

**THE UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL**

Department of Pathology

ANNUAL REPORT



1 July 2001 - 30 June 2002

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MEDICAL SCHOOL

Department of Pathology

ANNUAL REPORT



1 JULY 2001 - 30 JUNE 2002

LIST OF FACULTY

LIST OF FACULTY

<u>Name</u>	<u>Rank</u>	<u>Institutional Affiliation</u>
Abell, Murray R	Professor Emeritus	The University of Michigan
Abrams, Gerald D.	Professor	The University of Michigan
Annesley, Thomas M.	Professor	The University of Michigan
Appelman, Henry, D.	M.R. Abell Professor	The University of Michigan
Baker, James R.	Associate Professor	The University of Michigan
Barr Jr., Mason	Professor ⁺	The University of Michigan
Blaivas, Mila	Clinical Associate Professor	The University of Michigan
Capps, Rodney D.	Assistant Professor	The University of Michigan
Chamberlain, Priscilla	Clinical Instructor II	Veterans Affairs Medical Center
Chensue, Stephen W.	Associate Professor	Veterans Affairs Medical Center
Cho, Kathleen R.	Associate Professor*	The University of Michigan
Cooling, Laura	Clinical Assistant Professor	The University of Michigan
D'Amato, Constance J.	Assistant Professor Emeritus	The University of Michigan
Davenport, Robertson	Associate Professor	The University of Michigan
de la Iglesia, Felix	Adjunct Research Scientist***	Pfizer
Dressler, Gregory R.	Associate Professor	The University of Michigan
Duckett, Colin	Assistant Professor	The University of Michigan
Elner, Victor M.	Associate Professor ⁺⁺	The University of Michigan
England, Barry G.	Associate Professor	The University of Michigan
Fantone, Joseph C.	Godfrey D. Stobbe Professor in Pathology Education and Director, Anatomic Pathology	The University of Michigan
Fearon, Eric R.	Professor*	The University of Michigan
Finn, William	Clinical Associate Professor	The University of Michigan
Flint, Andrew	Professor	The University of Michigan
Friedman, Bruce A.	Professor	The University of Michigan
Fullen, Douglas R.	Clinical Assistant Professor	The University of Michigan
Giacherio, Donald	Assistant Professor	The University of Michigan
Gikas, Paul W.	Professor Emeritus	The University of Michigan
Giordano, Thomas J.	Clinical Associate Professor	The University of Michigan
Gordon, David	Adjunct Associate Professor	The University of Michigan
Greenson, Joel	Associate Professor and Director, Surgical Pathology	The University of Michigan
Headington, John T.	Professor Emeritus	The University of Michigan
Heidelberger, Kathleen P.	Professor Emeritus	The University of Michigan

<u>Name</u>	<u>Rank</u>	<u>Institutional Affiliation</u>
Hogaboam, Cory	Assistant Research Scientist	The University of Michigan
Inohara, Naohiro	Assistant Research Scientist	The University of Michigan
Johnson, Kent J.	Professor	The University of Michigan
Judd, W. John	Professor	The University of Michigan
Kaldjian, Eric	Adjunct Assistant Professor	Pfizer
Keller, Evan	Assistant Professor##	The University of Michigan
Keren, David F.	Clinical Professor	Warde Medical Laboratories
Killeen, Anthony A.	Clinical Associate Professor and Associate Director, Clinical Pathology	The University of Michigan
Killen, Paul D.	Associate Professor	The University of Michigan
Kleer, Celina	Assistant Professor	The University of Michigan
Kunkel, Steven L.	Endowed Professor of Pathology Research and Co-Director, Division of General Pathology	The University of Michigan
Lieberman, Andrew P.	Assistant Professor	The University of Michigan
Lieberman, Richard W.	Clinical Assistant Professor+++	The University of Michigan
Lowe, John B.	Professor	The University of Michigan
Lowe, Lori	Clinical Associate Professor	The University of Michigan
Lukacs, Nicholas	Assistant Research Scientist	The University of Michigan
McKeever, Paul E.	Associate Professor	The University of Michigan
Mellerick-Dressler, Dervla	Assistant Professor	The University of Michigan
Michael, Claire W.	Clinical Associate Professor	The University of Michigan
Midgley, A. Rees	Professor	The University of Michigan
Miller, Richard A.	Professor	The University of Michigan
Murphy, Hedwig S.	Assistant Professor	The University of Michigan
Naylor, Bernard	Professor Emeritus	The University of Michigan
Nunez, Gabriel	Professor	The University of Michigan
Oberman, Harold A.	Professor Emeritus	The University of Michigan
Paulino, Augusto F.	Clinical Assistant Professor	The University of Michigan
Phan, Sem H.	Professor	The University of Michigan
Pierson, Carl L.	Assistant Professor	The University of Michigan
Ramsburgh, Stephen R.	Clinical Assistant Professor	The University of Michigan
Rasche, Rodolfo	Clinical Assistant Professor	The University of Michigan
Remick, Daniel G.	Professor	The University of Michigan
Ross, Charles W.	Associate Professor	The University of Michigan
Roulston, Diane	Clinical Assistant Professor	The University of Michigan

<u>Name</u>	<u>Rank</u>	<u>Institutional Affiliation</u>
Rubin, Mark A.	Associate Professor#	The University of Michigan
Ruiz, Robert	Clinical Assistant Professor	The University of Michigan
Schmaier, Alvin	Professor	The University of Michigan
Schmidt, Robert W.	Professor Emeritus	The University of Michigan
Schnitzer, Bertram	Professor	The University of Michigan
Shah, Rajal B.	Clinical Assistant Professor	The University of Michigan
Silverman, Eugene M.	Clinical Associate Professor	The University of Michigan
Stoolman, Lloyd M.	Associate Professor	The University of Michigan
Su, Lyndon	Clinical Assistant Professor	The University of Michigan
Till, Gerd O.	Professor	The University of Michigan
Valdez, Riccardo	Clinical Assistant Professor	The University of Michigan
Varani, James	Professor	The University of Michigan
Vincenz, Claudius	Research Investigator	The University of Michigan
Ward, Peter A.	Godfrey D. Stobbe Professor and Chairman	The University of Michigan
Warren, Jeffrey S.	Warthin/Weller Professor and Director, Clinical Pathology	The University of Michigan
Wilson, Thomas	Assistant Professor	The University of Michigan

* Joint Appointment, Department of Internal Medicine

** Joint Appointment, Dental School

*** Clinical Appointment, Pfizer

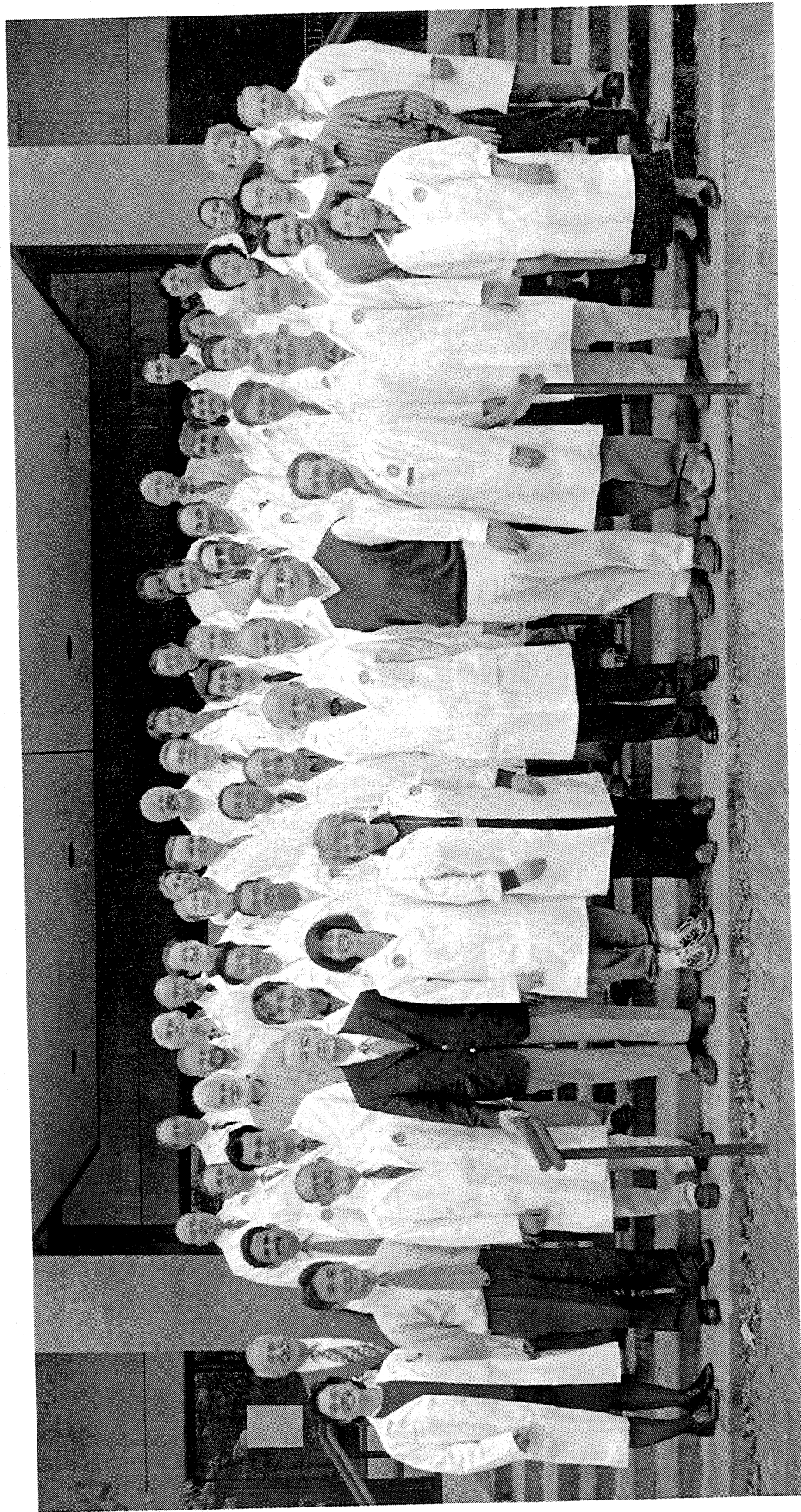
+ Joint Appointment, Department of Pediatrics and Communicable Diseases

++ Joint Appointment, Department of Ophthalmology

+++ Joint Appointment, Department of Obstetrics and Gynecology

Joint Appointment, Department of Urology

Joint Appointment, ULAM and Institute of Gerontology



**Faculty, Residents and Fellows
Department of Pathology
October, 2001**

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DEPARTMENTAL OVERVIEW

DEPARTMENTAL OVERVIEW 2001-2002

Introduction

The Department of Pathology remains in a strong position, academically, clinically and financially. Its teaching programs are very robust, with the more traditional teaching progressively being enhanced by computer-based learning. The diagnostic programs in Anatomic Pathology show a consistent annual increase (of approximately 4% per year) in volume, together with consistent demands for new procedures (such as those for prostate cancer, cutaneous melanoma, cytopathology, etc.). Similar demands exist in the areas of Clinical Pathology (Laboratory Medicine), especially as reflected by demands for new tests in the area of molecular diagnostic pathology. The Department has instituted aggressive new measures to reduce the cost of “send out” laboratory tests. This has resulted in substantial cost savings, as described below. In the area of blood products, we have also contained what otherwise would have been rapidly escalating costs of these products.

In the area of research, the Department’s plans for expansion of existing research are limited to borrowed space from other departments, until the new Basic Science Research Building is completed and occupied (in about another three years). During the past year three of our long-standing and highly productive faculty have retired (Drs. Abrams, Heidelberger and Oberman). Already, two replacement faculty are on site. We are also losing Drs. Alaa Afify, who is joining UC Davis as Director of Cytopathology, Dr. Anthony Killeen who will become Director of Clinical Laboratories at the University of Minnesota, and Dr. Mark Rubin, who is moving to the Brigham and Women’s Hospital in Boston. Active recruitments are underway to replace these faculty members. In Cytopathology, Dr. Barbara McKenna, a former trainee of ours, is already on site. Our relationship with Pfizer continues to mature as both institutions increase their collaborative ties. We are very pleased that, in the past summer (of 2002), we initiated the second medical student endowed scholarship, which has been named in honor of Professor Gerald Abrams (the first one having been named in honor of Professor Paul Gikas). In general, the Department of Pathology is very strong and robust.

Teaching Activities

Faculty members continue to fill leadership roles as course directors, sequence coordinators, and serve as Associate Dean for Medical Education in the Medical School curriculum. Several faculty members continue to be recognized as recipients of outstanding teaching awards and selection as graduation class marshals. Pathology laboratories continue to be a strength within the histology course and second year organ system sequences. Fourth year clerkships in Pathology and Laboratory Medicine are elected by approximately one fifth of the Medical School class each year and receive exceptional evaluations. The Department continues to present a semester-long Dental

Pathology course and a summer semester course to Medical Illustration students. Both courses continue to focus on the specific educational needs of these students and engage them in more inter-active learning activities, including the implementation of Web-based instruction. A significant number of undergraduate students complete honors theses under the direction of Pathology faculty.

The Pathology graduate program was successful in recruiting six new students. This represents an increase from our average of two over the past three years. Department faculty are actively involved in the Medical Scientist Training Program (MD/PhD) and combined graduate student recruitment activities associated with the Program in Biomedical Sciences (PIBS). Two students have completed their dissertation work and were awarded doctoral degrees (one in October 2001 and one in June 2002).

The Pathology residency and fellowship programs continue to prosper. Applications to the programs increased by approximately 25% this past year reversing a four-year national trend of declining student interest in pathology residency training. The program consists of 28 house officers and fellows. Last year all graduates of the house officer program found desirable positions, in both academia and private practice. Residents were selected for fellowships at several academic centers including; University of Michigan, M.D. Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, and Johns Hopkins Hospitals. One resident was awarded a prestigious 2-year Robert Wood Johnson Fellowship in transfusion medicine to be completed at the University of North Carolina.

Clinical Service Activities

The Anatomic and Clinical Pathology Laboratories continue to provide excellent, full-spectrum service as the UMHS has continued to experience clinical growth. 2001-2002 was marked by key faculty recruitments in AP and CP and several new laboratory initiatives. The laboratories continued their trend of increased laboratory volume (approximately 3%) while maintaining a constant number of staff. Efforts to aggressively control operating costs and laboratory utilization were successful as at least \$900,000 in incremental cost was avoided and the Laboratories completed FY 02 within budget. This success was achieved through improved operating efficiency the application of new technology, aggressive laboratory and send-out test utilization control, and an aggressive strategy to procure blood products at "best-in-region" prices. Augmentation of the capabilities of the Clinical Chemistry, Hematology, Molecular Diagnostics, and Cytogenetics Laboratories was particularly contributory to this process. In 2001-2002 the Laboratories performed more than 3.2 million laboratory analyses (billable units) and more than 55,000 surgical pathology cases. The maintenance of high quality service, in the face of increasing complexity of demands, is a testimony to the professionalism of the staff as well as the management capabilities of laboratory directors and senior laboratory personnel. Finally, as alluded to above, the Laboratories have continued to respond to the institutional initiative to expand clinical service. This activity has been coupled with expansion of on-site point-of-care testing and data handling activities. The Laboratories continue to support the successful M-Labs outreach program. The Laboratories successfully completed the tri-annual JCAHO inspection in October, 2001 and the bi-

annual College of American Pathologists (CAP) self inspection in May, 2002. Maintenance of the delicate balance among quality service, cost-effective testing, utilization control and research and development, which characterizes an academic institution, will be a continuing challenge.

Research Activities

The research activities in the Department of Pathology continue to be one of the many strengths of our academic mission. The Department's faculty successfully compete for extramural research support, attract outstanding graduate students and fellows from both the national and international scene, publish in highly visible, peer-reviewed scientific journals, and serve on numerous national and international scientific committees. During the past year, the expenditures of active grants and contracts credited to the Pathology Department's research efforts increased by approximately 2 million dollars when compared to the previous year's expenditures. The total research expenditures for 2001-2002 were over \$14 million; this included approximately \$9.9 million in direct expenditures and \$4.2 million in indirect expenditures. Faculty members in the Department of Pathology hold 88 individual grants from the National Institutes of Health (an increase of 16 funded applications over 00-01), 2 program projects, 2 MERIT Awards, and 2 training grants. In addition, other support originates from a variety of external non-federal sources including, the American Heart Association, the Pew Charitable Trusts, American Lung Association, the MEDC Life Science Corridor Fund, and contract grants from nearly a dozen pharmaceutical companies. This latter funding source includes a substantial investment from Pfizer for the support of the Genomic Pathology Laboratory and related activities.

Many of the Departmental faculty actively participate in the support of institutional initiatives, including the University of Michigan Cancer Center, Urology SPOR Program, Breast Cancer Program, Interstitial Lung Disease SCOR, and the acute lung injury SCOR. This blend of activity underscores the role of Pathology faculty in translational research, especially where DNA-based microarrays and tissue arrays are involved. These studies have resulted in publications dealing with solid tumors and inflammatory diseases. The faculty actively publish in both the clinical and experimental arena and cover very diverse scientific interests, including clinical pathology, anatomical pathology, and basic cellular and molecular mechanisms of disease. Our faculty participate in peer review of NIH grant applications and peer-review of submitted scientific articles for diverse journals.

Another index of the healthy academic research environment in the Pathology Department is the large number of post-doctoral fellows in the different laboratories, as over 40 post-doctoral fellows from many different countries are engaged in research activities and clinical fellowship. These post-doctoral scholars have actively sought positions in the Department of Pathology to enhance their research and clinical careers. Our faculty continue to provide expertise for both internal and external program review, which include serving as ad hoc and permanent members of NIH study sections, serving as committee members for site visit teams, providing expertise on government sponsored

special emphasis panels, and organizing or chairing clinical and experimental scientific conferences.

Respectfully submitted,

Peter A. Ward, M.D.
Professor and Chairman

Steven L. Kunkel, Ph.D.
Co-director, Division of General Pathology

Joseph C. Fantone, M.D.
Director, Division of Anatomic Pathology

Jeffrey S. Warren, M.D.
Director, Division of Clinical Pathology

INDIVIDUAL FACULTY REPORTS

**GERALD D. ABRAMS, M.D.
PROFESSOR OF PATHOLOGY**

**DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Surgical Pathology Services - 4 months.
- B. Necropsy Service - on call for consultation.
- C. Pathologist, Cardiac Transplant Team. Transplant biopsies - 9 months.
- D. Consultant for Gastrointestinal Pathology.
- E. Consultant for Cardiovascular Pathology.

II. TEACHING ACTIVITIES:

- A. Freshman Medical Class:
 - 1. Pathology 500, Course Director, Lecturer, "Basic Concepts of Disease" - 20 lecture hours.
 - 2. Multidisciplinary Conferences - 4 contact hours.
 - 3. Pathology 500, Histopathology Sequence, Sequence Director, Lecturer, Lab Instructor-32 contact hours (8 lectures, 24 lab hours).
- B. Sophomore Medical Class:
 - 1. Pathology Lab Instructor-all sequences. 50 contact hours.
- C. Clinical Radiology-Pathology correlation Elective Course-2 lecture hours.
- D. Dental School:
 - 1. Sophomore Dental Class (Path 580) - 2 lecture hours
- E. Undergraduate LS&A/Graduate:
 - 1. Biology 224 - 1.5 lecture hours.
- F. Hospital Conferences:
 - 1. Cardiovascular Pathology Conference - monthly.
 - 2. Cardiac biopsy review conference-monthly.
 - 3. Cardiac transplant biopsy review – weekly.
- G. House Officers:
 - 1. Training in Surgical and Necropsy Pathology.
- H. Community:
 - 1. Organizer, director, and lecturer of "Mini-Med. School", a six-week course for the public, Spring 2002.
- I. Invited Lectures:
 - 1. Keynote Address-UM Medical School White Coat Ceremony, August, 2001.
- J. Production of Teaching Materials:
 - 1. Production of CD-Rom and syllabus for Histopathology Lab sequence of Pathology 500.
- K. Honors:
 - 1. Elected class marshall, Class of 2002.
 - 2. "TAMS" award, Class of 2002.
 - 3. Fall 2001 Medical Student Award for Teaching Excellence.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Pathologic-Radiologic correlation in aortic disease, with D. Williams.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Member, Pathology House Officer Selection Committee.

MEDICAL SCHOOL/HOSPITAL/UNIVERSITY:

- A. Member, Component I Committee.
- B. Ombudsperson, Medical Faculty.
- C. Member, ad hoc Search Committee for Chair, Department of Medical Education.
- D. Member, Faculty Task Force to review Instructional Track.

REGIONAL AND NATIONAL:

- A. Editorial Board, Modern Pathology.
- B. Reviewer, Microbial Ecology in Health and Disease.

V. PUBLICATIONS:

**THOMAS M. ANNESLEY, PH.D.
PROFESSOR OF CLINICAL CHEMISTRY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Biochemistry Section, Clinical Pathology Laboratories.
- B. Consultant to Veterans Administration Hospital, Ann Arbor, Michigan.
- C. Laboratory Director, Chelsea Family Practice, M-Care Facility.
- D. Laboratory Director, Briarwood Medical Group, M-Care Facility.
- E. Laboratory Director, Briarwood Family Practice Facility.
- F. Laboratory Director, Chelsea Internal Medicine Associates.
- G. Laboratory Director, West Ann Arbor Health Care Facility.
- H. Staff Practitioner, The Toledo Hospital, Toledo, Ohio
- I. Consultant to Consultants in Laboratory Medicine, Toledo, Ohio

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. Course Director, Fundamentals of Laboratory Medicine (PTHCLNL.101) Component IV Medical School Curriculum.
 - 2. Lecturer, Minority Students Clerkship in Pathology.
- B. House Officers:
 - 1. Lecturer, Clinical Pathology Grand Rounds.
 - 2. Lecturer, Clinical Pathology Didactic Lecture Series.
 - 3. Daily Sign-out and Interpretation of Laboratory Results.
 - 4. Clinical Pathology Curriculum Committee.
 - 5. Coordinator, Clinical Pathology Block B.

III. RESEARCH ACTIVITIES:

- A. Visiting Scientists, Pfizer Global Research and Development, Ann Arbor Michigan.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Biochemistry Section, Clinical Pathology Laboratories.
- B. M-Labs Technical Group.
- C. Coordinator, Clinical Pathology Laboratory CME Program.
- D. Clinical Pathology Discretionary Incentive Funds Committee.

REGIONAL AND NATIONAL:

- A. Board of Directors, National Academy of Clinical Biochemistry (NACB).
- B. NACB/AACC Professional Activities Committee.
- C. Chair, NACB Awards Committee.
- D. Program Coordinating Commission, American Association for Clinical Chemistry
- E. House of Delegates, American Association for Clinical Chemistry.
- F. Steering Committee, House of Delegates, American Association for Clinical Chemistry.
- G. Membership Committee, American Association for Clinical Chemistry.
- H. Executive Committee/Journal Management Group, Clinical Chemistry Journal.
- I. Member, Academy of Clinical Laboratory Physicians and Scientists.
- J. Member, National Academy of Clinical Biochemistry.
- K. Member, Association of Clinical Scientists.
- L. Member, American Society for Mass Spectrometry.

V. OTHER RELEVANT ACTIVITIES:

JOURNAL EDITORSHIPS:

- A. Associate Editor, Clinical Chemistry.

EDITORIAL BOARDS:

- A. Clinical Chemistry, Editorial Board.
- B. Therapeutic Drug Monitoring, Editorial Board.
- C. Biomedical Chromatography, Editorial Board.

EDITORIAL REVIEW ACTIVITIES:

- A. Clinical Chemistry, Reviewer.
- B. Biomedical Chromatography, Reviewer.
- C. Therapeutic Drug Monitoring, Reviewer.
- D. Archives of Pathology and Laboratory Medicine, Reviewer.

AWARDS:

- A. National Leadership Award, The National Congressional Committee, 2001.
- B. Awardee, Who's Who in America, 2001.

INVITED LECTURES:

- 1. Glucuronidation of Prodrug Reactive Site: Isolation and Characterization of Oxymethylglucuronide Metabolite of Fosphenytoin, Rackham Graduate School, University of Michigan, September, 2001

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Annesley, T.M.: Medicinal Chemistry. Clin. Chem. 2002;48:684-685.
2. Frank, E.L., Schwarz, E.L., Juenke, J., Annesley, T.M., and Roberts, W.L.: Performance characteristics of four anticonvulsant immunoassays on the Immulite 2000 automated analyzer. Am. J.Clin. Path. 2002;118:124-31.
3. McMillin, G.A., Owen, W.E., Lambert, T.L., De, B.K., Frank, E.L., Bach P., Annesley, T.M., and Roberts, W.L.: Comparable effects of Digibind and DigiFab in thirteen digoxin immunoassays. Clin. Chem. 2002;48:, in press.
4. Annesley, T.M.: Disposition of toxic drugs and chemicals in man. Clin. Chem. 2002;48, in press.

ABSTRACTS:

1. Frank, E.L., Schwartz, E.L., Juenke, J.M., Annesley, T.M., and Roberts, W.L.: Performance characteristics of an automated chemiluminescent phenytoin assay. Clin. Chem. 2001;47:A76.

**HENRY D. APPELMAN, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. General surgical pathology - four and one-half months.
- B. Gastrointestinal and hepatic pathology services - six months.

II. TEACHING ACTIVITIES:

MEDICAL SCHOOL/HOSPITALS:

- A. Medical Students:
 - 1. Pathology 600 - 2 full class lectures and laboratory 2-4 hours per week
 - 2. Pathology 630 (dental) - one full class lectures.
 - 3. Senior Elective in Pathology: mentor, 4 weeks with daily conferences
- B. House Officers:
 - 1. Surgical pathology diagnosing room instruction for assigned house officer - 4 months
 - 2. Gastrointestinal and hepatic pathology tutoring - full time.
 - 3. Lectures in gastrointestinal and liver pathology, 2 hours
 - 4. Consult conferences, 4-5 hours
- C. Interdepartmental:
 - 1. G-I Tumor Conference - (3 hours per month).
 - 2. Liver Biopsy Conference - one hour every other month.
 - 3. Gastrointestinal Biopsy Conference for Gastrointestinal fellows and staff, 7 hours

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Are there specific histologic types of colonic adenomas that are more likely to recur, with Klaus Lewin (UCLA) and members of the National Cancer Institute, Chemoprevention Branch
- B. Clinical trial of difluoromethylornithine in Barrett's esophagus, with Dean Brenner of the U of Mich, Gary Stoner of Ohio State Univ, Stuart Spechler, and Edward Lee of University of Texas-Southwestern, and Anil Rustgi of Pennsylvania.
- C. Lymphocyte colitis, a comprehensive clinical/endoscopic/histologic study, with Rachel Vidal and members of the division of Gastroenterology.

- D. Anaplastic, lymphoma-like carcinoma arising in Barrett's mucosa, with BJ McKenna
- E. Adenomas of the duodenum: are there differences between sporadic and FAP-associated? With Paul Kowalski
- F. Is hyperplasia of the interstitial cells of Cajal a common reaction to intramural masses in the gut? With Neil Bavakaty and Meryem Koker
- G. The apoptotic form of microscopic colitis, with BJ McKenna
- H. The status of the squamous mucosa next to segments of Barrett's esophagus, with WL Lo and Jeffrey Barnett
- I. Are juvenile-like polyps in adults the same as in children? With Meryem Koker
- J. What is the yield of significant microscopic disease in colorectal biopsies of adult patients with chronic diarrhea and normal endoscopic findings? With BJ McKenna.
- K. Is there such a thing as ectopic antral mucosa in the duodenal bulb? With Wei Xin
- L. What is the cause of the autoimmune hepatitis-like recurrent hepatitis C in liver transplant recipients? With Wei Xin, Joel Greenson, and Robert Fontana
- M. What is the rate of neoplastic progression in Barrett's mucosa during surveillance endoscopy and biopsy at the University of Michigan? With John Inadomi
- N. What is the rate of neoplastic progression in ulcerative colitis during surveillance endoscopy and biopsy at the University of Michigan?

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Chairman, Advisory Committee on Appointments, Promotions and Tenure.

MEDICAL SCHOOL/HOSPITAL:

- A. Member, Cancer Work Group, University Hospital.
- B. Co-Coordinator, Gastrointestinal Sequence for 2nd year medical students.

REGIONAL AND NATIONAL:

- A. Member, Scientific Advisory Committee, and Board of Directors, International Organization for Statistical Studies of Diseases of the Esophagus, Paris, France.
- B. Central Pathologist, Polyp Prevention Trial, National Cancer Institute, Washington, DC
- C. Member, Editorial Board, Human Pathology.
- D. Member, Editorial Board, Modern Pathology.
- E. Member, Editorial Board, American Journal of Surgical Pathology.
- F. Ad hoc reviewer for American Journal of Pathology, Cancer, Gastroenterology, and American Journal of Gastroenterology.
- G. Member of the Council, member of the Ad hoc Nominating Committee, member of the Young Investigator's Committee, United States and Canadian Academy of Pathology, Inc
- H. Member, Lung and Esophagus Task Force, American Joint Committee on Cancer, 2001-present

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

1. "A whirlwind tour through esophagogastric inflammations and their complications" and "the role of the pathologist in the diagnosis and management of inflammatory bowel diseases, especially the colitides". Half day course, Pathology Update for Practicing Pathologists: Recent Advances and Selected Topics. American Society of Clinical Pathologists course, Montreal, Que, Canada, July 13, 2001
2. "New stuff in Barrett's mucosa and the gastric cardia"; "GI dysplasias, including Barrett's epithelium and ulcerative colitis"; "Idiopathic inflammatory bowel disease: changes with time and treatment"; "Gastrointestinal stromal tumors"; "Neoplasms of the appendix and anus"; Diagnosis of Gastrointestinal, Liver and Pancreatic Biopsies, California Pacific Medical Center Course, Mauna Kea, Hawaii, October 15-18, 2001
3. "The gastrointestinal biopsy report: What's right, what's wrong and what doesn't matter?" With BJ McKenna, half day course, Annual meeting, American Society of Clinical Pathologists, Philadelphia, PA, Oct 22, 2002;
4. GI biopsy reports I and II, with BJ McKenna, Annual fall meeting, The Arizona Society of Pathologists, Scottsdale, AZ, November 4, 2001
5. "Gastrointestinal stromal tumors: can we distinguish between benign and malignant?" The International Society of Bone and Soft Tissue Pathology, Chicago, IL, February 24, 2002
6. "Neoplastic diseases of the intestines", half day course, Pathology of the Gastrointestinal Tract, American Society of Clinical Pathologists, Montreal, Que, Canada, May 2, 2002

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Hinoi T, Tani M, Lucas PC, Caca C, Dunn RL, Macri E, Loda M, Appelman HD, Cho KR, Fearon ER: Loss of CDX2 expression and microsatellite instability are prominent features of large cell minimally differentiated carcinomas of the colon. Am J Pathol, 159:2239-2248, 2001
2. McKenna BJ, Appelman HD: Dysplasia of the gut: the diagnosis is harder than it seems. J Clin Gastroenterol, 34:111-116, 2002
3. Trupiano JK, Stewart RE, Misick C, Appelman HD, Goldblum JR: Gastric stromal tumors: a clinicopathologic study of 77 cases with correlation of features with non-aggressive and aggressive clinical behaviors. Am J Surg Pathol, 16:705-714, 2002
4. McKenna BJ, Appelman HD: Dysplasia can be a pain in the gut. Accepted for publication in Pathology, for publication December, 2002

CHAPTERS and BOOKS:

1. McKenna BJ, Appelman HD. Barrett's esophagus: morphologic considerations. Chapter 14 in Orringer MB, Heitmiller R, eds.: Shackelford's Surgery Of The Alimentary Tract - Vol 1, The

- Esophagus. W B Saunders, Philadelphia, 2002
2. McKenna BJ, Appelman HD, Neoplasms of the small intestine, in Quigley EE and Marsh MN, eds.: The Small Intestine, Blackwell Scientific, Cambridge, MA, in press

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

1. Kresty LA, Stoner GD, Normolle D, Beer D, Appelman H, et al: Analysis of cyclin D1 and EGFR in Barrett's esophagus patents. Annual meeting, American Association for Cancer Research, New Orleans, 2001

**MILA BLAIVAS, M.D., PH.D.
CLINICAL ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. 22 weeks of Surgical Neuropathology Service.
- B. 55 days of Autopsy Service including weekend autopsy calls.
- C. All muscle and nerve biopsies at the UMHS and referred by other hospitals in- and out-of-state throughout the year, including new anti-dystrophy workup (364 muscle biopsies and 102 nerve biopsies). 30% muscle biopsies with EM, 100% nerve biopsies with EM and 11 with teasing.
- D. Diagnostic EM on skin and other tissues for various rare disorders.
- E. Cutting autopsied brains with Pathology House Officers, microscopic evaluation with the residents for the diagnosis.
- F. Consulting on brain, muscle and nerve pathology, intradepartmental cases, VAH and other hospitals in MI and other states. 105 personal consults.

II. TEACHING ACTIVITIES:

- A. Instructed residents, fellows and staff in Neurology, Rheumatology and Pediatrics and students on muscle, nerve and brain biopsies.
- B. Lectures for medical and dental students; M-2 neuropathology labs.
- C. Taught Pathology Residents how to perform and read-out autopsies.
- D. Lectures on muscle, nerve and brain pathology to residents and fellows in Pathology, Neurology, Neurosurgery and Rheumatology.
- E. Conferences on muscle and nerve cases with Neurology Department.
- F. Neuropathology cases review with Pathology Residents.
- G. Weekly Conferences with Neuromuscular staff.
- H. Conferences and lectures for Neurosurgery Residents and staff.
- I. Pediatric Oncology conferences for brain tumor cases.
- J. Personal tutoring of neurology and pathology residents on Neuropathology – 5 persons.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Histology of animal models of rheumatoid arthritis with Arthritis and Rheumatology with Blake Roessler.
- B. Co-investigator on P.E. McKeever, M.D. grant “Glioma Tissue Markers of Potential Diagnostic and Prognostic Value.”

- C. National study group (ERSET), part of, for evaluation of temporal lobectomy/hippocampectomy cases.
- D. Collaboration with EMG group, neurosurgery, genetics, rheumatology, epilepsy and pulmonary/internal medicine on various projects.
- E. Supervision of histology/immunohistochemistry projects for residents, fellows and researchers in Neurosurgery, Neurology and Neuroscience labs.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Supervision of the muscle histochemistry and muscle and nerve biopsy handling.
- B. Continuing improvement of interdepartmental and interinstitutional coordination of muscle and nerve biopsy service.
- C. Improvements in immunoperoxidase stainings, expansion of anti-dystrophy workup.
- D. Daily monitoring muscle histochemistry group performance.

MEDICAL SCHOOL:

- A. Member of the Admissions Committee.

REGIONAL AND NATIONAL:

- A. Consulting with outside pathologists, neurologists and family practitioners on muscle and nerve biopsies performance and interpretation, brain biopsies.
- B. Member, American Association of Neuropathologists, IAP, CAP, PNS, and AAN.
- C. Attended the World Muscle Association meeting in September 2002.
- D. Ad-hoc reviewer for Archives of Pathology and Laboratory Medicine, Archives of Ophthalmology.

V. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN PEER REVIEWED JOURNALS:

1. Kish PE, Blaivas M, Strawderman M, Muraszko KM, Ross DA: Magnetic resonance imaging of ethyl-nitrosourea-induced rat gliomas: a model for experimental therapeutics of low-grade gliomas. *Journal of Neuro-Oncology*, 2001, 53 (3): 243-257
2. Flaherty KR, Wald J, Zeballos RJ, Blaivas M, Weisman IM, Schork MA, Zisman D, Rubenfire M, Martinez FJ: Unexplained exertional limitation: characterization in a large cohort discovered to have mitochondrial myopathy. *Am. J. of Resp. and Critical Care Medicine*, 2001 164 (3): 425-432
3. Rickman DS, Bobek MP, Misek DE, Kuick R, Blaivas M, Kurnit DM, Taylor J, Hanash SM. Distinctive molecular profiles of high-grade and low-grade gliomas based on oligonucleotide microarray analysis. *Cancer Research*, 2001, 61 (18): 6885-6891

ARTICLES SUBMITTED FOR PUBLICATION:

1. Rocheril SV, Blaivas M: Dego's Disease Mimicking Vasculitis. Submitted to: New England Journal of Medicine.

CHAPTER IN BOOKS

1. McKeever PE, Blaivas M, Gebarski SS: Nonadenomatous Pituitary Tumors. Chapter in: Diagnosis and Management of pituitary Tumors. Ed: Tharpark, Kovacs, Scheithauer B, Lloyd RV. Humana Press, 2001.
2. Martinez FJ, Blaivas M.: Mitochondrial disorders and exertional intolerance: Controversy continues. Chapter in: Progress in Respiratory Research, vol 32, (ed.) Bollinger CT, In Press.

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

1. Junck L, McKeever PE, Strawderman MS, Blaivas M, Tkaczyk A, Cates MA: Proliferation Index is Related to Patient Age in Glioblastoma. Submitted to: Meeting of the Society for Neuro-Oncology, November 2001.
2. Kocheril SV, Blaivas M, Ike R, McCune J: Dego's Disease Presenting as Abdominal Pain Mimicking Vasculitis. Presented at the European Association of Arthritis and Rheumatology Meeting, June 2002.
3. Lagrange H, Blaivas M, Gomez-Hassan D, Malow B. A very Novel Case of New-Onset Narcolepsy, Cataplexy, and Epilepsy in a 40-Year-Old Business Professor. Accepted to the American Epilepsy Society 56th Annual Meeting.

**PRISCILLA CHAMBERLIN, M.D.
CLINICAL INSTRUCTOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Surgical Pathology sign out – 6 months
- B. Director of Cytology with primary sign out responsibilities
 - 50% of Pap Smears
 - 50% of non-gynecological cases

II. TEACHING ACTIVITIES:

- A. Graduate students:
 - 1. Responsible during the current academic year for teaching activities for the following:
 - a. Sophomore pathology lab
 - b. Pathology residents
 - c. Lecture series for ENT residents

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

None.

PENDING:

None.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Medical Director of Microbiology, Immunology, Central Distribution and Chemistry labs at VA Hospital
- B. AP Imaging
- C. Ancillary Committee Chair
- D. Toledo VA Laboratory Director

MEDICAL SCHOOL/HOSPITAL:

- A. Admissions Committee

UNIVERSITY OF MICHIGAN:

None.

REGIONAL AND NATIONAL:

None.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

None.

HONORS AND AWARDS:

None.

PATENTS:

None.

INVITED LECTURES/SEMINARS:

None.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

None.

BOOKS/CHAPTERS IN BOOKS:

None.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

None.

**ARUL M. CHINNNAIYAN, M.D., Ph.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Board-Certified in Clinical Pathology (2002), Diplomate of the American Board of Pathology

II. TEACHING ACTIVITIES:

- A. Mentor, postdoctoral fellows: Chandan Kumar, Arun Sreekumar, Saravana Dhanasekaran, Sooryanaryana Varambally, Ira Maine (co-mentored with M. Rubin), Eric Albright (co-mentored with P.Ward)
- B. Mentor, medical student (research rotation): Dan Rhodes (M1)
- C. Mentor, graduate students (research rotations): Scott Tomlins (MSTP), Qi Cao (Pathology), Jianjun Yu (Bioinformatics), Chad Creighton (Bioinformatics), Patrick Lester (Pathology), Srikanth Kidambi (Chemistry)
- D. Mentor, high school student (research rotation): Angela Das (Plymouth)
- E. Mentor, Urology Resident: Atreya Dash (co-mentored with M. Rubin).
- F. Hosted international visiting scholars to train in microarray technology: Utpal Tatu (Indian Institute of Sciences), Tanuja Teni (Cancer Research Institute).

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Molecular Classification of Prostate Cancer"
American Cancer Society RSG-02-179-01-MGO, 07/01/02 – 06/30/06, 20% effort, \$180,000/yr direct costs
- B. Principal Investigator, "The Role of Polycomb Group Proteins in Prostate Cancer" NIH R01 CA97063, 07/01/02 – 06/30/07, 25% effort, \$178,000/yr direct costs
- C. Principal Investigator, "Transcriptome Analysis of Breast & Prostate Cancer Reveals Oncogenic Connections to Fatty Acid Metabolism",
V Foundation N003689, 03/29/02 – 03/28/04, 0% effort, \$50,000/yr direct costs.
- D. Principal Investigator, "Development of Breast Cancer biomarkers Using DNA and Protein Microarray Technologies", Mary Kay Ash Charitable Foundation N003813, 07/01/02 – 06/30/04, 0% effort, \$43,478/yr direct costs.
- E. Principal Investigator, "A Functional Genomics Approach to Cancer", PEW Charitable Trust, 07/01/02 – 06/30/06, 0% effort, \$55,556/yr direct costs

- F. Principal Investigator, "A Bioinformatics Approach to Cancer Profiling", Pilot Research Grant 2001N002824, University of Michigan, Bioinformatics Program, 07/01/01 – 12/31/02, 0% effort \$75,000
- G. Principal Investigator, "The Role of Hepsin in Prostate Cancer", CapCURE Foundation, 2001 CapCURE Award N003299 01/01/02 – 12/31/02, 0% effort, \$75,000
- H. Principal Investigator, "Molecular Classification of Prostate Cancer", Wendy Will Case Foundation, Bridging funds for re-submission of ACS grant, 12/01/01-11/31/02, 0%effort, \$25,000.
- I. Principal Investigator, "Functional Genomics Approach to Lethal Metastatic Prostate Cancer", Career Development Award, NCI P50 CA69568 (Pienta), 08/01/02 – 07/31/03, 25% effort, \$70,000/yr direct costs.
- J. Co-Principal Investigator, "Transcriptome Analysis of the EGFR Receptor in Breast Cancer, The Breast Cancer Foundation N003365 (Lippman), 10/01/01 – 09/30/02, 15% effort, \$250,000/yr
- K. Co-Investigator, "Biological Differences between prostate cancer cells that metastasize to the bone versus soft tissue sites", Department of Defense DAMD17-02-1-0098 (Pienta), 11/01/01 – 10/31/04 , 5% effort, \$141,563/yr direct costs
- L. Co-Investigator, "Protective Effects of Anti-C5a in Sepsis", NIH (Ward), 12/01/01- 11/30/06, 10% effort, \$225,000/yr direct costs.

PENDING:

- A. Principal Investigator, "Oncogenic connections to fatty acid metabolism", NIH RO1 CA097960-01, 12/01/02-11/30/07, 25% effort, \$200,000/yr direct costs.
- B. Principal Investigator, "Dysregulation of the Corepressor CtBP in Prostate Cancer", Department of Defense, DOD PC020322, 1/2/03- 12/31/05, 15% effort, \$125,000/yr direct costs
- C. Co-Principal Investigator, "Prostate Cancer Harbinger Genes: Aging, Race, and Ethnicity in Prostate Cancer." NIA RFA AG-02-003 (Rubin), 07/01/02 – 6/30/07, 10% effort, \$265,000/yr direct costs
- D. Co-Principal Investigator, MTOPS Molecular Profiling of Benign Prostatic Hyperplasia, NIDDK (Rubin), 10% effort,
- E. Principal Investigator, "Signature Lethal Biomarkers of Prostate Cancer", Project 3 NCI S.P.O.R.E. Bridging funds and competing renewal, NCI P50 CA69568 (Pienta), 15% effort, \$166,000/yr direct costs.
- F. Principal Investigator, "Tissue/Informatics Core", NCI S.P.O.R.E. Bridging funds and competing renewal, NCI P50 CA69568 (Pienta), 20% effort, \$250,000/yr direct costs.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Pathology student recruitment activities (lunch, poster session)
- B. Director of the Pathology DNA Microarray Research Lab.

MEDICAL SCHOOL/HOSPITAL:

- A. Member, MSTP Career Advisory Panel
- B. Bioinformatics student interviews
- C. Faculty Candidate Interviews for the Department of Urology and the Cancer Center
- D. MSTP student interviews

REGIONAL AND NATIONAL:

- A. Ad hoc reviewer for the following Journals: *Nature Genetics*, *American Journal of Pathology*, *Journal of Biomedical Informatics*, *Cancer Research*, *Neoplasia*, *Cell Death & Differentiation*, *Cytokine*, *Clinical Cancer Research*, *Molecular Diagnosis*, and the *Journal of Biological Chemistry*.
- B. External grant reviewer for the National Science and Technology Board Biomedical Research Council (Singapore) and the Cancer Society of New Zealand, Inc.

V. OTHER RELEVANT ACTIVITIES:

- A. Affiliated Faculty of the Bioinformatics Program
- B. Pew Scholars Program in the Biomedical Sciences, Pew Charitable Trusts
- C. Member, Michigan Comprehensive Cancer Center
- D. Joint Appointment in the Department of Urology

EDITORIAL BOARDS:

- A. None

HONORS AND AWARDS

- A. CapCURE Research Award, December 2001
- B. Wendy Will Case Cancer Fund Award, December 2001
- C. Excellence in Urologic Pathology Research, USCAP Annual Meeting, February 2002
- D. Pew Biomedical Scholar, June 2002

PATENTS:

- A. U.S. Provisional Application Serial no. 60/309,581 filed 8/02/01 and U.S. Provisional Application Serial no. 60/334,468 filed 11/15/01, "Prostate Cancer Biomarkers"

INVITED LECTURES/SEMINARS:

1. Cancer Center Seminar, University of Michigan Medical School, May 9, 2001.
2. Handy Lab, Inc., Invited Speaker, Ann Arbor, MI October 5, 2001
3. Medical Scientist Training Program Seminar for graduate students, University of Michigan Medical School, October 4, 2001

4. University of Minnesota, Department of Pharmacology, Invited Speaker, October 12, 2001.
5. Alexion Pharmaceuticals, Discovery Group, San Diego, Invited Speaker, October 26, 2001.
6. Nephrology Seminar Series, Department of Nephrology, Univ. of Michigan, Invited Speaker, Nov 13, 2001.
7. University of Windsor, Department of Biochemistry and Chemistry, Invited Speaker, November 30, 2001.
8. 21st Annual Convention of the Indian Association for Cancer Research, Bangalore, India, Invited Speaker, Jan 31-Feb 3, 2002.
9. Indian Institute of Sciences, Department of Biochemistry, Bangalore India, Invited Speaker, Feb 4, 2002.
10. Hematology-Oncology Seminar Series, Univ. of Michigan, Feb. 25, 2002.
11. Karmanos-Cancer Center, Wayne State University, Invited Speaker, Feb. 26, 2002.
12. Mt. Sinai School of Medicine, New York, Invited Speaker, March 4, 2002.
13. Genitourinary Research Seminar, University of Michigan, March 7, 2002
14. Pathology Research Seminar, University of Michigan, April 8, 2002.
15. Immunex, Seattle, Invited Speaker, May 13, 2002
16. Amersham Scientific Advisory Board, Invited Speaker, May 14, 2002.
17. ASCO Annual Meeting, Invited Speaker, May 21, 2002.
18. Plexxicon, Inc., Invited speaker, June 19, 2002

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1 **Chinnaiyan, A. M.***, Huber-Lang, M., Kumar, C., Barrette, T.R., Shankar, S. Sarma, V.J., Ward, P.A. (2001). Molecular Signatures of Sepsis: Multiorgan Gene Expression Profiles of Systemic Inflammation. *American Journal of Pathology* 159, 1199-1209. * Corresponding author.
2. Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, Pienta, K., Rubin, MA, **Chinnaiyan, A.M.** (2001) Delineation of prognostic biomarkers in prostate cancer. *Nature* 412(6849):822-6.
3. Sreekumar, A., Nyati, M.K., Varambally, S., Barrette, T.R., Ghosh, D., Lawrence, T.S., **Chinnaiyan, A.M.** (2001) Profiling of Cancer Cells Using Protein Microarrays: Discovery of Novel Radiation-Regulated Proteins, *Cancer Research*, 61, 7585-7593.
4. Ghosh D., **Chinnaiyan, A.M.** (2002) Model-based Clustering of Gene Expression Data from Microarray Experiments, *Bioinformatics*, 18(2):275-286.
5. Kumar-Sinha C, Varambally S, Sreekumar A, **Chinnaiyan AM.** (2002). Molecular cross-talk between the TRAIL and interferon signaling pathways. *J Biol Chem* 277:575-585.
6. Nyati MK, Sreekumar A, Li SP, **Chinnaiyan AM**, Rehemtulla A, Lawrence TS (2002). High and selective expression of yeast cytosine deaminase under a CEA promoter-enhancer. *Cancer Research*, 62:2337-42.
7. Rubin MA, Zhou M, Dhanasekaran SM, Varambally S, Barrette TR, Sanda MG, Pienta KJ, Ghosh D, **Chinnaiyan AM.** (2002). Alpha-Methylacyl-CoA Racemase as a Tissue Biomarker for Prostate Cancer. *JAMA*, 287:1662-70.

8. Rhodes, D.R., Barrette, T.R., Rubin, M.A., Ghosh, D., **Chinnaiyan, A.M.** (2002). Meta-analysis of Microarrays: Interstudy Validation of Gene Expression Profiles Reveals Pathway Dyregulation in Prostate Cancer. *Cancer Research*, 62: 4427-33.
9. Kuefer, R., Varambally, S., Zhou, M., Lucus, P.C., Loeffler, M., Wolter, H., Mattfeldt, T., Hautmann, R.E., Gschwend, J.E., Barrette, T.R., Dunn, R.L., **Chinnaiyan, A.M.**, Rubin, M.A. (2002) Alpha-Methylacyl-CoA Racemase: Expression levels of this novel cancer biomarker depend upon tumor differentiation. *American Journal of Pathology*, In Press.
10. Zhou, M., **Chinnaiyan, A.M.**, Kleer, C., Lucus, P., Rubin, M.A. (2002) Alpha-Methylacyl-CoA Racemase is a novel tumor marker over-expressed in several human cancers and their precursor lesions. *American Journal of Surgical Pathology*, 26:926-31.
11. Chay, C.H., Cooper, C.R., Gendernalik, J.D., Dhanasekaran, S.M., **Chinnaiyan, A.M.**, Rubin, M.A., Pienta, K.J. (2002) A functional thrombin receptor (PAR1) is expressed on bone-derived prostate cancer cell lines. *Urology*, In Press.
12. Xin, W., Rhodes, D.R., Ingold, C., **Chinnaiyan, A.M.**, Rubin, M.A. (2002) Dysregulation of the Annexin Protein Family is Associated with Prostate Cancer Progression. *American Journal of Pathology*, In Press.
13. Dash, A. Maine, I., Dhanasekaran, S.M., Barrette, T.R., **Chinnaiyan, A.M.**, Rubin, M.A. (2002) Changes in Differential Gene Expression Due to Warm Ischemia Time of Radical Prostatectomy Specimens. *American Journal of Pathology*. In Press.
14. Varambally S., Dhanasekaran, S.M., Barrette, T.R., Sanda, M.G., Ghosh, D., Pienta, K.J., Sewalt, R.G.A.B., Otte, A.P., Rubin, M.A., **Chinnaiyan, A.M.** (2002). The Polycomb Group Protein EZH2 is Involved in Prostate Cancer Progression. *Nature*, In Press.

REVIEW ARTICLES:

1. **Chinnaiyan AM**, Rubin MA (2002) Gene Expression Profiles of Hereditary Breast Cancer: On Hedenfalk Duggan, D, Chen Y, et al. *Adv. Anat. Path.* 9-1-6.
2. Rhodes, D.R. and **Chinnaiyan, A.M.** DNA Microarrays: Implications for Clinical Medicine. (2002) *Journal of Investigative Surgery*, In Press.
3. Sreekumar A. and **Chinnaiyan, A.M.** (2002) The Use of Protein Microarrays in the Study of Cancer. *Biotechniques*, In Press.

