Atty Docket No.: 197909US6SD

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FORM PTO-1595
1-31-92

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks. Please record the attached origi

1. Name of conveying party(ies):
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
6-21-02

Additional name(s) of conveying party(ies) attached? ☐Yes ☒No

2. Name and address of
Name: ATTO INSTRUMENTS, INC.
Address: 15010 Broschart Road
Rockville, MD 20850

3. Nature of Conveyance:
☐ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☒ Other –Exclusive License Agreement

Execution Date: March 6, 1992

Additional name(s) and address(es) attached? ☐Yes ☒No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)	B. Patent No.(s)
07/547,990	5,439,797; 5,661,035; 5,981,200; 6,197,928

Additional numbers attached? ☐Yes ☒No

5. Name and address of party to whom correspondence concerning document should be mailed:

22850

6. Total applications and patents involved: 4

7. Total fee (37 CFR 3.41): $40.00
☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit account number: 15-0030
(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

J. Derek Mason, Ph.D.
Name of Person Signing

Signature

6/21/02
Date

Registration Number: 35,270

Total number of pages including this cover sheet: 47

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Atty Docket No.: 197909US6SD

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FORM PTO-1595
1-31-92

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it and Trademark Office

102038001

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original ... copy thereof.

1. Name of conveying party(ies):

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

Additional name(s) of conveying party(ies) attached? □Yes ■No

2. Name and address of receiving party(ies):

Name: ATTO INSTRUMENTS, INC.

Address: 15010 Broschart Road
Rockville, Maryland 20850

3. Nature of Conveyance:

□ Assignment □ Merger
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Additional numbers attached? □Yes ■No

Name and address of party to whom correspondence concerning document should be mailed:

22850

6. Total applications and patents involved: 4

7. Total fee (37 CFR 3.41): $160.00
■ Enclosed
□ Authorized to be charged to deposit account

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(Attach duplicate copy of this page if paying by deposit account)

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To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

J. Derek Mason, Ph.D.
Name of Person Signing

Signature

3/26/02
Date

Registration Number: 35,270

Total number of pages including this cover sheet: 45

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EXCLUSIVE LICENSE AGREEMENT

between

ATTO INSTRUMENTS, INC.

and

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

TABLE OF CONTENTS

UC Case No(s).: 90-101-1

Draft Date: OCTOBER 1, 1991

EXCLUSIVE LICENSE AGREEMENT AND BAILMENT TO FLUORESCENT MARKERS FOR CYCLIC AMP

THIS LICENSE AGREEMENT ("Agreement") is made and is effective this 6th day of March, 1992 by and between THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a California corporation having its statewide administrative offices at 300 Lakeside Drive, 22nd Floor, Oakland, California 94612-3550, hereinafter referred to as "The Regents", and Atto Instruments, Inc., a Maryland corporation, having a principal place of business at 1500 Research Blvd., Rockville, Maryland 20850 hereinafter referred to as the "Licensee".

RECITALS

WHEREAS, certain inventions, generally characterized as "Fluorescent Sensors for Cyclic AMP" hereinafter collectively referred to as the "Invention", were conceived and developed in the course of research at the University of California, San Diego (UCSD) by Roger Tsien et al. and are covered by Regents' Property Rights and by Regents' Patent Rights as defined below;

WHEREAS, Brookhaven National Laboratory owns patent rights to an expression system that can be used in combination with the invention;

WHEREAS, Roger Tsien et al. used an expression system owned by Brookhaven National Laboratory in combination with the Invention;

WHEREAS, it is the intention of the Licensee to license said expression system from Brookhaven National Laboratory to practice the Invention;

WHEREAS, Licensee entered into a Secrecy Agreement (UC Agreement Control Number: 91-20-0099) with The Regents on March 15, 1991 and terminating on March 15, 1996.

WHEREAS, both parties recognize and agree that royalties due hereunder will be paid on Regents' Property Rights and both pending patent applications and issued patents contained in Regents' Patent Rights;

WHEREAS, the Licensee is a "small business firm" as defined in 15 U.S.C. 632;

WHEREAS, it is the intent of the parties to this Agreement to create a bailment, among other things, (as provided for in Paragraphs 2.2, 2.3 and 2.4 herein), for the Biological Materials as defined below;

WHEREAS, the Invention has utility for,including but not limited to, the detection of Cyclic AMP in cells (containing other cellular constituents), and the Licensee wishes to acquire licenses under Regents' Property Rights and Regents' Patent Rights to pursue commercial development of the Invention and to make, have made, use, and sell Products (as defined below); and

WHEREAS, The Regents is desirous that the Invention be

developed, utilized, and marketed to the fullest extent so that the Products therefrom and other benefits can be enjoyed by the general public;

the parties agree as follows:

1. DEFINITIONS

As used in this Agreement, the following terms shall have the meaning set forth below:

1.1 "Regents' Patent Rights" means all U. S. and foreign patents and patent applications, including any reissues, extensions, substitutions, continuations, divisions and continuations-in-part (only to the extent, however, that claims in the continuations-in-part are entitled to the priority filing date of the parent patent application) based on any subject matter claimed in or covered by any of the following:

(1.1a) U.S. Patent Application Serial Number 547,990 entitled " Detection of Analytes Using Fluorescent Energy Transfer" filed July 2, 1990 by Roger Y. Tsien et al. and assigned to The Regents, and the U.S. and foreign patents and patent applications specified in Exhibit A attached hereto and subject to Paragraph 13.4;

1.2 "Biological Material(s)" means gene sequences or any fragment thereof as derived from mammalian tissue and referenced as Recombinant Regulatory Subunit Type I Bovine and Recombinant Catalytic Subunit Type C alpha Mouse nomenclature of University of California, San Diego, and provided to the Licensee as part of

(a) any plasmid; (b) any other genetic construct; or (C) as a part of plasmids referenced as pLST1 and pLWS3, nomenclature of University of California, San Diego. pLWS3 was derived in part from pT7-7 (nomenclature of Brookhaven National Laboratory) and used and provided in combination with E-Coli strain DE3(BL21) as said expression system.

