in a mature or immature B cell line.

RATIONALE:

This screen is based on the assumption of cross-functionality between proliferative and apoptotic pathway members and is presented as a back-up strategy.

The outcome of BCR activation can be either apoptotic or proliferative, depending on the concentration and binding affinity of the antigen, the developmental stage of the B cells, and the coatimuli provided by T cells. Current understanding indicates that great similarities exist between the death and survival pathways. Based on this expectation of cross-functionality between pathways, an apoptotic approach was used to identify several important molecules in the TCR proliferative signaling pathway, including Lck, SLP-76 and LAT. Similarly, the apoptotic screening strategy described here will allow a rapid discovery of BCR signaling molecules that are involved Ig production and/or secretion in a system with low background. Specific secondary assays will then be used to confirm the cross functionality of the molecules in BCR-induced Ig secretion and B cell proliferation.

CELL LINE:

A mature or immature B cell line will be identified by the RMC that. is efficiently induced to apoptose upon hypercross-linking or cross-linking with different anti-Ig antibodies.

PEPTIDE LIBRARY SCREENING AND PROTEIN TARGET IDENTIFICATION:

The peptide scaffold for the primary libraries described in Screen I - 3 will be used to infect 10(8) to 10(9) B cells. Unlike the earlier screens; however, these libraries will not be under Tet control. The cells will be infected, allowed to express the peptide library, and stimulated with (alpha)-Ig (Appendix J). The survivors, containing inhibitory peptides or somatic mutations, will then be subjected to biorescue which transfers the peptide sequences to a naive population of cells (method of transfer described below). Multiple rounds of selection will be performed until the survival rate is sufficiently greater than that of the control. Somatic mutants that survive the initial selection will not be transferred when the peptides are reintroduced into a naive population.

To obtain phenotypic enrichment in the primary screens, the desired phenotype must be transferred from the enriched library-infected population to a naive population repeatedly. Historically, we have used RT-PCR to rescue library members from the phenotypically desirable cells of one round, then generated a new retroviral library and infected naive cells to enrich once again for the desired phenotype. Although this approach works, uneven amplification decreases overall amplification of real peptide hits from one round to another. Additional rounds of library enrichment can overcome this overall decrease of real hit amplification. However, to avoid the potential problems of RT-PCR and for more efficient transfer of phenotype from one round to the next, we are replacing RT-PCR amplification with a direct biological rescue (Appendix K). Biological rescue involves direct transfer of recombinant retroviral inserts from positively identified cell clones into naive cells for re-testing. By supplying retrovirus proteins gag-pol-env to library-enriched cells, integrated proviral transcripts encoding putative peptide hits are selectively re-packaged and secreted as

new virions capable of infecting new cells. Positive cells can be converted to retroviral producers by superinfection of gag-pol-env genes or alternatively, tetracycline-inducible packaging functions can be pre-engineered into target cell lines. By either strategy, peptides from enriched cells can be selectively transferred to new cells and re-tested for phenotypic effects, eliminating the time-intensive and potentially biased intermediary molecular cloning steps. Proof of principle demonstrating the feasibility of this approach is shown in Appendix L.

It will take approximately 3-4 rounds of enrichment to identify individual sequences capable of altering phenotype above background. For a discussion of the statistics associated with enrichment, see Appendix M. The most important factor that influences the number of enrichment rounds necessary to identify individual peptide hits is the ratio between real positive hits in the original library and heritable false positives. The frequency of real positive hits is dependent upon the qualitative ability of the over-expressed library member to alter the pathway .of interest. Enrichment of real positive peptides becomes less efficient with false positive rates above 2%. For this reason, great effort is placed in developing robust cell lines.

2. SECONDARY ASSAYS TO ASSESS PHYSIOLOGIC CHARACTERISTICS AND SPECIFICITY OF PRIMARY FUNCTIONAL PEPTIDE HITS.

2.1 Secondary assays measuring Ig secretion in B cell lines and primary human PBL B cells stimulated through the BCR.

After library enrichment, individual sequences shown to modulate BCR signaling and/or Ig secretion will be introduced into a standard set of secondary assays. The overall aim of these assays is to test the specificity and physiologic characteristics of the functional peptide hits. This will be a critical step in prioritizing hits for more intensive investigation. These assays will be performed in B cell lines and primary peripheral blood or splenic B cells. Of primary importance will be the ability of the hits to alter anti-Ig induced Ig secretion either by directly inhibiting secretion or indirectly by blocking activation events leading to Ig secretion. Inhibition of Ig by the hits will be measured by ELISA in both cell lines and primary human B cells. For further confirmation and to assess the mechanism of inhibition, the hits will be tested for their ability to block the alternative splicing of the secretory Ig transcript measured by PCR analysis. The block of the Ig secretory pathway will also be measured by western analysis for the cytoplasmic retention of the smaller form of the Ig heavy chain.

Functionally validated peptide hits will then be used as bait to isolate their interacting protein targets by genetic (yeast two-hybrid) screening technologies (see section 3 for yeast two-hybrid details). These new interacting partners can be cycled into the functional assays to assess their specific role in Ig secretion. In this manner, activation pathways that mediate multiple functions in Ig secretion can be deconvoluted in a step-wise manner.

2.2 Additional assays to further characterize the specificity of hits that block Ig secretion.

In addition to secondary assays directly targeting Ig secretion, a combination of generic assays for BCR proliferative responses will also be used to clarify the role or mechanism of the primary hits that block Ig secretion. Such assays (to be determined by P, MC) may include calcium influx, 3H-thymidine incorporation, NFAT reporter gene assay,

cell surface marker up-regulation markers (such as IL-1R, IL-2R, IL-6R, CD10, CD23, and CD25), and Ig switching. In addition, the specificity of the hits will be assessed based upon their ability to inhibit TCR-mediated .T cell activation, as well as LPS-induced macrophage activation.

Peptide hits validated in these activation, proliferation, and specificity assays will be cycled into yeast two-hybrid screens as described in section 2.1 and section 3.1.

PATHWAY MAPPING.

FUNCTIONAL MAPPING OF NOVEL B CELL SIGNALING PROTEINS.

3.1 Yeast two-hybrid screening to identify and map proteins that interact with functional peptide hits.

Peptides that modulate lymphocyte activation do so by binding to intracellular proteins that are members of signal transduction pathways which ultimately lead to diverse phenotypic endpoints in B cells. Identification of functional peptide-target protein pairs in these pathways will enable subsequent screening for low molecular weight compounds that alter T and B cell function.

Priority peptide hits from the library screens that alter BCR signaling will be subjected to yeast two-hybrid screening to identify their intracellular binding partners .(Appendix N). The libraries to be screened will be derived from various populations of B cells. The screening protocol for identification of interacting proteins is summarized in Appendix O. Briefly, sequences encoding the target peptides will be cloned into pAS2-1K to fuse to the C-terminal of' GAL4 DNA binding domain. The sequences can also be cloned into pAS2N to fuse to the N-terminal of GAL4 DNA binding domain. Both bait plasmids can be used for subsequent screenings. The bait plasmids will be transformed into the YI90 yeast strain. This yeast strain has the highest sensitivity for yeast, two-hybrid screening. Optimal 3AT concentration needed to suppress any HiS background expression will be determined on SD-WH+3AT plates. The cDNA libraries will be fused with the GAlA activation domain and transformed into the yeast already containing the bait plasmid. At least 20 million transformants from each library Bill be screened on SD-LWH+3AT plates. HIS+ and LacZ+ clones will be grown up in SD-L liquid medium to retrieve plasmid and for retransformation into Y 190 to verify the binding specificity.

Isolated proteins that are determined to interact with the functional sequence baits will be tested for their ability to affect BCR signaling in the previously discussed secondary assays. The various ways to determine function in the secondary assays is by simple overexpression of the putative target protein and any potential dominant-negative domains, and random mutagenesis to destroy functioning domains (Appendix P).

INITIAL STEPS FOR TARGET IDENTIFICATION/VALIDATION (SEE FLOWCHART IN APPENDIX QI AND Q2).

It is important to recognize that once a target protein/peptide pair has been identified, the relationship between that target protein and the pathway of interest for that particular cell type is defined by virtue of the functional screen that produced it. False positives arise only if the hit binds to additional proteins not related to the functional pathway of interest. The

binding peptide minimizes this possibility as it binds to only a portion of the cDNA in a manner that regulates the pathway of interest. Below is a protocol to discriminate false positives from pathway-specific protein/peptide target pairs.

Once the desired change in the phenotype of the library-infected cells is achieved, the cDNAs/peptides responsible will be sequenced. Individual sequences derived from the libraries, and subsequently two-hybrid approaches will be tested for their ability to alter B cell activation as described earlier in Sections 1 and 2. Initial targets are defined as functional cDNAs whose binding peptide can alter its influence on lymphocyte activation in a desired way.

The protein/peptide pairs can be subjected to numerous secondary assays to confirm their role and specificity in lymphocyte activation/regulation. The type of protein/peptide pairs identified will dictate the exact assays performed. These assays include over-expression in lymphocytes of the target protein, their individual functional domains, dominant negative mutants (large-scale mutagenesis of specific cDNAs to generate libraries of "mutant targets," see Appendix P) and anti-sense mRNA of the target protein sequence. The readouts will include changes in the expression of activation-up-regulated surface proteins, antibody production, cytokine production and proliferation as described in Section I and 2. In addition, the ability to revert the phenotype of activated lymphocytes by over-expressing the target protein in cells expressing the inhibitory binding peptide will be tested. These assays will assist the RMC in their determination of targets to be introduced into Novartis small molecule compound screens. Below is a brief description of the rationale and approach for each of the assays described above.

Over-expression of the full-length target protein or individual function, al domains may modulate B cell activation, thereby implicating the specific protein in one of the activation-coupled intracellular regulatory pathways. This can be accomplished very simply with Rigel's retroviral vector system. By using reporter genes downstream of the cDNA encoding the target protein or domain, we can track infected cells and determine the relative production of the target protein/domain. This will allow us to titrate its biological effect as a means to confirm the target protein's role in lymphocyte activation. If overexpression of the protein target influences lymphocyte activation, mutant libraries of the protein can then be screened for loss-of-function as described below.

Target proteins will be randomly mutated (see Appendix P) and screened in the FACS assays described in Section I for mutant proteins that alter lymphocyte activation. Two variations of this approach allow us to narrow our screen of mutant target proteins. One variation is to perform mutagenesis on the target cDNA and then subject the mutagenized target to a two-hybrid screen with the cognate peptide as bait to identify mutants that no longer bind the peptide. These mutant proteins can be tested for loss-of-function in mammalian cells. Alternatively, the peptide can be chemically crosslinked to the target protein to identify the region bound by the peptide using mass spectrometry.

Subsequently, the peptide-binding region of the target protein is randomly mutated and the clones screened for their ability to inhibit lymphocyte activation. The advantage of this variation is that the regulatory domain of the target protein is identified.

A third approach to confirm the role of the target protein in lymphocyte activation is to overcome peptide inhibition by overexpressing the target protein. The screening cell lines are infected with the peptide and its target protein where the target protein under the control

of an inducible promoter such as tetracycline or metallothionein. When the target protein is induced, its ability to outcompete inhibition by the peptide can be tested.

Some or all of the above methods can be employed to confirm that a protein/peptide pair, identified in the initial screen is functionally relevant. Because of our retroviral technology virtually any strategy of intracellular expression can be utilized to verify protein/peptide target pairs in living cells. It will be the task of the RMC to determine which assays are necessary to sufficiently define a functional protein/peptide pair for the next phase of development, specifically small molecular weight compound screening.

3.2 Additional levels of Yeast two-hybrid screening to identify and map proteins that interact with the functional cDNA target

The functional cDNA targets identified in 3.1 that bind to the inhibitory peptide will be used as bait to identify its binding partners. This second level of yeast two-hybrid analysis will identify cDNA "ligands" for the target proteins identified by the inhibitory peptides. These ligands will be assessed in a variety of assess to confirm their role in the pathway leading to Ig secretion and/or B cell activation as described in 3.1.

HEADCOUNT

To run optimally, the T cell project (Project I) and the B cell project (Project II) will each take 12 full-time Rigel FTEs. Listed here are the scientists who would begin working on the B cell project (see Appendix R for an amended list of the scientists who will begin working on the T cell project):

YING LUO: Dr. Luo is the project director and is the primary supervisor responsible for ensuring that the project hits milestones and objectives in a timely fashion. In addition, he is the head of Genomics and Target Discovery and is responsible for the supervision and data analysis resulting from YTH and HTS FACS analysis/sorting. He will also supervise all aspects of the various constructs, library generation, library enrichment steps, target validation, and target analysis.

H. MANCEBO: H. Mancebo will coordinate all communication between Rigel and Novartis. She will be responsible for the development of all primary and secondary assays for the screens. She will generate the IgH promoter survival cell lines and oversee their screening. She is responsible for analyzing the function of individual peptide and protein hits in cell lines and primary cells.

C.A. FU: Dr. Fu is a Scientist who is investigating functional B cell targets and two-hybrid hits. He is involved in developing many of the functional assays related to B cell function. . ,

TBH: A Scientist is required who will be in charge of retroviral library design and production. The individual will be responsible for the generation of all peptide libraries with their scaffold and localization sequences. He/she will perform library rescue and the subsequent subcloning of the individual peptide hits. The individual will also shuttle hits from the yeast two-hybrid screen to mammalian vectors for post two-hybrid functional analysis.

A. FRIERA: A. Friera is the Senior Research Associate in charge of retroviral production and tissue culture. She is responsible for conducting the library screens, which involves the generation of the infectious library for each round of enrichment screening and all aspects of tissue culture associated with the screening effort. She is also coordinating and performing biological rescue to transfer enriched peptide clones from one round to the next, as well as RT-PCR isolation of individual peptide sequences.

C. YOUNG: C. Young is the Research Associate responsible for retroviral vector design and testing. He will generate the retroviral constructs to be used in all the screens. He will be responsible for performing the peptide screens and conducting the rescue of the hits from those screens. He will be involved in the screening for proteins that bind the peptide hits.

TBH: An additional cell biology Research Associate will be required who

will be responsible for all the tissue culture work for the project. He will maintain all the different lymphocyte cell lines, the Phoenix packaging cell line, and the sorted cell populations.

M. FOX: M. Fox is the Research Assistant in charge of the sequencing core. He will be responsible for all DNA sequencing on this project. This includes sequencing of all rescued libraries to check for enrichment and contamination, all verified peptide hits, and two-hybrid hits. He will coordinate the data entry into the appropriate sequence databases.

ALEX ROSSI: A. Rossi is a Cell Biology Manager responsible for setting-up and implementing all the FACS-based assays. He will be responsible for adapting all assays for FACS-based sorting. He will perform these assays and sort the library hits. He will also supervise the FACS-associated bioinformatics for all the screens.

M. SHEN: M. Shen is the Senior Research Associate in charge of two-hybrid screening. She is responsible for setting up and carrying out all the two-hybrid assays, analyzing and isolating full-length clones, and generating the cDNA libraries

J. LASAGA: J. Lasaga is a molecular biology Research Associate in the target identification group. He is responsible for all the support work on the one- and two-hybrid analyses, including media prep, plate pouring, minipreps, colony picking, gel analysis, and subcloning.

RESEARCH ASSOCIATE TBH: An additional molecular biology Research Associate will be needed who will be responsible for all the subcloning of hits into expression vectors and execution of secondary assays to verify function in primary cells. This individual will also perform various labor-intensive tasks associated with the screening effort such as peptide rescue, library sequencing and tissue culture.

APPENDIX A

[DIAGRAM]

APPENDIX B

[DIAGRAM]

APPENDIX D

PROTOCOL FOR TRANSFECTION OF PHOENIX CELLS AND INFECTION OF NONADHERENT TARGET CELLS

[DIAGRAM]

Day 1:

Seed phoenix cells (Es or As) in 10cm plates at 5 x 10E6 cells in 6 ml (DMEM + 10% FBS + Pen/Strep) per plate the day before transfection.

Day 2:
Allow all reagents to reach room temperature 30 min. before staring. Add 50 mM chloroquine at 8 microliter/plate (50 microM final) before preparing the transfection solution.

Mix CaPO4 reagents in 15 ml polypropylene tube:
Per plate: 10 micrograms DNA
122 microliters 2M CaCl2
876 microliters H2O
1.0ml 2X HBS

Add 2X HBS and depress the expulsion button completely to bubble air through the mix for 10 secs. Immediately add mixture gently dropwise to plate. Incubate 3-8 hours.
Remove medium and replace with 6.0 ml DMEM-medium.

Day 3:
Change medium again to 6.0 mls of medium optimal for the cells to be infected. Move to 32 degrees C either in the morning of afternoon depending on the Phoenix cell confluency and whether you will infect at 48 or 72 hrs after transfection.

Day 4 or 5:

Collect virus supernatant form transfected plates (6.0 ml) into 50 ml tubes and add protamine sulfate to a final concentration of 5 micrograms/ml. Pass through a 0.45 microm filter. Count target cells and distriubte 10x7 cells per 10cm plate transfected to 50 ml tubes and pellet 5 min. Resuspend each pellet of target cells in virus supernatant and transfer to a 6 well plate at 1.0-1.2 ml per well. Seal plate with parafilm and centrifuge at RT for 30-90 min. at 2500 RPM. Remove parafilm and incubate plate over night at 37 degrees C.