BOOKS/CHAPTERS IN BOOKS:

1. None.

ABSTRACTS:

1. Several abstracts have been submitted from the Chinnaiyan Lab (during this period) to various national meetings including USCAP, American Association for Cancer Research (AACR), NCI S.P.O.R.E. meeting, and the Fall Research Symposium of the U of Michigan Cancer Center. Please refer to the published manuscripts that have resulted from these abstracts.

**KATHLEEN CHO, M.D.
ASSOCIATE PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Gynecological pathology consultation services and "Room G"/Gynecological Pathology sign out in surgical pathology – six months.

II. TEACHING ACTIVITIES:

- A. Postdoctoral Fellows:
Responsible during the academic year for the following:
 - 1. Donald Schwartz, Ph.D.
 - 2. Ya-Li Zhai, Ph.D.
- B. Graduate students:
Course Faculty, Pathology 581 – three lecture hours
Course Faculty, Pathology 580/630 – two lecture hours
Mentored laboratory rotation of PIBS student Neali Hendrix
- C. Undergraduate students:
Fan Yang
- D. House Officers:
Two staff consultation conferences
- E. Interdepartmental:
Multidisciplinary Gynecologic Oncology tumor board – one hour twice per month
Cancer Biology Journal Club: Faculty Supervisor
- F. Doctoral Thesis Committee Member for the following graduate students:
Tom Hlaing (Pathology)
Kenute Myrie (Human Genetics)
- G. National:
Course Faculty and Co-organizer: Molecular Biology in Clinical Oncology Workshop, American Association for Cancer Research, The Given Institute, Aspen, Colorado.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "FHIT Gene Alterations in Cervical Cancer Pathogenesis", NIH RO1 CA81587 (15% effort), September 1, 1998 - August 31, 2002. Final year is twelve month no cost extension.
- B. Principal Investigator, Project 2 ("Molecular Profiling of Ovarian Cancer", 15% effort). NIH: U19 CA84953 (Hanash). "Toward a Molecular Classification of Tumors," September 30, 1999 – March 31, 2004.
- C. Principal Investigator, "Oncogene Activation in Ovarian Cancer Pathogenesis", Department of Defense, OCRP OC000105 (15% effort), August 15, 2001 - August 14, 2004.

- D. Principal Investigator, "Molecular Pathogenesis of Ovarian Endometrioid Adenocarcinomas", NIH RO1 CA94172 (30% effort), February 1, 2002 – January 31, 2007.
- E. Co-Investigator (10% effort), "CDX2 Tumor Suppressor Pathway Defects in Colon Cancer", NIH R01 CA82223 (Fearon), August 15, 1999 – May 31, 2004.
- F. Co-Investigator (10% effort), "The Role of β -Catenin/Tcf Pathway Defects in Cancer." NIH R01 CA85463 (Fearon), June 1 2000 – May 31, 2005.
- G. Co-Investigator, Bioinformatics Pilot Grant (Lubman), University of Michigan, awarded June 2001. No salary support requested for Dr. Cho. Provides partial salary support for Dr. Donald Schwartz, post-doctoral fellow, Cho laboratory.

PENDING:

- A. National Institutes of Health: 1P50CA98252-01 (12/01/02 – 11/30/07). SPORE in Cervical Cancer (Program PI: T.C. Wu); Role in Program: Principal Investigator, Project 2, Molecular Markers of Invasion in Cervical Cancer Progression (20% effort). Co-Investigator, Project 1, Markers of Progression to Cervical Cancer in Rural India (5% effort). Application reviewed by IRG in 06/02, priority score 153, funding anticipated pending administrative approval.

PROJECTS UNDER STUDY:

- A. Molecular profiling of ovarian epithelial tumors using 2-D gel approaches and Affymetrix gene chip technologies.
- B. Identification and characterization of novel genes differentially expressed in ovarian carcinomas.
- C. Identification of novel genes amplified in ovarian carcinomas.
- D. Evaluation of the role of Wnt/ β -catenin/Tcf pathway defects in the pathogenesis of ovarian endometrioid adenocarcinomas.
- E. Identification of genes involved in cervical cancer progression

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

INSTITUTIONAL:

- A. Institutional Review Board, University of Michigan School of Medicine (IRB-MED), appointment from Feb 2001 – Jan 2005

REGIONAL AND NATIONAL:

- A. Special Emphasis Panel, Pathology B Study Section, National Institutes of Health/National Cancer Institute, teleconference review of RO1 applications, 2001
- B. Special Emphasis Panel, Oncological Sciences IRG, National Institutes of Health/National Cancer Institute, teleconference review of RO1 application (panel chair), 2001
- C. Member, Special Conferences Committee, American Association for Cancer Research, 1999-2002

- D. Co-Organizer, Molecular Biology in Clinical Oncology Workshop, American Association for Cancer Research, 2000-present
- E. Member, National Comprehensive Cancer Center Panel for establishment of endometrial and cervical cancer treatment guidelines, 1997-present
- F. Chairperson, AACR – Women in Cancer Research – Charlotte Friend Memorial Lectureship Selection Committee, American Association for Cancer Research, 2002

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

- A. Associate Editor, *Cancer Research*
- B. Associate Editor, *Clinical Cancer Research*
- C. Member, Editorial Board, *Human Pathology*
- D. Member, Editorial Board, *International Journal of Gynecological Pathology*
- E. Member, Editorial Board, *Molecular Diagnostic Pathology*
- F. Member, Editorial Board, *The Women's Oncology Review*
- G. Ad hoc reviewer for *American Journal of Pathology*, *British Journal of Cancer*, *Gynecologic Oncology*, *Laboratory Investigation*

INVITED LECTURES/SEMINARS:

- 1. Molecular Pathogenesis of Gynecologic Tumors, Advanced Molecular Pathology Special Course at the United States and Canadian Academy of Pathology Annual Meeting, Atlanta, Georgia, March 2001.
- 2. Molecular Biology of Gynecological Cancers. Molecular Biology in Clinical Oncology Workshop, American Association for Cancer Research, The Given Institute, Aspen, Colorado, July 2001.
- 3. Ovarian Cancer: Molecular Clues to Pathogenesis and Tumor Classification. University of Michigan Comprehensive Cancer Center Grand Rounds. Ann Arbor, Michigan, September 2001.
- 4. Cervical Cancer and Human Papillomaviruses. Annual Symposium of the Binford-Dammin Society of Infectious Disease Pathologists, United States and Canadian Academy of Pathology Annual Meeting, Chicago, Illinois, February 2002.
- 5. Ovarian Cancer: Molecular Clues to Pathogenesis and Tumor Classification: University of Michigan Department of Obstetrics and Gynecology. Ann Arbor, Michigan, May 2002.
- 6. Ovarian Cancer: Molecular Clues to Pathogenesis and Tumor Classification: Molecular Biology in Clinical Oncology Workshop, American Association for Cancer Research, The Given Institute, Aspen, Colorado, July 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Hough, C.D., Cho, K.R., Zonderman, A.B., Schwartz D.R., and Morin, P.J. Coordinately Up-Regulated Genes in Ovarian Cancer. *Cancer Research* 61:3869-76, 2001.
- 2. Ferguson, A.W., Katabuchi, H., Ronnett, B.M., and Cho, K.R. Glial Implants in Gliomatosis Peritonei Arise from Normal Tissue, Not from the Associated Teratoma *American Journal of Pathology* 159:51-56, 2001.
- 3. Giordano, T.J., Shedden, K.A., Schwartz, D.A., Kuick, R., Taylor, J.M.G., Lee, N., Misek, D.E., Greenson, J.K., Kardias, S.L.R., Beer, D.G., Rennert, G., Cho, K.R., Gruber, S.B., Fearon, E.R., and

- Hanash, S. Organ-Specific Molecular Classification of Primary Lung, Colon, and Ovarian Adenocarcinomas Using Gene Expression Profiles. American Journal of Pathology 159:1231-38, 2001.
4. Hinoi, T., Tani, M., Lucas, P.C., Caca, K., Dunn R.L., Macri, E., Loda, M., Appelman, H.D., Cho, K.R., and Fearon, E.R. Loss of CDX2 Expression and Microsatellite Instability are Prominent Features of Large Cell Minimally Differentiated Carcinomas of the Colon. American Journal of Pathology 159:2239-2248, 2001.
 5. Wu, R., Zhai, Y., Fearon, E.R., and Cho, K.R. Diverse Mechanisms of β -catenin Deregulation in Ovarian Endometrioid Adenocarcinomas. Cancer Research 61:8247-8255, 2001.
 6. Zhai, Y., Wu, R., Schwartz, D.R., Darrah, D., Kolligs, F.T., Nieman, M.T., Fearon E.R., and Cho, K.R. Role of β -catenin/TCF Regulated Genes in Ovarian Endometrioid Adenocarcinomas. American Journal of Pathology 160:1229-38, 2002.
 7. Kachman, M.T., Wang, H., Schwartz, D.R., Cho, K.R., and Lubman, D.M. A 2-D Liquid Separations/Mass Mapping Method for Interlysate Comparison of Ovarian Cancers. Analytical Chemistry 74:1779-1791, 2002.
 8. Kolligs, F.T., Nieman, M.N., Winer, I., Hu, G., van Mater, D.S., Feng, Y., Smith, I.M., Wu, R., Zhai, Y., Cho, K.R., and Fearon, E.R. ITF-2, a downstream target of the Wnt/TCF pathway, is activated in human cancers with β -catenin defects and promotes neoplastic transformation. Cancer Cell, 1:145-155, 2002.
 9. Leung, J.Y., Kolligs, F.T., Wu, R., Zhai Y, Kuick R., Hanash, S., Cho, K.R., and Fearon, E.R. Activation of AXIN2 Expression by β -catenin/TCF: A Feedback Repressor Pathway Regulating Wnt Signaling. Journal of Biological Chemistry, 277:21657-65, 2002.
 10. Wang, H., Kachman M.T., Schwartz, D.R., Cho, K.R., and Lubman, D.M. A protein molecular weight map of ES2 clear cell ovarian carcinoma cells using a 2-D liquid separations/mass mapping technique. Electrophoresis (in press, 2002).
 11. Schwartz, D.R., Kardia, S.L.R., Shedden, K.A., Kuick, R., Michailidis, G., Taylor, J.M.G., Misek, D.E., Wu, R., Zhai,Y., Darrah, D.M., Reed, H., Ellenson, L.H., Giordano, T.J., Fearon, E.R., Hanash, S.M., and Cho, K.R. Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. Cancer Research (in press, 2002).

ARTICLES SUBMITTED OR IN PREPARATION:

BOOKS/CHAPTERS IN BOOKS:

1. Cho, K.R. Cervical Cancer. Metabolic and Molecular Bases of Inherited Disease, 8th edition, in Part 4, "Cancer", ed. B. Vogelstein and K. Kinzler, McGraw-Hill, Inc., New York, New York, 2001.
2. Cho, K.R., and Ellenson L.H. Molecular Biology. In Blaustein's Pathology of the Female Genital Tract, 5th edition, ed. Robert J. Kurman, Springer-Verlag, New York, 2002.

**LAURA COOLING, M.D., M.S.
CLINICAL ASSISTANT PROFESSOR II
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 – 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Assistant Director, Transfusion Medicine
 - 1. Blood Bank, clinical coverage and administration
 - 2. Bone Marrow/Peripheral Stem Cell Collection and Processing
 - 3. Clinical Consultation/Management, Special Product Requests
 - 4. Clinical Coverage, Therapeutic Apheresis

II. TEACHING ACTIVITIES:

- A. Resident Education
 - 1. Responsible/Share didactic teaching activities for the following:
 - a. Blood Component Therapy
 - b. Transfusion Reaction Evaluation
 - c. Evaluation and Management of Platelet Refractoriness
 - d. Fundamentals of Clinical Apheresis (with nursing staff)
 - e. Evaluation and Management of Therapeutic Apheresis Requests
 - f. Administrative Issues on-call
 - 2. Clinical Teaching
 - Supervision Resident/ Visiting Fellow Activities (12 mo/yr)
 - a. Morning Report
 - b. Transfusion reaction sign-out
 - c. Clinical apheresis requests/patient management
 - d. Special product request evaluation and clinical follow-up
 - e. Case-based informal teaching
 - 3. Other Clinical Teaching
 - a. Hematology Fellows
 - b. Heme/Onc Nursing Staff (in-service lectures)
- B. Medical Students
 - 1. Transfusion Medicine. Senior Therapeutics Course, Dept. of Pharmacology

III. RESEARCH ACTIVITIES:

- A. The Regulation and Biology of Globo-Series Glycosphingolipids
 - 1. Chemical analysis of complex P and Luke related globo-gangliosides.
 - 2. Relationship of LKE phenotype on non-globo-glycoconjugates of human RBCs.
 - 3. Effect of inflammatory cytokines on P blood group and globo-ganglioside antigen expression in renal epithelial cells.
 - 4. Molecular basis and regulation of Pk and Luke antigen expression in LKE weak and negative phenotype.

SPONSORED RESEARCH:

CURRENT:

- A. Principal Investigator, "The Effect of TNF α on Renal Glycosphingolipid Synthesis". National Kidney Foundation of Michigan, \$27,960, Sept 1 2001-2002.

PENDING:

- A. Molecular Epidemiology of E. coli-Associated Hemolytic Uremic Syndrome in China. National Science Foundation of China. Principal Investigator, Yuan Gu MD, MPH, Associate Professor Epidemiology, Tongji Medical University, Wuhan, China. Consultant/Co-investigator, Laura Cooling, Univ. of Michigan.

NOT FUNDED:

- A. Molecular Analysis of Globo- and Lacto-Family Glycosyltransferases: Molecular Etiology of the LKE-negative and LKE-weak Phenotypes. National Blood Foundation. PI, Laura Cooling.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Associate Director, Transfusion Medicine

HOSPITAL:

- A. Transfusion Subcommittee

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

1. Invited Lecturer; Michigan Association of Blood Banks Annual Meeting: Saturday Night Fever: A Transfusion Reaction Review. September 12, 2001.
2. Invited Lecturer, Michigan Association of Blood Banks Teleconference: ABO, Platelets and Heredity: New Thoughts on ABO and Platelet Transfusion Therapy. October 2001.
3. Seminar, Clinical Pathology Grand Rounds, University of Michigan: Adverse Effects of Apheresis. October, 2001.
4. Invited Speaker, Hurley Medical Center. Review and Management of Transfusion Reactions. October, 2001.
5. Presenter, American Association of Blood Banks 55th Annual Meeting, San Antonio TX. Delayed Platelet Engraftment in Group O Patients after Autologous Stem Cell Transplantation.
6. Invited Speaker (with Dr. Judy Negele), Anesthesiology Rounds, University of Michigan: Not Another Case of Hypotension: Transfusion Related Acute Lung Injury. January, 2002.
7. Invited Lecturer, Internal Medicine Grand Rounds University of Michigan: Basics of Blood Transfusion Therapy. February, 2002.

8. Invited Lecturer, Internal Medicine Grand Rounds, University of Michigan: Transfusion Reaction Review. February, 2002.
9. Invited Lecturer, American Red Cross, Eastern Michigan University. Apheresis versus Whole Blood Derived Platelet Concentrates: Clinical and Laboratory Considerations. April, 2002.
10. Seminar, Clinical Pathology Grand Rounds, University of Michigan. Evaluation and Management of Platelet Refractoriness. May, 2002.
11. Lecturer, 30th Annual Current Topics in Blood Banking, University of Michigan: The Management of Platelet Refractoriness. June, 2002..
12. Invited Lecturer, American Red Cross, Detroit MI. ABO Antigens on Human Platelets: Role in Transfusion Therapy, Hematopoiesis and Donor Variability. June, 2002.

REVIEWER:

Conn's Current Therapy
Journal of Lipid Research
Journal, Transfusion
Journal, Thrombosis and Hemostasis
Journal, Thrombosis Research
Scientific Abstracts, American Association Blood Bank 55th Annual Meeting

PROFESSIONAL MEMBERSHIPS:

American Association of Blood Banks
Michigan Association of Blood Banks
American Society of Clinical Apheresis
Alpha Omega Alpha

VI. PUBLICATIONS:

JOURNALS:

1. Cooling LLW, Zhang DS, Naides NS, Koerner TAW. Glycosphingolipid expression in acute nonlymphocytic leukemia: common expression of shiga toxin and parvovirus B19 receptors on early myeloblasts. Blood, in press.
2. Cooling L. Transfusion related acute lung injury. JAMA 2002;288:315-316.
3. Cooling L, Kelly K. Inverse expression of P^k and LKE antigens on human RBCs. Transfusion July 2001;41:898-907.

BOOKS/CHAPTERS IN BOOKS:

1. Contributor, The Blood Group Antigen FACTS Book. Eds. M Reid, C. Lomas-Francis. Academic Press, Harcourt Brace & Co. London, UK. *In press.*

PEER REVIEWED ABSTRACTS:

1. Cooling L, Zhang DS, Koerner T. The receptor for shiga toxin is commonly expressed by immature myeloid cells. Transfusion, *in press.*
2. Cooling L, Gu Y. Increased expression of a para-Forssman-like glycosphingolipid on LKE-weak red cells. Transfusion, *in press.*

3. Cooling L, Gu Y, Copeland T. Identification of two new single nucleotide polymorphisms in FUT3 (Lewis), associated with the Lewis null phenotype in African Americans. *Transfusion*, *in press*.
4. Cooling L, Gu Y, Judd WJ, Copeland T. A missense mutation in β 3GalT5, the glycosyltransferase responsible for galactosylgloboside and Lewis c synthesis, may be associated with the LKE-weak phenotype in African Americans. *Transfusion*, *in press*.
5. Cooling, LW, Hoffmann S, Davenport R. Delayed platelet engraftment in group O patients after autologous stem cell transplant. *Transfusion* 2001;41:S113.
6. Steiner EA, Judd WJ, Combs MR, Watkins K, Weissman PB, Mann N, Casina, Cooling L. Prenatal antibody titers by the gel test. *Transfusion* 2001;41:S107.

**ROBERTSON D. DAVENPORT, M. D.
ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Medical Director, Blood Bank and Transfusion Service.
- B. Cytopathology staff.

II. TEACHING ACTIVITIES:

- A. Introductory Course in Blood Banking/Transfusion Medicine for Pathology House Officers.
- B. Daily teaching rounds for Pathology House Officers assigned to the Blood Bank.
- C. Current Topics in Blood Banking Conference, Towsley Center for Continuing Medical Education.
- D. M2 Hematology sequence, Blood Transfusion.
- E. Hematology fellows, blood transfusion.
- F. Clinical Pathology Grand Rounds: Statistics
- G. Clinical Pathology Grand Rounds: Ethical Issues in Transfusion Medicine.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Evaluation of Solvent/Detergent-Treated Plasma, Isoagglutinin Depleted, in Normal Healthy Volunteers", V. I Technologies, Inc.

PROJECTS UNDER STUDY:

- A. Pathophysiology of transfusion reactions.
- B. Transfusion risk perception.
- C. Safety of Isoagglutinin-depleted plasma.
- D. Heparin-induced thrombocytopenia

IV. ADMINISTRATIVE ACTIVITIES:

MEDICAL SCHOOL/HOSPITAL:

- A. Transfusion Committee.
- B. Blood Transfusion Process Improvement Team.

V. OTHER RELEVANT ACTIVITIES:

- A. Program Committee, Michigan Association of Blood Banks.
- B. Scientific Section Coordinating Committee, American Association of Blood Banks.
- C. Annual Meeting Program Planning Committee, American Association of Blood Banks.
- D. Medical Advisory Committee, American Red Cross Southeastern Michigan Region.
- E. Editorial Board, Transfusion.

- F. National Blood Foundation Grants Review Committee.
- G. Invited lecture: Transfusion Risk Perception. Blood-Borne HIV and Hepatitis: Optimizing the Donor Selection Process, Ottawa Canada, November 7 - 9, 2001

VI. PUBLICATIONS:

ARTICLES ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Davenport RD. Apheresis Treatment of Recurrent Focal Segmental Glomerulosclerosis after Kidney Transplantation: A Re-analysis of Published Case-Reports and Case-Series. J Clin Apher, 16:175-178, 2001.

ARTICLES SUBMITTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Davenport RD, Hanrard D. Public Perception of Transfusion Risks. Submitted to Transfusion.

ABSTRACTS AND PRESENTED PAPERS:

1. Davenport, RD. Public Perception of the Risk of Blood Transfusion. Transfusion 2001; 41:120S
2. Afenyi-Annan A, Downs T, Butch S, Deeb G. Transfusion Guidelines for Aortic Aneurysm Repair with Deep Hypothermic Circulatory Arrest. Transfusion 2001;41:56S
3. Cooling L, Hoffman S, Davenport RD. Delayed Platelet Engraftment in Group O Patients after Autologous Stem Cell Transplant. Transfusion 2001; 41:32S

BOOKS:

1. Contributing Editor. Blood Transfusion Therapy: A Physician's Handbook. 7th ed. American Association of Blood Banks. In Press.

**FELIX A. DE LA IGLESIA, M.D.
ADJUNCT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001-30 JUNE 2002**

I. CLINICAL ACTIVITIES:

II. TEACHING ACTIVITIES:

None.

III. RESEARCH ACTIVITIES:

Organizing a Cell Toxicity Laboratory.

SPONSORED SUPPORT:

- A. Research activities with intramural support from Dr. Ward.
- B. Collaborates with K. Johnson in the development of morphometric models for the evaluation of pathologic changes.
- C. NASA Grant – “Biosensors for real-time monitoring of radiation induced biologic effects in space.” (NAS-2-02069).

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

None.

MEDICAL SCHOOL/HOSPITAL:

None.

REGIONAL AND NATIONAL:

Member, Scientific Advisory Committee, NSF Center for Light Microscopy, Carnegie Mellon University, Pittsburgh, PA.
Member, Scientific Advisory Board, Cellomics Inc., Pittsburgh, PA.
Member, Scientific Advisory Board, Waratah Pharmaceutical, Boston.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

Editorial Board Member, Drug Metabolism Reviews.

INVITED LECTURES/SEMINARS:

1. Evolutionary Developments of Microscopy Towards Quantitation and Functional Relationships. Medical College of Ohio, Department of Pathology, May 15, 2002.
2. Coherent Multiprobes and Quantitative Spectroscopic Multimode Microscopy for the Study of Simultaneous Intracellular Events, Ohio State University, Nov. 20, 2001.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNALS:

1. M.M. Shi, M.R. Bleavins, F.A. de la Iglesia. Pharmacogenetic Application in Drug Development and Clinical Trials. Drug. Metab. Disp. 29:591-595, 2001.
2. J.R. Haskins, P. Rowse, R. Rahbari and F.A. de la Iglesia. Thiazolidinedione toxicity to isolated hepatocytes revealed by coherent multiprobe fluorescence microscopy and correlated with multiparameter flow cytometry of peripheral lymphocytes. Arch. Toxicol. 75:425-438, 2001.
3. S.J. Bulera, S.M. Eddy, E. Fergusson, T.A. Jatkoe, J.F. Reindel, M.R. Bleavins and F.A. de la Iglesia. RNA expression in the early characterization of hepatotoxicants in Wistar rats by high density DNA microarrays. Hepatology 33:1239-1259, 2001.
4. J.F. Reindel, A.W. Gough, G.D. Pilcher, W.F. Brobowski, G.P. Sobocinski and F.A. de la Iglesia. Systemic proliferative changes and clinical signs in cynomolgus monkeys administered a recombinant derivative of human epidermal growth factor. Toxicol. Pathol. 29:159-173, 2001.
5. J.R. Herman, L.A. Dethloff, E.J. McGuire, R.F. Parker, K.M. Walsh, A.W. Gough, H. Masuda and F.A. de la Iglesia. Rodent carcinogenicity with the thiazolidinedione antidiabetic agent troglitazone. Toxicol. Sci. 68:226-236, 2002.
6. H. Masuda, M.J. Adams, R.C. Secker, E. J. McGuire, J.R. Herman, D. Bailey and F.A. de la Iglesia. Reproductive Toxicology Studies with the Thiazolidinedione Antidiabetic Agent Troglitazone. J. Tox. Sci. In press, 2002.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Shi, M.M., Bleavins, M.R., Thompson, R.G., Chin, J.F., de la Iglesia, F.A, Candidate gene profiles for liver toxicity and metabolism in NIDDM patients receiving an antidiabetic thiazolidinedione (submitted, June 2002).
2. Bulera, S.J., Festerling, T.A., de la Iglesia, F.A. Gabapentin Activates MAP kinase In vivo and In vitro in pancreatic acinar cells from Wistar rats: a postulated mechanism for pancreatic acinar cell tumor formation (submitted, 2002).

3. FA. de la Iglesia, J. Haskins, D. Farkas, D. Wilson, G. Bearman. Coherent Multiprobes and Quantitative Spectroscopic Multimode Microscopy for the Study of Simultaneous Intracellular Events. (Submitted)
4. S.J. Bulera, T.A. Festerling, F.A. de la Iglesia, Gabapentin Activates MAP Kinase In Vivo and In Vitro in Pancreatic Acinar Cells from Wistar Rats: A Postulated Mechanism for Pancreatic Acinar Tumor Formation. (Submitted)

BOOKS/CHAPTERS IN BOOKS:

1. F.A. de la Iglesia, J.R. Haskins and G. Feurer. Hepatotoxicity of Cardiovascular and Antidiabetic Drugs. In: Drug-Induced Liver Disease. N. Kaplovitz (Ed.) M. Dekker Publ. New York. In press, 2002.

**ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR,
MISCELLANEOUS PUBLICATIONS IN UNREFERRED JOURNALS:**

None.

**GREGORY R. DRESSLER, Ph.D.
ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

None.

II. TEACHING ACTIVITIES:

- A. Pre-doctoral Students Supervised - Jing Mei Lin, Dept. of Pathology; Marc Prindle, CMB
- B. Post-doctoral Trainees Supervised - Yi Cai, M.D., Ph.D.; Patrick Brophy, M.D.; Sanj Patel, M.D.
- C. Ph. D. Thesis Committee Member - Igor Nasonkin, Dept. of Genetics; Kris Coulter, Dept. of Genetics; Hoonkyo Soo, Dept. of Genetics; Yue Ge, Dept. of Genetics; Bryan MacDonald, Dept of Genetics; Brian Gummow, CMB; Tom Hlaing, Dept of Pathology.
- D. Course Lectures - Path 581, 7.5 h; Path 582 course director; CDB 530, 3 h; CDB 680, 12h

MEDICAL SCHOOL/HOSPITALS:

- A. Second Year Medical Students - Renal Section, 1 h

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "PAX-2 in Normal and Cystic Epithelium Development", NIH/NIDDK R01 DK51043-02, (20%), September 30, 1995-August 31, 2001. no cost extension.
- B. Principal Investigator, "Cell Migration, Chemoattraction and the RET/GDNF Pathway", NIH/NIDDK 1 R01 DK54723-01 (30% effort), 1/1/99 - 12/31/03, Annual Direct Costs \$158,840.
- C. Principal Investigator, "PAX2 Interacting Proteins in Development and Disease", NIH/NIDDK 1 R01 DK54740-01 (30% effort), 1/1/99 - 12/31/02, Annual Direct Costs \$158,840.
- D. Principal Investigator, Project #3 (20% effort), "Functional Analysis of RET Signaling in Renal Epithelial Cells", NIH/NIDDK, 2 P50 DK39255-11A1, O' Brien Renal Center Grant, "Mechanisms of Glomerular and Tubular Injury", Dr. Roger C. Wiggins, PI. 9/1/98 - 8/31/03, \$76,066 Initial Budget Period.

PROJECTS UNDER STUDY:

- A. The identification of co-factors required for Pax protein mediated transcription activation.
- B. The development of novel methods for identifying genes regulated by Pax proteins.
- C. The role of Pax-2 in the initiation and progression of polycystic kidney disease.
- D. The GDNF/RET signaling pathway in the developing kidney.
- E. Wnt and Frizzled signaling in the developing kidney

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Dept. of Pathology - Preliminary Exam Committee, Curriculum Committee, Admissions Committee
- B. Center for Organogenesis - Interim Co-Director, Steering Committee, Training Grant Review Committee, Advisory Committee, Seminar Committee (Chair)
- C. Program in Biomedical Sciences (PIBS) - Admissions Committee

REGIONAL AND NATIONAL:

NIH Study Section, General Medicine B, Permanent Member
American Journal of Physiology, Editorial Reviews Board
Human Frontiers in Sciences Program, reviewer
Irish National Research Council, reviewer
Australian Medical Research council, reviewer

Reviewer for: Cell, Nature, Mechanisms of Development, Development, Proceedings of the National Academy of Sciences, Developmental Dynamics, Journal of Biological Chemistry, Nature, American J. of Physiology, Journal of Clinical Investigation, Molecular and Cellular Biology, Genes & Development, Kidney International, Journal of Cell Biology, Cell, Am. J. Pathology, Cancer Research

V. OTHER RELEVANT ACTIVITIES:

Membership in the American Society of Nephrology
Membership in Society for Developmental Biology
Membership in University of Michigan Comprehensive Cancer Center
Membership in the Center for Organogenesis, University of Michigan

INVITED LECTURES/SEMINARS:

- 1. Dept. of Molecular Genetics, Baylor College of Medicine, Houston, TX
- 2. Depts. of Pediatrics and Cell and Molecular Biology, Tulane Univ., New Orleans, LA
- 3. 8th International Workshop on Developmental Nephrology, Victoria, BC
- 4. American Society of Nephrology, Annual Meeting, San Francisco, CA
- 5. German Society for Nephrology, Annual Meeting, Muenster, Germany
- 6. Banbury Conference on Epithelial & Endothelial Tube Morphogenesis, Cold Spring Harbor, NY
- 7. Dept. of Cell Biology, Univ. of Alabama, Birmingham, AL

8. European Nephrogenesis Workshop IX, Royal College of Physicians, Dublin, Ireland
9. Developmental Gene Regulation, Max Planck Institute, Goettingen, Germany
10. Dept. of Anatomy, Indiana University School of Medicine, Indianapolis, IN

VI. **PUBLICATIONS:**

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Brophy, P.D, Ostrom, L., Lang, K.M. and Dressler, G.R. (2001) Regulation of Ureteric Bud Outgrowth by Pax2 Dependent Activation of the Glial Derived Neurotrophic Factor Gene. *Development* 128, 4747-4756.
2. Cai, Y., Lechner, M.S., Nihalani, D., Prindle, M., Holzman, L.B. and Dressler, G.R. (2002) Phosphorylation of Pax2 by the c-Jun N-terminal kinase and enhanced Pax2 dependent transactivation. *J. Biol Chem.* 277, 1217-1222.
3. Tang, M.J., Cai, Y., Tsai, S.J., Wang, Y.K. and Dressler, G.R. (2002) Ureteric Bud Outgrowth in Response to RET Activation is Mediated by Phosphatidylinositol-3 Kinase. *Dev. Biol.* 243, 128-136.
4. Silberstein, G. B, Dressler, G.R. and Van Horn, K. (2002) Expression of the Pax2 oncogene in human breast cancer and its role in progesterone dependent mammary growth. *Oncogene* 21, 1009-1016.
5. Hoffmeister, A., Ropolo, A., Vasseur, S., Mallo, G.V., Bodeker, H., Ritz-Laser, B., Dressler, G.R., Vaccaro, M.I., Dagorn, J.C., Moreno, S. and Iovanna, J.L. (2002) The HMG-I/Y-related protein p8 binds to p300 and Pax2 trans-activation-domain interacting protein to regulate the trans-activation activity of the Pax2A and Pax2B transcription factors on the glucagon gene promoter. *J. Biol. Chem.* 277, 22314-22319.
6. Dressler, G.R. (2002) Tubulogenesis in the developing mammalian kidney. *Trends Cell Biol.* 12, 390-395.

ARTICLES SUBMITTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Cai, Y., Brophy, P., Levitan, I. and Dressler, G.R. (2002) Suppression of Pax2 phosphorylation by the groucho protein Grg4, submitted.
2. Cho, E.A., Prindle, M.J. and Dressler, G.R. (2002) The BRCT domain protein PTIP is required for progression through mitosis, submitted.

BOOK CHAPTERS:

1. Dressler, G.R. (2002) The Development of the Excretory System. In: Mouse Development (J. Rossant and P. Tam, eds.) Academic Press, NY, pp395-420.
2. Cho, E.A. and Dressler, G.R. (2002) The Formation and Development of Nephrons. In: The kidney: Normal Development to Congenital Abnormalities (P. D. Vize, A. S. Woolf, J. B. L. Bard, eds) Academic Press, in press.

**COLIN S. DUCKETT, Ph.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
JULY 1 2001 – JUNE 30 2002**

I. CLINICAL ACTIVITIES:

None

II. TEACHING ACTIVITIES:

A. Research Mentor:

1. Jennifer Lewis, Ph.D., postdoctoral fellow, 1999 - present.
2. Ezra Burstein, M.D., Lecturer, Department of Internal Medicine 2001 - present.
3. John Wilkinson, Ph.D., postdoctoral fellow, 2002 - present.
4. Bettina Richter, Ph.D., postdoctoral fellow, 1997 - 2001.
5. Michiko Mandai, M.D., Ph.D., Fogarty Visiting Fellow (NIH), 2000-2001.
6. Stephanie Birkey Reffey, Ph.D., postdoctoral fellow 1997 - 2001.
7. Samy Mir, medical student, HHMI Research Scholars Program 1999 - 2001.

B. Thesis committee/examiner:

1. University of Melbourne, 2001 (student: M. Knight).
2. Johns Hopkins School of Public Health, 1999 - present (student: T. -T. Sheu).

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Role of X-linked IAP (XIAP) in TGF- β signal transduction pathways, in collaboration with Dr. Anita Roberts, National Cancer Institute.
- B. Analysis of the protective effects of XIAP in caspase-dependent and -independent cell death, in collaboration with Dr. Gerry Cohen, University of Leicester, England and Dr. Larry Boise, University of Miami.
- C. Characterization of VIAF, a novel IAP-associated factor, in collaboration with Dr. Pam Schwartzberg, National Human Genome Research Institute.
- D. Interaction of XIAP with Murr1, a factor whose gene is mutated in an inherited copper deficiency, in collaboration with Dr. Gary Nabel, National Institute of Allergy and Infectious Diseases, Dr. Cisca Wijmenga, University Medical Center, Utrecht, and Dr. George Brewer, University of Michigan.
- E. Use of agonistic antibodies directed against CD30 for the treatment of Hodgkin Disease and anaplastic large cell lymphoma, in collaboration with Dr. William Murphy, National Cancer Institute.

SPONSORED SUPPORT:

- 2002 - Present, (Principal Investigator), Startup funds from University of Michigan. Funding provided by Department of Pathology, UM Cancer Center and Biomedical Scholars Program.
- 2002 - 2003 (Mentor), "The Role of XIAP in the Regulation of Apoptosis," Cancer Biology Training Grant (Wilkinson).
- 2001 - (Principal Investigator), "Cooperative Research and Development Agreement (CRADA) for Developing a Screening Strategy for Inhibitors of Apoptosis (IAP) Inhibitory Compounds." Aegera, Inc. NIH Intramural Cooperative Research and Development Agreement.
- 1997 - 2001 (Principal Investigator), "Characterization of the Inhibitor of Apoptosis (IAP) Gene Family." Z01 SC 010358 NIH/NCI Intramural.
- 1997 - 2001 (Principal Investigator), "Induction of Apoptosis in Lymphoma Cells by Activation of CD30." Z01 SC 010287, NIH/NCI Intramural.

PENDING:

- 2003 - 2008 (Principal Investigator), "Control of Apoptosis and Signaling by XIAP," (30%). R01 GM067827-01 (NIGMS).
- 2003 - 2008 (Co-Investigator), "Prevention of Mammary Cancer in Her-2neu Transgenic Mice," (5%). R01 (P.I. Merajver).
- 2003 - 2005 (Co-investigator), "Structure-Based Approach for Discovery of Small Molecule Inhibitors of XIAP as Potential Novel Therapy for the Treatment of Prostate Cancer," (5%). Department of Defense Prostate Cancer Research Program.
- 2003 - 2005 (Co-Investigator), "Inhibition of the Anti-apoptotic Function of XIAP using Small Molecule Inhibitors as a Novel Target-specific Therapeutic Strategy for Breast Cancer Treatment," (2%). Department of Defense Breast Cancer Research Program IDEA award. (P.I. Wang).

IV. ADMINISTRATIVE ACTIVITIES:

- A. Organizing Committee, Gordon Research Conference on Cell Death, 2002.
- B. Scientific Advisory Board, Aegera Therapeutics, 2002 - Present.
- C. Temporary Reviewer, NIH Immunobiology Study Section, 2001.
- D. Temporary Reviewer, NIH CDF-5 Study Section, 2001.
- E. Temporary Reviewer, NIH CDF-6 Study Section, 2001.
- F. Co-chair, ASCB Symposium on Stress Regulation and Programmed Cell Death, 2001.
- G. Steering Committee, NIH-Oxford Scholars in Biomedical Research Program, 2001.
- H. Steering Committee, NCI Molecular Targets Faculty, 2000 - 2001.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL AND REVIEWING ACTIVITIES:

- A. Editorial Board: *Journal of Biological Chemistry*, 2002 - 2007

B. Reviewer (selected journals shown):

Blood,
Cancer Research,
Cell Death and Differentiation
Current Biology
Immunity
Journal of Biological Chemistry
Journal of Clinical Investigation
Nature Cell Biology
Nature Reviews Cancer
Oncogene
Proceedings of the National Academy of Sciences USA
Science

HONORS AND AWARDS:

Biomedical Scholar Award, University of Michigan, 2002.

NIH Intramural Research Award, 1999 - 2001.

INVITED LECTURES/SEMINARS:

1. Gordon Research Conference on Cell Death, 2002.
2. ASCB Minisymposium on Stress Regulation and Programmed Cell Death (co-chair), 2002
3. Wayne State University, 2002.
4. University of Texas, M.D. Anderson Cancer Center, 2001.
5. State University of New York at Stony Brook, 2001.
6. Washington University, St. Louis, 2001.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Clem, R. J., Sheu, T. -T., Richter, B. W. M., He, W. -W., Thornberry, N. A., Duckett, C. S. and Hardwick, J. M. cIAP-1 is cleaved by caspases to produce a pro-apoptotic C-terminal fragment. *J. Biol. Chem*, 276:7602-7608 (2001).
2. Harlin, H., Reffey, S.B., Duckett, C.S., Lindsten, T. and Thompson, C.B. Characterization of XIAP-deficient mice. *Mol. Cell. Biol.* 21:3604-3608 (2001).
3. Lewis, J., Eiben, L.J., Nelson, D.L., Cohen, J.I., Nichols, K.E., Ochs, H.D., Notarangelo, L.D. and Duckett, C.S. Distinct interactions of the X-linked lymphoproliferative syndrome protein SAP with cytoplasmic domains of members of the CD2 receptor family. *Clin. Immunol.* 100:15-23 (2001).
4. Richter, B.W.M., Mir, S.S., Eiben, L.J., Lewis, J, Frattini, A., Tian, L., Frank, S., Youle, R.J., Nelson, D.L., Notarangelo, L.D., Vezzoni, P., Fearnhead, H.O. and Duckett, C.S. Molecular cloning of ILP-2, a novel member of the inhibitor of apoptosis protein (IAP) family. *Mol. Cell. Biol.* 21:4292-4301 (2001).
5. Czar, M.J., Kersh, E., Mijares, L.A., Lewis, J., Yap, G., Chen, A., Sher, A., Duckett, C.S., Ahmed, R. and Schwartzberg, P. L. Altered lymphocyte responses and cytokine

- production in mice deficient in the X-linked lymphoproliferative disease gene SH2D1A/DSHP/SAP. *Proc. Natl. Acad. Sci. USA* 98:7449-7454 (2001).
- 6. Reffrey, S.B., Wurthner, J.U, Parks, W.T., Roberts, A.B and Duckett, C.S. X-linked inhibitor of apoptosis protein functions as a cofactor in transforming growth factor- β signaling. *J. Biol. Chem.* 276:26542-26549 (2001).
- 7. Kim, R.H., Flanders, K.C., Reffrey, S.B., Anderson, L.A., Duckett, C.S., Perkins, N.D., and Roberts, A.B. SNIP1 is a global inhibitor of the C/H1 domain of CBP/p300 transcriptional coactivators. *J. Biol. Chem.*, 276: 46297-46304 (2001).
- 8. Duckett, C. S. Apoptosis and NF- κ B: the FADD connection. *J. Clin. Invest.*, 109:579-580 (2002)
- 9. Salvesen, G.A. and Duckett, C.S. IAP proteins: Blocking the road to death's door. *Nature Rev Cell Mol Biol* 3: 401-410 (2002)
- 10. Bratton, S.B., Lewis, J., Butterworth, M., Duckett, C.S., and Cohen, G.M. Linker-BIR2 inhibition of caspase-3 preserves BIR3-caspase-9 interactions in XIAP-Apaf-1 apoptosome complexes. *Cell Death and Diff.*, In Press (2002).

BOOKS/CHAPTERS IN BOOKS:

- 1. O'Shea, J.J., Frucht, D.M. and **Duckett, C.S.** Cytokines: ligands, receptors, signaling, function and clinical relevance. In *Clinical Immunology*, ed R.R. Rich, **1**: 12.1-12.22 (2001).

**JOSEPH C. FANTONE, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Autopsy Service.

II. TEACHING ACTIVITIES:

- A. Director; Resident Training Program.
- B. Course Director; Pathology Teaching Laboratories.
- C. Laboratory Instructor; M1 Histopathology Sequence.
- D. Laboratory Instructor; M2 Pathology Labs.
- E. Lecturer and small group leader; M1 Host Defense Course.
- F. Medical Student Advisor (3rd and 4th year).

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Investigator, "Pulmonary Immune Responses to Inhaled Pathogens". NIH-RO1-HL5531601 (1998-2002)
- B. Principal Investigator, "An Integrated Curriculum for Multiculturalism, Spirituality, and End-of Life Care". Arthur Vining Davis Foundation. (2000-2002).
- C. Co-Investigator, "University of Michigan Integrative Curriculum for Medicine and Allied Health." National Institutes of Health. R25-AT00812-01 (2001-2006).
- D. Co-investigator, "Comprehensive Programs to Strengthen Physicians' Training in Geriatrics." The Donald Reynold's Foundation. (2001-2005).

PROJECTS UNDER STUDY:

- A. Mechanisms of phagocytic cell-mediated tissue injury.
- B. Outcomes measures of undergraduate medical education.
- C. Curriculum development in medical student education

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Anatomic Pathology.
- B. Coordinator - Educational Programs.
- C. Chairman's Advisory Committee.

- D. Department ACAPT Committee.
- E. Research Space Advisory Committee.
- F. Faculty Sexual Harassment Contact Person.

MEDICAL SCHOOL/HOSPITAL:

- A. Associate Dean for Medical Education.
- B. CD/ACD Education Committee (Chair).
- C. Curriculum Policy Committee (Chair).
- D. Medical Student Basic Science Academic Review Board (Chair).
- E. Medical Student Clinical Academic Review Board (Chair).
- F. Medical School Academic Hearing Committee (Chair).
- G. Medical School Curriculum Review Group (Chair)

REGIONAL AND NATIONAL:

- A. USMLE, Step 1 Test Committee, Chair.
- B. Pathology Residency Review Committee. ACGME.

V. AWARDS:

VI. OTHER RELEVANT ACTIVITIES:

VII. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNALS:

1. Tricia S. Tang, Ph.D.¹ Joseph C. Fantone, M.D.², Mary E. Bozynski, M.D.³, Barbara S. Adams, M.D.³ Teaching and Evaluating Undergraduate Curricula in "Sociocultural Medicine". Academic Medicine. 2002; 77: 578-583.
2. Mark A. Supiano, M.D., Casey B. White, B.A., and Joseph C. Fantone, M.D. The Geriatrics Educational Consultant. Academic Medicine (accepted for publication)

**WILLIAM G. FINN, M.D.
CLINICAL ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001- 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Hematopathology Section.
- B. Diagnostic Hematopathology (Bone marrow biopsies, lymph nodes, blood smears, body fluids).
- C. Clinical Flow Cytometry Laboratory.
- D. Clinical Molecular Diagnostics Laboratory.
- E. Hematopathology Consultation Cases (including M-Labs).

II. TEACHING ACTIVITIES:

- A. House Officers:
 - 1. Sign-out of bone marrow biopsies, aspirates, blood smears, and body fluids in Hematology Laboratory.
 - 2. Sign-out of lymph node biopsies and review of hematopathology consultation material.
 - 3. Flow Cytometry sign-out.
 - 4. Hematopathology case conferences (2).
 - 5. House Officer Teaching Award, 2001.
- B. Hematopathology teaching:
 - 1. Leukemia conference/biweekly.
 - 2. Lymphoma conference/weekly.
 - 3. Hematology conference/biweekly.
 - 4. Clinical Pathology Grand Rounds.
 - 5. Clinical Pathology Case Conference/weekly.
- C. Medical Students:
 - 1. M-2 Hematology Sequence: Section leader for laboratory sessions (12 hours).
 - 2. M-2 Hematology sequence: "Pathology and Classification of Lymphoma" (Lecture) – 1 hour.
 - 3. M-1 Histopathology Course (24 hours).
 - 4. Medical Student Award for Teaching Excellence, 2000.
- D. Dental and Graduate Students: Pathology 580/630: "Pathology of White Blood Cells" (Lecture) – 1 hour.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Gene expression profiling of chronic lymphoproliferative disorders.
- B. Finn WG, Peterson LC (eds): *Hematopathology in Oncology*. Kluwer Academic Publishers, Boston (Book under contract; scheduled publication 2003).

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Hematopathology Section.
- B. Clinical Pathology Resident Training.
- C. Interviewer of residency candidates.

REGIONAL/NATIONAL:

- A. Editorial Board, Cytometry (Clinical Cytometry).
- B. Manuscript reviewer, Human Pathology.
- C. Contributing Editor, Yearbook of Pathology and Laboratory Medicine, Mosby, 2002.
- D. Contributing Editor, Yearbook of Pathology and Laboratory Medicine, Mosby, 2003.
- E. American Society of Clinical Pathologists, Check Path Planning Committee (Hematopathology).
- F. College of American Pathologists, Hematology and Clinical Microscopy Resource Committee

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. "Lymphocyte Trafficking and Gene Expression Profiling in the Chronic B-Cell Leukemias." Cleveland Clinic Foundation, Cleveland, OH. October 29, 2001.
- 2. "Chronic Lymphocytic Leukemia: Gene Expression Profiling." Platform presentation, Society for Hematopathology Slide Workshop, Boston, MA, November 9, 2001.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Valdez R, Finn WG, Ross CW, Singleton TP, Tworek JA, Schnitzer B: Waldenstrom macroglobulinemia caused by extranodal marginal zone B-cell lymphoma: a report of six cases. *Am J Clin Pathol* 116(5):683-690, 2001.

2. Kansal R, Singleton TP, Ross CW, Finn WG, Padmore RF, Schnitzer B: Follicular Hodgkin's lymphoma: a histopathologic study. *Am J Clin Pathol*, 117: 29-35, 2002.
3. Mirza I, Macpherson N, Paproski S, Gascoyne RD, Yang B, Finn WG, Hsi ED: Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic and molecular features. *J Clin Oncol* 20(3):647-655, 2002.
4. Hans CP, Finn WG, Singleton TP, Schnitzer B, Ross CW: Utility of anti-CD117 in the flow cytometric analysis of acute leukemia. *Am J Clin Pathol* 117:301-305, 2002.
5. Uherova P, Ross CW, Finn WG, Singleton TP, Nangia R, Schnitzer B: Peripheral T-cell lymphoma mimicking marginal zone B-cell lymphoma. *Mod Pathol* 15:420-425, 2002.
6. Valdez R, Kroft SH, Ross CW, Schnitzer B, Peterson LC, Singleton TP, Finn WG: Cerebrospinal fluid involvement by mantle cell lymphoma. *Mod Pathol*, in press.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Valdez R, Thorson J, Finn WG, Kleer CG, Schnitzer B: Lymphocytic mastitis: a molecular, immunophenotypic, and clinicopathologic evaluation of eleven cases.
2. Kansal R, Ross CW, Kroft SH, Singleton TP, Finn WG, Schnitzer B: Histopathology of splenic small B-cell lymphomas. A study of 54 cases classified by flow cytometric immunophenotypic analysis or lymph node biopsy.
3. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience.

BOOKS AND CHAPTERS IN BOOKS:

1. Finn WG: Classification of lymphoma. In: *Hematology for the Medical Student*. Schmaier A, and Petruzzelli L, eds. Lippincott Williams & Wilkins, in press.
2. Finn WG: Hematolymphoid system. In: *Yearbook of Pathology and Laboratory Medicine 2002*. Raab SS, Bejarano PA, Bissell MG, Silverman JF, Stanley MW, eds. St. Louis, MO: Mosby, Inc., 2002: 335-356.
3. Finn WG: Hematolymphoid system. In: *Yearbook of Pathology and Laboratory Medicine 2003*. St. Louis, MO: Mosby, Inc., 2003, in press.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Finn WG: Alternative to histologic grading of cancer (letter). *Hum Pathol* 32:1277, 2001.
2. Uherova P, Ross CW, Schnitzer B, Finn WG: CD10 expression in diffuse large B-cell lymphoma (letter-reply). *Am J Clin Pathol*, 117:661-662, 2002.
3. Finn WG, Sreekumar A, Stoolman LM, Ross CW, Schnitzer B, Valdez R, Chinnaiyan A: Comparative gene expression profiling of B-cell lymphoproliferative disorders by cDNA microarray analysis: identification of genes preferentially upregulated in chronic lymphocytic leukemia. Platform presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):241A.
4. Guo G, Valdez R, Schnitzer B, Ross CW, Finn WG: The clinical spectrum of increased plasma viscosity: a retrospective study of 115 cases. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):242A.

5. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):267A.
6. Uherova P, Roulston D, Finn WG, Valdez R, Schnitzer B, Ross CW: CD56 expression in acute myeloid leukemia with monocytic differentiation: association with complex karyotype. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):267A.
7. Velankar M, Kansal R, Finn WG, Valdez R, Ross CW, Schnitzer B: Bcl-6 and CD10 paraffin section immunohistochemistry on bone marrow core biopsies to distinguish follicular lymphoma from other small B-cell non-Hodgkin lymphomas. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):268A.
8. Snyder ML, Roulston D, Ross CW, Finn WG, Schnitzer B, Valdez R: Cytogenetic, immunophenotypic, and clinical correlation in adult acute lymphoblastic leukemia: a single institution's experience. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):264A.
9. Valdez R, Thorson J, Finn WG, Kleer CG, Schnitzer B: Lymphocytic mastitis: a molecular, immunophenotypic, and clinicopathologic evaluation of eleven cases. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):268A.