1.3 "Biological Product(s)" means any product containing (a) any chemical structure produced by the Biological Material, including but not limited to a protein, the sequence of which is coded by the genetic sequence contained in the Biological Material; or (b) a chemical compound substantially similar to or identical to a compound in (a) immediately above produced by chemical synthesis or by any other method. The Biological Product produced from the Biological Material transferred to the Licensee under the terms of this Agreement including, but not limited to, FlCRhR, nomenclature of University of California, San Diego. Biological Product(s) may either be Patent Products or Non-Patent Products.

1.4 "Patent Products" means (a) any material comprising a Biological Product or any other material that is covered by Regents' Patent Rights, that is produced by the Licensed Method, or the manufacture, use or sale of which would constitute, but for the license granted to the Licensee pursuant to this Agreement, an infringement of any pending or issued claim within Regents' Patent Rights.

1.5 "Non-Patent Products" means any product containing a Biological Product to the extent that the manufacture, use, or sale of which does not infringe an issued or pending claim under Regents' Patent Rights.

1.6 "Products" means Patent Products and Non-Patent Products.

1.7 "Licensed Method" means any process or method that is covered by Regent's Patent Rights in the country in which such process or method is used, or the use or practice of which would constitute, but for the license granted to the Licensee pursuant to this Agreement, an infringement of any issued or pending claim under Regent's Patent Rights in that country in which the Licensed Method is used or practiced. Practice of the Licensed Method shall be subject to applicable government importation laws and regulations on Products made outside a particular country in which such Products are used or sold.

1.8 "Net Sales" means the total of the gross invoice prices of Products sold, less the sum of the following deductions that are customary and actually taken: (i) cash, trade or quantity discounts; (ii) sales, use, tariff, import/export duties or other excise taxes imposed upon particular sales; and (iii) transportation (and insurance charges associated with transportation) and allowances or credits to customers because of rejections or returns. For sales of Products to an Affiliate or Joint Venture (as defined in Paragraphs 1.9 and 1.10 below) that are provided by Licensee to the Affiliate or Joint Venture at a

reduced price from that customarily charged to an unrelated third party, then the royalty paid to The Regents will be based on the Net Sales of Products of the Affiliate or Joint Venture to the Affiliate's or Joint Venture's customers and subject to payment under Article 4 (ROYALTIES).

1.9 "Affiliate(s)" of a party means any entity which, directly or indirectly, controls such party, is controlled by such party or is under common control with such party, "control" for these purposes being defined as the actual, present capacity to elect a majority of the directors of such Affiliate, or if not, the capacity to elect a majority that controls at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors; provided, however, that in any country where the local law shall not permit foreign equity participation of a majority, then an "Affiliate" shall include any company in which the Licensee shall own or control, directly or indirectly, the maximum percentage of such outstanding stock or voting rights permitted by local law. Each reference to Licensee herein shall be meant to include its Affiliates.

1.10 "Joint Venture" means any separate entity established pursuant to an agreement between a third party and Licensee to constitute a vehicle for a joint venture, which separate entity purchases, sells or acquires Products from Licensee at prices substantially different from those at which Licensee would have charged other purchasers that deal at arms length with Licensee. If such separate entity is established, then The Regents shall

collect from Licensee royalties on the Net Sales of Products by the entity and shall not collect royalties on Net Sales of Products by Licensee. Each reference to Licensee herein shall be meant to include its Joint Venture.

1.11 "Regents' Property Rights" means all The Regents' personal proprietary rights covering the tangible personal property in Biological Materials licensed hereunder. In no case, however, shall Regents' Property Rights include Regent's Patent Rights.

2. GRANT

2.1 Subject to the limitations set forth in this Agreement, The Regents grants to Licensee an exclusive license under The Regents' Patent Rights to practice the Licensed Method, to make, have made, use, and/or sell Patent Products where Regents' Patent Rights exist.

2.2 Subject to the limitations set forth in this Agreement, The Regents grants to Licensee an exclusive license under Regents' Property Rights to make, have made, use, and/or sell Non-Patent Products throughout the world where The Regents may lawfully grant such a license.

2.3 The licenses granted under Regents' Property Rights set forth in Paragraph 2.2 immediately above expressly limit the rights granted to Licensee in the Biological Materials to those licenses expressly stated in this Agreement and for no other purpose.

2.4 Under Regents' Property Rights, Licensee's right to

transfer possession of the Biological Materials to third parties other than sublicensees, which Biological Materials Licensee possesses under the license granted in Paragraph 2.2 above, is expressly excluded from this Agreement. Licensee shall not attempt to sell, donate, abandon or otherwise transfer such Biological Material to any third party. Licensee acknowledges that title to the tangible material comprising such Biological Material is owned by The Regents and is not transferred to Licensee under this Agreement.

2.5 The Regents also grants to the Licensee the right to issue sublicenses to third parties to make, have made, use, and/or sell Licensed Products and to practice Licensed Method, provided the Licensee has current exclusive rights thereto under this Agreement. To the extent applicable, such sublicenses shall include all the rights of and obligations due to The Regents that are contained in this Agreement.

2.6 Licensee shall provide The Regents with a copy of each sublicense issued hereunder; collect and guarantee payment of all royalties due The Regents from sublicensees; and summarize and deliver all reports due The Regents from sublicensees.

2.7 Upon termination of this Agreement for any reason, The Regents, at its sole discretion, shall determine whether any or all sublicenses shall be canceled or assigned to The Regents.

2.8 The Regents expressly reserves the right to use the Invention, Biological Materials, and associated technology for solely educational and research purposes.

3. LICENSE ISSUE FEE

3.1 The Licensee shall pay to The Regents a License Issue Fee of Ten Thousand Dollars ($10,000.00) according to the following schedule:

(3.1a) Five Thousand Dollars ($5,000) upon the date of execution of this Agreement by Licensee. Said Five Thousand Dollars ($5,000) shall be sent by Licensee to The Regents together with two executed copies of this Agreement;

(3.1b) Five Thousand Dollars ($5,000) on or before the first anniversary of the effective date of this Agreement.

