NRC FORM 374
(7-94)

U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE

Amendment No. 01

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 36, 39, 40, and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations, and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

301897

Licensee	
1. Aastrom Biosciences	In accordance with letter dated September 27, 1996 3. License Number 21-26519-01 is amended in its entirety to read as follows:
2. P.O. Box 376 Ann Arbor, MI 48106	4. Expiration Date September 30, 2003
	5. Docket or Reference No. 030-33266

6. Byproduct, Source, and/or Special Nuclear Material	7. Chemical and/or Physical Form	8. Maximum Amount that Licensee May Possess at Any One Time Under This License
A. Phosphorus-32	A. Any	A. 30 millicuries
B. Phosphorus-33	B. Any	B. 30 millicuries
C. Sulfur-35	C. Any	C. 30 millicuries
D. Chromium-51	D. Any	D. 20 millicuries
E. Hydrogen-3	E. Any	E. 20 millicuries

9. Authorized Use:

A. through C. To be used as described in letter dated September 7, 1993.

D. and E. To be used as described in letter dated September 27, 1996.

CONDITIONS

10. Licensed material shall be used only at the licensee's facilities located at 24 Frank Lloyd Wright Drive, Domino's Farms, Lobby L, Ann Arbor, Michigan.

11. A. The Radiation Safety Officer: Douglas M. Smith, Ph.D.

B. Assistant Radiation Safety Officer: Timothy C. Jensen

12. Licensed material shall be used by, or under the supervision of, Douglas M. Smith, Ph.D. or Timothy C. Jensen.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number: 21-26519-01
Docket or Reference Number: 030-33266
Amendment No. 01

13. The licensee is authorized to hold radioactive material with a physical half-life of less than 65 days for decay-in-storage before disposal in ordinary trash provided:

A. Radioactive waste to be disposed of in this manner shall be held for decay a minimum of 10 half-lives.

B. Before disposal as ordinary trash, byproduct material shall be surveyed at the container surface with the appropriate meter set on its most sensitive scale and with no interposed shielding to determine that its radioactivity cannot be distinguished from background. All radiation labels shall be removed or obliterated.

C. A record of each disposal permitted under this License Condition shall be retained for 3 years. The record must include the date of disposal, the date on which the byproduct material was placed in storage, the radionuclides disposed, the survey instrument used, the background dose rate, the dose rate measured at the surface of each waste container, and the name of the individual who performed the disposal.

14. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents, including any enclosures, listed below. The U.S. Nuclear Regulatory Commission's regulations shall govern unless the statements, representations, and procedures in the licensee's application and correspondence are more restrictive than the regulations.

A. Letters dated September 7, 1993, September 27, 1996, and November 10, 1996.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

Date 11/20/96

By Kevin G. Null
Nuclear Materials Licensing Branch, Region III

BETWEEN:

License Fee Management Branch, ARM
and
Regional Licensing Sections

(FOR LFMS USE)
INFORMATION FROM LTS

Program Code: 03620
Status Code: 0
Fee Category: 3M
Exp. Date: 20030930
Fee Comments:
Decom Fin Assur Reqd: N

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
   Applicant/Licensee: AASTROM BIOSCIENCES
   Received Date: 960930
   Docket No: 3033266
   Control No.: 301897
   License No.: 21-26519-01
   Action Type: Amendment

2. FEE ATTACHED
   Amount: 590
   Check No.: 2053

3. COMMENTS

Signed D. Hersey
Date 10-2-96

1996 OCT -7 PM 1:43

B. LICENSE FEE MANAGEMENT BRANCH (Check when milestone 03 is entered /__/)

1. Fee Category and Amount: 3M #610

2. Correct Fee Paid. Application may be processed for:
   Amendment
   Renewal
   License

3. OTHER

Signed SC
Date 11/26/96

NOV 29 1996

Log Oct 3 III
Remitter
Check No. 11153 / 11689
Amount #590 + #20
Fee Category 3M
Type of Fee AMD
Date Check Rec'd 10/7/96
Date Completed 11/26/96
By: SC

NRC FORM 313 (10-94)
10 CFR 30, 32, 33
34, 35, 36, 39 and 40

U. S. NUCLEAR REGULATORY COMMISSION

APPLICATION FOR MATERIAL LICENSE

APPROVED BY OMB: NO. 3150-0120
EXPIRES 5-31-96

ESTIMATED BURDEN PER RESPONSE TO COMPLY WITH THIS INFORMATION COLLECTION REQUEST: 9 HOURS. SUBMITTAL OF THE APPLICATION IS NECESSARY TO DETERMINE THAT THE APPLICANT IS QUALIFIED AND THAT ADEQUATE PROCEDURES EXIST TO PROTECT THE PUBLIC HEALTH AND SAFETY. FORWARD COMMENTS REGARDING BURDEN ESTIMATE TO THE INFORMATION AND RECORDS MANAGEMENT BRANCH (T-6 F33), U.S. NUCLEAR REGULATORY COMMISSION, WASHINGTON, DC 20555-0001, AND TO THE PAPERWORK REDUCTION PROJECT (3150-0120), OFFICE OF MANAGEMENT AND BUDGET, WASHINGTON, DC 20503.

INSTRUCTIONS: SEE THE APPROPRIATE LICENSE APPLICATION GUIDE FOR DETAILED INSTRUCTIONS FOR COMPLETING APPLICATION. SEND TWO COPIES OF THE ENTIRE COMPLETED APPLICATION TO THE NRC OFFICE SPECIFIED BELOW.