**ANDREW FLINT, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Surgical Pathology Rotations, July (1/5), August (2/4), September (1/4), October (2/4), November (1/4), December (2/5), January (1/4), Mar (1/4), Apr (1/4), May (2/4), June (2/4)
- B. Ophthalmic Pathology Service – 52 weeks/year

II. TEACHING ACTIVITIES:

- A. Pathology 600
 - 1. Obstructive Lung Disease - November, 2001
 - 2. Pulmonary Neoplasms - November, 2001
 - 3. Pathology of ARDS - November 2001
 - 4. Tissue Reactions to Infectious Agents - November, 2001
 - 5. Pulmonary Pathology Review for Medical Students November, 2001
 - 6. General Pathology Review for Medical Students - June, 2002
 - 7. Laboratory Instructor, October, 2001 - May, 2002
 - 8. Medical student question and answer sessions, October, 2001 - May, 2002
 - 9. Histology Tutorial for Medical Students, January, 2002 – May, 2002
 - 10. Histology Tutorial for Dental Students, October, 2001 – December, 2001
- B. Pathology 630:
 - 1. Respiratory Disease I - October, 2001
 - 2. Respiratory Disease II - November, 2001
- C. Residency Training:
 - 1. Topics in Medical Ethics, 2001
 - 2. Consultant's Seminar, December, 2001, May, 2002
- D. Other educational activities:
 - 1. M4 student elective mentor, August 2001, March, 2002
 - 2. Center for Research on Learning and Teaching Workshops: "Technology and Teaching", May, 2002
 - 3. Center for Research on Learning and Teaching Workshops: "Teaching as Theatre", October, 2001
 - 4. Member, M-2 Respiratory Sequence Committee
 - 5. Course Director, M-4 Student Pathology Clerkships
 - 6. Radiology - Pathology Correlation Course Co-Director, April, 2002
 - 7. M1 student mentor, January – May, 2002
 - 8. M2 student mentor, September, 2001 - present

9. Nominated for American Association of Medical Colleges Humanism in Medical Education Award, 2002
10. "Thoracic Pathology," Department of Surgery, April, 2002

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. A Murine Model of Graft-Vs-Host Disease Lacrimal Gland Inflammation and Destruction: Histopathology, Immunopathology, and Intervention (Midwest Eye-Banks and Transplantation Center), Victor M. Elner, MD, PH.D (Principal Investigator), Andrew Flint MD (Co-Investigator)
- B. "Effect of Gamma Interferon Therapy on the Clinical Course of Patients with Idiopathic Pulmonary Fibrosis. Fernando Martinez, MD (Principal Investigator).
- C. "Lung Image Database Consortium (IU01 CA91099-01). Chuck Meyer, PhD (Principal Investigator)

PROJECTS UNDER STUDY:

- A. The separation of usual interstitial pneumonitis from nonspecific interstitial pneumonitis
- B. Interactive Teaching in Pathology
- C. Pathology teaching materials production

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

None.

V. OTHER RELEVANT ACTIVITIES:

- A. Member, Admissions Committee of the University of Michigan Medical School, 1995 - present
- B. Member, Rules Committee, Senate Advisory Committee on University Affairs, 2000 – 2003
- C. Resolution Officer, Office of Student Conflict Resolution, Division of Student Affairs, University of Michigan, 2001 – 2002
- D. Reviewer, Journal of Neuro-Ophthalmology

EDITORIAL BOARDS:

None

INVITED LECTURES/SEMINARS:

None

VI. PUBLICATIONS:

1. Flaherty K, Thwaite E, Kazerooni E, Gross B, Toews G, Colby T, Travis WD, Mumford J, Murray S, Flint A, Lynch JP, Martinez FJ: Radiologic vs. Histologic diagnosis in UIP & NSIP: survival implications. *Thorax* (accepted)
2. Flaherty KR, Toews GB, Travis WD, Colby TB, Kazerooni EA, Gross BH, Jain A, Strawderman III RL, Paine R, Flint A, Lynch III JP, Martinez FJ: Clinical significance of histopathological classification in patients with suspected idiopathic interstitial pneumonia: Results of a large, well characterized cohort. *Eur Respir J* 2002; 19: 275-283

VII. SUBMITTED PUBLICATIONS:

1. Moroi SE, Gokhale PA, Schteingart MT, Sugar A, Downs CA, Shimizu S, Krofchak C, Fuse N, Elner, SG, Elner V, Flint A, Epstein MP, Boehnke, M, Richards, JE: A prominent retrocorneal membrane on an Intraocular Lens in a case with posterior polymorphous corneal dystrophy. (*J Ophth*)
2. Doerr TD, Marentette LJ, Flint A, Elner V: uPAR expression in adenoid cystic carcinoma of the skull base. (*Arch Otolaryngology-Head and Neck Surgery*)
3. JA, Murray S, Flint A, Lynch III JP, Martinez FJ: Radiologic vs. histologic diagnosis Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TB, Travis WD, Mumford in UIP and NSIP: Survival implications

VIII. ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Flaherty K, Colby T, Travis W, Toews G, Flint A, Gay S, Strawderman R, Jain A, Lynch III JP, Martinez FJ: Differential presence of fibroblastic foci in usual interstitial pneumonia patients with or without connective tissue disease. *Am J Respir Crit Care Med* 2001; 163:A983
2. Martinez FJ, Flaherty KR, Travis WD, Colby TV, Kazerooni EA, Gross BH, Jain A, Strawderman III RL, Flint A, Lynch III JP, Toews GB: Quantifying risk of mortality in idiopathic interstitial pneumonia (UIP). Accepted for European Respiratory Society 2001
3. Flaherty KR, Thwaite E, Kazerooni E, Gross B, Toews GB, Colby T, Travis WD, Mumford J, Murray S, Flint A, Lynch III JP, Martinez FJ: Radiologic vs. histologic diagnosis in UIP and NSIP: Clinical implications. *Am J Respir Crit Care Med* 2002; 165: A138.

**DOUGLAS R. FULLEN, M.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Dermatology Service – 12 months
- B. Dermatology Consultation Service – 12 months
- C. Immunofluorescence evaluation of skin biopsies

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. Dermatology laboratory instructor, MS II Dermatology Sequence
 - 2. Dermatology, Pathology Clerkship, MS IV
 - 3. Dermatology, Dermatology Clerkship, MS IV (3 lectures)
- B. House Officers:
 - 1. Dermatology sign-out (dermatology and pathology sign-out)
 - 2. Review of dermatology consultation material
 - 3. Dermatology teaching conference (pathology residents – weekly)
 - 4. Dermatology teaching conference (dermatology residents – weekly)
 - 5. Anatomic Pathology Grand Rounds (one lecture)
 - 6. Review of immunofluorescence on skin biopsies (interesting cases)
- C. Diagnostic Conference, Department of Dermatology (weekly)

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Immunohistochemical evaluation of sentinel lymph nodes for micrometastases: patterns of involvement and sensitivity of S100, HMB45 and melan-A immunostains (D. Karimipour, M.D., L. Lowe, M.D., L. Su, M.D., T. Johnson, M.D.)
- B. S100 A6 protein expression in neurothekeomas (L. Su, M.D.)
- C. Microsatellite instability in Spitz nevi, atypical Spitz tumors and Spitz-like melanoma (S. Gruber, M.D., L. Lowe, M.D. and L. Su, M.D.)
- D. University of Michigan (UMMC 2000-0713): Molecular, biochemical and cellular basis of melanoma and other melanocytic lesions: Tissue Bank (T. Johnson, M.D., T. Wang, M.D., J. Schwartz, M.D., J. Voorhees, M.D., A. Dlugosz, M.D., L. Lowe, M.D., L. Su, M.D., C. Bradford, M.D., V. Cimmino, M.D.)
- E. Patient examination with Mela Find TM System developed by Electro-Optical Sciences, Inc., (EOS), 2001 (J. Schwartz, M.D., T. Johnson, M.D., T. Wang, M.D., D. Karimipour, M.D., J. Orringer, M.D., L. Lowe, M.D., L. Su, M.D., C. Bichakjian, M.D., M. Rabe, R.N.)

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

Director of Histology Laboratory, Department of Pathology

REGIONAL AND NATIONAL:

- I. Ad hoc manuscript reviewer, Journal of Cutaneous Pathology
- II. Ad hoc manuscript reviewer, Journal of the American Academy of Dermatology

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

None

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Fullen, D.R., Reed, J.A., Finnerty, B., McNutt, N.S.: S100 A6 expression in fibrohistiocytic lesions. J Cutan Pathol 28: 229-34, 2001.
- 2. Fullen, D.R., Reed, J.A., Finnerty, B., McNutt, N.S.: S100 A6 preferentially labels type C nevus cells and nevic corpuscles: additional support for Schwannian differentiation of dermal nevi. J Cutan Pathol 28: 393-9, 2001.
- 3. Murphy, M., Fullen, D., Carlson, J.A.: Low CD7 expression in benign and malignant cutaneous lymphocytic infiltrates: experience with an antibody reactive with paraffin-embedded tissue. Am J Dermatopathol 24: 6-16, 2002.
- 4. Su, L., Fullen, D.R., Lowe, L., Uherova, P., Schnitzer, B., Valdez, R.: CD117 (kit receptor) expression in Merkel cell carcinoma. Am J Dermatopathol (in press).

BOOKS/CHAPTERS IN BOOKS:

None

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

- 1. Fullen, D.R., Burger, J.H., Novice, F.M., Lowe, L.: An unusual case of bilateral upper extremity interstitial granulomatous (granuloma annulare-like) infiltrates with concomitant secondary low-grade B-cell lymphoma. (accepted for poster presentation, American Society of Dermatopathology, September, 2001 – meeting canceled).

**DONALD A. GIACHERIO, Ph.D.
ASSISTANT PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Chemistry Laboratory
- B. Sign-out and interpretation of electrophoresis results.
- C. Direct the operation of blood gas/electrolyte analyzers, coagulation testing meters, and hematology analyzers in the Emergency Department and the operating rooms of Main, Mott, and Kellogg Hospitals.
- D. Direct the workgroup overseeing the quality assurance programs for bedside blood glucose testing in the Medical Center.
- E. Planning group for the approval and establishment of alternate site testing programs.
- F. Technical Director for laboratories at U-M Health Centers off-site clinics.
- G. Sign out of Triple Marker Screen results from maternal serum testing.

II. TEACHING ACTIVITIES:

MEDICAL SCHOOL/HOSPITAL:

- A. Pathology House Officers:
 - 1. Clinical Pathology Grand Rounds (2 lectures)
 - 2. Coordinator, Pathology House Officer rotation through Chemistry Lab.
 - 3. Review sign-out and interpretation of electrophoresis results.
 - 4. Review of selected topics in Clinical Chemistry with Block B residents.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Clinical Study of 1,25 DihydroxyVitamin D determination by radioimmunoassay (sponsored by Diasorin, Inc.)
- B. Evaluation of meters and data management systems for point of care testing.
- C. Evaluation of HPLC-MS methods for immunosuppressant drugs Tacrolimus and Sirolimus.
- D. PSA and Percent free PSA levels in an African-American population (Flint Mens Health Study).
- E. Evaluation of an enzymatic method for homocysteine determination.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Incentive Committee
- B. Quality Assurance Committee
- C. Laboratory Reorganization / Automation Work Group
- D. Director, Chemistry Laboratory
- E. Director, Point of Care Testing

MEDICAL SCHOOL /HOSPITAL:

- A. Planning Group for Brighton Health Center Infusion Center.
- B. Renal Replacement Therapy Workgroup.

REGIONAL AND NATIONAL:

- A. Executive Committee, Michigan Section AACC.
- B. Treasurer, Michigan Section AACC.
- C. Lipids and Lipoproteins Division Member, AACC
- D. Pediatric Clinical Chemistry Division Member, AACC.
- E. Ad hoc reviewer, Clinical Chemistry.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- A. The New NCEP Guidelines for Cholesterol Screening. Promedica Health System, Consultants in Laboratory Medicine, Toledo, OH. Jan 10, 2002.
- B. Prenatal Screening: The Triple Test versus the Quad Test. MSCLS Annual Meeting, Kalamazoo, MI. April 17, 2002.
- C. Prenatal Screening for Down Syndrome. Toledo Hospital. May 20, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Palaniappan, L., Anthony, M., Mahesh, C., Elliott, M., Killeen, A., Giacherio, D., and Rubenfire, M.: Cardiovascular risk factors in ethnic minority women aged ≤ 30 years. Am. J. Cardiol. 2002; 89:524-529.
2. Clive, D., Rao, D., Giacherio, D., Gupta, M., Sackrison, J.L., and MacFarlane, G.D.: Analytical and clinical validation of a radioimmunoassay for the detection of 1,25 dihydroxyvitamin D. Clinical Biochemistry 2002 (accepted for publication)

SUBMITTED PUBLICATIONS:

1. McBryde, K.D., Kudelka, T.L., Gardner, J.J., Kershaw, D.B., Bieniewicz, J.C., Mueller, B.A., Giacherio, D.A., and Smoyer, W.E.: Clearance of amino acids by hemodialysis in argininosuccinic synthetase deficiency. *Journal of Pediatrics*.

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

1. McBryde, K.D., Kudelka, T. L., Kershaw, D. B., Bienkiewicz, J.C., Mueller, B. A., Giacherio, D.A., and Smoyer, W.E. Clearance of Arginine for urea cycle defects by intermittent hemodialysis. Presented at the American Society of Nephrology annual meeting, Oct 2001, San Francisco, CA.
2. Clive, D.R., MacFarlane, G.D., Rao, D., Giacherio, D., Gupta, M., and Sackrison, J.: Clinical Utility of a 1,25 dihydroxyvitamin D RIA in the management of end-stage renal disease patients. *Clin. Chem.* 2002; 48(S6):A144.
3. Clive, D.R., MacFarlane, G.D., Rao, D., Giacherio, D., Gupta, M., and Sackrison, J.: Hypovitaminosis D in midwestern urban centers. *Clin. Chem.* 2002; 48(S6):A145.

**PAUL W. GIKAS, M.D.
EMERITUS PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Autopsy Service – 10 days.

II. TEACHING ACTIVITIES:

- A. Histopathology Lab Section for M1 medical students – 16 hours.
B. Urinary Sequence Lab for M2 medical students – 12 hours.

III. RESEARCH ACTIVITIES:

None.

PROJECTS UNDER STUDY:

None.

IV. SERVICE ACTIVITIES:

DEPARTMENTAL:

MEDICAL SCHOOL/HOSPITAL:

- A. Member of Medical School Admissions Committee.

REGIONAL AND NATIONAL:

- A. Chairman, Board of Directors, Public Citizen, Inc. (Ralph Nader, Initial Chairman and Founder).
B. Reviewer for the “Journal of Urology” and “Urology”.

V. OTHER RELEVANT ACTIVITIES:

None.

**THOMAS J. GIORDANO, M.D., Ph.D.
CLINICAL ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. General Surgical Pathology - four months.
- B. Endocrine Surgical Pathology, Departmental and Outside Consultation - 12 months.
- C. Immunoperoxidase Service - Outside Consultation - 12 months.
- D. M-Labs Surgical Pathology Consultation - 12 months.

II. TEACHING ACTIVITIES:

MEDICAL SCHOOL/HOSPITALS:

- A. Medical Students:
 - 1. Sequence Co-Coordinator – Component II Endocrine Sequence.
 - 2. Component II Endocrine Sequence - 2 lectures on Endocrine Pathology.
 - 3. Endocrine Pathology Laboratories - preparation of course materials.
 - 4. Component IV Pathology Elective mentor – one month.
- B. House Officers:
 - 1. General Surgical Pathology - 4 months.
 - 2. Endocrine Surgical Pathology - 12 months as needed.
 - 3. Consultation Conferences - four.
 - 4. Molecular Pathology lectures.
 - 5. Endocrine Pathology lectures.
- C. Dental and Graduate Students:
 - 1. Endocrine Pathology lecture.
- D. Interdepartmental:
 - 1. Endocrine Conference, Department of Surgery - monthly.
 - 2. Adrenal Cancer Conference - monthly.

EXTERNAL:

- A. Michigan State Medical School.
 - 1. Endocrine Pathology - 2 lectures.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Principal Investigator, "University of Michigan Endocrine Bank", Millie Schembechler Adrenal Cancer Research Fund, 1/1/01 to 12/31/02 (\$100,000 direct costs), with Dr. Paul Gauger, Department of Surgery, 5% effort
- B. Co-Investigator, "Great-Lakes-New England Clinical and Epidemiology Center", NCI CA-99-007, 4/1/00 to 03/31/05 (\$4,987,159 total direct costs), with Dr. Dean Brenner, Department of Internal Medicine, 5% effort
- C. Co-Principal Investigator, "Towards a Molecular Classification of Tumors", NCI U19-CA84953, 9/99 to 3/04 (\$951,282/yr direct costs for 4.5 yrs), with S. Hanash, Department of Pediatrics, Pathology Core Director, 20% effort
- D. Co-Principal Investigator, "Proteomics Biomarker Development Laboratory", NCI U01-CA84982, 9/99 to 8/04 (\$304,900/yr direct costs for five years), with S. Hanash, Department of Pediatrics, 10% effort
- E. Director, "Tissue Procurement Contract", Genentech, Inc., 5/99 to 5/2001 (\$92,346 direct costs/year), 10% effort
- F. Core Director, The University of Michigan Comprehensive Cancer Center, Tissue Procurement Service, 7-98 to present, 10% effort
- G. Core Director, The University of Michigan Comprehensive Cancer Center, Laser Capture Microdissection Core, 1-99 to present

PROJECTS UNDER STUDY:

- A. Principal Investigator, "Gene Expression Profiles of Adrenal Cortical Neoplasms."
- B. Principal Investigator, "Molecular Studies of Soft Tissue Sarcomas."
- C. Principal Investigator, "Gene Expression Profiles of Thyroid Neoplasms."
- D. Co-Investigator with Dr. Jim Baker, "Molecular Studies of Thyroiditis."
- E. Co-Investigator, "Molecular Classification of Ovarian, Colonic and Thoracic Neoplasms."
- F. Principal Investigator, "Gene Expression Profiles of Adrenomedullary Neoplasms."

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL and INSTITUTIONAL:

- A. House Officer Candidate Interviews.
- B. Faculty Candidate Interviews.
- C. Sequence Co-Coordinator – Component II Endocrine Sequence
- D. Director, Tissue Procurement Service
- E. Director, Frozen Tumor Bank
- F. Director, Laser Capture Microdissection Core
- G. Medical Institutional Review Board (IRB-Med), *ad hoc* member.
- H. MSTP Career Advisory Panel

NATIONAL:

A. Editorial Board, *Endocrine Pathology*

V. OTHER RELEVANT ACTIVITIES:

1. Consultant, Eli Lilly & Co.
2. Pathology Consultant, Asterand Corporation.

INVITED LECTURES/SEMINAR:

1. "Molecular Classification of Tumors by Gene Expression Profiling," A. James French Society of Pathologists, Ann Arbor, Michigan
2. "Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles", Director's Challenge PI Meeting, Bethesda, Maryland
3. "Towards a Molecular Classification of Human Neoplasia", Eli Lilly and Co., Indianapolis, Indiana
4. "Towards a Molecular Classification of Human Neoplasia", University of Alabama, Birmingham, Alabama

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN PEER-REVIEWED JOURNALS:

1. Schteingart DE, Giordano TJ, Benitez R, Burdick M, Starkman MN, and Strieter RM. Overexpression of CXC-chemokines by an adrenocortical carcinoma: A novel clinical syndrome. J Clin Endocrinol Metab 2001;86:3968-3974.
2. Brichory FM, Misek DE, Yim A-M, Krause MC, Giordano TJ, Beer DG, and Hanash SM. An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer. Proc Natl Acad Sci USA 2001;98:9824-9829.
3. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JMG, Lee N, Misek DE, Greenson JK, Kardia SLR, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles. Am J Pathol 2001;159:1231-1238.
4. Brichory F, Beer D, Le Naour F, Giordano T, and Hanash S. Proteomics-based identification of protein gene product PGP9.5 as a tumor antigen that induces a humoral immune response in lung cancer. Cancer Res 2001;61:7908-7912.
5. Le Naour F, Misek DE, Krause MC, Deneux L, Giordano TJ, Scholl S, Hanash SM. Proteomics-based identification of RS/DJ-1 as a novel circulating tumor antigen in breast cancer. Clin Can Res 2001;7:3328-3335.
6. Thomas DT, Giordano TJ, Sanders D, Biermann JS, Baker L. Absence of Her2/neu expression in osteosarcoma and skeletal Ewing's sarcoma. Clin Cancer Res 2002;8:788-793.
7. Koch CA, Vortmeyer AO, Diallo R, Poremba C, Giordano TJ, Sanders D, Bornstein SR, Chrousos GP, Pacak K. Survivin: a novel neuroendocrine marker for pheochromocytoma. Eur J

Endocrinol 2002;146:381-188.

8. Bretz JD, Mezosi E, Giordano TJ, Gauger PG, Thompson NW, Baker Jr. JR. Inflammatory cytokine regulation of TRAIL-mediated apoptosis in thyroid epithelial cells. Cell Death Diff 2002;9:274-286.
9. Chen G, Gharib TG, Huang C-C, Shedden K, Taylor JMG, Misek DE, Kardias SLR, Giordano TJ, Iannettoni MD, Orringer MB, Hanash S, Beer DG. Discordant protein and mRNA expression in lung adenocarcinomas. Molecular and Cellular Proteomics 2002;1:304-313.
10. Chen G, Gharib TG, Huang C-C, Thomas DG, Shedden KA, Taylor JMG, Kardias SLR, Misek DE, Giordano TJ, Iannettoni MD, Orringer MB, Hanash SM, Beer DG. Proteomic analysis of lung adenocarcinoma: Identification of a highly expressed set of proteins in tumors. In press: Clin Cancer Res
11. Beer DG, Kardias SLR, Huang C-C, Giordano TJ, Levin AL, Misek DE, Lin L, Chen G, Gharib TG, Thomas DG, Lizyness ML, Kuick R, Hayasaka S, Taylor JMG, Iannettoni MD, Orringer MB, Hanash S. Gene expression profiles predict survival of patients lung adenocarcinoma. In press: Nat Med.
12. Gharib TG, Chen G, Wang H, Huang C-C, Prescott MS, Misek DE, Thomas DG, Giordano TJ, Taylor JMG, Kardias S, Yee J, Orringer MB, Hanash S, Beer DG. Proteomic analysis of cytokeratin isoforms uncovers association with survival in lung adenocarcinoma. In press: Neoplasia.
13. Schwartz DR, Kardias SLR, Shedden KA, Kuick R, Michailidis G, Taylor JMG, Misek DE, Wu R, Zhai Y, Darrah DM, Reed H, Ellenson LH, Giordano TJ, Hanash SM, Cho KR. Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. In press: Cancer Research.

ARTICLES SUBMITTED FOR PUBLICATION IN PEER-REVIEWED JOURNALS:

1. Chen G, Gharib TG, Huang C-C, Thomas DG, Shedden KA, Taylor JMG, Kardias SLR, Misek DE, Giordano TJ, Iannettoni MD, Orringer MB, Hanash SM, Beer DG. Proteomic analysis of lung adenocarcinomas using 2D-PAGE mass spectrometry with correlation to mRNA abundance.
2. Dhaini HR, Thomas DG, Giordano TJ, Johnson TD, Biermann JS, Leu K, Hollenberg PF, Baker LH. Delineation of cytochrome P450 CYP3A4/5 expression as a biomarker of therapeutic response in osteosarcoma.
3. Giordano TJ, Thomas DT, Kuick R, Lizyness M, Misek DE, Smith A, Sanders D, Gauger P, Thompson N, Taylor JMG, Hanash S. Distinct molecular profiles of adrenocortical tumors uncovered by DNA microarray analysis.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFERRED JOURNALS:

1. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JMG, Lee N, Misek DE, Greenon JK, Kardias SLR, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles. Presented at the 2001 Fall Cancer Research Symposium, University of Michigan.
2. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JMG, Lee N, Misek DE, Greenon

- JK, Kardia SLR, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles. Presented at the 2001 Director's Challenge PI Meeting, Bethesda, Maryland.
3. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JMG, Lee N, Misek DE, Greenson JK, Kardia SLR, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles. J Mol Diag 2001;3;206.
 4. Thomas DG, Sanders DL, Biermann JS, Baker L, Giordano T. Her2/erbB2 expression in synovial sarcoma. Sarcoma 2001;5;S29.
 5. Thomas DG, Leu KM, Hewitt S, Khanna Chand, Helman L, Giordano TJ, Baker L. Autocrine and paracrine regulation of metastatic growth in canine osteosarcoma. Sarcoma 2001;5;S30.
 6. Giordano TJ, Thomas DG, Sanders D, Lizyness M, Kuick R, Misek D, Hanash S. Comprehensive gene expression profiles of papillary thyroid carcinoma. Mod Pathol 2002;15;115A.
 7. Giordano TJ, Thomas DG, Lizyness M, Sanders D, Kuick R, Misek D, Hanash S. Comprehensive gene expression profiles of adrenal cortical thyroid tumors. Mod Pathol 2002;15;115A.
 8. Dhaini H, Thomas D, Giordano T, Hollenberg P, Baker L. Quantitative double-staining immunofluorescence of drug-resistance related-enzymes in human osteosarcomas using high-throughput tissue microarray blocks. Presented at the 2002 Annual Meeting of the AACR.
 9. Chen G, Gharib TG, Prescott MS, Huang C-C, Shedden KA, Taylor JM, Giordano TJ, Thomas DG, Kuick RD, Iannettoni MD, Hanash SM, Beer DG. Protein expression profiles predict patient survival in Stage I lung adenocarcinoma. Presented at the 2002 Annual Meeting of the AACR.
 10. Thomas DG, Giordano TG, Sanders D, Biermann JS, Pollack RE, Baker L. Tyrosine kinase expression in synovial sarcoma. Presented at the 2002 Annual Meeting of the AACR.
 11. Golembeski C, Thomas D, Lizyness M, Sanders D, Smith A, Giordano T. Evaluation of galectin-3 as a marker of thyroid malignancy using gene expression profiling and immunohistochemistry. Presented at the 2002 Department of Internal Medicine Research Symposium.

**JOEL K. GREENSON, M.D.
ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. General surgical pathology – eighteen weeks.
- B. Gastrointestinal and hepatic pathology consultation services - six months.
- C. Liver transplant pathology - six months.

II. TEACHING ACTIVITIES:

MEDICAL SCHOOL/HOSPITALS:

- A. Medical Students:
 - 1. Pathology 600 - Laboratory Instructor (25 contact hours).
 - 2. GI Pathology Sequence, assisted Dr. Appelman (ten contact hours).
 - 3. GI Pathology Sequence, 2 hours full class lecture
- B. Dental Students:
 - 1. Pathology 630-631 one full class lecture (one contact hour).
- C. House Officers:
 - 1. Surgical pathology diagnosing room instruction for house officers - four months.
 - 2. Two didactic lectures on gastrointestinal pathology - April, 2002.
 - 3. Gastrointestinal and hepatic pathology tutoring - six months.
 - 4. Five consultation conferences.
- D. Interdepartmental:
 - 1. Liver biopsy conference - one hour per month.
 - 2. Multidisciplinary GI tumor board - 1hour every other week.
 - 3. GI pathology teaching sessions with GI fellows - one hour/week.
 - 4. GI and Liver path teaching to GI and transplant fellows – 3 hours/year

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Investigator R01CA81488-01 (\$4,547,772) “Molecular Epidemiology of Colorectal Cancer”, 20% Salary Support, years 1-4, Stephen Gruber, M.D., Ph.D. Principal Investigator.
- B. Co-Investigator N01-DK-9-2323 (\$1,433,559) “Hepatitis C Clinical Trial”, 7% Salary Support, Anna Lok, M.D. Principal Investigator.

- C. Co-investigator in GI Study Group awarded \$15,955.00 grant for a workshop on "Reproducibility of the diagnosis of dysplasia in ulcerative colitis."
- D. Co-investigator with Hari Conjeevaram M.D., "Study of viral resistance to antiviral therapy of chronic hepatitis c (virahep-c) - clinical centers" (7.5% salary support year 2, 3% years 3 and 4), University of Michigan Grant NIH-NIDDK-01-007

PROJECTS UNDER STUDY:

- A. Study of Small cell carcinomas of the colon with GI Study Group
 - B. Study of fatty liver and steatohepatitis with Hari Conjeevaram in Division of Gastroenterology..
 - C. NIH study of HCV with Anna Lok in Division of Gastroenterology.
 - D. NIH study of the Molecular Epidemiology of Colon Cancer in Israel.
 - E. Study of molecular classification of tumors with Stephen Gruber and Thomas Giordano
 - F. Study of molecular genetic changes in pancreas cancer with Diane Simione and Craig Logsdon
- Study of Yersinia and Crohn's disease with Laura Lamps at the University of Arkansas.
Study of UC dysplasia grading with GI Study Group.
Study of Neuroendocrine Tumors of the Gut with Murray Resnick, M.D. Haifa, Israel
Study of Focal Active Colitis in children with Wei Xin

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Surgical Pathology Fellowship Program.
- B. Quality Assurance Officer for Surgical Pathology
- C. Member, Residency Selection Committee
- D. Member, Departmental Incentive Committee
- E. Member, University Hospital Tissue Committee

REGIONAL AND NATIONAL:

- A. Reviewer, Cancer.
- B. Reviewer, Archives of Pathology and Laboratory Medicine.
- C. Reviewer, Gastroenterology.
- D. Reviewer, Human Pathology.
- E. Reviewer and Editorial Board member, American Journal of Surgical Pathology.
- F. Reviewer, American Journal of Pathology.

- G. Reviewer, Modern Pathology
- H. Reviewer, Cancer Research
- I. Education Committee member, USCAP.
- J. President, Gastrointestinal Pathology Society.
- K. Editorial Board member, The Online Journal of Digestive Diseases
- L. American Board of Pathology, Test Question Committee
- M. Reviewer, American Journal of Gastroenterology
- N. Reviewer, British Journal of Cancer
- O. Reviewer, Journal of Clinical Oncology

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. Invited Speaker, A. James French Society of Pathologists biannual meeting, Ann Arbor, MI. Oct. 2001
- 2. Invited Speaker, Johns Hopkins University School of Medicine, Current Topics in Gastrointestinal Pathology, Baltimore, MD, Nov. 2001.
- 3. Visiting Professor, The Cleveland Clinic Foundation, Cleveland, Ohio, Dec. 2001
- 4. Invited Speaker, USCAP long course on GI pathology, Chicago, Illinois, Feb. 27, 2002
- 5. Faculty Member, ASCP Workshop – Surgical Pathology of the Gastrointestinal Tract, Montreal, Canada May 2002.
- 6. Invited Speaker, GI Pathology Companion meeting at DDW, San Francisco, May 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Quallich LD, Greenson JK, Haftel HM, Fontana RJ. Is it Crohn's disease? Severe systemic granulomatous reaction to sulfasalazine in a patient with rheumatoid arthritis. BMC Gastroenterology 1:8, 2001.
- 2. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JMG, Lee N, Misek DE, Greenson JK, Kardia SLR, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon and ovarian adenocarcinomas using gene expression profiles. Am J pathol 159:1231-1238, 2001.
- 3. Bavikatty NR, Goldblum JR, Nielsen S, Abdul-Karim FW, Greenson JK. Florid Vascular Proliferation of the Colon Related to Intussusception and Mucosal Prolapse: Potential Diagnostic Confusion with Angiosarcoma. Modern Pathol 14:1114-1118, 2001.
- 4. Montgomery E, Bronner MP, Greenson JK, Haber MM, Hart J, Lamps LW et al. Are Ulcers a Marker for Invasive Carcinoma in Barrett's Esophagus (BE)? Data from A Diagnostic Variability Study with Clinical Follow-up. Am J Gastroenterol 91:27-31, 2002.
- 5. Greenson JK. Infections of the Esophagus. Pathology Case Reviews 7:19-26, 2002. (Invited paper)
- 6. Greenson JK. Dysplasia in Inflammatory Bowel Disease. Seminars in Diagnostic Pathology 19:31-37, 2002. (Invited paper).
- 7. Watanabe H, Jass J, Geboes K, Greenson J, Day SM, Lewin KJ, et al. Comparison between Japanese and foreign pathologists in their diagnoses of cap polyposis of the colorectum. Stomach and Intestine 37:715-726, 2002.

8. Brown RS, Goodman TM, Zasadny KR, Greenson JK, Wahl RL. Expression of hexokinase II and Glut-1 in untreated human breast cancer. *Nuclear Medicine and Biology* 29:443-453, 2002.
9. Washington K, Greenson JK, Montgomery E, Shyr Y, Crissinger K, Polk DB, Barnard J, Lauwers GY. Histopathology of Ulcerative Colitis in Initial Rectal Biopsy in Children. Accepted to *Am J Surg Pathol*.
10. Chiles MC, Madhusudhan KT, Greenson JK, Pierce RH, Scott MA, Dean PJ, Lamps LW. *Yersinia Enterocolitica* DNA is Detected in Crohn's Disease. Accepted to *Am J Surg Pathol*.

ARTICLES SUBMITTED FOR PUBLICATION IN PEER-REVIEWED JOURNALS:

1. Resnick MB, Herzog Y, Brodzky A, Greenson JK, Eldar S, Gluzman-Poltorak Z, Newfeld G, Tzafrir C. Neuropilin-2 is a Novel Neuroendocrine Marker Expressed in Pancreatic Islet Cells and Islet Cell Tumors. Submitted to *Modern Pathology*.
2. Lauwers GY, Goldblum JR, Burgart LJ, Bhan AK, Vauthey JN, Greenson JK. Expression Of Neurotrophin Receptors And Ret Protein In Duodenal Gangliocytic Paraganglioma: A Study Of 12 Cases. Submitted to *Am J Surg Pathol*.
3. Scheiman JM, Greenson JK, Lee, J, Cryer B. Impact of COX-2 Specific Inhibition on Human *Helicobacter Pylori* (HP) Gastritis: Implications for Ulcerogenesis and Carcinogenesis. Submitted to *Gastroenterol*.
4. Fontana RJ, Hamidullah H, Nghiem H, Greenson JK, Hussain H, Marrero J, Rudich S, McClure LA, Arenas J. Radiofrequency Thermal Ablation of Hepatocellular Carcinoma is an effective bridge to Liver Transplantation: A prospective series. Submitted to *Liver Transplantation*.
5. Gruber SB, Scott KK, Almog R, Bonner JD, Gryfe R, Cleary S, Tomsho LP, Low M, Rennert H, Greenson JK, Rennert G. *BLM* Haploinsufficiency and the Risk of Colorectal Cancer. Submitted to *Science*.
6. Askari FK, Greenson JK, Dick RD, Johnson VD, Brewer G. Treatment of Wilson's Disease with Zinc XVIII. Initial Treatment of the Hepatic Decompensation Presentation with Trientine and Zinc. Submitted to *Journal of Laboratory and Clinical Medicine*

BOOKS/CHAPTERS IN BOOKS:

1. Inflammatory Diseases of the Colon, in *Surgical Pathology of the Gastrointestinal Tract, Liver, Biliary tract, and Pancreas*. Edited by Robert D. Odze, John R. Goldblum, and James Crawford. Harcourt Health Sciences. In Press.
2. *Sternberg's Diagnostic Surgical Pathology, Fourth Ed.* Edited by Mills SM, Carter D, Greenson JK, Oberman HA, Reuter V, and Stoler MH. Lippincott, Williams & Wilkins, Philadelphia, PA. In preparation.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Conjeevaram HS, Huang M, Greenson J, Felton-Church A, Lok AS. Prevalence and severity of steatosis and steatohepatitis in adult and pediatric patients undergoing liver biopsies. Poster presentation at ASLD meeting, Dallas 2001. *Hepatology* 34:461A;2001.
2. Greenson JK, Bonner JD, Ben-Yzhak O, Cohen HI, Miselevich I, Resnick MB, Trougouboff P, Rennert G, Gruber SB. Well-differentiated colorectal cancers are often microsatellite unstable. Platform presentation at USCAP meeting 2002, *Mod Pathol* 15:128A, 2002.
3. Bronner M, Emond M, Burgart L, Goldblum J, Greenson J, Haber M, Hart J, Lauwers G, Lazenby A, Lewin D, Robert M, Washington K, Montgomery E. Diagnostic accuracy in ulcerative colitis. Platform presentation at USCAP meeting 2002, *Mod Pathol* 15:124A, 2002.
4. Chiles MC, Madhusudhan KT, Greenson JK, Scott MA, Bronner MP, Havens JM, Dean PJ, Lamps LW. Pathogenic *Yersinia pseudotuberculosis* and *Yersinia enterocolitica* DNA is

- detected in bowel and mesenteric nodes from Crohn's disease patients. Platform presentation at USCAP meeting 2002, Mod Pathol 15:125A, 2002.
5. Lauwers GY, Goldblum JR, Burgart LJ, Bhan AK, Greenson JK. Expression of neurotrophin receptors and RET protein in duodenal gangliocytic paraganglioma: A study of 12 cases. Poster presentation at USCAP meeting 2002, Mod Pathol 15:134A, 2002.
 6. Hanh NT, Son LB, Zhang S, Perez-Perez G, Greenson J, Nguyen K, Vinh NT, Thanh NN, Olivares AZ, Mao HV, Chey W, Merchant JL. Antigenicity of *Helicobacter pylori* Outer Membrane Protein HP1125 in the Vietnamese Population. Poster presentation at DDW 2002, Gastroenterol 122:A-203, 2002.
 7. Logsdon C, Simeone D, Arumugam T, Binkley C, Ji B, Greenson JK, Misek DE, Kuick R, Hanash S. Molecular Profiling of Pancreatic Adenocarcinoma and Chronic Pancreatitis Identifies Multiple Genes Differentially Regulated in Pancreatic Cancer. Poster presentation at DDW 2002, Gastroenterol 122:A-492, 2002.
 8. Scheiman J, Greenson J, Cryer BL. Impact of COX-2 Specific Inhibition on Human *Helicobacter pylori* (HP) Gastritis: Implications for Ulcerogenesis and Carcinogenesis . Oral presentation at DDW 2002, Gastroenterol 122:A-87, 2002.

CORY M. HOGABOAM, Ph.D.
ASSISTANT RESEARCH SCIENTIST
DEPARTMENT OF PATHOLOGY

ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002

I. CLINICAL ACTIVITIES:

None.

II. TEACHING ACTIVITIES:

A. Graduate Students:

1. Ph.D. Dissertation Committees, University of Michigan
 - a. Cynthia Bone-Larson (Thesis successfully defended July 31, 2001)
 - b. Claudia Jakubzick
 - c. Allison Miller
2. Undergraduate Students, University of Michigan
 - a. Esther Choi
3. PIBS Graduate Student Laboratory Rotations, University of Michigan
 - a. Mr. Vilasack Thammavongsa, BS
4. Preliminary Examiner for Ph.D. Program, Dept. of Pathology
 - a. Yayi Chang
5. Formal Teaching, Dept. of Pathology
 - a. Pathology 582: Inflammation

B. Postdoctoral Fellows:

1. Jane Schuh, Ph.D.
2. Claudia Benjamin, Ph.D.
3. Traci Ness, Ph.D.
4. Simona Neff, M.D.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

Co-investigator, *Stem Cell Factor and mast cells in allergic airway disease*. R01 HL58178 (15%), \$135 000 per annum, 9/1/99 - 8/30/03.

Co-investigator, *Monokine gene expression/regulation in lung injury*. R01 HL31237 (10%), \$200 000 per annum, 4/01/00 - 3/31/05.

Principal Investigator, *Specialized Centers of Research - Pathobiology of Fibrotic Lung Disease*. Project 1: Chemokines and chemokine receptors in IPF. P50 HL56402-04 (20%), \$185 917 per annum for Project 1, 12/01/01-11/30/06.

Principal Investigator, *Role of CXCR4 During Allergic Airway Fibrosis*. Research Contract from AnorMED, Inc. \$23 135.00 per annum, 02/16/01 - 02/16/02.

Co-investigator, *Monocyte/Macrophage Signals in Lung Granuloma*. R01 (15%), \$250 000 per annum, 07/01/01 - 06/30/06.

Principal Investigator, *Caspase Inhibition in the Context of Experimental CLP-induced Sepsis*. Research Contract from Idun Pharmaceuticals, \$22 081 per annum, 07/01/01-06/30/02.

Co-investigator, *SCF in Liver Repair after Hepatectomy or Toxic Injury*. R01 (10%), \$225 000 per annum, 07/01/02-11/30/07.

Principal Investigator, *Targeting of IL-4 and IL-13 responsive cells in the treatment of allergy and asthma*. Biomedical Research Council (BMRC) University of Michigan \$23 654 per annum, 06/01/02-05/31/03.

Co-investigator, *Role of chemokines in acute experimental acute hepatitis* Canadian Institutes of Health Proof of Principle Initiative Grant on Hepatitis C. \$100 000 (CAN) per annum, 07/01/02-06/30/05.

Principal Investigator, *Therapeutic Targeting of RANTES/CCL5 during Chronic Fungal Asthma*. R01 HL69865-01 (40%), \$175 000 per annum, 12/01/02 – 03/31/07.

Pending:

Principal Investigator, *IL-13 fusion cytotoxin as a targeted therapeutic for IIP*. R01 (25%), \$275 000 per annum, 07/01/03-06/30/07.

PROJECTS UNDER STUDY:

Role of chemokines in airway remodeling due to allergic airway disease and asthma.

Role of chemokine receptors in airway remodeling due to allergic airway and asthma.

Role of chemokines and chemokine receptors in human interstitial fibrotic disease.

Novel approaches to targeting IL-4 and IL-13 in chronic allergic airway disease.

Role of IL-4 and IL-13 in chronic interstitial fibrotic disease.

Novel approaches to targeting IL-4 and IL-13 in human interstitial fibrotic disease.

Regulation of fibroblast activities during idiopathic interstitial pneumonias.

Role of chemokines in liver regeneration.

Role of SCF in acute and chronic inflammation.

Role of CC chemokines in acute and chronic pulmonary inflammation.

IV. ADMINISTRATIVE ACTIVITIES:

REGIONAL AND NATIONAL:

A. Membership in Professional Associations

1. American Association of Immunologists (AAI)
2. American Society for Investigative Pathology (ASIP)
3. American Thoracic Society (ATS)

B. Journal peer-review

1. Journal of Immunology (Associate Editor - July 1, 2002 – July 1, 2004)
2. American Journal of Physiology
3. American Journal of Pathology
4. Journal of Clinical Investigation

5. Journal of Leukocyte Biology
6. Journal of Clinical Immunology
7. American Journal of Respiratory Cell and Molecular Biology
8. Infection and Immunity
9. Blood
10. Journal of Experimental Medicine
11. Nature

C. Grant peer-review

1. National Institutes of Health, National Heart, Lung and Blood Institute.
2. Department of Veterans Affairs, Merit Review.
3. University of Michigan. Office of the Vice President for Research.

V. **OTHER RELEVANT ACTIVITIES:**

NHLBI, Division of Extramural Affairs, Review Branch
100. Program Project Review. July 18, 2001

FASEB, New Orleans, LA. April 20, 2002
Chair of ASIP Poster Discussion session: '*Airway inflammation and injury.*'

INVITED LECTURES/SEMINARS:

1. Canadian Association of Gastroenterology, CDDW, Montreal, QC, Canada. February 1-3, 2002. Title: '*Chemokines in Immunopathology and Repair.*'
2. Immunex Corporation, Seattle, WA. March 26-27, 2002. Title: '*The role of MCP-1 and CCR2 in innate and acquired immune responses associated with experimental lung injury.*'
3. Pulmonary Research Group, University of Alberta, Edmonton, AB. April 16-18, 2002. Title: '*Chemokine receptors in allergic asthma: where is the redundancy?*'
4. Chemotactic Cytokines Conference, El Escorial, Madrid, Spain. May 4-10, 2002. Title: '*Chemokines and Innate Immunity: lessons learned from the opportunistic fungus Aspergillus fumigatus.*'
5. Medical College of Wisconsin, Milwaukee, WI. May 16-17, 2002. Title: '*Chemokine receptors in allergic asthma: still looking for the redundancy.*'
6. University of Louisville, Louisville, KY. June 24-25, 2002. Title: '*Linking innate and acquired immunity: importance in chronic fungal asthma.*'

PATENTS

IL-13 receptor-targeted immunotoxins ameliorates symptoms of asthma and of allergy.
University of Michigan and the FDA.
Filed March 1, 2002
Docket Number 015280-448000

Method of treating allergen-induced airway disease.
University of Michigan and Micromet Inc.

Filing pending for August 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICAITON IN REFERRED JOURNALS.

1. Lukacs N.W., Hogaboam C.M., Chensue S.W., Blease K., Kunkel S.L. Type 1/Type 2-cytokine paradigm and the progression of pulmonary fibrosis. *Chest*, 120 (1): S5-8, 2001.
2. Carollo M., Hogaboam C.M., Kunkel S.L., Delaney S., Christie M.I., Perretti M. Analysis of the temporal expression of chemokines and chemokine receptors during experimental granulomatous inflammation: role and expression of MIP-1alpha and MCP-1. *Br. J. Pharmacol.* Nov 6; 134(6): 1166-1179, 2001.
3. Blease K., Jakubzick C., Schuh J.M., Joshi B.H., Puri R.K., Hogaboam C.M. Interleukin-13 fusion cytotoxin ameliorates chronic fungal-induced allergic airway disease in mice. *J. Immunol.*, 167: 6583-6592, 2001.
4. Bone-Larson C.L., Hogaboam C.M., Strieter R.M., Kunkel S.L. IP-10/CXCL10 is hepatoprotective during acute liver injury through the induction of CXCR2 on hepatocytes. *J. Immunol.*, 167: 7077-7083, 2001.
5. Blease K., Kunkel S.L., Hogaboam C.M. IL-18 modulates chronic fungal asthma; putative involvement of toll-like receptor-2. *Inflamm. Res.*, 50: 552-560, 2001.
6. Schuh J.M., Blease K., Hogaboam C.M. The role of CC Chemokine Receptor 5 (CCR5) and RANTES/CCL5 during chronic fungal asthma in mice. *FASEB J.*, 16: 228-230, 2002.
7. Matsukawa A, Lukacs N.W., Hogaboam C.M., Knibbs R.N., Bullard D.C., Kunkel S.L., Stoolman L.M. Mice genetically lacking endothelial selectins are resistant to the lethality in septic peritonitis. *Exp. Mol. Pathol.*, 72(1): 68-76, 2002.
8. Schuh J.M., Blease K., Hogaboam C.M. CXC Chemokine receptor-2 (CXCR2) is necessary for the development and persistence of chronic fungal asthma in mice. *J. Immunol.*, 168: 1447-1456, 2002.
9. Blease K., Schuh J., Jakubzick C., Lukacs N.W., Kunkel S.L., Joshi B.H., Puri R.K., Kaplan M., Hogaboam C.M. Stat6-deficient mice develop airway hyperresponsiveness and airway remodeling during chronic fungal-induced asthma. *Am. J. Pathol.*, 160: 481-490, 2002.
10. Schuh J.M., Blease K., Kunkel S.L., Hogaboam C.M. Eotaxin/CCL11 is involved in acute, but not chronic, allergic airway responses to *Aspergillus fumigatus*. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 283: L198-204, 2002.
11. Schuh J.M., Kunkel S.L., Power C.A., Proudfoot A., Lukacs N.W., Hogaboam C.M. Airway hyperresponsiveness but not airway remodeling is attenuated during chronic pulmonary allergic responses to *Aspergillus* in CCR4-/- mice. *FASEB J.*, published Jun 21, 2002, online.
12. Jakubzick C., Kunkel S.L., Lukacs N.W., Joshi B.H., Puri R.K., Hogaboam C.M. Interleukin-13 fusion cytotoxin arrests *Schistosoma mansoni* egg-induced pulmonary granuloma formation in mice. *Am. J. Pathol.*, in press.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Jakubzick C., Puri R.K., Kunkel S.L., Hogaboam C.M. Impact of interleukin-13-responsiveness on the synthetic and proliferative properties of Th1- and Th2-type pulmonary granuloma fibroblasts. *J. Immunol.*
2. Schuh J.M., Jakubzick C., Blease K., Bruhl H., Xing Z., Mack M., Hogaboam C.M. Therapeutic intrapulmonary targeting of RANTES/CCL5-responsive cells prevents chronic fungal asthma. *Am. J. Pathol.*
3. Ajuebor M.N., Hogaboam C.M., Le T., Swain M.G. Novel anti-inflammatory role of CCL2/MCP-1 in acute T cell-mediated hepatitis in the mouse. *J. Clin. Invest.*

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Matsukawa A., Lukacs N.W., Hogaboam C.M., Lira S.A., Kunkel S.L. Resistance to septic peritonitis in mice lacking CC chemokine receptor 8 via augmenting innate immune response. *J. Leuk. Biol.* 182 Suppl. S, 2001.
2. Jakubzick C., Campbell E., Westwick J., Evanoff H., Hogaboam C.M., Kunkel S.L. IL-13 modulates the phenotypic profile of type 1 and type 2 fibroblasts. *FASEB J.*, 16(4): A457.24, 2002.
3. Schuh J.M., Blease K., Hogaboam C.M. CXC chemokine receptor-2 is necessary for the development and persistence of chronic fungal asthma in mice. *FASEB J.*, 16(4): A245.1, 2002.
4. Schuh J.M., Blease K., Kunkel S.L., Power C.A., Proudfoot A., Lukacs N.W., Hogaboam C.M. Airway hyperresponsiveness, but not airway remodeling, is attenuated during chronic pulmonary allergic responses to *Aspergillus* in CCR4-/- mice. *FASEB J.*, 16(4): A245.2, 2002.
5. Jakubzick C., Kunkel S.L., Joshi B.H., Puri R.K., Hogaboam C.M., IL-13 fusion cytotoxin arrests *Schistosoma mansoni* egg-induced pulmonary granuloma formation in mice. *FASEB J.*, 16(4): A459.15, 2002.
6. Ness T.L., Strieter R.M., Hogaboam C.M., Kunkel S.L. The role of CXCR2 in murine models of sepsis. *FASEB J.*, 16(4): A520.2, 2002.
7. Ajuebor M.N., Hogaboam C.M., Le T., Swain M.G. Novel protective effects of the CC Chemokine CCL2/MCP-1 in concanavalin A-induced acute hepatitis. *Gastroenterology* 122 (4): 238, 2002.
8. Ren X., Hogaboam C.M., Colletti L.M. Stem cell factor plays a role in hepatic regeneration following partial hepatectomy and may be involved in IL-6-mediated hepatocyte proliferation. *Gastroenterology* Plenary Poster presentation.

**NAOHIRO INOHARA, Ph.D.
ASSISTANT RESEARCH SCIENTIST
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

None.

I. TEACHING ACTIVITIES:

Supervised Junya Masumoto, a postdoctoral fellow, Namit Kumar, a Graduate student.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

Active:

Principal Investigator , Nod1: An Apaf-like Activator of Apoptosis and NF- κ B; R01 GM60421-01A2 (Jul. 1 01-Jun 30, 06); NIH

PATENTS:

"Compositions and methods for identifying apoptosis signaling pathway inhibitors and activators" # 6,348,573

DISCLOSURES:

Composition and Methods to identify and study BH3 domains of Bcl-2 family members

PROJECT UNDER STUDY:

1. Regulation of NF- κ B and caspase activation by novel signaling molecules including Nod, Bimp and kinase protein family members.
2. Molecular mechanism of inflammatory and infectious diseases
3. Discovery of novel signaling pathways by bioinformatics and molecular biology

IV. ADMINISTRATIVE ACTIVITIES:

None.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES AND SEMINARS:

1. Invited Speaker, "Regulation of Inflammation and Apoptosis" International Medical Center of Japan, Tokyo, Japan Sept. 2th., 2001
2. Invited Speaker, "Nod protein family and chronic inflammatory diseases" Yamanouchi Pharmaceutical, Tsukuba, Japan, Sept. 3th
3. Invited Speaker, "Regulation of immunity by Nod family", Tokyo Univ., Tokyo, Japan, Sept 4th.
4. Invited Speaker, " Regulation of Inflammation and Apoptosis by Nods and Bimps", Juntendo Univ., Tokyo, Japan, Sept. 5th.
5. Invited Speaker, " Nod2 and Crohn's disease", Conference of Inflammatory Bowel Diseases, Tokyo, Japan, Sept. 6th-7th
6. Invited Speaker, "Regulation of immunity by Nod family", Hyogo Med. School., Hyogo, Japan, Sept. 10th
7. Invited Speaker, "Regulation of Inflammation and Apoptosis", Shinshu Univ., Nagano, Japan, Sept 11th.
8. Invited Speaker, "Regulation of Inflammation and Apoptosis", Riken, Wako, Japan, Sept 12th.