3.2 These fees are non-refundable, non-creditable and not an advance against royalties.

4. ROYALTIES

4.1 As consideration for the licenses granted herein, Licensee shall also pay to The Regents an earned royalty in an amount equal to the following percentages of the Net Sales of Products sold by the Licensee.

(4.1a) Ten Percent (10%) on the Net Sales of Patent Products;

(4.1b) Ten percent (10%) on the Net Sales of Non-Patent Products;

In no case will a royalty of greater than ten percent (10%) be charged to Licensee by The Regents.

4.2 Earned royalties for Products under Paragraph 4.1 shall accrue in each country for the duration of Regents' Patent Rights in that country.

4.3 Products shall be considered sold when invoiced or, if

not invoiced, when delivered to a third party.

4.4 In the event that the Licensee is required to license an expression system from Brookhaven National Laboratory in order to practice Regents' Patent Rights and Regents' Property Rights, then The Regents shall reduce the earned royalty set forth in Paragraphs 4.1a and 4.1b above to eight percent (8%) on the Net Sales of Patent Products and eight (8%) on the Net Sales of Non-Patent Products sold by Licensee for the period that the Licensee is required to pay royalties to Brookhaven National Laboratory.

4.5 If the Licensee is no longer paying royalties to Brookhaven National Laboratory, then the earned royalty paid to The Regents shall revert back to that specified in Paragraphs 4.1a and 4.1b herein.

4.6 Earned Royalties accruing to The Regents shall be paid to The Regents quarterly on or before the following dates of each calendar year:

February 28	for the preceding calendar quarter ending December 31.
May 31	for the preceding calendar quarter ending March 31.
August 31	for the preceding calendar quarter ending June 30.
November 30	for the preceding calendar quarter ending September 30.

Each such payment will be for royalties which accrued within the Licensee's most recently completed calendar quarter.

4.7 Beginning in the calendar year 1993, Licensee shall pay to The Regents a minimum annual royalty as set forth below:

1993 - Five Thousand Dollars ($5,000);

1994 - Ten Thousand Dollars ($10,000).

In each succeeding calendar year after the year 1994, Licensee shall pay a minimum annual royalty of Ten Thousand Dollars ($10,000) for the life of this Agreement. These minimum annual royalties shall be paid to The Regents by February 28 each year and shall be credited against earned royalties quarter to quarter until consumed for that year.

4.8 All monies due The Regents shall be payable in United States Dollars. When Products are sold for currency other than United States Dollars, the earned royalties will first be determined in the foreign currency of the country in which such Products were sold and then converted into equivalent United States Dollars. The exchange rate will be that published by the Bank of America in New York, New York on the last day of the calendar quarter and will be quoted in local currency per U.S. dollar.

4.9 Royalties earned with respect to sales on Products shall not be reduced by any value-added taxes, fees or other charges imposed by the government of any country. The Licensee shall also be responsible for all bank transfer charges.

4.10 If at any time legal restrictions prevent the prompt remittance of part or all royalties by the Licensee with respect to any country where a Product is sold, the Licensee shall have the right and option to make such payments by depositing the amount thereof in local currency to The Regents' account in a

bank or other depository in such country.

4.11 The Regents will use its best efforts to transfer the monies held in the account specified in Paragraph 4.8 to the United States. If after one year from the date of the first deposit into that account there are still legal restrictions that prevent The Regents from transferring the monies, The Regents shall transfer the impounded funds back to the Licensee, and the Licensee shall convert the amount owed to The Regents into United States funds and shall pay The Regents directly from its U.S. source of funds for the amount impounded. The Licensee shall then pay all future royalties due to The Regents from its U.S. source of funds so long as the legal restrictions of Paragraph 4.8 still apply.

4.12 In the event that any patent or any claim thereof included within the Regents' Patent Rights expires or shall be held invalid in a final decision by a court of competent jurisdiction and last resort and from which no appeal has been or can be taken, all obligation to pay royalties for Products based on, covered by, or made using such patent or claim, or any claim patentably indistinct therefrom, shall cease as of the date of such expiration or final decision. The Licensee shall not, however, be relieved from paying any royalties that accrued before such expiration or decision or from paying royalties on Products that are based on, covered by, or are made using another patent or claim not expired or involved in such decision or are covered by Regents' Property Rights.

5. DUE DILIGENCE

5.1 The Licensee, upon execution of this Agreement, shall use diligent commercial efforts to proceed with the development, manufacture and sale of Products and shall use diligent commercial efforts to market the same within a reasonable time after execution of this Agreement and in quantities sufficient to meet the market demands therefor.

5.2 The Licensee shall be entitled to exercise prudent and reasonable business judgment in meeting its due diligence obligations hereunder.

5.3 The Licensee shall endeavor to obtain all necessary governmental approvals for the manufacture, use, and sale of all Products.

5.4 If the licensee is unable to perform any of the following:

(5.4a) manufacture Products according to the following specifications (which specifications are provided in more detail in Appendix D attached hereto and incorporated herein)

i. produce Biological Product containing one protein having two fluorescently labeled bands with apparent molecular weight of 39-42 kD for the catalytic and 49kD for the type I regulatory subunit on a 12% SDS polyacrylamide sequencing gel (Appendix D, paragraph 1); or

ii. produce Biological Product containing another protein having two fluorescently labeled bands with apparent molecular weight of 56-58 kD for the catalytic and 49kD for the type II regulatory subunit on a 12% SDS-polyacrylamide sequencing gel (Appendix D, paragraph 1); and

iii. produce said proteins (set forth in Subparagraphs i and ii above) having a fluorescence emission ratio inducible by cAMP of 1.3 or greater (Appendix D, paragraph 3);

iv. produce such proteins having kinase activity less than twenty percent (20%) before the addition of 50 um CAMP of that obtained after addition of CAMP (Appendix D, paragraph 4);

v. produce such proteins having more than eighty percent (80%) of the initial fluorescence as supernatant after centrifugation of said proteins (Appendix D, paragraph 5)

(5.4b) introduce all Products produced in (i-v above) to the market by March 1, 1993;

then The Regents has the right and option to terminate this Agreement or reduce Licensee's licenses to nonexclusive licenses. This right by The Regents supersedes the rights granted in Article 2 (GRANT).

