EXHIBIT 6

(1985. 11. 27付)

AGREEMENT

between

GENETICS INSTITUTE, INC.

and

CHUGAI PHARMACEUTICAL CO., LTD.

TABLE OF CONTENTS

Page

(4)

(3)

AGREEMENT

AGREEMENT dated as of November 27, 1985 between GENETICS INSTITUTE, INC., a Delaware corporation, having its principal place of business at 87 CambridgePark Drive, Cambridge, Massachusetts 02140 (hereinafter referred to as "GI") and CHUGAI PHARMACEUTICAL CO., LTD., a Japanese corporation having its principal place of business at 5-1, 5-chome, Ukima, Kita-ku, Tokyo, Japan (hereinafter referred to as "Chugai").

INTRODUCTION

1. GI has research and development facilities and experienced scientists, research associates and assistants and other personnel which enables it to conduct research and development activities in the area of recombinant DNA technology and the application thereof to the development, production and processing of recombinant DNA and to the production and expression of products using that technology.

2. Pursuant to an Agreement dated June 29, 1984 between GI and Chugai (the "1984 Agreement"), GI, on behalf of and in collaboration with Chugai, has undertaken a research and development project utilizing recombinant DNA technology for producing erythropoietin on a commercially feasible basis.

3. In accordance with the research steps set forth in the 1984 Agreement, GI has cloned and expressed erythropoietin in several cells and is working to develop an improved expression level as well as a purification and cell culture process for the production of erythropoietin.

390

(6)

4. In light of current competition in the field of erythropoietin recombinant DNA technology development, GI and Chugai believe there is a need for early market introduction of erythropoietin developed under the 1984 Agreement. In order to expedite the market introduction of erythropoietin, GI and Chugai have decided to undertake a secondary project relating to the development of commercial production processes for erythropoietin, as more fully described herein.

In consideration of the mutual covenants and promises contained in this Agreement and other good and valuable consideration, GI and Chugai hereby agree as follows:

Article I. DEFINITIONS

As used in this Agreement, the following terms, whether used in the singular or plural, shall have the following meanings:

1.1. "Affiliate" means any corporation, company, partnership, joint venture and/or firm which controls, is controlled by or is under common control with Chugai. For purposes of this Section 1.1, "control" shall mean (a) in the case of corporate entities, direct or indirect ownership of at least fifty percent (50%) of the stock or shares entitled to vote for the election of directors; and (b) in the case of non-corporate entities, direct or indirect ownership of at least fifty percent (50%) of the equity interest with the power to direct the management and policies of such noncorporate entities.

1.2. "Confidential Information" means Manufacturing Know-How, as defined in Section 1.7 below, and any other information designated by the disclosing Party as confidential or proprietary.

(2)

whether or not related to the commercial manufacture and production of EPO, EPO Products, Manufactured Compounds and/or Manufactured Products.

1.3. "EPO" means "Licensed Compounds" as such term is defined in the 1984 Agreement.

1.4. "EPO Products" means "Licensed Products" as such term is defined in the 1984 Agreement.

1.5. "Manufactured Compounds" means (a) any and all kinds of compounds or substances other than EPO which is covered by any of the Manufacturing Patent Rights and/or embodies any Manufacturing Know-How, or (b) any and all kinds of compounds or substances other than EPO manufactured or developed by the use of any manufacturing procedure, process, product or other technology which is covered by any of the Manufacturing Patent Rights and/or embodies any Manufacturing Know-How.

1.6. "Manufactured Products" means any and all kinds of formulations, mixtures and/or compositions for whatever use which contain Manufactured Compounds.

1.7. "Manufacturing Know-How" means all technical information of GI, patentable or otherwise, relating to the commercial manufacture and production of EPO which is used by GI in the Project and is required for Chugai, its Affiliates and sublicensees to manufacture, use and/or sell EPO, EPO Products, Manufactured Compounds and/or Manufactured Products. As used in this Agreement, "Manufacturing Know-How of Chugai" shall have the meaning stated in this Section 1.7, but as applied to Chugai rather than GI.

1.8. "Manufacturing Patent Rights" means all patents and patent applications of GI (which for all purposes of this Agreement shall be deemed to include certificates of invention and applications for certificates of invention) throughout the world, relating to the commercial manufacture and production of EPO which are based on subject matter used in the Project and are required by Chugai, its Affiliates or sublicensees to manufacture, use and/or sell EPO, EPO Products, Manufactured Compounds and/or Manufactured Products.

1.9. "Net Sales" means the total invoice price billed or otherwise charged by Chugai, its Affiliates and sublicensees from or on account of the sale of Manufactured Products, whether such sales are made directly to end users, wholesalers or distributors, in each case less price adjustments, returned goods, billing corrections, cash, trade and contract discounts, excises and sales taxes imposed upon and paid with respect to such sales. Net Sales shall not include any transfer between Chugai and any of its Affiliates or sublicensees for resale but shall include the resale from an Affiliate to an independent third party.

1.10. "Party" means GI or Chugai; "Parties" means GI and Chugai.

1.11. "Project" means the program jointly conceived, planned, organized, controlled and performed by GI and Chugai relating to the development of commercial production processes for EPO as more fully set forth in Article II hereof.

1.12. "Territory" shall have the meaning ascribed to such term in the 1984 Agreement.

(9)

Article II. THE PROJECT AND PROJECT FUNDING

2.1. General. Subject to the terms and conditions contained in this Agreement, GI agrees to undertake the Project on a best efforts basis. In consideration of such services to be performed by GI with regard to the Project, Chugai shall make the payments to GI as specified in this Article II. Except to the extent necessary for GI to render appropriate technical assistance and training to Chugai, the Project shall be conducted at and/or coordinated from the facilities of GI under a team of scientists, research associates and/or assistants assembled by GI. GI shall be responsible for the administrative management and fiscal control of the Project.