IV. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Inohara N, Ogura Y, Chen FF, Muto A, Nuñez G: Human Nod1 confers responsiveness to lipopolysaccharides. *J. Biol. Chem.* 276: 2551-2554 (2001)
2. Ogura Y, Inohara N, Benito A, Chen, FF, Yamaoka S, Nunez G: Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. *J. Biol. Chem.* 276: 4812-4818 (2001)
3. Nickerson K*, Sisk TJ*, Inohara N*, Yee CSK, Kennell J, Cho M-C, Yannie PJ, Nunez G, Chang C-H: Dendritic cell specific CIITA contains a caspase-recruitment domain that confers potent transactivation activity. *J. Biol. Chem.* 276: 19089-19093 (2001)
4. Lucas PC, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, Yamaoka S, Seto M, Nunez G: Bcl10 and MALT1, independent targets of chromosomal translocation in MALT lymphoma, cooperate in a novel NF-kappaB signaling pathway. *J. Biol. Chem.* 276:19012-19019 (2001)
5. Ogura Y, Bonen, DK, Inohara N, Nicolae DL, Chen F, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH: Susceptibility to Crohn's disease by a frameshift mutation in nod2, resulting in lipopolysaccharide hyporesponsiveness. *Nature* 411: 603-606 (2001)
6. McAllister-Lucas LM*, Inohara N*, Lucas PC*, Ruland J, Li Q, Chen S, Chen FF, Yamaoka S, Verma IM, Mak TW, Nunez G: Bim1, a MAGUK family member linking PKC activation to Bcl10-mediated NF-kappaB induction. *J. Biol. Chem.* 276: 30589-30597 (2001)
7. Inohara N, Nunez G: Signaling Molecules Containing Nucleotide-binding Oligomerization Domains. *Oncogene* 20:6473-81 (2001)

8. Nair RP, Stuart P, Ogura Y, Inohara N, Chia NVC, Young L, Henseler T, Jenisch S, Christophers E, Voorhees JJ, Nunez G, Elder JT: Lack of association between NOD2 3020InsC frameshift mutation and psoriasis. *J. Invest. Dermatol.* 117: 1671-1672 (2001)
9. Kobayashi K, Inohara N, Hernandez LD, Galan JE, Nunez G, Janeway CA, Medzhitov R, Flavell RA: RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. *Nature* 416:194-199 (2002)
10. Inohara N: Molecular functions and related pathologies of Nod proteins. Cold Spring Harbor Meeting, Programmed Cell Death. (2001)
11. Inohara N, Nunez G: ML- a conserved domain involved in innate immunity and lipid metabolism. *Trends Biochem. Sci.* 27: 219-221 (2002)
12. Inoue N, Tamura K, Kinouchi Y, Fukuda Y, Takahashi S, Ogura Y, Inohara N, Nunez G, Kishi Y, Koike Y, Shimosegawa T, Shimoyama T, Hibi T: Lack of Common NOD2 Variants in Japanese Patients With Crohn's Disease *Gastroenterology* 123: 86-91 (2002).
13. Muto A, Ruland J, McAllister-Lucas LM, Lucas PC, Lic Q, Verma PM, Yamaoka S, Chen FF, Mak TW, Nunez G and Inohara N: PKK mediates Bcl10-independent NF-kB Activation Induced by Phorbol Ester. *J. Biol. Chem.* (in press).
14. Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, Inohara N, Nunez G, Tromp G, Williams CJ. NOD2/CARD15 mutations in familial granulomatosis syndromes: A study of the original Blau syndrome kindred and other families with large vessel arteritis and cranial neuropathy *Arthritis Rheum.* (in press)

BOOKS AND CHARTERS IN BOOKS:

None.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Inohara N: Functions of Bcl-2 family members. *Immunology Frontier.* 12: 6-22 (2001)
2. Inohara N: Molecular Mechanism of Apoptosis, An Overview from Structure Analyses of Apoptosis. *Jikken-igaku* 19:1615-1621 (2001)
3. Ogura Y, Inohara, N: Genes for susceptibility of inflammatory bowel diseases. *BIO Clinica* 17: 23-27. (2002)
4. Inohara, N: Nod family proteins and related diseases. *Molecular Medicine* 39: 652-659 (2002)
5. Inohara N: Nod family and inflammatory bowel diseases *Molecular Medicine* (in press)
6. Beck, B., Jones, M.L., Schimmer, R.C., Schmal, H., Friedl, H.P. and Ward, P.A.: Cloning and expression of rat intercellular adhesion molecule-1 (ICAM-1) in the pET and baculovirus systems. *FASEB J.* 9:A37, 1995.

**KENT J. JOHNSON, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Immunopathological evaluation of skin and renal biopsies.
- B. Director, Morphology Core.
- C. Renal pathology.
- D. Autopsy coverage.

II. TEACHING ACTIVITIES:

- A. Lecturer Genitourinary Pathology - Second Year Pathology Course.
- B. Lectures on Renal Pathology - Nephrology Fellows.
- C. Lectures on Renal and Skin Immunopathology - Pathology Residents.
- D. Lectures on Genitourinary Pathology - Dental Pathology Course.
- E. Laboratory Instructor - Second year Pathology Course.
- F. Lecturer Genitourinary Pathology – Second Year Pathology Course, Michigan State University Medical School

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Principal Investigator, "Pathophysiology of Aspiration Pneumonitis", with Paul Knight, Anesthesia , R01, National Institutes of Health - Budget - \$720,866; \$187,518 annual, 08/96 - 07/04.
- B. Principal Investigator, "Inflammatory Cells and Lung Injury", Core C, National Institutes of Health, \$291,025.
- C. Co-Investigator, "Nanomolecule-Based Agents for Pathogen Countermeasure", with James Baker, Allergy, 03/01/97 – 02/28/01, Dept of Defense.
- D. Co-Investigator, "A New Approach to Treat Lupus Nephritis", with Gary Glick, Chemistry. National Institutes of Health, 02/22/00 – 02/21/04.
- E. Principal Investigator, "Mechanisms of Vasculitis", Pfizer, Inc., 5/02 – 5/04

PENDING SUPPORT:

- A. Co-Principal Investigator, "MMPs in Prostate Cancer" NIH
- B. Co-Principal Investigator, "Mechanisms of MMP Involvement in Acute Lung Injury" NIH

PROJECTS UNDER STUDY:

- A. Pathogenesis of IgG and IgA immune complex lung injury.
 - 1. Role of oxygen radicals.
 - 2. Role of proteases.
 - 3. Role of terminal components of the complement system.
- B. Oxidant and protease interaction in inflammation.
- C. Pathogenesis of aspiration pneumonitis.
- D. Pathogenesis of viral pneumonitis.
- E. Pathogenesis of pancreatitis and pancreatitis induced ARDS.
- F. Adhesion molecules and cytokines in inflammation.
- G. Cyclosporin-induced nephrotoxicity.
- H. Role of heme oxygenase in renal injury.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Immunopathology Fellowship Program.
- B. Renal Pathology Conference - Biweekly.
- C. Space Utilization Committee.
- D. Stobbe Funds Committee.

REGIONAL AND NATIONAL:

- A. Associate Editor - Laboratory Investigation.
- B. Reviewer for the following journals:
 - 1. American Journal of Pathology.
 - 2. American Review of Respiratory Diseases.
 - 3. American Journal of Respiratory Cell and Molecular Biology
- C. Consultant/Grant reviewer for the Veteran's Administration.
- D. NIH NHLBI Study Section.

V. INVITED LECTURES AND SEMINARS:

- 1. Invited Main Speaker – 5 Ali Conference, Tokyo, Japan.
- 2. Invited Speaker- Mechanisms of Human Vasculitis, Milan, Italy.
- 3. Invited Speaker – Human Vasculitis, Pathogenesis – Pfizer, Inc., LaJolla, California.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Yung, R., Ray, D., Eisenbraun, J., Deng, C., Attwood, J., Eisenbraun, M., Johnson, K., Miller, R., Hanash, S., and Richardson, B.: Unexpected effects of a heterozygous DNMT1 null mutation on age-dependent DNA hypomethylation and autoimmunity. *J. Gerontology:Biological Sciences*. 2001;56(6):B268-B276.
2. Warner, R.L., Beltran, L., Younkin, E.M., Lewis, C.S., Weiss, S.J., Varani, J., and Johnson, K.J.: Role of stromelysin 1 and gelatinase B in experimental acute lung injury. *Am J of Respir Cell and Mol Biol*, 2001;24:537-544.
3. Warner, R.L., Lewis, C.S., Beltran, L., Younkin, E.M., Varani, J., and Johnson, K.J.: The role of metalloelastase in immune complex-induced acute lung injury. *Am J of Pathol*. 2001;158:2139-2144.
4. Varani, J., Hattori, Y., Dame, M.K., Schmidt, T., Murphy, H.S., Johnson, K.J., Wojno, K.J.: Matrix metalloproteinases (MMPs) in fresh human prostate tumour tissue and organ-cultured prostate tissue: levels of collagenolytic and gelatinolytic MMPs are low, variable and different in fresh tissue versus organ-cultured tissue. *Br J Cancer*. 2001;84:1076-83.
5. O'Shea, S., Johnson, K., Clark, R., Sliwkowski, M.X., Erickson, S.L.: Effects of in vivo heregulin beta1 treatment in wild-type and ErbB gene-targeted mice depend on receptor levels and pregnancy. *Am J Pathol*. 2001;158:1871-80.
6. Yung, R., Kaplan, M., Ray, D., Schneider, K., Mo, R.R., Johnson, K.J. and Richardson, B.: Autoreactive murine Th1 and Th2 cells kill syngeneic macrophages and induce autoantibodies. *Lupus* 2001;10:539-546.
7. Lewis, D.A., Colton, D., Johnson, K.J., and Hirschl, R.B.: Prevention of ventilator-induced lung injury with partial liquid ventilation. *J Pediatr Surg* 2001;36:1333-1336.
8. Sawada, S., Matsuda, Younger, J., Johnson, K.J., Bartlett, Hirschl, R.B.: Effects of partial liquid ventilation on unilateral lung injury in dogs. *Chest* 2002 Feb;121(2):566-72.
9. Benzodiazepine-induced superoxide signals B cell apoptosis: Mechanisitic insight and potential therapeutic utility. Accepted for publication JCI, 2002.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Kershaw, D.B., Bunchman, T.E., Johnson, K.J., Sedman, A.B., Kelsch, R.C.: Crescentic glomerulonephritis with subsequent hemolytic uremic syndrome in a child. Submitted for publication.
2. Varani, J., Hirschl, R., Dame, M. and Johnson, K.: Neutrophil infiltration is reduced during liquid ventilation: II. In Vitro analysis. Submitted for publication to *Amer. J. Respiratory & Critical Care Medicine*.
3. Sawyer, R.G., Chenault, R.H., Merion, R.M., Johnson, K.J., Kuta, E.G., and Hebert, C.A.: Antibody to interleukin-8 decreases systemic and pulmonary sequelae of sepsis: evidence for early chemokine regulation of cytokine activity in a porcine model of bacteremia. Submitted for publication.
4. Reuter, J.D., Myc, A., Cao, Z., Johnson, K.J., Wright D.C., Brisker, J., and Baker, J.R.: Prevention of influenza A virus infection by non-ionic surfactant nanoemulsions in a murine model. Submitted for publication.
5. Heard, P.L., Bleavins, M.R., Johnson, K.J., Shi, M. and de la Iglesia, F.A.: Induction of Alanine Aminotransferase Gene Expression by Tacrine in Hep G2 Cells. Submitted for publication.

6. Yung, R., Kaplan, M., Ray, D., Schneider, K., Ru-Ran, M., Johnson, K.J., and Richardson, B.: Common Effector functions of autoreactive Th1 and Th2 cells suggest a mechanism for tolerance abrogation and autoantibody induction. Submitted for publication.
7. Yung, R., Kaplan, M., Ray, D., Schneider, K., Ru-Ran, M., Johnson, K.J. and Richardson, B.: Autoreactive murine Th1 and Th2 cells kill syngeneic macrophages and induce autoantibodies. Submitted for publication.

BOOKS AND CHAPTERS IN BOOKS:

1. Warren, J.S., Johnson, K.J. and Ward, P.A.: Phagocytes and reactive oxygen substances as mediators of acute lung injury, in, Hyers, T. (ed), Diffuse Alveolar Damage and Respiratory Failure, Futura Press, New York, In Press.
2. Till, G.O., Johnson, K.J. and Ward, P.A.: Oxygen free radicals in inflammation, in, Messmer, K. and Hammersen, F. (eds), Prog. Appl. Microcirc., Volume 9, Karger, Basel, In Press.
3. Ward, P.A., Warren, J.S. and Johnson, K.J.: Oxygen radicals, inflammation and tissue injury, in, Pryor, W. and Godber, S.L. (eds), Free Radical Biology and Medicine, In Press.
4. Varani, J. and Johnson, K.J.: Modulation of endothelial cell injury by all-trans retinoic acid: Role of the anti-inflammatory effects of RA, in, Jesaitis, A. (ed), Molecular basis of oxidative damage by leukocytes. CRC Press, In Press.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Varani, J., Dame, M., Johnson, K.J., and Wojno, K.J.: Elaboration of matrix metalloproteinases by fresh human prostate tissue and by prostate tissue in organ culture. *Experimental Biology* 15(4):475.12, 2001.
2. Warner, R.L., Lukacs, N.W., Lewis, C.S., Varani, J., and Johnson, K.J.: Role of matrix metalloproteinases in a model of allergic inflammation in mice. *Experimental Biology* 15(4):50.1, 2001.
3. Burmeister, W., Varani, J., Bleavins, M., Dame, M., and Johnson, K.J.: Effects of three matrix metalloproteinase inhibitors (PD-159879, PD-166793 and marimastat) on proliferation of fibroblasts from human, marmoset, cynomolgus monkey, and rat. *Experimental Biology*, 15(4):131.11, 2001.
4. Johnson, K.J., Warner, R.L., Beltran, L., Younkin, E.M., Lewis, C.S., and Varani, J.: Role of stromelysin-1 and gelatinase B in experimental acute lung injury. *Experimental Biology*, 15(4):71.5, 2001.
5. Delnomdedieu, M., Reily, M., Johnson, K., Roffi, C., and Bleavins, M.: NMR of human biofluids: a promising tool to monitor health status. *Metabolic Profiling: Pathways to Discovery*, Dec. 2001.
6. Roffi, C., Butler, A., Dednomdedieu, M., Johnson, K.J., Bleavins, M.: NMR of human biofluids: metabolites quantitation and correlation to metabolic pathways 43rd ENC (Experimental Nuclear Magnetic Resonance Conference), April 2002.
7. Johnson, K.J., Warner, R.L., Varani, J.: Role of stromelysin-1 in experimental acute lung injury. *FASEB J.* 16(4): A590.456.7, 2002.
8. Warner, R.L., Johnson, K.J., Varani, J.: Role of metalloelastase (MMP-12) in a model of experimental asthma. *FASEB J.* 16 (4) A590.456.8, 2002.

9. Warner, R.L., Younkin, E., Beltran, L., Johnson, K.J., Varani, J.: Lung parenchymal cells as a source of matrix metalloproteinases in lung inflammation. *FASEB J.* 16(4) A1207.909.6, 2002.

**W. JOHN JUDD, F.I.B.M.S., M.I.BIOL.
PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001- 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Blood Bank Reference Laboratory
- B. Consultant, Veteran's Administration Medical Center, Ann Arbor.

II. TEACHING ACTIVITIES:

Resident Training/Contact Hours

- A. Clinical Pathology Grand Rounds:
 - 1. Program Director (CME Accredited Program 10016)
 - 2. Presented lecture on Special Methods in Antibody Identification
- B. Anatomical pathology Conferences:
 - 1. Program Coordinator (CME Accredited Program 10004)
- C. Core-Lecture Series in Blood Banking for 1st-year Pathology House Officers:
 - 1. Program Coordinator
 - 2. Presented lectures on:
 - a) Pretransfusion testing 4 hours
 - b) Prenatal/perinatal testing 4 hours
 - c) Immune hemolysis 4 hours
 - d) Antibody identification 4 hours
- D. Clinical Pathology Case Study Conference (CME Accredited Program 10021)
 - 1. Program Coordinator
 - 2. Participant 40 hours
- E. Management Lecture Series
 - 1. Developed/coordinated series of 8 lectures on laboratory management issues relative to Pathology Residents
- F. Ethics
 - 1. Departmental liaison, GME ethics program
 - 2. Incorporated four 1-hour sessions on ethical issues into the Residency Training Program
- G. Transfusion Medicine Fellowship Program
 - 1. Program Coordinator
 - 2. Araba Afenyi-Annan, MD – Transfusion Medicine Fellow, July 2001 – June 2002 (50 contact hours); RWJ Fellow, University of North Carolina, Chapel Hill, NC
- H. Residency Training
 - 1. Provided instruction in immunohematology to six house-officers during their Blood Bank Rotation (over 150 contact hours)

2. Provided instruction in immunohematology to seven hematology/oncology fellows (21 hours).
- I. Current Topics in Blood Banking Conference, Towsley Center for Continuing Medical Education:
 1. Program Director – Planned and coordinated the June, 2002 Current Topics in Blood Banking Symposium and Preconference Workshops 11 hours
 2. Presented Workshop entitled: From Chemicals to Columns and Clones to Codons (1 5 contact hours)
 3. Presented Workshop entitled: Transfusing Incompatible Blood (1 contact hour)
 4. Presented talk entitled: Recommendations for Prenatal/Perinatal Testing, Revisited (1 contact hour)
 5. Moderated morning session on Transfusion Medicine topics

III. RESEARCH ACTIVITIES:

- A. Steiner EA, Judd WJ, Combs MR, et al. Prenatal antibody titers by the gel test (abstract). *Transfusion* 2001;41(S):31.
- B. Judd WJ, Dake LR. Enzyme tests using anti-IgG gels. Accepted for presentation at the Congress of the International Society for Blood Transfusion, Vancouver, BC, August 2002.
- C. Afenyi-Annan A, Judd WJ. Cefotetan-induced immune-mediated hemolysis complicated by thrombocytopenia: alloimmune or thrombotic? Accepted for presentation at the Annual Meeting of the American Association of Blood Banks, Orlando, FL, October 2002.
- D. Dake LR, Judd WJ. Weak D testing DAT-positive infants born to Rh-negative women in cases of fetal-maternal ABO incompatibility. Accepted for presentation at the Annual Meeting of the American Association of Blood Banks, Orlando, FL, October 2002.
- E. Judd WJ, Moulds M, Schlanser G. Reactivity of FDA-approved monoclonal anti-D reagents with partial D RBCs. Accepted for presentation at the Annual Meeting of the American Association of Blood Banks, Orlando, FL, October 2002.
- F. Boonenberg C, Dake LR, Butch SH, Judd WJ. Effective removal of isohemagglutinins from AS-3 red blood cells for use in ABO incompatible heart transplants. Accepted for presentation at the Annual Meeting of the American Association of Blood Banks, Orlando, FL, October 2002.
- G. Cooling L, Judd WJ, Copeland T. A missense mutation in β 3GalT5, the glycosyltransferase responsible for galactosylgloboside and Lewis c Synthesis, may be associated with the LKE-weak phenotype in African Americans. Accepted for presentation at the Annual Meeting of the American Association of Blood Banks, Orlando, FL, October 2002.
- H. With Irwin Goldstein, PhD. Studies on the α -D-galactose-binding lectin from *Marasmius oreades*.
- I. With Tom Annesley, PhD. Studies on the second example of Paraben anti-D.

IV. SERVICE ACTIVITIES:

DEPARTMENTAL:

- A. Blood Bank Daily Rounds.
- B. Weekly Blood Bank Communication Meetings.
- C. Monthly Clinical Pathology Faculty Meetings.

REGIONAL/NATIONAL/INTERNATIONAL:

- A. Michigan Association of Blood Banks:
 - 1. Member, Annual Meeting Program Committee.
- B. American Association of Blood Banks:
 - 1. Member, Scientific Abstract Review Committee.
 - 2. Member, Editorial Board, Transfusion.
- C. Reviewer of articles submitted for publication in Transfusion, Immunohematology, Transfusion Medicine and Vox Sanguinis.
- D. International Society of Blood Transfusion
 - 1. Member, WHO Committee on Blood Group Nomenclature

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES:

- 1. The blood bank of the future. Annual Meeting of the Michigan Association of Blood Banks, Detroit, MI, September, 2001.
- 2. Practice guidelines for prenatal and perinatal immunohematology, revisited. . Annual Meeting of the Michigan Association of Blood Banks, Detroit, MI, September, 2001.
- 3. Approaches to antibody identification. University of Western Ontario, London, Canada, October, 2001.
- 4. Compatibility testing – past, present and future. 50th Anniversary of the Danish Blood Transfusion Service, Odense, Denmark, November, 2001
- 5. Clinical insignificance of a positive direct antiglobulin test. AABB Annual Meeting, San Antonio, TX. November, 2001
- 6. Transfusing in the face of coldreactive autoantibodies. AABB Annual Meeting, San Antonio, TX. November, 2001
- 7. Modern approaches to antibody detection and identification. Joint Annual Meeting of the American Society for Clinical Pathology and the Clinical Laboratory Management Association, New Orleans, LA, June 2002.

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN PEER-REVIEWED JOURNALS:

1. Lee S, Russo DC, Reiner AP, Lee JH, Sy MY, Telen MJ, Judd WJ, Simon P, Rodrigues MJ, Chabert T, Poole J, Jovanovic-Srzentic S, Levene C, Yahalom V, Redman CM. Molecular defects underlying the Kell null phenotype. *J Biol Chem* 2001;276:27281-9.
2. Judd WJ, Dake L. PEG adsorption of autoantibodies causes loss of concomitant alloantibodies. *Immunohematology* 2001;17:82-5.
3. Judd WJ. Practice guidelines for prenatal and perinatal immunohematology revisited. *Transfusion* 2001;41:1445-52.

CHAPTERS IN BOOKS:

1. Judd WJ. Pretransfusion testing. In: McClatchey KD, ed. *Clinical laboratory medicine*, ed 2. Philadelphia: Lippincott Williams & Wilkins, 2002:1533-1544.
2. Judd WJ. Red cell immunology and compatibility testing. *Rossi's Principles of Transfusion Medicine*, ed 3. Philadelphia: Lippincott Williams & Wilkins, 2002:69-88.

**CELINA G. KLEER, M.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
JULY 1, 2001 - JUNE 30, 2002**

I. CLINICAL ACTIVITIES:

- A. General surgical pathology, including frozen sections, and biopsies in diagnostic rooms I, II, and C with residents and fellows – 4 months
- B. Breast pathology transfer and consultation service – 12 months
- C. Review of all breast cancer cases to be presented in the Breast Care Conference – 12 months

I. TEACHING ACTIVITIES:

- A. Undergraduate Students
Mentored Tammy Chang for 6 months in the laboratory and in writing her graduation thesis.
- B. Medical Students (M2 and M4)
Radiology-Pathology course for M4 students – 3 contact hours
Mentored five M4 students - 1 month
Reproductive Pathology Sequence, M2 students – 10 contact hours
- C. Pathology House Officers and Fellows
Surgical pathology diagnosing room instruction for house officers - 4 months
Two slide conferences on interesting cases in breast pathology – 2 contact hours
Two didactic lectures on breast pathology – 2 contact hours
- D. Interdepartmental
Breast Care Clinic tumor board – 2 hours every week for 12 months
Breast Surgical Oncology Fellow - Kathleen Diehl, M.D. Review of interesting breast pathology cases – 1 month

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

ACTIVE

- 1. **Principal Investigator - USAMRMC DAMD17-00-1-0636, \$75,000, 9/15/00 - 9/14/02 0%**
- 2. **"LIBC (Lost in Inflammatory Breast Cancer) Gene Targeted Mice: A Novel Model to Develop and Test Gene Targeted Therapies for Inflammatory Breast Cancer"**
- 3. **Principal Investigator - Research Grant (Kleer CG) John and Suzanne Munn funds \$10,000, 8/1/01 - 7/31/03 0%**
- 4. **"Protein Expression Profile Analysis of Human Breast Cancer Progression by Use of High Density Tissue Microarrays".**

5. **Principal Investigator - USAMRMC-Career Development Award DAMD17-02-1-0490**, \$355,152 4/17/02 – 4/16/05, 50%
6. "Detection of Metastatic Potential in Breast Cancer by RhoC-GTPase and WISP3 Proteins"
7. **Principal Investigator - USAMRMC-Clinical Bridge Award DAMD17-02-1-491**, \$451,531, 4/17/02 – 4/16/06, 30%
8. "Detection of Metastatic Potential in Breast Cancer by RhoC-GTPase and WISP3 Proteins"
9. **Co-Investigator** – Proteomics alliance project, 5% (PI: Gilbert Ommenn).

PENDING

1. **Principal Investigator –NIH, K08 CA090876-01A2 (Kleer, CG)**, \$630,000, 80%
"Role of LIBC (WISP3) in the Development of the Inflammatory Breast Cancer Phenotype"

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

None

REGIONAL AND NATIONAL:

Reviewer, Cancer Research
Reviewer, Endocrine pathology
Reviewer, Modern Pathology

V. INVITED LECTURES:

1. Grand Rounds "Detection of Metastatic Potential in Breast Cancer by RhoC GTPase and WISP3 proteins" MD Anderson Cancer Center, Houston, TX. March 8th, 2002.
2. Invited Speaker "Role of RhoC in the Detection of Aggressive Breast Cancer" The World Congress in Breast Cancer, Victoria, Canada. June 7th, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Kleer CG, van Golen KL, Braun T, Merajver SD. Persistent E-cadherin expression in inflammatory breast cancer. Modern Pathology. Mod Pathol 14: 458-464, 2001.
2. Kleer CG, van Golen KL, Zhang Y, Wu Z-F, Rubin MA, Merajver SD. Characterization of RhoC Expression in Benign and Malignant Breast Disease: A Potential New Marker for Small Breast Carcinomas with Metastatic Potential. Am J of Pathol. 160(2), 579-584, 2002.
3. Kleer CG, Zhang Y, Pan Q, van Golen KL, Wu Z-F, and Merajver SD. WISP3 Is a Novel Tumor Suppressor Gene of Inflammatory Breast Cancer. Oncogene 21, 3172-3180, 2002.

4. Zhou M, Chinnaiyan AM, Kleer CG, Lucas PC and Rubin MA. Alpha-Methylacyl-CoA racemase: a novel tumor marker overexpressed in several human cancers and their precursor lesions. *Am J Surg Pathol*. 26(7): 926-931, 2002.
5. Kleer CG, Tseng MD, Gutsch DE, Rochford AR, Wu Z-F, Joynt LK, Helvie MA, Chang T, van Golen KL, Merajver SD. Epstein-Barr virus is implicated in the pathogenesis of breast fibroadenomas in immunocompromised hosts. *Modern Pathology* 15(7):759-764, 2002.
6. Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bais C, De Carvalho M, Mesri EA, Robins DM, Dick R, Brewer GJ and Merajver SD. Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. *Cancer Research* 62(17), 2002 In Press.

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

1. Kleer, CG and Rubin, MA. Increased expression of α -methylacyl-CoA racemase (AMACR) is associated with tumor size and lymph node metastases in breast cancer. Presented at the IAP meeting, February 2002, Chicago, IL.
2. Kleer, CG and Afify, AM. HER-2/neu over-expression: comparison between three immunohistochemical assays. Presented at the IAP meeting, February 2002, Chicago, IL.
3. Valdez, R, Thorson, J, Finn, WG, Schnitzer, B, and Kleer, CG. Lymphocytic mastitis/diabetic mastopathy: a molecular, immunophenotypic and clinicopathologic evaluation of eleven cases. Presented at the IAP meeting, February 2002, Chicago, IL.
4. Kleer CG, van Golen KL, Zhang Y, Wu Z-F, Rubin MA, Merajver SD. RhoC expression in benign and malignant breast disease: a promising marker of metastatic potential in small tumors. Presented at the AACR meeting, April 2002, San Francisco, CA.
5. Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bais C, De Carvalho M, Mesri EA, Robins DM, Dick R, Brewer GJ and Merajver SD. Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Presented at the AACR meeting, April, 2002, San Francisco, CA.
6. Kleer CG, van Golen KL, Zhang Y, Wu Z-F, Rubin MA, Merajver SD. RhoC expression in benign and malignant breast disease: a promising marker of metastatic potential in small tumors. ASCO meeting, May 18th 2002, Orlando, FL.

**CYNTHIA KRUEGER, M.D.
LECTURER
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Cytopathology Service:
1. Fine Needle Aspiration Service – 8 weeks
 2. Gynecologic and Non-gynecologic Cytology Service – 5 weeks

II. TEACHING ACTIVITIES:

- A. House Officers:
1. Fine Needle Aspiration Cytology – 8 weeks
 2. Gynecologic and Non-gynecologic Cytology Service – 5 weeks
 3. Cytopathology Teaching Conference – 1 hour

**STEVEN L. KUNKEL, Ph. D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

None

II. TEACHING ACTIVITIES:

- A. Host Defense Sequence, First Year Medical School
- B. Case Reports First Year Medical Students
- C. Grand rounds: Rheumatology, Pediatrics
- D. Academic Advisor, Immunology graduate program
- E. Member, Molecular mechanisms of Microbial Pathogenesis training grant program committee
- F. Operating committee Graduate Program in Immunology
- G. Member, Pathology graduate program committee
- H. Member, Lung Immunopathology Post-doctoral Training Program (Pathology)
- I. Member, Experimental Immunopathology Training Program (Pathology)
- J. Member, Pulmonary Cellular and Molecular Biology Training Program
- K. Member, Pediatric Training Grant "Cellular and Molecular Biology in Pediatrics"
- L. Member, Systems and Integrative Biology Training Program (Physiology)
- M. Chair, Pathology Graduate Examination committee
- N. Member, Graduate Teaching Award Review Committee
- O. Supervised/serve on thesis committee for the following postdoctoral fellows, graduate students, medical students and undergraduates:
Fellows: Jane Schuh, Claudia Benjamim, Steven Lundy, Traci Ness, Robert Edwards
Graduate Students ; Sara Cheng, Claudia Jakubzick
Medical students: Matt Steinhauser
Undergraduate Students: Ester Choi, Kristin Carpenter, Nicholas Martens, Ron Harris, Joe Nosel
- P. Doctoral Thesis Committee Member/Orals Committee for the following graduate students: Molly Thomas, (Pathology), Allison Miller (Pathology), Joyce J. Lai (Public Health), Sara Cheng (MSTP, CMB), Anavelys Ortiz-Suarez (CMB) Tania Gourley (Micro/Immuno), Tina Yee (Micro/Immunology), Phil Schaner (MSTP, Cell and Developmental Biology), John Marrow (MSTP, Neuroscience), Yayi Chang (Pathology)
- Q. Oral preliminary examination committee
- R. Facilitator SROP Conference Research Roundtable

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. NIH - Macrophage/Monocyte Signals in Lung Granuloma Formation; HL-RO1-35276; Principal Investigator MERIT Grant
- B. NIH - Monokine Gene Expression/Regulation in Lung Injury HL-RO1-31237; Principal Investigator
- C. NIH - Inflammatory Cells and Lung Injury; Program Project HL-31963; Principal Investigator for Section II
- D. SCOR Occupational and Immunological Lung Disease, P50HL-46487 Principal Investigator for Project 3
- E. SCOR Acute Lung Injury, P50HL60289, Principal Investigator Project 3

PROJECTS UNDER STUDY:

- A. Role of cytokines in acute inflammation
- B. Regulation of chemokine gene expression
- C. Macrophage-lymphocyte interactions in the initiation, maintenance, and resolution of chronic inflammation

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Operating committee Pathology graduate program
- B. Space utilization and research committee
- C. Interview candidates for graduate program
- D. Divisional Co-Director of General Pathology
- E. Chair, Graduate Program's Examination committee
- F. Member, Department of Pathology ACAPT committee
- G. Chair, Medical School Selection Tuition Selection Committee

MEDICAL SCHOOL/HOSPITAL/UNIVERSITY:

- A. Member, Committee on medical student research
- B. Medical school admission interview committee
- C. Medical scientist training program interviewer
- D. Member, Research Council of the Office of the Vice President for Research
- E. Member, Michigan cancer center
- F. Grant reviewer, Biomedical Research Council
- G. Member, Advisory Committee Cancer Center Animal Core
- H. Associate Dean for Interdisciplinary Programs, Rackham Graduate School
- I. CMB Advisory Committee
- J. Dean's Research Advisory Board
- K. Medical School Space master Plan Steering Committee

- L. Medical School Communications Advisory Committee
- M. Member, Advisory committee on Medical School appointments, promotions, and tenure
- N. Member, Human Research Coordinating Council
- O. Member, Dean's Task Force on Rodent Populations
- P. Committee of associate chairs for research

REGIONAL AND NATIONAL:

- A. Associate Editor, Journal of Clinical Investigation
- B. Associate Editor, American Journal of Pathology
- C. Associate editor, American Journal of Respiratory Cell and Molecular Biology
- D. Associate Editor, Experimental and Molecular Pathology
- E. Associate Editor, Shock
- F. Editorial board, Mediators of Inflammation
- G. Co-Chair 2003 Keystone Conference on Biology of Chemokines
- H. Co-Chair 2002 International Chemokine Conference
- I. Reviewer for the following journals: American Journal of Pathology, American Review of Respiratory Disease, Circulation, Infection and Immunity, Laboratory Investigation, Science, Journal of Immunology, American Journal of Respiratory Cell and Molecular Biology
- J. Grant Reviewer, The Arthritis Society
- K. Grant Reviewer, Veterans Administration
- L. National Institutes of Health Study Section, Lung Biology and Pathology (ad hoc)

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES AND SEMINARS:

- 1. Visiting Professor, Division of Allergy and Immunology, University of Texas Medical Branch, Galveston, Texas, August 2001.
- 2. Invited speaker, Lilly Pharmaceutical Co, September 2001
- 3. Invited speaker, session chair Inflammation Research Association "Chemokines: Progress on therapeutic outcomes", November 1, 2001, Boston, MA
- 4. Invited Speaker and session chair, British Pharmacological Society, Chemokine and their antagonist. December 2001, London
- 5. Invited lecture, Burroughs-Wellcome lectureship National Institute of Health; January 2002, Bethesda, MD
- 6. Invited lecture, Heidelberg Nephrology Forum, June, 2002, Heidelberg, Germany

VI. PUBLICATIONS:

ARTICLES PUBLISHED IN REFEREED JOURNALS:

- 1. Belperio JA, Keane MP, Burdick MD, Lynch JP 3rd, Xue YY, Berlin A, Ross DJ, Kunkel SL, Charo IF, Strieter RM. Critical role for the chemokine MCP-1/CCR2 in the pathogenesis of bronchiolitis obliterans syndrome. J Clin Invest. 2001, 108:547-56.

2. Blease, K., Kunkel, S.L. Hogaboam, C.M. IL-18 modulates chronic fungal asthma in a murine model; putative involvement of Toll-like receptor-2. *Inflammation Res* 2001; 50:552-560.
3. Godessart, N., Kunkel, S.L. Chemokines in autoimmune disease. *Current Opinion in Immunol* 2001; 13:670-675.
4. Yoshida, A., Elner, S.G., Bian, Z.M., Kunkel, S.L., Lukacs, N.W., Elner, V.M. Thrombin regulates chemokine induction during human retinal pigment epithelial cell/monocyte interaction. *Am. J. pathol.* 2001; 159:1171-1180.
5. Carollo, M., Hogaboam, C.M., Kunkel, S.L., Delaney, S., Christie, M.I., Perretti, M. Analysis of the temporal expression of chemokines and chemokine receptors during experimental granulomatous inflammation: role and expression of MIP-1 alpha and MCP-1. *Brit. J., Pharmacol.* 2001; 134:1166-1179.
6. Bone-Larson, C.L., Hogaboam, C.M., Evanoff, H., Strieter, R.M., Kunkel, S.L. IFN-gamma inducible protein-10 (CXCL10) is hepatoprotective during acute liver injury through the induction of CXCR2 on hepatocytes. *J. Immunol.* 2001; 167:7077-7083.
7. Blease K, Schuh JM, Jakubzick C, Lukacs NW, Kunkel SL, Joshi BH, Puri RK, Kaplan MH, Hogaboam CM. Stat6-deficient mice develop airway hyperresponsiveness and peribronchial fibrosis during chronic fungal asthma. *Am J Pathol.* 2002 Feb;160(2):481-90.
8. Cheng SS, Lukacs NW, Kunkel SL. Eotaxin/CCL11 Suppresses IL-8/CXCL8 Secretion from Human Dermal Microvascular Endothelial Cells. *J Immunol.* 2002 Mar 15;168(6):2887-94.
9. Belperio JA, DiGiovine B, Keane MP, Burdick MD, Ying Xue Y, Ross DJ, Lynch JP 3rd, Kunkel SL, Strieter RM. Interleukin-1 receptor antagonist as a biomarker for bronchiolitis obliterans syndrome in lung transplant recipients. *Transplantation.* 2002;73(4):591-9.
10. Matsukawa A, Lukacs NW, Hogaboam CM, Knibbs RN, Bullard DC, Kunkel SL, Stoolman LM. Mice genetically lacking endothelial selectins are resistant to the lethality in septic peritonitis. *Exp Mol Pathol.* 2002;72(1):68-76.
11. Hay RV, Skinner RS, Newman OC, Kunkel SL, Lyle LR, Shapiro B, Gross MD. Scintigraphy of acute inflammatory lesions in rats with radiolabelled recombinant human neutrophil-activating peptide-2. *Nucl Med Commun.* 2002;23(4):367-372.
12. Shang XZ, Chiu BC, Stolberg V, Lukacs NW, Kunkel SL, Murphy HS, Chensue SW. Eosinophil Recruitment in Type-2 Hypersensitivity Pulmonary Granulomas: Source and Contribution of Monocyte Chemotactic Protein-3 (CCL7). *Am J Pathol.* 2002 Jul;161(1):257-66.
13. Schuh JM, Blease K, Kunkel SL, Hogaboam CM. Eotaxin/CCL11 is involved in acute, but not chronic, allergic airway responses to *Aspergillus fumigatus*. *Am J Physiol Lung Cell Mol Physiol.* 2002 Jul;283(1):L198-204.
14. Schuh JM, Power CA, Proudfoot AE, Kunkel SL, Lukacs NW, Hogaboam CM. Airway hyperresponsiveness, but not airway remodeling, is attenuated during chronic pulmonary allergic responses to *Aspergillus* in CCR4-mice. *FASEB J.* 2002 Aug 1;16(10):1313-1315.
15. Shang, X.Z., Chiu, B.C., Stolberg, V., Lukacs, N.W., Kunkel, S.L. Murphy, H.S., Chensue, S.W. Eosinophil recruitment in type 2 hypersensitivity pulmonary granulomas. Source and contribution of monocyte chemotactic protein-3 (CCL7). *Am. J. Pathol.* 2002 161:257-266.

**ANDREW P. LIEBERMAN, M.D., PH.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Diagnostic surgical neuropathology, 6 weeks
- B. Autopsy evaluation of brains submitted to the Michigan Alzheimer's Disease Research Center

II. TEACHING ACTIVITIES:

- A. Graduate students and postdoctoral fellows:
 - 1. Responsible during the current academic year for teaching activities for the following:
 - a. Monzy Thomas, Ph.D. (Post-Doctoral Fellow)
 - b. Valerie Drews (member of thesis committee)
- B. Undergraduate students:
 - 1. Abhishek Aphale
- C. Lecturer on Neurodegenerative disease, Pathology house officers
- D. Lecturer and laboratory instructor, M2 Pathology, Neuroscience Sequence
- E. Instructor, Pathology/Radiology elective for M4 students
- F. Lecturer, Pathology 581
- G. Lecturer, Biology 201 (LS&A)
- H. Member, Neuroscience Graduate Program

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Altered Androgen Receptor Function Due to CAG Expansion", K02 NS44047 (75%), \$156,250/year (\$681,250/five years), July 1, 2002 – June 30, 2007.
- B. Principal Investigator, "Altered Androgen Receptor Function in Kennedy's Disease", Muscular Dystrophy Association (5%, no salary support), \$73,409/year (\$219,000/three years), July 1, 2002 – June 30, 2005.
- C. Principal Investigator, "Oxidative Injury in a Model of Motor Neuron Disease", Michigan Alzheimer's Disease Research Center (0%, no salary support), \$30,000/year, January 1, 2002 – December 31, 2002.
- D. Co-director, "Neuropathology Core, Michigan Alzheimer's Disease Research Center", P50 AG08671 (S. Gilman, P.I.) (15%), \$47,043/year.

PROJECTS UNDER STUDY:

- A. Mechanisms of neurodegeneration in Kennedy's disease.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Ad-hoc member, Pathology Graduate Program Admissions Committee

MEDICAL SCHOOL/HOSPITAL:

- A. Co-director, Neuropathology Core, Michigan Alzheimer's Disease Research Center
- B. Member, Medical Scientist Training Program Advisory Committee
- C. PIBS student interviews and recruitment dinners

UNIVERSITY OF MICHIGAN:

- A. None

REGIONAL AND NATIONAL:

- A. Manuscript review for:
 - 1. Human Molecular Genetics
 - 2. Journal of Neurochemistry
 - 3. The Lancet

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

- A. None

HONORS AND AWARDS

- A. None

PATENTS:

- A. None

INVITED LECTURES/SEMINARS:

- 1. "Kennedy's Disease", Neuroscience Graduate Program Seminar, University of Michigan, October 2001.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Puls I, Lieberman AP, Fischbeck KH. Impact of the human genome sequence on neurology and neuroscience. Arch Neurol, 58:1750-1751, 2001.
2. Lieberman AP, Harmison G, Strand AD, Olson JM, Fischbeck KH. Altered transcriptional regulation in cells expressing the expanded polyglutamine androgen receptor. Hum Mol Genet, in press.

BOOKS/CHAPTERS IN BOOKS:

1. Taylor JP, Lieberman AP, Fischbeck KH. Repeat expansion and neurological disease. In: Diseases of the Nervous System, 3rd Ed. (Asbury AK, McKhann GM, McDonald WI, Goadsby P, McArthur J, eds). Cambridge University Press, Cambridge, in press.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Lieberman AP, Harmison G, Strand A, Olson J, Fischbeck KH. Altered androgen receptor function caused by polyglutamine expansion. Am J Hum Genet, 69:35, 2001.

**RICHARD W. LIEBERMAN, M.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENTS OF PATHOLOGY AND
OBSTETRICS & GYNECOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Gynecologic Pathology Consultation - twelve months.
- B. Gynecologic Oncology Semimonthly Tumor Planning Conference - twelve months.
- C. Autopsy service – twelve months (14 weeks, 6 weekends).
- D. Gynecologic Oncology – Colposcopy Clinic, one half day/week, twelve months.
- E. Placental Pathology – twelve months.

II. TEACHING ACTIVITIES:

- A. Residents:
 - 1. Sign-out - Gynecologic Pathology, Placentas, and Autopsy cases.
 - 2. Review cases and supervise presentation of semimonthly Gynecologic Oncology Tumor Planning Conference – twelve months.
 - 3. Instruction in the Gross Examination, frozen section diagnosis, and processing of Gynecologic Surgical specimens and Placentas, July 2001.
 - 4. Instruction and supervision in the performance, presentation and sign-out of autopsy cases.
 - 5. Teaching Conferences- lecture in Gyn Pathology, Jan 2001.
 - 6. Consult Case Conference - two/year.
 - 7. Miscellaneous resident evening conferences in Gyn Path
 - 8. Resident resource web page in Gyn Pathology (<http://gynonc.path.med.umich.edu>) – Web access to Gyn Pathology Grossing Manual, lecture slides, “Blue Book” Online guide to Gynecologic Oncology, and other resources
 - 9. Morbidity and Mortality Conferences – Internal Medicine, General Surgery, and Obstetrics & Gynecology
- B. University of Michigan Medical Students:
 - 1. M2, Obstetrics & Gynecology Sequence: Five hours Gynecologic Pathology lectures; preparation of examination questions.
 - 2. M2, Obstetrics & Gynecology Sequence: Laboratory instruction.
 - 3. M2 resource web page in Gyn Pathology (– Web access to Gyn Pathology laboratory, lecture slides, and other resources
 - 4. M3 – Teaching during weekly Colposcopy Clinic.
- C. Michigan State University Medical Students
 - 1. M2 School of Human Medicine, Obstetrics & Gynecology Sequence: Three hours Gynecologic Pathology lectures; preparation of examination questions.
 - 2. M2 School of Osteopathic Medicine, Obstetrics & Gynecology Sequence: Two hours Gynecologic Pathology lectures; preparation of examination questions.
- D. Ob/Gyn Residents and Gynecologic Oncology Fellow:
 - 1. Semimonthly Tumor Planning Conference – twelve months.
 - 2. Colposcopy clinic staff – one-half day per week (twelve months).
 - 3. Operating Room Instruction – approximately one-half day per week.
 - 4. Lectures in Gynecologic Pathology to Gyn Oncology Service – two/year.

5. Gyn Pathology Rotation for 3rd year Gyn Oncology Fellow – one month.

III. RESEARCH ACTIVITIES:

SOFTWARE DEVELOPMENT:

PathView Image Database – Software Disclosure (U of Michigan 2000)

Profiler, Tissue Microarray & Genomics DB Module (under PathView) – Disclosure Pending

Diagnostic Hierarchy – schema development in MS Access, with link to Oracle 8i

SPONSORED SUPPORT:

None

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Member, Pathology Bioinformatics, Department of Pathology.

MEDICAL SCHOOL/HOSPITAL:

Member of Picture Archiving and Communication System Committee (PACS).

UNIVERSITY OF MICHIGAN:

None.

REGIONAL AND NATIONAL:

- A. Member, College of American Pathologists, Informatics Committee.
- B. Member, NCI Microtissue Array Working Group.
- C. Co-Chairperson, Medical Informatics Committee, Gynecologic Oncology Group.
- D. Member, Pathology Committee, Gynecologic Oncology Group.
- E. Member, Tissue Utilization Committee, Gynecologic Oncology Group.
- F. Member, National Comprehensive Cancer Network (NCCN) Cervical/Endometrial Cancer Screening Panel.
- G. Editorial Reviewer, Obstetrics and Gynecology.
- H. Editorial Reviewer, Cancer.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. “Web-based Imaging for Interactive Microscopy: Potential Applications for the Anatomic Pathologist” ASCP/CAP 2001 Meeting in Philadelphia, Pennsylvania. October 22, 2001.
- 2. Ob/Gyn Grand Rounds: Highlights in Gynecologic Pathology: Clinical Pathologic Correlations of selected cases at the University of Michigan and Innovations in Web-based Imaging Technologies in Pathology and Medicine. The Grand Rapids Medical Education and Research Core. 17 April 2002.

3. "Managing High Throughput Tissue Microarray Data: The University of Michigan SPORE Model" Anatomic Pathology Informatics, Imaging, and the Internet (APIII) Meeting in Pittsburgh, Pennsylvania. October 6, 2001.
4. Automated Information Management in the Clinical Laboratory (AIMCL). "Innovations in Digital Imaging Technology in the Pathology Laboratory". May 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED IN REFEREED JOURNALS:

None.

ARTICLES SUBMITTED TO REFEREED JOURNALS:

None.

BOOKS/CHAPTERS IN BOOKS:

None.

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

PUBLICATIONS (non-peer reviewed):

1. Vulva: Benign and Inflammatory Conditions. Haefner, H (editor), Lieberman, R (Web Editor/developer), et al. <http://www.asccp.org/edu/practice/vulva.shtml>.
2. Vulva: HPV and VIN. Haefner, H (editor), Lieberman, R (Web Editor/developer), et al. http://gynonc.path.med.umich.edu/ASCCP/HPV_VIN/default.htm.
3. Vulva: HPV and VIN. Haefner, H (editor), Lieberman, R (Web Editor/developer), et al. http://gynonc.path.med.umich.edu/ASCCP/HPV_VIN/default.htm.
4. On-line Gynecologic Pathology Manual. GOG Pathology Committee: Benda J (Chair), Lieberman R (Web Editor) <http://www.gog.org>.

**JOHN B. LOWE, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Clinical Immunology Diagnostic Service - sign out of serum and urine protein electrophoresis, immunofixation, and immunoelectrophoresis.