5.5 At the request of either party, any controversy or claim arising out of or relating to the diligence provisions of this Agreement shall be settled by arbitration conducted in San Francisco, California in accordance with the then current Licensing Agreement Arbitration Rules of the American Arbitration Association. The parties shall use a single, mutually-acceptable arbitrator in any arbitration contemplated under this Paragraph.

5.6 To exercise the right to terminate this Agreement or reduce Licensee's exclusive licenses to nonexclusive licenses for lack of diligence required in Paragraphs 5.1, 5.3 and 5.4, The Regents must give the Licensee prior written notice of the deficiency. The Licensee thereafter has ninety (90) days to cure

the deficiency or ninety (90) days to request arbitration under Paragraph 5.6. If The Regents has not received a written request for arbitration within ninety (90) days or satisfactory tangible evidence that the deficiency has been cured within the ninety (90) day period, then The Regents may, at its option, either terminate this Agreement or reduce the Licensee's exclusive licenses to nonexclusive licenses by giving written notice to the Licensee. These notices shall be subject to Article 20 (Notices).

6. PROGRESS AND ROYALTY REPORTS

6.1 Beginning August 31, 1992 and quarterly thereafter, the Licensee shall submit to The Regents a progress report covering the Licensee's activities related to the development and testing of all Products necessary for marketing in order to determine that the provisions in Article 5 (Diligence) have been met. These progress reports shall be made for each Product until the first commercial sale of that Product occurs anywhere in the world.

6.2 The progress reports submitted under section 6.1 should include, but not be limited to, the following topics:

- summary of work completed;
- key scientific discoveries;
- summary of work in progress;
- current schedule of anticipated events or milestones;
- market plans and introduction of Products; and

- a summary of resources (dollar value) spent in developing the invention during the reporting period;

- any activities relating to the formation of a Joint Venture.

6.3 After the first commercial sale of a Product, the Licensee will provide The Regents with quarterly royalty reports on or before each February 28, May 31, August 31 and November 30 of each year. Each such royalty report will cover the Licensee's most recently completed calendar quarter and will show:

(6.3a) the gross sales and Net Sales of Products sold by the Licensee and reported to Licensee as sold by its sublicensees during the most recently completed calendar quarter;

(6.3b) the number of each type of Product sold by Licensee and reported to Licensee as sold by its sublicensees;

(6.3c) the royalties, in U.S. dollars, payable hereunder with respect to Net Sales; and

(6.3d) the exchange rates used, if any.

6.4 If no sales of Products have been made during any reporting period after the first commercial sale of Products, a statement to this effect shall be required.

7. BOOKS AND RECORDS

7.1 The Licensee shall keep books and records accurately showing all Products manufactured, used, and/or sold under the terms of this Agreement. Such books and records shall be preserved for at least five (5) years from the date of the

royalty payment to which they pertain and shall be open to inspection by representatives or agents of The Regents at reasonable times.

7.2 The costs of such an examination shall be borne by The Regents. However, if an error in royalties of more than five percent (5%) of the total royalties due for any year is discovered by such an examination, the cost of the examination shall be borne by the Licensee.

8. LIFE OF THE AGREEMENT

8.1 Unless otherwise terminated by operation of law or by acts of the parties in accordance with the terms of this Agreement, this Agreement shall be in force from the effective date recited on page one and shall remain in effect for the life of the last-to-expire patent licensed under this Agreement or, in the event no patent issues, for a period of eight (8) years from market introduction for the last to be introduced Non-Patent Product in the United States.

8.2 In the event this Agreement remains in effect for the entire term specified in Paragraph 8.1 above, and is not otherwise terminated under the provisions of Articles 5 (DUE DILIGENCE, 9 (TERMINATION BY REGENTS), or 10 (TERMINATION BY LICENSEE) Licensee is hereby granted an option for renewal of this Agreement for a period of ten (10) years from the date of its termination. Said option for renewal shall be automatically exercised provided that the Licensee has not notified The Regents

to the contrary prior to the option renewal date. The renewal licenses will be for the same terms and conditions as set forth in this Agreement, except that such licenses shall be royalty-free

8.3 In the event this Agreement is terminated for any reason whatsoever not including expiration, Licensee shall provide to The Regents, in writing and at no cost to The Regents, all technical information, data, and know-how developed by Licensee and directly relating to the Biological Products within ninety (90) days of such termination. The Regents shall be free to transfer the technical information, data, and know-how to third parties.

8.4 Any termination of this Agreement shall not affect the rights and obligations set forth in the following Articles:

Article 7	Books and Records
Article 8	Life of the Agreement
Article 12	Disposition of the Biological Material(s) and Products on Hand Upon Termination
Article 15	Use of Names and Trademarks
Article 19	Indemnification
Article 22	Late Payments
Article 24	Failure to Perform
Article 29	Confidentiality

9. TERMINATION BY REGENTS

9.1 If the Licensee should violate or fail to perform any term or covenant of this Agreement, then The Regents may give

written notice of such default (Notice of Default) to the Licensee. If the Licensee should fail to repair such default within ninety (90) days of the effective date of such notice, The Regents shall have the right to terminate this Agreement and the licenses herein by a second written notice (Notice of Termination) to the Licensee. If a Notice of Termination is sent to the Licensee, this Agreement shall automatically terminate on the effective date of such notice. Such termination shall not relieve the Licensee of its obligation to pay any royalty or license issue fees or prosecution costs (subject to Article 13.3) owing at the time of such termination and shall not impair any accrued right of The Regents. These notices shall be subject to Article 20 (NOTICES).

10. TERMINATION BY LICENSEE

10.1 The Licensee shall have the right at any time to terminate this Agreement in whole or as to any portion of Regents' Patent Rights or Regents' Property Rights by giving notice in writing to The Regents. Such notice of termination shall be subject to Article 20 (NOTICES) and termination of this Agreement, or termination of any specified portion of the Agreement, shall be effective ninety (90) days from the date of such notice. Such termination shall not relieve Licensee of its obligation to pay prosecution costs (subject to Paragraph 13.3).