APPLICATION FOR DISTRIBUTION OF EXEMPT PRODUCTS FILE APPLICATIONS WITH:

DIVISION OF INDUSTRIAL AND MEDICAL NUCLEAR SAFETY
OFFICE OF NUCLEAR MATERIALS SAFETY AND SAFEGUARDS
U.S. NUCLEAR REGULATORY COMMISSION
WASHINGTON, DC 20555-0001

ALL OTHER PERSONS FILE APPLICATIONS AS FOLLOWS:

IF YOU ARE LOCATED IN:

CONNECTICUT, DELAWARE, DISTRICT OF COLUMBIA, MAINE, MARYLAND, MASSACHUSETTS, NEW HAMPSHIRE, NEW JERSEY, NEW YORK, PENNSYLVANIA, RHODE ISLAND, OR VERMONT, SEND APPLICATIONS TO:

LICENSING ASSISTANT SECTION
NUCLEAR MATERIALS SAFETY BRANCH
U.S. NUCLEAR REGULATORY COMMISSION, REGION I
475 ALLENDALE ROAD
KING OF PRUSSIA, PA 19406-1415

ALABAMA, FLORIDA, GEORGIA, KENTUCKY, MISSISSIPPI, NORTH CAROLINA, PUERTO RICO, SOUTH CAROLINA, TENNESSEE, VIRGINIA, VIRGIN ISLANDS, OR WEST VIRGINIA, SEND APPLICATIONS TO:

NUCLEAR MATERIALS LICENSING SECTION
U.S. NUCLEAR REGULATORY COMMISSION, REGION II
101 MARIETTA STREET, NW, SUITE 2900
ATLANTA, GA 30323-0199

IF YOU ARE LOCATED IN:

ILLINOIS, INDIANA, IOWA, MICHIGAN, MINNESOTA, MISSOURI, OHIO, OR WISCONSIN, SEND APPLICATIONS TO:

MATERIALS LICENSING SECTION
U.S. NUCLEAR REGULATORY COMMISSION, REGION III
801 WARRENVILLE RD.
LISLE, IL 60532-4351

ALASKA, ARIZONA, ARKANSAS, CALIFORNIA, COLORADO, HAWAII, IDAHO, KANSAS, LOUISIANA, MONTANA, NEBRASKA, NEVADA, NEW MEXICO, NORTH DAKOTA, OKLAHOMA, OREGON, PACIFIC TRUST TERRITORIES, SOUTH DAKOTA, TEXAS, UTAH, WASHINGTON, OR WYOMING, SEND APPLICATIONS TO:

NUCLEAR MATERIALS LICENSING SECTION
U.S. NUCLEAR REGULATORY COMMISSION, REGION IV
611 RYAN PLAZA DRIVE, SUITE 400
ARLINGTON, TX 76011-8064

PERSONS LOCATED IN AGREEMENT STATES SEND APPLICATIONS TO THE U.S. NUCLEAR REGULATORY COMMISSION ONLY IF THEY WISH TO POSSESS AND USE LICENSED MATERIAL IN STATES SUBJECT TO U.S. NUCLEAR REGULATORY COMMISSION JURISDICTIONS.

1. THIS IS AN APPLICATION FOR *(Check appropriate item)*
   - [ ] A. NEW LICENSE
   - [x] B. AMENDMENT TO LICENSE NUMBER 21-26519-01
   - [ ] C. RENEWAL OF LICENSE NUMBER _____

2. NAME AND MAILING ADDRESS OF APPLICANT *(Include Zip code)*
   Douglas M. Smith, Ph.D.
   Aastrom Biosciences, Inc.
   24 Frank Lloyd Wright Dr. Box 376
   Ann Arbor Michigan 48106

3. ADDRESS(ES) WHERE LICENSED MATERIAL WILL BE USED OR POSSESSED
   Same as above, item 2.

4. NAME OF PERSON TO BE CONTACTED ABOUT THIS APPLICATION
   Douglas M. Smith, Ph.D.
   TELEPHONE NUMBER
   313-930-5784

SUBMIT ITEMS 5 THROUGH 11 ON 8-1/2 X 11" PAPER. THE TYPE AND SCOPE OF INFORMATION TO BE PROVIDED IS DESCRIBED IN THE LICENSE APPLICATION GUIDE.

5. RADIOACTIVE MATERIAL.
   a. Element and mass number, b. chemical and/or physical form; and c. maximum amount which will be possessed at any one time.

6. PURPOSE(S) FOR WHICH LICENSED MATERIAL WILL BE USED.

7. INDIVIDUAL(S) RESPONSIBLE FOR RADIATION SAFETY PROGRAM AND THEIR TRAINING EXPERIENCE.

8. TRAINING FOR INDIVIDUALS WORKING IN OR FREQUENTING RESTRICTED AREAS.

9. FACILITIES AND EQUIPMENT.

10. RADIATION SAFETY PROGRAM.

11. WASTE MANAGEMENT.

12. LICENSEE FEES *(See 10 CFR 170 and Section 170.31)*
    FEE CATEGORY
    AMOUNT ENCLOSED $ 590.00

13. CERTIFICATION *(Must be completed by applicant)* THE APPLICANT UNDERSTANDS THAT ALL STATEMENTS AND REPRESENTATIONS MADE IN THIS APPLICATION ARE BINDING UPON THE APPLICANT.

THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATION ON BEHALF OF THE APPLICANT, NAMED IN ITEM 2, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PARTS 30, 32, 33, 34, 35, 36, 39 AND 40, AND THAT ALL INFORMATION CONTAINED HEREIN IS TRUE AND CORRECT TO THE BEST OF THEIR KNOWLEDGE AND BELIEF.

WARNING: 18 U.S.C. SECTION 1001 ACT OF JUNE 25, 1948 62 STAT. 749 MAKES IT A CRIMINAL OFFENSE TO MAKE A WILLFULLY FALSE STATEMENT OR REPRESENTATION TO ANY DEPARTMENT OR AGENCY OF THE UNITED STATES AS TO ANY MATTER WITHIN ITS JURISDICTION.