II. TEACHING ACTIVITIES:

- A. Supervision of three postdoctoral fellows (Jonathon Homeister, M.D., Ph.D., Lan Zhou, M.D., Ph.D., and Stephanie Chervin, Ph.D.)
- B. Supervision of two MSTP students (Daniel Becker and David Kim)
- C. Lecturer – Postdoctoral Research Training Program
- D. Member of four Ph.D. thesis committees (Stacey Arnold, Anavelys Ortiz-Suarez, Gallia Levy and Qin Li)
- E. Member, Cell and Molecular Biology Program Committee
- F. Member, Pathology Department Ph.D. Program Committee

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. "Glycoconjugate function in mammals". Source of award: Howard Hughes Medical Institute
- B. Program Project - Project #2 Principal Investigator, "Carbohydrate-dependent adhesion of normal and tumor cells", NIH - CA71932 (20% effort), \$732,109/five years direct cost, 07/08/96 - 02/28/07
- C. Large Scale Collaborative Project Award "Protein-carbohydrate interactions in cell communication". Bridging Project Title "Fucosylated Glycan Structure and Function" (Lowe). NIH GM62116 (Paulson) (5% effort) \$300,000/five year direct cost, 09/01/01 – 08/31/06

PROJECTS UNDER STUDY:

- A. Structure and regulation of mammalian oligosaccharide genes. Efforts are focused on the isolation and analysis of gene(s) for human and murine glycosyltransferases, using mammalian gene transfer techniques, and on characterization of immune defects in glycosyltransferase knock-out mice.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Chair, Biomedical Scholars Program Committee
- B. Member, Department of Pathology's Graduate Program Committee
- C. Member, University of Michigan Technology Transfer Committee
- D. Member, Biomedical Research Core Facilities Advisory Committee
- E. Member, Biomedical Science Research Building Committee
- F. Member, Life Sciences Institute Advisory Board

REGIONAL AND NATIONAL:

- A. Deputy Editor, The Journal of Clinical Investigation
- B. Member, Scientific Advisory Board, The Ara Parseghian Medical Research Foundation (Niemann-Pick disease type C)
- C. Member, Editorial Board of the European Journal of Biochemistry
- D. Consulting Reviewer for Proceedings of the National Academy of Sciences USA, Journal of Cell Biology, Journal of Experimental Medicine, Biochemistry, Journal of Immunology, Glycoconjugate Journal, Cell, Nature Genetics, Immunity, Nature Immunology, Blood, and Transfusion

V. OTHER RELEVANT ACTIVITIES:

- A. Howard Hughes Medical Institute, Investigator

VI. INVITED LECTURES AND SEMINARS:

- 1. Molecular determinants of L-selectin-dependent lymphocyte adhesion. 11th International Congress of Immunology, Stockholm, Sweden. July 2001
- 2. Defective selectin-dependent leukocyte trafficking, and altered innate immunity in mice with targeted deletions in fucosyltransferase genes. Schering AG, Berlin, Germany. October 2001
- 3. Leukocyte adhesion defects in glycosylation-deficient mice. Complex Carbohydrate Research Center, University of Georgia, Athens, Georgia. November 2001
- 4. Glycosylation and the adaptive immune response. Society for Glycobiology Meeting, San Francisco, CA. November 2001
- 5. Fucosyltransferases and blood group antigens. Glycogenomics: the Impact of Genomics and Informatics in Glycobiology. York, UK. December 2001.
- 6. Glycosylation and the adaptive immune response. The San Diego Glycobiology Symposium, San Diego, CA. January 2002
- 7. Aberrant leukocyte biology in mice with targeted deletions of glycosylation loci. American Society of University Pathologists (Pluto Club) Annual Meeting, Turks and Caicos Islands. February 2002
- 8. Glycosylation loci that control leukocyte adhesion and myelopoiesis. University of California at San Diego, La Jolla, CA. March 2002
- 9. Genetic control of glycan dependent events required for leukocyte adhesion and function. Symposium: Regulation of development and immunity by glycoconjugates. FASEB, New Orleans, LA. April 2002

10. Fucosylation and selectin ligands. Molecular Mechanisms of Leukocyte Trafficking. Keystone Symposium, Steamboat Springs, CO. April 2002

VII. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Domino SE, Zhang L, Gillespie PJ, Saunders TL, and Lowe JB. Deficiency of reproductive tract $\alpha(1,2)$ fucosylated glycans and normal fertility in mice with targeted deletions of the FUT1 or FUT2 $\alpha(1,2)$ fucosyltransferase loci. *Mol Cell Biol* 21:8336-8345, 2001.
2. Pendl GG, Robert C, Steinert M, Thanos R, Eytner R, Borge E, Fuhlbrigge RC, Kupper TS, Lowe JB, Vestweber D, and Grabbe S. Immature mouse dendritic cells enter inflamed tissue, a process that requires E- and P-selectin, but not PSGL-1. *Blood* 99:946-956, 2002.
3. Erdmann I, Scheidegger EP, Koch FK, Heinzerling L, Odermatt B, Burg G, Lowe JB, and Kundig TM. Fucosyltransferase-VII deficient mice with defective E-, P- and L-selectin ligands show impaired CD4+ and CD8+ T cell migration into the skin but normal extravasation into visceral organs. *J Immunol* 168:2139-2146, 2002.
4. Mazo IB, Quackenbush EJ, Lowe JB, and von Andrian UH. Total body irradiation causes profound changes in endothelial traffic molecules for hematopoietic progenitor cell recruitment to bone marrow. *Blood* 99:4182-4191, 2002.
5. Chervin SM, Lowe JB, and Koreeda M. Synthesis and biological evaluation of a new sialyl Lewis x mimetic derived from lactose. *J Org Chem* 2002, in press.
6. Smith PL, Myers JT, Rogers CE, Zhou L, Petryniak B, Becker DJ, Homeister JW, and Lowe JB. Conditional control of selectin ligand expression and global fucosylation events in mice with a targeted mutation at the FX locus. *J Cell Biol*, 2002, in press.
7. Thomsson KA, Hinojosa-Kurtzberg M, Axelsson KA, Domino SE, Lowe JB, Gendler SJ, and Hansson GC. Intestinal mucins from cystic fibrosis mice show increased fucosylation due to an induced Fuc α 1-2 glycosyltransferase. *Biochem J*, 2002, in press.
8. Lowe JB. Glycosylation in the control of selectin counter-receptor structure and function. *Immunol Rev*, 2002, in press.
9. Becker DJ, Myers JT, Ruff MM, Smith PL, Gillespie BW, Ginsburg D, and Lowe JB. Strain-specific modification of lethality in fucose-deficient mice. *Mammalian Genome*, 2002, in press.

ARTICLES SUBMITTED OR IN PREPARATION:

1. Smith PL, Rogers CE, Myers JM, Petryniak B, and Lowe JB. Dysregulated expression of selectin ligands on fetal thymocytes in mice with a targeted disruption of the Galgt2 GalNAc transferase locus. In preparation.
2. Hiraiwa N, Domino S, Saunders T, and Lowe JB. Dominant pre-implantation lethality in mice directed by aberrant expression of an $\alpha(1,2)$ fucosyltransferase cDNA. In preparation.
3. Legault DJ, Kelly RJ, Smith PL, and Lowe JB. Glycan epitope recovery defines amino acid sequence requirements for $\alpha(1,3/1,4)$ fucosyltransferase acceptor substrate specificity. In preparation.
4. Pipia GG, Kale S, Smith PL, Kelly RJ, Rogers CM, Lowe JB, and Long MW. Selectin ligand pairs: negative modulators of human hematopoiesis. In preparation.
Masayoshi Oh-eda M, Tsuboi S, Petryniak B, Lowe JB, and Fukuda M. Expression of E-selectin ligand oligosaccharides on Chinese hamster ovary cells by mouse fucosyltransferase IV and VII. In preparation.
5. Kale S, Chervin SM, Pipia G, Kelly RJ, Datta NS, Smith PL, Lowe JB, and Long MW. Selectin ligand-dependent homeostatic control of hematopoiesis. In preparation.

BOOKS AND CHAPTERS IN BOOKS:

1. Lowe JB. Glycosyltransferases and glycan structures contributing to the adhesive activities of L-, E-, and P-selectin counter-receptors. *Biochem J*, 2002, in press.

LORI LOWE, M.D.
CLINICAL ASSOCIATE PROFESSOR OF PATHOLOGY AND DERMATOLOGY
DEPARTMENTS OF PATHOLOGY AND DERMATOLOGY

ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002

I. CLINICAL ACTIVITIES:

- A. Dermatopathology Service – 12 months.
- B. Dermatopathology Consultation Service (including MLabs and Veterans Administration Hospital) – 12 months.

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. Lecturer, MS II Dermatology Sequence (2 hours full class lecture)
 - 2. Dermatopathology laboratory director and instructor, MS II Dermatology Sequence (2 contact hours)
 - 3. Dermatopathology, Pathology Clerkship, MS I and MS IV students (4 students).
- B. House Officers:
 - 1. Dermatopathology sign-out.
 - 2. Review of dermatopathology consultation material.
 - 3. Dermatopathology teaching conference/weekly.
- C. Diagnostic Conference, Department of Dermatology (weekly).
- D. Director of Diagnostic Conference, Department of Dermatology – (2 hours/month)
- E. Hospital Conferences:
 - 1. Multidisciplinary Melanoma Conference (twice monthly).
- F. Honors:
 - 1. Listed in *Best Doctors* for 2001-2002

III. RESEARCH ACTIVITIES:

Sponsored Support:

Patient Examination with MelaFind™ system developed by Electro-Optical Sciences, Inc. (EOS). 2001 Jennifer L. Schwartz, M.D., Timothy M. Johnson, M.D., Timothy S. Wang, M.D., Darius J. Karimipour, M.D., Jeffrey S. Orringer, M.D., Lori Lowe, M.D., Lyndon Su, M.D., Doug Fullen, M.D., Christopher Bichakjian, M.D., Mitzi Rabe, R.N. 4/1/01-9/30/01 (Study ongoing through 2002.) \$5,750.

Projects under Study:

- A. Genes, environment and melanoma (GEM) study (Mulicenter collaborative investigation); local principal investigator: Stephen B. Gruber, M.D., Ph.D., MPH 2000-2001.
- B. University of Michigan (UMMC 2000-0713): Molecular, biochemical, and cellular basis of melanoma and other melanocytic lesions: Tissue Bank. Timothy M. Johnson, M.D., Timothy S. Wang, M.D., Jennifer L. Schwartz, M.D., John J. Voorhees, M.D., Anj Dlugosz, M.D., Lori Lowe, M.D., Lyndon Su, M.D., Doug Fullen, M.D., Carol Bradford, M.D., Vincent Cimmino, M.D.
- C. University of Michigan (UMCC 2-15): A phase III randomized double-blind pivotal trial of immunotherapy with BCG plus a polyvalent melanoma vaccine, CancerVaxTM vaccine versus BCG plus a placebo as a post-surgical treatment for Stage III melanoma. Principal investigator: Michael Sabel, M.D.
- D. Treatment of Kaposi's sarcoma by topical application of interferon- α 2 expression plasmid DNA in a nanoemulsion: A Phase I trial. Blake J. Roessler, M.D., Sewon Kang, M.D., Lori Lowe, M.D.
- E. Histologic features of thick non-metastasizing melanomas (cohort study – North American Melanoma Pathology Study Group).

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Dermatopathology Service.
- B. Quality Assurance/Quality Control Program. Cutaneous Surgery and Oncology Unit.

REGIONAL AND NATIONAL:

- A. Member, North American Melanoma Pathology Study Group.
- B. Member, American Medical Women's Association Mentorship Program
- C. Member, American Academy of Dermatology's Minority Medical Student Mentor Program
- D. Invited formal observer at 2002 Annual American Academy of Dermatology Meeting (C102 – Basic Self-Assessment)
- E. Ad hoc manuscript reviewer, Journal of Cutaneous Pathology.
- F. Ad hoc manuscript reviewer, The American Journal of Dermatopathology.
- G. Ad hoc manuscript reviewer, Journal of the American Academy of Dermatology.
- H. Ad hoc manuscript reviewer, Archives of Dermatology.
- I. Ad hoc manuscript reviewer, Dermatologic Surgery
- J. Ad hoc manuscript reviewer, Cancer.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. Basic Self-Assessment in Dermatopathology, faculty, American Academy of Dermatology Annual Meeting, New Orleans, LA, February, 2002.

2. Advanced Self-Assessment in Dermatopathology, faculty, American Academy of Dermatology Annual Meeting, New Orleans, LA, February, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Anderson KW, Lowe L, Su LD, Baker SR, Johnson TM: A staged excision approach for lentigo maligna and lentigo maligna melanoma of the head and neck: The "square" procedure. *Arch Facial Plast Surg* 3: 202-206, 2001.
2. Su LD, Lowe L, Bradford CR, Johnson TM, Yahanda AI, Sondak VK: Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. *J Am Acad Dermatol* 46: 661-666, 2002.
3. Guitart J, Lowe L, Piepkorn M, Prieto VG, Rabkin MS, Ronan SG, Shea CR, Tron VA, White W, Barnhill RL: Histologic characteristics of thin metastasizing melanomas: A case-control study of 43 cases. *Arch Dermatol* 138: 603-608, 2002.
4. Fader DJ, Lowe L: Concomitant use of a high-energy pulsed CO₂ laser and a long-pulsed (810 nm) diode laser for squamous cell carcinoma in situ. *Dermatol Surg* 28: 97-99, 2002.
5. Altman JF, Lowe L, Redman B, Esper P, Schwartz JL, Johnson TM, Haefner HK: Placental metastasis of maternal melanoma. *J Am Acad Dermatol* (in press).
6. Bezanis G, Wang TS, Johnson TM, Lowe L: Verrucous plaques on the leg. *Arch Dermatol* (in press).
7. Schwartz JL, Wang TS, Hamilton TA, Lowe L, Sondak VK, Johnson TM: Thin primary cutaneous melanomas: associated detection patterns, lesion and patient characteristics. *Cancer* (in press).
8. Su LD, Fullen DR, Lowe L, Uherova P, Schnitzer B, Valdez R: CD117 (kit receptor) expression in Merkel cell carcinoma. *Am J Derm Pathol* (in press).
9. Sheng H, Goich S, Wang A, Grachtchouk M, Lowe L, Mo R, Lin K, de Sauvage FJ, Sasaki H, Hui C, Dlugosz AA: Dissecting the oncogenic potential of Gli2: Deletion of an amino-terminal fragment alters skin tumor phenotype. *Cancer Res* (in press).
10. Barr KL, Lowe L, Su LD: Mycobacterium marinum infection simulating interstitial granuloma annulare: A report of 2 cases. *Am J Dermatopathol* (in press).

ARTICLES SUBMITTED FOR PUBLICATION:

1. Grover AC, Moon J, Lowe L, Sondak VK, Yahanda AM, Cimmino V, Chang AE, Taylor JMG, Johnson TM: Clinical and histopathological factors associated with a positive sentinel lymph node in primary cutaneous melanoma: generation of probabilistic model. *Cancer* (submitted).
2. Pacella SJ, Lowe L, Bradford C, Johnson TM, Rees R: The utility of sentinel lymph node biopsy in head and neck melanoma in the pediatric population. *Plast Reconstr Surg* (submitted).
3. Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L: Sentinel lymph node biopsy for problematic spitzoid melanocytic lesions: a report of 18 cases. *Cancer* (submitted).
4. Fullen DR, Lowe L, Su LD: Antibody to S100 A6 protein is a sensitive immunohistochemical marker for neurothekeoma. *J Cutan Pathol* (submitted).

ABSTRACTS, BOOK REVIEWS, PRELIMINARY COMMUNICATIONS, PANEL DISCUSSIONS:

1. Sheng H, Goich S, Wang A, Lowe L, Sasaki H, Dlugosz A: Induction of multiple types of skin tumors in mice overexpressing an activated Gli2 mutant. *J Invest Dermatol* 117: 471, 2001.
2. Fullen DR, Burger JH, Novice FM, Lowe L: An unusual case of bilateral upper extremity interstitial granulomatous (granuloma annulare-like) infiltrates with concomitant secondary low-grade B-cell lymphoma. *J Cutan Pathol* 28: 567, 2001.
3. Dubay D, Cimmino V, Lowe L, Johnson TM, Sondak VK: Low recurrence rate for wide excision of dermatofibrosarcoma protuberans. American Society of Clinical Oncology, Orlando, FL, May, 2002.
4. Cho S, Lowe L, Hamilton T, Voorhees J, Kang S: Long-term treatment with topical tretinoin improves cellular atypia in photoaged skin. Society for Investigative Dermatology Annual Meeting, May, 2002.

**NICHOLAS W. LUKACS, Ph.D.
ASSOCIATE PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENT REPORT
1 JULY 2001-30 JUNE 2002**

I. CLINICAL ACTIVITIES:

None.

II. TEACHING ACTIVITIES:

- A. Pathology 585, Lecturer, Inflammation section, Summer, 2001, 2002
- B. Pathology 580, Dental School. Lectures on Inflammation, cytokines and Chemokines
- C. Pathology 581, Graduate Students. Lectures on Inflammation and Immune responses.
- D. Pathology 643, Course Director, Immune mechanisms of Disease, Fall, 2001.
- E. Post-doctoral fellows-Alison John, Steve Lundy, Kavita Ramen
- F. Graduate Students- Allison Miller, Molly Thomas, Matt Schaller, Brian Rudd

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

Active

- A. Principal Investigator, "Role of C-C chemokines in eosinophil airway inflammation", RO1, 5/1/01-4/30/06, National Institutes of Health.
- B. Principal Investigator, "SCF and mast cells in allergic airway inflammation", NIH R01. 9/1/99-8/30/03.
- C. Principal Investigator, "Cockroach allergen-induced airway inflammation" NIH Program Project, Project IV with P.A. Ward, M.D., Program Director 3/1/99-2/28/04.
- D. Principal Investigator; Section III, "Rational Design of Adhesion Blocking Anti-Inflammatories" NIH SBIR grant. (Ligocyte Pharmaceuticals, Inc.) 7/1/00 to 6/30/02.
- E. Co-Investigator, "Acute Lung Injury", Project 2, NIH Special Centers of Research (SCOR) grant, with Steven L. Kunkel, Ph.D., Ted Standiford, M.D. SCOR Director. 12/01/98 to 11/30/04.
- F. Co-Investigator, "Fibrotic cytokine phenotypes in interstitial lung disease" Project 3, NIH Special Centers of Research (SCOR) grant, with Steven L. Kunkel, Ph.D. Galen B. Towes, M.D. SCOR Director.
- G. Co-Investigator, "RETINAL CELL/LEUKOCYTE BINDING INDUCES CXC/CC CHEMOKINES", with Victor Elner, M.D., Ph.D. NIH RO1. 9/01/98 to 8/30/03.

PROJECTS UNDER STUDY:

- A. Regulation of cytokine and chemokines during eosinophilic airway inflammation.

- B. Role of mast cells in chronic inflammation.
- C. Regulation of chemokine production during cell-to-cell interactions.
- D. Role of chemokines in autoimmune responses.
- E. Adhesion molecules in chronic inflammatory responses.
- F. Role of stem cell factor (SCF) in acute and chronic inflammation

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- 1. Departmental representative- Curriculum Committee for Joint Medical School Graduate program, PIBS.
- 2. Admissions Committee- Immunology Graduate Program in PIBS.
- 3. Curriculum Committee for Pathology Graduate Program.
- 4. Preliminary exam committee for Pathology Graduate Program.
- 5. Immunology graduate examination Committee

REGIONAL AND NATIONAL:

-Section Editor

Journal of Immunology

-ASIP Program Committee for Experimental Biology 2001

-Reviewer for the following Journals:

- 1. Journal of Immunology
- 2. American Journal of Pathology
- 3. American Journal of Respiratory Cell and Molecular Biology
- 4. Infection and Immunity
- 5. Immunology Today
- 6. European Respiratory Journal
- 7. Journal of Experimental Medicine
- 8. Hepatology
- 9. Shock
- 10. Journal of Leukocyte Biology
- 11. Cellular Immunology
- 12. BLOOD
- 13. Journal of Clinical Investigation
- 14. Journal of Clinical Allergy

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. The role of cytokines and chemokines in asthma. Anormed Inc. Annual Meeting. Seattle, WA. July 27th, 2001.
- 2. Cytokines in Disease Progression. Central Society for Clinical Research. Chicago, IL. Sept. 8, 2001.

3. The role of SCF for mast cell and eosinophil activation. Brazilian Society of Inflammation. Rio de Janeiro, Brazil. November 8-9, 2001.
4. Chemokine and chemokine receptors in airway inflammation and hyperreactivity. Texas Southwestern, Dept. of Pediatrics, Div. of Infectious Diseases, Dallas, TX. March 15th, 2002.
5. Chemokine and Inflammation: Redundancy or coordinated effort? Experimental Biology Symposium on Inflammation. New Orleans, LA. 4/20/02.
6. Chemokines and their receptors in the pathophysiology of airway disease. Euroconference on Chemokine Biology. Madrid, Spain. 5/5/02 to 5/9/02.

PATENTS AND DISCLOSURES

The role of CXCR2 in mucus production in the airway. Nicholas W. Lukacs, Steven L. Kunkel, Cory Hogaboam, and Allison Miller. 2002. Disclosure.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERREED JOURNALS:

1. Tekkanat, K.K., Hussein Maassab, David Cho, Joyce Lai, Aaron A. Berlin, Mark H. Kaplan, and N. W. Lukacs. Role of IL-12 and STAT4 in regulation of airway inflammation and hyperreactivity in RSV infection. *Am. J. Pathol.* 159(2):631-8, 2001.
2. André Klein; André Talvani; Patrícia M.R. Silva; Marco A. Martins; Tim N.C. Wells; Amanda Proudfoot; N.W. Lukacs & Mauro M. Teixeira. SCF-induced leukotriene B₄ production cooperates with eotaxin to mediate the recruitment of eosinophils during allergic pleurisy in mice. *J. Immunol.* 167(1):524-31, 2001.
3. Yoshida A, Elner SG, Bian ZM, Kunkel SL, Lukacs NW, Elner VM. Thrombin regulates chemokine induction during human retinal pigment epithelial cell/monocyte interaction. *Am. J Pathol.* 159(3):1171-80, 2001.
4. Lukacs, N.W. Role of chemokines in the pathogenesis of asthma. *Nature Reviews Immunology* 1:108-116, 2001.
5. Fife, BT, MC Paniagua, NW Lukacs, SL Kunkel, and WJ Karpus. Selective CC Chemokine receptor expression by central nervous system-infiltrating encephalitogenic T cells during experimental autoimmune encephalomyelitis. *J Neurosci Res* 66:705-714, 2001.
6. Matsukawa, A., NW Lukacs, CM Hogaboam, RN Knibbs, DC Bullard, SL Kunkel, and LM Stoolman. Mice genetically lacking endothelial selectins are resistant to the lethality in septic peritonitis. *Exp. Mol Pathol.* 72:68-76, 2001.
7. Blease, K., NW Lukacs, CM Hogaboam, and SL Kunkel. Chemokines and their role in airway hyper-reactivity. *Respir Res* 1:54-61, 2000.
8. Matzer, SP, T Baumann, NW Lukacs, M Rollinghoff, and HU Beuscher. Constitutive expression of macrophage-inflammatory protein 2 (MIP-2) mRNA in bone marrow gives rise to peripheral neutrophils with preformed MIP-2 protein. *J. Immunol.* 167:4635-4643, 2001.
9. Nicholas W. Lukacs, Aaron Berlin, Dominique Schols, Renato T. Skerlj, and Gary J. Bridger. The role of CXCR4 in allergic airway inflammation and airway hyperreactivity. *Am J. Pathol.* 160(4):1353-60, 2002.
10. Oliveira, S.H.P., S. Lira, M. Miekowski, L. Sullivan, and N.W. Lukacs. Increased responsiveness of murine eosinophils to MIP-1b (CCL4) and TCA3 (CCL1) is mediated by their specific receptors, CCR5 and CCR8. *J. Leuk. Biol.* 71:1019-1025, 2002.

11. Mancuso, P., A. Gottschalk, S. M. Phare, M. Peters-Golden, N. W. Lukacs, and G. B. Huffnagle. Leptin-deficient mice exhibit impaired host defense in Gram-negative pneumonia. *J Immunol* 168:4018, 2002.
12. Cheng, S. S., N. W. Lukacs, and S. L. Kunkel. Eotaxin/CCL11 suppresses IL-8/CXCL8 secretion from human dermal microvascular endothelial cells. *J Immunol* 168:2887, 2002.
13. Blease, K., J. M. Schuh, C. Jakubzick, N. W. Lukacs, S. L. Kunkel, B. H. Joshi, R. K. Puri, M. H. Kaplan, and C. M. Hogaboam. Stat6-deficient mice develop airway hyperresponsiveness and peribronchial fibrosis during chronic fungal asthma. *Am J Pathol* 160:481, 2002.
14. Shang, XZ, K.A. Frait, N.W. Lukacs, S.L. Kunkel, and S.W. Chensue. Eosinophil mobilization to type-2 (Schistosomal antigen-induced) hypersensitivity pulmonary granulomas: Role of eotaxin and Monocyte chemotactic protein-3 (MCP-3). *Am J. Pathol.* 161:257-266, 2002.
15. Lukacs, N.W., A. John, A. Berlin, D.C. Bullard, R. Knibbs, and LM Stoolman. E- and P-Selectins are essential for the development of cockroach allergen-induced airway responses. *J. Immunol.* 169:2120-2125, 2002.

Articles Accepted for Publication

1. Sandra H.P. Oliveira, D.D. Taub, J. Nagel, R. Smith, and N.W. Lukacs. Stem cell factor (SCF) induces eosinophil activation and degranulation: mediator and gene array analysis. *Blood* (In Press).
2. Kim K. Tekkanat, Aaron A. Berlin, Hussein Maassab, Steven L. Kunkel, Pam Lincoln, Holly Evanoff, and Nicholas Lukacs. Role of RANTES in the primary RSV infection and Lung function. *Eur. J. Immunol.* (In Press).

BOOKS/CHAPTERS IN BOOKS:

1. Lukacs NW, Hogaboam C, Chensue SW, Blease K, Kunkel SL. Type 1/type 2 cytokine paradigm and the progression of pulmonary fibrosis. *Chest*. 2001. 120(1 Suppl):S5-8.
2. Cytokine, chemokines and Asthma. *CLI Journal*. October, 2002. (In Press).
3. Hogaboam, Schuh, John and Lukacs. The role of chemokines in asthmatic airway responses. IN: *Chemokines in Pulmonary Disease*. ED. RM Strieter, SL Kunkel, and TJ Standiford. (In Press).

**PAUL E. McKEEVER, M.D., Ph.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 – 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Daily weekday and weekend 24 hour surgical neuropathology call. Individual case follow up, immunohistochemical and special stains. and electron microscopic neuropathology; weekly Brain Tumor Board, review of neurosurgical, neuroradiologic, neuropathologic and clinical-pathologic correlation, 27 weeks. This is an 11% increase in personal cases over last year, and is four times the national average.
- B. Consultations on neuropathology from other hospitals.
- C. Diagnostic neuropathology consultant, Veterans Administration Hospital.
- D. Examination of all University Hospital autopsy neuropathologic material – brain cutting, sampling, microscopic examination, and special stains.
- E. General autopsies, 13 days.

II. TEACHING ACTIVITIES:

DEPARTMENTAL:

- A. Neuroscience Sequence, Neuropathology for Second Year Medical Students. Prepared two laboratories and two lectures on brain tumors; toxic, metabolic, demyelinating and infectious diseases. Taught four laboratories.
- B. House Officers:
 - 1. Brain cutting, sampling, microscopic examination and special stain instruction of pathology House Officers.
 - 2. Individual instruction of Pathology House Officers on neurosurgical biopsy material, 27 weeks.
 - 3. Review all neurosurgically removed material in the hospital in CME-approved biweekly conference, 27 weeks.
 - 4. Invited presentations of neuropathologic observations at Rheumatology, Ophthalmology and other joint clinical conferences.
 - 5. Pathology Resident's Tuesday AP Conference rotated with other faculty.
 - 6. One month House Officer Electives for Neurosurgery, Neurology, and Pathology.
 - 7. Pathology Resident's Monday Special Conferences rotated with other faculty.
 - 8. Combined Neurosurgery, Neuroradiology, Neuropathology CPC.
 - 9. Autopsy call.
 - 10. Pathology Gross Conference.
 - 11. Various other conferences
- C. Review laboratory techniques with Research Assistants and UMMC Histologists.
- D. Other Faculty: Brain Tumor Board, CPC, and other joint clinical conferences.

REGIONAL AND NATIONAL:

Faculty, "New Methods of Brain Tumor Analysis": 40th Annual AFIP Kenneth M. Earle Memorial Neuropathology Review, Armed Forces Institutes of Pathology, Rockville, Maryland, 2002.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

National Institutes of Health, Principal Investigator, "Glioma Markers of Potential Diagnostic and Prognostic Value" (\$562,806 for entire cost of project).

PROJECTS UNDER STUDY:

- A. Characterization of Rosai-Dorfman disease in brain with Drs. Michael Boland and Karin Muraszko.
- B. Viral vectors in glioma therapy with Drs. Julian Hoff and Brian Ross.
- C. Effects of BCNU on histopathology and MRI signals in experimental rat brain tumors with Drs. Brian Ross and Thomas Chenevert.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Chief, Section of Neuropathology.
- B. Director, Neuropathology Residency Training. Full accreditation from the Accreditation Council for Graduate Medical Education obtained in 1996, status inactive for lack of funds.
- C. Member, Photography Committee.
- D. Member, Immunoperoxidase Committee.

MEDICAL SCHOOL/HOSPITAL:

- A. Organization and scheduling of Pathology, Neurology, Neuroradiology and Neurosurgery House Officer Neuropathology teaching conferences, individual instruction and consultation review.
- B. Organization of call logistics, specimen handling, and schedules for coverage of diagnostic neuropathology by staff.
- C. Interaction with Chiefs and Staff of other clinical services, particularly Neurosurgery, Neurology, Nuclear Medicine, Radiation Oncology, Neuro-oncology and Neuroradiology.
- D. Quality control of microscopic, ultrastructural and immunodiagnostic neuropathology. This included various ad hoc reviews requested by faculty.

REGIONAL AND NATIONAL:

- A. Editorial Board, Journal of Histochemistry and Cytochemistry.
- B. Editor, Histochemical Society Newsletter.
- C. Editorial Board, Journal of Neuro-Oncology.
- D. Primary Review Pathologist, Children's Cancer Study Group CCG 9897 nationwide study of childhood low grade gliomas.
- E. Reviewer for the following journals:
 - 1. Journal of Neuropathology and Experimental Neurology.
 - 2. Journal of Histochemistry and Cytochemistry.
 - 3. American Journal of Pathology.
 - 4. Archives of Pathology and Laboratory Medicine.
- F. Member, Brain Tumor/EMF Study Scientific Advisory Panel, National Cancer Institute, Jonathan Samet, Chairman.
- G. Member, Review Panel, Program for Treatment of Malignant Brain Tumors, National Cancer Institute, William Jewell, Chairman.
- H. Member, Review Panel, Molecular Markers of Glioma Initiation and Progression, National Cancer Institute, Susan Naylor, Chairwoman.
- I. M-Labs Neuropathology Services.

V. OTHER RELEVANT ACTIVITIES:

PROFESSIONAL ORGANIZATIONS:

- A. Faculty of Graduate Program of Department of Pathology.
- B. Member of the University of Michigan Cancer Center.
- C. Member, International Academy of Pathology, 1972 --.
- D. Member, Alpha Omega Alpha, Eta Chapter, 1972 --.
- E. Member, American Association of Neuropathologists, 1978 --.
- F. Member, Society of Neuroscience, 1983 --.
- G. Member, American Association of Pathologists, 1984 --.
- H. Member, Children's Cancer Study Group, 1985 --.
 - 1. Pathology Committee, 1989 --.
 - 2. Primary Review Pathologist for astrocytoma study, 1991 --.
Review and determine correct diagnoses on cases put on study protocol.
- I. Member, Histochemical Society, 1989 --.
 - 1. Constitution Advisor 1996 --.
Make certain that Council functions in accord with constitution.
- J. Lieutenant Colonel, U.S. Army Reserve Medical Corps, 1997 --.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. McKeever PE, Junck L, Strawderman MS, Blaivas M, Tkaczyk A, Cates MA, Yan, M, Li L.: Proliferation index is related to patient age in glioblastoma. *Neurology* 56: 1216-1218, 2001.

2. Xin W, Rubin MA, McKeever PE.: Differential expression of cytokeratin 8 and 20 differentiate between craniopharyngioma and Rathke cleft cyst. Arch Pathol Lab Med 2002 (in press).
3. Valdez R, McKeever PE, Finn WG, Ross CW, Schnitzer B.: Composite germ cell tumor and high-grade B-cell lymphoma arising in the sella turcica: a report of one case. Human Pathol 2002 (in press).
4. Youkilis AS, Park P, McKeever PE, Chandler WF.: Parasagittal ependymoma resembling falcine meningioma. Am. J. Neuroradiol: 22: 1105-8, 2001.
5. Song DK, Boulis NM, McKeever PE, Quint DJ.: Angiotropic large cell lymphoma with imaging characteristics of CNS vasculitis. Am. J. Neuroradiol.: 23: 239-42, 2002.
6. Jain R, Mukherji SK, Garton H, Gujar S, McKeever PE, Robertson P.: Imaging findings of childhood primary intracranial squamous cell carcinoma. Am. J. Neuroradiol. 2002.
7. Lin PT, Bijwaard K, McKeever PE.: Adult peripheral primitive neuroectodermal tumor of the cauda equina diagnosed by a combined immunohistochemical and molecular genetic analysis. (in preparation)
8. McKeever PE, Junck L, Li L, Mena H, Tkaczuk A, Yan M.: Block age affects MIB-1 proliferation indices. (in preparation).

BOOKS/CHAPTERS IN BOOKS:

1. McKeever PE: New Methods of Brain Tumor Analysis. In: *Kenneth M. Earle Memorial Neuropathology Review*. Armed Forces Institute of Pathology, Washington, D.C., 2002, pp.1-54.
2. McKeever PE: Glial cell pathology. In: *Encyclopedia of Neuroscience, Elsevier Science, 3rd edition*. Smith BH and Adelman A, eds., (in press).
3. McKeever PE, Blaivas M, Gebarski SS: In: *Pituitary Tumors, Chapter 23*. Thapar K, Kovacs K, Scheithauer BW, Lloyd RV (Eds). The Humana Press Inc., Totowa, New Jersey, 2000. (in press).
4. McKeever PE: Laboratory methods. In: *Principles and Practice of Neuropathology*. Nelson JS, Parisi J, Schochet S (Eds). Oxford, New York (in press).
5. McKeever PE: The nervous system. In: *Comprehensive Diagnostic Immunohistochemistry*. Dabbs DJ (Ed). Harcourt Brace & Co., Orlando (in press).
6. McKeever PE, Boyer P: The brain, spinal cord, and meninges. In: *Diagnostic Surgical Pathology, 4th edition*. Sternberg SS, Antonioli DA, Carter D, Mills SE, Oberman HA (Eds). Lippincott, Philadelphia (in press).

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Junck L, McKeever PE, Blaivas M, Tkaczuk A: The shorter survival of older patients with glioblastoma is partly due to more rapid tumor cell proliferation. World Federation on Neuro-Oncology First Quadrennial Meeting/Society for Neuro-Oncology Sixth Annual Meeting, Washington D.C., 2001.
2. Xin W, Rubin MA, McKeever PE: Differential expression of cytokeratin 8 and 20 distinguish craniopharyngioma from Rathke cleft cyst. ASCP Annual Meeting, 2001, Amer J Clin Pathol (in press).

**CLAIRE W. MICHAEL, M.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Cytopathology - six months.
- B. Breast Cancer Clinic, Cytopathology – twelve months.
- C. Cytopathology Consultation Service, Department of Pathology - twelve months.
- D. Necropsy Service - four weekends.

II. TEACHING ACTIVITIES:

- A. Medical School Students:
 - Mentor for medical students' senior clerkship – six weeks.
 - Introduction to cytology, second year medical students (30 minute lecture)
- B. Residents and Cytopathology Fellow:
 - 1. Sign out; Gynecologic and Non-Gynecologic Cytology cases.
 - 2. Instruction in the performance and interpretation of fine needle aspirates.
 - 4. Monthly Cytopathology Resident Conference.
 - 5. Weekly Cytopathology Fellowship Conference
 - 6. Consult Case Conference.
 - 7. Anatomic Pathology Conference: 2/year-Review of Cytopathology
- C. Other Education Activities:
 - Cytotechnologists - Cytopathology Slide Conferences.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

Co-Investigator (Principle Investigator: E-J Wamsteker, M.D.) ASGE Endoscopic Research Award (\$25,000) "Approaches to improve the cytologic diagnosis of pancreatobiliary malignancy by ERCP", 0% effort, American Society for Gastrointestinal Endoscopy.

PROJECTS UNDER STUDY:

- 1. Hayes, D, Michael CW. Ductal lavage pilot study.
- 2. Fine needle aspiration of squamous lesions; Diagnostic features and pitfalls.
- 3. Dai Y, Michael CW. Application of Beta Catenin and Cyclin D1 in mesothelial lesions.
- 4. Sturm C, Michael CW. Cytologic features of microglandular hyperplasia.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Cytopathology Laboratory.
- B. Director, Cytopathology Fellowship.
- C. Member, Residency Review Board.

MEDICAL SCHOOL/HOSPITAL:

None.

REGIONAL AND NATIONAL:

- A. Member, Editorial Board, Diagnostic Cytopathology
- B. Reviewer, Diagnostic Cytopathology.
- C. Reviewer, Cancer Cytopathology.
- D. Secretary, Papanicolaou Society of Cytopathology.
- E. Chair, Committee of Public Information, American Society of Cytopathology.
- F. Member, Task Force for Patient Advocacy, American Society of Cytopathology.
- G. Member, Abstract review committee, United States and Canadian Academy of Pathology.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. Bedrossian, CWM, Michael CW. "Pleural mesothelioma in situ: The concept, the diagnosis, the dilemmas". Pulmonary Pathology Society. Washington Seattle, August 17, 2001.
- 2. "Neuroendocrine tumors of the lung: differential diagnosis and diagnostic pitfalls". Teleconference, American Society of Clinical Pathology, September 20, 2001.
- 3. "Cytolpathology in the new millennium". French Society of Pathology, Ann Arbor, MI. October 6, 2001.
- 4. "Cytopathology of the Lung. Differential Diagnosis and Diagnostic Pitfalls". Workshop, American Society of Clinical Pathology, October 20, 2001.
- 5. "The interpretation of Fine needle aspirates prepared by the ThinPrep technique". American Society of Cytopathology, Kansas City, KA. November 9, 2001.
- 6. "The interpretation of cytologic specimens prepared by the ThinPrep technique". Short Course, United States and Canadian Academy of Pathology. Chicago, IL. March 1, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNALS:

- 1. Michael CW Buschman B. Can true papillary neoplasms and their mimickers be accurately classified by cytology. Cancer (Cancer Cytopathol) 2002;96:92-100.

2. Hammoud MM, Haefner HK, Michael CW, Ansbacher R. Atypical glandular cells of undetermined significance: histologic findings and proposed management. *The Journal of Reproductive Medicine. J Reprod Med* 2002;47:266-270.
3. Akdas Barkan G, Rubin MA, Michael CW. Diagnosis of melanoma aspirates on ThinPrep®: The University of Michigan experience. *Diagn. Cytopathol.* 2002;26:334-339.
4. Bavikatty NR, Michael CW. The cytologic features of small cell carcinoma on ThinPrep. *Diagn. Cytopathol.* (Accepted).
5. Abdul-karim F, Michael CW, Koscick RL, Cheng L. Cytopathology, Book chapter in "Essentials of anatomic Pathology" edited by Cheng L and Bostwick DG. Humana press Totowa, New Jersey. 6 (1-63), first edition, 2002.

ARTICLES SUBMITTED FOR PUBLICATION IN PEER-REVIEWED JOURNALS:

1. Liu J, Michael CW. Fibroadenoma versus ductal carcinoma in breast aspirates: The grey zone. *Diagn Cytopathol*
2. McConnell J, Silverman E, Michael CW. Psammoma bodies on pap smears: Differential diagnosis and diagnostic pitfalls. *ACTA Cytologica*

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

1. Barkan GA, Michael CW. Diagnostic features for malignant salivary gland tumors prepared by ThinPrep technique: a reappraisal of criteria. *Mod Pathol* 2002;15 (1): 66A.
2. Michael CW, Bedrossian U. Morphologic and immunostaining performance in cytologic cell blocks prepared by three different methods. *Mod Pathol* 2002;15 (1):81A.
3. Tan LC, Bavikatty N, Michael CW. The role of immunohistochemical staining in distinguishing squamous cell carcinoma from mesothelioma and adenocarcinoma. *Mod Pathol* 2002;15 (1):88A.
4. Xin W, Raab SS, Michael CW. Low grade urothelial carcinoma: Reappraisal of the cytologic criteria on ThinPrep. *Mod Pathol* 2002;15 (1):93A.

**RICHARD A. MILLER, M.D., Ph.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY
SENIOR RESEARCH SCIENTIST
INSTITUTE OF GERONTOLOGY
RESEARCH SCIENTIST
ANN ARBOR V.A. MEDICAL CENTER**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2000 - 30 JUNE 2001**

I. CLINICAL ACTIVITIES:

None.

II. TEACHING ACTIVITIES:

A. Graduate students:

1. Responsible during the current academic year for teaching activities for the following:
 - a. Human Growth and Development Course "Biology of Aging", 1 hour.
 - b. PIBS 502, Research Responsibility Course, 2 hours.
2. Program Director, "Experimental Immunopathology Training Grant."
3. Ph.D. Dissertation Committees, University of Michigan:
 - a. Pamela Bennett-Baker
 - f. Yadira Hernandez
4. Ph.D. Dissertation Advisor:
 - a. Anavelys Ortiz-Suarez
 - b. Scott Berger
 - c. Adam Salmon
 - d. Yayi Chang

B. Postdoctoral Fellows:

- a. James Harper
- b. Amir Sadighi-Akha
- c. Shin Murakami

C. In Lab:

1. Gonzalo Garcia, Ph.D.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, R. A. Miller "Genetic Control of Longevity in Mice," NIH/NIA 1-R01-AG11687-08 (15%), \$325,008 direct costs/year, 9/1/93–11/30/03. Quantitative trait locus mapping areas of the mouse genome that contribute disproportionately to longevity in a heterogeneous stock. Collaborators: Burke, Monnier, Wolf, Lipman.
- B. Principal Investigator, R. A. Miller, "Genetics of Age-Sensitive Traits in Mice", NIH/NIA 1-P01-AG-16699-03 (20%), \$634,394 direct costs/year, 5/99–4/04. A program project to map quantitative trait loci that regulate age-sensitive traits, and to see which of these traits are mutually correlated. The program includes studies of immunity (Miller, 10% effort), muscles (Sue Brooks), bones (Steve Goldstein), protein folding (Ari Gafni), and collagen modification (Monnier), and includes four cores: Administration (Miller, 5% effort), Genotyping (David Burke), Animals (Miller, 5% effort), and Analysis (Andrzej Galecki). Support for research in Miller lab = \$82,000/year.
- C. Principal Investigator, R. A. Miller, "Wild Derived Mouse Stocks: New Models for Aging Research," NIH/NIA R01-AG13711-04A1 (10%), \$175,000 direct costs/year, 9/1/00 - 8/31/05. Lifespan, genetics, and biomarker analysis of specific-pathogen-free mice derived from wild-trapped progenitors.
- D. Principal Investigator, R. A. Miller, "Activation Defects in T Cells of Aged Mice," NIH/NIA R01-AG19619-01 (15%), \$250,000 direct costs/year, 9/30/00 – 8/31/05. Studies of protein kinase pathways in T lymphocytes from aged mice, using confocal microscopy and immunoprecipitation methods.
- E. Principal Investigator, J. Faulkner, "Nathan Shock Center for the Basic Biology of Aging -Gene Expression Profile Core," NIH P30-AG13283-06, \$139,394 direct costs/year, 7/1/00 – 6/30/05. Dr. Miller directs the Gene Expression Profiling Core of the Nathan Shock Center, which provides assistance for UM researchers wishing to make use of gene expression array scanning. Miller also directs the "Laboratory for Anti-Geric Testing, Evaluation and Research" which evaluates compounds purported to increase life span in mice.
- F. Principal Investigator, J. Halter, "Claude D. Pepper Older Americans Independence Center", NIH P30-AG08808-13 (20%), \$146,000 direct costs/year, 9/1/99 - 8/31/04. Dr. Miller directs the Pepper Center's Core Facility for Aged Rodents, which provides animals to all OAIC research scientists. He directs the Research Development Core, which coordinates the selection of pilot grant projects for junior faculty scientists and annual research retreat conferences in the area of Geriatric Research. He also directs a research project on "Weight Gain Trajectory and Life Span in Mice" which focuses on studies of dw/dw dwarf mice. Direct costs in Miller laboratory are about \$146,000 annually.
- G. Principal Investigator, Andrzej Bartke, "Research Training in Experimental Immunopathology", NIH R01-AG19899-01 (2%), \$175,000; Miller \$32,894, 12/1/01 – 11/30/06. Interaction of caloric restriction with longevity genes (Bartke, PI). Subcontract: Gene expression and biomarkers in dwarf mice (Miller). Studies of gene expression and immune biomarkers in Ames dwarf mice (genotype df/df), submitted by

- A. Bartke at Southern Illinois University. Includes a subcontract to Miller (\$32,894/year) to support (a) analyses of gene expression in these mice, using microarray methods; and (b) analyses of T cell subset patterns.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Experimental Immunology Training Program.

MEDICAL SCHOOL/HOSPITAL:

- A. Director, Core Facility for Aging Rodents
- B. Member, Cancer Biology Training Program
- C. Member, Rheumatology Training Program
- D. Director, Research Development Core, Geriatrics Center
- E. Associate Director for Research, Geriatrics Center
- F. Director, Gene Expression Profiling Core, Nathan Shock Center
- G. Director, Animal Intervention Core, Nathan Shock Center
- H. Operating Committee, Immunology PhD program
- I. Associate Director, Nathan Shock Center for Aging

REGIONAL AND NATIONAL:

- A. Board of Scientific Advisors, Buck Center for Research on Aging
- B. Chair, Research Committee, American Federation for Aging Research
- C. Vice-President, American Federation for Aging Research

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

- A. Journal of Gerontology: Biological Sciences.
- B. Aging: Clinical and Experimental Research
- C. Mechanisms of Ageing and Development
- D. Experimental Gerontology

HONORS AND AWARDS:

- A. None.

INVITED LECTURES/SEMINARS:

2001

1. Immunology Program, Tufts University School of Medicine. "Signal Transduction Defects in Aging T Cells." January 18.

2. Department of Veterinary Pathology, Michigan State University. "New Animal Models for Research on Aging." February 2.
3. 2nd International Meeting on Aging and Immunity, Cordoba, Spain. "Genetic and Biomarker Analysis of Immune Aging in Mice." March 23 – 25.
4. University of Michigan School of Nursing. "New Animal Models for Aging Research." April 11.
5. NIH "Science and the Public Health" Seminar Series, Bethesda, MD. "Biology of Aging and Longevity: Evidence from the Laboratory and the Jungle." April 17.
6. International Longevity Center conference on Anti-Aging Medicine, Tucson, AZ. "Hope From Bottles: Rising Expectations of Longevity." May 3 – 6.
7. Summer Training Course in Aging Research, San Antonio, TX. "Animal Models for Aging" and "Introduction to Aging Research." June 2 – 7.
8. University of Kentucky Sixth Annual Symposium on the Biology of Aging, Lexington, KY. "Genetics and Biomarkers of Aging in Mice." October 4 – 5.
9. International Longevity Center conference on Longevity Genes, Tucson, AZ. "Genetics of Longevity in Mice." October 5 – 7.
10. Shock Center Workshop on Gene Expression Screening, Rochester, NY. "Gene Expression Patterns in Long-Lived Dwarf Mice." October 20 – 21.
11. Aspects Scientifiques, Medicaux, et Sociaux de la Longevité et du Vieillissement, Paris, France. "Biology of Aging and Longevity." October 29 – 30.
12. Gerontological Society of America Annual Meeting, Chicago, IL. "Gene Expression Screening in Snell Dwarf Mice." November 15.
13. NIA Workshop on Mutant Screening, Bethesda, MD. "Biomarkers and Gene Filters." December 17.

2002

1. 19th Annual Alberta Horse Owners and Breeders Conference, Red Deer, Alberta. "Biology of Aging." January 11 – 13.
2. Biological Mechanisms in Social Connectedness and Health, Tucson, AZ. "Overview of Aging Mechanisms." January 21 – 23.
3. Kronos Research Foundation, Phoenix, AZ. "Genetics and Biomarker Analysis of Aging in Mice." January 24
4. University of Michigan Hematology/Oncology seminar series. "Genetic and Gene Expression Analysis of Aging in Mice." February 4
5. NIA Symposium on Comparative Biology of Aging, Bethesda, MD. "Issues in the Comparative Biology of Aging." February 6.
6. UM Life Sciences Outreach Series, Ann Arbor, MI. "Are There Genes for Aging?" February 10.
7. University of Michigan Department of Anesthesiology seminar series. "Cellular and Genetic Analyses of Aging." February 13.
8. UM Life Sciences Outreach Series, Ann Arbor, MI. "Extending Life Span: Scientific Prospects and Political Obstacles." February 17.
9. University of Maryland Surgery Department, Baltimore, MD. "Gene Mapping and Gene Expression Studies of Aging." March 8.
10. UM School of Social Work, Ann Arbor, MI. "Extending Life Span: Scientific Prospects and Political Obstacles." March 21.

11. CDC Conference on Emerging Infectious Diseases, Atlanta, GA. "Biology of Immune Senescence." March 27.
12. Conference on Genomics of Aging, Seville, Spain. "Gene Mapping in Aging Mice." April 24 – 27.
13. Lanekenau Medical Research Institute, Philadelphia, PA. "Gene expression and gene mapping studies of aging mice." May 16.
14. University College, London (United Kingdom). "Gene expression and gene mapping of aging mice." May 24.
15. Summer Training Course in Aging Research, Ann Arbor, MI. "Animal Models for Aging" and "Introduction to Aging Research." June 2 – 6.
16. 7th Annual Paul Beeson Physician Faculty Scholars meeting, Blaine, WA. "Is Aging a Disease?" June 8 – 11.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Bartke, A., J. C. Wright, J. A. Mattison, D. K. Ingram, R. A. Miller, and G. S. Roth. 2001. Extending the lifespan of long-lived mice. *Nature* 414: 412.
2. Jackson, A. U., A. T. Galecki, D. T. Burke, and R. A. Miller. 2002. Mouse loci associated with life span exhibit sex-specific and epistatic effects. *J. Gerontol. Biol. Sci.* 57:B9-B15.
3. Chiu, B., X. Shang, K. A. Frait, J. Hu, E. Komuniecki, R. A. Miller and S. W. Chensue. 2002. Differential effects of aging on cytokine and chemokine responses during Type-1 (mycobacterial) and Type-2 (Schistosomal) pulmonary granulomatous inflammation in mice. *Mechanisms of Ageing and Development* 123:313-326.
4. Miller, R. A., C. Chrisp, A. U. Jackson, A. T. Galecki, and D. T. Burke. 2002. Coordinated genetic control of neoplastic and non-neoplastic diseases in mice. *J. Gerontol. Biol. Sci.* 56A:B3-B8.
5. Ortiz-Suarez, A., and R. A. Miller. In vivo expansion of aged T cells from an IFN-producing CD8 subset with atypically high CD28 levels. *Clinical Immunology*, in press.
6. Dozmorov, I., A. Galecki, Y. Chang, R. Krzesicki, M. Vergara and R. A. Miller. 2002. Gene expression profile of long-lived Snell dwarf mice. *J. Gerontol. Biol. Sci.* 57A:B99-B108.
7. Bartke, A. J. C. Wright, J. A. Mattison, D. K. Ingram, R. A. Miller, and G. S. Roth. 2002. Letter: Dietary restriction and life span. *Science* 296: 2141 – 2142.
8. Miller, R. A. and C. Chrisp. T cell subset patterns that predict resistance to spontaneous lymphoma, mammary adenocarcinoma, and fibrosarcoma in mice. *J. Immunol.*, in press.
9. Miller, R. A., A. U. Jackson, A. T. Galecki, and D. T. Burke. Genetic polymorphisms in mouse genes regulating age-sensitive and age-stable T cell subsets in mice. *Genes and Immunity*, in press.
10. Miller, R. A., J. M. Harper, R. C. Dysko, S. J. Durkee, and S. N. Austad. 2002. Longer life spans and delayed maturation in wild-derived mice. *Experimental Biology and Medicine* 227:500-508.
11. Miller, R. A., J. M. Harper, A. Galecki, and D. T. Burke. Big mice die young: early-life body weight predicts longevity in genetically heterogeneous mice. *Aging Cell*, in press.

12. Miller, R. A., Y. Chang, A. T. Galecki, K. Al-Regaiey, J. J. Kopchick, and A. Bartke. Gene expression patterns in calorically restricted mice: partial overlap with long-lived mutant mice. *Molecular Endocrinology*, in press.
13. Miller, R. A. 2001. New paradigms for research on aging and late-life illness. *Mechanisms of Ageing and Development* 122: 130- 132. .
14. Miller, R. A., A. Galecki, and R. J. Shmookler-Reis. 2001. Letter to the editor on "Interpretation, Design, and Analysis of Gene Array Expression Experiments." *J. Gerontol. Biol. Sci.* 56A:B329 – B330.
15. Miller, R. A. 2002. Extending life: scientific prospects and political obstacles. *Milbank Quarterly* 80:155 – 174.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Murakami, S., A. Salmon, and R. A. Miller. Multiplex stress resistance in cells from long-lived dwarf mice. Submitted.
2. Volkman, S. K. A.T. Galecki, D. T. Burke, M. R. Paczas, M. R. Moalli, R. A. Miller, and S. A. Goldstein. Quantitative trait loci for femoral size and shape in a genetically heterogeneous mouse population. Submitted.
3. Garcia, G. G., and R. A. Miller. O-Sialoglycoprotein endopeptidase corrects age-associated defects in mouse T cell synapse formation without altering CD43 exclusion. Submitted.
4. Garcia, G. G., and R. A. Miller. Age-dependent defects in TCR-triggered cytoskeletal rearrangement in CD4⁺ T cells. Submitted.