10.2 Any termination pursuant to the above Paragraph 10.1 shall not relieve the Licensee of any obligation or liability

established hereunder prior to such termination or rescind anything done by the Licensee or any payments made to The Regents hereunder prior to the time such termination becomes effective, and such termination shall not affect in any manner any rights of The Regents arising under this Agreement prior to such termination.

11. SUPPLY OF THE BIOLOGICAL MATERIAL

11.1 The Regents shall initially supply Licensee with viable samples of the existing Biological Material and Biological Products such as FlCRhR (samples of each where "R" is made from both type 1 and type 2 regulatory sub-units), subject to the receipt of written approval by Brookhaven National Laboratory to The Regents, within thirty (30) days of the effective date of this Agreement. To the extent Licensee requires and requests additional samples from The Regents during the term hereof (due to failure of the initial supply of the Biological Material or otherwise), and The Regents has such additional samples in its possession, The Regents agrees to supply such additional samples. Licensee shall pay the actual handling and shipping costs for any additional samples provided.

12. DISPOSITION OF THE BIOLOGICAL MATERIAL AND PRODUCTS ON HAND UPON TERMINATION

12.1 Upon termination of this Agreement, the Licensee shall have the privilege of disposing all previously made or partially made Products, but no more, for a period of one hundred and

twenty (120) days following the effective date of termination, provided, however, that the sale of such Products shall be subject to the terms of this Agreement including, but not limited to, the payment of royalties at the rate and at the time provided herein and the rendering of reports in connection therewith.

12.2 Upon termination of this Agreement for any reason, Licensee agrees to destroy the Biological Material in its possession within fifteen (15) days following the effective date of termination. Licensee shall provide The Regents within thirty (30) days following said termination date with written notice that the Biological Material has been destroyed.

13. PATENT PROSECUTION AND MAINTENANCE

13.1 The Regents shall diligently prosecute and maintain the United States and foreign patents under Regents' Patent Rights using counsel of its choice. The Regents shall provide Licensee with copies of all relevant documentation so that licensee may be informed and apprised of the continuing prosecution and the Licensee agrees to keep this documentation confidential in accordance with Article 29 herein. The Regents' counsel will take instructions only from The Regents.

13.2 The Regents shall use all reasonable efforts to amend any patent application to include claims reasonably requested by Licensee and required to protect the Products contemplated to be sold under this Agreement.

13.3 All past, present and future costs of preparing,

filing, prosecuting and maintaining all United States and foreign patent applications and resulting patents contemplated by this Agreement shall be born by Licensee. This includes patent prosecution costs for this Invention incurred by The Regents prior to the execution of this Agreement and shall be payable in two installments. Such prosecution costs will be approximately Twelve Thousand, Eight Hundred Dollars ($12,800).The first installment (half of said patent prosecution costs) shall be paid at the time payment of the first installment of the License Issue Fee is due. The remainder of the patent prosecution costs shall be paid on or before the six month anniversary date of this Agreement. The Regents shall elect to file Chapter II under the Patent Cooperation Treaty (PCT), designating Japan, Canada, Australia, and EPO (designating all member countries), covering the foreign patent applications at the appropriate time and at the expense of the Licensee.

13.4 The Licensee shall have the right to request that The Regents obtain national phase patent protection in Japan and/or protection under the European Patent Organization if available and if it so desires. The Licensee must notify The Regents within five (5) months of the filing of the corresponding PCT Chapter II procedure of its decision to obtain foreign patents. This notice concerning foreign filing shall be in writing and must identify the countries desired. The absence of such a notice from the Licensee to The Regents shall be considered an election not to secure foreign rights.

13.5 The Licensee's obligation to underwrite and to pay patent prosecution cost shall continue for so long as this Agreement remains in effect, provided, however, that the licensee may terminate its obligations with respect to any given patent application or patent upon three (3) months written notice to The Regents. The Regents will use its best efforts to curtail patent costs when such a notice is received from the Licensee. The Regents may continue prosecution and/or maintenance of such application(s) or patent(s) at its sole discretion and expense; provided, however, that the Licensee shall have no further right or licenses thereunder.

13.6 The Regents shall have the right to file patent applications at its own expense in any country in which the Licensee has not elected to secure patent rights, and such applications and resultant patents shall not be subject to this Agreement.

13.7 The Licensee shall have a continuing responsibility to keep The Regents informed of the large/small entity status (as defined by the United States Patent and Trademark Office) of itself and its sublicensees.

14. PATENT MARKING

14.1 The Licensee agrees to mark all Patent Products made, used, or sold under the terms of this Agreement, or their containers, in accordance with the applicable patent marking laws

15. USE OF NAMES AND TRADEMARKS

15.1 Nothing contained in this Agreement shall be construed as conferring any right to use in advertising, publicity, or other promotional activities any name, trade name, trademark, or other designation of either party hereto (including any contraction, abbreviation or simulation of any of the foregoing). Unless required by law or consented to in writing by the Director, Office of Technology Transfer, of The Regents, the use of the name, "The Regents of the University of California" or the name of any campus or laboratory of the University of California is expressly prohibited.

15.2 It is understood that The Regents shall be free to release to the inventors and senior administrative officials employed by The Regents the terms and conditions of this Agreement upon their request. If such release is made, The Regents shall request that such terms and conditions not be disclosed to others. It is further understood that should a third party inquire whether a license to Regents' Patent Rights or Regents' Property Rights is available, The Regents may disclose the existence of this Agreement and the extent of the grant in Article 2 (GRANT) to such third party, but shall not disclose the name of the Licensee, except where The Regents is required to release such information under either the California Public Records Act or other applicable law.

16. LIMITED WARRANTY

16.1 The Regents warrants to the Licensee that it has the lawful right to grant this license and bailment.

16.2 The Licensed Method, Regents' Patent Rights and Regents' Property Rights are provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. THE REGENTS MAKES NO REPRESENTATION OR WARRANTY THAT THE PRODUCTS OR LICENSED METHODS WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

16.3 IN NO EVENT WILL THE REGENTS BE LIABLE FOR ANY INCIDENTAL, SPECIAL OR CONSEQUENTIAL DAMAGES RESULTING FROM EXERCISE OF THIS LICENSE OR THE USE OF THE LICENSED METHOD OR PRODUCTS.