CERTIFYING OFFICER – TYPED/PRINTED NAME AND TITLE	SIGNATURE	DATE
Douglas M. Smith, Ph.D. Research Scientist	Douglas M. Smith	Sept. 26, 1996

FOR NRC USE ONLY

TYPE OF FEE	FEE LOG	FEE CATEGORY	AMOUNT RECEIVED	CHECK NUMBER	COMMENTS
			$		RECEIVED
APPROVED BY				DATE	SEP 30 1996

NRC FORM 313 (10-94) PRINTED ON RECYCLED PAPER

REGION III

PM: 9-27-96

301897

Douglas M. Smith, Ph.D.
AASTROM Biosciences Inc.
24 Frank Lloyd Wright Drive
Ann Arbor, Michigan 48106
Telephone: 313-930-5789
FAX: 313-665-0485

September 27, 1996

Mr. William Reichhold
U.S. Nuclear Regulatory Commission
Region III
801 Warrenville Rd.
Lisle, IL 60532-4951

Dear Mr. Reichhold,

I am writing to request amendments regarding NRC Material License Number 21-26519-01.

Recently, I have been nominated to replace Sue A. Rummel, Ph.D. as Radiation Safety Officer at Aastrom Biosciences, Inc. In addition, I would like to appoint Mr. Timothy Jensen as Assistant Radiation Safety Officer. My experience with radioisotopes includes Hydrogen-3, Chromium-51, Indium-111, Iodine-125, Lead-212 and Bismuth-212; Mr. Jensen is familiar with the use of Carbon-14, Phosphorus-32, Phosphorus-33, Sulfur-35 and Iodine-125. I have received radiation safety training at The University of Chicago; Mr. Jensen has received similar training at The University of Michigan. Current resumes for Mr. Jensen and myself are enclosed.

In addition, I have enclosed a completed application form and fee of $590.00 for amendment of NRC Material License Number 21-26519-01 to include Chromium-51 and Hydrogen-3. It is necessary to use these radioisotopes for projects currently in progress. If possible, we would like to expedite this application to permit use of these radioisotopes within one month.

Please contact me if you require additional information. Thank you for your assistance in these matters.

Sincerely,

Douglas M. Smith, Ph.D.
Research Scientist

CC: Thomas Muller, Ph.D., Vice President of Regulatory Affairs
Alan Smith, Ph.D., Vice President of Research
R. Douglas Armstrong, Ph.D., President & CEO

Enclosures

5.0 RADIOACTIVE MATERIALS

a. Element and Mass Number	b. Chemical and/or Physical form	c. Maximum amount to be possessed at any one time
Chromium-51	Any	20 mCi
Hydrogen-3 (Tritium)	Any	20 mCi

6.0 PURPOSE FOR WHICH LICENSED MATERIAL WILL BE USED

Sodium Chromate will be used to label target cells for use in standard Cytolytic T-cell assays. Lytic activity will be measured by determination of Cr-51 release from labeled target cells in microwell cultures.

3[H]thymidine will be used to measure cellular proliferation in a standard thymidine incorporation assay. Labeled cells will be harvested from microwells and incorporation of label into DNA will be determined by liquid scintillation counting.

7.0 INDIVIDUAL(S) RESPONSIBLE FOR THE RADIATION SAFETY PROGRAM AND THEIR TRAINING EXPERIENCE

Dr. Douglas Smith is the person responsible for the Radiation Safety Program. He will be assisted in his duties by Mr. Timothy Jensen. The resumes of these two individuals are attached to this application amendment.

8.0 TRAINING OF INDIVIDUALS

The training program is described in Section F of the Radiation Safety Manual which is included in the currently existing License, Number 21-26519-01.

9.0 FACILITY DESCRIPTION AND EQUIPMENT

Aastrom Biosciences, Inc. is a privately held Biotechnology company that was founded in partnership with the University of Michigan in August, 1989. The company has developed proprietary technology for growing human stem and hematopoietic progenitor cells, T-lymphocytes and other cell types.

Aastrom Biosciences, Inc. currently leases approximately 20,000 square feet of space at the address listed in Item 3 of this application and employs approximately 60 people. The office and laboratory areas are located on the second floor while the waste storage area is in a secure room located on the first floor. The floor-plan indicating areas for use and storage of radioactive materials is shown in Attachment B of the existing License, Number 21-26519-01.

10.0 RADIATION SAFETY PROGRAM

The radiation safety program is described in the Radiation Safety Manual which is included in section F-1 of the existing License, Number 21-26519-01.

11.0 WASTE MANAGEMENT

Chromium-51 will be stored on site until decay to background; waste will be stored for at least 10 half-lives.

Scientific Ecology Group, (SEG), Inc. P.O. Box 2530, 1560 Bear Creek Road, Oak Ridge TN 37831-2530, telephone: (423-481-0222) will dispose of liquid and solid waste containing 3[H]thymidine.

Timothy C. Jensen

9416 Houghton Livonia, MI 48150 (313) 432-0931

Education

1988-1990 Bowling Green State University, Bowling Green, Ohio.
Masters of Science in **Biology**
course work in **Biochemistry and Molecular Biology**
Masters Thesis: Characterization of the major LHC chlorophyll a/b proteins of *Prochlorothrix hollandica*.

1984-1988 Bowling Green State University, Bowling Green, Ohio.
Bachelors of Science in **Biology**

1985-1986 Institute des Etudes Francaise de Touraine, Tours, France.
Certificate of Language

Laboratory Skills

Radioisotope handling	Transgenic Mouse work
Cell Culture	Protein Electrophoresis (SDS PAGE, IEF, Westerns)
Immunoprecipitation	Thin Layer Chromatography
PCR, DNA Sequencing	DNA and RNA blotting/hybridization
Library screening	*in situ* hybridization

Related Work Experience

Research Associate, Aastrom Biosciences Inc., Ann Arbor, Michigan.