Day 5:

Collect and pellet each well of target cells. Resuspend in 3 ml medium and transfer back to same 6 well plate. Infection can be repeated by refeeding the Phoenix cells with 6ml fresh medium and reinfecting the same cells agains up to 3 times to increase % of cells infected (for instance at 48, 56, and 72 hours)

Day 7 or Day 8:

At 48 to 72 hrs. post infection, target cells are ready to analyze for expression.

14.

APPENDIX E

[DIAGRAM]

15.

APPENDIX F

[DIAGRAM]

16.

APPENDIX G

[DIAGRAM]

17.

APPENDIX H

[DIAGRAM]

18.

APPENDIX I

[DIAGRAM]

19.

APPENDIX J

[DIAGRAM]

20.

APPENDIX K

[DIAGRAM]

21.

APPENDIX L

[DIAGRAM]

22.

APPENDIX M

[DIAGRAM]

23.

APPENDIX N

[DIAGRAM]

24.

APPENDIX O

[DIAGRAM]

25.

APPENDIX P(1)

[DIAGRAM]

26.

APPENDIX P(2)

[DIAGRAM]

27.

APPENDIX Q1 FLOW CHART FOR FUNCTIONAL SCREENS
(IDENTIFICATION OF TARGET PROTEIN/PEPTIDE PAIRS)

[DIAGRAM]

28.

APPENDIX Q2

TARGET VALIDATION STEPS

[DIAGRAM]

29.

RIGEL/NOVARTIS COLLABORATION TIMELINE

[DIAGRAM]

30.

EXHIBIT B

<TABLE>
<CAPTION>

	PROJECT	NUMBER OF FTES	COMMENCEMENT DATE
<S>		<C>	<C>
B-1	T-Cell Project	12	Effective Date
B-2	B-Cell Project	12	To be determined

</TABLE>

EXHIBIT C

LICENCE TERMS UNDER ARTICLES 5.6 AND 6.4

1. DEFINITIONS:

For purposes of this Exhibit C the term

- - "Direct Product" shall mean a product developed by Novartis based upon a Rigel-supplied compound or a derivative thereof, the manufacture, use or sale of which in the absence of a licence, would infringe a valid claim (to be defined in a full agreement) of Rigel.

- - "Indirect Product" shall mean a product developed by Novartis based upon a

Rigel-supplied compound or a derivative thereof and which is not a Direct Product.

2. CONSIDERATION DUE FOR EACH DIRECT PRODUCT:

(A) LICENSE EXECUTION AND MILESTONE PAYMENTS

Upon execution of license	$250,000
Upon start of Phase I Clinical Trials	$500,000
Upon NDA submission	$1,000,000
Upon NDA approval	$2,000,000

(B) ROYALTIES ON ANNUAL NET SALES OF DIRECT PRODUCTS DURING PATENT TERM*:

up to $300 Million	4%
on incremental sales from $300 Million to $500 Million	5%
on incremental sales from $500 Million to $750 Million	6%
on incremental sales from $750 Million to $1 Billion	7%
on incremental sales above $1Billion	8%

*subject to a deduction from royalty payments of an amount corresponding to 50% of the milestone payments made to Rigel under 2(a), provided, that each royalty payment shall not be reduced by more than 50% of the amount due prior to applying the milestone payment credit

3. CONSIDERATION DUE FOR EACH INDIRECT PRODUCTS:

- - License execution and milestone payments equal to 50% of the amounts set forth in 2.(a) above for Direct Products;

- - No royalties.

EXHIBIT D

THIRD PARTY LICENSES

Agreement between the Board of Trustees of the Leland Stanford Junior University and Rigel Pharmaceuticals, Inc. dated October 7, 1996

AGREEMENT

Effective as of October 7, 1996 ("Effective Date"), THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California ("STANFORD") and RIGEL PHARMACEUTICALS, INC., a Delaware corporation having a principle place of business at 24 Windsor Drive, Hillsborough, CA 94010 ("RIGEL"), agree as follows:

1. BACKGROUND.

1.1 STANFORD has an assignment of U.S. Patent Application No. 08/589,109, entitled "Methods for Screening for Transdominant Effector Peptides and RNA Molecules" (the "Nolan/Rothenberg Patent Application") claiming an invention developed in the laboratory of Dr. Garry Nolan (the "Invention"), and any Licensed Patent(s), as hereinafter defined, which may claim such Invention.

1.2 STANFORD has certain biological materials and other know-how ("Know-How"), as herein defined, pertaining to the Invention.

1.3 STANFORD desires to have the Know-How and Invention perfected and marketed at the earliest possible time in order that products resulting therefrom may be available for public use and benefit.

1.4 RIGEL desires a license under said Know-How, Invention, and Licensed Patent(s) in the field of use of gene transfer technologies, including retrovirally mediated nucleic acid libraries, for drug development, drug delivery, drug screening, and target analysis and discovery associated with the development, manufacture, use and sale of Licensed product(s), as defined below.

1.5 RIGEL acknowledges that certain of the Cell Lines (as defined below) were made in the course of research supported by Progenesys.

1.6 The patent application entitled "Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules," which claims technology useful in the field and which was developed in the laboratory of Dr. Garry Nolan (the "Nolan Patent Application"), has previously been assigned to RIGEL.

2. DEFINITIONS.

2.1 "LICENSED BIOLOGICAL MATERIALS" means the materials listed on Exhibit A, including certain vector libraries ("Vector Libraries") and cell lines ("Cell Lines") set forth therein, as amended from time to time upon the parties' mutual written consent.

2.2 "LICENSED KNOW-HOW" means all know-how necessary or useful for the commercial exploitation of the Licensed Patents in the Licensed Field of Use, including without limitation all know-how, trade secrets, protocols, information, processes or other subject matter which is either disclosed in the Nolan/Rothenberg Patent Application, or necessary or useful to

practice the licenses granted to RIGEL in this Agreement with respect to the Invention. Licensed Know-How excludes the Licensed Patents and includes the Licensed Biological Materials.

2.3 "LICENSED PATENT(S)" means (i) any Letters Patent, both foreign (subject to Section 7) and domestic, issued upon the Nolan/Rothenberg Patent Application STANFORD's U.S. Patent Application, Serial Number 08/589,109 filed January 23, 1996, (ii) any substitutions, divisionals, continuations, and continuations-in-part (to the extent such continuations-in-part claim subject matter disclosed or claimed in the Nolan/Rothenberg Patent Application as filed on January 23, 1996and to the extent that the practice of an invention claimed in a Licensed Patent issuing from a patent application other than such continuation-in-part would infringe a claim of Licensed Patent issuing from such continuation-in-part), and (iii) any foreign counterparts of (i) or (ii).

2.4 "LICENSED TECHNOLOGY" means the Licensed Patent(s) and the Licensed Know-How.

2.5 "LICENSED PRODUCT(S)" means:

(a) any product, the manufacture, use, sale, offer for sale or import of which:

(1) is covered by a valid claim of an issued, unexpired Licensed Patent(s) directed to the Invention (claim of an issued, unexpired Licensed Patent(s) shall be presumed to be valid unless and until it has been held to be invalid by a final judgment of a court of competent jurisdiction from which no appeal can be or is taken), or

(2) is covered by any claim being prosecuted in a pending application directed to the Invention, which claim has not been pending for more than three (3) years from first filing of such claim;

(b) any product which directly incorporates any of the Licensed Biological Materials; or

c) any product which would not, but for the use of the Licensed Biological Materials, have been identified, discovered, or developed.

2.6 "NET SALES" means the gross revenue derived by RIGEL and/or RIGEL's sublicensee(s) from the sales of Licensed Product(s), less the following items but only insofar as they actually pertain to the disposition of such Licensed Product(s) by RIGEL or RIGEL's sublicensee(s), are included in such gross revenue, and are separately billed:

a) Import, export, excise and sales taxes, and custom duties;
b) Credit for returns, allowances, trades, or retroactive price adjustments;
c) Transportation charges, issuances and allowances;
d) Discounts actually allowed; or
e) Royalties payable to third parties on the manufacture, use, sale, offer for sale or import of Licensed Products.

2.7 "LICENSED FIELD OF USE" means the use of gene transfer technologies, including retrovirally mediated nucleic acid libraries, for drug development, drug delivery, and target

analysis and discovery. Solely with respect to the phiNX Cell Lines set forth on Exhibit A, the Licensed Field of Use excludes the use of such Cell Lines,

derivatives or vectors thereof or other tangible products that are a direct lineal descendent from such Cell Lines (although obtained in any manner therefrom), wherein cells treated with any one or more of the aforementioned materials are contained within a human subject or are subsequently transplanted into a human subject.

2.8 "EXCLUSIVE" means that, subject to Article 4, STANFORD shall not grant further licenses in the Licensed Field of Use.

3. GRANT.

3.1 STANFORD hereby grants and RIGEL hereby accepts a worldwide license in the Licensed Field of Use under STANFORD's right, title and interest in the Licensed Patents and the Vector Libraries to make, use, sell, offer for sale and import Licensed Product(s).

3.2 The license granted in Section 3.1 is Exclusive, including the right to sublicense pursuant to Article 13, in the Licensed Field of Use for a term (the "Exclusivity Term") commencing as of the Effective Date and ending on the first to occur of the following:

(a) twenty (20) years from the Effective Date; or

(b) ten (10) years from the date of first commercial sale of a Licensed Product(s) by RIGEL or RIGEL's sublicensee(s). RIGEL agrees to promptly inform STANFORD in writing of the date of first commercial sale of Licensed Products. After expiration of the Exclusivity Term, said license shall become nonexclusive and continue indefinitely.

3.3 STANFORD additionally grants, and RIGEL hereby accepts, a worldwide, nonexclusive license in the Licensed Field of Use under STANFORD's right, title and interest in the Licensed Know-How other than the Vector Libraries to make, use, sell, offer for sale and import Licensed Product(s). The term of such nonexclusive license shall commence upon the Effective Date and, continiue indefinitely.

3.4 Notwithstanding the Exclusive license granted to RIGEL, pursuant to Sections 3.1 and 3.2, STANFORD shall have the right to practice the Licensed Patents and to use the Vector Libraries for non-commercial, academic research purposes.

4. GOVERNMENT RIGHTS.

This Agreement is subject to all of the terms and conditions of Title 35 United States Code Sections 200 through 204, including an obligation that Licensed Product(s) sold or produced in the United States be "manufactured substantially in the United States," and RIGEL agrees to take all reasonable action necessary on its part as licensee to enable STANFORD to satisfy its obligation thereunder, relating to the Invention. STANFORD agrees to provide reasonable assistance to RIGEL in the event RIGEL decides to seek a waiver under such domestic manufacture requirement.

5. DILIGENCE.

5.1 As an inducement to STANFORD to enter into this Agreement, RIGEL agrees to use all reasonable efforts and diligence to proceed with the development, manufacture, and sale of Licensed Product(s) and to diligently develop markets for the Licensed Product(s). RIGEL shall demonstrate such diligence to STANFORD by achieving proof of principle through written documentation of the following within eighteen (18) months after the Effective Date:

a) Construction of a retroviral vector library;

b) Infection of cells with such vector library;

c) Detection of a physiological response to such infection in an infected cell; and

d) Isolation and analysis of the peptide eliciting such physiological response from the cell.

5.2 If RIGEL is unable to demonstrate proof of principle within eighteen (18) months Licensed after the Effective Date, STANFORD may elect to narrow the definition of the Licensed Field of Use to include only the use of retrovirally mediated nucleic acid libraries for drug development, drug delivery, drug screening, and target analysis and discovery, by providing written notice to RIGEL thereof. Additionally, RIGEL shall provide to STANFORD within eighteen (18) months after the Effective Date a plan for the development and commercialization of Licensed Products (a "Development Plan"). STANFORD shall comment upon and approve such plan, which approval shall not be unreasonably withheld. After the Development Plan is approved by STANFORD, RIGEL shall use

reasonable efforts to diligently perform its obligations under such Development Plan. If Stanford reasonably believes that RIGEL is not using reasonable efforts to perform the Development Plan, STANFORD may so notify RIGEL. The parties shall promptly thereafter meet to discuss RIGEL's progress under the Development Plan, and shall develop a mutually agreeable plan for remedying any such lack of diligence (the "Proposed Remedy"). If RIGEL fails to perform the Proposed Remedy within one hundred and eighty (180) days after the Proposed Remedy is agreed upon, STANFORD may elect to narrow the definition of the Licensed Field of Use to include only the use of retrovirally mediated nucleic acid libraries for drug development, drug delivery, and target analysis and discovery by providing written notice to RIGEL. If RIGEL then fails to perform the Proposed Remedy within ninety (90) days after receiving STANFORD's notice that it has elected to so narrow the Licensed Field of Use definition, then STANFORD may elect to convert the Exclusive License granted to RIGEL pursuant to Sections 3.1 and 3.2 to a nonexclusive license for the remaining term of this Agreement.

5.3 PROGRESS REPORT. On or before each anniversary of the Effective Date until RIGEL markets a Licensed Product(s), RIGEL shall make a written annual report to STANFORD covering RIGEL's progress during the preceding year toward commercial use of Licensed Product(s). Such report shall include, as a minimum, information sufficient to enable STANFORD to satisfy relevant reporting requirements of the U.S. Government and to ascertain progress by RIGEL toward meeting the diligence requirements of this Article 5.

6. ROYALTIES.

6.1 RIGEL agrees to pay to STANFORD a noncreditable, nonrefundable license issue royalty of Twenty Thousand Dollars ($20,000) half of which shall be paid within forty-five (45) days after the Effective Date and the balance of which shall be on the first anniversary of the Effective Date.

6.2 Upon each anniversary of the Effective Date, RIGEL shall also pay to STANFORD a Minimum Annual Royalty as follows:

Anniversary of Effective Date	Minimum Annual Royalty Due
First and Second	$10,000
Third through Seventh	$20,000
Eighth and Thereafter	$40,000

Said Minimum Annual Royalty payments are nonrefundable but they are creditable against earned royalties to the extent provided in Paragraph 6.5. The foregoing Minimum Annual Royalty payment shall be decreased by fifty percent (50%) if either:

(i) Stanford abandons all patent applications from which Licensed Patent(s) could issue prior to the time that any Licensed Patent(s) issue; or

(ii) Stanford elects to narrow the definition of the Licensed Field of Use pursuant to Section 5.2.

6.3 If Rigel grants to a third party a sublicense under the Licensed Technology solely for research, and not commercialization purposes (a "Research Sublicense"), Rigel shall also pay to STANFORD a milestone payment equal to one percent (1%) of any research milestone payment that RIGEL receives as consideration for the grant of such Research Sublicense. RIGEL shall pay such amount to STANFORD within sixty (60) days after RIGEL receives such research milestone payment.

If RIGEL grants to a third party a sublicense under the Licensed Technology which includes the right to sell and offer for sale Licensed products (a "Commercialization Sublicense"), RIGEL shall pay to STANFORD a sublicense fee as follows:

First Sublicense Granted	$10,000
Second Sublicensed Granted	$20,000
Each Additional Sublicense Granted	$30,000

RIGEL shall pay such sublicense fees to STANFORD within sixty (60) days after the effective date of each Commercialization Sublicense.

6.4 In addition, RIGEL shall pay STANFORD earned royalties equal to (i) 0.5% of Net Sales of Licensed Products set forth in Sections 2.5(a) and 2.5(b), or 0.25% of Net Sales of Licensed Products which can only be categorized under Section 2.5(c). If a Licensed product

can be included in more than one of Sections 2.5(a), 2.5(b) or 2.5(c), the royalty rate due to STANFORD on Net Sales of such Licensed Product shall be 0.5%.

6.5 As further consideration for the license granted to RIGEL under this Agreement, RIGEL shall issue to STANFORD forty thousand (40,000) shares of Preferred Stock of RIGEL, pursuant to a Stock Purchase Agreement. If such number of shares shall equal less than three tenths of one percent (0.3%) of the total outstanding shares of RIGEL's stock at any time during the period from the date of issuance of such stock until one (1) year thereafter, STANFORD and RIGEL shall discuss whether RIGEL shall adjust the number of shares issued to Stanford under this Section 6.5.

6.6 Creditable payments under this Agreement shall be an offset to RIGEL against up to fifty percent (50%) of each earned royalty payment which RIGEL would be required to pay pursuant to Paragraph 6.4 until the entire credit is exhausted.

6.7 If this Agreement is not terminated in accordance with other provisions hereof, RIGEL's obligation to pay royalties hereunder shall continue until ten (10) years after first commercial sale of Licensed Products.

6.8 The royalty on sales in currencies other than U.S. Dollars shall be calculated using the appropriate foreign exchange rate for such currency quoted by the Bank of America (San Francisco) foreign exchange desk, on the close of business on the last banking day of each calendar quarter. Royalty payments to STANFORD shall be in U.S. Dollars. All non-U.S. taxes related to royalty payments shall be paid by RIGEL and are not deductible from the payments due STANFORD.

6.9 Within thirty (30) days after receipt of a statement from STANFORD, RIGEL shall reimburse STANFORD for all costs incurred by STANFORD, including those costs incurred prior to the Effective Date, in connection with the preparation, filing and prosecution of all patent applications and maintenance of patents corresponding to the Invention.

