

**LLOYD M. STOOLMAN, M.D.**  
**ASSOCIATE PROFESSOR OF PATHOLOGY**  
**DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT**  
**1 JULY 1999 - 30 JUNE 2000**

**I. CLINICAL ACTIVITIES:**

- A. **Flow Cytometry Diagnostic Service** - interpretation of cell surface marker studies in the evaluation of hematologic disorders, primary and secondary immune deficiencies and autoimmune processes.
- B. **Autopsy Service**

**II. TEACHING ACTIVITIES:**

- A. **Research supervisor for undergraduate, post-doctoral and research-track investigators:**
  - 1. **Nobuhiro Takeshita, M.D., post-doctoral fellow (April 1998-present):** Dr. Takeshita is jointly supported by the L.M. Stoolman (Pathology) and A.E. Chang laboratories (Surgical Oncology) for work on T-cell trafficking during adoptive cellular immunotherapy for metastatic cancer. His research indicates that T-lymphoblasts grown from tumor-draining lymph node cells expressing binding site for the adhesion receptor P-selectin (so-called Plig<sup>high</sup> cells) are 10-100 fold more potent than cells derived from unfractionated populations. Both the CD8, CD4 and NK-T cells contribute to the anti-tumor activities. As few as  $1 \times 10^6$  cultured Plig<sup>high</sup> cells completely suppress pulmonary metastases generated by infusion of  $3 \times 10^5$  murine sarcoma cells. Their potency is further increased by pretreatment with proinflammatory cytokines that increase the recruitment of the adoptively transferred cells into tumor-bearing organs. The potency of the cultured Plig<sup>high</sup> cells exceeds that reported for all previous forms of adoptive immunotherapy in the murine sarcoma model. Current efforts focus on defining the effector cell populations and activities that mediated the increased anti-tumor activities of the Plig<sup>high</sup> population. In addition, pre-clinical studies in humans have begun (a focus of new P01 and R01 submissions).
  - 2. **Randall Knibbs, Ph.D., Research Scientist (January, 1994-present)** - Dr. Knibbs continued development of a microcarrier-based, high capacity transient transfection system. In addition, he developed a rapid purification system for the selectin-chimeras used in the adoptive immunotherapy project and purified several milligrams of these vital reagents for Dr. Takeshita's project. Dr. Knibbs assisted the PI in development of an SBIR project that will develop and test novel selectin inhibitors in several models of immunologically mediated disease in rodents. The project (coordinated by

Jon Nagy, PhD at Ligocyte and Lloyd Stoolman, MD at the University of Michigan) was recently funded by the NIAID.

3. **Summer Research Opportunity Program Summer 1999, mentor:** Mentored Ms. Genese Reynolds (sophomore undergraduate), a pre-medical honors student interested in a career in pediatrics.
  4. **Undergraduate research assistants:** Hosted three undergraduate students in the laboratory during the academic year. These students actively participate in one of several ongoing research projects in the laboratory.
  5. **Graduate research assistants:** Hosted one Masters of Public Health student in the research laboratory.
- B. **Computerworld-Smithsonian Award Finalist for development of Internet-based courseware entitled: The Virtual Microscope-Interactive Laboratory Syllabii for Medical and Dental Pathology Courses.** This Award Program is jointly sponsored by the Smithsonian Institution and Computerworld Magazine. It solicits Case Studies from companies and individuals that illustrate the benefits of information technology to society as a whole. Thousands of Case Studies are submitted each year for consideration. In 1999, ~400 Case Studies were selected for inclusion in the American History Museum's Information Age Exhibit and added to the Smithsonian's Permanent Research Collection. **The Virtual Microscope** was selected as one of five finalists for the Computerworld-Smithsonian Award from the 75 Laureates in the Education and Academia Category. Judging criteria included the application's "benefit to society, difficulty, originality and the primacy of information technology in the definition or resolution of the task addressed". It was one of 15 Laureates in the category from the University of Michigan and the first from any unit of the institution to be selected as a Finalist in the Program.
- C. **Director, General Pathology Laboratory Course for Dental Students (Pathology 631) and co-director, General Pathology Lecture Course (Pathology 630):** The third generation Virtual Microscope Pathology Laboratory Interactive Syllabus was deployed for the course (<http://141.214.6.12/cyberscope631/>). The site incorporates high resolution (1900 X 1300 pixel) photographs of gross and microscopic specimens into an on-line version of the laboratory syllabus. An NT-Server in the Pathology Department houses the Livepicture Image Server dedicated to this project. The Livepicture Server software allows the user to pan across a low-power image and then magnify selected regions. Focus is maintained to the limits of photographic resolution. This "active" learning modality allows students to interact with specimens and slides much as they will in the laboratory. Consequently, it provides a unique approach to preview and review of laboratory material.
- D. **Co-director and lecturer, Hematology Sequence in Component II (Medical School 2<sup>nd</sup> year curriculum)-** Administered pathology component of sequence and co-directed course with Alvin Schmier, M.D. (Department of Internal Medicine and Pathology). The third generation of