- Utilize short and long term bone marrow tissue culture to study the effects of clinical treatments on cell expansion
- Establish protocols to measure lymphocyte proliferation in response to antigen presenting cells
- Utilize Good Laboratory Practices in experiments, record keeping and training
- Present results in both formal and informal group meetings and in written reports

Research Associate, University of Michigan, Ann Arbor, Michigan. 1990-1996

- Extensively use SDS-PAGE, Western blotting and Immunoprecipitation to study cell receptor activity
- Study gene regulation of matrix degrading proteases in tissue and cell culture systems
- Isolate and characterize genes by library screening, PCR, cloning and DNA sequencing
- Maintain, screen and perform experiments with a transgenic mouse colony
- Computer analysis of DNA sequence from subtractive library clones

- Published four papers and four abstracts
- Train and supervise new employees and medical students
- Make regular presentations of research data

Research/Teaching Assistant, Bowling Green State University, Bowling Green, Ohio. 1988-1990

- Characterized an important photosynthetic protein by Western blotting, isolation techniques and DNA sequence analysis
- Presented data at an international convention
- Published thesis results
- Demonstrated techniques to new graduate students
- Instructed undergraduate students in Introductory Biology course; presented lectures, prepared laboratory, and demonstrated a large variety of techniques and experiments to students

Research Assistant, Heinz USA Agricultural Research, Bowling Green, Ohio. 1988-1989

- Used a hydroponics system that I helped develop to monitor growth of tomato plants under mineral stress conditions
- Worked closely with supervisors to design experiments and present data to company officials

Quality Control Technician, PPG Industries, Coatings and Resins Division, Delaware, Ohio. 1987

- Performed tests on paint samples to assure that customer specifications were achieved prior to shipment

Other Experiences

- Bowling Green State University Admissions
  Telephoned perspective students to answer questions and promote the University
  Gave campus tours to perspective students
- Bowling Green State University Ambassadors
  Represented the University at alumni events
  Hosted university alumni visiting campus
- Drivers Education Instructor (two years, part time)
- Northville Players, Delaware Theater Association (community theater groups)

Publications

1. Majmudar, G., B.R. Nelson, T.C. Jensen, and T. M. Johnson. 1994. Increased expression of matrix metalloproteinase-3 (stromelysin-I) in cultured fibroblasts and basal cell carcinomas of nevoid basal cell carcinoma syndrome. Molecular Carcinogenesis. .

2. Majmudar, G., T.C. Jensen, J.J. Voorhees and T. M. Johnson. 1994. Stromelysin-3: A novel metalloproteinase is overexpressed in basal cell carcinomas. Molecular Carcinogenesis. 9:17-23.

3. Johnson, T.M., B.R. Nelson, T.C. Jensen and G. Majmudar. 1993. Matrix metalloproteinases in local tumor invasion in nonmeloanoma skin cancer. The Cancer Bulletin. 45:238-244.

4. Klein, S.B., G.S. Fisher, T.C. Jensen, J. Mendelsohn, J.J. Voorhees and J.T. Elder. 1992. Regulation of the TGF-alpha expression in human keratinocytes: PKC-dependent and independent pathways. Journal of Cell Physiology. 151:326-336

5. Bullerjahn, G.S., T.C. Jensen, D. M. Sherman and L.A. Sherman. 1990. Immunological characterization of the *Prochlorothrix hollandica* and *Prochloron sp.* chlorophyll a/b antenna proteins. FEMS Microbiology. Leters. 67:99-106.

Abstracts Published

1. Majmudar, G., T.C. Jensen, J. Trent, J. Voorhees, B. Nelson, and T. Johnson, 1993. Increased Expression of Stromelysin-1 in skin fibroblasts and basal cell carcinomas in nevoid basal cell carcinoma syndrome. Journal of Investigative Dermatology (program abstracts).

2. Majmudar., T.C. Jensen, J.J. Voorhees and T. M. Johnson. 1992. Stromelysin-3: A novel metalloproteinase is over expressed in most (17 of 21) basal cell but in few (3 or 13) squamous cell carcinomas. Journal of Investigative Dermatology (program abstracts).

3. Elder, J.T. and T.C. Jensen. 1991. EGF and TGF-alpha rapidly stimulate tyrosine phosphorylation in normal human keratinocytes. Clinical Research (program abstracts).

4. Bullerjahn, G.S., T.C. Jensen, D.M. Sherman and L.A Sherman. 1989. Characterization of the prochlorophyte chlorophyll a/b antenna. Plant Physiology 89:154 (supplement).

5. Jensen, T.C., D.H. Lee, R. Noble and D. Emmaty. 1989. Tolerance to low phosphorus levels in an anthocyaninless tomato variety (*lycopersicon esculentum*). Plant Physiology. 89:120 (supplement).

6. Ruff, B.S., T.C. Jensen and R. Noble. 1989. Relationship between duration of exposure to selected growth hormones and rate of shoot formation in tomato leaf disks. The Ohio Journal of Science. (program abstracts). 89:8.

DOUGLAS M. SMITH

Home Address:

1466 Astor Drive
Ann Arbor, Michigan 48104
313-332-4270

Business Address:

Aastrom Biosciences, Inc.
P.O. Box 376
Ann Arbor, Michigan 48106
313-930-5555

EDUCATION:

Ph.D., Immunology, University of Chicago, 1987
Dissertation: "Cellular Pathways for Rejection of Class I MHC Disparate Allografts."
Thesis advisor: Frank W. Fitch, M.D., Ph.D.
B.Sc., Microbiology/Immunology, McGill University, 1979

EXPERIENCE:

1996-Present: Research Scientist, Aastrom Biosciences, Inc.