7. PATENT RIGHTS.

STANFORD shall have the obligation to file, prosecute and maintain all patent applications and patents included in the Licensed Patents. STANFORD will provide RIGEL with an opportunity to review and comment upon the prosecution strategy and to consult with STANFORD on the content of patent filings, and will provide copies of any correspondence relating to patent applications and patents included in the Licensed Patents to RIGEL or a designee of RIGEL. RIGEL shall have the right to designate, in its sole discretion, those foreign countries in which STANFORD will file, prosecute and maintain patents and patent applications included in the Licensed Patents. STANFORD may propose to file, prosecute and maintain a Licensed Patent in a country which RIGEL has not designated pursuant to this Section 7. If RIGEL agrees to such designation, it shall reimburse STANFORD costs of such filing, prosecution of maintenance of such patent or patent applications pursuant to Section 6.9 and such patent or patent applications shall be included in the Licensed Patents. If RIGEL does not agree to such proposal, STANFORD may elect to proceed with such filing, prosecution or

maintenance at its own expense, and such patent or patent applications shall not be included in the Licensed Patents.

8. ROYALTY REPORTS, PAYMENTS, AND ACCOUNTING.

8.1 QUARTERLY EARNED ROYALTY PAYMENT AND REPORT. Beginning with the first sale of a Licensed Product, RIGEL shall make written reports (even if there are no sales) and earned royalty payments to STANFORD within thirty (30) days after the end of each calendar quarter. This report shall be in the form of the report of Appendix B and shall state the number, description, and aggregate Net Sales of Licensed Product(s) during such completed calendar quarter, and resulting calculation pursuant to Paragraph 6.4 of earned royalty payment due STANFORD for such completed calendar quarter. Concurrent with the making of each such report, RIGEL shall include payment due STANFORD of royalties for the calendar quarter covered by such report.

8.2 ACCOUNTING. RIGEL agrees to keep and maintain records for a period of three (3) years showing the manufacture, sale, use, and other disposition of products sold or otherwise disposed of under the license herein granted. Such records will include general ledger records showing cash receipts and expenses, and records which include production records, customers serial numbers and related information in sufficient detail to enable the royalties payable hereunder by RIGEL to be determined. RIGEL further agrees to permit its books and records to be examined by STANFORD from time to time to the extent necessary to verify reports provided for in Paragraph 8.1. Such examination is to be made by STANFORD or its designee, at the expense of STANFORD, except in the event that the results of the audit reveal an underreporting of royalties due STANFORD of five percent (5%) or more, then the audit costs shall be paid by RIGEL.

9. NEGATION OF WARRANTIES.

9.1 Nothing in this Agreement is or shall be construed as:

a) A warranty or representation by STANFORD as to the validity or scope of any Licensed Patent(s);

b) A warranty or representation that anything made, used, sold, or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights, and other rights of third parties;

c) An obligation to bring or prosecute actions or suits against third parties for infringement, except to the extent and in the circumstances described in Article 13;

d) Granting by implication, estoppel, or otherwise any licenses or rights under patents or other rights of STANFORD or other persons other than Licensed Patent(s), regardless of whether such patents or other rights are dominant or subordinate to any Licensed Patent(s); or

e) An obligation to furnish any technology or technological information other than the Licensed Technology.

9.2 Except as expressly set forth in the Agreement STANFORD MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE LICENSED PRODUCT(S) WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER RIGHTS, OR ANY OTHER EXPRESS OR IMPLIED WARRANTIES.

9.3 RIGEL agrees that nothing in this Agreement grants RIGEL any express or implied license or right under or to:

a) U.S. Patent No. 4,237,224, "Process for Producing Biologically Functional Molecular Chimeras"; U.S. Patent No. 4,468,464 and U.S. Patent No. 4,740470, both entitled, "Biologically Functional Molecular Chimeras" (collectively known as the Cohen/Boyer patents), or reissues thereof; or

b) U.S. Patent 4,656,134 "Amplification of Eucaryotic Genes" or any patent application corresponding thereto.

9.4 STANFORD warrants that it has all right, power and authority necessary to grant the licenses set forth in Article 3 to RIGEL, and that it has not, and will not during the term of this Agreement, grant any right to any third party which would conflict with the rights granted to RIGEL hereunder.

10. INDEMNITY.

10.1 RIGEL agrees to indemnify, hold harmless, and defend STANFORD and Stanford Health Services and their respective trustees, officers, employees, students, and agents against any and all claims by third parties for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale, or other disposition of the Invention, Licensed Technology, or Licensed Product(s) by RIGEL or RIGEL's sublicensee(s) or customers.

10.2 STANFORD shall not be liable for any indirect, special, consequential or other damages whatsoever, whether grounded in tort (including negligence), strict liability, contract or otherwise. STANFORD shall not have any responsibilities or liabilities whosoever with respect to Licensed Product(s).

10.3 RIGEL shall at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering any and all employees with respect to activities performed under this Agreement.

10.4 In addition to the foregoing, RIGEL shall maintain Comprehensive General Liability Insurance, with reputable and financially secure insurance carrier(s) to cover the activities of RIGEL and its sublicensee(s) in the amounts and during the periods specified herein. Such insurance shall provide minimum limits of liability of One Million Dollars ($1,000,000) as of the first anniversary of the date upon which RIGEL first leases a facility in which it will

conduct research and development activities, and of Five Million Dollars ($5,000,000) as of the commencement of human clinical trials of Licensed Products. Such insurance shall include STANFORD, Stanford Health Services, their trustees, directors, officers, employees, students, and agents as additional insureds. Such insurance shall be written to cover claims incurred, discovered, manifested, or made during or after the expiration of this Agreement. At STANFORD's request, RIGEL shall furnish a Certificate of Insurance evidencing

primary coverage and requiring thirty (30) days prior written notice of cancellation or material change to STANFORD. RIGEL shall advise STANFORD, in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All such insurance of RIGEL shall be primary coverage; insurance of STANFORD or Stanford Health Services shall be excess and noncontributory.

11. MARKING.

Prior to the issuance of patents on the Invention, RIGEL agrees to mark Licensed Product(s) (or their containers or labels) made, sold, or otherwise disposed of by it under the licenses granted in this Agreement with the words "Patent Pending," and following the issuance of one or more patents, with the numbers of the Licensed Patent(s).

12. STANFORD NAMES AND MARKS.

RIGEL agrees not to identify STANFORD in any promotional advertising or other promotional materials to be disseminated to the pubic or any portion thereof or to use the name of any STANFORD faculty member, employee, or student or any trademark, service mark, trade name, or symbol of STANFORD or the Stanford University Hospital, or that is associated with either of them, without STANFORD's prior written consent, except as required by law. STANFORD shall not unreasonably hold consent under this Section 12.

13. INFRINGEMENT BY OTHERS: PROTECTION OF PATENTS.

13.1 RIGEL shall promptly inform STANFORD of any suspected infringement of any Licensed Patent(s) by a third party. During the Exclusive period of this Agreement, STANFORD and RIGEL each shall have the right to institute an action for infringement of the Licensed Patent(s) against such third party in accordance with the following:

a) If STANFORD and RIGEL agree to institute suit jointly, the suit shall be brought in both their names, the out-of-pocket costs thereof shall be borne equally, and any recovery or settlement shall be shared equally. RIGEL and STANFORD shall agree to the manner in which they shall exercise control over such action. STANFORD may, if it so desires, also be represented by separate counsel of its own selection, the fees for which counsel shall be paid by STANFORD;

b) In the absence of agreement to institute a suit jointly, STANFORD may institute suit, and, at its option, join RIGEL as a plaintiff. If STANFORD decides to institute suit, then it shall notify RIGEL in writing. STANFORD shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement; and

c) In the absence of agreement to institute a suit jointly and if STANFORD notifies RIGEL that it has decided not to join in or institute a suit, as provided in (a) or (b) above, RIGEL may institute suit and, at its option, join STANFORD as a plaintiff. RIGEL shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement, provided, however, that any recovery in excess of litigation costs shall be deemed to be Net Sales, and RIGEL shall pay STANFORD royalties thereon at the rates specified herein.

13.2 Should either STANFORD or RIGEL commence a suit under the provisions of Paragraph 12.1 and thereafter elect to abandon the same, it shall give timely notice to the other party who may, if it so desires, continue prosecution of such suit, provided, however, that the sharing of expenses and any recovery in such suit shall be as agreed upon between STANFORD and RIGEL.

14. SUBLICENSE(S).

14.1 RIGEL may grant sublicense(s) under its Exclusive license rights during the Exclusivity Term. RIGEL may grant sublicense(s) under nonexclusive license rights, if such sublicense is in conjunction with a sublicense of other RIGEL proprietary technology.

14.2 If RIGEL is unable or unwilling to serve or develop a potential market or market territory for which there is a willing sublicense(s), RIGEL will, at STANFORD's request negotiate in good faith a sublicense(s) hereunder on commercially reasonable terms.

14.3 Any sublicense(s) granted by RIGEL under this Agreement shall be subject and subordinate to terms and conditions of this Agreement, except:

a) Sublicense terms and conditions shall reflect that any sublicensee(s) shall not grant a sublicense to a third party; and

b) The earned royalty rate specified in the sublicense(s) may be at higher rates than the rates in this Agreement.

Any such sublicense(s) also shall expressly include the provisions of Articles 8, 9, and 10 for the benefit of STANFORD and provide for the transfer of all obligations including the payment of royalties specified in such sublicense(s), to STANFORD or its designee, in the event that this Agreement is terminated.

14.4 RIGEL agrees to provide STANFORD a copy of any sublicense(s) granted pursuant to this Article 14.

15. TERMINATION.

15.1 RIGEL may terminate this Agreement by giving STANFORD notice in writing at least thirty (30) days in advance of the Effective Date of termination selected by RIGEL.

15.2 STANFORD may terminate this Agreement if RIGEL:

a) Is in default in payment of royalty or providing of reports;

b) Is in material breach of any provision hereof; or

c) Intentionally provides any false report;

and RIGEL fails to remedy any such default, breach, or false report within thirty (30) days after written notice thereof by STANFORD.

15.3 Surviving any termination are:

a) RIGEL's obligation to pay royalties accrued or accruable;

b) Any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party; and

c) The provisions of Articles 8, 9, and 10.

16. ASSIGNMENT.

This Agreement may not be assigned by either party without the express written consent of the other party, except that RIGEL may assign the Agreement in connection with a merger, consolidation or sale of all or substantially all of RIGEL's assets.

17. DOUBLE PATENTING CONTINGENCY.

If the PTO rejects either the Nolan/Rothenberg Patent Application for double patenting in view of the claims of the Nolan Patent Application, or the claims of the Nolan Patent Application for double patenting in view of the claims of the Nolan/Rothenberg Patent Application, then RIGEL may elect to assign its right, title and interest in the Nolan Patent Application to STANFORD, in which case STANFORD shall grant to RIGEL an irrevocable, exclusive, worldwide, royalty-free license under STANFORD's right, title and interest in the Nolan Patent Application for all purposes.

18. ARBITRATION.

18.1 Any controversy arising under or related to this Agreement, and any disputed claim by either party against the other under this Agreement excluding any dispute relating to patent validity or infringement arising under this Agreement, shall be settled by arbitration in accordance with the Licensing Agreement Arbitration Rules of the American Arbitration Association.

18.2 Upon request by either party, arbitration will be by a third party arbitrator mutually agreed upon in writing by RIGEL and STANFORD within thirty (30) days of such arbitration request. Judgement upon the award rendered by the arbitrator shall be final and nonappealable and may be entered in any court having jurisdiction thereof.

18.3 The parties shall be entitled to discovery in like manner as if the arbitration were a civil suit in the California Superior Court.

18.4 Any arbitration shall be held at Stanford, California, unless the parties hereto mutually agree in writing to another place.

19. NOTICES.

All notices under this Agreement shall be deemed to have been fully given when done in writing and deposited in the United States mail registered or certified, and addressed as follows:

To STANFORD: Office of Technology Licensing
Stanford University
900 Welch Road, Suite 350
Palo Alto, CA 94304-1850

Attention: Director

To RIGEL: 24 Windsor Drive
Hillsborough, CA 94010

Attention: Dr. Donald G. Payan

Either party may change its address upon written notice to the other party.

20. WAIVER

None of the terms of this Agreement can be waived except by the written consent of the party waiving compliance.

21. APPLICABLE LAW.

This Agreement shall be governed by the laws of the State of California applicable to agreements negotiated, executed and performed wholly within California.

22. SEVERABILITY.

If any provision or provisions of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby.

23. ENTIRE AGREEMENT.

This Agreement, together with the Exhibits attached hereto, embodies the entire understanding of the parties and shall supercede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof. No amendment or modification hereof shall be valid or binding upon the parties unless made in writing and signed by duly authorized representatives of both parties.

24. COUNTERPARTS.

This Agreement may be executed in counterparts, with the same force and effect as if the parties had executed the same instrument.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement in duplicate originals by their duly authorized officers or representatives.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

Signature /s/ Katherine Ku
Name Katherine Ku
Title Director, Technology Licensing
Date October 7, 1996

RIGEL

Signature /s/ Donald G. Payan
Name Donald G. Payan
Title President & CEO
Date 10/9/96

EXHIBIT A

MATERIALS FROM NOLAN LAB TO BE LICENSED TO RIGEL

Vector Libraries
- ----------

1. Random peptide library in pMSCU & Bst X1
2. SH-3 first generation library
3. CPP32 inhibitor peptide library
4. SH-3 second generation library
5. Coiled-coil library

Plasmids
- --------

1. pMSCU SD & Bst X1
2. pBabe Pur
3. pMSCU SD - IRES neo Bst X1
4. p5 & MD

Cell Lines
- ----------

1. phiNX cell lines - gp, eco, ampho
2. 293 T

EXHIBIT B

SAMPLE REPORTING FORM

Stanford Docket No. S_____-_____

This report is provided pursuant to the license agreement between Stanford University and _____.

License Agreement Effective Date: _____

Report Covering Period	_____
Fixed Fees (Annual Minimum Payment)	$_____
Number of Sublicense Executed	_____
Net Sales	$_____
Royalty Calculation	_____
Royalty Subtotal	$_____
Credit	$_____
Royalty Due	$_____

Comments:

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED AND FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO RULE 406 OF THE SECURITIES ACT OF 1933, AS AMENDED.

EXHIBIT 10.9

LICENSE AND RESEARCH AGREEMENT

THIS LICENSE AND RESEARCH AGREEMENT (the "Agreement") is made and entered into as of 2 September, 1999, (the "Effective Date") by and between Rigel Pharmaceuticals, Inc., a corporation organized under the laws of Delaware and having a principal place of business at 240 East Grand Avenue, South San Francisco, CA 94080 ("Rigel") and Cell Genesys, Inc. a corporation organized under the laws of Delaware and having a principal place of business at 342 Lakeside Drive, Foster City, CA 94404 ("CG"). Rigel and CG may be referred to collectively as the "Parties," or individually as a "Party."

RECITALS

WHEREAS, CG owns patents relating to [*] cell lines [*] and [*] cell lines (Rockefeller), and related technology; and

WHEREAS, Rigel has a license to the [*] cell lines, associated vectors and vector libraries under intellectual property rights owned by Stanford University; and

WHEREAS, CG and Rigel desire to enter into an agreement granting each other licenses under such patents and other intellectual property rights as provided herein; and

WHEREAS, Rigel is in the business of, among other things, providing services for identifying molecules which bind together in intracellular signaling pathways, and CG desires that Rigel perform such services for CG to identify peptides, proteins and/or Genetic Material (as defined below) that modulate angiogenesis in endothelial tissues.

NOW THEREFORE, in consideration of the foregoing premises and the covenants and promises contained in this Agreement, the Parties agree as follows:

ARTICLE 1

DEFINITIONS

1.1 "AFFILIATE" shall mean, with respect to a Party to this Agreement, any other entity, whether de jure or de facto, which directly or indirectly controls, is controlled by, or is under common control with, such Party. A business entity or Party shall be regarded as in control of another business entity if it owns, or directly or indirectly controls, at least fifty percent (50%) (or such lesser percentage which is the maximum allowed to be owned by a foreign entity in a particular jurisdiction) of the voting stock or other ownership interest of the other entity, or if it

[*] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED AND FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO RULE 406 OF THE SECURITIES ACT OF 1933, AS AMENDED.

directly or indirectly possesses the power to direct or cause the direction of the management and policies of the other entity by any lawful means whatsoever.

1.2 "CG COLLABORATION PARTNERS" means those third parties which enter into a research or development agreement with CG under which CG conducts substantial research or development activities in collaboration with such third party and grants a license to such third party under patents and/or know-how owned or controlled by CG in addition to a sublicense under the Rigel Biological Materials or Rigel Know-How, which licenses and sublicense are for the further development and commercialization of the results of such collaborative research or development.

1.3 "CG [*] FIELD" means human Gene Therapy and animal Gene Therapy.

1.4 "CG KNOW-HOW" means all Information Controlled by CG as of the Effective Date that is necessary or useful for practicing the CG Patents.

1.5 "CG LICENSE" means the license agreement between CG and Rockefeller University as in effect as of the Effective Date and attached hereto as

Appendix A.

1.6 "CG PATENTS" means the Patents and applications listed on Appendix B, to the extent the same as Controlled by CG.

1.7 "CG PROGRAM FIELD" means the research, development or commercialization of human or animal therapeutic products and services, which products and/or services are comprised of peptides, proteins or Gene Therapy.