2.2. Base Technology Development. GI shall undertake the development of a technology (including cell culture, cell separation and purification and isolation of EPO) capable of large scale commercial production of EPO in accordance with the program design steps and time frames set forth on Schedule A hereto (the "Base Technology"). The quality of the EPO produced by such Base Technology shall meet the standards established by the United States and Japan for use in connection with pre-clinical studies and clinical trials. GI shall also use its best efforts to assure that the EPO produced by such Base Technology has specific activity in vivo and in vitro as good as or better than that of other available forms of EPO produced through the utilization of recombinant DNA technology. GI shall disclose its Manufacturing Know-How in confidence to Chugai to the extent necessary to enable Chugai to use the Base Technology to commercially produce EPO, EPO Products, Manufactured Compounds and/or Manufactured Products, and

shall render such technical assistance to Chugai with respect to the Base Technology as is set forth on Schedule A hereto. Promptly after the completion of the final program design step set forth on Schedule A hereto, GI shall notify Chugai in writing of such completion. Unless Chugai otherwise notifies GI in writing within 45 days after receipt of the notice of completion, the program design steps set forth on Schedule A hereto shall be deemed to have been satisfactorily achieved for all purposes of this Agreement. In consideration of the foregoing Base Technology development, Chugai shall pay to GI, as set forth on Schedule B hereto, an aggregate of $1,200,000, which shall be due as of the signing of this Agreement. GI shall invoice Chugai accordingly. The terms are cash payment net 30 days.

2.3. EPO Technology Development. During the development of the program design steps set forth on Schedule A hereto, GI shall undertake the development of a Master Cell Bank (a generic name for an EPO cell line to be mutually selected by the Parties) with the objective of achieving an EPO output of 187,500,000 units of EPO per ton (it being understood by the Parties that the specific activity of EPO from such Master Cell Bank shall be no less than 75,000 units of EPO per milligram). The term "units of EPO per ton" shall mean the number of units of purified EPO obtained from 1,000 liters of conditioned medium. Units of EPO shall be measured by both Parties at the facilities of GI or Chugai in accordance with the standards set forth on Schedule D hereto. GI shall disclose and transfer its Manufacturing Know-How in confidence to Chugai to the extent necessary to enable Chugai to use the Master Cell Bank to commercially produce EPO. In

(11)

consideration of the foregoing EPO technology development achieved by GI, Chugai shall pay to GI an amount, as set forth on Schedule B hereto, dependent upon the actual EPO output of the Master Cell Bank measured in terms of units of EPO per ton. The quality of such EPO shall meet the standards established by the United States and Japan for use in connection with pre-clinical and clinical trials. GI shall also use its best efforts to assure that the EPO produced by such EPO technology has specific activity in vivo and in vitro as good as or better than that of other available forms of EPO produced through the utilization of recombinant DNA technology. The amount payable to GI shall be determined on June 30, 1986 or such earlier date as GI shall select (the "measurement date") based upon the level of EPO output of the Master Cell Bank achieved as of the measurement date. In the event that the actual EPO output of the Master Cell Bank as of the measurement date is less than 112,500,000 units of EPO per ton, GI shall continue to use its best efforts for a period of one year following the measurement date to achieve an EPO output of 187,500,000 units of EPO per ton. GI shall not be entitled to any payment under this Section 2.3 for such continued EPO technology development after the measurement date.

2.4. Technology Improvements. For a period of one year following the measurement date, each Party shall disclose to the other Party at no additional cost to such other Party any process improvements developed by such Party during such one-year period relating to the Project. In addition, in the event that GI fails to achieve an EPO output of 187,500,000 units of EPO per ton within the one-year period following the measurement date, but

(12)

subsequently achieves an EPO output of 187,500,000 units of EPO per ton, GI shall disclose to Chugai at no additional cost to Chugai such process improvements. During the one-year period following the measurement date, to the extent that GI develops or otherwise acquires the right to grant a license covering any such process improvement, the licenses set forth in Sections 4.1 and 4.2 hereof shall apply to such process improvements, and such process improvements shall be considered to be Manufacturing Patent Rights or Manufacturing Know-How as the case may be. During the one-year period following the measurement date, to the extent that Chugai develops or otherwise acquires the right to grant a license covering any such process improvement, Chugai hereby grants a non-exclusive, royalty-free, world-wide license to GI to make, have made, use or sell such process improvement, subject, however, to the rights of Chugai set forth in this Agreement and the 1984 Agreement.

2.5. Flexibility. In carrying out the Project, GI shall have and maintain sufficient flexibility to shift effort and emphasis within the overall scope of the Project in a manner that will, in the opinion of GI, after consultation with and giving due consideration to the advice of Chugai, best result in the development of large scale commercial technology for the production of EPO.

AM 17 108670

2.6. Technical Assistance and Training. For a period of one year following the measurement date, GI shall, upon request from Chugai, make available to Chugai members of the technical staff of GI assigned to the Project (to the extent available as determined by GI in its sole discretion) in order to further assist Chugai in

(13)

the transfer of the Project Technology (as defined herein) as it relates to the commercial production and manufacture of EPO, provided that such assistance shall not be required to be in excess of 40 man hours per month per person (such amount being subject to extension by mutual agreement of the Parties). GI shall be reimbursed for any "Additional Expenses" incurred in rendering such assistance and training. As used in this Section 2.6, the term "Additional Expenses" means (a) costs incurred by GI in carrying out such assistance and training, including without limitation, reasonable travel and living expenses of GI's staff when away from their normal place of business, the costs of direct materials and equipment, and other reasonable expenses incurred by GI which are allocable to such activities, and (b) the related salaries of the professional staff and personnel of GI and quantifiable fringe benefits associated therewith, multiplied, in the case of costs and expenses, described in (a) above, by 1.15, and, in the case of costs and expenses described in (b) above, by 2.10. GI shall invoice Chugai for such reimbursements and Additional Expenses and Chugai shall pay such invoices within 30 days after receipt thereof.

2.7. Consultation. Each Party shall have the right to arrange for its employees and outside consultants involved in the Project to visit the other Party at its offices and laboratories, and to discuss Project work and its results in detail with the technical personnel and consultants of the other Party; provided that such visits shall be during normal business hours and shall not unreasonably interrupt the operations of the other Party.

2.8. Patent and Confidential Information Agreements. GI shall require all scientists, research associates and assistants, technicians and technical personnel assigned to the Project to execute an agreement for the assignment of inventions and for the protection of Confidential Information in such reasonable form as may from time to time be used by GI for such purpose. Chugai shall require all scientific and other employees working on or involved in the Project to execute an agreement for the assignment of inventions in Joint Technology (as defined in Section 3.1 hereof) and for the protection of Confidential Information in such reasonable form as may from time to time be used by Chugai for such purpose.