16.4 Nothing in this Agreement shall be construed as:

(16.4a) a warranty or representation by The Regents as to the validity or scope of any of Regents' Patent Rights; or

(16.4b) 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 of third parties; or

(16.4c) an obligation to bring or prosecute actions or suits against third parties for patent infringement, except to the extent and in the circumstances described in Article 17; or

(16.4d) conferring by implication, estoppel or otherwise any license or rights under any patents of The Regents other than Regents' Patent Rights as defined herein;or

(16.4e) an obligation to furnish any know-how not provided in Regents' Patent Rights or Regents' Property Rights.

17. PATENT INFRINGEMENT

17.1 In the event that the Licensee shall learn of the substantial infringement of any patent licensed under this Agreement, the Licensee shall call The Regents' attention thereto in writing and shall provide The Regents with reasonable evidence of such infringement. Both parties to this Agreement agree that during the period and in a jurisdiction where the Licensee has exclusive rights under this Agreement, neither will notify an infringing third party of the alleged infringement of any of Regents' Patent Rights without first obtaining consent of the other party, which consent shall not be unreasonably denied. Both parties shall use their reasonable efforts in cooperation with each other to terminate such infringement without litigation.

17.2 The Licensee may request that The Regents take legal action against the infringement of Regents' Patent Rights. Such request shall be made in writing and shall include reasonable evidence of such infringement and damages to the Licensee. If the infringing activity has not been abated within ninety (90) days following the effective date of such request, The Regents shall have the right to:

(17.2a) commence suit on their own account; or

(17.2b) refuse to participate in such suit;

and The Regents shall give notice of their election in writing to the Licensee by the end of the one-hundredth (100th) day after receiving notice of such request from the Licensee. The Licensee

may thereafter bring suit for patent infringement if and only if The Regents elects not to commence suit (other than as nominal party plaintiff) and if the infringement occurred during the period and in a jurisdiction where the Licensee had exclusive rights under this Agreement. However, in the event the Licensee elects to bring suit in accordance with this Paragraph, The Regents may thereafter join such suit at its own expense.

17.3 Such legal action as is decided upon shall be at the expense of the party on account of whom suit is brought and all recoveries recovered thereby shall belong to such party, provided, however, that legal action brought jointly by The Regents and the Licensee and fully participated in by both shall be at the joint expense of the parties and all recoveries shall be shared jointly by them in proportion to the share of expenses paid by each party.

17.4 Each party agrees to cooperate with the other in legal proceedings (including without limitation, signing and arranging for the signature on documents, joining actions as nominal party and similar actions), instituted hereunder but at the expense of the party on account of whom suit is brought. Such legal proceedings shall be controlled by the party bringing the action, except that The Regents may be represented by counsel of its choice, at Licensee's expense, in any action brought by the Licensee.

18. MAINTENANCE OF THE BIOLOGICAL MATERIAL

18.1 The Regents agrees to instruct Roger Tsien and Susan Taylor that if The Regents circulates the Biological Material to third parties for noncommercial research purposes, it shall only do so under the terms and conditions set forth in the biological material transmission letter attached hereto as Appendix A. The Regents expressly reserves the right to transfer the Biological Material strictly for noncommercial research purposes in the manner set forth above. The Regents agrees that it will not otherwise transfer Biological Material. The Licensee acknowledges that The Regents' right to so transfer the Biological Material could lead to the diminution of the commercial value of the Biological Material.

19. INDEMNIFICATION

19.1 The Licensee agrees to (and require its sublicensees to) indemnify, hold harmless and defend The Regents, its officers, employees, and agents; the sponsors of the research that led to the Invention; the inventors (and their employers) of any invention covered by any patents and patent applications under Regents' Patent Rights and Regents' Property Rights and Products contemplated thereunder against any and all claims, suits, losses, damage, costs, fees, and expenses resulting from or arising out of exercise of this license or any sublicense.

19.2 The Regents shall promptly notify Licensee in writing of any claim or suit brought against The Regents in

respect of which The Regents intends to invoke the provisions of this Article 19 (INDEMNIFICATION). Licensee will keep The Regents informed on a current basis of its defense of any claims pursuant to this Article 19 (INDEMNIFICATION).

20. NOTICES

20.1 Any notice or payment required to be given to either party shall be deemed to have been properly given and to be effective (a) on the date of delivery if delivered in person or (b) five (5) days after mailing if mailed by air mail certified mail, postage paid, to the respective addresses given below, or to such other address as it shall designate by written notice given to the other party in the manner provided above.

In the case of the Licensee:	Atto Instruments, Inc. 1500 Research Blvd. Rockville, Maryland 20850 Attention: President
In the case of The Regents:	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (C/N #90-101-1) Suite 150 1320 Harbor Bay Parkway Alameda, CA 94501 Attention: Director--Office of Technology Transfer

21. ASSIGNABILITY

21.1 This Agreement is binding upon and shall inure to the benefit of the parties hereto and their respective successors and assigns, provided, however, this Agreement shall be personal to

the Licensee and shall be assignable by the Licensee only with the written consent of The Regents, which consent shall not be unreasonably withheld.

22. LATE PAYMENTS

22.1 In the event royalty payments or fees are not received by The Regents when due, the Licensee shall pay to The Regents interest charges at a rate of ten percent (10%) compounded interest per annum. Such interest shall be calculated from the date payment was due until actually received by The Regents. Acceptance by The Regents of any late payment interest from Licensee under this Paragraph 22.1 shall in no way affect the provision of Article 23 (WAIVER) herein.

23. WAIVER

23.1 It is agreed that no waiver by either party hereto of any breach or default of any of the covenants or agreements herein set forth shall be deemed a waiver as to any subsequent and/or similar breach or default.

24. FAILURE TO PERFORM

24.1 In the event of a failure of performance due under the terms of this Agreement and if it becomes necessary for either party to undertake legal action (or arbitration in accordance with Article 5 [DUE DILIGENCE]) against the other on account thereof, then the prevailing party shall be entitled to

reasonable attorney's fees in addition to costs and necessary disbursements.