1.8 "CONTROL" OR "CONTROLLED" means ownership of, or a license to, a particular item, material or intellectual property right with the ability to grant to the other Party access to and/or a license or sublicense as provided for herein without violating the terms of any agreement with a Third Party under which such rights were acquired from such Third Party.

1.9 "FIELD OF RESEARCH" means identification of peptides, proteins and/or Genetic Material that modulate angiogenesis in endothelial tissues.

1.10 "FTE" means a full-time employee or consultant of Rigel or the equivalent thereof.

1.11 "FTE YEAR" means the amount of time one FTE would spend working during one (1) calendar year.

1.12 "GENE THERAPY" means a product or service for the treatment or prevention of a disease that utilizes ex vivo or in vivo delivery (via viral or nonviral gene transfer methods or systems) of Genetic Material, including any cell incorporating Genetic Material.

1.13 "GENETIC MATERIAL" means a nucleotide sequence, including DNA, RNA and complementary and reverse complementary nucleotide sequences thereto, whether coding or noncoding and whether intact or a fragment.

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1.14 "INFORMATION" means any and all information, including without limitation techniques, inventions, practices, methods, knowledge, know-how, skill, experience, test data, analytical and quality control data, compositions and assays, and any business, marketing, personnel or financial information or matters.

1.15 "PATENT" means an issued, valid, unexpired patent, including any extension, registration, confirmation, reissue, re-examination or renewal thereof, or a pending application for a patent, in any country, region or jurisdiction.

1.16 "PROGRAM KNOW-HOW" shall mean any Information developed in the Research relating to the development of Therapeutic Candidates, excluding Information relating to Targets.

1.17 "PROGRAM PATENT" shall mean a Patent claiming inventions or discoveries in the Program Know-How.

1.18 "PROGRAM TECHNOLOGY" shall mean Program Know-How and Program Patents.

1.19 "RESEARCH" shall have the meaning provided in Section 3.1(a).

1.20 "RESEARCH PLAN" shall have the meaning provided in Section 3.1(a).

1.21 "RIGEL BIOLOGICAL MATERIALS" means the [*] cell lines, associated vectors and vector libraries set forth in Appendix C.

1.22 "RIGEL COLLABORATION PARTNERS" means those third parties which enter into a research or development agreement with Rigel under which Rigel conducts substantial research or development activities in collaboration with such third party and grants a license to such third party under patents and/or know-how owned or controlled by Rigel in addition to a sublicense under CG Patents and/or CG Know-How, which licenses and sublicense are for the further development and commercialization of the results of such collaborative research or development.

1.23 "RIGEL FIELD" means the creation and use of virally produced peptide and protein libraries for the screening of transdominant effector peptides and RNA molecules as claimed in the patent applications set forth on Appendix D as well as any processes, techniques and applications disclosed in the foregoing patents applications; it is understood that the foregoing technology is to be used for (a) the discovery, validation and development of targets for human or animal therapeutics, and (b) the discovery, testing, development and commercialization of therapeutic, diagnostic and drug

delivery products. For purposes of this Section 1.23, "disclosed in" shall mean disclosed in the specifications of such patent applications as necessary to practice the invention claimed and not solely as part of the description of the prior art.

1.24 "RIGEL KNOW-HOW" means all Information Controlled by Rigel as of the Effective Date necessary or useful for the use or modification of the Rigel Biological Materials.

1.25 "RIGEL LICENSE" means the license agreements between Rigel and Stanford University as in effect as of the Effective Date and attached hereto as Appendix E.

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1.26 "RMC" shall have the meaning provided in Section 3.2.

1.27 "SUCCESS CRITERIA" shall have the meaning provided in Section 3.1(b).

1.28 "TAIL END PERIOD" shall mean the period of six (6) months after the end of the Research Period, the purpose of which is to permit the RMC to identify Therapeutic Candidates; provided, however, that if this Agreement is terminated prior to or during the Tail End Period, the Tail End Period shall be deemed to end upon such termination date.

1.29 "TARGET" shall mean a molecule occurring naturally in the body that is shown during the Research to directly or indirectly cause or impede angiogenesis in endothelial tissue, to the extent such molecule (or its binding to another molecule) is agonized or antagonized by a Therapeutic Candidate. It is understood that a particular protein, peptide of Genetic Material could be both a Therapeutic Candidate and a Target, and in such case such molecule shall be treated as a "Target" hereunder to the extent that such molecule is used as a drug discovery target, and shall at the same time be treated as a "Therapeutic Candidate" hereunder to the extent such molecule is used as a drug or therapy.

1.30 "THERAPEUTIC CANDIDATE" shall mean a peptide, protein or Genetic Material discovered, identified, produced or tested during the Research Period pursuant to the Research, or identified during the Tail End Period, which meets the Success Criteria, and any homologues or derivatives thereof. For such purposes, it is understood that if a protein or peptide meets the Success Criteria, Genetic Material that codes for such protein or peptide (or its homologues or derivatives) shall be within the definition of Therapeutic Candidate (and vice-versa).

1.31 "[*] PATENTS" means the patents listed in Appendix F.

ARTICLE 2

LICENSES

2.1 CG LICENSE GRANTS.

(a) Subject to the terms of license of the CG License, CG hereby grants to Rigel a royalty-free, non-exclusive, worldwide license, with the right to sublicense to Rigel Collaboration Partners, under and to CG's right, title and interest in any Program Technology owned solely by CG, all for purposes solely within the Rigel Field; and hereby waives any claims against Rigel for the practice and use of the CG Patents and CG Know-How within the Rigel Field prior to the Effective Date. Any sublicense granted hereunder to Rigel Collaboration Partners shall be limited to the purposes of such collaboration (as such purposes are described in Section 1.22 above).

(b) CG hereby grants to Rigel a royalty-free, exclusive, worldwide license, with the right to grant and authorize sublicenses, under CG's right, title and interest in the Program Technology that is owned jointly by the Parties under Section 4.1(d) below, and Targets

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that are similarly owned jointly with Rigel, all to make and use the Targets for purposes outside the CG Program Field.

(c) CG has entered into a license agreement with the [*] concerning the [*] Patents which includes the right to sublicense (the "[*] Agreement"); as of the Effective Date, however, the terms under which CG may grant sublicenses under the [*] Agreement make impractical a sublicense to Rigel under the [*] patents for purposes of the Rigel Field. In the event that CG successfully renegotiates the terms of the [*] Agreement such that such sublicense would be practical, CG agrees to discuss in good faith the grant of a sublicense to Rigel under the [*] patents. The Parties understand and agree, however, that CG is not and shall not be obligated to enter into any agreement with Rigel concerning the [*] Patents, that failure to reach such an agreement for any reason shall not be deemed a breach of this Agreement and that this Section 2.1(C) shall not be deemed to preclude CG form entering into an agreement with a third party of any type or at any time concerning the [*] Patents.

2.2 RIGEL LICENSE GRANTS.

(a) Subject to the terms and prior to the termination or expiration of the Rigel License, the Parties agree that Rigel shall grant to CG, at CG's sole option and upon CG's request, a royalty-free, non-exclusive, worldwide license, without the right to sublicense, under Rigel's right, title and interest in the Rigel Know-How and Rigel Biological Materials, to make, have made, use sell, offer for sale and import products in the CG [*] Field. It is understood that in no event will CG have any obligation to obtain such license from Rigel. Rigel will give CG thirty (30) days prior written notice of the termination of the Rigel License by Rigel.

(b) Rigel hereby grants to CG:

(i) a royalty-free, exclusive, world-wide license, with the right to grant and authorize sublicenses, under Rigel's right, title and interest in the Program Technology (including without limitation the Therapeutic Candidates) owned solely by Rigel or jointly with CG, to make, have made, use, sell, offer for sale and import products, and otherwise exploit the Program Technology, in each case for purposes solely within the CG Program Field; and

(ii) subject to rights previously granted to third parties, a royalty-free, non-exclusive, worldwide license, with the right to grant sublicenses, under Rigel's right, title and interest in and to all Patents with priority dates prior to the Effective Date that claim Therapeutic Candidates, or the manufacture or use thereof, to make, have made, use and sell products in Gene Therapy incorporating such Therapeutic Candidates.

(c) In addition, Rigel hereby grants to CG a royalty-free, non-exclusive license, without the right to sublicense to CG Collaboration Partners, under Rigel's right, title and interest in the Targets to make and use the Targets solely to for the research and development of Therapeutic Candidates in the Field of Research. For clarity, it is understood and agreed that the licenses garanted to CG under this Section 2.2 specifically exclude the performance by CG of research on or with a Target which is outside the Field of Research. Any sublicense granted hereunder to CG Collaboration Partners shall be limited to the purposes of such collaboration.

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2.3 RIGEL COVENANT. Rigel hereby covenants that neither Rigel nor its Affiliates will make any claims against CG, its permitted sublicensees, distributors and customers in the chain of title with CG or its permitted sublicensees for Patent infringement as a result of activities which are explicitly permitted under the terms of this Agreement, nor shall Rigel or its Affiliates authorize a third party to make such a claim, and Rigel agrees to cooperate with CG in the defense against any such claim by licensees of Rigel.

2.4 NO OTHER LICENSE. No right or license is granted by either Party to the other under any other intellectual property other than those items expressly included in the licenses granted in this Article 2. Accordingly, no license shall be deemed granted by implication, estoppel or otherwise, if such license is not expressly and specifically granted in this Article 2.

ARTICLE 3

RESEARCH

3.1 RESEARCH.

(a) Rigel agrees to (i) use diligent efforts to conduct research within the Field of Research (the "Research"), in accordance with the research plan (the "Research Plan") incorporated hereby in, and appended to, this Agreement as Appendix G, as amended from time to time by written agreement of the Parties; and (ii) use diligent efforts to meet the goals of the Research Plan according to the timetables set forth therein. Without limiting the foregoing, the Research shall commence of the Effective Date and terminate upon the earlier of three (3) years after the Effective Date or the termination of the Agreement (the "Research Period"). Rigel will commit [*] during each year of the Research Period, or such other allocation as the RMC may decide, provided that in the event the RMC decides to reallocate FTEs between years, Rigel shall have no obligation to commit more than [*] in total over the entire Research Period. The individual FTEs who will conduct the Research are listed in Appendix H and may be replaced by Rigel, as reasonably agreed by the Parties, with other FTEs of comparable skill and expertise. Rigel agrees to test against the Success Criteria during the Research Period any proteins, peptides and Genetic Material produced or evaluated in connection with the Research as contemplated in the Research Plan.

(b) The Parties shall reasonably establish criteria for determining whether a particular peptide, protein or Genetic Material modulates angiogenesis in endothelial tissue in assays performed at Rigel, as such criteria are contemplated in the Research Plan (the "Success Criteria").

3.2 RESEARCH MANAGEMENT COMMITTEE. The Parties shall form a research management committee (the "RMC") comprised of four (4) individuals, two (2) being Rigel employees appointed and replaced by Rigel at its discretion, and two (2) being CG employees appointed and replaced by CG at its discretion. The size and composition of the RMC may be modified by mutual agreement of the Parties. The RMC shall evaluate the results of the Research set forth in the research reports pursuant to Section 3.4(a) to assess whether a peptide, protein or

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Genetic Material is a Therapeutic Candidate, and perform such other duties as specifically delegated to the RMC by mutual written agreement of the Parties.

3.3 RMC MEETINGS AND ACTIONS. RMC Meetings shall take place at such times and places as shall be determined by the RMC in order for the RMC to fulfill its obligations under Section 3.2. It is expected that the meetings will alternate between appropriate offices of each Party, or at such other convenient locations as agreed. If agreed by its members, the RMC may conduct meetings by telephone or video conference or other acceptable electronic means, provided that any decisions made during such meeting are recorded in writing and confirmed by signature of at least one (1) of the RMC members from each of the Parties. All decisions of or actions taken by the RMC shall be by unanimous approval of all the members of the RMC, and voting on any matters shall be reflected in the minutes of the meeting at which the vote was taken. If the RMC is unable to reach unanimous decision on any particular matter or issue, such matter or issue shall be referred to the chief executive officer of each Party or their designees for resolution. It is understood that for purposes of determining the Parties' rights and obligations under this Agreement, the authority of the RMC shall be limited to deciding those specific issues specifically delegated to the RMC in other Article of this Agreement (i.e., other than the general matters described in this Article 3).

3.4 REPORTS; DISCLOSURE.

(a) Rigel shall keep CG fully informed of the progress and results of the Research and shall provide written reports at or before each RMC meeting describing its activities, the level of effort applied to, and the results of, the Research, specifically including Rigel's determination as to which peptides, proteins or Genetic Material as of the date of such report meet the Success Criteria. Such RMC reports shall be in such form and contain such detail as the RMC shall determine. Rigel agrees to fully disclose to CG the Program Technology and the Targets, and to provide CG with reasonable quantities of Targets and Therapeutic Candidates generated or utilized in connection with the Research.

(b) Rigel agrees to maintain records of its activities in performing the Research, in good scientific manner, and to permit CG to have access to such records upon ten (10) days written notice to Rigel and during regular business hours, to the extent reasonably necessary to verify that Rigel has met its obligations under this Section 3.4.

3.5 EXCLUSIVITY OF EFFORTS. Rigel agrees that neither Rigel nor any of

its Affiliates shall directly or indirectly conduct or sponsor any research, develop or otherwise commercialize any products or technologies within the Field of Research, other than pursuant to the Research Plan, during the Research Period and for a period of one (1) year following the Research Period. Without limiting the foregoing, Rigel shall not appoint or license any third party to develop market, sell or otherwise distribute such products until after the expiration of one (1) year following the Research Period.

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ARTICLE 4

INTELLECTUAL PROPERTY MATTERS

4.1 OWNERSHIP AND PROSECUTION. Subject to the terms of this Agreement, as between the Parties hereto:

(a) It is understood that CG retains its entire right, title and interest in the CG Patents and CG Know-How, subject only to the rights expressly granted to Rigel hereunder, and shall have the right, but not the obligation, to file, prosecute and maintain any Patents related thereto at its expense.

(b) It is understood that Rigel retains its entire right, title and interest in the Rigel Biological Materials and Rigel Know-How, subject only to the rights expressly granted to CG hereunder, and shall have the right, but not the obligation, to file, prosecute and maintain any Patents related thereto at its expense.

(c) It is understood that, subject only to the rights expressly granted to the other Party hereunder, each Party retains its entire right, title and interest in and to any inventions, discoveries, know-how, trade secrets, and other information made or developed solely by such Party and/or its consultants in the course of the performance of this Agreement ("Sole Inventions"), and, subject to subsection (e) below, shall have the right, but not the obligation, to file, prosecute and maintain any Patents claiming its Sole Inventions ("Sole Patents") in all countries of the world.

(d) Both Parties shall jointly own any inventions, discoveries, know-how, trade secrets, and other information, that are made jointly by the Parties in the course of the performance of this Agreement ("Joint Inventions"). Subject to subsection (e) below, the RMC shall designate the Party which shall be responsible for filing, prosecuting and maintaining Patents claiming Joint Inventions ("Joint Patents"). All costs and expenses of filing, prosecuting and maintaining such Joint Patents will be borne equally by the Parties. The Party designated by the RMC to perform patenting activities shall seek the comments of the other Party and shall keep the other informed of the progress of such prosecution by providing quarterly status reports and copies of all correspondence between their patent counsel and the patent offices of the countries where such applications were filed. Such other Party shall reasonably assist the Party designated by the RMC in the prosecution of Joint Patents, including, without limitation, by executing any necessary powers of attorney. Subject to the rights and licenses granted to the other Party in Section 2.1(b) and 2.2(b), it is understood that neither Party shall have any obligation to account to the other, or obtain the consent of the owner, with respect to the commercialization, licensing or enforcement of any Joint Patents, and hereby waives any right it may have under the laws of any country to require such accounting or consent.

(e) CG shall have the right but not the obligation (either itself or through its designee) to file, prosecute and maintain Patents claiming Therapeutic Candidates ("Candidate Patents"); provided, however, that for any molecule that is a Therapeutic Candidate and a Target: (i) CG shall have the right but not the obligation (either itself or through its designee) to file, prosecute and maintain Patents claiming uses of such molecule in the CG Program Field and

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such Patents also shall be Candidate Patents; and (ii) Rigel shall have the right, but not the obligation, to file, prosecute and maintain any patents claiming the composition of matter of such molecule or claiming any use of the molecule outside the CG Program Field or in the Rigel Field. All costs and expenses of filing, prosecuting and maintaining Candidate Patents will be

borne by the Party that undertakes such prosecution. The Party undertaking such prosecution shall seek the comments of the other Party and shall keep the other Party informed of the progress of such prosecution by providing quarterly status reports and copies of all correspondence between their patent counsel and the patent offices of the countries where such applications were filed. Each Party shall reasonably assist the other Party in the prosecution of Candidate Patents, including, without limitation, by executing any necessary powers of attorney and other document, necessary for such prosecution.

(f) Each Party agrees to keep the other Party fully informed as to prosecution and maintenance (including without limitation any interference, opposition or other prosecution or other proceedings) with respect to patents claiming and disclosing subject matter within the Program Technology. In the event that a Party elects not to prosecute or maintain any patent rights in a Sole Invention comprising Program Technology, it shall promptly notify the other Party and authorize the other Party to seek or continue such prosecution and maintenance at such other Party's expense. In such case the owner of Sole Invention shall cooperate fully with the other Party to facilitate such prosecution and maintenance.