Article III. INTELLECTUAL PROPERTY RIGHTS

3.1. Ownership of Technology. GI shall own the entire right, title and interest in and to all Manufacturing Patent Rights and Manufacturing Know-How developed solely by employees or consultants of GI in the course of the Project (hereinafter "Sole Technology"). Chugai shall own the entire right, title and interest in and to all patents, patent applications and Manufacturing Know-How of Chugai developed solely by employees or consultants of Chugai at any time which relate to the Project, including those developed for and in the course of the Project. Unless otherwise agreed in particular instances, GI shall own the entire right, title and interest in and to all patent and other rights in any product, method or apparatus conceived, reduced to practice or developed jointly by GI and Chugai in the course of the Project (hereinafter "Joint Technology"), subject to the

(15)

license granted to Chugai under this Agreement. As used in this Agreement, the term "Project Technology" shall mean the Sole Technology and Joint Technology, collectively.

3.2. Responsibility for Patenting of Project Technology.

(a) GI shall have the right and responsibility to:

(i) decide on whether or not to seek or continue to seek or maintain patent protection in any country on any Project Technology, subject to subparagraph (b) below; and

(ii) file for, procure and maintain patents in any country on any Project Technology, subject to subparagraph (b) below.

(b) Copies of all substantive communications to and from all patent offices regarding applications or patents on any Project Technology shall be provided to Chugai promptly after the receipt thereof, and copies of all proposed substantive communications to such patent offices shall be provided to Chugai in sufficient time before the due date in order to enable Chugai an opportunity to comment on the content thereof. GI shall discuss with Chugai and shall give due consideration to Chugai's comments on all proposed substantive communications to patent offices. GI shall bear the costs incurred by it in carrying out its responsibilities pursuant to subsection (a) above.

(c) Chugai shall make available to GI or its authorized attorneys, agents or representatives, such of its employees whom GI in its reasonable judgment deems necessary in order to assist it in obtaining patent protection for the Project Technology.

(16)

Chugai shall sign or use its best efforts to have signed all legal documents necessary to file and prosecute patent applications or to obtain or maintain patents at no charge to GI.

Article IV. PATENT AND KNOW-HOW LICENSES

4.1. Exclusive Licenses. Subject to the payment of the royalty provided for in Article VI of the 1984 Agreement and the fulfillment of the terms and conditions of this Agreement, GI hereby grants to Chugai and its Affiliates:

(a) an exclusive license (even as to GI) in the Territory under the Manufacturing Patent Rights, and

(b) an exclusive license (even as to GI) to use the Manufacturing Know-How in the Territory, including the right to grant sublicenses, for the sole and exclusive purpose of manufacturing, having manufactured for Chugai and its Affiliates, using and selling EPO and/or EPO Products in the Territory. Notwithstanding the foregoing, GI and its Affiliates shall have the right under the Manufacturing Patent Rights and the right to use the Manufacturing Know-How, including the right to grant sublicenses, to manufacture and have manufactured EPO and/or EPO Products in the United States, provided that in no event shall such manufactured EPO or EPO Products be sold in the United States or any other country in the Territory except by Chugai, its Affiliates and sublicensees. The license granted pursuant to subsection (a) above shall continue in effect until the expiration of the last patent licensed to Chugai under such subsection and the license granted pursuant to subsection (b) above shall continue in effect until the expiration of the know-

17

how licenses granted to Chugai under the terms of Section 5.2 of the 1984 Agreement. Upon the expiration of the know-how licenses granted to Chugai under the terms of Section 5.2 of the 1984 Agreement, the license granted pursuant to subsection (b) above shall become a fully paid non-exclusive license. Chugai may upon such expiration elect to continue in effect the exclusive nature of the license in any country in the Territory by paying to GI the exclusivity royalty provided for under the terms of the 1984 Agreement. Such exclusive license shall remain in effect as long as Chugai pays such royalty; if and when such royalty payments are terminated, the license shall become a fully paid, non-exclusive license with respect to such Manufacturing Know-How in such country. A copy of each sublicense granted by Chugai under this Section 4.1 shall be furnished to GI promptly after execution thereof.

4.2 Non-Exclusive Licenses. Subject to the payment of the royalty provided for in Article V of this Agreement and the fulfillment of the other terms and conditions of this Agreement, GI hereby grants to Chugai and its Affiliates:

(a) a world-wide, non-exclusive license under the Manufacturing Patent Rights, and

(b) A world-wide, non-exclusive license to use the Manufacturing Know-How,

for the sole and exclusive purpose of manufacturing, using and selling Manufactured Compounds and/or Manufactured Products. Chugai shall have the following limited right to grant sublicenses under the foregoing licenses granted pursuant to this Section 4.2. To the extent that Chugai owns (independent of this

Agreement) the technology necessary to produce a specific compound or substance other than EPO or has the right to grant (independent of this Agreement) sublicenses to third parties for the manufacture, use and sale of a specific compound or substance other than EPO, Chugai shall have the right to grant sublicenses to its sublicensees of such technology under the foregoing licenses granted pursuant to this Section 4.2 for the sole and exclusive purpose of manufacturing, using and/or selling such specific compound or substance other than EPO. In no event shall Chugai have the right to grant a general sublicense to the Manufacturing Patent Rights and/or Manufacturing Know-How under the foregoing licenses granted pursuant to this Section 4.2. The license granted pursuant to subsection (a) above shall continue in effect until the expiration of the last patent licensed to Chugai under such subsection; the license granted pursuant to subsection (b) above shall continue in effect as provided in Sections 5.1(c) of this Agreement.

Article V. PATENT AND KNOW-HOW ROYALTIES

5.1. Royalties.

(a) Chugai shall pay to GI earned royalties for calendar years 1986 through 1997 at the rates set forth on Schedule C hereto on all Net Sales in such years by Chugai, its Affiliates and sublicensees of Manufactured Products which fall within the definition of Manufactured Products by virtue of involving the Manufacturing Patent Rights or Manufacturing Know-How. If a Manufactured Product involves both Manufacturing

(19)

Patent Rights and Manufacturing Know-How, only one royalty shall be due with respect to each sale of such Manufactured Product.