- Responsible for determination of the functional characteristics of human CD8+ T-lymphocytes produced in large scale bioreactors.
- Develop and utilize controled flow rate technology for retroviral-mediated gene transfer to human T-lymphocytes.

1991-1996: Research Associate, University of Chicago, Department of Surgery

- Responsible for directing research laboratory that derives and characterizes novel monoclonal antibodies for human transplant therapy.
- Devised new assays for antibody screening and selection.
- Three mAbs selected for commercialization by the University of Chicago.
- Conducting research on class I MHC signalling pathways leading to apoptosis of human lymphocytes and tumor cells.
- Expertise in cellular immunology including flow cytometry, T-cell cloning technology, signal transduction, lymphokine release, proliferation and cytolysis.
- Supervision of technicians, medical students and undergraduate students.

1987-1991: Post Doctoral Fellow and Cytogen Corporation Scholar, University of Chicago, Department of Surgery

- Interacted with industrial research and development laboratories at Cytogen Corporation leading to application of technology for site specific conjugation of mAbs with chelators for alpha emitting radionuclides.
- Directed a group of 2 technicians and a Surgery Resident in the evaluation of the immunoreactivity, stability and biodistribution of radiolabeled mAbs and lymphocytes in vitro and in vivo.
- Determined the immunosuppressive effects of Pb-212 labeled lymphocytes on the immune response to murine skin allografts.
- Established a mouse model for bone marrow purging of fibrosarcoma tumor cells.
- Produced mAbs in hollow fiber bioreactors.

EXPERIENCE (Continued):

1981-1982: Teaching Assistant, University of Chicago, Department of Biology, Common Core Biology Laboratory

- Assisted in all aspects of an undergraduate laboratory course in basic biology, organized experiments, lead discussions, tutored students and graded papers.

1979-1981: Research Assistant, Yale University School of Medicine, New Haven, Connecticut

- Conducted research defining the relationship between Epstein-Barr virus and human lymphoproliferative disease.
- Studies focused on the early events of EBV transformation of human B-lymphocytes and on the state of differentiation and potential for malignancy of infected cells in the peripheral blood of patients with infectious mononucleosis.

HONORS AND AWARDS:

1983-1986: National Institutes of Health, National Research Service Award, Immunology Training Grant

PROFESSIONAL ACTIVITIES:

1991: Consultant, Cytogen Corporation, Princeton, NJ
Member: American Association for the Advancement of Science

PROFESSIONAL PUBLICATIONS:

Articles:

1. Robinson, J., **D. Smith** and J. Niedermann. 1980. Mitotic EBNA-positive lymphocytes in the peripheral blood during infectious mononucleosis. **Nature.** 287:334.

2. Robinson, J., **D. Smith** and J. Niedermann. 1981. Plasmacytic differentiation of circulating Epstein-Barr virus-infected B lymphocytes during acute infectious mononucleosis. **J. Exp. Med.** 153:235.

3. Robinson, J. and **D. Smith**. 1981. Infection of human B lymphocytes with high multiplicities of Epstein-Barr virus: kinetics of EBNA expression, cellular DNA synthesis, and mitosis. **Virology.** 109:336.

4. Miller, G., E. Grogan, L. Heston. J. Robinson and **D. Smith**. 1981. Epstein-Barr viral DNA: infectivity for human placental cells. **Science.** 212:452.

Articles (Continued):

5. **Smith, D.**, F. Stuart, G. Wemhoff, J. Quintans and F. Fitch. 1988. Cellular pathways for rejection of class I MHC disparate skin and tumor allografts. **Transplantation.** 45:168.

6. **Smith, D.** and F. Fitch. 1989. Cellular stimuli for rejection of Sarcoma I tumor allografts by BALB/c recipient mice. **Cell. Immunol.** 118:358.

7. **Smith, D.**, M. McKisic, F. Stuart and F. Fitch. 1989. Rejection of H-2K or H-2I region disparate skin allografts by either Lyt-2^+ or L3T4^+ T-lymphocyte subset. **Transplant. Proc.** 21:162.

8. **Smith, D.**, O. Ojogho and F. Stuart. Regulation of allograft rejection by anti- idiotypic responses. In: Burdick, J. et al. eds. **Kidney Transplant Rejection**, Second Edition. New York: Marcel Dekker, Inc., 1992: 235-260.

9. **Smith, D.,** J. Bluestone, D. Jeyarajah, M. Newberg, V. Engelhard, J. Thistlethwaite, Jr. and E. Woodle. 1994. Inhibition of T cell activation by a monoclonal antibody reactive against the $\alpha 3$ domain of human MHC class I molecules. **J. Immunol.** 153:1054.

10. **Smith, D.**, J. Bluestone, J. Thistlethwaite, Jr., and E. Woodle. 1995. Inhibition of T cell activation by an anti-human class I MHC reactive monoclonal antibody occurs at a point distal to TCR-CD3 mediated signal transduction. **Transplant. Proc.** 27:395.

11. **Smith, D.**, W. Kirkman, E. Skowronski, D. Green, J. Bluestone and E. Woodle. Anti-human Class I MHC antibodies induce apoptosis by a pathway which is distinct from the Fas antigen-mediated pathway. **Submitted for publication.**

12. **Smith, D.**, R. Atcher and F. Stuart. Specific immunosuppression of anti-transplant responses after administration of lead-212-labeled allogeneic lymphocytes to recipient mice. **Manuscript in preparation.**

13. **Smith, D.**, J. Bluestone, W. Kirkman, and E. Woodle. Induction of apoptosis in selective human T-lymphocyte subsets after signal transduction through TCR/CD3 and Class I MHC molecules. **Manuscript in preparation.**

Abstracts:

1. **Smith, D.** and F. Fitch. 1986. Interleukin 2 down-regulates cytolytic activity in a murine helper-independent cytolytic T lymphocyte clone. **Fed. Proc.** 45:996.