4.2 INFRINGEMENT AND SIMILAR ACTIONS. As between the Parties hereto:

(a) CG shall have the sole and exclusive right, at its expense, to prosecute any and all infringement or wrongful use of the CG Patents and CG Know-How, and (subject to paragraph (c) below) Sole Patents owned by CG and/or to enter settlements, judgments or other arrangements respecting such infringement or wrongful use. CG may retain all damages and other amounts recovered as a result of any such action, settlement, judgment or other arrangement.

(b) Rigel shall have the sole and exclusive right, at its expense, to prosecute any and all infringement or wrongful use of the Rigel Know-How, the Rigel Biological Materials, and (subject to paragraph (c) below) Sole Patents owned by Rigel and/or to enter settlements, judgments or other arrangements respecting such infringement or wrongful use. Rigel may retain all damages and other amounts recovered as a result of any such action, settlement, judgment or other arrangement.

(c) With respect to infringement of any Program Patents in the CG Program Field, CG shall have the right, but not the obligation (directly or through designees), to institute, prosecute and control at its own expense and for its own benefit, any action or proceeding with respect to such infringement. With respect to infringement of any Program Patents (i.e., outside the CG Program Field), Rigel shall have the right, but not the obligation, (directly or through designees) to institute, prosecute and control, at its own expense and for its own benefit, any action or proceeding with respect to such infringement. If a Party with the right to do so fails to bring an action or proceeding against a suspected infringer within a reasonable period after receiving a written request by the other Party to do so, such other Party shall have the right to

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bring and control an action against such infringer by counsel of its own choice and retain for its own account any amounts recovered from third parties. If one Party brings any such action or proceeding, the other Party agrees to be joined as a Party plaintiff if necessary to prosecute the action and to give the first Party reasonable assistance and authority to file and prosecute the suit.

(d) Each Party shall promptly notify the other in writing of any alleged or threatened infringement of Joint Patents of which it becomes aware and which may adversely impact the rights of the Parties hereunder. Promptly upon such notification, the Parties shall meet to discuss the strategy and appropriate steps to be taken to deal with such infringement. Any recovery obtained by settlement or otherwise shall be disbursed as follows: first, any reasonable expenses incurred in connection with such action (including counsel fees) by both Parties are reimbursed; thereafter, the net recovery shall be shared between the Parties according to the ratio of their respective contributions to the litigation costs. This paragraph shall not be deemed to limit the Parties' respective rights to enforce Joint Patents, or to limit the rights granted under paragraph (c) above.

4.3 THIRD PARTY CLAIMS.

(a) Except to the extent expressly warranted in Article 7, and subject to the indemnification obligation in Article 5, CG shall have no liability to Rigel with respect to any claim, suit or action alleging that the practice of the license rights granted by CG under Section 2.1 infringes

any intellectual property or other right of a third party. Except to the extent expressly warranted in Article 7, and subject to the indemnification obligation in Article 5, Rigel shall have no liability to CG or its Affiliates with respect to any claim, suit or action alleging that the practice of the license rights granted under Section 2.2 infringes any intellectual property or other rights of a third party.

(b) Rigel hereby agrees to provide reasonable assistance to CG, at its request, in defending any action or claim initiated by a third party against CG arising from any claim that the use or practice of the Rigel Know-How, Rigel Biological Materials or the Target by CG or its Affiliates infringes that third party's proprietary rights. CG hereby agrees to provide Rigel reasonable assistance, at its request and expense, in defending any action or claim initiated by a third party against Rigel or its Affiliates arising from any claim that the use or practice of the CG Patents or CG Know-How by Rigel or its Affiliates infringes that third party's proprietary rights.

(c) If a third party asserts against CG that a patent, trademark or other intangible right owned by it is infringed by any product in the CG Program Field derived or resulting from or incorporating Program Technology, CG will be solely responsible for defending against any such assertions at its cost and expense. Each Party will give prompt written notice to the other of any such claim. Rigel will assist in the defense of any such claim as reasonably requested by CG, at CG's expense, and may retain separate counsel at its own expense at any time.

(d) Neither Party shall enter into any settlement of any such claim which would admit the invalidity of Patents within the Program Technology without the other Party's prior written consent, which consent shall not be unreasonably withheld or delayed.

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4.4 PASS-THROUGH ROYALTIES. In consideration for the licenses granted herein:

(a) Rigel agrees to pay any amounts which CG is required to pay to Rockefeller University under the CG License as a result of CG's grant to Rigel of license rights to CG Patents or CG Know-How to Rigel or the exercise of the license rights granted by CG under the CG License.

(b) Rigel agrees to pay CG (i) [*] for the license granted to Rigel hereunder to CG Patents related to the [*] cell lines, and (ii) [*] for each sublicense granted by Rigel under this Agreement.

(c) CG agrees that in the event CG exercises its option to obtain a license pursuant to Section 2.2(a) above, CG will pay any amounts which Rigel is required to pay to Stanford University under the Rigel Licesne as a result of Rigel's grant to CG of license rights to Rigel Biolgoical Material or Rigel Know-How to CG or the exercise of the license rights granted by Rigel under the Rigel License. It is understood that unless and until CG obtains such license rights from Rigel, CG shall not be obligated to pay to Rigel or to Stanford University any amounts that Rigel is required to pay to Stanford University under the Rigel License.

ARTICLE 5

INDEMNIFICATION

5.1 CG INDEMNITY. CG agrees to indemnify, hold harmless and defend Rigel, its Affiliates, agents and employees from and against any and all liabilities, losses, damages, costs, fees and expenses, including reasonable legal expenses and attorneys' fees (collectively, "Losses") arising out of suits, claims, actions, or demands, brought or made by a third party ("Third Party Claim") against Rigel, its Affiliates, agents and employees, based on (i) CG's use and practice of the Rigel Know-How, Rigel Biological Materials, the Program Technology or the Targets, or (ii) breach of CG's warranties under Article 7 below, or (iii) the manufacture, use, handling, storage, sale or other disposition of Rigel Biological Materials, Program Technology, the Targets or any products resulting or derived from the Rigel Biological Materials or the Program Technology by CG, it Affiliates, agents, employees or sublicensees, all except to the extent such Losses or Third Party Claims result from the negligence or willful misconduct of Rigel or a breach of Rigel's warranties under Article 7 below.

5.2 RIGEL INDEMNITY. Rigel agrees to indemnify, hold harmless and defend CG, its Affiliates, agents and employees from and against any and all Losses arising out of any Third Party Claims against CG, its Affiliates, agents and employees based on (i) Rigel's use or practice of the CG Patents the CG Know-How or the Program Technology, (ii) breach of Rigel's warranties under Article 7 below, or (iii) the manufacture, use, handling, storage, sale or other disposition of Program Technology, the Targets or any products resulting or derived from the Program Technology by Rigel, its Affiliates, agents, employees or sublicensees, all except to the extent such Losses or Third Party Claims result from the negligence or willful misconduct of CG, or a breach of CG's warranties under Article 7 below.

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5.3 In the event that a Party is seeking indemnification under this Article 5, it shall inform the other Party of a claim or suit as soon as reasonably practicable after it receives notice of the claim or suit, shall permit the indemnifying Party to assume direction and control of the defense of the claim or suit (including the right to settle the claim or suit solely for monetary consideration), and shall cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the claim or suit. Neither Party will enter into any settlement or claim pursuant to this Section 5.3 which is materially adverse to the rights of the other Party herein, without the other Party's prior written consent, which will not be unreasonably withheld or delayed.

ARTICLE 6

CONFIDENTIALITY

6.1 CONFIDENTIALITY. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, for the term of this Agreement and for five (5) years thereafter, the Party receiving any Information or materials furnished to it by the other Party pursuant to this Agreement (collectively, "Confidential Information") shall keep confidential and shall not publish or otherwise disclose or use such Confidential Information for any purpose other than as provided for in this Agreement.

6.2 EXCEPTIONS. The obligations in Section 6.1 shall not apply to any Information or materials to the extent that the receiving Party can establish by competent proof that such Information or materials:

(a) was already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the other Party;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the receiving Party;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the receiving Party in breach of this Agreement; or

(d) was disclosed to the receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the disclosing Party not to disclose such information to others.

6.3 AUTHORIZED DISCLOSURE. Each Party may disclose the other's Confidential Information to the extent such disclosure is reasonably necessary (i) to exercise the rights granted to such Party hereunder (including the right to grant sublicenses as permitted by this Agreement provided that prior to any disclosure to a sublicensee, such sublicensee has executed a confidentiality agreement with terms corresponding to this Article 6); and (ii) to file or prosecute patent applications, to prosecute or defend litigation, to comply with applicable governmental

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regulations or to conduct preclinical or clinical trials; provided that if a Party is required by law or regulation to make any such disclosure of the other Party's Confidential Information it will, except where impracticable for necessary disclosures, for example in the event of medical emergency, give reasonable advance notice to the other Party of such disclosure requirement and, except to the extent inappropriate in the case of patent applications, will use its best efforts to secure confidential treatment of such Confidential Information required to be disclosed.

6.4 SURVIVAL. This Article 6 shall survive the termination or expiration of this Agreement for a period of five (5) years.

ARTICLE 7

WARRANTY MATTERS

7.1 LIMITED WARRANTIES. CG hereby represents and warrants to Rigel that CG has the full right and power to grant the licenses granted to Rigel under Section 2.1(a). Rigel hereby represents and warrants to CG that Rigel has the full right and power to grant the licenses granted to CG under Section 2.2.

7.2 GENERAL WARRANTIES. Each of the Parties hereby represents and warrants to the other that (i) it is a corporation duly organized and validly existing in good standing under the laws of its state of incorporation, (ii) it is duly qualified and authorized to enter into and perform its obligations under this Agreement, (iii) it has full power, authority and legal right to enter into and perform this Agreement, and (iv) the execution, delivery, and performance of this Agreement has been duly authorized by all necessary corporate action on the part of each Party and does not contravene any law binding on it, its Articles of Incorporation or Bylaws, any indenture, mortgage, contract or other agreement to which it is a Party or by which it is bound or any laws, governmental rule, regulation or order.

7.3 INTELLECTUAL PROPERTY WARRANTIES.

(a) Each of the Parties hereby represents and warrants to the other that (i) it does not Control any Patens that would dominate the Patents licensed to the other Party hereunder, (ii) it is not aware of any claims of a third party which would call into question the rights of such Party in the licensed subject matter or its right to grant the licenses granted to the other Party hereunder, (iii) it has provided the other Party with all information concerning royalty obligations pertinent to the licenses granted to the other Party hereunder; and (iv) it will use commercially reasonable efforts to keep in force any license agreement from which the license or sublicense granted to the other Party under this Agreement is derived to the extent that such license agreement does not provide for a survival of any sublicenses granted by such Party.

(b) Rigel further warrants to CG that as of the Effective Date (i) to the best of its knowledge, Rigel's conduct of the Research, and the manufacture, sale and use of Therapeutic Candidates will not infringe any third party intellectual property rights, and without limiting the foregoing, Rigel warrants that Rigel's conduct of the Research will not infringe any of the

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patents listed in Appendix I hereto; (ii) Rigel does not know of any third party other than Stanford University having a claim in the Rigel Biological Materials; and (iii) Rigel has the right to grant to CG a license under the Rigel Biological Materials and the Rigel Know-How to make, use and sell products in the CG [*] Field.

(c) CG further warrants to Rigel that CG has the right to grant to Rigel a license under the CG Patents and CG Know-How to make, use and sell products within the Rigel Field.

(d) Rigel warrants that it has not as of the Effective Date entered into an agreement with any third party licensing or granting right to Rigel technology in the Field of Research.

7.4 LIMITATION ON WARRANTIES. EXCEPT AS PROVIDED IN SECTIONS 7.1, 7.2, AND 7.3 ABOVE, NEITHER PARTY MAKES ANY WARRANTIES TO THE OTHER PARTY, WHETHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE AS TO ANY PRODUCT OR PROCESS, OR AS TO THE VALIDITY OR SCOPE OF ANY PATENTS, OR THAT ANY LICENSED BIOLOGICAL MATERIALS, PATENTS OR KNOW-HOW WILL BE FREE FROM INFRINGEMENT OF

PATENTS OF ANY THIRD PARTY, OR THAT NO THIRD PARTIES ARE INFRINGING SAME.

ARTICLE 8

TERM AND TERMINATION

8.1 TERM OF AGREEMENT. Unless earlier terminated as otherwise provided in this Article 8, this Agreement shall remain in effect until the expiration of the last to expire of the CG Patents or Program Patents.

8.2 TERMINATION FOR BREACH. A Party may terminate this Agreement prior to the expiration of the Agreement in the event that the other Party is in breach of or default under a material term of the Agreement, and the breaching Party does not cure such breach or default within thirty (30) days of written notice thereof from the non-breaching Party. Subject to Section 8.3 below, upon any such termination, all the licensees granted by and between the Parties herein shall terminate; provided that any sublicense granted by a Party hereunder to a third party prior to such termination shall survive such termination, so long as the sublicensee agrees to be bound by the applicable terms of this Agreement.

8.3 SURVIVAL. Upon expiration or termination of this Agreement the rights and obligations under Articles 5 and 6 and Sections 7.4, 8.3, 9.2, 9.3, 9.7 and 9.10 shall continue. In addition, upon expiration or termination of this Agreement after the end of the Research Period, the license granted under Article 2 above and the rights and obligations under Article 4 shall survive. Further, subject to Section 2.1(b) and 2.2(b) if they survive the termination or expiration of this Agreement as provided above, neither Party shall have any obligation to account to the

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other, or obtain the consent of the owner, with respect to the commercialization, licensing or enforcement of any Joint Patents, and hereby waives any right it may have under the laws of any country to require such accounting or consent.

ARTICLE 9

MISCELLANEOUS

9.1 RELATIONSHIP OF THE PARTIES. This Agreement creates only licensor-licensee and sublicensor-sublicensee relationships between Rigel and CG. No partnership or other legal relationship is created hereunder. Neither Party is, or will be deemed to be, an agent or legal representative of the other Party for any purpose. Neither Party will be entitled to enter into any contracts in the name of or on behalf of the other Party, and neither Party will be entitled to pledge the credit of the other Party in any way or hold itself out as having authority to do so.

9.2 ASSIGNMENT. This Agreement may not be assigned by either Party without the prior written consent of the other Party, which consent shall not be unreasonably withheld; provided, however, that a Party may assign this Agreement without such consent to any Affiliate or to a successor in interest by way of merger, acquisition, sale or transfer of substantially all of its business or assets pertaining to the subject matter of this Agreement. The Agreement will be binding upon and inure to the benefit of all permitted successors and assignees of the Parties hereunder, and the name of each Party appearing herein will be deemed to include the names of such Party's successors and assignees.

9.3 USE OF NAMES. No Party hereto may use the name of the other Party in public announcements without the prior consent of the other Party as required by law or regulation.

9.4 AMENDMENT. No amendment, modification or supplement of any provision of the Agreement will be valid or effective unless made in writing and signed by a duly authorized officer of each Party.

9.5 WAIVER. No provision of the Agreement will be waived by any act, omission or knowledge of a Party or its agents or employees except by an instrument in writing expressly waiving such provision and signed by a duly authorized officer of the waiving Party.

9.6 HEADINGS. The headings for each article and section in this Agreement have been inserted for the convenience of reference only and are

not intended to limit or expand on the meaning of the language contained in the particular article or section.

9.7 NOTICES. Any notice or other communication required or permitted to be given to either Party hereto shall be in writing unless otherwise specified and shall be deemed to have been properly given and to be effective on the date of delivery if delivered in person or by facsimile or three (3) days after mailing by registered or certified mail, postage paid, to the other Party at the following address:

If to Rigel: Rigel, Inc.
240 East Grant Avenue
South San Francisco, CA 94080
Attn: Secretary
Fax: 650.624.1101

Copy to: Cooley Godward, LLP
Five Palo Alto Square, 4th Floor
3000 El Camino Real
Palo Alto, CA 94306
Attn: Patrick A. Pohlen, Esq.
Fax: 650.857.0663

If to CG: Cell Genesys, Inc.
342 Lakeside Drive
Foster City, CA 94404
Attn: Chief Executive Officer
Fax: 650.358.0803

9.8 SEVERABILITY. Whenever possible, each provision of the Agreement will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of the Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of the Agreement.

9.9 ENTIRE AGREEMENT OF THE PARTIES. The Agreement will constitute and contain the complete, final and exclusive understanding and agreement of the Parties with respect to the subject matter hereof and cancels and supersedes any and all prior negotiations, correspondence, understandings and agreements, whether oral or written, between the Parties respecting the subject matter. Each Party hereto was represented by counsel in drafting and negotiating this Agreement, and all Parties are deemed to have contributed to the drafting hereof.

9.10 GOVERNING LAW. This Agreement shall be governed by and construed in accordance with the laws of the State of California excluding only laws and rules relating to "choice of law". All Parties to this Agreement hereby consent to the jurisdiction of the courts of the State of California and the Federal District Court for the Northern District of California for resolution of any disputes that arise hereunder.

9.11 COUNTERPARTS. This Agreement may be executed in any number of counterparts, each of which shall be an original, but all of which together shall constitute one instrument.