BOOKS/CHAPTERS IN BOOKS:

1. Miller, R. A. 2001. Genetics of increased longevity and retarded aging in mice. *Handbook of the Biology of Aging*, 5th Edition; E. J. Masoro and S. N. Austad, editors; Academic Press, NY. Chapter 14, pp. 369 – 395.
2. Miller, R. A. 2001. Biomarkers and genetics of aging in mice. In: *Cells and Surveys*; C. E. Finch, J. W. Vaupel, and K. Kinsella, eds, National Academy Press, Washington, DC. Chapter 8, pp 180 – 212.
3. Miller, R. A. 2001. Du bon usage des puces en biogérontologie (Gene expression profiling in biogerontology.) *Biofutur*, October 2001, p. 38.
4. Allison, D. B., R. A. Miller, S. N. Austad, C. Bouchard, R. Leibel, S. Klebanov, T. Johnson, and D. E. Harrison. 2001. Genetic variability in responses to caloric restriction in animals and in regulation of metabolism and obesity in humans. *J. Gerontol. Biol. Sci.* 56A: Special Issue 1, 55 – 65.
5. Miller, R. A. 2002. Biochemical and genetic analyses of T cell aging in mice. *Springer Seminars in Immunopathology* 24:61-73.

**HEDWIG S. MURPHY, M.D., Ph.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Chief, Histopathology, Pathology and Laboratory Medicine Service, VAAHS. Responsibilities include supervision of tissue processing and staining for surgical and autopsy tissue. Evaluation of procedures, equipment, quality control and personnel.
- B. Chief, Clinical Electron Microscopy, Pathology and Laboratory Medicine Service, VAAHS. Responsibilities include supervision of tissue processing, review of all semi-thin sections and selection for ultrastructural analysis. Ultrastructural diagnosis of patient tissue and research specimens. Evaluation of procedures, equipment, quality control and personnel.
- C. Surgical Pathology Diagnosis (17 weeks/year), Pathology and Laboratory Medicine Service, VAAHS
- D. Surgical Frozen Section Diagnosis (17 weeks/year), Pathology and Laboratory Medicine Service, VAAHS
- E. Autopsy Service, (13 weeks/year) Pathology and Laboratory Medicine Service, VAAHS
- F. Case presentations at Tumor Board VAAHS
- G. Case presentations at Morbidity and Mortality Conferences. VAAHS
- H. Case presentations at weekly Urologic Pathology Conferences VAAHS

II. TEACHING ACTIVITIES:

- A. House Officers
 - 1. Pathology house officers, Autopsy supervision and instruction (13 weeks /year)
 - 2. Pathology house officers, Surgical Pathology supervision and instruction, (5 months/year)
 - 3. Urology house officers, Lecture and Case presentations at weekly Urologic Pathology Conferences
- B. Post-graduate
 - 1. Kyriaki Zebecoglou, M.D., Ph.D. , Visiting Scholar
- C. Graduate students:
 - 1. Course Director, Pathology 585, Lecture and Laboratory course for Medical Illustration Graduate students (20 hrs)
 - 2. Laboratory Instructor, pathology 600 (M2 pathology course) (10 hrs)
- D. Coordinator, "Topics in Pathology", CME accredited lecture series

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Investigator "Gender-specific T cell homing and autoimmunity"
(B. Richardson, Internal Medicine, PI) NIH 12/98 - 11/03 (\$1,760,000)
- B. Co-Investigator, "Host Defense of the Lung" Research Enhancement Award Program
(REAP) Veteran's Administration 11/98-10/03 (\$1,350,000)
- C. Co-investigator, "Metabolic imaging of Renal and Prostate Cancer using C-11 Acetate"
RO1-CA089448-01 12/00 -11/03 (\$750,000)
- D. Co-Investigator. Lung Injury by Oxygen Metabolites NIH/NIGMS R37 GM29507.
National Institute of Health (Peter A. Ward, Principal Investigator).7/97-6/01.
(\$1,123,824)

PROJECTS UNDER STUDY:

- A. Endothelial cell responses in inflammation
 - 1. The enzyme source of endothelial cell oxidants
 - 2. The role of endothelial cell derived oxidants in signaling and cell injury
 - 3. Repertoire of endothelial cell derived cytokines and their role in inflammation
- B. Gender-specific effects of hormones on T cells in autoimmunity
- C. Gender-specific effects of hormones on Dendritic Cells
- D. Gender-specific effects of hormones on endothelial cells
- E. Role of prostate endothelial cells in malignancy

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Chief, Histopathology, Pathology and Laboratory Medicine, VAAHS
- B. Chief, Clinical Electron Microscopy, Pathology and Laboratory Medicine, VAAHS

MEDICAL SCHOOL/HOSPITAL:

- A. Member, Admissions committee of the University of Michigan Medical School, 1999-present
- B. Member, Research and Development Committee, Veterans Affairs Medical Center, 1999-present

REGIONAL AND NATIONAL:

- A. Manuscript Review for
 - Clinical Immunology and Immunopathology
 - Biochemical Pharmacology
 - Shock
 - Free Radical Biology and Medicine
 - American Journal of Pathology
 - Microvascular Research

- B. Membership in National organizations
American Association for the Advancement of Science (1991)
New York Academy of Science (1991)
American Society for Investigative Pathology (Fellow, 1995)
1996 Institutional Liason to University of Michigan
American Society of Clinical Pathologists (Fellow, 1995)
American Association of University Women (1995)
The A. James French Society of Pathologists (1996)
Society for Experimental Biology and Medicine (2000)
The Oxygen Society (2001)
Society for Free Radical Research International (2001)
The Nitric Oxide Society (2001)

V. **OTHER RELEVANT ACTIVITIES:**

- A. Case presentations at Tumor Board
B Case presentations at Morbidity and Mortality Conferences.
C Case presentations at Urologic Pathology Conferences
D. Light microscopic tissue evaluation for clinical researchers.
E. Electron microscopic tissue evaluation for clinical researchers.

VI. **PUBLICATIONS:**

BOOK CHAPTERS:

1. Ward, P.A. H.S. Murphy Role of Complement in Endothelial Cell Activation. in Molecular and Cellular Basis of Inflammation. C.N Serhan and P.A. Ward, (eds.) Humana press, Inc., Totowa NJ. 1999.
2. Murphy, H. S., J. Varani and P. A. Ward (in press). Biology of Endothelial Cells: Role of the Endothelium in Lung Inflammation. Middleton's Allergy: Principles and Practice. N. F. Adkinson. St Louis, Mosby
3. Murphy, H.S. and P.A. Ward. (in press) Inflammation. Pathology 4th Ed. E. Rubin. Lipincott Williams and Wilkins.

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1 Varani, J., Y. Hattori, M. K. Dame, T. Schmidt, H. S. Murphy, K. J. Johnson and K. J. Wojno. Matrix metalloproteinases (MMPs) in fresh human prostate tumour tissue and organ-cultured prostate tissue: levels of collagenolytic and gelatinolytic MMPs are low, variable and different in fresh tissue versus organ-cultured tissue. *British Journal of Cancer* 84(8): 1076-83, 2001.
2. Robey, T.C., Valimaa, T., Murphy, H.S., Mooney, D.J., Weatherly, R.A The use of internal "Knitted-type" stents in a rabbit tracheal reconstruction model. *Arch. Otolaryng* (accepted for publication).
3. Shang, X-Z, Chiu, B-C, Stolberg, V, Lukacs, N.W., Kunkel, S. L., Murphy, H.S., Chensue, S. W. Eosinophil Recuritment in Type-2 (Schistosomal Antigen-Induced) Hypersensitivity Pulmonary

Granulomas: Source and Contribution of Monocyte Chemotactic Protein-3 9CCL7). Am. J. Path. (accepted for pub.)

4. Hattori, Y., N. Hattori, H. S. Murphy, L. Su, T. Johnson, M and J. Varani. Expression of MMP-139 Collagenase-3) in microvascular endothelial cells of normal human skin and basal cell carcinoma. *Microvascular Research* (accepted for publ.)

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Robey, T., Valimaa, T. Murphy, H.S., Tormala, P., Mooney, D.J., Weatherly.R.A. Bioabsorbable PLLA stents and their use in a rabbit tracheal reconstruction model. Am Soc Ped. Otolaryn. Meeting, May , 2001.
2. Murphy, M.E., Chensue, S. W., Murphy, H.S. Effect of Endogenous Nitric Oxide on Vascular Endothelial Cell Cytokines. FASEB J 15:217, 2001
3. Murphy, B.A., Yu, C., Richardson, B.C., Murphy, H.S. Effect of Estrogen on Adhesion Molecules of Spleen Endothelial Cells. FASEB J 15: 526, 2001
4. Murphy, B.A., Yu, C., Richardson, B.C., Murphy, H.S. Effect of Estrogen on Spleen Dendritic Cells in Short-term Culture. FASEB J 15:272, 2001
5. Laudes, I.J., Huber-Lang, M, Speyer, C., Albrecht, E., Chu, J, Murphy, H.S., Riedemann, N., Sarma, V., Ward, P.A. C5a receptor expression on rat endothelial cells. FASEB J 15:926, 2001.
6. Speyer, C.S., Ward, P.A., Murphy, H.S. Analysis of Nitric Oxide Synthase Activity in Mouse Dermal and Lung Microvascular Endothelial Cells. FASEB J. 16: A594 2002.

**BERNARD NAYLOR, M.D.
PROFESSOR EMERITUS OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Consultation Service: Cytopathology/pulmonary pathology - 12 months.
- B. Autopsy Service, occasional coverage.

II. TEACHING ACTIVITIES:

- A. Pathology residents – Diagnostic consultations and lectures.
- B. Dental and graduate students - Lectures (Dermatopathology).

III. RESEARCH ACTIVITIES:

- A. History of cytopathology.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Advisory Committee on Appointments and Promotions.

REGIONAL AND NATIONAL:

- A. Cytopathology, Editorial Advisory Board.
- B. Acta Cytologica
 - Associate Editor
 - Editorial Advisory Board
 - North American Review Board
- C. International Academy of Cytology:
 - International Board of Cytopathology, Member
- D. Awards Committee, American Society of Cytopathology

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES AND SEMINARS:

1. Naylor, B.: a). Cytopathology of serous fluids, b). Mesothelioma, c). Transthoracic fine needle aspiration cytology, c) History of cytopathology. Lectures, Cytotechnology Training Program, Henry Ford Hospital, Detroit, Michigan, 2002.

— **HONORS AND AWARDS:**

None.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Naylor, B., Tasca, L., Bartziota, E.V., and Schneider, V.: In Romania It's the Méthode Babeş-Papanicolaou. Acta Cytol, 2002, 46:1-12.

BOOKS/CHAPTERS IN BOOKS:

None.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Naylor, B.: Pathogenesis of nodular histiocytic hyperplasia in serous effusions. Letter to the Editor. Diagn Cytopathol., 2002, 26:68.

**GABRIEL NUÑEZ, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Autopsy Service (two weeks and one weekend on-call).

II. TEACHING ACTIVITIES:

- A. Supervised, Adalberto Benito, Theresa Dowds, Peter Lucas, Rebecca Liu, Jacques Nör, Linda McAllister-Lucas, Akihiro Muto, Tsuyoshi Tanabe, Yasumasa Nishito, and Yasunori Ogura, Postdoctoral Fellows.
- B. Department of Pathology, Graduate Program Course 581, University of Michigan, Ann Arbor, Michigan, (2 lectures).
- C. Instructor, Microbiology and Immunology 553, Cancer Biology Training Program, University of Michigan, (1 lecture).
- D. Instructor, Cell Biology Course 530 for Graduate Students, University of Michigan (1 lecture).

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

CURRENT

- A. Principal Investigator, "Genetic regulation of apoptotic cell death," National Institutes of Health, \$813,000 (total direct costs), 6/1/99-5/31/04.
- B. Principal Investigator, "HRK, A novel apoptosis regulatory gene," National Institutes of Health, \$746,005 (total annual direct costs), 3/1/98-2/28/02.
- C. Principal Investigator, "Role of Apaf-1/Caspase-9 Pathway in tumor development in the breast" US Army Medical Grant; \$50,000.
- D. Principal Investigator, "Ciper: a novel NF- κ B-activating gene involved in Cancer," National Institutes of Health, \$1,000,000 (total direct costs), 1/7/00-6/30/05.
- E. Principal Investigator, "Characteriation of chimeric c-IAP2/MALT-1 in Lymphoma", Michigan Life Science Corridor Fund, \$620,507 (total direct costs), 2/15/01-2/14/04.
- F. Principal Investigator, "Nod2: A Susceptibility Gene for Crohn's Disease" National Institutes of Health, \$1,000,000 (total direct costs), 7/1/02-6/30/04

PROJECTS UNDER STUDY:

- A. Role of Ciper/Bcl10 Pathway in Signal transduction and lymphoma development.
- B. Molecular regulation of apoptosis by Bcl-2 family members.
- C. Role of Nod Family in Innate Immunity and Crohn's disease

IV. DEPARTMENTAL:

- A. Member, Comprehensive Examination Committee, Pathology Graduate Program, University of Michigan, Ann Arbor, MI.
- B. Member, Admissions Committee, Molecular and Cellular Biology, Graduate Program, University of Michigan, Ann Arbor, MI.

MEDICAL SCHOOL/HOSPITAL:

- A. Co-Director, Cell Biology Program, University of Michigan Cancer Center.
- B. Member, Faculty Search Committee, Rheumatology Division, and Department of Microbiology/Immunology.
- C. Reviewer, Departmental Grants and Summer Student Scholarship Program.
- D. Member, Biomedical Research Core Facilities (BRCF), University of Michigan, Ann Arbor, Michigan.
- E. Member, Biomedical Research Council, University of Michigan, Ann Arbor, Michigan.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARD:

- A. Reviewer for the following journals: American Journal of Pathology; Cancer Research; Cell; Cell Death and Differentiation; Immunity; Journal of Biological Chemistry; Journal of Cell Death and Differentiation; Journal of Immunology; Oncogene; Journal of Cell Biology; Laboratory Investigation; Proceedings of National Academy of Science USA; Science, Nature Cell Biology.

INVITED LECTURES AND SEMINARS:

UNIVERSITY OF MICHIGAN:

- 1. Invited Speaker, "Regulation of Apoptosis by the Apaf-1-Caspase-9 Pathway," Michigan Diabetes Research and Training Center, Sheldon Auditorium, Towsley Center, University of Michigan Medical School,
- 2. Invited Speaker, "Regulation of the Cell Death Machinery," Department of Pathology Research Lecture Series, University of Michigan Medical School
- 3. Invited Speaker, "Regulation of the Cell Death Machinery from Mammals and Worms," Department of Biology, University of Michigan
- 4. Invited Speaker, "Nods: Regulators of the Host Response to Pathogens" Division of Hematology/Oncology Research Seminar, University of Michigan Medical Center
- 5. Invited Speaker, "Nods: Regulators of the Host Response to Pathogens" Division of Rheumatology Research Seminar, University of Michigan Medical Center

NATIONAL AND INTERNATIONAL:

- 1. Invited Speaker, "Nods: cytosolic plant R gene Homologs Regulating the Host Response to Pathogens" Sainsbury Laboratory, Norwich, England, July 19, 2001.

2. Invited Speaker, "Nods: Apaf-1-like Molecules Regulating the Host Response to Pathogens," Millenium Pharmaceuticals, Cambridge, MA, August 7, 2001.
3. Invited Speaker, "Nods: Apaf-1-like Molecules Regulating the Host Response to Pathogens," Corixa Pharmaceuticals, Seattle, WA, September 5, 2001.
4. Invited Speaker, "Nods: Apaf-1-like Molecules Regulating the Host Response to Pathogens" Biogen, Cambridge, MA, September 26, 2001.
5. Invited Speaker, "Apoptosis," II International Symposium on Novel Molecular Targets for Cancer Therapy, Buenas Aires, Argentina, October 4, 2001.
6. Invited Speaker, "A Novel NF- κ B Pathway in MALT Lymphoma" Pfizer, Groton, CT, October 1, 2001.
7. Invited Speaker, "Nods: Apaf-1-like Molecules Regulating the Host Response to Pathogens" Washington University, St. Louis, MO, October 15, 2001.
8. Invited Speaker, "Nod2 and Crohn's Disease", Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, Cambridge, MA, November 16, 2001.
9. Invited Speaker, "Activation of NF- κ B by Intracellular LPS Receptor Nod1/2", Symposium on NF- κ B in Host Defense: Genetics, Biochemistry and Function, Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, Cambridge, MA, November 17, 2001.
10. Invited Speaker, "Apaf-1-like Molecules Regulating the Host Response to Pathogens", American Society of Hematology Meeting, Orlando, FL, December 8, 2001.
11. Invited Speaker, "NOD Receptors and Intracellular Immunity, Immunity, Cologne Spring Meeting, University of Cologne, Germany, March 14, 2002.
12. Invited Speaker, "Nods: Apaf-1-Like Molecules Regulating the Host Response to Pathogens, Second Annual Workshop on Immunogenetic Mechanisms of Intestinal Inflammation: Genetics and Functional Genomics, University of Virginia, Charlottesville, VA, March 23, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNAL:

1. Inohara N, Ogura Y, Chen FF, Muto A, Nuñez G.: Human Nod1 Confers Responsiveness to Bacterial Lipopolysaccharides. *J Biol Chem.* 276:2551-2554 (2001).
2. Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nuñez G.: Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF κ B. *J Biol Chem.* 276:4812-4818 (2001).
3. Nickerson K, Sisk TJ, Inohara N, Yee CS, Kennell J, Cho MC, Yannie PJ, Nuñez G, Chang CH. Dendritic cell specific CIITA contains a caspase-recruitment domain that confers potent transactivation activity. *J. Biol. Chem* 276:19089-93 (2001).
4. Lucas PC, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, Yamaoka S, Seto M, Nuñez G: Bcl10 and MALT1, independent targets of chromosomal translocation in MALT lymphoma, cooperate in a novel NF-kappaB signaling pathway. *J. Biol. Chem* 276:19012-19019 (2001).
5. Hernandez-Alcoceba R, Pihajla M, Nuñez G, Clarke MF: Evaluation of a new dual-specificity promoter for selective induction of apoptosis in breast cancer cells. *Cancer Gene Therapy* 8:298-07 (2001).

6. Kulik G, Carson JP, Vomastek T, Overman K, Gooch BD, Srinivasula S, Alnemri E, Nuñez G, Weber MJ: Tumor necrosis factor alpha induces BID cleavage and bypasses antiapoptotic signals in prostate cancer LNCaP cells. *Cancer Res* 61:2713-9 (2001).
7. Mitra RS, Benedict MA, Qian D, Foreman KE, Ekhterae D, Nickoloff BJ and Nuñez G. Killing of sarcoma cells by pro-apoptotic Bcl-X_S: Role of the BH3 domain and regulation by Bcl-X_L. *Neoplasia* 23:437-445 (2001).
8. Yasunori O, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar J-P, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G* and Cho JH* (*joint senior authors). A frameshift mutation in Nod2 associated with susceptibility to Crohn's disease. *Nature* 411:603-606 (2001).
9. McAllister-Lucas LM, Inohara N, Lucas PC, Ruland J, Benito A, Li Q, Chen S, Chen FF, Yamaoka S, Verma IM, Mak TW and Nuñez G. Bimp1, a MAGUK Family Member Linking PKC Activation to Bcl10-Mediated NF- κ B Induction. *J Biol Chem* 276: 30589-30597 (2001).
10. Nair RP, Stuart P, Ogura Y, Inohara N, Chia NVC, Young L, Henseler T, Jenisch S, Christophers E, Voorhees JJ, Nuñez G, Elder JT. Lack of association between NOD2 3020InsC frameshift mutation and psoriasis. *J Invest Dermatol* 117:1671-1672 (2001).
11. Lin J, Page C, Jin X, Sethi AO, Patel R, Nuñez G. Suppression activity of pro-apoptotic gene products in cancer cells, a potential application for cancer gene therapy. *Anticancer Res* 21:831-839 (2001).
12. Kobayashi K, Inohara N, Hernandez LD, Galan JE, Nuñez G, Janeway C, Medzhitov R, Flavell RA. RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. *Nature* 416:194-199 (2002).
13. Liu JR, Opipari AW, Tan L, Jiang Y, Zhang Y, Tang H, Nuñez G. Dysfunctional apoptosome activation in ovarian cancer: Implications for chemoresistance. *Cancer Res.* 62:924-931 (2002).
14. Nor JE, Hu Y, Song W, Spencer DM, Nuñez G. Ablation of microvessels in vivo upon dimerization of iCaspase-9. *Gene Therapy* 2002 (*in press*).
15. Inohara N, Nuñez G. A conserved domain in MD-2 related protein family involved in innate immunity and lipid metabolism. *Trends Biochem Sci* 2002 (*in press*).

**AUGUSTO FELIX G. PAULINO, M.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. General Surgical Pathology – six months.
- B. Head and Neck Surgical Pathology, Departmental and Outside Consultation Services – 12 months.
- C. Bone and Soft Tissue Surgical Pathology, Departmental and Outside Consultation Services – 12 months.
- D. M-Labs Surgical Pathology Consultation – 12 months

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. M2: Musculoskeletal Sequence
 - 2. M4: Radiology-Pathology Correlation
 - 3. M4: Preceptor for Pathology Elective
- B. House Officers:
 - 1. General Surgical Pathology – 6 months.
 - 2. Head and Neck Surgical Pathology – 12 months as needed.
 - 3. Bone and Soft Tissue Surgical Pathology – 12 months as needed.
 - 4. Consultation Conferences
 - 5. Salivary Gland Pathology Lecture.
 - 6. Bone Pathology Lecture.
 - 7. Elective in Bone and Soft Tissue/Head and Neck Pathology.
- C. Interdepartmental:
 - 1. Pathology Conference for Oral/Maxillofacial Surgery Residents – monthly.
 - 2. Sarcoma Tumor Board – weekly.
 - 3. Pathology Conference for ENT Residents.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-investigator for Head and Neck SPORE

- B. Co-investigator for “Predicting response to therapy and early detection of recurrent oral cancer” (NIH 89570), Thomas E. Carey (principal investigator).
- C. Co-investigator for “Evaluating Neck Dissection Specimens” (U-M, Faculty Group Practice Plan, Academic Award – September 2001), Douglas Chepeha, M.D. (principal investigator)

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. House Officer Candidate Interviews.

UNIVERSITY OF MICHIGAN:

- A. Co-chair, Homer H. Stryker Orthopaedic Pathology Conference.

REGIONAL AND NATIONAL:

- A. Member, Head and Neck Task Force, American Joint Committee on Cancer.
- B. Reviewer, Cancer.
- C. Reviewer, Journal of Surgical Oncology.
- D. Reviewer, Head & Neck

V. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Xin W, Paulino AFG. Prognostic factors in malignant mixed tumors of the salivary gland: correlation of immunohistochemical markers with histologic classification. Ann Diagn Pathol (in press).
2. D'Silva NJ, Kurago Z, Polverini PJ, Hanks CT, Paulino AF. Malignant melanoma of the oral mucosa in a 17 year old female. Arch Pathol Lab Med (in press).
3. Muler JH, Paulino AF, Roulston D, Baker LH. Myxoid malignant fibrous histiocytoma with multiple primary sites. Sarcoma 2002;6:51-55.
4. Afify AM, Al-Khafaji BM, Paulino AFG, Davila RM. Diagnostic utility of muscle markers in the cytologic evaluation of serous fluids. Applied Immunohistochem Molec Morphol 2002;10:178-182.
5. Guo G, Paulino AFG. Lipomatous variant of nasopharyngeal angiofibroma: a case report. Arch Otolaryngol Head Neck Surg 2002;128:448-450.
6. Chhieng DC, Paulino AF. Cytology of myoepithelial carcinoma of salivary gland: a study of 4 cases. Cancer Cytopathol 2002;96:32-36.

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

1. Kowalski PJ, Paulino AFG. Perineural invasion in adenoid cystic carcinoma: its causation/promotion by brain-derived neurotrophic factor. Poster at the USCAP meeting, Feb 2002.
2. McKenney JK, Paulino AFG, Arbiser J, Folpe AL, Weiss SW. Angiosarcoma – one disease or many? A comparison of clinical subtypes. USCAP meeting, Feb 2002.
3. Paulino AFG, Afify AM. Her2/neu is preferentially expressed in squamous cell carcinoma of the tonsil compared to other squamous cell carcinomas of the head and neck. Poster at the USCAP meeting, Feb 2002.
4. Xin W, Paulino AFG. Prognostic factors in malignant mixed tumors of the salivary gland: correlation of immunohistochemical markers with histologic classification. Poster at the USCAP meeting, Feb 2002.
5. Akdas-Barkan G, Paulino AFG. Are epidermal and transforming growth factors responsible for pseudoepitheliomatous hyperplasia associated with granular cell tumors? Poster at the USCAP meeting, Feb 2002.

**SEM H. PHAN, Ph.D., M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Autopsy Service.

II. TEACHING ACTIVITIES:

- A. Lecturer, Pathology 580/630 and Pathology 581
- B. Training of postdoctoral fellows
- C. Member, Pathology Graduate Program thesis committees
- D. House officer training in autopsy service
- E. Pathology graduate program student counseling

III. RESEARCH ACTIVITIES:

- A. Principal Investigator, "Mechanisms of pulmonary fibrosis," NIH, R37, HL28737 MERIT Award.
- B. Principal Investigator, "Myofibroblasts in pulmonary fibrosis," NIH, RO-1, HL 52285.
- C. Project Leader, Project III, "Macrophage function in lung injury and fibrosis," NIH, PO-1, HL 31963.
- D. Co-investigator, SCOR in Human idiopathic pulmonary fibrosis, NIH, P-50 HL 56402.

PROJECTS UNDER STUDY:

- A. Mechanisms of lung injury and fibrosis.
- B. Cytokine regulation of fibroblast function.
- C. Smad regulation of the α -smooth muscle actin promoter and gene expression.
- D. Myofibroblast differentiation and its regulation by cytokines.
- E. Microarray analysis of lung gene expression in lung fibrosis.
- F. Induction and regulation of telomerase expression in lung fibrosis.
- G. Role of eosinophils in pulmonary fibrosis.
- H. Characterization of FIZZ1 and its role in myofibroblast differentiation

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Pathology Graduate Program.
- B. Member, Graduate Program Committee.
- C. Member, Departmental Research and Space Advisory Committee.
- D. Member, Pathology House Officer Selection Committee.

MEDICAL SCHOOL/HOSPITAL:

- A. Member, Medical Scientist Training Program Operating Committee.
- B. Member, Program in Biomedical Sciences Admissions Committee.

REGIONAL AND NATIONAL:

- A. Associate Editor, American Journal of Pathology.
- B. Reviewer for the following journals:
 - 1. American Journal of Respiratory and Critical Care Medicine.
 - 2. American Journal of Pathology.
 - 3. Journal of Immunology.
 - 4. American Journal of Physiology.
 - 5. American Journal of Respiratory Cell and Molecular Biology.
 - 6. Journal of Clinical Investigation,
 - 7. Experimental Cell Research.
 - 8. Journal of Applied Physiology.
 - 9. Lung.
- C. Reviewer/site visitor for NIH Program Project/Study Sections and VA grant proposals.

INVITED LECTURES/SEMINARS:

- 1. Invited Speaker, "Myofibroblasts in pulmonary fibrosis", Lovelace Respiratory Research Institute 2001 Annual Symposium, "Remodeling and repair in respiratory disease", Santa Fe, NM, 2001
- 2. Invited Speaker, "Pathogenesis of lung fibrosis", 7th International workshop on Scleroderma Research, Woods Hole, MA, 2002

V. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNALS:

- 1. Peters-Golden, M., Bailie, M., Marshall, T., Wilke, C., Phan, S.H., Toews, G.B.: Protection from pulmonary fibrosis in leukotriene-deficient mice. *Am. J. Resp. Crit. Care Med.* 2002; 165: 229-235.

2. Liu, T., Ullenbruch, M., Nozaki, Y., and Phan, S.H.: Regulation of telomerase activity in lung fibroblasts. *Am. J. Resp. Cell Molec. Biol.* 2002; 26: 534-540.
3. Huaux, F., Arras, M., Tomasi, D., Barbarin, V., Delos, M., Coutelier, J., Vink, A., Phan, S.H., Renauld, J., and Lison D.: A profibrotic function of IL-12p40 in experimental pulmonary fibrosis. *J. Immunol.* 2002; 169: 2653-2661.

BOOKS/CHAPTERS IN BOOKS/REVIEWS:

1. Guharoy, S., Phan, S.H.: Lung repair, remodeling and fibrosis, in, Wong, H.R., and Shanley, T.P. (Eds.) *Molecular biology of acute lung injury*, Kluwer Academic Publishers, Boston, MA, 2001; pp. 213-227.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Huaux F, Liu T, McGarry B, Ullenbruch M, Phan SH: Dual roles of interleukin-4 (IL-4) in bleomycin-induced lung injury and fibrosis. *FASEB J.* 2002;16:A556
2. Liu T, Dhanasekaran S, Ullenbruch M, Chinnaiyan AM, Phan SH: Microarray analysis in a model of lung injury shows a dramatic increase in FIZZ1 expression. *FASEB J.* 2002;16:A605
3. Gharaee-Kermani M, Ullenbruch M, McGarry B, Phan SH: The effects of estrogen on fibrotic lung fibroblasts. *Am. J. Resp. Crit. Care Med.* 2002;165:A167
4. Nozaki Y, Hasegawa Y, Shimamoto K, Hashimoto N, Nishiwaki K, Shimokata K, Phan SH: Telomerase activity in human alveolar fibroblasts from interstitial pneumonias patients. *Am. J. Resp. Crit. Care Med.* 2002;165:A360
5. Liu T, Ullenbruch M, Phan SH: Telomerase induction and myofibroblast differentiation in bleomycin-induced pulmonary fibrosis. 2002;165:A360
6. Huaux F, Gharaee-Kermani M, Liu T, McGarry B, Ullenbruch M, Xing Z, Phan SH: Role of CC chemokine receptor 3 (CCR3) and eotaxin in pulmonary responses to bleomycin in mice. *Am. J. Resp. Crit. Care Med.* 2002;165:A551

CARL L. PIERSON, Ph.D.
ASSISTANT PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY

ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002

I. CLINICAL ACTIVITIES:

- A. Director, Clinical Microbiology/Virology Laboratories.
- B. Director, UMHC Saline Health Center Clinical Laboratory
- C. Director, UMHC Ypsilanti Family Practice Health Care Center Clinical Laboratory.
- D. Coordinator, Infectious Disease Microbiology Laboratory Rounds.
- E. Technical Consultant - M-Labs.
- F. New clinical test development, verification and implementation.

II. TEACHING ACTIVITIES:

- A. Instructor, Pathology House Officer Microbiology/Virology Program.
- B. Lecturer, Clinical Pathology Grand Rounds.
- C. Coordinator, Clinical Microbiology/Virology In-service Program.
- D. Instructor, Infectious Disease Laboratory Rounds.
- E. Preceptor for M-4 elective in Pathology.
- F. Lecturer, Epidemiology 680, "Hospital Epidemiology"

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. "Trends in Antimicrobial Resistance for Clinical Isolates of *Bacteroides sp.*", Principal Investigator: D. R. Snyderman, New England Medical Center, Boston, Massachusetts.
- B. "In Vitro activity of Moxifloxacin against Clinically Significant Anaerobic Bacteria", Principal Investigator: Carl Pierson, Dept. of Pathology, University of Michigan.
- C. "Susceptibility and Surveillance Study of Antimicrobial Resistance of Common Respiratory Pathogens", a multicenter study.
- D. *Streptococcus pneumoniae*-Targeted Surveillance: A Two Phase Study. Protocol: 1351-SKB-00ED". Principal Investigator: Carl Pierson, Dept. of Pathology, University of Michigan.
- E. "Prospective Resistant Organism Tracking for the Ketolide Telithromycin-United States: 2000-2001 PROTEKT-US Survey". Principal Investigator: Carl Pierson, Dept. of Pathology, University of Michigan.

PROJECTS UNDER STUDY:

- A. Use of the Cobas Monitor for the quantitation of CMV in BMT patients.

- B. "Real-Time" PCR for the rapid diagnosis of infectious diseases.
- C. Use of the Cobas Monitor for the quantitation of HBV in patients with hepatitis.
- D. Prospective comparison of antimicrobial profiles of bacteria isolated from ICU patients.
- E. Use of the HandyLab bedside PCR device for detecting *Streptococcus agalactiae* during pregnancy.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Clinical Pathology Laboratory Directors Committee.
- B. Quality Assurance Committee
- C. Chair, Clinical Microbiology/Virology Senior Staff committee.
- D. UMHC Health Care Centers Laboratory Committee.
- E. Consultant for "Consultants in Laboratory Medicine", ProMedica Health System, Toledo, OH.

MEDICAL SCHOOL/HOSPITAL:

- A. Hospital Infection Control Committee.
- B. Antimicrobial Use subcommittee of the Pharmaceutical & Therapeutics Committee.
- C. Hospital Biodisaster Planning Committee
- D. College of Pharmacy Infectious Disease Program Planning Committee

REGIONAL/NATIONAL:

- A. Executive Board, South Central Association for Clinical Microbiology.
- B. Executive Board, Michigan Branch-American Society for Microbiology

V. OTHER RELEVANT ACTIVITIES:

PROFESSIONAL ORGANIZATIONS:

- A. American Society for Microbiology.
- B. European Congress for Clinical Microbiology and Infectious Diseases.
- C. Infectious Disease Society of America.
- D. South Central Association for Clinical Microbiology.
- E. Pan American Society for Clinical Virology.

INVITED LECTURES/ SEMINARS:

- 1. "Tick-Borne Infections in the USA", UMHS Dept. of Dermatology Continuing Education Series, March, 2002.
- 2. "The relationship of Human Papillomavirus infection and cancer." ProMedica Laboratory CME, Toledo, OH, March, 2002

3. Coordinated Roche-sponsored seminar: "NCCLS Guidelines 2002, Microbiological Recommendations and Clinical Relevance", April, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Manning, SD, MD Pearlman, P Tallman. CL Pierson and B Foxman. "Frequency of antibiotic resistance among Group B *Streptococcus* isolated from healthy college students". Clin. Infect. Dis., 2001;33:e137-139.

BOOKS/ CHAPTERS IN BOOKS:

1. "Antimicrobial susceptibility testing". In Clinical Laboratory Medicine, K.D. McClatchey, ed., Lippincott Williams & Wilkins, 2nd Ed, Chapter 55, p. 1221-1235.
2. "Collection and transport of gynecologic microbiology specimens". In Emergency Care of the Woman, M.D. Pearlman and J.E. Tintinalli, ed., McGraw Hill, 2nd Ed. *In press*.

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

1. Pierson, CL. "Measurement of Cytomegalovirus Viral Load", M-Labs Spectrum, 15(3):1-3,2001
2. Pierson, CL. "West Nile Virus in Michigan", M-Labs Spectrum, 15(4):1-3, 2001
3. Turner N and Pierson, CL. "Celiac disease testing", M-Labs Spectrum 16(2):3, 2002.

**RODOLFO F.H. RASCHE, M.D.
CLINICAL ASSISTANT PROFESSOR II
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2000 - 30 JUNE 2001**

I. CLINICAL ACTIVITIES:

- A. Surgical Pathology coverage of M-Labs cases, including most from the following hospitals/clinical practices:
 - 1. Trillium Community Hospital, Albion, MI (closed 2/5/02);
 - 2. Forest Health Medical Center, Ypsilanti;
 - 3. University of Michigan Health Service;
 - 4. Livonia SurgiCenter and other University of Michigan Clinics and satellite sites;
 - 5. Other clients such as clinics outside of Washtenaw County.
- B. Outside consults to a growing list of pathologists. These are stat consults and we provide fast turn around times. Most of these cases are shown in consultation to other faculty.
- C. Autopsy coverage at the University Hospitals, for weekdays and weekends. Autopsy coverage is also provided to Trillium Hospital, in Albion and Forest Health Medical Center, Ypsilanti.
- D. Perform bone marrow aspiration and biopsies at Trillium Hospital, Albion, MI (closed 2/5/02).
- E. Review peripheral smears at Forest Health Hospital and University of Michigan Health Service.
- F. Clinical Pathology consults for M-Labs client hospitals.
- G. Cytopathology: provide coverage in gynecologic, non-gyn and FNA services (performance of aspirate/interpretation) at U of M Hospitals for 20 weeks.
- H. Occasional frozen sections at Trillium Hospital (closed 2/5/02) and at Livonia Surgical Center (U of M Facility).

II. TEACHING ACTIVITIES:

- A. Supervise performing of autopsies by residents and sign out M-Labs and University of Michigan cases.
- B. Organize and lecture at the M-labs Symposium (17th Symposium in October 2001), a one day-long event with lectures and case presentations for pathologists (most are M-Labs clients). CME credits are provided. Held twice a year (October/April).
- C. Sign-out in cytopathology, with residents, fellow and, occasionally with medical students.
- D. In-service teaching to laboratory staff at Trillium Community Hospital (closed 2/5/02) and the University of Michigan Health Service (UHS).
- E. Monthly colposcopy meetings with the Gyn medical staff at UHS.

III. RESEARCH ACTIVITIES:

Ongoing collaborative study with Department of Radiology (Lawrence Kuhn, M.D.) and Hematology/Oncology (Valerie Castle, M.D.) on "Detection of Lymph Node Metastasis Using Ultrasound". – postponed to current academic year.

IV. ADMINISTRATIVE ACTIVITIES:

- A. Associate Director, M-Labs: (for more details, see M-Labs' Annual Report). Participate in planning, marketing and implementation of M-Labs programs.

Department of Pathology Annual Report

- a. Contacts with pathologists from client hospitals and others, as part of our support to pathologists; this includes providing occasional coverage;
- b. Laboratory network activity:
 - Joint Venture Hospital Laboratory – (JVHL) QA committee, which meets approximately once every three months.
 - Great Lakes Network – (GLN) Medical Affairs Committee, which meets as needed.
- c. M-Labs Network for M-care members. Coordinating M-Labs QA activities with D. Moss; monthly review of occurrence reports.
- B. Medical Director of the University of Michigan Health Service Laboratory, and Forest Health Medical Center in Ypsilanti.
- C. Active medical staff member at Forest Health Medical Center, Community Health Center of Branch Co (Coldwater) and Hillsdale Community Hospital. Conduct Tissue Review and Transfusion Review meetings. Attend their medical staff meetings.
- D. Intra-departmental meetings (e.g., Cytopathology)

V. OTHER:

- A. Inspector, for the CAP Accreditation Program. Performed two inspections.
- B. QA Review through Peer Review Organization of Michigan (PROM), for other hospitals in Michigan.

**DANIEL G. REMICK, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Autopsy Service.
- B. Director, Electron Microscopy Service
- C. Supervision of Autopsies- 8 weeks, signed out 66 autopsies, 28 day turnaround.
- D. Coordinator, Trauma/burn autopsy conference monthly
- E. Coordinator of Senior Staff Autopsy Call Schedule.
- F. Coordinator, Medical Examiner Investigators, University of Michigan until Oct 2001
- G. Deputy Medical Examiner, Washtenaw County.

II. TEACHING ACTIVITIES:

- A. Coordinator, Biweekly Pathology Gross Conference.
- B. Lectures to Pathology House Officers in Anatomic and Clinical Pathology.
- C. Lecturer, Pathology 600 Course, 1 contact hour
- D. Lecturer, Pathology 580 course (Dental School), 1 contact hour
- E. Pathology 600, Provided written critiques of student autopsy write-ups (167).
- F. Course Director, Pathology 800 Research Seminar Series in Pathology
- G. Lecturer, Pathology 581 Tissue, cellular and Molecular Basis of Disease, 3 contact hours
- H. Laboratory Instructor, Histopathology Laboratory for M1 students, 20 contact hours
- I. Laboratory Instructor, Pathology 600 (M2 pathology course), year long
- J. Thesis Committee - Andrew Merry, Kellie Breen, Department of Physiology
- K. Mentored research of Stewart Wang, M.D., Ph.D. (Department of Surgery), Grace Su, M.D., (Department of Medicine), Jean Nemzek, D.V.M. (Unit for Lab Animal Medicine), Postdoctoral fellows, Jiyou Kim, Ph.D., Liyu Xin, M.D., Ph.D., Hong Yan Xiao, M.D., Ekram El Laban, M.D.
- L. Medical Students – Elizabeth Owloski
- M. Graduate Students – Andrew Merry, Kellie Breen, Laura McKinley, Jill Murtha
- N. Undergraduate Students - Andrew Riskin

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Regulation of gene expression of soluble mediators of inflammation using the following models:
 - 1. Endotoxin-stimulated human whole blood.

2. Endotoxin injection in mice.
3. Cecal ligation and puncture.
4. 2 hit model of acid aspiration induced lung injury
- B. Toxic effects of immunomodulators.
- C. Pathophysiology of septic shock.
- D. Quantitation of mediators in septic shock.
- E. Cloning, sequencing, and expressing cytokines including mTNF, hTNF, mIL-6, hIL-8, mIL-18, mIL-1ra.
- F. Oxidant regulation of chemokine gene expression.
- G. Chemokines in the pathogenesis of murine asthma

SPONSORED SUPPORT:

- A. Principal Investigator, "The Role of Cytokines in Sepsis and Trauma", GM44918 \$906,182, 1990-2004. 30% effort
- B. Principal Investigator, "Regulation of IL-8 gene expression: four years, GM50401 \$870,822, 1995- 2004. 20% effort
- C. Principal Investigator, "Chemokines in the Pathogenesis of Asthma", ES09589, project #3, \$1,180,00, 1998 – 2002. 10% effort
- D. Co-Investigator, "Inflammation and the Host Response to Injury", GM-99-007, Ronald Tompkins, M.D. Principal Investigator Mass. General Hospital. Protein Analysis and Cell Biology Core, \$613,115, 2001 – 2006, 5% effort.
- E. Co-Investigator, "Inflammation and the Host Response to Injury", GM-99-007, Ronald Tompkins, M.D. Principal Investigator Mass. General Hospital. Protein Analysis and Cell Biology Core, \$613,115, 2001 – 2006, 10% effort.
- F. Co-Investigator, "Can Paraoxonase be Used to Treat Endotoxemia and Sepsis", Life Sciences Initiative, Bert LaDu Principal Investigator, \$150,000, 2000-2003. 2% effort
- G. Co-Investigator, NIH HD040112, "Neuroimmunology/Cytokine Alterations In Vulvodynia" Principal Investigator, Barbara Reed, \$375,000, 2000 – 2003

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director - Autopsy Service.
- B. Director, Electron Microscopy Service.
- C. Interviewer - Candidates for faculty, house officer, postdoctoral, and graduate student positions.
- D. Co-ordinator of call schedule, both weekend and weekday, autopsy service.
- E. Member, Paul W. Gikas Scholarship Selection Committee

MEDICAL SCHOOL/HOSPITAL:

- A. Member, Medical School Admissions Committee
- B. Member, Executive Committee, Medical School Admissions Committee
- C. Member, Task Force on Promotions and Tenure – Instructional Track

- D. Member, Institutional Review Board
- E. Member, Biomedical Research Council Undergraduate Research Council
- F. Reviewer, Biomedical Research Council grants
- G. Pathology representative to Medical Device Explant Committee
- H. Representative for Pathology to Program in Biomedical Sciences (PIBS) Admissions Committee

REGIONAL AND NATIONAL:

- A. Executive Committee, Michigan Association of Medical Examiners.
- B. Deputy Medical Examiner for Washtenaw County.
- C. Regular member National Institutes of Health, Surgery, Anesthesiology and Trauma Study Section Oct 1999 to June 2003
- D. Chair, NIH Special Emphasis Panel, Feb 2001
- E. Chair, NIH Special Emphasis Panel, June 2001
- F. Member, American Society of Investigative Pathology Education Committee
- G. Member, Michigan Coalition on Donation
- H. Publications Committee, International Cytokine Society
- I. Awards Committee, Shock Society
- J. Organizer, Shock Society Young Investigator's Research Forum
- K. Member, Michigan Association of Medical Examiners, Shock Society, American Association of Immunologists, A. James French Society, American Society of Investigative Pathologists, United States-Canadian Academy of Pathology.

V. OTHER RELEVANT ACTIVITIES:

- A. Editorial Board: Shock
- B. Reviewer:
 - 1. Journal of Immunology
 - 2. Journal Leukocyte Biology
 - 3. American Journal of Pathology
 - 4. Shock, reviewed
 - 5. American Journal of Physiology
 - 6. American Journal of Respiratory Cell and Molecular Biology
 - 7. American Journal of Respiratory and Critical Care Medicine
 - 8. Cellular Immunology
 - 9. Journal of Endotoxin Research
 - 10. Cytokine
 - 11. Grant Reviewer, Veterans Administration

INVITED LECTURES/SEMINARS:

- 2001 Visiting Professor, Institute Mario Negri, Milan, Italy, *Using the Inflammatory Response to Sepsis to Guide Therapy*
- Invited presentation, Esperion Therapeutics, Ann Arbor, Michigan *The Immunopathology of Sepsis*

- Visiting Professor, Department of Pathology, State University of New York, Stony Brook, *Understanding the Inflammatory Response in Sepsis to Guide Patient Therapy*
 Visiting Professor, North Shore University Hospital, Manhasset, New York, *Six at Six, Understanding the Inflammatory Response to Guide Therapy*
 2002 Visiting Professor, Washington State University, Pullman, Washington, *Understanding the Inflammatory Response to Sepsis to Guide Therapy*
 Chair, Experimental Biology Poster Discussion Session Pulmonary Inflammation, New Orleans
 Chair Experimental Biology Poster Discussion Session, Vascular Biology, New Orleans

VI. PUBLICATIONS:

ARTICLES PUBLISHED:

1. Remick DG, Call DR, Ebong SJ, Newcomb DE, Nybom P, Nemzek JA, Bolgos GE. Combinant immunotherapy with soluble tumor necrosis factor receptors plus interleukin 1 receptor antagonist decreases sepsis mortality. *Critical Care Medicine* 2001, 29:473-481
2. Call DR, Nemzek JA, Ebong SJ, Bolgos GR, Newcomb DE, Remick DG. Ratio of local to systemic chemokine concentrations regulates neutrophil recruitment. *American Journal of Pathology* 2001, 158:715-721
3. Call DR, Nemzek JA, Ebong SJ, Bolgos GR, Newcomb DE, Wollenberg GK, Remick DG. Differential local and systemic regulation of the murine chemokines KC and MIP2. *Shock* 2001, 4:278-284
4. Ebong SJ, Goyert SM, Nemzek JA, Kim J, Bolgos GL, Remick DG. Critical role of CD14 for production of proinflammatory cytokines and cytokine inhibitors during sepsis with failure to alter morbidity or mortality. *Infection & Immunity* 2001, 69:2099-106
5. Stern SA, Wang X, Mertz M, Chowanski ZP, Remick DG, Kim HM, Dronen SC. Under-resuscitation of near-lethal uncontrolled hemorrhage: effects on mortality and end-organ function at 72 hours. *Shock* 2001, 15:16-23
6. Nemzek JA, Siddiqui J, Remick DG. Development and optimization of cytokine ELISAs using commercial antibody pairs. *J Immunol Methods* 2001, 255:149-57
7. Mosher B, Dean R, Harkema J, Remick D, Palma J, Crockett E. Inhibition of Kupffer cells reduced CXC chemokine production and liver injury. *J Surg Res* 2001, 99:201-10
8. Steinstraesser L, Klein RD, Aminlari A, Fan MH, Khilanani V, Remick DG, Su GL, Wang SC. Protegrin-1 enhances bacterial killing in thermally injured skin. *Crit Care Med* 2001, 29:1431-7
9. Steinstraesser L, Fohn M, Klein RD, Aminlari A, Remick DG, Su GL, Wang SC. Feasibility of biolistic gene therapy in burns. *Shock* 2001, 15:272-7
10. Moon SE, Dame MK, Remick DG, Elder JT, Varani J: Induction of matrix metalloproteinase-1 (MMP-1) during epidermal invasion of the stroma in human skin organ culture: keratinocyte stimulation of fibroblast MMP-1 production. *Br J Cancer* 2001, 85:1600-1605.
11. Miura M, Fu X, Zhang QW, Remick DG, Fairchild RL: Neutralization of Gro alpha and macrophage inflammatory protein-2 attenuates renal ischemia/reperfusion injury. *Am J Pathol* 2001, 159:2137-2145.
12. Steinstraesser L, Tack BF, Waring AJ, Hong T, Boo LM, Fan MH, Remick DG, Su GL, Lehrer RI, Wang SC: Activity of novispirin G10 against *Pseudomonas aeruginosa* in vitro and in infected burns. *Antimicrob Agents Chemother* 2002, 46:1837-1844.

13. Remick DG, Bolgos GR, Siddiqui J, Shin J, Nemzek JA: Six at six: interleukin-6 measured 6 h after the initiation of sepsis predicts mortality over 3 days. *Shock* 2002, 17:463-467.

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

1. Remick D.G.: Protein Analysis and Bioassays of Cytokines and Cytokine Receptors. *Manual of Clinical and Laboratory Immunology*. Edited by Rose N.R., Hamilton R.G., Detrick B. Washington, D.C., ASM Press, 2002, pp 320-337
2. Remick D.G.: Mediators of Sepsis. *Sepsis and Multiple Organ Dysfunction*. Edited by Deitch E.A., Vincent J.L., Windsor A. New York, New York, W.B. Saunders, 2002, pp 63-72
3. Why Septic Mice Die: The SIRS-CARS Transition. D. Remick, G. Bolgos, J. Siddiqui, J. Nemzek, *Shock Society*, Big Sky Montana June 2002
4. Differential Gene Induction of Cytokines with Gram-Positive and Gram-Negative Bacterial. Preliminary Screening with Proteomics. S.Copeland, J. Siddiqui and D. Remick, *Shock Society*, Big Sky Montana June 2002
5. Improved Sensitivity of Colorimetric (COL) Compared to Chemiluminescence (CMIL) ELISAS for Cytokine Assays. Daniel Remick and Javed Siddiqui, *Experimental Biology*, New Orleans April 2002
6. Dimethyl Sulfoxide Increases LPS-Induced IL-1 β Production of Peripheral Blood Mononuclear Cells. Liyu Xing and Daniel G. Remick *Experimental Biology*, New Orleans April 2002
7. Neutralization of CXC Chemokines KC and MIP-2 Reduces Airway Hyperresponsiveness in a Novel House Dust Model of Asthma. Laura McKinley, Jiyou Kim, Javed Siddiqui, Gerald Bolgos, and Daniel Remick, *Experimental Biology*, New Orleans April 2002
8. Steroid Treatment Prevents Pulmonary Inflammation and Airway Hyperresponsiveness (AHR) in Mice Immunized and Challenged with House Dust Containing High Levels of Cockroach Allergens. Jiyou Kim, Javed Siddiqui, Laura McKinley, Gerry Bolgos, Daniel Remick, *Experimental Biology*, New Orleans April 2002
9. Mortality in Mice by CLP Induced Sepsis is not Due to Multiorgan Failure. G. Bolgos, J. Siddiqui, D. Remick, *Experimental Biology*, New Orleans April 2002
10. CXC Chemokine Redundancy Ensures Local Neutrophil Recruitment During Acute Inflammation. DG Remick, LB Green, DE Newcomb, SJ Garg, GL Bolgos, & DR Call. *International Cytokine Society*, Hawaii, November 2002.