(b) In no event shall Chugai be obligated to pay royalties on the manufacture, use and/or sale of EPO or EPO Products by virtue of involving Manufacturing Patent Rights or Manufacturing Know-How; provided, however, that Chugai shall be obligated to pay royalties on the manufacture, use and/or sale of EPO and EPO Products under the 1984 Agreement.

(c) Upon the expiration of the royalty obligations set forth in Section 5.1(a) with respect to any of the Manufacturing Know-How in any country, the license granted under Section 4.2 with respect to such Manufacturing Know-How in such country shall become a fully paid non-exclusive license.

5.2. Reports and Payment. Chugai shall deliver to GI within 45 days after the end of each calendar quarter a written report showing its computation of royalties due under this Agreement upon Net Sales by Chugai, its Affiliates and sublicensees during such calendar quarter. All Net Sales shall be segmented in each such report according to sales by Chugai and each Affiliate and sublicensee, as well as on a country-by-country basis, including the rates of exchange used to convert such royalties to United States dollars from the currency in which such sales were made. For the purposes hereof, the rates of exchange to be used for converting royalties hereunder to United States dollars shall be those in effect for the purchase of dollars at Tokyo, Japan, on the day on which payment is due. Chugai, simultaneously with the delivery of each such report,

shall tender payment in United States dollars of all royalties shown to be due thereon.

5.3. Foreign Royalties. Where royalties are due to GI hereunder for sales of Manufactured Products in a country where, by reason of currency regulations or taxes of any kind, it is impossible or illegal for Chugai or any Affiliate or any sublicensee to transfer royalty payments to GI for Net Sales in that country, such royalties shall be deposited in whatever currency is allowable by the person or entity not able to make the transfer for the benefit or credit of GI in an accredited bank in that country that is acceptable to GI.

5.4. Records. Chugai shall keep, and shall require all Affiliates and sublicensees to keep, full, true and accurate books of accounts and other records containing all information and data which may be necessary to ascertain and verify the royalties payable hereunder. During the period in which royalties are payable hereunder as set forth in Sections 5.1(a) hereof and for a period of one year thereafter, GI shall have the right from time to time (not to exceed twice during each calendar year) to inspect, or have an agent, accountant or other representative inspect, such books, records and supporting data.

5.5. Withholding Tax. If any income or other taxes are imposed by the Japanese government on the payment to GI of the amounts set forth on Schedules B and C hereto, and such income or other taxes are required to be withheld therefrom, such taxes shall be withheld from the account of GI. Chugai shall pay such taxes on behalf of GI to the appropriate tax office of Japan and

shall furnish GI with the certificate evidencing each payment of tax so made by Chugai.

Article VI. PATENT AND KNOW-HOW INFRINGEMENT

6.1. Infringement.

(a) Each Party shall promptly report in writing to the other Party during the term of this Agreement any (i) known infringement or suspected infringement of any of the Manufacturing Patent Rights, or (ii) unauthorized use or misappropriation of Manufacturing Know-How by a third party of which it becomes aware, and shall provide the other Party with all available evidence supporting said infringement, suspected infringement or unauthorized use or misappropriation.

(b) GI shall have the right to initiate an infringement or other appropriate suit in any country against any third party who at any time has infringed, or is suspected of infringing, any of the Manufacturing Patent Rights or of using without proper authorization all or any portion of the Manufacturing Know-How. GI shall give Chugai sufficient advance notice of its intent to file said suit and the reasons therefor, and shall provide Chugai with an opportunity to make suggestions and comments regarding such suit. GI shall keep Chugai promptly informed, and shall from time to time consult with Chugai regarding the status of any such suit and shall provide Chugai with copies of all documents filed in, and all written communications relating to, such suit.

AM 17 108679

(c) GI shall have the sole and exclusive right to select counsel for any suit referred to in paragraph (b) above

(22)

and shall pay all expenses of the suit, including without limitation attorneys' fees and court costs. GI shall be entitled to retain any damages, royalties, settlement fees or other consideration resulting therefrom. Chugai shall offer reasonable assistance to GI in connection therewith at no charge to GI except for reimbursement of reasonable out-of-pocket expenses, including salaries of Chugai's personnel, incurred in rendering such assistance. If necessary, Chugai shall join as a party to the suit but shall be under no obligation to participate except to the extent that such participation is required as the result of being a named party to the suit. In the event that it is necessary for Chugai to join as a party to the suit, Chugai shall have the right to be represented in any such suit by its own counsel, provided that any such representation shall be at Chugai's own expense.

6.2. Claimed Infringement. AM 17 108680

(a) In the event that a third party at any time provides written notice of a claim to, or brings an action, suit or proceeding against either Party or any of their respective Affiliates or sublicensees, claiming infringement of its patent rights or unauthorized use or misappropriation of its technology, based upon an assertion or claim arising out of the manufacture, use or sale of Manufactured Products, such Party shall promptly notify the other Party of the claim or the commencement of such action, suit or proceeding, enclosing a copy of the claim and/or all papers served. Each Party shall have sole and exclusive responsibility for the selection of counsel for and the defense of any such suit or proceeding brought against it, provided that

GI agrees to make available to Chugai its advice and counsel regarding the technical merits of any claim brought against Chugai.

(b) If Chugai or its Affiliates, in order to operate under or exploit the licenses granted under Article IV of this Agreement, must make payments (including without limitation royalties, option fees or license fees) to one or more third parties to obtain a license or similar right in the absence of which the Manufactured Compounds and/or Manufactured Products could not legally be manufactured or sold in such country, Chugai may deduct from royalties thereafter payable to GI on Net Sales in such country an amount equal to up to 50% of such third party payments, provided that the total royalties otherwise due to GI on Net Sales in such country in any year shall not be reduced by more than 50% as a result of such deduction.

(c) The foregoing states the entire responsibility of GI in the case of any claimed infringement or violation of any third party's rights or unauthorized use or misappropriation of any third party's technology.

Article VII. CONFIDENTIAL INFORMATION

7.1. Treatment of Confidential Information. Each Party hereto shall maintain the Confidential Information of the other Party in confidence, and shall not disclose, divulge or otherwise communicate such Confidential Information to others, or use it for any purpose, except pursuant to, and in order to carry out, the terms and objectives of this Agreement, and hereby agrees to exercise every reasonable precaution to prevent and restrain the unauthorized disclosure of such Confidential Information by any

of its directors, officers, employees, consultants, Affiliates, subcontractors, sublicensees, distributors or agents.