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IN WITNESS WHEREOF, the Parties hereto have duly executed this Agreement as of the date first written above.

CELL GENESYS, INC. RIGEL PHARMACEUTICALS, INC.

By: /s/ Stephen A. Sherwin By: /s/ Donald W. Perryman

Name: Stephen A. Sherwin, M.D.	Name: Donald W. Perryman
Title: Chairman & Chief Executive Officer	Title: VP, Business Development

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APPENDIX A
EXCLUSIVE LICENSE AGREEMENT

EXCLUSIVE LICENSE AGREEMENT made as of January 31, 1996 (the "Effective Date"), by and between Cell Genesys, Inc. ("Company"), a corporation organized and existing under the laws of the State of Delaware, having an office at 322 Lakeside Drive, Foster City, California 94404, and The Rockefeller University ("Rockefeller"), a nonprofit education corporation organized and existing under the laws of the State of New York, having an office at 1230 York Avenue, New York, New York 10021-6395.

WITNESSETH:

WHEREAS, Rockefeller is the owner by assignment from Warren S. Pear, Martin L. Scott, Garry M. Nolan and David Baltimore ("Inventors") of the entire right, title and interest in United States Patent Application Serial No. 08/023,909, filed February 22, 1993, entitled Production of High Titer Helper-Free Retroviruses by Transient Transfection, and in the inventions described and claimed therein ("Licensed Patent Rights"), and in the Biological Materials and related Know-How, as defined below;

WHEREAS, Rockefeller and the Company entered into a license agreement effective as of October 25, 1994 (the "Prior Agreement"), pursuant to which Rockefeller granted to the Company a non-exclusive license to use the Licensed Patent Rights, Know-How and Biological Materials for research and commercial purposes;

WHEREAS, the parties have agreed to expand the scope of the license and rights granted to the Company and therefore have agreed to terminate the Prior Agreement as of the Effective Date, and enter into this Agreement;

WHEREAS, Rockefeller wishes to offer and grant the Company an exclusive license with regard to the Licensed Patent Rights, Know-How and the Biological Materials for research and commercial purposes, and seeks to be compensated for the transfer and use of such rights; and

WHEREAS, the Company wishes to license from Rockefeller the Licensed Patent Rights, Biological Materials and Know-How for commercial development and application as herein defined.

NOW, THEREFORE, in consideration of the mutual benefits to be derived hereunder, the parties hereto agrees as follows:

1. DEFINITIONS.

The following terms will have the meanings assigned to them below when used in this Agreement.

1.1 "AFFILIATE" shall mean:

(a) any entity owning or controlling, directly or indirectly, at least forty-nine percent (49%) of the stock normally entitled to vote for election of directors of a party; or

(b) any entity at least forty-nine percent (49%) of whose stock

normally entitled to vote for election of directors is owned or controlled, directly or indirectly, by a party.

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1.2 "BIOLOGICAL MATERIALS" shall mean (i) the ecotropic producer cell line named [*] which producer cell line was deposited with the American Type Culture Collection as of [*] and has been assigned Accession No. [*] and any viruses produced thereby; (ii) _____ Biological Materials shall also include any direct progeny, mutant, or derivatives of the [*] _____ cell lines and the viruses produced thereby.

1.3 "IMPROVEMENT TECHNOLOGY" means all patent and other intellectual property rights, and materials relating to inventions, discoveries or improvements to the Licensed Technology licensed to Rockefeller by any academic institution, governmental and other not-for-profit entity to which Rockefeller grants a non-exclusive research license with regard to the Licensed Technology pursuant to Section 6.3 herein.

1.4 "KNOW-HOW" shall mean information and data not generally known which are owned and in the possession of or available to Rockefeller and which it is free to divulge as of the Effective Date regarding the preparation and use of Biological Materials, and pharmacological, biological and clinical properties of Biological Materials. It is understood that Know-How shall not include any information or data known by the Company prior to receipt of such information or data from Rockefeller, as shown by reasonable evidence.

1.5 "LICENSED PATENT RIGHTS" shall mean:

(a) the patent application(s) concerning the subject matter of this Agreement which are listed on Exhibit A attached hereto;

(b) all patent applications which are divisions, substitutions, continuations, continuations-in-part, renewals, or additions of the patent applications described in (a) hereof,

(c) all foreign counterparts of the applications listed in (a) and (b) hereof; and

(d) all patents, including reissues, re-examinations and extensions, which may issue on any of the preceding.

1.6 "LICENSED PRODUCTS" shall mean any and all products the manufacture, use or sale of which but for the license granted herein would infringe a Valid Claim or are within the scope of a Pending Claim in the country in which such products are made or sold.

1.7 "LICENSED TECHNOLOGY" shall mean the Licensed Patent Rights, Biological Materials and Know-How.

1.8 "NET SALES" shall mean [*], where [*] shall mean the amount invoiced by the Company or its sublicensees to customers for Licensed Products less: (i) all trade, cash and quantity credits, discounts, refunds or government rebates, (ii) amounts for claims, allowances or credits for returns; retroactive price reductions; chargebacks or the like; (iii) packaging, handling fees and prepaid freight, sales taxes, duties and other governmental charges (including value added tax), but excluding what is commonly known as income taxes; and (iv) provisions for

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uncollectible accounts determined in accordance with reasonable accounting practices, consistently applied to all products of the selling party. [*] shall not include sales by the Company to its Affiliates for resale, provided that if the Company sells a Licensed Product to an Affiliate for resale, [*] shall include the amounts invoiced by such Affiliate to third parties on the resale of such Licensed Product. Notwithstanding the foregoing. [*] shall include charges for the separation, transduction and/or expansion of cells

comprising Licensed Products, but notwithstanding any of the foregoing, shall not include charges for apheresis, reinfusion, surgical procedures, hospital stays or other charges not directly attributed to the Licensed Product or to the ex vivo preparation of the Licensed Product.

1.9 "PARTY" shall mean the Company or Rockefeller, and "Parties" shall mean both the Company and Rockefeller.

1.10 "PENDING CLAIM" shall mean a claim of a pending patent application within the Licensed Patent Rights.

1.11 "TERRITORY" shall mean the entire world.

1.12 "VALID CLAIM" shall mean a claim of an issued and unexpired patent included within the Licensed Patent Rights, which has not been held unenforceable or invalid by a court or other governmental agency of competent jurisdiction, and which has not been admitted to be invalid or unenforceable through reissue, disclaimer or otherwise.

2. LICENSED RIGHTS

2.1 Subject to Section 2.2 below, Rockefeller grants to the Company and its Affiliates the following licenses:

(a) an exclusive, worldwide, royalty-bearing license under the Licensed Technology, with the right to grant and authorize sublicenses, to make, have made, import, have imported, use, sell, offer for sale and otherwise exploit the Licensed Products in any country of the Territory; and

(b) a non-exclusive, worldwide, royalty-free, irrevocable license under the Improvement Technology, with the right to grant and authorize sublicenses, to make, have made, import, have imported, use, sell, offer for sale and otherwise commercialize products and services in any country of the Territory.

2.2 The licenses granted by Rockefeller in Section 2.1 (a) above are subject to any limitations on Rockefeller's rights arising under the provisions of the following:

(a) 35 United States, Section 201 et seq., and regulations and rules promulgated thereunder and any agreements implementing the provisions thereof, or

(b) other applicable laws or regulations to which Rockefeller may be subject; or

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(c) Rockefeller's Institutional Patent Agreement with the United States Department of Health and Human Services, dated June 15, 1973, as amended, which is its formal agreement with the United States Government to implement the cited provisions of the U.S. Code.

2.3 Rockefeller shall promptly notify the Company of any Improvement Technology of which it acquires knowledge and provide the Company all available information relating thereto.

2.4 The licenses herein granted shall continue for the lives of any issued patents hereunder as the same or the effectiveness thereof may be extended by any governmental authority, rule or regulation applicable thereto.

3. TRANSFER OF BIOLOGICAL MATERIALS AND KNOW-HOW

3.1 The parties acknowledge that pursuant to the Prior Agreement, Rockefeller transferred to the Company a quantity of Biological Materials and such Know-How to allow the Company to establish a viable cell culture of said Biological Materials for the Company's purposes. The Company is permitted to cultivate and use said Biological Materials, subject to the terms and conditions of this Agreement On the Effective Date, Rockefeller shall notify the American Type Culture Collection ("ATCC") that the Company is authorized to receive samples of the Biological Materials deposited with the ATCC and to deliver such materials to the Company at the Company's request, and that the Company has the right to authorize third parties to receive one or more samples of the Biological Materials, on such terms as the Company may indicate to the ATCC.

3.2 Should the Company exhaust the quantity of Biological Materials within six (6) months of the date of execution hereof, so that a viable cell

culture of said Biological Materials no longer exists, Rockefeller shall authorize the ATCC to provide the Company with a quantity of Biological Materials sufficient to reestablish the Company's viable colony thereof.

3.3 Within sixty (60) days of the Effective Date, Rockefeller shall deliver to the Company tangible copies of all existing Know-How which it did not previously provide to the Company pursuant to the Prior Agreement.

4. PAYMENTS

4.1 In consideration of the rights and licenses granted hereunder, the Company shall pay or cause to be paid to Rockefeller amounts as follows:

(a) _____

(b) _____

(c) _____

(d) a royalty of [*] of Net Sales of Licensed Products sold by the Company within the scope of a Valid Claim within the Licensed Patent Rights in the country they are made or sold.

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Notwithstanding the above, the royalty due Rockefeller on Net Sales of Licensed Products, the manufacture, use or sale of which would not infringe a Valid Claim in the country for which they are sold but which are within the scope of a Pending Claim in such country, shall be fifty percent (50%) of the royalty due under Section 4.1(d).

4.2 In the event that a Licensed Product is sold in combination as a single product with another product whose sale and use are not covered by the Licensed Patent Rights in the country for which the combination product is sold, Net Sales from such sales, for purposes of calculating the amounts due under Section 4.1 above, shall be calculated by multiplying the Net Sales of that combination by the fraction A/(A + B), where A is the gross selling price of the Licensed Product, as the case may be, sold separately, and B is the gross selling price of the other product sold separately. In the event that no such separate sales are made by the Company, Net Sales for royalty determination shall be as reasonably allocated by the Company between such Licensed Product and such other product, based upon their relative importance and proprietary protection.

4.3 Licensed Products sold, leased or otherwise distributed by the Company's sublicensees shall be considered to be sales, leases or disposals of Licensed Products by the Company for purposes of royalty payments and reports under this Agreement. The obligation to pay royalties pursuant to this Agreement is imposed only once with respect to the sale of a particular Licensed Product regardless of the number of claims or patents that cover such Licensed Product. The Company shall have no obligation to pay royalties on Licensed Products used in research and development, in clinical trials or other noncommercial purposes, or distributed as samples.

4.4 The Company's obligation to pay royalties hereunder shall continue on a country-by-country basis until (i) the expiration of the last-to-expire issued patent within the Licensed Patent Rights in such country, or (ii) [*] following the first commercial sale of a Licensed Product in a country, if no patent covering such Licensed Product has been issued in such country. Thereafter, the Company shall have a fully paid up license under Licensed Patent Rights, Biological Materials and Know-How to make, have made, use, sell, lease, import, have imported, offer for sale or otherwise exploit the Licensed Product(s) for any use in that country.

4.5 _____

4.6 _____

4.7 Unless this Agreement is terminated earlier, within sixty (60) days following the first achievement by the Company or a sublicensee of the following milestones with respect to the first Licensed Product within the scope of a Valid Claim within the Licensed Patent Rights, the Company shall pay to Rockefeller [*] milestone payments as follows:

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<TABLE>
<CAPTION>

EVENT	Payment
<S>	<C>
Enrollment of first patient in a Company-sponsored [*] clinical trial of a Licensed Product	$ [*]
Enrollment of first patient in a Company-sponsored [*] clinical trial of a Licensed Product	$ [*]
Approval of NDA in U.S. of a Licensed Product	$ [*]

</TABLE>

4.8 Upon commencement of commercial sales of any Licensed Products which generate a royalty to Rockefeller pursuant to this Agreement, the Company shall within ninety (90) days of the close of the fiscal semi-annual period, provide semi-annual reports to Rockefeller showing the total Net Sales of Licensed Products sold, leased or otherwise disposed of during such period and the calculation of royalties thereon. Any royalty then due and payable shall be included with such report. All reports provided hereunder by the Company shall be the Confidential Information of the Company, subject to Section 7 herein. The Company's records shall be open to inspection by an independent certified public accountant designated by Rockefeller for three (3) years from the submission of such reports and payments, subject to execution of a confidentiality agreement reasonably acceptable to the Company, once per calendar year at reasonable times, at Rockefeller's expense, for the sole purpose of verifying the accuracy of the reports and royalty payments made by the Company. The accountant shall report to Rockefeller only whether there has been an underpayment and, if so, the amount thereof.

5. TIMES AND CURRENCIES OF PAYMENT

5.1 Royalty payments shall be made in United States dollars or if sales are made in the currency of other countries, royalties shall be calculated in the currency of such other country and be converted into United States dollars using the applicable exchange rate for sale of U.S. dollars listed by the foreign exchange desk of the Bank of America on the last day of the applicable reporting period.

5.2 If at any time legal restrictions prevent the prompt remittance of part or all royalties by the Company with respect to any country where a Licensed Product is sold, the Company shall have the right and option to make such payment by depositing the amount thereof in local currency to an account in the name of Rockefeller in a bank or other depository in such country.

6. SUBLICENSEES

6.1 The Company and its Affiliates shall have the right to grant and authorize sublicenses under the Licensed Technology and Improvement Technology to commercial entities for research purposes and for commercial purposes, including without limitation, to make, have made, import, have imported, use, lease, offer for sale and sell Licensed Products in the Territory.

6.2 The Company shall have the sole discretion to determine the financial and other terms on which any sublicenses shall be granted under the Licensed Technology, subject to the

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provisions herein. Any sublicense(s) granted by the Company under this Agreement shall be subject and subordinate to the terms and conditions of this Agreement, except the financial terms of the sublicense(s) may require greater payments than the financial terms in this Agreement.

6.3 Notwithstanding Section 2.1 above, Rockefeller, on behalf of the Company, may continue to grant limited, non-transferable, research sublicenses to academic institutions, governmental and other not-for-profit entities using the form sublicense agreement attached hereto as Exhibit B. Rockefeller shall not enter into or agree to enter into any agreement with such an entity which deviates in any way from the form agreement set forth in

Exhibit B, without the prior written consent of the Company. Rockefeller shall provide the Company with a copy of each such research license entered by Rockefeller promptly following the execution of such agreement.

6.4 In the event of any termination of this Agreement, any sublicenses granted under or this Agreement shall also terminate unless such sublicensees provide Rockefeller written notice that they will abide by the applicable terms of this Agreement.

6.5 In no event shall a default or breach of a sublicensee of a sublicense granted by the Company pursuant to this Agreement constitute by a default or breach by the Company of this Agreement or be deemed a valid basis for the termination of this Agreement.

7. CONFIDENTIAL INFORMATION

7.1 Each Party and its Affiliates and sublicensees shall treat as confidential all Confidential Information received from the other Party hereto, shall not use such Confidential Information except as expressly set forth herein or otherwise authorized in writing, shall implement reasonable procedures to prohibit the disclosure, unauthorized duplication, misuse or removal of such Confidential Information and shall not disclose such Confidential Information to any third party except as may be necessary and required in connection with the rights and obligations of such party under this Agreement, and subject to confidentiality obligations at least as protective as those set forth herein. Without limiting the foregoing, each of the parties shall use at least the same procedures and degree of care which it uses to prevent the disclosure of its own confidential information to prevent the disclosure of Confidential Information of the other Party. As used herein, the term "Confidential Information" shall mean any information expressly designated as Confidential Information in this Agreement and information disclosed by one Party to another pursuant to this Agreement which is in written, graphic, machine readable or other tangible form and is marked "Confidential" to indicate its confidential nature. Confidential Information may also include oral information disclosed by one Party to another pursuant to this Agreement, provided that such information is designated as confidential at the time of disclosure and within thirty (30) days after its oral disclosure is reduced to a written summary by the disclosing Party, which summary is marked in a manner to indicate its confidential nature and delivered to the receiving Party.

7.2 Notwithstanding the above, neither Party has any obligation of confidence under this Agreement with respect to any information which:

(i) may be demonstrated to have been known to the receiving Party prior to the time of disclosure thereof by the disclosing Party; or

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(ii) without breach of this Agreement, has been published or is otherwise available to the public at any time whether before or after the time of disclosure to such Party; or

(iii) is at any time lawfully received by such Party from a third party who has no obligation of confidence to a Party in respect hereof.

7.3 Each Party hereto may disclose another's Confidential Information to the extent such disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, complying with applicable governmental regulations or otherwise submitting information to tax or other government authorities, making a permitted sublicense or other exercise of its rights hereunder or conducting clinical trials, provided that if a Party is required to make any such disclosure of another Party's secret or Confidential Information, other than pursuant to a confidentiality agreement, it will give reasonable advance notice to the latter Party of such disclosure requirement and, will use its best efforts to secure confidential treatment of such information prior to its disclosure (whether through protective orders or otherwise).