**CHARLES W. ROSS, M.D.
ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001- 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Clinical Flow Cytometry Laboratory.
- B. Diagnostic Surgical Pathology, Hematopathology.
- C. Clinical Hematology Laboratory.
- D. Clinical Molecular Diagnostics Laboratory.
- E. Hematopathology Consultation Cases (including M-Labs and Veterans Administration Hospital).

II. TEACHING ACTIVITIES:

- A. Medical Students and Dental Students:
 - 1. Lecturer, M2 Hematology Sequence.
 - 2. Laboratory Instructor, M2 Hematology Sequence.
 - 3. Lecturer, Dental School Pathology 630.
 - 4. Laboratory Instructor, M1 Histopathology Course.
 - 5. Instructor, hematology portion of clinical pathology rotation, M4 clerkship in general pathology.
- B. House Officers:
 - 1. Sign-out of bone marrow biopsies, aspirates, blood smears, and body fluids in Hematology Laboratory.
 - 2. Sign-out of lymph node biopsies and review of hematopathology consultation material.
 - 3. Flow Cytometry sign-out.
 - 4. Molecular Diagnostics sign-out.
 - 5. Hematopathology case conferences.
 - 6. Hematopathology lecturer.
- C. Hematopathology teaching:
 - 1. Leukemia conference/biweekly.
 - 2. Lymphoma conference/weekly.
 - 3. Hematology conference/biweekly.
 - 4. Clinical Pathology Grand Rounds (one lecture).
 - 5. Clinical Pathology Case Conference/weekly.
 - 6. Cutaneous Lymphoma Conference/monthly.
 - 7. Lecturer in flow cytometry to hematology/oncology fellows, Department of Internal Medicine.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Immunophenotyping in acute and chronic leukemias.
- B. Radioimmunotherapy for B-cell lymphoma.
- C. Gene expression profiling of chronic lymphoproliferative disorders.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Clinical Flow Cytometry Laboratory.
- B. Coordinator, CP resident teaching program.
- C. Clinical Pathology Incentive Distribution Committee.
- D. Pathology Faculty Incentive Committee.
- E. Interviewer of residency candidates.

REGIONAL/NATIONAL:

- A. Central pathology reviewer, multicenter study of I¹³¹ anti-B1 radioimmunotherapy for B-cell lymphoma, Corixa Pharmaceutical.
- B. Hematology Council Member, Commission on Continuing Education, American Society of Clinical Pathologists.
- C. American Society of Clinical Pathologists, CheckPath Expert Review Panel, Hematopathology.
- D. Manuscript Reviewer, Archives of Pathology and Laboratory Medicine.

V. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Valdez R, Finn WG, Ross CW, Singleton TP, Tworek JA, Schnitzer B. Waldenström macroglobulinemia caused by extranodal marginal zone B-cell lymphoma. Am J Clin Pathol 116:683-690, 2001.
- 2. Hans CP, Finn WG, Singleton TP, Schnitzer B, Ross CW. Usefulness of anti-CD117 in the flow cytometric analysis of acute leukemia. Am J Clin Pathol 117:301-305, 2002.
- 3. Kansal R, Singleton TP, Ross CW, Finn WG, Padmore RF, Schnitzer B. Follicular Hodgkin's lymphoma: A histopathologic study. Am J Clin Pathol 117:29-35, 2002.
- 4. Uherova P, Ross CW, Finn WG, Singleton TP, Kansal R, Schnitzer B. Peripheral T cell lymphoma mimicking marginal zone B-cell lymphoma. Mod Pathol 15(4):420-425, 2002.
- 5. Valdez R, Kroft SH, Ross CW, Schnitzer B, Peterson LC, Singleton TP, Finn WG: Cerebrospinal fluid involvement by mantle cell lymphoma. Mod Pathol, in press.

ARTICLES SUBMITTED FOR PUBLICATION:

- 1. Kansal R, Ross CW, Kroft SH, Singleton TP, Finn WG, Schnitzer B. Histopathology of splenic small B-cell lymphomas: a study of 54 cases classified by flow cytometric immunophenotypic analysis or lymph node biopsy.
- 2. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience.

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

1. Finn WG, Sreekumar A, Stoolman LM, Ross CW, Schnitzer B, Valdez R, Chinnaiyan A: Comparative gene expression profiling of B-cell lymphoproliferative disorders by cDNA microarray analysis: identification of genes preferentially upregulated in chronic lymphocytic leukemia. *Mod Pathol* 2002;15(1):241A.
2. Guo G, Valdez R, Schnitzer B, Ross CW, Finn WG: The clinical spectrum of increased plasma viscosity: a retrospective study of 115 cases. *Mod Pathol* 2002;15(1):242A.
3. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience. *Mod Pathol* 2002;15(1):267A.
4. Uherova P, Roulston D, Finn WG, Valdez R, Schnitzer B, Ross CW: CD56 expression in acute myeloid leukemia with monocytic differentiation: association with complex karyotype. *Mod Pathol* 2002;15(1):267A.
5. Velankar M, Kansal R, Finn WG, Valdez R, Ross CW, Schnitzer B: Bcl-6 and CD10 paraffin section immunohistochemistry on bone marrow core biopsies to distinguish follicular lymphoma from other small B-cell non-Hodgkin lymphomas. *Mod Pathol* 2002;15(1):268A.
6. Snyder ML, Roulston D, Ross CW, Finn WG, Schnitzer B, Valdez R: Cytogenetic, immunophenotypic, and clinical correlation in adult acute lymphoblastic leukemia: a single institution's experience. *Mod Pathol* 2002;15(1):264A.
7. Uherova P, Ross CW, Schnitzer B, Finn WG: CD10 expression in diffuse large B-cell lymphoma (letter-reply). *Am J Clin Pathol*, 117:661-662, 2002.
8. Ross CW. Book review: *Flow Cytometry: First Principles*, 2nd ed., by Alice Longobardi Givan. *Arch Pathol Lab Med* 126(3):384-385, 2002.
9. Ross CW, Roulston D, Vandyke D, Finn WG, Schnitzer B, Nangia R. AML M2 with a complex variant t(8;21). *Proceedings of the Society for Hematopathology Meeting, Genetic and Molecular Genetic Studies in Human Hematologic Malignancies*. Boston, November 2001.
10. Valdez R, Finn WG, Nangia R, Ross CW, Schnitzer B: Cyclin D1-negative mantle cell lymphoma. *Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies*, Boston, MA, Nov. 2001.
11. Valdez R, Gulley ML, Ross CW, Nangia R, Finn WG, Schnitzer B: Classical Hodgkin's disease post-transplant. *Society for Hematopathology. Genetic and Molecular Genetics in hematologic Malignancies*, Boston, MA, Nov. 2001.
12. Valdez R, Gully ML, Ross CW, Nangia R, Finn WG, Schnitzer B: T-cell rich large B-cell lymphoma primary in CNS. *Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies*, Boston, MA, Nov. 2001.
13. Schnitzer B, Finn WG, Nangia R, Roulston D, Ross CW: Cytogenetically-confirmed Burkitt lymphoma of orbit. *Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies*, Boston, MA, Nov. 2001.
14. Finn WG, Sreekumar A, Ross CW, Schnitzer B, Nangia R, Chinnaiyan A: Gene expression profiling in B-cell chronic lymphocytic leukemia. *Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies*, Boston, MA, Nov. 2001.
15. Uherova P, Finn WG, Nangia R, Ross CW, Schnitzer B. Peripheral T-cell lymphoma mimicking MALT lymphoma. *Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies*, Boston, MA, Nov. 2001.

16. Nangia R, Ross CW, Finn WG, Gulley ML, Schnitzer B: Atypical lymphoid proliferation preceding peripheral T-cell lymphoma. Society for Hematopathology. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2001.

**DIANE ROULSTON, Ph.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2000 - 30 JUNE 2001**

I. CLINICAL ACTIVITIES:

- A. Director, Clinical Cytogenetics Laboratory

II. TEACHING ACTIVITIES:

- A. House Officers and Fellows
1. Rotations in Cytogenetics
 - a. Pathology (N=6)
 - b. Genetics (N=1)
 - c. Hematology/Oncology (N=1)
- B. Genetic Counselors (Human Genetics 644 – Interdisciplinary Care)
1. Lecture and Interactive Training in Clinical Cytogenetics – 2 hours
- C. Clinical Cytogenetics teaching
1. Abnormal Cytogenetics Case Conference (Biweekly) for technologists, residents, fellows, and faculty
 2. Leukemia Conference (Biweekly)
 3. Pediatric Genetics Post-clinic Conference (Weekly)
 4. Joint Genetics Conference (Monthly - 2 case presentations)
 5. Clinical Pathology Grand Rounds
 - a. “Evolving Technologies in Cytogenetics” 3/15/02
 6. Anatomic Pathology Residents Conference
 - a. “Molecular Cytogenetics” 2/12/02
 7. Hematology/Oncology Fellows Conference
 8. “Cancer Cytogenetics” 4/17/02
 - a. “Cancer Cytogenetics” 4/17/02

III. RESEARCH ACTIVITIES:

- A. Cytogenetic and FISH analysis for “A Phase II Study of Oral Tetrathiomolybdate (TM), an Inhibitor of Angiogenesis, for the Treatment of Multiple Myeloma.” (GCRC Protocol Mo1-RR00042) Harry Erba, MD, PhD, Principal Investigator.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Clinical Cytogenetics Laboratory
- B. Interviewer
1. Pathology Residency Candidates
 2. Hematopathology Fellow Candidates
- C. Search Committee for Assistant Director, Clinical Cytogenetics
- D. Clinical Pathology Laboratory Organization Committee

UNIVERSITY OF MICHIGAN:

- A. Interviewer
 - 1. Clinical Genetics Residency/Fellowship Candidates

REGIONAL AND NATIONAL:

- A. Fellow, American College of Medical Genetics
- B. Peer Review: *Leukemia; Genes, Chromosomes & Cancer; Int. J Cancer*
- C. Children's Oncology Group (COG)
 - 1. Cytogenetics Committee member: review cases for national study group
 - 2. Director of an Approved Laboratory; submit clinical cases for review
- D. Southwest Oncology Group (SWOG)
 - 1. Director of an Approved Laboratory; submit cases for review

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Muler JH, Paulino AF, Roulston D, Baker LH. Case report of myxoid malignant fibrous histiocytoma with multiple primary sites. *Sarcoma* 1:51-55. 2002.
- 2. Wechsler DW, Alexander BM, Engstrom LD, Motto DG, Roulston D. A novel inversion of 11q in an infant leukemia fuses *MLL* to *CALM*, a clathrin assembly protein gene. *Genes Chromosomes & Cancer*, in press.

ABSTRACTS:

- 1. Baida G, Chim CS, Pomykala H, Roulston D, Larson RA, Olopade OI. *LUN*, a novel transcription factor on 9p21, is frequently deleted in human leukemia. *Blood* 98; 98a: 2001
- 2. Alexander BM, Engstrom LD, Motto DG, Roulston D, Wechsler DW. A novel inversion of chromosome 11 in an infant acute myeloid leukemia fuses *MLL* to *CALM*, a clathrin assembly protein gene. *Blood* 98; 576a: 2001.
- 3. Uherova P, Roulston D, Finn WG, Valdez R, Schnitzer B, Ross CW. CD56 expression in acute myeloid leukemia (AML) with monocytic differentiation: association with complex karyotype. United States and Canadian Academy of Pathology Annual Meeting Feb 23-March 1, 2002. Abstracts, p. 267A.
- 4. Snyder ML, Roulston D, Ross CW, Finn WG, Schnitzer B, Valdez R. Cytogenetic, immunophenotypic, and clinical correlation in adult acute lymphoblastic leukemia: a single institution's experience. United States and Canadian Academy of Pathology Annual Meeting Feb 23-March 1, 2002. Abstracts, p. 264A.
- 5. Dagenais SL, Cox B, Stempek L, Innis JW, Carels H, Robertson J, Roulston D, Glover TW. Interstitial deletion of 4p in a three-generation family with minimal phenotypic effects. Association of Genetics Technologists Annual Meeting, June 20-23, 2002. Abstracts, p.150.

**ROBERT E. RUIZ, M.D., PH.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 AUGUST 2001 – 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Consultant, pediatric surgical pathology, full time
- B. Consultant, pediatric autopsy pathology, full time
- C. Consultant, placental pathology, as needed
- D. Consultant, Teratology Service histology, as needed
- E. Pathology co-ordinator, Children's Oncology Group cases
- F. Diagnostic Hematopathology, 1 week/month (since 1/2002)

II. TEACHING ACTIVITIES:

- A. Pathology House Officers:
 - 1. Pathology Consult Conference, Neuroblastoma (1 hour)
 - 2. Pathology Teaching Conferences, Hirschsprung's Disease, Wilms tumor (2 hours)
 - 3. Hematopathology Signout (~1 week per month, ~3 hours per day with residents, since 1/2002)
 - 4. Placental Pathology Signout (~0.5-1 hour per week with residents)
 - 5. Pediatric Surgical Pathology Signout (~0.5-1 hour per week with residents)
 - 6. Pediatric Autopsy Pathology Signout (~0.5-1 hour per week with residents)
- B. Interdepartmental:
 - 1. Pediatric Hematology-Oncology Fellow Pathology Tutorials (3 hours)
 - 2. Pediatric Hem-Onc Tumor Board (2 hours per month)
 - 3. Pediatric Radiology/Surgery/Pathology Conference (1 hour per month)
 - 4. Pediatric Morbidity & Mortality Conference (1 hour per quarter)
 - 5. Pediatric Gastrointestinal Pathology (1-2 hours per month)

RESEARCH ACTIVITIES:

- A. Case study of intestinal infantile fibrosarcoma with Drs. Islam and Geiger of Pediatric Surgery (manuscript in preparation)
- B. Case study of Burkitt lymphoma in Williams syndrome with Drs. Thornburg and Mody of Pediatric Hematology-Oncology (manuscript in preparation)
- C. Collaborator in ongoing studies of neuroblastoma with Dr. Castle of Pediatric Hematology-Oncology

IV. ADMINISTRATIVE ACTIVITIES:

Executive Committee, Mott Hospital

V. PUBLICATIONS:

1. B.P. Rubin, S. Singer, C. Tsao, A. Duensing, M. L. Lux, R. Ruiz, M.K. Hibbard, C.-J. Chen, S. Xiao, D. A. Tuveson, G. D. Demetri, C.D.M. Fletcher, J.A. Fletcher. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Research* 2001 61: 8118-8121.
2. D.R. Genest, R.E. Ruiz, S. Weremowicz, R.S. Berkowitz, D.P. Goldstein, D.M. Dorfman. Do non-triploid partial hydatidiform moles exist? A histologic and flow cytometric reevaluation of nontriploid specimens. (Manuscript submitted.)

ALVIN H. SCHMAIER, M.D.
PROFESSOR
DEPARTMENTS OF PATHOLOGY AND INTERNAL MEDICINE

ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 – 20 JUNE 2002

I. CLINICAL ACTIVITIES:

- A. Professor of Internal Medicine.
- B. Professor of Pathology.
- C. Director, Coagulation Laboratory

II. TEACHING ACTIVITIES (DEPARTMENT OF PATHOLOGY):

- A. Pathology House Officers:
 - 1. Responsible during the current academic year for teaching activities for the following:
 - a. Residents participated in weekly sign-out rounds by laboratory direct of specialized coagulation testing.
 - b. Formal lecture for 4th year medical student elective clinical pathology course.
- B. Medical School: M2 Hematology Course Director

III. RESEARCH DESCRIPTION:

Dr. Schmaier's major investigative work this year on the physiology and functional of the plasma kallikrein/kinin system (KKS) has made great progress this year. The Schmaier laboratory made a fundamental discovery that the endothelial cell enzyme prolylcarboxypeptidase activates plasma prekallikrein when bound to high molecular weight kininogen (*JBC* 277:17962-17969, 2002). This discovery answers a 30 year question in this field as to what is the physiologic activator of the plasma kallikrein/kinin system. Prolylcarboxypeptidase previously has only been known as the enzyme to degrade angiotensin II, the vasoactive peptide of the renin angiotensin system. Determining that prolylcarboxypeptidase is an activator of prekallikrein at a K_m 5 orders of magnitude lower than inactivation of angiotensin II indicates that its interaction is physiologically important. This discovery also allows for a new hypothesis on the physiologic activity of the plasma KKS. We hypothesize that the plasma KKS is the physiologic counterbalance of the renin angiotensin system. This notion was presented as a Commentary in the *J. of Clinical Investigation* (*JCI* 109:1007-1009, 2002) and will be the working hypothesis for this project for years to come.

Second, the research efforts to develop a novel class of selective inhibitors of α -thrombin activation of platelet have made good progress. An agent termed "thrombostatin" has been developed as an inhibitor of α -thrombin cleaving the cloned thrombin receptors, PAR1. Four proof-of-concept animal studies have been completed showing that our model agent prevents

coronary thrombosis in dogs and carotid thrombosis in mice. A lead compound has been identified for toxicology studies and Phase I clinical studies. Dr. Schmaier's start-up biotechnology company, Thromgen, Inc., has received good funding to continue its work. Thromgen, Inc. is a recipient of a new Phase II STTR from NIH and a grant from the Michigan Life Science Corridor. Major progress has been made to complete the licensing agreement between Thromgen, Inc. and the University of Michigan.

A third major investigative effort is to create mouse models for intracerebral hemorrhage. At present, we have created two transgenic mice that over-express the 751 form of the amyloid β -protein precursor (A β PP) in brain vasculature. By both PCR and histologic studies on brain endothelium, A β PP is specifically expressed in brain endothelium. Anticoagulant challenge studies are planned on these animals to determine if those animals which over-express A β PP have a lower threshold for brain hemorrhage.

IV. HONORS & AWARDS:

None

V. IMPORTANT LECTURES:

1. 3/1/01: Medical University of South Carolina: Symposium for Harry Margolius, Charleston SC "*Revised Hypothesis of the Kallikrein/Kinin System*"
2. 3/22/01: University of Miami Hemostasis Conference, Miami FL "*Disseminated Intravascular Coagulation*"
3. 9/6/01: Central Society for Clinical Research, Chicago, IL, "*Faculty Start-up Companies: The Academic Conundrum*".
4. 12/9/01: American Society of Hematology, Orlando, FL: Medical School Course Directors Meeting: Presentation about "*Hematology for the Medical Student*".
5. 1/17/02: SE Blood Center Milwaukee, Milwaukee WI, "*Interaction Between the Kallikrein/Kinin System and the Renin Angiotensin System*"
6. 1/26/02: ASH Update Course, Dearborn, MI, "*Hemostasis and Thrombosis*"
7. 3/4/02: University Health Service, University of Michigan, "*Outpatient Management of Coumadin & Low Molecular Weight Heparin*"
8. 3/16/02: Biomedical Research Council, University of Michigan, "*What To Do To Get Your NIH Grant Funded*"
9. 4/15/02: Pfizer, Ann Arbor, MI, "*Thrombostatin*"
10. 5/28/02: International Kallikrein/Kinin Meeting, Charleston SC, "*Revised Hypothesis for the Kallikrein/Kinin System*"
11. 5/31/02: International Kallikrein/Kinin Meeting, Charleston SC, "*Mechanism of Action of Thrombostatin*"
12. 6/5/02: Blood Banking CME Course, Department of Pathology, "*New Antiplatelet Agents and Their Relation to Blood Banking*"

VI. NATIONAL OR REGIONAL COMMITTEE ASSIGNMENTS:

1. Chairman: Scientific Subcommittee on Clinical Laboratory Hematology, American Society of Hematology, 2002
2. Central Society for Clinical Research: Hematology/Oncology Subspeciality Chairman
3. NASCOLA: North American Specialized Coagulation Laboratory Association – Executive Committee, “Member-at-Large”

VII. INDIVIDUAL EDITORIAL:

1. Advisory Board: Journal of Thrombosis & Haemostasis
2. Editorial Board: Thrombosis and Haemostasis, Section Editor

VIII. NIH STUDY SECTIONS OR OTHER FEDERAL ADVISORY:

1. NIH NHLBI: PPG Review Committee, 2002
2. NIH NHLBI: ZRG1 SSS-0 10B and SSS-0 12B Special Emphasis Panel Study Section, 2001-2004

IX. PEER-REVIEWED PUBLICATIONS:

1. Shariat-Madar, Z., Mahdi, F., Schmaier, A.H. Factor XI assembly and activation on human umbilical vein endothelial cells in culture. *Thromb. Haemost.* 85:544-551, 2001.
2. Zhao, Y., Qui, Q., Mahdi, F., Shariat-Madar, Z., Rojkaer, R., Schmaier, A.H. Assembly and activation of the HK.PK complex on endothelial cells results in bradykinin liberation and NO formation. *Amer. J. Physiol. Hear Circ Physiol.* 280:H1821-H1829, 2001.
3. Mahdi, F., Shariat-Madar, Z., Todd III, R. F., Figueroa, C.D., Schmaier, A.H. Expression and co-localization of cytokeratin 1 and urokinase plasminogen activator receptor on endothelial cells. *Blood.* 97:2342-2350, 2001.
4. Schmaier, A.H., Srikanth, S., Elghetany, M.T., Normolle, D., Gokhale, S., Feng, H.M., Walker, D.H. Hemostatic/fibrinolytic protein changes in C3H/HeN mice infected with *Rickettsia conorii* – A model for Rocky Mountain Spotted Fever. *Thrombosis and Haemostasis.* 86:871-879, 2001.
5. Motta, G., Shariat-Madar, Z., Mahdi, F., Sampaio, C.A.M., Schmaier, A.H. Assembly and activation of high molecular weight kininogen and prekallikrein on cell matrix. *Thrombosis and Haemostasis.* 86:840-847, 2001.
6. Hasan, A.A.K., Schmaier, A.H., Warnock, M., Normolle, D., Driscoll, E., Lucchesi, B.R., Werns, S.W. Thrombostatin inhibits cyclic flow variations in stenosed canine coronary arteries. *Thrombosis and Haemostasis.* 86:1296-1304, 2001.
7. Hasan, A.A.K., Warnock, M., Srikanth, S., Schmaier, A.H. Developing peptide inhibitors to thrombin activation of platelets from bradykinin analogs. *Thrombosis Research*, 104:451-465, 2001.
8. Prieto, A.R., Ma, H., Huang, R., Khan, G., Schwartz, K.A., Hage-Korban, E.E., Schmaier, A.H., Hasan, A.A.K., Abela, G. S. Thrombostatin, a metabolite of bradykinin, reduces platelet activation in a model of arterial wall injury. *Cardiovascular Research.* 53:984-992, 2002.

9. Lima, A.P.C.A., Almeida, P.C., Tersariol, I.L.S., Schmitz, V., Schmaier, A.H., Juliano, L., Hirata, I.Y., Muller-Esterl, W., Chagas, J.R., Scharfstein, J. Heparin sulfate modulates kinin release by *Trypanosoma cruzi* through the activity of cruzipain. *J. Biol. Chem.* 277:5875-5881, 2002.
10. Mahdi, F., Shariat-Madar, Z., Figueroa, C.D., Schmaier, A.H. Factor XII interacts with the multiprotein assembly of urokinase plasminogen activator receptor, gC1qR, and cytokeratin 1 on endothelial cell membranes. *Blood.* 99:3585-3596, 2002.
11. Shariat-Madar, Z., Mahdi, F., Schmaier, A.H. Identification and characterization of prolylcarboxypeptidase as an endothelial cell prekallikrein activator. *J. Biol. Chem.* 277:17962-17969, 2002.
12. Laudes, I.J., Chu, J.C., Srikanth, S., Huber-Lang, M., Guo, R.-F., Riedemann, N., Sarma, J.V., Schmaier, A.H., Ward, P.A. Anti-C5a ameliorates coagulation/fibrinolytic protein changes in a rat model of sepsis. *Amer. J. Pathol.* 160:1867-1875, 2002.
13. Moreira, C.R., Schmaier, A.H., Mahdi, F., da Motta, G., Nader, H.B., Shariat-Madar, Z. Identification of prolylcarboxypeptidase as the cell matrix-associated prekallikrein activator. *FEBS Letters.* 523:167-170, 2002.
14. Chay, C.H., Cooper, C.R., Gendernalik, J.D., Dhanasekaran, S.M., Chinnaiyan, A.M., Rubin, M.A., Schmaier, A.H., Pienta, K.J. A functional thrombin receptor (PAR1) is expressed on bone-derived prostate cancer cell lines. *Urology.* In Press, 2002.
15. Abela GS, Huang R, Ma H, Prieto AR, Lei M, Schmaier AH, Schwartz KA, Davis JM. Laser-light scattering (LLS), a new method for continuous monitoring of platelet activation in circulating fluid. *J. Lab. Clin. Med.* In Press, 2003.

X. CURRENT GRANT SUPPORT:

1. PO1-HL57346, 1997-2002, "Molecular Genetics of Coagulation Disorders", D. Ginsburg, P.I. Core A. (\$296,000 Direct Costs to Dr. Schmaier)
2. R42-HL61981, 2001-2003, "Thrombostatin in the Folts Model", AH Schmaier, PI, Subcontract to the University of Michigan (\$344,976 Total Costs to Dr. Schmaier at U of M subcontract)
3. RO1-HL65194, 2000-2004, "Plasma Protein Phenotyping of Prothrombotic Mice", A.H. Schmaier, P.I. (\$604,128 Total Costs)
4. Michigan Life Science Corridor Grant, 2001-2004, "Thrombostatin-A Novel Anti-Platelet Agent", AH Schmaier, P.I., (\$745,793 subcontract to U of Michigan, HI Mosberg, and BR Lucchesi PI)
5. RO1-HL52779, 2001-2005, "Regulation of Kinin Delivery on HUVEC", A.H. Schmaier, P.I. (\$1,678,075 Total Costs)
6. P01 CA69568, 2002-2003, "The Role of Protease Activated Receptor-1 (PAR-1) in Prostate Cancer Metastasis", K. Pienta, P.I. (\$16,670 Direct Costs to Dr. Schmaier)

**BERTRAM SCHNITZER, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Hematopathology Fellowship Training Program
- B. Diagnostic Surgical Pathology, Hematopathology (12 months).
- C. Diagnostic Hematopathology Consultant, Veterans Administration Hospital.
- D. Diagnostic Hematopathology of M-Labs clients.
- E. Consultant for external and transfer Hematopathology cases.
- F. Review of lymphoma cases entered into Children's Cancer Study Group protocols.

II. TEACHING ACTIVITIES:

MEDICAL SCHOOL/HOSPITALS:

- A. Daily sign-out of bone marrow biopsies and aspirates.
- B. Daily review of blood smears and body cavity and joint fluids in the Hematology Laboratory.
- C. Daily review of in-house and consultation hematopathology cases and correlation with flow cytometry data and immunoperoxidase studies.
- D. Daily review of outside consultation cases.
- E. House Officer Conferences in Hematopathology, Clinical Pathology Grand Rounds.
- F. Biweekly House Office Hematopathology Conference.
- G. Monthly lectures to house officers on acute leukemias, lymphomas, and benign lymphadenopathy.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

None.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Diagnostic Surgical Pathology, Hematopathology.
- B. Diagnostic Clinical Pathology, Hematology.

MEDICAL SCHOOL/HOSPITALS:

- A. Director of Hematopathology Fellowship Training Program

REGIONAL AND NATIONAL:

- A. Society for Hematopathology, Executive Committee
1. Past President.
- B. Children's Cancer Study Group: Review of in-house cases of lymphoma cases.
- C. Member, Hematology Workshop Review Committee, American Society of Clinical Pathologists.
- D. Hematology Planning Committee, American Society of Clinical Pathologists.
- E. Bylaws Committee, Society for Hematopathology.
- F. Chair, Hematology Check-Path Committee, American Society of Clinical Pathologists.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARD:

- A. Human Pathology. Designated reviewer.
- B. American Journal Clinical Pathology. Designated reviewer.

INVITED LECTURES/SEMINARS:

1. "A Practical Approach to Diagnostic Hematological Problems," ASCP Educational Course, Lectures given included a) Reactive Lymphadenopathies: Diagnosis and Differential Diagnosis; b) Non-Hodgkin's Lymphomas and their Differential Diagnosis; c) Hodgkin's Disease; d) Differential Diagnosis of Hodgkin's Disease; e) A Practical Approach to Diagnosis and Classification of Lymphomas and Leukemias by Immunohistochemistry, Flow Cytometry and Molecular Genetic Analysis; f) Extranodal Lymphomas and, g) Acute Lymphoblastic Leukemias, Las Vegas, NV, November 2001.
2. "Reactive Lymphadenopathies," Tutorial on Neoplastic Hematopathology, Department of Laboratory Medicine and Pathology, Cornell University, Miami, Florida, February, 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Valdez R, Finn WG, Ross CW, Singleton TP, Tworek JA, Schnitzer B: Waldenstrom's macroglobulinemia caused by extranodal marginal zone B-cell lymphoma. Am J Clin Pathol 116:898-904, 2001.
2. Alkan S, Beals TF, Schnitzer B: Primary diagnosis of Whipple's disease manifesting as lymphadenopathy. Use of polymerase chain reaction for detection of *Tropheryma whipplei*. Am J Clin Pathol 116:898-904, 2001.
3. Hans CP, Finn WG, Singleton TP, Schnitzer B, Ross CW: Usefulness of anti-CD117 in the flow cytometric analysis of acute leukemia. Am J Clin Pathol 117:301-305, 2002.

4. Kansal R, Singleton TP, Ross CW, Finn WG, Padmore RF, Schnitzer B: Follicular Hodgkin's Lymphoma. A histopathologic study. *Am J Clin Pathol* 117:29-35, 2002.
5. Uherova P, Ross CW, Finn WG, Singleton TP, Kansal R, Schnitzer B: Peripheral T-cell lymphoma mimicking marginal zone B-cell lymphoma. *Mod Pathol* 15:420-425, 2002.
6. Plumbley JA, Fan H, Eagan PA, Ehsan A, Schnitzer B, Gulley ML: Lymphoid tissue from patients with infectious mononucleosis lack monoclonal B and T cells. *J Mol Diagn* 4:37-43, 2002.
7. Valdez R, McKeever P, Schnitzer B: Composite germ cell tumor and high-grade B-cell lymphoma arising in the sella tursica. *Human Pathol*. In press, 2002.
8. Su, LD, Fullen DR, Lowe L, Uherova P, Schnitzer B, Valdez R: CD117 (KIT receptor) expression in Merkel cell carcinoma. *Am J Dermatol*. In press, 2002.
9. Valdez, R, Kroft SH, Ross CW, Schnitzer B, Peterson LC, Singleton TP, Finn WG: Cerebrospinal fluid involvement by mantle cell lymphoma. *Mod Pathol*, in press.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Kansal R, Ross CW, Kroft SH, Singleton TP, Finn WG, Schnitzer B: Histopathology of splenic small B-cell lymphomas: A study of 54 cases classified by flow cytometric immunophenotypic analysis or lymph node biopsy. *Am J Clin Pathol* (submitted for publication).
2. Uherova P, Valdez R, Ross CW, Schnitzer B, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: An immunophenotypic reappraisal based on a single-institution experience. *Am J Clin Pathol* (submitted for publication).
3. Valdez R, Thorson J, Finn WG, Kleer CG, Schnitzer B: Lymphocytic mastitis: a molecular, immunophenotypic, and clinicopathologic evaluation of eleven cases. *Am J Clin Pathol* (submitted for publication).

BOOKS AND CHAPTERS IN BOOKS:

1. Reactive Lymphadenopathies. In: Knowles, D. (ed). *Neoplastic Hematopathology*, 2nd Ed. Williams & Wilkins, 2001.
2. Hsi ED, Schnitzer B. In Jaffe ES, Harris NL, Vardiman J (eds). *Diagnostic Hematopathology*. Harcourt Health Sciences, 2003.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Schnitzer B, Finn WG, Nangia R, Roulston D, Ross CW: Burkitt's lymphoma. Case 65. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
2. Valdez R, Gulley ML, Ross CW, Nangia R, Finn WG, Schnitzer B: T-cell rich large B-cell lymphoma primary in CNS. Case 72. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
3. Nangia R, Ross CW, Finn WG, Gulley ML, Schnitzer B: Atypical lymphoproliferative process with prominent non-caseating granulomatous reaction and clonal T-cell receptor gene rearrangement followed by peripheral T-cell lymphoma. Case 98. Society for Hematopathology

- Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
4. Finn WG, Sreekumar A, Ross CW, Schnitzer B, Nangia R, Chinnaiyan A: B-cell chronic lymphocytic leukemia. Case 89. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
 5. Valdez R, Gulley ML, Ross CW, Nangia R, Finn WG, Schnitzer B: Classical Hodgkin's disease occurring in post-transplant setting. Case 87. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
 6. Uherova P, Finn WG, Nangia R, Ross CW, Schnitzer B. Peripheral T-cell lymphoma. Case 39. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
 7. Ross CW, Roulston P, Vandyke D, Finn WG, Schnitzer B, Nangia R: AML M2 presenting with characteristic morphology and flow cytometric immunophenotype but having a complex variant t(8;21) by conventional cytogenetics. Case 5. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
 8. Uherova P, Ross CW, Schnitzer B, Finn WG: CD10 expression and survival. *Am J Clin Pathol* 117: 661-662, 2002 (Letter to the Editor).
 9. Finn WG, Sreekumar A, Stoolman LM, Ross CW, Schnitzer B, Valdez R: Comparative gene expression profiling of B-cell lymphoproliferative disorders by cDNA microarray analysis: Identification of genes preferentially upregulated in chronic lymphocytic leukemia. *Mod Pathol* 15:241A, 2002.
 10. Valdez R, Thomson J, Finn WG, Kleer CG, Schnitzer B: Lymphocytic mastitis: A molecular, immunophenotypic, and clinicopathologic evaluation of eleven cases. *Mod Pathol* 15: 268A, 2002
 11. Velenkar M, Kansal R, Finn WG, Valdez R, Ross CW, Schnitzer B: Bcl-6 and CD paraffin section immunohistochemistry in marrow core biopsies to distinguish follicular lymphoma from other B-cell non-Hodgkin's lymphomas. *Mod Pathol* 15:368A, 2002
 12. Uherova P, Roulston D, Finn WG, Valdez R, Schnitzer B, Ross CW. CD56 expression in acute myeloid leukemia (AML) with monocytic differentiation: Association with complex karyotype. *Mod Pathol* 15:267A, 2002.
 13. Guo G, Valdez R, Schnitzer B, Ross CW, Finn WG. The clinical spectrum of increased plasma viscosity: A retrospective study of 115 cases. *Mod Pathol* 15:242, 2002.
 14. Snyder ML, Roulston D, Ross CW, Finn WG, Schnitzer B, Valdez R: Cytogenetic, immunophenotypic, and clinical correlation in adult acute lymphoblastic leukemia: A single institution experience. *Mod Pathol* 15:264A, 2002.
 15. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocytic predominant Hodgkin's lymphoma: An immunophenotypic reappraisal based on a single-institution experience. *Mod Pathol*: 267A, 2002

EUGENE M. SILVERMAN, M.D.
CLINICAL ASSOCIATE PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY

ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002

I. CLINICAL ACTIVITIES:

- A. Surgical Pathology Coverage of M-Labs cases, including most cases from:
 - 1. Trillium Hospital, Albion, Michigan (including frozen sections) through February, 2002.
 - 2. University of Michigan Health Service, non-dermatology cases, Ann Arbor, Michigan.
 - 3. Forest Health Medical Center, Ypsilanti, Michigan.
 - 4. Other various clients including numerous satellite sites and University acquired practices.
- B. Autopsy Coverage for Trillium Hospital, Albion, Michigan, (through February, 2002, and Forest Health Medical Center, Ypsilanti, Michigan.
- C. Rotation with other staff pathologists:
 - 1. Coverage at the University Hospitals of weekend autopsy call.
- D. Perform bone marrow aspiration and biopsies at Trillium Hospital, Albion, Michigan through February, 2002.
- E. Clinical Pathology consults for M-Labs clients.
- F. Surgical Pathology "Quickie" Anatomic Pathology consults for pathologists at M-Labs client hospitals and others.

II. TEACHING ACTIVITIES:

- A. Review of microscopic material with residents in interesting M Labs surgical pathology cases.

III. RESEARCH ACTIVITIES:

None.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Michigan Health Corporation representative to Joint Venture Hospital Labs (JVHL).
- B. Director, M-Labs:
 - 1. Provide leadership for and participate in planning, marketing, and implementation of M-Labs programs.
 - 2. Growth. In FY 2002, M Labs added 13 new physician offices and specialty service practices to our client list. The majority of these are related to our

contract to provide coverage to MCare patients. Some are for specialty services (dermatopathology, flow cytometry, muscle and nerve biopsy), and a few were UMHS acquired practices. There were also two new full reference laboratory accounts, one, a hospital in northern Ohio, and the other, a health Alliance composed of several small hospitals in southeastern Michigan. Two contracts for services were terminated, one because of closure of the hospital.

This fiscal year, gross billings for clinical pathology services increased by 5% and gross billing for anatomic pathology services increased by 17%. Total combined expected revenue from CP and AP billing increased by 12% over our last fiscal year.

M Labs submitted 1 proposal to a prospective new client during FY2002 which was rejected.

The department of Pathology rejected a business opportunity to provide dermatopathology services to a new prospective client.

3. Managed Care Activities

We have successfully implemented our renegotiated contract of 4/1/01 with M Care to provide outpatient lab services for all groups and products for M Care's commercial and Medicare products. M Labs prepares quarterly QA reports on lab services for M Care's QA department and have conducted a Physician Satisfaction Survey for M Labs subcontracted providers and reported the results to M Care. We assist M Care with resolution of laboratory service issues. We are actively engaged in contracting for delivery of HEDIS data for M Care to assist them in meeting requirements of the NCQA.

4. Networks. MLabs is a member of 2 laboratory networks, Great Lakes Laboratory Network (GLN) which consists of 28 hospital laboratories, predominantly in the western and northern parts of Michigan, and Joint Venture Hospital Laboratories (JVHL) which has grown to include 9 equity members and 72 participating member laboratories located in Michigan. JVHL has contracts for laboratory services with 14 managed care organizations including BCN.

I serve on the JVHL Executive committee which is striving to improve the financial rewards to its provider members, including UMHS, by reducing "leakage" to non-contracted providers and increasing reimbursement for contracted services.

MLabs coordinates the Pathology Department's issues concerning contractual obligations to JVHL and GLN. These include such items as BCN critical value list and HEDIS reporting.

- C. Member Department of Pathology Incentive Committee.
- D. Member, University of Michigan Networking Leads Committee.
- E. Department of Pathology representative to Managed Care Committee.
- F. Director, Laboratory at Trillium Hospital, Albion, Michigan, through February, 2002.
- G. Chair, Tissue/Transfusion and Infection Control Committees, Trillium Hospital through February, 2002.
- H. Member, Surgical and Medicine/Family Practice Committees, Trillium Hospital through February, 2002.
- I. Member, Peer Review Committee, Forest Health.

V. OTHER RELEVANT ACTIVITIES:

None.

VI. PUBLICATIONS:

None.

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

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

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 mentor:

1. Nobuhiro Takeshita, M.D., post-doctoral fellow (4/99-4/02) and Ronald Craig, PhD, Research Associate (1/91-present): Dr. Takeshita was 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, conducted jointly with Dr. Craig, indicates that T-lymphoblasts grown from tumor-draining lymph node cells expressed binding sites for the adhesion receptor P-selectin (so-called Plig^{high} cells) are 10-100 fold more potent than cells derived from unfractionated populations against pulmonary and subcutaneous tumor implants. The potency of these cells was further enhanced through intra-tumoral inoculation of chemokines that enhance trafficking of the adoptively transferred Tc1 effector cells. This work resulted in 3 abstracts, 1 published manuscript and 2 manuscripts in preparation.
2. Randall Knibbs, Ph.D., Research Scientist (1/94-present) - Dr. Knibbs completed toxicologic and functional studies on several novel inhibitors of the selectin family under an NIAID funded SBIR contract from Ligocyte, Inc. (project coordinated by Jon Nagy, PhD at Ligocyte and Lloyd Stoolman, MD at the University of Michigan). In addition, Dr. Knibbs and Melissa Allen in the laboratory developed adenoviral transfection vectors containing a gene-segment encoding a mutant, non-shedding form of murine L-selectin. This vector conferred high levels of L-selectin expression and function on cultured murine dendritic cells. Studies are underway to test the hypothesis that tumor-antigen pulsed, cultured murine dendritic cells expressing high levels of L-selectin will traffic more efficiently to lymph nodes and confer higher levels of tumor immunity in murine models. Dr. Knibbs and Dr. Craig participated in several collaborative projects investigating selectin ligand structure and function. This work resulted in 2 abstracts, 6 published manuscripts and 2 submitted manuscripts.
3. Joseph Skitzki, MD (8/01-present) post-doctoral fellow – Dr. Skitzki is a trainee under the Surgical Oncology Training Grant who recently completed clinical training at Case Western Reserve. He is developing methodologies that precisely measure the

influx, in-situ proliferation, in-situ apoptosis and efflux of tumor-reactive T-cells from experimental murine subcutaneous and pulmonary neoplasms. The studies to date indicate that adoptively transferred, ex-vivo expanded populations containing tumor-specific effector and regulatory cells traffick to the tumor, secondary lymphoid organs and uninvolved visceral organs initially. One or more sub-populations then proliferate in vivo increasing the delivery/accumulation of T-cells in tumors and tumor-bearing organs. The functional characteristics of the proliferating, adoptively transferred T-cells, the molecular basis for their trafficking behavior and their impact on tumor clearance are currently under investigation.

4. Graduate research assistants: Mentored one Ph.D. and one MD/ Ph.D. candidate during laboratory rotations.
5. Undergraduate research assistants: Mentored two undergraduate students in the laboratory participating in work/study programs.
- B. Director, General Pathology Laboratory Course for Dental Students (Pathology 631) and co-director, General Pathology Lecture Course (Pathology 630): The 5th generation of the "Virtual Microscope- Pathology Laboratory On-line Interactive Syllabus" was deployed for the course (<http://141.214.6.12/cyberscope631/>).
- C. Co-director and lecturer, Hematology Sequence in Component II (Medical School 2nd year curriculum)- Administered pathology component of sequence and co-directed course with Alvin Schmier, M.D. (Department of Internal Medicine and Pathology). The 5th generation of the "Virtual Microscope- Hematopathology Interactive On-line Syllabus" was deployed for the course (<http://141.214.6.12/virtualheme99>).
- D. M1 Host Defense Sequence: Lectured and developed CD-based courseware for lecture syllabus and case presentations.
- E. Advanced Topics in Immunology: Lecturer.
- F. Pathology 581: Co-director and lecturer.

III. **RESEARCH ACTIVITIES:**

ACTIVE SUPPORT (60-70% funded effort):

- A. Principal Investigator- T Cell Trafficking in Adoptive Cellular Immunotherapy; NIH, R01CA73059, 30% effort, \$196,000 (annual, direct); April 2001 -Mar 2006
- B. Co-investigator on Project 2 and Co-director of the Immunology Core (with J. Mule, B. Redman and A.E. Chang, Surgical Oncology Division, University of Michigan)- Cellular Vaccines for Cancer Immunotherapy, NIH P01CA59327, 15% effort, \$1,000,000 (annual, direct); June 2001-April 2006.
- C. Co-investigator (with B. Redman and A. E. Chang, Surgical Oncology Division, University of Michigan)- T-Cell Therapy of Human Renal Cell Cancer; NIH R01CA69102, \$250,000 (annual, direct), 10% effort, April 2001 -Mar 2006.
- D. 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.
- E. 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, June 1999-Jan 2002.
- F. Co-investigator (with B. Richardson, Rheumatology Division, University of Michigan)- "Gender specific T-cell homing and autoimmunity"; NIH, R01AI42753, 0% effort, \$187,000 (annual, direct); Apr 1998-Mar 2003.
- G. Trainer on three funded pre-/post-doctoral training grants: Translational Immunology (J. Mule, PI); Surgery Oncology Research (A.E. Chang, PI) and Immunopathology (R. Miller, PI).

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 Millenium). Participated in the consolidation of Clinical Flow Cytometry and Hematology Laboratories. Managed the operation of the research flow cytometry instrument.
- B. Director, General Pathology Laboratory Course for Dental Students (Pathology 631) and co-director, General Pathology Lecture Course (Pathology 630) - see educational activities.
- C. Co-Director, Hematology Sequence in Component II - see educational activities.
- D. Member, Dental School Curriculum Accreditation Task Force
- E. Member, Medical School Curriculum Review Group
- F. Member, Abnormal Organ Systems Task Force for Curriculum Redesign
- G. Member, Medical School Admissions Committees
- H. Member, Pathology/Immunology Graduate Program Admissions Committee

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL ACTIVITIES:

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

VI. PUBLICATIONS:

ARTICLES IN PEER REVIEWED PUBLICATIONS:

1. 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. 2001. J. Immunol.167: 3089

2. A. Matsukawa, N.W. Lukacs, C.M. Hogaboam, R.N. Knibbs, D.C. Bullard, S.L. Kunkel and L.M. Stoolman: Mice Genetically Lacking Endothelial Selectins are Resistant to the Lethality in a Murine Model of Septic Peritonitis. Exper. & Mol. Path. 2002. 72: 68.
3. B. Walcheck, A. Leppanen, R.N. Knibbs, L.M. Stoolman, S.R. Alexander, R.P. McEver. Sialyl-Lex formed on core 2-modified O-glycans is recognized by the mAb CHO-131: Distinction of cells expressing high affinity glycan ligands for P-selectin. 2002. Blood. 99:4063.
4. N. W. Lukacs, R.N. Knibbs, A. Johns, L.M. Stoolman: E- and P-selectin molecules are involved in the inflammatory responses during allergen-induced airway hyperractivity. 2002. J. Immunol. 169: 2120.
5. M. Jutila, S. Kurk, L. Turk, R.N. Knibbs, L.M. Stoolman: L-selectin can serve as an E-selectin ligand on human T-cells. 2002. J. Immunol. 169: 1768.
6. Jeffrey L. Curtis, Joanne Sonstein, Ronald A. Craig, Jill Todt, Randall N. Knibbs, Timothy Polak, Daniel C. Bullard, and L.M. Stoolman: Altered Lung Lymphocyte Recruitment in response to intratracheal particulate antigen challenge in mice lacking endothelial selectins is subset specific. 2002. J. Immunol. (in press).
7. Wusi Maki, William G. Telford, Randall N. Knibbs, L.M. Stoolman and Sam T. Hwang: CC chemokine receptor-6 (CCR6) co-localizes with CD18 and enhances adhesion to activated endothelial cells in CCR6-transduced Jurkat T cells. J. Immunol. (in press)

ARTICLES SUBMITTED TO PEER REVIEWED PUBLICATIONS:

1. Stoolman. L.M. 2002. Hematopoietic differentiation and the development of neoplastic diseases, in *Hematology for Medical Students*, A. Schmaier (ed.)
2. R.N. Knibbs, M. Dame, M.R. Allen, Y. Ding, W.J. Hillegas, J. Varani, L.M. Stoolman. Sustained high yield production of recombinant proteins on transiently-transfected COS-7 cells grown on trimethylamine coated microcarrier beads.
3. 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.
4. Daniel, Myers DVM, Dianna Farris LVT, Angela Hawley MS, Shirley Wroblewski BS, Amy Chapman BS, L.M. Stoolman MD, Randy Knibbs PhD, Robert Strieter MD, Thomas Wakefield MD: Selectins and Interleukin-10 Influence Acute Thrombus Formation in a Mouse Model of Venous Thrombosis.

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

1. LM Stoolman, Michael Lougee, Douglas Gibbs and Tom Peterson. 2000/2001. 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..
2. LM Stoolman, Michael Lougee, Douglas Gibbs, Tom Peterson and Gerald Abrams. 2000/2001. 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. New this year are high resolution digital “maps” covering 20-50% of the microscopic section. These “webslides” emulate glass slides more precisely than single photographs. The features are as described above. 1999 Computerworld-Smithsonian Award Finalist.
 3. LM Stoolman. 2002. Hematopathology Unknown Exercises. Interactive, CD-based excercises for medical student (M2) Hematopathology laboratory. CD-based publication used in M2-Heme sequence.
 4. LM Stoolman. 2002. 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).