The Virtual Microscope-Hematopathology Interactive Syllabus was deployed for the course (<http://141.214.6.12/virtualheme99>). This site utilizes the image server and the general approach outlined above for the Dental Pathology Laboratory Website. New this year were two CD-based PowerPoint exercises. In addition, an image server capable of delivering completely digitized "Webslides" was developed so that alpha testing could begin in the Fall of 2000.

- E. **M1 Host Defense Sequence:** Lectured and developed CD-based courseware for lecture syllabus and case presentations.
- F. **Advanced Topics in Immunology:** Lecturer.
- G. **Pathology 581:** Co-director and lecturer.

### III. RESEARCH ACTIVITIES:

#### ACTIVE SUPPORT (70% funded effort):

- A. **Principal Investigator- T Cell Trafficking in Adoptive Cellular Immunotherapy;** NIH, R01CA73059, 30% effort, \$180,000 (annual, direct); Apr 1998-Mar 2001.
- B. **Co-investigator and coordinator for Pathology Department section- "Rational Design of Adhesion Blocking Anti-Inflammatories"** (Jon O. Nagy, PI, Ligocyte Pharmaceuticals, Inc.); NIH, SBIR R43AI/GM43789, \$988,598 (annual, direct), 10% effort, Dec 99-Nov. **NEW**
- C. **Principal Investigator, project 3- "Structure of selectin-ligands synthesized by human T-lymphoblasts"**, NIH, P01AI33189 (Oligosaccharides as Anti-inflammatory Agents; PA Ward, Program Director), 15% effort, \$90,000 (annual, direct for the sub-project); Sept 1996-Aug 2000.
- D. **Co-investigator (with B. Richardson, Rheumatology Division, University of Michigan)- "Gender specific T-cell homing and autoimmunity"**; NIH, R01AI42753, 15% effort, \$187,000 (annual, direct); Apr 1998-Mar 2003 (**NEW**).
- E. **Co-investigator (with A. E. Chang, Surgical Oncology Division, University of Michigan)-"T-cell Activation for Cancer Immunotherapy"**; NIH R01CA82529, \$211,282 (annual, direct); 5% effort, Jul 1999-June 2004 (**NEW**).
- F. **Co-investigator (with G. Kansas, Department of Microbiology/Immunology, Northwestern University)- "Leukocyte Recognition of P-selectin"**, American Cancer Society, \$120,000 (annual, direct), 5% effort, Jul 1999-June 2001.

### IV. ADMINISTRATIVE ACTIVITIES:

- A. **Director of Research Flow Cytometry Laboratory and Co-Director of Clinical Flow Cytometry Laboratory-** managed the development of new software to interface clinical flow cytometry instruments with the Laboratory Information System

(Cerner Milleneum). Participated in the consolidation of Clinical Flow Cytometry and Hematology Laboratories. Managed the operation of the research flow cytometry instruments (provided access for departmental investigators with grant support for flow cytometry).