8. REPRESENTATIONS AND WARRANTIES

8.1 Rockefeller represents and warrants that: (i) it is a nonprofit corporation duly organized, validly existing and in good standing under the laws of New York (ii) the execution, delivery and performance of this Agreement have been duly authorized by all necessary action on the part of Rockefeller; (iii) it is the sole and exclusive owner of all right, title and interest in the Licensed Patent Rights; (iv) the Licensed Patent Rights are free and clear of any lien, security interest or restriction on transfer or

license; (v) Rockefeller has not previously granted, and will not grant during the term of this Agreement, any right, license or interest in and to the Licensed Patent Rights, Biological Materials and Know-How, or any portion thereof, in conflict with the rights, exclusive license and interest granted to the Company herein; (vi) it has complied fully with all requirements of 35 U.S.C. Section 201 et seq. and all implementing regulations with respect to perfecting its interest in the Licensed Patent Rights; (vii) Exhibit A contains a complete and accurate listing of all Licensed Patent Rights existing as of the Effective Date; and (viii) there are no actions, suits, investigations, claims or proceedings pending in any way relating to the Licensed Patent Rights, Biological Materials or Know-How.

8.2 The Company represents and warrants that: (i) it is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware; and (ii) the execution, delivery and performance of this Agreement have been duly authorized by all necessary corporate action on the part of the Company.

8.3 ROCKEFELLER EXPRESSLY DISCLAIMS ANY AND ALL IMPLIED OR EXPRESS WARRANTIES AND MAKES NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR ANY PARTICULAR PURPOSE OF BIOLOGICAL MATERIALS, LICENSED PROCESSES OR LICENSED PRODUCTS CONTEMPLATED BY THIS AGREEMENT. FURTHER, ROCKEFELLER HAS MADE NO FORMAL INVESTIGATION AND THEREORE CAN MAKE NO REPRESENTATION THAT BIOLOGICAL MATERIALS SUPPLIED BY IT OR THE METHODS USED IN MAKING OR

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USING SUCH MATERIALS ARE NOW OR WILL REMAIN FREE FROM LIABILITY FOR PATENT INFRINGEMENT.

9. _____

9.1 _____

9.2 _____

10. PUBLICITY

The Company will not use either directly or by implication the name of Rockefeller, or the name of any member of the faculty or staff thereof for any commercial or promotional purposes without prior notification and written agreement of Rockefeller. Except as expressly provided herein, the Parties agree not to disclose the terms of this Agreement to any third party without the prior written consent of the other Party to the fact and form of such disclosure, except as required by securities or other applicable laws, to prospective investors and to such party's accountants, attorneys and other professional advisors. Notwithstanding the above, the Company may disclose the existence of this Agreement and issue a press release, reasonably acceptable to Rockefeller, describing this Agreement and the rights granted the Company by Rockefeller under this Agreement, and disclose to actual and potential sublicensees the rights granted the Company by Rockefeller under this Agreement.

11. PATENTS

11.1 Except as set forth in Section 11.4, the Company shall have the sole right to control the preparation, filing, prosecution and maintenance of the Licensed Patent Rights, and any interference or opposition proceeding relating thereto, using patent counsel of its choice. The Company shall consult with Rockefeller regarding the prosecution of any such patent applications, by providing Rockefeller a reasonable opportunity to review and comment on all proposed submissions to any patent office before submittal, and provided further that the Company shall keep Rockefeller reasonably informed as to the status of such patent applications by promptly providing Rockefeller copies of all communications relating to such patent applications that are received from any patent office. If the Company informs Rockefeller in writing that the Company no longer wishes to conduct such activities with regard to any such patent applications or patents in any country, then Rockefeller will be free, at its discretion and expense to either abandon the subject patent applications or to continue such activities, and the Company shall have no further rights with respect to the applicable patent applications or patents in such countries.

11.2 During the term of the Agreement, the Company shall be responsible for one hundred percent (100%) of the expenses incurred in connection with the activities set forth in Section 11.1. above.
_____ With respect to patent-related costs

incurred after the Effective Date, the Company shall reimburse Rockefeller within thirty (30) days following invoice for such costs, in a form reasonably acceptable to the Company.

11.3 If either Party hereto becomes aware that any Licensed Patent Rights are being or have been infringed by any third party, such Party shall promptly notify the other Party hereto in

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writing describing the facts relating thereto in reasonable detail. The Company shall have the initial right, but not the obligation, to institute, prosecute and control any action, suit or proceeding (an "Action") with respect to such infringement, including any declaratory judgment action, at its expense, using counsel of its choice; provided, however, during the pendency of any such Action, the Company shall be entitled to place any royalties otherwise due Rockefeller hereunder in a separate account controlled by the Company. If the pertinent Licensed Patent Rights are found invalid or unenforceable in such an Action, or any appeal thereof, the Company may retain the amounts placed in such account without further obligation to Rockefeller with regard thereto. If the Licensed Patent Rights are not held invalid or unenforceable in such an Action, or any appeal thereof, the Company shall promptly pay the amounts deposited in such account to Rockefeller. Any amounts recovered from third parties in any such Action shall be retained by the Company. In the event the Company fails to initiate or defend any Action involving the Licensed Patent Rights within one (1) year of receiving notice of any commercially significant infringement, Rockefeller shall have the right, but not the obligation, to initiate and control such an Action, and the Company shall cooperate reasonably with Rockefeller, at Rockefeller's request, in connection with any such Action. Any amounts recovered in such Action shall be used first to reimburse the Company and Rockefeller for the expenses incurred in connection with such Action, and any remainder retained by Rockefeller.

11.4 In the event the parties believe an interference may be declared or an interference is declared between any patent application or patent within the Licensed Patent Rights and any patent application or patent owned or controlled by the Company relating to the production of high titer retroviruses, the parties agree to amicably settle any such prospective or actual interference in accordance with the procedure set forth on Exhibit C. The Company shall have the exclusive right to initiate such settlement procedure after consultation with Rockefeller. In the event of any such prospective or actual interference and the settlement thereof, each Party shall pay its own costs associated therewith and the parties shall equally share the costs of any arbitration, including without limitation, administration and arbitrator fees. It is understood and agreed that in the event an interference is declared, neither Patty shall have an obligation to participate in such a proceeding, but each hereby acknowledges that it understands that a failure to participate may result in an adverse outcome which could have a material adverse impact on such Party. It is further understood and agreed that any patent applications and patents within the Licensed Patent Rights which are involved in any interference shall remain subject to the license granted the Company herein.

12. LICENSED PRODUCT LIABILITY

The Company agrees to indemnify, defend and hold harmless Rockefeller and its trustees, officers, agents, faculty, employees, and students (the "Indemnitees"), from any and all liability arising from injury or damage to persons or property resulting directly or indirectly from the Company's acquisition, use, manufacture, sublicense or sale of any Licensed Product covered by Licensed Patent Rights or Know-How licensed hereunder. Notwithstanding the foregoing, the Company expressly retains any and all claims it may have against Indemnitees arising from indemnitees' negligence or willful misconduct. The Company's obligation to indemnify the Indemnitees under this Section 11 shall not apply unless the indemnified Party promptly notifies the Company of any claim or liability subject to this Section 12 and cooperates fully with the Company in the defense of any such claim or proceeding. The Company further agrees to obtain, prior to the first

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commercial sale of a Licensed Product, and maintain in force for at least fifteen (15) years following the last sale of a Licensed Product, product liability insurance coverage of at least one million ($1,000,000) dollars or a lesser amount as appropriate to the risk as determined by reference to reliable standards in the industry, such insurance to specifically name Rockefeller as an additional insured.

13. NOTICES

Any notice required to be given pursuant to this Agreement shall be in writing and may be made by personal delivery or by registered or certified mail, return receipt requested, by one Party to the other Party at the addresses noted below:

In the case of the Company, notice should be sent to:

Cell Genesys, Inc.
322 Lakeside Drive
Foster City, California 94404
Attn: Senior Vice President, Corporate Development

In the case of Rockefeller, notice should be sent to:

The Rockefeller University
1230 York Avenue
New York, New York 10021
Attn: Office of the General Counsel

14. LAW TO GOVERN

This Agreement shall be interpreted and governed in accordance with the laws of the State of New York.

15. ASSIGNMENT

This Agreement may not be assigned by either Party without the prior written consent of the other; PROVIDED, HOWEVER, the Company may assign this Agreement in connection with the transfer of all or substantially all of its business relating to the subject matter of this Agreement whether by sale, merger, operation of law or otherwise.

16. TERMINATION

16.1 The Company shall have the right to terminate this Agreement at any time with respect to any Licensed Patent Right or any country upon ninety (90) days prior written notice to Rockefeller. Such termination shall automatically terminate the license rights provided in Section 2 with respect to such Licensed Patent Rights hereof in such country but shall not relieve the Company of the obligation to pay royalties for any period prior to the effective date of termination.

16.2 Either Party may terminate this Agreement in the event of a material breach by the other Party which is not cured within a reasonable time, provided only that the offending Party is given notice of the breach and not less than ninety (90) days in which to cure such breach.

16.3 Sections 2.4, 6.4 and 24.3 and Articles 7, 8, 10, 12, 14, 17 and 25 shall survive expiration or termination of this Agreement for any reason.

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17. RESOLUTION OF DISPUTES

The Parties agree that in the event of it dispute between them arising from, concerning, or in any way relating to this Agreement, the Parties shall undertake good faith efforts to resolve the same amicably between themselves.

18. FORCE MAJEURE

The Parties shall not be liable in any manner for failure or delay in fulfillment of all or part of this Agreement, directly or indirectly caused by acts of God, governmental orders or restrictions, war, war-like conditions, revolution, riot, looting, strike, lockout, fire, earthquake, flood or other similar or dissimilar cause or circumstances beyond the nonperforming Party's control. The nonperforming Party shall promptly notify the other Party of the cause or circumstance and shall recommence its performance of its obligations as soon as practicable after the cause or circumstance ceases.

19. BINDING UPON SUCCESSORS AND ASSIGNS

Subject to the limitations on assignment herein, this Agreement shall be binding upon and inure to the benefit of successors in interest or assigns of Rockefeller and the Company. Any such successor or assignee of a Party's interest shall expressly assume in writing the performance of all the terms and conditions of this Agreement to be performed by said Party.

20. INDEPENDENT CONTRACTORS

The relationship between Rockefeller and the Company is that of independent contractors. Rockefeller and the Company are not joint venturers, partners, principal and agent, master and servant, employer or employee, and have no other relationship other than independent contracting parties. Rockefeller shall have no power to bind or obligate the Company in any manner, other than as is expressly set forth in this Agreement. Likewise, the Company shall have no power to bind or obligate Rockefeller in any manner, other than as is expressly set forth in this Agreement.

21. SEVERABILITY

If any provision of this Agreement is ultimately held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not in any way be affected or impaired thereby.

22. NO WAIVER

Any delay in enforcing a Party's rights under this Agreement or any waiver as to a particular default or other matter shall not constitute a waiver of such Party's rights to the future enforcement of its rights under this Agreement, excepting only as to an express written and signed waiver as to a particular matter for a particular period of time.

23. NO IMPLIED OBLIGATIONS

It is understood and agreed that nothing in this Agreement shall be deemed to prevent the Company from commercializing technology or products similar to or competitive with the Licensed Technology or the Licensed Products. Nor shall anything in this Agreement impair the

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right of the Company to independently acquire, license, develop or have others develop for it technology performing similar or equivalent functions as the Licensed Technology, or to develop, market or distribute products based on such technology in addition to or in lieu of the Licensed Products.

24. COMPLIANCE WITH LAWS. REGULATIONS AND STANDARDS

24.1 The Company recognizes that the use of Biological Materials carries with it certain safety risks to both the environment and the population that are inherent in such materials, and shall exercise prudent scientific laboratory procedures in the use of said Biological Materials.

24.2 The inventors and Rockefeller recognize and have advised that the Biological Materials may be used to create infectious retroviruses with a broad host range, that the supplied materials may be used to create retroviruses that can infect human cells in both vitro and in vivo, that the Biological Materials and all materials derived thereof should be handled and used with all due care in accordance with generally acceptable scientific guidelines establishing appropriate precautions and approved by the Institutional Biosafety Committee or similar authority at the Company.

24.3 The Company shall bear all risk to the Company and/or to any others resulting from use, directly or indirectly, to which the Company puts the Biological Materials or any progeny or cells or cell lines derived from it.

25. NO CONSEQUENTIAL DAMAGES

IN NO EVENT SHALL EITHER PARTY BE LIABLE FOR SPECIAL, INCIDENTAL OR CONSEQUENTIAL DAMAGES ARISING OUT OF ANY BREACH OF THIS AGREEMENT.

26. ENTIRE UNDERSTANDING

This Agreement with its Exhibits represents the entire understanding between the Parties with respect to the subject matter hereof and supersedes any other

agreement, expressed or implied, by the Parties with respect to the Licensed Patent Rights, Biological Materials, Know-How and Improvement Technology, and supersedes and merges all prior negotiations, discussions and agreements, including without limitation, the Prior Agreement between the parties. This Agreement may not be amended or modified except in a written document signed by authorized representatives of the Parties.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be duly executed as of the day and year first above written.

CELL GENESYS, INC.

By: /s/ R. Scott Greer

Title: Senior Vice President
Corporate Development

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Date: February 2. 1996

The Rockefeller University

By: /s/ William H. Griesar

Title: Vice President and General Counsel
January 31, 1996

Date: January 31, 1996

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EXHIBIT "A"

LICENSED PATENT RIGHTS

United States Serial No. 08/023,909

PCT Application No. PCT/US94/01983

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AMENDMENT TO EXCLUSIVE LICENSE AGREEMENT

This Amendment to Exclusive License Agreement ("Amendment"), effective as of November 3, 1998, by and between Cell Genesys, Inc.,("Company"), a corporation organized and existing under the laws of the State of Delaware, having an office at 342 Lakeside Drive, Foster City, California 94404, and The Rockefeller University ("Rockefeller"), a nonprofit education corporation organized and existing under the laws of the State of New York, having an office at 1230 York Avenue, New York, New York 10021-6395 (Company and Rockefeller collectively, the "Parties").

BACKGROUND

The Parties desire to amend that certain Exclusive License Agreement by and between Company and Rockefeller effective as of January 31, 1996 (the "Agreement") as set forth herein below.

NOW, THEREFORE, the Parties agree as follows:

1. AMENDMENT. This Amendment hereby amends the Agreement to incorporate the terms and conditions set forth in this Amendment. The relationship of the Parties shall continue to be governed by the terms and conditions of the Agreement, as amended herein; and in the event that there is any conflict between the terms and conditions of the Agreement and this Amendment, the terms and conditions of this Amendment shall control. As used in this Amendment, all capitalized terms shall have the meanings defined for such terms in this Amendment or, if not defined in the Amendment, the meanings defined in the Agreement.

2. MODIFICATION TO THE AGREEMENT.

2.1 Section 4.6 of the Agreement is hereby amended to read in its entirety as follows:

"4.6 COMMERCIAL SUBLICENSES. It is understood and agreed that Company shall have the right, at its sole discretion, to grant Commercial Sublicenses to third parties _____. As used herein, "Commercial Sublicense" shall mean Commercial Target Sublicenses and any other sublicense right granted under the Licensed Technology, provided, however, Commercial Sublicenses shall exclude rights granted by Company to a third party pursuant to an agreement substantially in the form of Exhibit D to this Agreement (i.e., research sublicenses)."

2.2 The Agreement is hereby amended to add the following new Section 4.9:

"4.9 COMMERCIAL TARGET SUBLICENSES. Subject to the terms and conditions set forth in this Section 4.9 below and without limiting the provisions of Section 4.6 above or Article 6 below, Company shall have the right to grant and authorize Commercial Target Sublicenses to third parties (each such third party, a "Commercial Target Sublicensee") on terms and conditions as Company deems appropriate in its sole discretion.

(a) MILESTONE AND MAINTENANCE FEES. In addition to amounts payable

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pursuant to Section 4.3 above and in consideration of Company's right to grant and authorize Commercial Target Sublicenses pursuant to this Section 4.9 _____. Payments due under this Section 4.9(a) shall be due and payable within sixty (60) days after the calendar quarter in which the Milestone Fee or Maintenance Fee, as applicable, is received by Company _____.

(b) TERMS. For purposes of this Section 4.9 the following capitalized terms shall have the following meanings. "Commercial Target Sublicense" shall mean a sublicense under the Licensed Technology that includes the right to conduct Target Validation using the Licensed Technology. "Target Validation" shall mean the process by which the function of nucleotide sequences are identified, determined and/or confirmed; and/or the function of nucleotide sequences are identified, determined and/or confirmed as being significant in a disease or other biological pathway in which pharmacological or other intervention is sought to affect the function of that pathway. _____.

(c) SURVIVAL. Subject to Section 6.4 below, Commercial Sublicenses, including Commercial Target Sublicenses, shall survive the termination of this Agreement, provided that the Commercial Sublicensee or Commercial Target Sublicensee, as the case may be, agrees to be bound by the applicable terms and conditions of this Agreement."

3. ENTIRE AGREEMENT. Together the Agreement (including the Exhibits thereto) and this Amendment constitute the entire agreement between the Parties in connection with the subject matter thereof and supersede all prior and contemporaneous agreements, understandings, negotiations and discussions, whether oral or written, of the Parties.

IN WITNESS WHEREOF, the Parties have executed this Amendment.