7.2. Release from Restrictions. The provisions of Section 7.1 shall not apply to any Confidential Information disclosed hereunder which:

(a) was known or used by the receiving Party prior to its date of disclosure to the receiving Party, as evidenced by the prior written records of the receiving Party; or

(b) either before or after the date of the disclosure to the receiving Party is lawfully disclosed to the receiving Party by an independent, unaffiliated third party rightfully in possession of the Confidential Information; or

(c) either before or after the date of the disclosure to the receiving Party becomes published or generally known to the public through no fault or omission on the part of the receiving Party or its Affiliates; or

(d) is required to be disclosed by the receiving Party to comply with applicable laws, to defend or prosecute litigation or to comply with governmental regulations, provided that the receiving Party provides prior written notice of such disclosure to the other Party and takes reasonable and lawful actions to avoid and/or minimize the degree of such disclosure.

7.3 Publications. The following restrictions shall apply with respect to the disclosure in scientific journals or publications by any Party or any Affiliate, employee, sublicensee, consultant or agent of any Party relating to any scientific work performed as part of the Project:

(a) A Party (the "publishing Party") shall provide the other Party with an advance copy of any proposed publication of results arising from the Project, and such other Party shall have a reasonable opportunity to recommend any changes it reasonably believes are necessary to preserve Manufacturing Patent Rights or Manufacturing Know-How belonging in whole or in part to GI, and the incorporation of such recommended changes shall not be unreasonably refused; and

(b) If such other Party informs the publishing Party, within 30 days of receipt of an advance copy of a proposed publication, that such publication in its reasonable judgment could be expected to have a material adverse effect on any Manufacturing Patent Rights or Manufacturing Know-How belonging in whole or in part to GI, the publishing Party shall, to the extent permitted by its agreements with its employees and consultants, delay or prevent such publication as proposed. In the case of inventions, the delay shall be sufficiently long to permit the timely preparation and filing of a patent application(s) or application(s) for a certificate of invention on the information involved.

Article VIII. TERMINATION

8.1. Term. This Agreement shall remain in effect until terminated in accordance with the provisions of Article VIII or until the last to expire of the licenses granted pursuant to Article IV hereof.

(26)

8.2. Termination for Breach. Each Party shall be entitled to terminate this Agreement by written notice to the other Party in the event that the other Party shall be in default of any of its obligations hereunder, and shall fail to remedy any such default within 60 days after notice thereof by the non-breaching Party. Upon termination of this Agreement pursuant to this Section 8.2, neither Party shall be relieved of any obligations incurred prior to such termination. If GI elects to terminate this Agreement pursuant to this Section 8.2, all rights in the Project Technology shall vest in GI. If Chugai elects to terminate this Agreement pursuant to this Section 8.2 after the completion of the program design steps set forth on Schedule A hereto but prior to the development of the EPO technology described in Section 2.4 hereof, Chugai shall remain entitled to use the Base Technology in the production of Manufactured Compounds and Manufactured Products subject to Chugai's obligation to pay royalties as set forth in this Agreement.

8.3. Termination by Chugai. Chugai shall be entitled to terminate this Agreement in the event that due to the fault of GI the program design steps set forth on Schedule A hereto shall not have been completed by March 31, 1986. Upon termination of this Agreement pursuant to this Section 8.3, Chugai shall not be relieved of any obligations incurred prior to such termination. If Chugai elects to terminate the Agreement pursuant to this Section 8.3, all rights in the Project Technology shall vest in GI.

(27)

8.4. Termination by GI of Exclusive Licenses.

(a) In the event that Chugai shall be in default of any of its obligations under the terms of the 1984 Agreement and GI shall terminate the 1984 Agreement for breach, the licenses granted to Chugai pursuant to Section 4.1 of this Agreement shall be terminated immediately.

(b) In the event that GI shall terminate the exclusivity of the licenses granted to Chugai under the 1984 Agreement, then upon written notice by GI:

(i) GI shall receive from Chugai non-exclusive rights in and to all Manufacturing Know-How of Chugai;

(ii) All licenses granted herein by GI to Chugai pursuant to Section 4.1 of this Agreement shall become non-exclusive; and

(iii) All other terms and conditions of this Agreement not inconsistent with this Section 8.4, shall remain in effect.

8.5. Disposition of Manufactured Products. Upon any termination of this Agreement pursuant to Sections 8.2, Chugai shall within 30 days of the effective date of such termination notify GI in writing of the amount of Manufactured Products which Chugai and its Affiliates then have completed on hand, the sale of which would, but for the termination, be subject to royalty, and Chugai and its Affiliates shall thereupon be permitted during the six months following such termination to sell that amount of Manufactured Products, provided that Chugai shall pay the aggregate royalty thereon at the conclusion of the earlier of the

last such sale or such six months period. All sublicenses granted by Chugai shall forthwith terminate upon the termination of this Agreement.

8.6. Survival of Obligations; Return of Confidential Information. Notwithstanding any termination of this Agreement, the obligations of the Parties under Article VII, as well as under any other provisions which by their nature are intended to survive any such termination, shall survive and continue to be enforceable. Upon any termination of this Agreement pursuant to Sections 8.2 or 8.3, each Party shall promptly return to the other Party all written Confidential Information, and all copies thereof, of the other Party.

Article IX. MISCELLANEOUS

9.1. Filing of Agreement. Chugai shall be responsible for, and shall make, all filings of this Agreement with the appropriate Japanese authorities necessary to give full force and effect to the provisions hereof.

9.2. Publicity. Neither Party shall originate any publicity, news release or other public announcement, written or oral, relating to this Agreement, the Project or the existence of an arrangement between the Parties, without the prior written approval of the other Party except as otherwise required by law.

9.3 Assignment. Neither this Agreement nor any of the rights or obligations hereunder may be assigned by either Party without the prior written consent of the other Party, except to a party who acquires all or substantially all of the business of the assigning Party by merger, sale of assets or otherwise.

(29)

9.4. Governing Law. This Agreement shall be governed by and interpreted in accordance with the laws of the Commonwealth of Massachusetts.