Abstracts (Continued):

2. **Smith, D.**, F. Stuart and F. Fitch. 1987. Cellular pathways for rejection of class I MHC disparate skin and tumor allografts. **Fed. Proc.** 46:756.

3. McKisic, M., **D. Smith**, F. Stuart and F. Fitch. 1989. Cytolytic activity of some murine T cell clones cycle in response to IL-2. **FASEB Journal** 3:A478.

4. **Smith, D.**, O. Ojogho, M. Buckingham, R. Atcher and F. Stuart. 1991. Specific Reduction of the Immune Response to Alloantigens after Administration of Lead-212-Labeled Allogeneic Lymphocytes to Recipient Mice. **Antibody Immunoconjugates and Radiopharmaceuticals** 4:217.

5. **Smith, D.**, D. Jeyarajah, S. Hussain, E. Woodle, J. Thistlethwaite, Jr. and J. Bluestone. 1993. Human T-lymphocyte activation in response to anti-CD3 monoclonal antibody, alloantigen or xenoantigen is inhibited by a monoclonal anti-HLA class I reactive antibody. **J. Immunol.** 150:269A.

6. **Smith, D.**, J. Thistlethwaite, Jr. and E. Woodle. 1994. Inhibition of T-cell activation by a mAb reactive against the α3 domain of human MHC class I molecules. **13th Annual Meeting of the American Society of Transplant Physicians.** Chicago, Illinois.

7. **Smith, D.**, J. Bluestone, W. Kirkman and E. Woodle. 1995. Induction of apoptosis in normal and transformed human lymphocytes by a monoclonal antibody reactive against the α3 domain of class I MHC molecules. **9th International Congress of Immunology.** San Francisco, California.

8. **Smith, D.**, J. Bluestone, W. Kirkman and E. Woodle. 1995. A monoclonal antibody reactive against the α3 domain of class I MHC molecules induces apoptosis of human lymphocytes. **4th Basic Sciences Symposium of the Transplant Society.** Noordwijkerhout, The Netherlands.

9. Woodle, E., **D. Smith,** J. Bluestone, D. Green, E. Skowronski. 1996. Class I MHC mediates programmed cell death in a Fas-independent manner. **14th Annual Meeting of the American Society of Transplant Physicians.** Dallas, Texas.

NRC FORM 577
(1-95)

U.S. NUCLEAR REGULATORY COMMISSION

LICENSE FEE REQUIREMENTS

LICENSE FEE AND DEBT COLLECTION BRANCH
DIVISION OF ACCOUNTING AND FINANCE
OFFICE OF THE CONTROLLER
U.S. NUCLEAR REGULATORY COMMISSION
WASHINGTON, DC 20555-0001

AASTROM BIOSCIENCES, INC.
ATTN: DR. DOUGLAS M. SMITH
RESEARCH SCIENTIST
24 FRANK LLOYD WRIGHT DRIVE
BOX 376
ANN ARBOR, MICHIGAN 48106

TYPE OF ACTION

- ☐ NEW LICENSE
- ☐ RENEWAL OF LICENSE
- ☒ AMENDMENT TO LICENSE

REQUESTED DATE: 9-26-96

LICENSE NUMBER: 21-26519-01

CONTROL NUMBER: 301897

I. APPLICATION FEE DUE

Your request for a licensing action is subject to the fee(s) in the category(ies) noted below in accordance with Section 170.31 of the enclosed Federal Register notice. Payment of the fee is required prior to the issuance of the license, renewal, or amendment.

FEE CATEGORY	APPLICATION	RENEWAL	AMENDMENT
3M	$	$	$ 610.00
	$	$	$
	$	$	$
	$	$	$
	$	$	$
	$	$	$
	$	$	$
	$	$	$
	$	$	$
	$	$	$

FEE(s) DUE	$ 610.00
PAYMENT RECEIVED	$ 590.00
AMOUNT DUE	$ 20.00

☐ Your request was received without the prescribed application fee.

☒ We received your Check No. 11153 in the amount of $ 590.00. Payment of the additional fee noted above is required.

☐ Your request will increase the scope of your license program. Therefore, your request is subject to the application fee(s) noted above. Refer to Section 170.31 and Footnote 1(d)(2).

☐ Your license expired prior to the receipt of your application for renewal. Therefore, your request is subject to the application fee(s) noted above. Refer to Section 170.31 and Footnote 1(a).

MAKE PAYMENT OF THE FEE(S) TO THE U.S. NUCLEAR REGULATORY COMMISSION AND MAIL THE PAYMENT TO THE ADDRESS LISTED AT THE TOP OF THIS FORM. IF WE DO NOT RECEIVE A REPLY FROM YOU WITHIN 30 CALENDAR DAYS FROM THE DATE LISTED BELOW, WE SHALL ASSUME THAT YOU DO NOT WISH TO PURSUE YOUR APPLICATION AND WILL VOID THIS ACTION.

II. FEE NOT REQUIRED

☐ Enclosed is Check No. _____ which accompanied your request. The fee is not required because:

☐ We received your Check No. _____ in payment of the fee.

☐ The Licensing staff has informed us that your request is to be considered as a continuation of your request dated _____, Control No. _____.

☐ Your request was combined, prior to review, with your _____ request, Control No. _____.