- B. **Co-Director, Hematology Sequence in Component II and General Pathology 580/630/631-** see educational activities.
- C. **Member, Learning Resources Center Oversight Committee**
- D. **Member, Medical School InfoTech Committee**
- E. **Member, Medical School and MD/PhD Admissions Committees**
- F. **Member, Pathology/Immunology Graduate Program Admissions Committee**
- G. **Participant, Retreat on Medical School Sequence II Content**
- H. **Member, Pathology Website Committee**

V. **OTHER RELEVANT ACTIVITIES:**

**EDITORIAL ACTIVITIES:**

- A. Journal of Clinical Investigation.
- B. Journal of Biological Chemistry.
- C. Journal of Laboratory Investigation.
- D. Nature.
- E. Cell.
- F. Journal of Experimental Medicine.
- G. American Journal of Pathology.
- H. Journal of Immunology (Associate Editor).

VI. **PUBLICATIONS:**

**ARTICLES IN PEER REVIEWED PUBLICATIONS:**

1. Tanigawa, K., Craig, R.A., **Stoolman, L.M.**, Chang A.E. Effects of TNF- $\alpha$  on the in vitro maturation of tumor-reactive effector T-cells. 2000. J. Immunotherapy. Curtis JL, Wolber FM, Sonstein J, Craig
2. RA, Polak T, Knibbs RN, Todt J, Seitzman GD, **Stoolman LM**. Lymphocyte-endothelial cell adhesive interactions in lung immunity: lessons from the murine response to particulate antigen. 2000. Immunopharmacology (in press).
3. K. Tanigawa, K. Phillips, N. Takeshita, R.A. Craig, R.N. Knibbs, A.E. Chang and **L.M. Stoolman**. Tumor-specific responses in lymph nodes draining murine sarcomas are concentrated in cells expressing P-selectin binding sites (submitted).
4. **L.M. Stoolman**, R.A. Craig, M.J. Cameron, A.E. Chang. Ex-vivo expansion of human T-lymphocytes for adoptive immunotherapy: optimal growth conditions for expression of selectin ligands and attachment to vascular endothelium under shear (submitted).

**ABSTRACTS, BOOK REVIEWS, LETTERS TO THE EDITOR, MISCELLANEOUS UNREFEREED PUBLICATIONS:**

1. K. Tanigawa, K. Phillips, R.A. Craig, R.N. Knibbs, A.E. Chang, **L.M. Stoolman**. Tumor-specific responses in lymph nodes draining murine sarcomas are concentrated in cells expressing P-selectin binding sites. 2000. Poster/Discussion session. AACR Annual Meeting, San Francisco, CA.
2. **LM Stoolman**, Michael Lougee, Douglas Gibbs and Tom Peterson. 1999. The Virtual Microscope- Interactive web-based syllabus for medical student (M2) Hematopathology laboratory. URL= <http://141.214.6.12/virtualheme99/>. The site incorporates high resolution (1900 X 1300 pixel) photomicrographs of blood smears, bone-marrow aspirates and lymph node sections in an interactive laboratory syllabus. Unique software allows user to pan across low-power images then magnify regions of interest. Questions (and answers) covering the pathophysiology, diagnosis and treatment of the hematologic malignancies are incorporated into the exercises. This "active" learning experience captures the essentials of the in-class laboratory exercises providing students with a flexible tool for preview and review. **1999 Computerworld-Smithsonian Award Finalist.**
3. **LM Stoolman**, Michael Lougee, Douglas Gibbs, Tom Peterson and Gerald Abrams. 1999. The Virtual Microscope- Interactive web-based syllabus for General and Organ systems pathology for dental students (D2). URL= <http://141.214.6.12/cyberscope631/> This sites incorporates several hundred, high resolution (1900 X 1300 pixel) photographs of gross and microscopic specimens into an interactive laboratory syllabus. The features are as described above. **1999 Computerworld-Smithsonian Award Finalist.**
4. **LM Stoolman**. 1999. Hematopathology Unknown Exercises. Interactive, CD-based excercises for medical student (M2) Hematopathology laboratory. CD-based publication used in M2-Heme sequence.
5. **LM Stoolman**. 1999 & 2000. Leukocyte Pathophysiology and Leukocyte Trafficking. Interactive, CD-based syllabus and exercises including video clips and animations. CD-based publication used in Pathology 581 (Graduate Course) and Host Defense Sequence (M1 sequence).