9.5. Force Majeure. In the event that either Party is prevented from performing or is unable to perform any of its obligations under this Agreement due to any act of God; fire; casualty; flood; war; strike; lockout; failure of public utilities; injunction or any act, exercise, assertion or requirement of governmental authority, including any governmental law, order or regulation permanently or temporarily prohibiting or reducing the level of research, development or production work hereunder or the manufacture, use or sale of EPO, EPO Products, Manufactured Compounds or Manufactured Products; epidemic; destruction of production facilities; riots; insurrection; inability to procure or use materials, labor, equipment, transportation or energy sufficient to meet experimentation or manufacturing needs; or any other cause beyond the reasonable control of the Party invoking this Section 9.5 if such Party shall have used its best efforts to avoid such occurrence, such Party shall give notice to the other Party in writing promptly, and thereupon the affected Party's performance shall be excused and the time for performance shall be extended for the period of delay or inability to perform due to such occurrence. Upon receipt of such notice from GI, Chugai may delay payment of the amounts set forth on Schedule B hereto for the period of delay or inability of GI to perform its obligations under this Agreement.

9.6. Waiver. The waiver by either Party of a breach or a default of any provision of this Agreement by the other Party

(30)

shall not be construed as a waiver of any succeeding breach of the same or any other provision, nor shall any delay or omission on the part of either party to exercise or avail itself of any right, power or privilege that it has or may have hereunder operate as a waiver of any right, power or privilege by such Party.

9.7. Notices. Any notice or other communication in connection with this Agreement must be in writing and if by mail, by certified mail, return receipt requested, and shall be effective when delivered to the addressee at the address listed below or such other address as the addressee shall have specified in a notice actually received by the addressor.

If to GI:
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, Massachusetts 02140
Attention: President

If to Chugai:
Chugai Pharmaceutical Co., Ltd.
1-9, Kyobashi 2-chome, Chuo-Ku,
Tokyo, 104 Japan
Attention: International Division

9.8. No Agency. Nothing herein shall be deemed to constitute either Party as the agent or representative of the other Party, or both Parties as joint venturers or partners for any purpose. GI shall be an independent contractor, not an employee or partner of Chugai, and the manner in which GI renders its services under this Agreement shall be within GI' sole discretion. Neither Party shall be responsible for the acts or omissions of the other Party, and neither Party will have authority to speak for, represent or obligate the other Party in any way without prior written authority from the other Party.

(31)

9.9. Entire Agreement; Relationship to 1984 Agreement. This Agreement and the Schedules hereto (which Schedules are deemed to be a part of this Agreement for all purposes) contain the full understanding of the Parties with respect to the subject matter hereof and supersede all prior understandings and writings relating thereto. No waiver, alteration or modification of any of the provisions hereof shall be binding unless made in writing and signed by the Parties by their respective officers thereunto duly authorized. The Parties hereto have entered into the 1984 Agreement, a related agreement which shall, subject to the provisions thereof, remain in full force and effect.

9.10. Headings. The headings contained in this Agreement are for convenience of reference only and shall not be considered in construing this Agreement.

9.11. Severability. In the event that any provision of this Agreement is held by a court of competent jurisdiction to be unenforceable because it is invalid or in conflict with any law of any relevant jurisdiction, the validity of the remaining provisions shall not be affected, and the rights and obligations of the Parties shall be construed and enforced as if the Agreement did not contain the particular provisions held to be unenforceable.

9.12. Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of the Parties hereto and their successors and permitted assigns.

9.13. Counterparts. This Agreement may be executed in any number of counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same instrument.

(32)

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed as a sealed instrument in their names by their properly and duly authorized officers or representatives as of the date first above written.

[SEAL] GENETICS INSTITUTE, INC.

By: Gabriel Schmergel

[SEAL] CHUGAI PHARMACEUTICAL CO., LTD.

By: Kimio Uyeno

417

(33)

SCHEDULE A

PROGRAM DESIGN STEPS AND TIME FRAMES

Activities	Time Frame
Meeting 1: (Cambridge)	
- Detailed design review - Specification of remaining equipment - Transfer of procedures for preparation of Standard Operating Procedures (SOP's forwarded as available)	July 1985
Chugai visits GI (one week, two-man weeks)	
Meeting 2: (Tokyo)	
- Review of on-site construction and installation plans	November 1985
GI visits Chugai (one week, two man-weeks)	
Meeting 3: (Cambridge)	
- Process scale-up - Training - Culture in 1,600 liter bioreactor - Cell separation and purification of EPO	During EPO production in pilot plant.
Chugai visits GI (three weeks, six to 12 man-weeks)	
	Estimated to be as early as possible before January 31, 1986
Meeting 4: (Tokyo)	
- Training - Bioreactor commissioning qualification - Bioreactor process validation/start-up - Cell separation, purification and isolation process validation/start-up	Estimated to be as early as possible after Meeting 3
GI visits Chugai (eight weeks, 12 to 16 man-weeks)	

AM 17 108691

Acknowledged:

GENETICS INSTITUTE, INC.

By: Gabriel Schmergel

CHUGAI PHARMACEUTICAL CO., LTD.

By: Kimio Ugeno

418

(34)

SCHEDULE B

PAYMENT SCHEDULE

Year	Base Technology	EPO Technology[1]	Total Min.	Total Max.
1985	due as of signing of Agreement			
1986				
1987		(if less than 112,500,000 units/ton) (if more than 112,500,000 units/ton)[2] (if more than 187,500,000 units/ton)[3] (if more than 262,500,000 units/ton)[4]		

[1] Achievement shall be determined as of the measurement date. The specific activity of EPO from the Master Cell Bank shall be no less than 75,000 units per milligram.

[2] Payable as follows: by August 31, 1986 and by November 30, 1986.

[3] Payable as follows: by August 31, 1986, by November 30, 1986, by February 28, 1987 and by May 31, 1987.

[4] Payable as follows: by August 31, 1986, by December 30, 1986, payable by February 28, 1987 and payable by May 31, 1987.

AM 17 108692

(35)

Acknowledged:

GENETICS INSTITUTE, INC.

By: Gabriel Schmergel

CHUGAI PHARMACEUTICAL CO., LTD.

By: Kimio Myasa

CHUSA CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER
ITC INV. NO. 337-TA-281
420

AM 17 108693

AM-ITC 00435818

(36)

SCHEDULE C

ROYALTIES

Patent Rights and Know-How Royalty on Manufactured Products

for calendar years 1986 through 1991

for calendar years 1992 through 1997

Acknowledged:

GENETICS INSTITUTE, INC.