III. CHECK RETURNED

☐ Enclosed is Check No. _____ which was returned to us by the bank for:

- ☐ INSUFFICIENT FUNDS
- ☐ ACCOUNT CLOSED
- ☐ OTHER

MAIL THE REPLACEMENT CHECK TO THE ADDRESS LISTED AT THE TOP OF THIS FORM AND REFERENCE THE ABOVE CONTROL NUMBER.

IV. LICENSE ISSUED WITHOUT THE REQUIRED FEE

☐ License No. _____, Amendment No. _____, issued on _____ was issued without the required fee being collected. The fee required is noted in Section I of this form.

☐ The scope of your licensed program was increased. Therefore, your request is subject to the application fee(s) noted in Section 1 of this form. Refer to Section 170.31 and Footnote 1(d)(2).

☐ Because of the urgency of your request, the license was issued without remittance of the prescribed fee noted in Section 1 of this form.

SIGNATURE – LICENSE FEE ANALYST	LFDCB	LFDCB
Shirley Crutchfield	SC	
SHIRLEY CRUTCHFIELD	10/7/96	

Distribution: OC/DAF/LFF
Pending Fee File OC/DAF/SF(LF-3.2.7)
LFARB R/F (2) Region 3

DATE: Oct. 9, 1996

NRC FORM 577 (1-95)

This form was electronically produced by Elite Federal Forms, Inc.

NOV 2 1 1996

Douglas M. Smith, Ph.D.
Radiation Safety Officer
Aastrom Biosciences
P.O. Box 376
Ann Arbor, MI 48106

Dear Dr. Smith:

Enclosed is Amendment No. 01 to your NRC Material License No. 21-26519-01 in accordance with your request.

Please review the enclosed document carefully and be sure that you understand all conditions. If there are any errors or questions, please notify the U.S. Nuclear Regulatory Commission, Region III office at (630) 829-9887 so that we can provide appropriate corrections and answers.

Please note we have extended the expiration date of the license for five years in accordance with the regulations (10 CFR 30.36).

Also note, we have removed the license condition requiring decommissioning records because this requirement is in the regulations.

Please be advised that your license expires at the end of the day, in the month, and year stated in the license. Unless your license has been terminated, you must conduct your program involving byproduct materials in accordance with the conditions of your NRC license, representations made in your license application, and NRC regulations. In particular, note that you must:

1. Operate in accordance with NRC regulations 10 CFR Part 19, "Notices, Instructions and Reports to Workers; Inspections," 10 CFR Part 20, "Standards for Protection Against Radiation," and other applicable regulations.

2. Notify NRC, in writing, within 30 days:

   a. When the Radiation Safety Officer permanently discontinues performance of duties under the license or has a name change; or

   b. When the licensee's mailing address changes (no fee is required if the location of byproduct material remains the same).

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3. In accordance with 10 CFR 30.36(b) and/or license condition, notify NRC, promptly, in writing, and request termination of the license when you decide to terminate all activities involving materials authorized under the license.

4. Request and obtain a license amendment before you:

   a. Change Radiation Safety Officers;

   b. Order byproduct material in excess of the amount, or radionuclide, or form different than authorized on the license;

   c. Add or change the areas of use or address or addresses of use identified in the license application or on the license; or

   d. Change ownership of your organization.

5. Submit a complete renewal application with proper fee or termination request at least 30 days before the expiration date of your license. You will receive a reminder notice approximately 90 days before the expiration date. Possession of byproduct material after your license expires is a violation of NRC regulations. A license will not normally be renewed, except on a case-by-case basis, in instances where licensed material has never been possessed or used.

In addition, please note that NRC Form 313 requires the applicant, by his/her signature, to verify that the applicant understands that all statements contained in the application are true and correct to the best of the applicant's knowledge. The signatory for the application should be the licensee or certifying official rather than a consultant.

You will be periodically inspected by NRC. Failure to conduct your program in accordance with NRC regulations, license conditions, and representations made in your license application and supplemental correspondence with NRC will result in enforcement action against you. This could include issuance of a notice of violation, or imposition of a civil penalty, or an order suspending, modifying or revoking your license as specified in the General Policy and Procedures for NRC Enforcement Actions. Since serious consequences to employees and the public can result from failure to comply with NRC requirements,

prompt and vigorous enforcement action will be taken when dealing with licensees who do not achieve the necessary meticulous attention to detail and the high standard of compliance which NRC expects of its licensees.

Sincerely,

Original Signed By
W. P. Reichhold
Nuclear Materials Licensing Branch

License No.: 21- 3519-01
Docket No.: 030-33266

Enclosure: Amendment No. 01

DOCUMENT NAME: M:\03033266.CL6

To receive a copy of this document, indicate in the box: "C" = Copy without attachment/enclosure "E" = Copy with attachment/enclosure "N" = No copy

OFFICE	DNMS/RIII									
NAME	WREICHHOLD:jaw									
DATE	11/18/96									

OFFICIAL RECORD COPY

Douglas M. Smith, Ph.D.
AASTROM Biosciences Inc.
24 Frank Lloyd Wright Drive
Ann Arbor, Michigan 48106
Telephone: 313-930-5789
FAX: 313-665-0485
E-mail: dsmith@aastrom.com

November 10, 1996

Mr. William Reichhold
U.S. Nuclear Regulatory Commission
Region III
801 Warrenville Rd.
Lisle, IL 60532-4951
Phone: 630-829-9839
FAX: 630-515-1259

Dear Mr. Reichhold,

I am writing to provide the additional information required for amendment of NRC Material License Number 21-26519-01 as requested in your Fax message dated October 10, 1996 (mail control **301897**).