25. GOVERNING LAWS

25.1 THIS AGREEMENT SHALL BE INTERPRETED AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF CALIFORNIA, but the scope and validity of any patent or patent application licensed under this Agreement shall be governed by the applicable laws of United States of America or other country in which that patent was granted or in which that patent application is pending.

26. FOREIGN GOVERNMENT APPROVAL OR REGISTRATION

26.1 If this Agreement or any associated transaction is required by the law of any nation to be either approved or registered with any governmental agency, the Licensee shall assume all legal obligations to do so and the costs in connection therewith. The Regents shall fully cooperate with the Licensee, to the extent it is able to do so within the law and established Regents' policy, to provide documentation and testimony to obtain such approval or registration.

27. EXPORT CONTROL LAWS

27.1 The Licensee shall observe all applicable United States and foreign laws and regulations with respect to the transfer of Products and related technical data to foreign countries,

including, without limitation, the International Traffic in Arms Regulations (ITAR) and the Export Administration Regulations.

28. FORCE MAJEURE

28.1 The parties to this Agreement shall be excused from any performance required hereunder if such performance is rendered impossible or unfeasible due to any catastrophes or other major events beyond their reasonable control,, including, without limitation, war, riot, and insurrection; laws, proclamations, edicts, ordinances or regulations; strikes, lock-outs or other serious labor disputes; and floods, fires, explosions, or other natural disasters. When such events have abated, the parties' respective obligations hereunder shall resume.

29. CONFIDENTIALITY

29.1 With regard to confidential information ("Data"), which can be oral or written or both, received from The Regents regarding this Invention, the Licensee agrees:

(29.1a) not to use the Data except for the sole purpose of performing under the terms of this Agreement;

(29.1b) to safeguard Data against disclosure to others with the same degree of care it exercises with its own data of a similar nature;

(29.1c) not to disclose Data to others (except to its employees, agents or consultants who are bound to Licensee by a like obligation of confidentiality) without the express written permission of The Regents, except that Licensee shall not be prevented from using or disclosing any of the Data:

(i) which Licensee can demonstrate by written records was previously known to it;

(ii) which is now, or becomes in the future, public knowledge other than through acts or omissions of Licensee; or

(iii) which is lawfully obtained by Licensee from sources independent of The Regents; and

(29.1d) that the secrecy obligations of Licensee with respect to Data shall continue for a period ending five (5) years from the termination date of this Agreement.

31. MISCELLANEOUS

31.1 The headings of the several sections are inserted for convenience of reference only and are not intended to be a part of or to affect the meaning or interpretation of this Agreement.

31.2 This Agreement will not be binding upon the parties until it has been signed below on behalf of each party, in which event, it shall be effective as of the date recited on page one.

31.3 No amendment or modification hereof shall be valid or binding upon the parties unless made in writing and signed on behalf of each party.

31.4 This Agreement embodies the entire understanding of the parties with respect to the subject matter herein and shall supersede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof, including the Secrecy Agreement.

31.5 In case any of the provisions contained in this Agreement shall be held to be invalid, illegal or unenforceable

in any respect, such invalidity, illegality or unenforceability shall not affect any other provisions hereof, but this Agreement shall be construed as if such invalid or illegal or unenforceable provisions had never been contained herein.

IN WITNESS WHEREOF, both The Regents and the Licensee have executed this Agreement, in duplicate originals, by their respective officers hereunto duly authorized, on the day and year hereinafter written.

ATTO INSTRUMENTS, INC

By _____ (Signature)

Name Gary Brooker, Phd.

Title President

Date 3/2/92

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

By _____ (Signature)

Name Carl B. Wootten

Title Director, Office of Technology Transfer

Date _____

Approval as to legal form: _____ Date
P. Martin Simpson, Jr., Resident Counsel
Office of Technology Transfer
University of California

University of California

Instructions for Standard Letter Transmitting
Biological Materials to Universities and
Nonprofit Institutions

The attached letter is authorized for use by University of California Principal Investigators and Administrators only with Scientists at other universities and nonprofit research institutions when transmitting cell lines, plasmids, amoeba and the like for non-commercial research purposes.

1. Choose the appropriate form of university or nonprofit research institutions in paragraph 2.

2. Choose whether or not to include the phrase "our cooperative" in paragraph 2.

3. Insert in paragraph 4 the amount of processing charge. If the material is to be shipped at no charge, insert the words "no charge".

4. Send the letter in duplicate to the other scientists.

5. Do not send biological materials until you receive the duplicate copy executed by both the scientist and the other institution.

6. Send a copy of the fully executed letter agreement to:

   Carl B. Wootten (c/n 91-101)
   Director
   Office of Technology Transfer
   1320 Harbor Bay Parkway
   Suite 150
   Alameda, CA 94501

7. Any changes in the wording of this standard letter must be reviewed by the Director of the Patent, Trademark and Copyright Office before acceptance.

Note: Do not use this letter for the exchange of living plants. A separate "Testing Agreement for the Plant Varieties" is available for that purpose.

SAMPLE LETTER FOR USE PRIOR TO TRANSMISSION OF BIOLOGICAL MATERIALS TO INVESTIGATORS AT UNIVERSITIES OR NON-PROFIT RESEARCH INSTITUTIONS

(date)

IN DUPLICATE

To: _____

This is to (acknowledge receipt of your letter) (confirm our telephone conversation) in which you requested certain research materials developed in this laboratory be sent to you for scientific research purposes. The materials concerned, which belong to The Regents of the University of California are: _____. While I cannot transfer ownership of these materials to you, I will be pleased to permit your use of these materials within your (university) (Non-Profit Research Institution) laboratory for (our cooperative) scientific research. However, before forwarding them to you, I would like your agreement that the materials will be received by you only for use in (our cooperative work) (scientific research), that you will bear all risk to you or any others resulting from your use, and that you will not pass these materials, their progeny or derivatives, on to any other party or use them for commercial purposes without the express written consent of The Regents of the University of California. You understand that no other right or license to these materials, their progeny or derivatives, is granted or implied as a result of our transmission of these materials to you.

These materials are to be used with caution and prudence in any experimental work, since all of their characteristics are not known.