By: Gabriel Schmergel

CHUGAI PHARMACEUTICAL CO., LTD.

By: Kisuke Ueno

(37)

SCHEDULE D

STANDARDS FOR MEASURING UNITS OF EPO

The determination of the in vivo activity of EPO samples for documenting achievement of EPO output as set forth in Section 2.3 of the Agreement shall be performed as follows:

- The polycythemic mouse in vivo EPO assay described by Kazal and Erslev, Am. Clin. Lab. Sci. Vol. 5, p. 91 (1975) will be employed.

- A urinary standard will be employed that has been carefully calibrated versus the WHO international standard 2 by dose response comparison. Dose response analysis will, in all assays, be performed with four points using four animals per point. The four standard doses will be 0.1, 0.25, 0.5 and 1.0 u/ml with 1 ml injected per mouse.

- Samples for assay will also be analyzed by dose response analysis performed within the same assay set as a urinary standard. At least three points within the dose response curve containing different two-fold dilutions of the sample must have values that fall within the range of the standard dose response curve.

- Using least squares analysis, a line will be drawn for both the standard and the sample dose response curves. The sample dilution which results in an assay value equivalent to one unit/ml (from the standard dose/response line) will be interpolated and used to calculate the in vivo activity of the sample.

Acknowledged:

GENETICS INSTITUTE, INC.

By: Gabriel Schmergel

CHUGAI PHARMACEUTICAL CO., LTD.

By: Kiyoshi Ogawa

000339

AMENDMENT

AMENDMENT dated as of November 27, 1985 to an Agreement dated as of June 29, 1984 (the "Agreement") between Genetics Institute, Inc., a Delaware corporation ("Genetics") and Chugai Pharmaceutical Co., Ltd., a Japanese corporation ("Licensee").

For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Genetics and Licensee agree as follows:

1. Section 5.1 of the Agreement is amended to read in its entirety as follows:

> "5.1. Patent Licenses. Subject to the payment of the royalty provided in Article VI and the fulfillment of the other terms and conditions of this Agreement, Genetics hereby grants to Licensee and its Affiliates:
>
> (a) an exclusive license (even as to Genetics) in the Territory under the Project Patent Rights, and
>
> (b) a non-exclusive license in the Territory under the Genetics Patent Rights,
>
> including the right to grant sublicenses, for the sole and exclusive purpose of manufacturing, having manufactured for Licensee and its Affiliates, using and selling Licensed Compounds and/or Licensed Products in the Territory; provided, however, that Licensee and its Affiliates may not sell Licensed Products to a Distributor for ultimate resale in Japan, Canada, the United States or Mexico. The licenses granted pursuant to this Section 5.1 shall continue in effect until the expiration of the last patent licensed to the Licensee hereunder. Notwithstanding the foregoing, Genetics and its Affiliates shall have the right under the Project Patent Rights, including the right to grant sublicenses, to manufacture and have manufactured Licensed Compounds and Licensed Products in the United States; provided that in no event shall such manufactured Licensed Compounds and/or Licensed Products be sold in the United States or any other country in the Territory except by Licensee or its Affiliates."

2. Section 5.2 of the Agreement is amended to read in its entirety as follows:

(37)

"5.2. Know-How Licenses. Subject to the payment of the royalty provided in Article VI and the fulfillment of the other terms and conditions of this Agreement, Genetics hereby grants to Licensee and its Affiliates:

(a) an exclusive license (even as to Genetics) to use the Project Know-How in the Territory, and

(b) a non-exclusive license to use the Genetics Know-How in the Territory,

including the right to grant sublicenses, for the sole and exclusive purpose of manufacturing, having manufactured for Licensee and its Affiliates, using and selling Licensed Compounds and/or Licensed Products in the Territory; provided, however, that Licensee and its Affiliates may not sell Licensed Products to a Distributor for ultimate resale in Japan, Canada, the United States or Mexico. The licenses granted pursuant to this Section 5.2 shall continue in effect for a period of 20 years from the date of the completion of the Final Benchmark set forth on Schedule A hereto. Notwithstanding the foregoing, Genetics and its Affiliates shall have the right to use the Project Know-How, including the right to grant sublicenses, to manufacture and have manufactured Licensed Compounds and/or Licensed Products in the United States; provided that in no event shall such manufactured Licensed Compounds and/or Licensed Products be sold in the United States or any other country in the Territory except by Licensee or its Affiliates."

3. Section 9.1 of the Agreement is amended to read in its entirety as follows:

"9.1 Treatment of Confidential Information. Each Party hereto shall maintain the Confidential Information of the other Party in confidence, and shall not disclose, divulge or otherwise communicate such Confidential Information to others, or use it for any purpose, except pursuant to, and in order to carry out, the terms and objectives of this Agreement and hereby agrees to exercise every reasonable precaution to prevent and restrain the unauthorized disclosure of such Confidential Information by any of its directors, officers, employees, consultants, Affiliates, subcontractors, sublicensees, distributors or agents. Notwithstanding the foregoing, Genetics may disclose

(40)

Confidential Information pertaining to the Project, the obtaining of regulatory approvals and the development of Licensed Products in confidence to its Affiliates, other licensees or research sponsors in the field of erythropoeitin for use outside the Territory or for manufacture of Licensed Compounds and/or Licensed Products within the Territory, provided that such Licensed Compounds and/or Licensed Products are not sold within the Territory except by Licensee or its Affiliates."

4. Capitalized terms used herein and not otherwise defined shall have the meanings given them in the Agreement.

IN WITNESS WHEREOF, the Parties hereto have caused this Amendment to be executed as a sealed instrument in their names by their properly and duly authorized officers or representatives as of the date first written above.

(Seal) GENETICS INSTITUTE, INC.

By: Gabriel Schmergel
Title:

(Seal) CHUGAI PHARMACEUTICAL CO., LTD.