1. We would like an Assistant RSO to support the RSO in ensuring the competency of all radioisotope users including compliance with rules for safe use of radioactive materials. Timothy Jensen, the Assistant RSO, currently spends 90% of his time working in the lab where direct observation of radioisotope users is possible. The Assistant RSO also is needed to assume duties during times when the RSO is away from the Company, when traveling on business or during vacation. Therefore, it is important that a second person in addition to the RSO is familiar with the safe use and monitoring of radioisotopes at Aastrom Biosciences.

   The following duties will be assigned to the Assistant RSO:

   - Assist RSO in surveillance of use of radioisotopes including routine laboratory surveys.
   - Assist RSO in determining compliance with rules and regulations of license conditions.
   - Assist RSO in monitoring use, storage and disposal of radioactive materials including record keeping and tracking of radioisotopes from time of receipt to waste disposal.
   - Assure proper maintenance and operation of cell harvesting equipment including monitoring of radioactive and non-radioactive waste effluents.
   - Assist in maintenance of radiation detecting equipment.
   - Assist in receiving and opening shipments of radioactive materials arriving at Aastrom, and packaging and shipping of materials leaving the facility.

2. Dr. Douglas Smith and Timothy Jensen should be authorized to use 3-hydrogen (tritium), 51-chromium, phosphorus-32 and sulfur-35.

3. The radiation safety training and experience with radionuclides for Dr. Douglas Smith and Timothy Jensen have included:

   A. The principles and practices of radiation protection: discussions included use of proper shielding, protective clothing, use of film badges, time of exposure, distance from the source, proper working conditions including prevention of contamination and spills, contamination detection and control, emergency procedures, reporting of spills or accidents.

   B. Radioactivity measurements, standardization and monitoring techniques and instruments. Training included: atomic structure and types of radiation, units of measure, principles of liquid scintillation counting, cpm/dpm, use of beta and gamma counters, use of Geiger counter, survey of lab work areas for contamination, test swipes.

   C. Mathematics and calculations basic to the use and measurement of radioactivity: Radioactive decay, decay constant, half life.

   D. Biological effects of radiation: Genetic effects/risks, damage to tissues, DNA damage, carcinogenesis, induction of cell death.

   E. Description of radioisotopes used:
   Dr. Douglas Smith has used Hydrogen-3 for cell proliferation and cytotoxicity studies (18 years experience, McGill University, Yale University and The University of Chicago), Chromium-51 for standard cytolytic T-cell assays (Cr-51 release) (15 years experience, The University of Chicago), Indium-111 for cell labeling and biodistribution studies *in vivo*, (5 years experience, The University of Chicago), Iodine-125 for protein labeling/immunoprecipitation (2 years experience, The University of Chicago), Lead-212 for cell labeling and biodistribution studies in mice (5 years experience, The University of Chicago) and Bismuth-212 for preparation of radiolabeled monoclonal antibody immunoconjugates (5 years experience, The University of Chicago). All radioisotopes were handled in quantities of 5-10 mCi; Pb-212 or Bi-212 were eluted from Radium-224 generators at the University of Chicago.

   Mr. Jensen has used Hydrogen-3 for protein labeling studies (1 year experience), Carbon-14 for CAT assays/molecular biology (2 years experience), Phosphorus-32 for nucleotide labeling/molecular biology (7 years experience), Sulfur-35 for nucleotide labeling/molecular biology and protein labeling studies (7 years experience) and Iodine-125 labeled-protein A for Western blot analysis or I-125 labeled monoclonal antibody for immunoprecipitation studies (7 years experience). The quantities of radioisotopes handled were less than 1 mCi except for P-32 which was handled in quantities of 5 mCi. Mr. Jensen has received basic radiation safety training with annual re-training by a certified RSO and training through experienced laboratory personnel at Bowling Green State University and The University of Michigan.

4. Gamma emitting radionuclides (Cr-51) will be shielded in a cave built with lead bricks (2" x 4" x 8") and/or behind sheet lead which is available in 1/4" thickness (2-3 layers of sheet lead will be used).

Please contact me if you require additional information.

Sincerely,

Douglas M. Smith, Ph.D.
Research Scientist

UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
801 WARRENVILLE ROAD
LISLE, ILLINOIS 60532-4351

October 8, 1996

Douglas M. Smith, Ph.D.
Radiation Safety Officer
Aastrom Biosciences Incorporated
P. O. Box 376
24 Frank Lloyd Wright Drive
Ann Arbor, MI 48106

SUBJECT: ACKNOWLEDGEMENT OF CORRESPONDENCE
(Letter & Application Dated 09/27/96 & 09/26/96)

Dear Licensee:

In response to your request, we have completed the initial processing, which is an administrative review of your application for a(n):

___ New License X Amendment ___ Renewal
___ Termination ___ Auth User (Amendment not required)
___ Other_____

No administrative deficiencies were identified during this initial review. However, it should be noted that a technical review may identify omissions in the submitted information.

It appears that your request is nonroutine and has been assigned to Bill Reichhold for an expedited review. If you should have any questions please contact Mr. Reichhold at (630) 829-9887.

1. New and amendment actions are normally processed within 90 days, unless we find major deficiencies, or policy issues requiring central program office assistance.

2. Renewal actions are normally processed within 180 days, however, under timely filing (before expiration), you may continue to operate under your existing license.

3. Termination actions are normally processed within 90 days, unless confirmatory surveys following decontamination/decommissioning activities are involved.

A copy of your correspondence has been forwarded to our Licensing Fee and Debt Collection Branch (301/415-6097) for approval of the fee category and amount, if required.

If you have a compelling safety or business-related reason for requesting expedited review, please contact the Materials Licensing Branch at (630) 829-9887. We will try to complete your request as soon as practicable. Any correspondence about this request should reference the control number.

Nuclear Materials Support Branch

Mail Control No. 301897
License No. 21-26519-01