As you recognize, there is a processing cost to us involved in providing these materials to you. We will bill you for our processing costs, which will amount to $_____.

If you agree to accept these materials under the above conditions, please sign the enclosed duplicate copy of this letter, then have it signed by an authorized representative of your institution, and return it to me. Upon receipt of that confirmation I will forward the material(s) to you.

(Note: other paragraphs discussing the relevant literature, the nature of the work, hazards relating to materials to be sent etc. may be appropriate. These will vary depending on the individual circumstances and the relationship between the two parties previously established. Be sure to retain a signed copy when received and send a photocopy of the completed agreement to the University of California Patent Administrator, Office of Technology Transfer, 1320 Harbor Bay Parkway, Suite 150, Alameda, CA 94501)

Sincerely yours,

ACCEPTED:

RESEARCH INVESTIGATOR

_____
(Signature)

_____
Date

PRINCIPAL INVESTIGATOR

_____
(Signature)

_____
Date

RESEARCH UNIVERSITY OR
NON-PROFIT INSTITUTION

_____
Printed Name

_____
(Signature)

_____
Date

APPENDIX B

The INVENTOR and PRINCIPAL INVESTIGATOR listed below understand and agree to abide by the terms and conditions of Article 18 of the License Agreement between The Regents of the University of California and Atto Instruments, Inc. effective _____ and to instruct all relevant personnel working within their laboratory to act accordingly. Said paragraph reads, in part, as follows:

> "18.1 The Regents agrees to instruct Dr. Roger Tsien and Dr. Susan Taylor that if The Regents circulates the Biological Materials to third parties for noncommercial research purposes, it shall only do so under the terms and conditions set forth in the biological material transmission letter attached hereto as Appendix A.

The Biological Materials is defined in said Agreement as follows:

> "1.2 "Biological Material" means a gene sequence or any fragment thereof as derived from mamalian tissue and referenced as _____, nomenclature of University of California, San Diego, and provided to the Licensee in combination with (a) any plasmid; (b) any other genetc construct; or as a part of plasmid ____ and plasmid____."

By _____ Jan. 11 1994
Dr. Roger Tsien — Date

By _____ March 17 1993
Dr. Susan Taylor — Date

APPENDIX C

Martin Rachmeler, Director of the Technology Transfer Office at the University of California at San Diego, has read and approved the terms and conditions of the License Agreement titled "Exclusive License Agreement and Bailment to Fluorescent Markers for Cyclic Amp".

By Martin Rachmeler Date 3/13/92

Martin Rachmeler
Director
University of California
San Diego

PRODUCT SPECIFICATIONS

1 SDS-polyacrylamide gel electrophoresis is performed with a twelve percent (12%) separating gel as described by U.K. Laemmli (1970) *Nature 227*:680. Correctly prepared fluorescently labeled protein made from type I holoenzyme should give two fluorescently labeled bands, with apparent molecular weight (calibrated against conventional protein standards) of 39-42 kD for the catalytic and 49 Kd for the type I regulatory subunit. When viewed with 365 nm illumination from a mercury handlamp, these bands should show green and red fluorescence respectively. The same bands should co-stain for protein with Coomassie Blue. Bands of lower molecular weight should constitute less than ten percent (10%) of the total protein.

2 For type II holoenzyme, the same should apply except that the apparent molecular weight of the type II regulatory subunit should be 56-58 Kd.

3 Change in fluorescence emission ratio: Dissolve fluorescently labeled protein to a final concentration of 10-20 nM in a buffer consisting of 135 mM KCl, 10mM MOPS, 5mM $MgCl_2$, and 3 mM ATP, adjusted to Ph 7.3 using KOH. Excite at 490 nm, measure the emission spectrum from 500 to 600 nm using a bandpass of less than 5 nm, and calculate the ratio of emission amplitudes at 520 nm to that at 580 nm. Define this ratio to be A. Add 0.2 uM cyclic AMP Na or K salt, then measure the 520:580 nm emission ratio again (=B). Finally, add 50 uM cyclic AMP and measure the ratio again (=C). C/A should be 1.30 or greater (this measures the maximal change in ratio inducible by CAMP). B should be greater than (A + C)/2 (this is a crude test of the apparent K_m for CAMP).

4 Change in kinase activity: Measure the activity of fluorescently labeled protein to phosphorylate the synthetic peptide H_2N-Leu-Arg-Arg-Ala-Ser-Leu-Gly-OH (commonly known as Kemptide) in a coupled assay using pyruvate kinase and lactate dehydrogenase linked to NADH, as described by Cook et al (1982), *Biochemistry* 21:5794. The assay medium contains 5 - 10 nM holoenzyme in 100 mM K-MOPS pH 7.1-7.2, 100 mM KCl, 10 mM $MgCl_2$, 1mM phosphoenolpyruvate, 1 mM ATP, 15 units/ml lactate dehydrogenase, 7.1 units/ml pyruvate kinase, 0.2 mM NADH, and 0.25 mM Kemptide. Transfer of phosphate groups from ATP to Kemptide makes ADP; ADP plus phosphoenolpyruvate makes ATP plus pyruvate; pyruvate plus NADH makes lactate plus NAD; kinase activity is therefore detected by loss

of NADH measured by UV spectrophotometry or fluorometry. Kinase activity before addition of cAMP should be less than twenty percent (20%) of that obtained after addition of 50 uM cAMP. The latter activity should be at least 5 umol NADH min^{-1}(mg catalytic subunit)$^{-1}$.

5 Solubility: Measure the fluorescence before and after centrifuging the protein at equal to or greater than 15,000 x g for 20 minutes at 4 C. More than eighty percent (80%) of the initial fluorescence should remain in the supernatant after centrifugation.

Case No. 90-101-I "Detection of Analytes Using Flourescent Energy Transfer"

Patent Applications

Country	Application No	Filing Date
United States	547,990	7/2/90
PCT designating	PCT/US91	1/7/91
Austria		
Belgium		
Switzerland & Lichtenstein		
Germany (Federal Republic)		
Denmark		
Spain		
France		
United Kingdom		
Greece		
Italy		
Japan		
Luxembourg		
Netherlands		
Sweden		

[redacted]

[redacted]A