By: Kimio Uyeno
Title:

CHUSA CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER
ITC INV. NO. 337-TA-281
425

AM 17 108698

CHUGAI PHARMACEUTICAL CO.,LTD.
1-9, Kyobashi 2-chome, Chuo-ku
Tokyo, 104 Japan
Tel:(03)281-6611
Telex:J26681 CSKPHARM
Cable:CSKPHARM TOKYO

Statement of Intent
For EPO Technology Development

Chugai Pharmaceutical Co., Ltd. (hereinafter referred to as Chugai) has been interested in developing erythropoietin (EPO) for the treatment of anemia patients. Because of the inadequate amounts of EPO available in anemia patients, Chugai has requested and worked with Genetics Institute (hereinafter referred to as G.I.) to solve the availability problem of EPO by G.I.'s recombinant DNA technology.

G.I. entered into an agreement with Chugai to develop a recombinant EPO, and later cloned and expressed it in several cells. G.I. has been working to improve the expression level as well as to develop a downstream purification and cell culture process for the production of the recombinant EPO.

Whereas both Chugai and G.I. realize that the timing of the development for rEPO is critically important in light of the competition and the need for early market introduction, and have exchanged views and decided to cooperate with each other to seek ways to early commercial developments, including pre-clinical sample production by G.I. for Chugai and technology transfer of cell culture process technology relating to the scale-up of commercial production at Chugai;

In order for both parties to proceed further toward the commercial production of rEPO at Chugai, they set forth the following understanding and agreement before an official, legal agreement is prepared and signed.

CHUGAI PHARMACEUTICAL CO., LTD.

(142)

This Statement of Intent will specify 3 areas of agreement between Chugai and G.I., i.e., (1) Supply of pre-clinical material, (2) Technology development and transfer, (3) Supply of commercial processes. It will also discuss and agree on the payment schedule and other considerations.

1. Technology Development and Transfer

Technology development and transfer necessary for Chugai will be discussed in the attached Schedule A in terms of major activities and time frame. The program specifies major steps necessary from detailed design review at an early stage in the first part of July through process validations and start-up scheduled for late this year or early next year. The payment schedule is attached in Schedule B.

2. Pre-clinical Material

G.I. will make its best effort to supply 300-600 milligrams of EPO for pre-clinical testing by the end of November, 1985, using Master Cell Bank A (1-2 mgs/liter).

a. Chugai would like to receive a minimum partial amount of EPO as early as possible before November, 1985.

b. The specific delivery schedule may be discussed and changed by mutual agreement between the two parties.

c. will be paid by Chugai for this material in 1986, as shown in attached Schedule B.

d. The quality of the material should be acceptable for the requirements of the Japanese and US authorities. Further details will be specified in the Agreement.

CHUGAI PHARMACEUTICAL CO.,LTD.

(143)

3. Supply of Commercial Process

Upon the completion of the development and transfer to Chugai of the large scale technology provided by G.I. for the production of rEPO described above, Chugai will expect that the new process will meet a certain level of efficiency in the March-June period, 1986, using Master Cell Bank B (5-10 mgs/liter).

a. The payments will be linked to the level of output of the G.I. process in terms of grams of purified EPO/ton during the March-June, 1986 period. See Schedule B.

b. For the 12 months period July 86-June 87 G.I. will transfer to Chugai any process improvements without additional payment. Chugai will likewise transfer to G.I. process improvements for the same period without charge.

c. "Purified" described in (a) means the quality of the material should be acceptable for the requirements of the Japanese and US authorities. Further details will be specified in the Agreement.

4. Payment Terms

The payment terms for (1) pre-clinical material, (2) technology development and transfer, and (3) supply of commercial processes are specified in Schedule B.

5. Royalties

Chugai will pay royalties to G.I. at the rate of between 1987-1991 and between 1992-1997 on the basis of Chugai's net sales of all products produced by any of the foregoing technology excluding EPO.

6. Other Considerations

a. The technology being discussed here is applicable to mammalian as well as other culture/fermentation systems.

AM 17 108701

CHUGAI PHARMACEUTICAL CO., LTD.

(44)

b. Additional technical assistance beyond the scope of Schedule A will be separately discussed, should there be a particular need for it.

c. The subject fermentation process technology was developed by G.I. and G.I. is unaware of any third party patents thereon.

d. Chugai may terminate this program and the subsequent payment in the middle of the program. The method of termination will be faithfully discussed by the both parties and will be stipulated in the Agreement.

With this Statement of Intent and understanding, both parties believe that a major step toward the commercialization of EPO will begin shortly.

Date: July 9, 1985

Chugai Pharmaceutical Co., Ltd. Genetics Institute, Inc.

By: _____ By: _____

Osamu Nagayama

Title: Executive Director Title: PRESIDENT

CHUSA CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER
ITC INV. NO. 337-TA-281
429

AM 17 108702

CHUSA CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER
ITC INV. NO. 337-TA-281
430

SCHEDULE A

TECHNOLOGY DEVELOPMENT AND TRANSFER:

ACTIVITIES	TIME FRAME
Meeting 1: (Cambridge) - Detailed Design Review - Specification of Remaining Equipment - Transfer of procedures for preparation of Standard Operating Procedures - SOP's forwarded as available	Estimated to be in early July.
Chugai visits G.I. (1 week)	Estimated to be some time in July - August.
Meeting 2: (Tokyo) - Review of on-site construction and installation plans	During EPO production in pilot plant for pre-clinical material (GMP). Estimated to be some time as early as possible before November
G.I. visits Chugai (3 days)	
Meeting 3: (Cambridge) - Process scale-up - Training	
Chugai visits G.I. (2 weeks)	
Meeting 4: (Tokyo) - Training - Bioreactor Commissioning/Qualification - Bioreactor Process Validation/Startup - Isolation Process Validation/Startup	Estimated to be end of November - December
G.I. visits Chugai (1 man month)	

AM 17 108703

(46)

SCHEDULE B

TRANSFER OF PAYMENTS
($000)

	Technology Development & Transfer	Pre-clinical Material	Support Commercial Process	Total Min. - Max.
1985	at signing of Agreement payable by Nov. 30, 1985			
1986		payable by Feb. 28, 1986 payable by May 31, 1986		
			(if less than 1.5g/ton*) or	
			(if more than 1.5g/ton*)	
1987			(if more than 2.5g/ton*) or	
			(if more than 3.5g/ton*)	

* - Achievement level during March-June, 1986
** - Will be payable in quarterly installments

CHUSA CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER
ITC INV. NO. 337-TA-281

431

AM 17 108704

AM-ITC 00435829