CELL GENESYS, INC.	The Rockefeller University
By: /s/ Bruce A. Hironaka	By: /s/ William A. Griesar
Title: Vice President, Corp. Devel.	Title: Vice President and General Counsel
Date: November 16, 1998	Date: 11/3/98

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APPENDIX B

BOSC 23 CELL LINE

<TABLE>
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CGI Docket Number	Application, Patent Number or Publication Number	Filling Date, Grant Date, or Publication Date	Title/Inventors
The Rockefeller University	PCTWO94/19478 (US application corresponding to the PCT)		Production of High Titer Helper-Free Retroviruses by Transient Transfection Pear at al.
The Rockfeller University	US 08/693,160	June 12, 1996	Production of High Titer Helper-free Retroviruses by Transient Transfection Pear, at al.
CELL 13.0 Virus &	US 5,834,256	November 10, 1998	Method for Production of High Titer

	(Patent)		High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
CELL 13.1 Virus &	US 5,686,279 (Patent)	November 11, 1997	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
CELL 13.1 PCT Virus &	WO 94/29438	December 22, 1994	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
CELL 13.2 Virus &	US 5,858,740 (Patent)	January 12, 1999	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
CELL 13.3 Virus &	US 08/517,488	August 21, 1995	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.

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KAT-TM-

CGI Docket Number	Application, Patent Number or Publication Number	Filling Date, Grant Date, or Publication Date	Title/Inventors
CELL 13.3 PCT Virus &	WO 97/07225	February 21, 1997	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
CELL 13.5 Virus & (will be dropped if 13.3 is allowed)	US 09/266.956	March 11, 1999	Method for Production of High Titer High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.
	US 08/914,893	August 20, 1997	Method for Production of High Titer Virus & High Efficiency of Retroviral Mediated Transduction of Mammalian Cells Finer at al.

APPENDIX C

RIGEL BIOLOGICAL MATERIALS

[*] Vectors:

[*]

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APPENDIX D

NOLAN AND NOLAN/ROTHENBERG PATENTS

U.S. Patent Application No. 08/589,109, entitled "Methods for Screening for Transdominant Effector Peptides and RNA Molecules" (the Nolan/Rothenberg Patent Application).

U.S. Patent Applications Nos. 08/789,333, 08/589,911 and 08/963,368, entitled, "Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules" (the Nolan Patent Application).

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APPENDIX E

LICENSE AGREEMENT

BY AND BETWEEN

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

AND

RIGEL PHARMACEUTICALS, INC.

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APPENDIX E

LICENSE AGREEMENT

Effective as of June 1, 1999 (the "Effective Date"), THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California ("STANFORD") and RIGEL PHARMACEUTICALS, INC., a Delaware corporation having a principle place of business at 240 East Grand Avenue, South San Francisco, CA 94080 ("RIGEL"), agree as follows:

RECITALS

A. STANFORD owns certain [*] cell lines and derivatives thereof and biological components related thereto.

B. RIGEL desires to obtain a non-exclusive license to such materials for use in the Field, with the right to grant one non-exclusive sublicense to Cell Genesys, Inc.

1. DEFINITIONS.

1.1 "CELL GENESYS" means Cell Genesys, Inc., a Delaware corporation, having a principal place of business at 342 Lakeside Drive, Foster City, CA 94404.

1.2 "FIELD" means any and all fields of use, including, without limitation, any research or commercial field of use.

1.3 "LICENSED BIOLOGICAL MATERIALS" means the materials listed on Exhibit A.

1.4 "LICENSED KNOW-HOW" means:

(a) any and all tangible or intangible know-how, trade secrets, inventions (whether or not patentable), processes, data, and other information owned by STANFORD as of the Effective Date that are necessary or useful for the use of the Licensed Biological Materials; and

(b) any modifications or progeny of the information and materials in subsection (a) above that STANFORD may elect to provide to RIGEL at STANFORD's sole and exclusive discretion.

1.5 "PATENT" shall mean all foreign and domestic patents (including, without limitation, extensions, reexaminations, reissues, renewals and inventors certificates) and patents issuing from patent applications (including substitutions, provisionals, divisionals, continuations and continuations-in-part).

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2. GRANT; TRANSFER OF LICENSED BIOLOGICAL MATERIALS.

2.1 STANFORD hereby grants, and RIGEL hereby accepts, a worldwide, non-exclusive license (without the right to sublicense except to Cell Genesys in the field of human and/or animal gene therapy as provided in Article 8) under STANFORD's right, title and interest in the Licensed Biological Materials to conduct research and development and to use the Licensed Biological Materials to make, have made, use, import, offer for sale and sell products in the Field.

2.2 STANFORD hereby grants, and RIGEL hereby accepts, a worldwide, non-exclusive license (without the right to sublicense except to Cell Genesys in the field of human and/or animal gene therapy as provided in Article 8) under STANFORD's right, title and interest in the Licensed Know-How to use the Licensed Know-How in the Field.

2.3 STANFORD shall have the right to use the Licensed Know-How and the Licensed Biological Materials for its own bona fide research, including sponsored research and collaborations. In addition, STANFORD shall have the right to distribute the Licensed Biological Materials.

2.4 Promptly after the Effective Date, STANFORD shall transfer to RIGEL such quantities of the Licensed Biological Materials as RIGEL shall reasonably request. Thereafter, STANFORD shall transfer to RIGEL such additional quantities of Licensed Biological Materials as RIGEL shall reasonably request in the event that RIGEL's stock of the Licensed Biological Materials is destroyed or contaminated.

3. LICENSE ROYALTIES.

3.1 In partial consideration for the license granted by STANFORD to RIGEL under Section 2.1, RIGEL agrees to pay to STANFORD the following:

(a) An initial, nonrefundable license issue royalty of [*], which amount shall be paid within thirty (30) days after the Effective Date.

(b) A royalty payment equal to [*] on each of the first three (3) anniversaries of the Effective Date.

After the third (3rd) anniversary of the Effective Date, the sublicense shall be considered perpetual and fully paid-up.

3.2 If RIGEL grants to Cell Genesys a sublicense under the Licensed Biological Materials to use and sell products in the field of human and/or animal gene therapy, RIGEL shall pay to STANFORD during the term of such sublicense a sublicense fee as follows:

Upon signing of the sublicense	$[*]
On each of the first three (3) anniversaries of the effective date of such sublicense	$[*]
On the 4th, 5th and 6th anniversaries of the effective date of such sublicense	$[*]

After the sixth (6th) anniversary of the effective date of such sublicense, the sublicense shall be considered perpetual and fully paid-up.

4. PATENTS; NEW INVENTIONS.

Subject to the terms and conditions of this Agreement, any patentable inventions or discoveries conceived or reduced to practice by the employees, agents or consultants of one party during the course of the Agreement ("Sole Inventions") shall be the property of such party. Any patentable inventions or discoveries conceived or reduced to practice jointly by employees, agents or consultants of STANFORD and RIGEL as determined in accordance with United States rules of inventorship ("Joint Inventions") during the course of and pursuant to this Agreement shall be owned jointly by STANFORD and RIGEL, each to own an undivided one-half (1/2) interest in such Joint Invention. Each party shall cooperate with the other in completing any patent applications relating to Joint Inventions, and in executing and delivering any instrument required to assign, convey or transfer to such other party its undivided one-half (1/2) interest.

5. WARRANTIES.

5.1 STANFORD's Office of Technology Licensing represents and warrants that to the best of its knowledge as of the Effective Date, STANFORD has not sought or obtained patent protection of the Licensed Biological Materials or any use thereof in the Field.

5.2 STANFORD's Office of Technology Licensing represents and warrants that as of the Effective Date, it has no knowledge of claims by third parties that the use of the Licensed Biological Materials infringes any patents, copyrights or other rights of third parties.

5.3 STANFORD represents and warrants that it has all right, power and authority necessary to grant the licenses set forth in Article 2 to RIGEL.

5.4 RIGEL agrees that nothing in this Agreement grants RIGEL any express or implied license or right under or to:

(a) U.S. Patent 4,656,134, entitled "Amplification of Eucaryotic Genes" or any patent application corresponding thereto; or

(b) U.S. Patent 5,070,012, entitled "Monitoring of Cells and Trans-Activating Transcription Elements" or any patent application corresponding thereto; or

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(c) U.S. Patent 5,804,387, entitled "FACS-Optimized Mutants of the Green Fluorescent Protein (GFP) or any patent application corresponding thereto.

5.5 STANFORD agrees that nothing in this Agreement grants STANFORD any express or implied license or right under or to U.S. Patent Application Nos. 08/789,333, 08/589,911, or 08/963,368, entitled "Method for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules," or any continuations, divisionals or continuation-in-parts thereof or any patents which may issue therefrom.

5.6 Except as provided in Sections 5.1, 5.2 and 5.3 and as otherwise expressly set forth in this Agreement, nothing in this Agreement will be construed as a warranty or representation that anything made, used, sold, or

otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights, and trademarks of third parties; conferring rights to use in advertising, publicity, or otherwise any trademark or the name of "STANFORD"; or granting by implication, estoppel, or otherwise any licenses or rights under patents of STANFORD.

5.7 EXCEPT AS EXPRESSLY SET FORTH IN THE AGREEMENT, STANFORD MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE LICENSED BIOLOGICAL MATERIALS OR LICENSED KNOW-HOW WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER RIGHTS, OR ANY OTHER EXPRESS OR IMPLIED WARRANTIES.

6. INDEMNITY.

6.1 RIGEL agrees to indemnify, hold harmless, and defend STANFORD, UCSF-Stanford Health Care and Stanford Health Services and their respective trustees, officers, employees, students, and agents against any and all claims by third parties for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale, or other disposition of the Licensed Biological Materials or any products arising or derived from Licensed Biological Materials, by RIGEL or RIGEL's sublicensee(s) or customers.

6.2 STANFORD shall not be liable for any indirect, special, consequential or other damages whatsoever, whether grounded in tort (including negligence), strict liability, contract or otherwise. STANFORD shall not have any responsibilities or liabilities whatsoever with respect to products arising or derived from Licensed Biological Materials by RIGEL.

6.3 RIGEL shall at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering any and all employees with respect to activities performed under this Agreement.

6.4 In addition to the foregoing, RIGEL shall maintain Comprehensive General Liability Insurance, including Products Liability Insurance, with reputable and financially secure

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insurance carrier(s) to cover the activities of RIGEL and its sublicensee(s) in the amounts and during the periods specified herein. Such insurance shall provide minimum limits of liability of One Million Dollars ($1,000,000) as of the first anniversary of the date upon which RIGEL first leases a facility in which it will conduct research and development activities, and of Five Million Dollars ($5,000,000) as of the commencement of human clinical trials. Such insurance shall include STANFORD, UCSF-Stanford Health Care and Stanford Health Services, their trustees, directors, officers, employees, students, and agents as additional insureds. Such insurance shall be written to cover claims incurred, discovered, manifested or made during or after the expiration of this Agreement. At STANFORD's request, RIGEL shall furnish a Certificate of Insurance evidencing primary coverage and requiring thirty (30) days prior written notice of cancellation or material change to STANFORD. RIGEL shall advise STANFORD, in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All such insurance of RIGEL shall be primary coverage; insurance of STANFORD, UCSF-Stanford Health Care or Stanford Health Services shall be excess and noncontributory.

7. STANFORD NAMES AND MARKS.

RIGEL agrees not to identify STANFORD in any promotional advertising or other promotional materials to be disseminated to the pubic or any portion thereof or to use the name of any STANFORD faculty member, employee, or student or any trademark, service mark, trade name, or symbol of STANFORD, UCSF-Stanford Health Care or Stanford Health Services, or that is associated with any of them, without STANFORD's prior written consent, except as required by law. STANFORD shall not unreasonably withhold consent under this Section 7.

8. SUBLICENSE(S).

8.1 Subject to the provisions of this Article 8, RIGEL may grant a sublicense to the license rights granted to RIGEL by STANFORD in Sections 2.1 and 2.2 to Cell Genesys solely in the field of human and/or animal gene therapy.

8.2 Any sublicense granted by RIGEL to Cell Genesys under this Agreement shall be subject and subordinate to terms and conditions of this Agreement,

except:

(a) Sublicense terms and conditions shall reflect that any sublicensee(s) shall not grant a sublicense to a third party; and

(b) The financial obligations of any sublicensee to RIGEL specified in the sublicense(s) may be different from those obligations set forth in this Agreement.

Any such sublicense(s) also shall expressly include the provisions of Articles 5 and 6 for the benefit of STANFORD and shall survive any termination of this Agreement.

8.3 RIGEL agrees to provide STANFORD with a copy (with financial terms redacted) of any sublicense granted to Cell Genesys pursuant to this Article 8 and written notice

of the effective date of any termination of such sublicense prior to the expiration of the Term (as defined in Section 9.1).

9. TERM AND TERMINATION.

9.1 The term of this Agreement shall commence upon the Effective Date and shall expire upon the later of: (a) the expiration of the last to expire of any Patents owned by STANFORD at any time which claim inventions in the Licensed Biological Materials or the Licensed Know-How; or (b) twenty (20) years from the Effective Date (the "Term"). In addition, RIGEL may terminate this Agreement prior to the expiration of the Term by giving STANFORD notice in writing at least thirty (30) days in advance of the effective termination date selected by RIGEL.

9.2 Either party may terminate this Agreement prior to the expiration of the Term if the other party is in material breach of any provision hereof and fails to remedy any such default or breach within thirty (30) days after written notice thereof to the breaching party.

9.3 Surviving the expiration of the Term are:

(a) Any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party prior to the expiration of the Term; and

(b) Articles 4, 5, 6, 7 and 11; and

(c) Article 8 and Sections 2.1 and 2.2; and the licenses granted thereunder shall be deemed perpetual and fully paid-up.

9.4 Surviving any termination of this Agreement are:

(a) Any cause of action or claim of RIGEL or STANFORD, accrued or to accrue, because of any breach or default by the other party prior to the termination of this Agreement; and

(b) Articles 4, 5, 6, 7, 8 and 11 and Section 3.2; and

(c) Sections 2.1 and 2.2 if RIGEL has fulfilled all of its payment obligations to STANFORD under Section 3.1 prior to such termination; and the licenses granted thereunder shall be deemed perpetual and fully paid-up.

10. ASSIGNMENT.

This Agreement may not be assigned by either party without the express written consent of the other party, except that RIGEL may assign the Agreement in connection with a merger, consolidation or sale of all or substantially all of RIGEL's assets.

11. ARBITRATION.

11.1 Any controversy arising under or related to this Agreement, and any disputed claim by either party against the other under this Agreement excluding any dispute relating to patent validity or infringement arising under this Agreement, shall be settled by arbitration in accordance with the Licensing Agreement Arbitration Rules of the American Arbitration Association.

11.2 Upon request by either party, arbitration will be by a third party arbitrator mutually agreed upon in writing by RIGEL and STANFORD within thirty (30) days of such arbitration request. Judgment upon the award rendered by the arbitrator shall be final and nonappealable and may be entered in any court having jurisdiction thereof.

11.3 The parties shall be entitled to discovery in like manner as if the arbitration were a civil suit in the California Superior Court.

11.4 Any arbitration shall be held at Stanford, California, unless the parties hereto mutually agree in writing to another place.

12. NOTICES.

All notices under this Agreement shall be deemed to have been fully given when done in writing and deposited in the United States mail registered or certified, and addressed as follows:

To STANFORD: Office of Technology Licensing
Stanford University
900 Welch Road, Suite 350
Palo Alto, CA 94304-1850
Attention: Director

To RIGEL: Rigel Pharmaceuticals, Inc.
240 East Grand Ave.
South San Francisco, CA 94080
Attention: President

Either party may change its address upon written notice to the other party.

13. WAIVER.

None of the terms of this Agreement can be waived except by the written consent of the party waiving compliance.

14. APPLICABLE LAW.

This Agreement shall be governed by the laws of the State of California applicable to agreements negotiated, executed and performed wholly within California. Any claim or controversy arising out of or related to this Agreement or any breach hereof shall be submitted to a court of applicable jurisdiction in the State of California, and each party hereby consents to the

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jurisdiction and venue of such court.

15. DISCLAIMER OF AGENCY.

Neither party is, or will be deemed to be, the legal representative or agent of the other, nor shall either party have the right or authority to assume, create, or incur any third party liability or obligation of any kind, express or implied, against or in the name of or on behalf of another except as expressly set forth in this Agreement.

16. SEVERABILITY.

If any provision or provisions of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby.

17. ENTIRE AGREEMENT.

This Agreement, together with the Exhibit attached hereto, embodies the entire understanding of the parties and shall supersede all previous communications, representations or understandings, either oral or written,

between the parties relating to the subject matter hereof. No amendment or modification hereof shall be valid or binding upon the parties unless made in writing and signed by duly authorized representatives of both parties.

18. COUNTERPARTS.

This Agreement may be executed in counterparts, with the same force and effect as if the parties had executed the same instrument.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement in duplicate originals by their duly authorized officers or representatives.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY	RIGEL PHARMACEUTICALS, INC.
By: /s/ Katherine Ku	By: /s/ Donald W. Perryman
Name: Katherine Ku	Name: Donald W. Perryman
Title: Director, Technology Licensing	Title: VP, Business Development June 1999

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EXHIBIT A

LICENSED BIOLOGICAL MATERIALS

[*] Vectors:

[*]

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