**LYNDON SU, M.D.
CLINICAL ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Dermatopathology Service – (University Hospital and Transfer cases) – 12 months
- B. Dermatopathology Consultation Service (including personal, M-Labs, and Veterans Administration Hospital consultations) – 12 months

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. Medical students – (on elective rotation in dermatopathology)
 - 2. Instructor in medical student laboratories
- B. House Officers:
 - 1. Dermatopathology daily sign-out (dermatology and pathology residents, and medical students)
 - 2. Review of dermatopathology consultation material
 - 3. Dermatopathology Teaching conference – (dermatology residents-weekly)
 - 4. Dermatopathology Teaching conference – (pathology residents-3 per year)
 - 5. Anatomic Pathology Core Conference – (2 per year)
 - 6. Anatomic Pathology Consultation Conference – (2 per year)
- C. Diagnostic Conference, Department of Dermatology – (weekly)
- D. Cutaneous T-Cell Lymphoma Conference—(monthly)

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Role of BCL-XL in Merkel cell carcinoma and effects of BL-193 (BCL-XL inhibitor) on its growth. (Dr. Maria Soengas, Dr. Lina Wasserman, Dr. Daniel Remick, Dr. Shaomeng Wang)
- B. Effects of PS341 proteasome inhibitor on Merkel cell carcinoma growth. (Dr. Maria Soengas, Dr. Dan Remick, Dr. Lina Wasserman)
- C. M-RNA expression microarray of Merkel cell carcinoma and other neuroendocrine tumors. (Dr. Tom Giordano, Dr. Lina Wasserman)
- D. Efficacy of sentinel lymph node biopsy for detecting early metastasis of eccrine carcinomas. (Dr. Paul Bogner, Dr. Lori Lowe, Dr. D. Fullen, Dr. Augusto Paulino, Dr. Vernon Sondak, Dr. Sybil Biermann)
- E. Utility and sensitivity of standard immunostains and serial sectioning for melanoma sentinel lymph node biopsy. (Dr. Darius Karimipour, Dr. Lori Lowe, Ted Hamilton, Dr. Vernon Sondak, Dr. Timothy Johnson, Dr. D. Fullen)
- F. Role of S100A6 in neurothekeoma. (Dr. D. Fullen, Dr. Lori Lowe)
- G. Role of RhoGTPase in melanoma metastasis. (Dr. Sofia Merajver, Dr. Celina Kleer)

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Co-director, Dermatopathology Service

REGIONAL AND NATIONAL:

- A. Ad hoc manuscript reviewer, Journal of Cutaneous Pathology
B. Ad hoc manuscript reviewer, Journal of the Academy of Dermatology
C. Ad hoc manuscript reviewer, Cancer

V. OTHER RELEVANT ACTIVITIES:

VI. PUBLICATIONS:

ARTICLES PUBLISHED, ACCEPTED OR SUBMITTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Cherny, S., Mraz, S., Su, L., Harvell, J., Kohler, S.: Heteroduplex analysis of T-cell receptor gamma gene rearrangement as an adjuvant diagnostic tool in skin biopsies for erythroderma. J Cutan Pathol 28(7):351-55, 2001.
2. Cowper, S.E., Su, L.D., Bhawan, J., Robin, H.S., Leboit, P.E.: Nephrogenic Fibrosing Dermopathy. Am J Dermatopathol 2001;23(5):383-93.
3. Anderson, K.W., Johnson, T.M., Lowe, L., Su, L., Baker, S.R.: Treatment of head and neck melanoma, lentigo maligna subtype: a practical surgical technique. Arch Facial Plast Surg 2001;3:202-6.
4. Su, L., Kim, Y., Swetter, S., LeBoit, P., Kohler, S.K.: Interstitial mycosis fungoides, a variant of mycosis fungoides resembling inflammatory morphea and granuloma annulare. J Cutan Pathol 2002;29(3):135-41.
5. Su, L.D., Lowe, L., Bradford, C.R., Yahanda, A.I., Johnson, T.M., Sondak, V.K.: Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. J Am Acad Dermatol 2002;46:661-6.
6. Su, L.D., Fullen, D.F., Lowe, L., Uherova, P., Schnitzer, B., Valdez, R. CD117 (KIT receptor) expression in Merkel cell carcinoma. Am J Dermatopathology 2002; 24(2):289-293.
7. Barr, K.L., Lowe, L., Su, L.D. Mycobacterium marinum infection simulating interstitial granuloma annulare: a report of 2 cases. (Accepted for publication, American Journal of Dermatopathology)
8. Su, L.D., Fullen, D.F., Sondak, V.K., Johnson, T.M., Lowe, L. Sentinel lymph node biopsy for problematic spitzoid melanocytic lesions: a report of 18 cases. (Accepted for publication, Cancer)
9. Winer, I., Normolle, D.P., Shureiqi, I., Sondak, V. K., Johnson, T.M., Su, L.D., Brenner, D.E. Expression of 12-lipoxygenase as a biomarker for melanoma carcinogenesis. (Accepted for publication, Melanoma Research)
10. Swartz RD, Crofford LJ, Phan SH, Ike RW, Su LD. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. (Submitted to American Journal of Medicine)
11. Petro, A., Wegman, P.A., Su, L.D. Acral and ear papules and arthritis: a report of a case of fibroblastic rheumatism. (Submitted to Archives of Dermatology)
12. Woo, J., Su, L., Kohler, S., Bowen, G.M.: Pseudolymphoma developing at the sites of subcutaneous vitamin K injections. A case report. (Submitted to Archives of Dermatology)

ABSTRACTS AND PRESENTED PAPERS:

1. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. Swartz RD, Crofford LJ, Phan SH, Ike RW, Su LD. (Accepted by the American Society of Dermatopathology for presentation at the 39th annual meeting).
2. Lymphatic mapping and sentinel lymph node biopsy detects early metastasis of eccrine carcinoma. Bogner, P., Lowe, L., Fullen, D., Biermann, J., Paulino, A.F., Sondak, V., Su, L.D. (Accepted by the American Society of Dermatopathology for presentation at the 39th annual meeting)

**GERD O. TILL, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. None

II. TEACHING ACTIVITIES:

- A. Instructor, General Pathology for Dental Students and Graduate Students (Pathology 630/580)
B. Mentor, graduate student - Lai Ming Lee
C. Mentor, NIH Training Grant in Trauma, Burn and Wound Healing Research (T32 GM08616)

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Investigator, "Mechanisms and Prevention of Lung Injury Caused by Mustard Gas" (U.S. DOD, Meharry Medical College)
B. Co-Investigator, "Liquid Ventilation in ARDS" (NIH HL-54224)
C. Co-Investigator, "Lung Injury Produced by Oxygen Metabolites", (NIH GM-29507).
D. Senior Mentor, "Training Grant in Burn, Trauma and Wound Healing Research" (NIH)

PENDING SUPPORT:

- A. Mechanism and Prevention of Lung Injury Caused by Mustard Gas (II) (U.S. DOD)

PROJECTS UNDER STUDY:

- A. Lung injury caused by 2-chloroethyl ethyl sulfide.
B. Pathomechanisms of ischemia-reperfusion injury.
C. Pathophysiologic role of complement activation products in secondary lung injury

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Interviewed candidates for faculty and postdoctoral positions

- B. Participation in undergraduate research program

MEDICAL SCHOOL/HOSPITAL:

- A. Course Director, Pathology 580/630
- B. Member Medical School Committee on Student Biomedical Research Programs
- C. Member Doctoral Thesis Committee
- D. Interviewed candidates for faculty positions
- E. Consultant for clinical research programs
- F. Reviewer of intra-departmental grant proposals

REGIONAL AND NATIONAL:

None

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/SEMINARS:

- 1. Invited Speaker, "Role of complement in organ injury"; Conference on Advanced Technology Applications for Combat Casualty Care, September 9-14, 2001, Fort Walton, Florida
- 2. Speaker, "Mechanisms and prevention of lung injury caused by 2-chloroethyl ethyl sulfide.", Departmental Seminar Series, December 3, 2001
- 3. Invited Speaker, "Protection from lung injury caused by the vesicant, 2-chloroethyl ethyl sulfide"; US Army Medical Defense Bioscience Review, June 2-7, 2002, Hunt Valley, Maryland

EDITORIAL BOARDS:

- A. Member Editorial Board, International Immunopharmacology, 1998-present
- B. Member Editorial Advisory Board, Immunobiology, 1980- present
- C. Reviewer for the following scientific journals:
 - 1. American Journal of Pathology
 - 2. American Journal of Physiology
 - 3. British Journal of Pharmacology
 - 4. International Immunopharmacology
 - 5. Journal of Applied Physiology
 - 6. Journal of Leukocyte Biology
 - 7. Journal of Pharmacology and Experimental Therapeutics
 - 8. Shock

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. McClintock SD, Till GO, Smith MG, Ward PA. Protection from half-mustard-gas-induced acute lung injury in the rat. J. Appl. Toxicol. (in press)
2. McClintock SD, Till GO, Smith MG, Ward PA. Attenuation by liposome-associated antioxidants of lung injury caused by 2-chloroethyl ethyl sulfide. (to be submitted)
3. Till GO, McClintock SD, Elford HL, Ward PA. Protective effects of polyhydroxyphenyl compounds on 2-chloroethyl-ethyl-sulfide-induced lung injury (to be submitted)

BOOKS AND CHAPTERS IN BOOKS:

None

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

1. Till GO: Role of complement in organ injury. Proceedings of the ATACCC Conference, September 11-13, 2001, Fort Walton, Florida
2. McClintock SD, Till GO, Smith MG, Ward PA: Protection from liposome-associated antioxidants against mustard gas-induced acute lung injury in the rat. FASEB J. 16:A1206, 2002
3. McClintock SD, Till GO, Smith MG, Ward PA: Protection from lung injury caused by the vesicant, 2-chloroethyl ethyl sulfide. Proceedings of the US Army Medical Defense Bioscience Review, pp 225; June 2-7, 2002, Hunt Valley, Maryland
4. Till GO. Book review in Arch. Pathol. Lab. Med. 125:710-710, 2001. "Therapeutic Interventions in the Complement System" Edited by . Lambris JD and Holers VM. Humana Press, 2000.

**RICCARDO VALDEZ, M.D.
CLINICAL ASSISTANT PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001- 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Diagnostic Hematopathology (including peripheral blood and body fluid smears).
- B. Clinical Hematology Laboratory.
- C. Clinical Flow Cytometry Laboratory.
- D. Hematopathology Consultation Cases (including M-Labs and Veteran's Hospital).
- E. Tissue Typing/Histocompatibility Laboratory.
- F. Diagnostic Heart Transplant Biopsies (ad hoc, 52 cases).
- G. Blood Bank, attending coverage (ad hoc, 1 week).

II. TEACHING ACTIVITIES:

- A. Medical Students:
 - 1. Laboratory Instructor, M2 General Pathology Course (28 hours).
 - 2. Laboratory Instructor, M1 Histopathology (2 hours).
 - 3. Black Medical Student Association/Latin American-Native American Medical Student Association Career Seminars Series Lecture (1 hour)
- B. House Officers:
 - 1. Sign-out of bone marrow biopsies, aspirate smears, peripheral blood smears, and body fluids in Hematology Laboratory.
 - 2. Sign-out of lymph node biopsies and review of Hematopathology Consultation material.
 - 3. Flow Cytometry sign-out.
 - 4. Hematopathology case conferences (2).
- C. Hematopathology teaching:
 - 1. Leukemia conference/biweekly.
 - 2. Lymphoma conference/weekly.
 - 3. Hematology conference/biweekly.
 - 4. Clinical Pathology Grand Rounds (one lecture).
 - 5. Clinical Pathology Case Conference/weekly.
- D. Laboratory Staff:
 - 1. Hematology Laboratory monthly CME coordinator.
 - 2. Tissue Typing Laboratory Journal Club.

III. RESEARCH ACTIVITIES:

PROJECTS UNDER STUDY:

- A. Gene expression profiling in small B-cell lymphoproliferative disorders.
- B. Effects of novel hematopoietic malignancy therapies on bone marrow morphology.
- C. Immunophenotyping of hematopoietic neoplasms.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Clinical Pathology Resident Training.
Tissue Typing/Histocompatibility Laboratory, Director in training.

REGIONAL/NATIONAL:

- A. College of American Pathologists Laboratory Accreditation Program Inspector,
Hematology and Flow Cytometry, Oklahoma City, OK, 2002

V. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Valdez R, Finn WG, Ross CW, Singleton TP, Tworek JA, Schnitzer B. Waldenström macroglobulinemia caused by extranodal marginal zone B-cell lymphoma. *Am J Clin Pathol* 116:683-690, 2001.
2. Munshi HG, Merajver SD, Valdez R, Baker LH, Cooney KA. Metastatic dedifferentiated chordoma with elevated b-hCG. *Am J Clin Oncol* 25:274-276, 2002.
3. Su LD, Fullen DR, Lowe L, Uherova P, Schnitzer B, Valdez R. CD117 expression (KIT receptor) expression in Merkel cell carcinoma. *Am J Dermatol*. 24:289-293, 2002.
4. Muler JH, Valdez R, Hayes C, Kaminski M. Acute megakaryocytic leukemia presenting as hypercalcemia with skeletal lytic lesions. *Eur J Haematol*. In press, 2002.
5. Valdez R, Kroft SH, Ross CW, Schnitzer B, Singleton TP, Peterson LC, Finn WG. Cerebrospinal fluid involvement in mantle cell lymphoma. *Mod Pathol*. In press, 2002.
6. Valdez R, McKeever P, Finn WG, Gebarski S, Schnitzer B. Composite germ cell tumor and high-grade B-cell lymphoma arising in the sella turcica. *Human Pathol*. In press, 2002.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Valdez R, Thorson J, Finn WG, Schnitzer B, Kleer CG. Lymphocytic mastitis: a molecular, immunophenotypic, and clinical evaluation of eleven cases. Submitted for publication.

2. Uherova P, Valdez R, Ross CW, Schnitzer B, Finn WG. Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience. Submitted for publication.

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

1. Valdez R, Thomson J, Finn WG, Kleer CG, Schnitzer B: Lymphocytic mastitis: a molecular, immunophenotypic, and clinicopathologic evaluation of eleven cases. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):268A.
2. Finn WG, Sreekumar A, Stoolman LM, Ross CW, Schnitzer B, Valdez R, Chinnaiyan A: Comparative gene expression profiling of B-cell lymphoproliferative disorders by cDNA microarray analysis: identification of genes preferentially upregulated in chronic lymphocytic leukemia. Platform presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):241A.
3. Guo G, Valdez R, Schnitzer B, Ross CW, Finn WG: The clinical spectrum of increased plasma viscosity: a retrospective study of 115 cases. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):242A.
4. Uherova P, Schnitzer B, Valdez R, Ross CW, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma: an immunophenotypic reappraisal based on a single-institution experience. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):267A.
5. Uherova P, Roulston D, Finn WG, Valdez R, Schnitzer B, Ross CW: CD56 expression in acute myeloid leukemia with monocytic differentiation: association with complex karyotype. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):267A.
6. Velankar M, Kansal R, Finn WG, Valdez R, Ross CW, Schnitzer B: Bcl-6 and CD10 paraffin section immunohistochemistry on bone marrow core biopsies to distinguish follicular lymphoma from other small B-cell non-Hodgkin lymphomas. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):268A.
7. Snyder ML, Roulston D, Ross CW, Finn WG, Schnitzer B, Valdez R: Cytogenetic, immunophenotypic, and clinical correlation in adult acute lymphoblastic leukemia: a single institution's experience. Poster presentation, United States and Canadian Academy of Pathology Annual Meeting, Chicago, IL, 2002. *Mod Pathol* 2002;15(1):264A.
8. Valdez R, Gulley ML, Ross CW, Nangia R, Finn WG, Schnitzer B: T-cell rich large B-cell lymphoma primary in CNS. Case 72. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
9. Valdez R, Gulley ML, Ross CW, Nangia R, Finn WG, Schnitzer B: Classical Hodgkin's disease occurring in post-transplant setting. Case 87. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.
10. Valdez R, Finn WG, Nangia R, Ross CW, Schnitzer B: Cyclin D1 negative mantle cell lymphoma with t(11;14)(q13;q32). Case 50. Society for Hematopathology Workshop. Genetic and Molecular Genetics in Hematologic Malignancies, Boston, MA, Nov. 2002.

**JAMES VARANI, PH.D.
PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. None.

II. TEACHING ACTIVITIES:

- A. Mentor for students who worked in my laboratory over the past year, including five post-doctoral fellows, one pathology graduate student, one medical student, three undergraduate students and two high school students.
B. Course director – Pathology 581. Tissue, cellular and molecular basis of disease.
C. Instructor – Pathology 581 – Tissue, cellular and molecular basis of disease.
D. Instructor – Pathology 600 – Pathology course for dental students.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Squamous Epithelial Invasion in Organ Culture," NIH CA60958.
B. Principal Investigator, "Retinoids for Diabetic Foot Ulcers," NIH DK59169.
C. Principal Investigator, "Co-polymer – "Microcarrier culture system for human influenza vaccind production" HHH AI 50315
D. Principal Investigator on Project 10, "Retinoic Acid and Cells of the Skin," Johnson and Johnson Corporation.
E. Principal Investigator, "Cell culture, media, microcarrier system for Marek's Disease Vaccine" NIH AI 46876.
F. Principal Investigators, "Novel therapeutic approach to psoriasis" NIH AR 44767.

PROJECTS UNDER STUDY:

- A. The biology of human squamous carcinoma cell invasion.
B. The biology of collagen destruction and potential repair in diabetic skin
C. The development of a microcarrier-based protocol for production of human influenza vaccine..
D. Biological basis of photoaging and natural aging in skin.
E. Development of a bioreactor culture system for Marek's disease vaccine.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Member, Department of Pathology Advisory Committee on Appointments, Promotions and Tenure.
- B. Member, Department of Pathology Graduate Program Committee
- C. Member, Pathology Graduate Program Steering Committee
- D. Member and chairman – Pathology Graduate Program Curriculum Revision Committee.
- E. Member, Department of Pathology Graduate Program Comprehensive Exam Committee.

MEDICAL SCHOOL/HOSPITAL:

- A. Member, Medical School Committee on Summer Research Opportunities.
- B. Member, University of Michigan Cancer Center Basic Research Committee.
- C. Member, Cancer Biology Research Training Grant Scientific Steering Committee.
- D. Member, Department of Dermatology Research Training Grant Steering Committee.
- E. Member, University Committee on Use and Care of Animals (UCUCA).
- F. Member, Program in Biomedical Sciences (PIBS) Curriculum Committee
- G. Member, Program in Biomedical Sciences (PIBS) Admissions Committee
- H. Member, Program in Biomedical Sciences (PIBS) Steering Committee

UNIVERSITY:

- A. Member, Graduate School Task Force on Non-Academic Misconduct

REGIONAL AND NATIONAL:

- A. Editorial Board of Invasion and Metastasis.
- B. Manuscript Review for:
 - 1. American Journal of Pathology.
 - 2. Cancer Research.
 - 3. Experimental Cell Research.
 - 4. International Journal of Cancer.
 - 5. Journal of Investigative Dermatology.
 - 6. Laboratory Investigation.
 - 7. Invasion and Metastasis.
- C. National Institutes of Health Review Panels
 - 1. National Institutes of Health Study Section (ZRG1SMB04), April, 2002.
 - 2. National Institutes of Health Study Section (ZDK1 GRB-5(M1)), May, 2002
 - 3. National Institutes of Health Study Section (ZRG1SRB08), June, 2002.

V. OTHER RELEVANT ACTIVITIES:

INVITED LECTURES/PRESENTATIONS:

1. Invited speaker, Department of Pathology and Laboratory Medicine, MD Anderson Cancer Center, March 16, 2001.
2. Invited speaker, Johnson & Johnson Retinoid Symposium, Philadelphia PA, June 6-8, 2001.
3. Invited speaker, Cell Culture Engineering VI, Snowmass, CO, April 1-5, 2002
4. Invited speaker, Johnson & Johnson Retinoid Symposium, New York, NY, June 14, 2002.
5. Hamchung Lecturer, National University of Korea, Seoul, Korea, September 14, 2002

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFERRED JOURNALS:

1. Varani J, Hattori Y, Dame MK, Murphy HS, Johnson KJ, Wojno KJ: Elaboration of matrix metalloproteinases by human prostate tissue in organ culture: Relationship to invasion in culture and to tumor spread. *Brit. J. Cancer* 84:1076-1083, 2001.
2. Riser B.L., Varani J., Cortes P., Yee J., Dame M.K., Sharba A.K.: Cyclic mechanical strain on mesangial cells upregulates intracellular adhesion molecule 1 (ICAM-1) and leukocyte adherence: Possible role in hypertension-induced nephropathy. *Amer. J. Pathol.* 158:11-18, 2001.
3. Varani J, Spearman D, Perone P, Fligiel SEG, Datta SC, Wang ZQ, Shao Y, Kang S, Fisher GJ, Voorhees JJ: Inhibition of type I procollagen synthesis by damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. *Amer. J. Pathol* 158:931-942, 2001.
4. Lewis C, Warner RL, Varani J, Johnson KJ. The role of metalloelastase in immune complex-induced acute lung injury. *Amer. J. Pathol.* 158:2135-2144, 2001
5. Zeigler ME, Chi Y, Tumas D, Bodary S, Tang H, Varani J. Anti-CD11a ameliorates disease in the human skin – SCID mouse transplant model: Comparison with Cyclosporin A and clobetasol propionate. *Lab. Invest.* 81:1253-1261, 2001.
6. Varani J, Fligiel SEG. Human squamous epithelial cell invasion under in situ conditions in a human skin organ culture model. *Histology & Histopath.* (in press).
7. Warner RL, Lewis CS, Beltran L, Younkin E, Varani J, Johnson KJ: The role of metalloelastase in immune complex-induced acute lung injury. *Am. J. Pathol.* 158:2139-2144, 2001.
8. Riser BL, Varani J, Cortes P, Yee J, Dame MK, Sharba AK: Cyclic mechanical strain on mesangial cells upregulates intracellular adhesion molecule 1 (ICAM-1) and leukocyte adherence: Possible role in hypertension-induced nephropathy. *Am J Pathol* 158:11-18, 2001.
9. Varani J, Hattori Y, Dame MK, Schmidt T, Murphy HS, Johnson KJ, Wojno KJ: Elaboration of matrix metalloproteinases by human prostate tissue in organ culture: Relationship to invasion in culture and to tumor spread. *Brit. J. Cancer* 84: 1076-1083, 2001.
10. Moon SE, Dame MK, Remick DR, Elder JT, Varani J. Induction of matrix metalloproteinase-1 (MMP-1) during epidermal invasion of the stroma in human skin organ culture: Keratinocyte stimulation of fibroblast MMP-1 production. *Brit. J. Cancer* 85:1600-1605, 2001.
11. Varani J, Zeigler ME, Dame MK, Kang S, Fisher GJ, Voorhees JJ, Stoll SW, Elder JT. HB-EGF activation of keratinocyte ErbB receptors mediates epidermal hyperplasia following retinoid treatment: A prominent side effect of retinoid therapy. *J. Invest. Dermatol* 117:1335-1341, 2001.

12. Varani J, Petryniak J, Takagaki M, Dame MK, Petryniak B, Goldstein IJ. Differential expression of an a-galactosyl-containing trisaccharide on high- and low-malignant murine sarcoma cells: Identification and regulation. *Clin. Exp. Metastasis* 19:1-8, 2002.
13. Moon SE, Bagavathula R, Varani J. Induction of matrix metalloproteinase-1 (MMP-1) during epidermal invasion of the stroma in human skin organ culture: Regulation through activation of MAPK pathways. *Brit. J. Cancer* (in press) 2002.
14. Varani J, Perone P, Fligiel SEG, Fisher GJ, Voorhees JJ. Inhibition of type I procollagen production in photodamage: Correlation between presence of high molecular weight collagen fragments and reduced procollagen synthesis. *J. Invest. Dermatol.* (in press) 2002.
15. Varani J, Perone P, Merfart MG, Moon SE, Larkin D, Stevens MJ. All-trans retinoic acid improves structure and function of diabetic rat skin in organ culture. *Diabetes* (in press) 2002.
16. Knibbs RN, Dame M, Allen MR, Ding Y, Hillegas WJ, Varani J, Stoolman L. Sustained high yield production of recombinant proteins in transiently-transfected COS-7 cells grown on trimethylamine-coated microcarrier beads. *Biotech. Progress* (in press) 2002.
17. Hattori Y, Hattori N, Murphy HS, Su L, Wang TS, Johnson TM, Varani J. Expression of MMP-13 (collagenase-3) in microvascular endothelial cells of basal cell carcinoma and normal human skin. *Endothelium* (in press) 2002.
18. Fligiel SEG, Datta SH, Fisher GJ, Voorhees JJ, Varani J. Ultrastructural and biochemical features of collagen damage in photoaged skin and by MMP-1 in vitro. *J. Invest. Dermatol.* (in press) 2002.

BOOKS AND CHAPTERS IN BOOKS:

1. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, Voorhees. Mechanisms of Photoaging and Chronological Skin Aging. *Arch. Dermatol* (in press).
2. Varani J, Mezick J. Retinoids and skin repair. In: *Mechanisms and Treatment of Aging*. Marcell-Dekker (in press).

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Varani J. Expression of matrix metalloproteinases in fresh human prostate tissue and following organ culture. *Exp. Biol.* 2001.
2. Warner RO, Lewis CS, Beltran L, Varani J, Johnson KJ. Immune complex-induced lung injury in MMP-3 and MMP-9 gene-deleted mice: Evidence for two separate mechanisms of action. *Exp. Biol.* 2001.
3. Johnson KJ, Lewis C, Warner RO, Beltran L, Varani J. The role of metalloelastase in immune complex-induced acute lung injury. *Exp. Biol.* 2001.
4. Zeigler ME, Bhagavathula N, Varani J. (2001) MAPK signaling mediates properties of collagen-stimulated epidermal keratinocytes. *AACR Proceed*, 42,147, 2001.
5. Varani J, Zeigler ME, Dame MK, Kang S, Fisher GJ, Voorhees JJ, Stoll SW, Elder JT. HB-EGF activation of keratinocyte ErbB receptors mediates epidermal hyperplasia following retinoid treatment: A prominent side effect of retinoid therapy. *J. Invest. Dermatol.* 2001.
6. Moon SE, Dame MK, Remick DR, Elder JT, Varani J. Induction of matrix metalloproteinase-1 (MMP-1) during epidermal invasion of the stroma in human skin organ culture: Keratinocyte stimulation of fibroblast MMP-1 production. *J. Invest. Dermatol.* 2001.

7. Fligiel SEG, Perone P, Varani J. Collagen destruction induced by metalloproteinase (MMP) treatment in vitro is similar to dermal collagen damage in photodamaged skin: An ultrastructural analysis. *J. Derm. Pathol.* 2002.
8. Varani J, Perone P, Fligiel SEG, Fisher GJ, Voorhees JJ. Inhibition of collagen production in photodamage. *J. Invest. Dermatol.* 2002.

**CLAUDIUS VINCENZ, PhD
RESEARCH INVESTIGATOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

None.

II. TEACHING ACTIVITIES:

A. Graduate students:

Michael Zeidler, Student of the "Freie Universitaet in Berlin, Germany"

B. Courses: Pathology 581: Lectures on cellular pathology; Pathology 582: Module on poly-glutamine expansion disease (4 sessions).

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

PENDING:

None

PROJECTS UNDER STUDY:

A. Studies on the biological activities and molecular mechanisms of NRADD, a novel transmembrane protein with a death domain.

B. Characterization of the polyglutamine gain of function activity in cellular systems.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

None

MEDICAL SCHOOL/HOSPITAL:

Member, University of Michigan Cancer Center

Member, University of Michigan Diabetes Research and Training Center

UNIVERSITY OF MICHIGAN:

None

REGIONAL AND NATIONAL:

Grant reviews: Ad hoc member for NIH June CDF5 study section
NSF (MCB-Biomolecular processes) one grant

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS:

Reviewer for the following journals: The Journal of Cell Biology, Journal of Clinical Investigation, Cell Death and Differentiation, Trends in Immunology.

HONORS AND AWARDS:

None

PATENTS:

None

INVITED LECTURES/SEMINARS:

None

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Malhotra, R., Lin, Z., Vincenz, C., and Brosius, F.C., 3rd. Hypoxia induces apoptosis via two independent pathways in Jurkat cells: differential regulation by glucose. Am J Physiol Cell Physiol 281, C1596-603, 2001.
2. Weber, C.H., Vincenz, C.: The death domain superfamily: a tale of two interfaces. TIBS, 26:475-481, 2001.
3. Wang, X., Bauer, J. H., Li, Y., Shao, Z., Zetoune, F. S., Cattaneo, E., and Vincenz, C.: Characterization of a p75NTR apoptotic signaling pathway using a novel cellular system. J Biol Chem 276: 33812-33820, 2001

BOOKS/CHAPTERS IN BOOKS:

None

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

Meeting Abstracts:

1. Keystone Meeting on Cellular Motility and signaling in the wiring and plasticity of nervous systems. March 2002, Taos New Mexico. NRADD, a novel membrane protein with a death domain mediates apoptosis in response to ER stress in neurons.

**PETER A. WARD, M.D.
PROFESSOR AND CHAIRMAN
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. These have been chiefly related to administrative responsibility for all clinical service functions of the Department.

II. TEACHING ACTIVITIES:

- A. Post-doctoral fellows (2001-02):
1. Ren-Feng Guo, M.D.
 2. Neils Reidemann, M.D.
 3. Ines Laudes, M.D.
 4. Cecelia Speyer, Ph.D.
 5. Eric Albrecht, Ph.D.
 6. Thomas Neff, M.D.
 7. Jayne Reuben, Ph.D.
- B. Graduate students
1. Tommy Hlaing (Completed thesis 6/02)
- C. UROP Undergraduate Students:
1. Kari Dilley, Junior
 2. Jennifer Loussia, Sophomore
 3. Stephanie McGuire, Senior
- D. Research mentoring of two Research Scientists (Drs. Younger and Vincenz)
- E. Undergraduate students:
1. Lecture, College Honors Seminar 250 (LS&A), three hours.

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT

- A. Principal Investigator, "Lung Immunopathology" (Training Grant) HL07517, \$227,536/yr., (5%) 06/01/96 - 05/31/06
- B. Principal Investigator, "Inflammatory Cells and Lung Injury" NIH/NHLBI PO1-HL31963, \$246,249 /yr. (25%) \$816,953/yr (all projects) 03/01/99 - 02/29/04
- C. Principal Investigator; "Lung Injury by Oxygen Metabolites (MERIT) RO1- GM29507 NIH/NIGMS, (20%) \$204,700/yr, 07/01/01 - 06/30/05
- D. Principal Investigator, "Protective Effects of Anti-C5a in Sepsis," NIH/NIGMS RO1-GM61656, (20%) \$204,700/yr; 01/01/02 - 05/31/07

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Chair, Department of Pathology.

MEDICAL SCHOOL/HOSPITAL:

- A. Advisory Committee for the Howard Hughes Medical Institute.
- B. Clinical Council.
 - Conflict of Interest Committee.
 - Technology Transfer Committee
- C. Dean's Advisory Council.
- D. Geriatric Center Executive Committee.
- E. Howard Hughes Medical Institute Dean's Advisory Committee.
- F. Internal Medicine Advisory Committee for the University of Michigan George M. O'Brien Renal and Urologic Center.
- G. Michigan Eye Bank Research Review Committee.
- H. Undergraduate Research Opportunity Program, University of Michigan.
- I. University of Michigan Cancer Center Executive Committee.

UNIVERSITY OF MICHIGAN:

- A. Senate Advisory Committee on University Affairs, 1998 – June 2002
- B. Michigan League Board of Governors, September, 1997 – June 2002

REGIONAL AND NATIONAL:

- A. American Association of Immunologists.
- B. American Society for Clinical Investigation.
- C. Association of American Physicians.
- D. American Thoracic Society.
- E. Association of Pathology Chairmen
- F. A. James French Society of Pathologists, 1988-present.
- G. Health Policy Agenda for the American People, Advisory Committee.
- H. Institute of Medicine, National Academy of Sciences, July, 1990-present.
- I. Michigan Society of Pathologists.
- J. Michigan Thoracic Society, 1988-present.
- K. National Research Council.
 - a. Chair and member, Institute of Laboratory Animal Research.
- L. Universities Associated for Research and Education in Pathology, Inc., Board of Directors.

V. OTHER RELEVANT ACTIVITIES:

EDITORIAL BOARDS

- A. American Journal of Pathology, Editorial Board, 1982-present.
- B. American Review of Respiratory Diseases, Consulting Editor, 1977-present.
- C. Biological Signals, Consulting Editor.
- D. Free Radical Biology & Medicine, Editorial Board, 1995-present.
- E. Journal of Clinical Investigation, Consulting Editor.
- F. Journal of Experimental and Molecular Biology, 1999 – present
- G. Toxicologic Pathology, Editorial Board, 1988-present.

INVITED LECTURES/SEMINARS:

- 1. Invited Speaker, “C5a in Inflammatory Responses: Just Right or Too Much?” Therapeutic Approaches session at Complement Associated Diseases, Animal Models, and Therapeutics in Santorini, Greece, October 2001
- 2. Invited Speaker, “Regulation of Cytokine-Mediated Lung Injury”, University of Arizona, Tucson, Arizona; February 2002
- 3. Invited Speaker, ASTS-American Transplant Congress; Washington, DC; May 2002
- 4. Invited Speaker; “Signaling Defects in Neutrophils During Experimental Sepsis”, 25th Annual Conference on Shock, Big Sky, Montana, June 2002

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS

- 1. Martinez-Mier, G., Toledo-Pereyra, L.H., McDuffie, J.E., Warner, R.L., and **Ward, P.A.**: Neutrophil depletion and chemokine response after liver ischemia and reperfusion. *J Invest Surg.* 2001;14:99-107.
- 2. Lentsch, A.B., **Ward, P.A.** Regulation of experimental lung inflammation. *Respir Physiol.* 2001;128(1):17-22.
- 3. Martinez-Mier, G., Toledo-Pereyra, L.H., **Ward, P.A.** Adhesion molecules and hemorrhagic shock. *J Trauma.* 2001;51(2):408-415.
- 4. Chinnaiyan, A.M., Huber-Lang, M., Kumar-Sinha, C., Barrette, T.R., Shankar-Sinha, S., Sarma, V.J., Padgaonkar, V.A., **Ward, P.A.** Molecular signatures of sepsis: multiorgan gene expression profiles of systemic inflammation *Am J Pathol* 2001;159(4):1199-1209.
- 5. Fernandez, R., Sarma, V., Younkin, E., Hirschl, R.B., **Ward, P.A.**, Younger, J.G.: Exposure to perflubron is associated with decreased Syk phosphorylation in human neutrophils. *J Appl Physiol.* 2001;91:1941-1947.
- 6. Riedemann, N.C., and **Ward, P.A.**: Les modèles animaux du sepsis. *BIOFUTUR* 2117 Numéro spécial, Decembre 2001.
- 7. Rivera-Chavez, F.A., Toledo-Pereyra, L.H., Dean, R.E., Crouch, L., and **Ward, P.A.**: Exogenous and endogenous nitric oxide but not iNOS inhibition improves function and survival of ischemichally injured livers. *J Inv Surg* 2001;14:267-273.

8. Jordan, J.A., Guo, R.F., Yun, E.C., Sarma, V., Warner, R.L., Crouch, L.D., Senaldi, G., Ulich, T.R., and **Ward, P.A.**: Role of IL-18 in acute lung inflammation. *J Immunol.* 2001;15,167(12):7060-7068.
9. Beck-Schimmer, B., Schimmer, R.C., Madjdpour, C., Bonvini, J.M., Pasch T., and **Ward, P.A.**: Hypoxia mediates increased neutrophil and macrophage adhesiveness to alveolar epithelial cells. *Am J Respir Cell Mol Biol.* 2001;25(6):780-787.
10. Riedemann, N.C., Guo, R.F., Sarma, V.J., Laudes, I.J., Huber-Lang, M., Warner, R.L., Albrecht, E.A., Speyer, C.L., and **Ward, P.A.**: Expression and function of the C5a receptor in rat alveolar epithelial cells. *J Immunol.* 2002;168:1919-1925.
11. Riedemann, N.C., Guo, R.F., Laudes, I.J., Keller, K., Sarma, V.J., Padgaonkar, V., and **Ward, P.A.**: C5a receptor and thymocyte apoptosis in sepsis. *FASEB J. Express*; 2002;16(8):887-888.
12. Laudes, I.J., Chu, J.C., Sikranth, S., Huber-Lang, M., Guo, R.F., Riedemann, N., Sarma, J.V., Schmaier, A.H., and **Ward, P.A.**: Anti-C5a ameliorates coagulation/fibrinolytic protein changes in a rat model of sepsis. *Am J Pathol.* 2002;160: 1867-1875.
13. Anaya-Prado, R., Toledo-Pereyra, T., Lentsch, A.B., Guo, R.F. and **Ward, P.A.**: Understanding ischaemia/reperfusion injury. *Recent Res Devel Resp Critical Care Med.*, 2002;(2):47-54.
14. Riedemann, N.C., Guo, R.F., Neff, T.A., Laudes, I.J., Keller, K.A., Sarma, J.V., Markiewski, M.M., Mastellos, D., Strey, C.W., Pierson, C.L., Lambris, J.D., Zetoune, F.S., and **Ward, P.A.**: Increased C5a receptor expression in sepsis. *J. Clin. Invest.*, 2002;110:101-108.
15. Anaya-Prado, R., and Ramos-Kelly, J.R., Toldeo-Pereyra, L.H., Walsh, J., and **Ward, P.A.**: Multiple selectin blockade with a small-molecule selectin inhibitor does not affect survival after a second inflammatory challenge with nonlethal LPS. *J Invest. Surg.*, 2002;15:171-180.
16. Guo, R.F., Riedemann, N.C., Laudes, I.J., Sarma, V.J., Kunkel, R.G., Dilley, K.A., Paulauskis, J.D., and **Ward, P.A.**: Altered neutrophil trafficking during sepsis. *J Immunol.*, 2002;169(1):307-314.
17. **Ward, P.A.** and Lentsch, A.B.: Endogenous regulation of the acute inflammatory response. *Molecular and Cellular Biochemistry*, 2002;234/235:225-228.
18. Beck-Schimmer, B., Madjdpour, C., Kneller, S., Ziergler, U., Pasch, T., Wuthrich, R.P., **Ward, P.A.**, and Schimmer, R.C.: Role of alveolar epithelial ICAM-1 in lipopolysaccharide-induced lung inflammation. *Eur Respir J* 2002 19(6):1142-1150.
19. Guo, R.F., and **Ward, P.A.**: Mediators and regulation of neutrophil accumulation in inflammatory responses in lung: Insights from the IgG immune complex model. *Free Radical Biology and Medicine.* 2002 33:303-310.
20. Guo, R.F., Lentsch, A.B., Sarma, J.V., Sun, L., Riedemann, N.C., McClintock, S.D., McGuire, S.R., Van Rooijen, N., and **Ward, P.A.**: Activator protein-1 activation in acute lung injury. *Am J Pathol.* 2002 161:275-282.
21. Anaya-Prado, R., Toledo-Pereyra, L.H., Lentsch, A.B., and **Ward, P.A.**: Ischemia/reperfusion injury. *J Surg Res.* 2002 105:248-258.

**JEFFREY S. WARREN, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. Director, Division of Clinical Pathology/Clinical Laboratories, May 1993-present.
- B. Director, Clinical Immunopathology Service; September 1989-present.
- C. Interim Director, Clinical Cytogenetics Laboratory; September 1999-August 2000.
- D. Interim Director, Tissue Typing Laboratory; March 2000-present.
- E. Microbiology Laboratory; review of peripheral blood parasite smears; July 1996-present.
- F. Molecular Diagnostics Laboratory; signout of cases (3 weeks/year); July 1997-present.

II. TEACHING ACTIVITIES:

- A. "Current Topics in Immunopathology" journal club series: pathology residents, M4 students (41 contact hours).
- B. "Current Management Problems for Pathology Residents" series: pathology residents (14 contact hours).
- C. Clinical Pathology Grand Rounds:
 - 1. "Cases and Images in Immunopathology" (12/8/00).
 - 2. "Amyloidosis" (12/15/00).
- D. Immunopathology signout: pathology residents, M-4 medical students, EMU medical technology students (three times/week; 26 weeks/year).
- E. Immunopathology component of Block B (Clinical Pathology); ad hoc topical reviews: pathology residents (68 contact hours).
- F. M-1 Host Defense sequence; "Autoimmunity and tumor immunology" (5/18/01); (1 contact hour); Case Studies (5/17/01; 5/18/01); (2 contact hours).
- G. Supervision of Research activities for:
 - 1. Anjali Desai, Ph.D. (Research Investigator); (6/15/96-present).
 - 2. Hernan Gomez, M.D. (Assistant Professor; Emergency Medicine, University of Michigan); (6/1/96-6/30/01).
 - 3. Jessica Dong (Undergraduate, University of Michigan); November-May, 2000.
 - 4. Rachna Arora (Undergraduate; University of Michigan); (6/11/01-8/15/01).
 - 5. Melanie Hoekstra, Undergraduate, University of Michigan, January-August, 2002; (sponsored in Undergraduate Research Opportunities Program).

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Oxidant-Induced Beta Chemokines in Granuloma Formation", NIH (RO1-HL48287), (40% effort), \$877,511; direct costs, 7/1/96-6/30/01.

PROJECTS UNDER STUDY:

- A. Role of cellular redox status and neutrophil-derived mediators in MCP-1-mediated pulmonary granulomatous vasculitis.

- B. Modulation of proinflammatory endothelial and smooth muscle cell functions by erythropoietin, reactive oxygen intermediates, and reactive nitrogen intermediates.
- C. Pathophysiologic role of oxidants in uremia and its complications (collaboration with Rajiv Saran, M.D., Department of Internal Medicine, University of Michigan Medical School).
- D. Ischemia-reperfusion injury in perinatal rat brain (collaboration with Faye Silverstein, M.D., Departments of Pediatrics and Neurology, University of Michigan Medical School).
- E. Pathogenesis of Loxosceles reclusa venom-induced cell activation (collaboration with Hernan Gomez, M.D., Department of Surgery, Section of Emergency Medicine, University of Michigan, Ann Arbor, Michigan).

IV. ADMINISTRATIVE ACTIVITIES:

MEDICAL SCHOOL:

- A. Member, Operations Improvement Committee, University of Michigan Health System 2000-present
- B. Member, Professional Billing Compliance Committee, University of Michigan Medical School 1999-present.
- C. Member, Executive Committee, University of Michigan Medical School, 1999-present.
- D. Finance Subcommittee, advisory to Faculty Group Practice (FGP) Executive Committee, 1997-present.
- E. Member, Task Force on Faculty Administrative Services, advisory to FGP Executive Committee and Chief Executive Officer, University of Michigan Health System, 1998-2001.
- F. Member, Professional Billing Compliance Committee, 1999-present.
- G. Member, Operations Improvement Committee, 2000-present.
- H. Dean's Advisory Committee (ad hoc substitute for Dr. Peter Ward), 1994-present.
- I. Clinical Council (ad hoc substitute for Dr. Peter Ward), 1996-present.

DEPARTMENTAL:

- A. Interviewer of Pathology Residency Candidates, 1989-present.
- B. Interviewer of Pathology Graduate Program Candidates, 1990-present.
- C. Chairman, Laboratories Communications Committee, 1993-present.
- D. Chairman, Department of Pathology Quality Assurance Committee, 1993-present.
- E. Clinical Associate and Advisory Committee for Medical Technology Program, Eastern Michigan University, 1993-present.
- F. Chairman, Category Risk II Faculty Salary Planning Committee, Department of Pathology, 1996-present.

REGIONAL AND NATIONAL:

- A. Ad hoc referee for:
 - 1. American Journal of Pathology.
 - 2. Laboratory Investigation.
 - 3. Human Pathology.
 - 4. Journal of Applied Physiology.
 - 5. Lung.
 - 6. Blood.
 - 7. Journal of Laboratory and Clinical Medicine.
 - 8. Pediatric Research.

9. Journal of Leukocyte Biology.
10. American Review of Respiratory Disease.
11. Chest.
12. Journal of Pharmacology and Experimental Therapeutics.
13. Circulation.
14. Ophthalmology.
15. American Journal of Respiratory Cell and Molecular Biology.
16. Clinical Immunology and Immunopathology.
17. Circulation Research.
18. Journal of Immunology.
19. Surgery.
20. Reviews of Infectious Diseases.
21. Infection and Immunity.
22. Experimental Lung Research.
23. Journal of Rheumatology.
24. Clinical Infectious Diseases.
25. Journal of Clinical Investigation.
26. Cytometry.
27. Biological Signals.
28. Metabolism.
29. Molecular Medicine Today.
30. American Journal of Respiratory and Critical Care Medicine.
31. The Cancer Journal.
32. British Journal of Pharmacology.
33. Kidney International
- B. Member, Test Committee for Clinical Pathology, American Board of Pathology, 1999-present.
- C. Member, Council for Diagnostic Immunology and Molecular Pathology, American Society of Clinical Pathologists, 1998-present.
- D. Ad hoc Reviewer; Clinical Trials Review Committee; National Institutes of Health (NHBLI); Bethesda, MD; September 27-28, 2000.

V. INVITED LECTURES/SEMINARS:

1. Warren JS: Mechanisms of pulmonary granuloma formation. Festschrift in Honor of Larry Roth. Indiana University, Indianapolis, IN, June 14, 2001.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Miller MJ, Gomez HF, Snyder RJ, Stephens EL, Czop RM, Warren JS: Detection of Loxosceles venom in lesional hair shafts and skin: application of a specific immunoassay to identify dermonecrotic arachnidism. Am J Emerg Med 18:626-628, 2000.
2. Galasso JM, Miller MJ, Cowell RM, Harrison JK, Warren JS, Silverstein FS: Acute excitotoxic injury induces expression of monocyte chemoattractant protein-1 and its receptor CCR2 in neonatal rat brain. Exp Neurol 165:295-305, 2000.
3. Gomez HF, Miller MJ, Waggener MW, Warren JS: Antigenic cross-reactivity of venoms from medically important North American Loxosceles spider species. Toxicon 39:817-824, 2001.

4. Desai A, Lankford HA, Warren JS: Homocysteine augments cytokine-induced chemokine expression in human vascular smooth muscle cells: implications for atherogenesis. *Inflammation* 25:79-86, 2001.
5. Desai A, Lankford HA, Warren JS: *Loxosceles deserta* spider venom induces the expression of vascular endothelial growth factor (VEGF) in keratinocytes. *Inflammation* (in press).
6. Townson DH, Bowen JM, Remick DG, Warren JS, Keyes PL: Prolactin-induced regression of the rat corpus luteum: the effect of dexamethasone. *J Endocrinology* (in press).

ARTICLES SUBMITTED FOR PUBLICATION:

1. Szaflarski J, Liu XH, Warren JS, Silverstein FS: Treatment with antibody to monocyte chemoattractant protein-1 attenuates excitotoxic brain injury in perinatal rats. *J Neuroscience* (submitted).
2. Miller MJ, Desai A, Huang X, Warren JS: Nitric oxide modulates monocyte chemoattractant protein-1 expression in endothelial cells: implications for the pathogenesis of glucan-induced granulomatous vasculitis. *Am J Pathol* (submitted).
3. Whetstone WD, Gomez HF, Ernsting KS, Miller MJ, Marks RM, Warren JS: Inhibition of dermonecrotic arachnidism with interleukin-8 monoclonal antibody. *Acad Emerg Med* (submitted).
4. Gomez HF, Greenfield DM, Miller MJ, Warren JS. Direct correlation of dermal inflammatory effects with intradermal migration of *Loxosceles reclusa* venom (submitted).
5. Saran R, Novak JE, D'Alecy LG, Desai A, Weitzel W, Abdulhayoglu E, Warren JS, Rajagopalan S: Impact of vitamin E on plasma asymmetric dimethylarginine (ADMA) in chronic kidney disease (CKD): A pilot study. *Nephrology, Dialysis, Transplantation* (submitted).

BOOKS/CHAPTERS IN BOOKS:

1. Warren JS, Ward PA: The inflammatory response, in Beutler E, Lichtman MA, Collier BS, Kipps TJ and Seligsohn U (eds.) *Williams' Hematology*, 6th Edition, McGraw-Hill, New York, NY, 2001, pp. 67-77.
2. Warren JS: Leukocyte functional assays by flow cytometry, in Keren DF, McCoy JP, Carey JL, and Hanson CA (eds.) *Flow Cytometry and Clinical Diagnostics*, 3rd Edition, ASCP Press, Chicago, IL, (in press).
3. Warren JS: Immunodeficiency disease, in McClatchey KD (ed.) *Clinical Laboratory Medicine*, 2nd Edition, Lippincott Williams and Wilkins, Philadelphia, PA, (in press).

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFERRED JOURNALS:

1. Desai A, Lankford HA, Warren JS. Homocysteine augments cytokine-induced chemokine expression in human vascular smooth muscle cells: Implications for atherogenesis. *Experimental Biology*, Orlando, FL, (abstract), March 31-April 4, 2001.
2. Hoekstra M, Desai A, Lankford H, Warren JS. Erythropoietin alters nitric oxide regulated MCP-1 production in endothelial cells. *The University of Michigan Student Biomedical Research Forum*, Ann Arbor, MI (abstract), November 6, 2001.

3. Desai A, Lankford HA, Warren JS. Nitric oxide suppresses erythropoietin-mediated augmentation of cytokine-induced MCP-1 expression: implications for atherogenesis in chronic renal failure. Experimental Biology, Orlando, FL (abstract), April 20-24, 2002.

**THOMAS WILSON, M.D., Ph.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PATHOLOGY**

**ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. CLINICAL ACTIVITIES:

- A. None

II. TEACHING ACTIVITIES:

- A. Mentor, postdoctoral fellows: John Vance, Rajashree Deshpande, Anandi Srinivasan
- B. Mentor, graduate student: Phil Palmbos (MSTP)
- C. Mentor, undergraduate students: Anthony Iacco, Monica Heger
- D. Path 581, 2 lectures
- E. Path 582, 1 lecture, 1 discussion section
- F. Member, thesis committees: Tammy Morrish (Human Genetics), Jonathan Rios-Doria (CMB), Marc Prindle (CMB)
- G. Member, preliminary examination committee: Sarah Sutter (CMB), Brian Gentry (Pharmacology)
- H. Member, Cellular and Molecular Biology Training Program
- I. Full week course in molecular biology and DNA repair, University of Michigan Postdoctoral Research Training Program
- J. Coursemaster Path 850, research seminar series for graduate students

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Principal Investigator, "Disposition of DNA Double-Strand Breaks Among Multiple Pathways of Repair", Pew Scholars Program in the Biomedical Sciences (8%), \$60,000/year (\$240,000/four years), 7/1/2000-6/30/2004.
- B. Mentor, "Lung Immunopathology Training" (Training Grant), NIH 5T32HL07517, John R. Vance, Ph.D., postdoctoral fellow, 3/1/2000-2/28/2002.
- C. Principal Investigator, "End Processing in DNA Double-Strand Break Repair", NIH/NCI 1 R01 CA90911-01 (27%), \$166,000/current year (\$601,750/four years), 4/1/2001-3/31/2005.
- D. Principal Investigator, "Probing the mechanisms of gemcitabine action using a yeast genomic approach", University of Michigan Comprehensive Cancer Center Munn Research Grant (0%, no salary support), \$15,000/year (\$15,000/one year), 9/1/2001-8/31/2002.

PENDING:

- A. Principal Investigator, "Mutational Analysis of NHEJ", NIH R01 in preparation.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Pathology student recruitment activities (lunch, poster session)
- B. Chair and organizer, Pathology Research Seminar Series
- C. Member, Pathology Graduate Program Curriculum Committee

MEDICAL SCHOOL/HOSPITAL:

- A. Member, MSTP Career Advisory Panel
- B. Faculty candidate interviews: R. Stephen Lloyd (Chair, Biological Chemistry), Paul Nghiem (Radiation Oncology)
- C. PIBS student interviews and recruitment dinners
- D. MSTP student interviews

UNIVERSITY OF MICHIGAN:

- A. Grant review, Michigan Biomedical Research Council, Veterans Administration

REGIONAL AND NATIONAL:

- A. Manuscript review, Neoplasia, Nucleic Acids Research, Mol. Cell. Biol
- B. Pew Scholars Annual Meeting Planning Committee

V. OTHER RELEVANT ACTIVITIES:

- A. Biological Sciences Scholars Program, University of Michigan
- B. Pew Scholars Program in the Biomedical Sciences, Pew Charitable Trusts
- C. Member, Michigan Comprehensive Cancer Center

EDITORIAL BOARDS:

- A. None

HONORS AND AWARDS

- A. None

PATENTS:

- A. None

INVITED LECTURES/SEMINARS:

1. "Repair of DNA strand breaks with complex and damaged termini: Implications for chromosomal rearrangement", Pathology Research Seminar, University of Michigan, September, 2001.
2. "NHEJ in yeast", CMB Program Seminar, University of Michigan, April 2002.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

1. Karathanasis E, **Wilson TE**. Enhancement of *Saccharomyces cerevisiae* end-joining efficiency by stationary phase transition but not by impairment of recombination. *Genetics* 161: 1015-27 (2002).
2. Vance JR, **Wilson TE**. Yeast Tdp1 and Rad1-Rad10 function as redundant pathways for repairing Top1 replicative damage. *Proc Natl Acad Sci USA* in press.
3. **Wilson TE**. A genomics-based screen for yeast mutants with an altered recombination/end-joining repair ratio. *Genetics* in press.

ARTICLES SUBMITTED OR IN PREPARATION:

1. Karathanasis E, Thimmarayappa J, **Wilson TE**. Roles of Pol4 and Mre11 in microhomology searching and end-processing during nonhomologous end-joining. In preparation.

BOOKS/CHAPTERS IN BOOKS:

1. None

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. **Wilson TE**. A genomics-based screen for yeast mutants with an altered recombination/end-joining competitive repair ratio. Presented at the Genetics Society of America conference "Yeast Genetics and Molecular Biology", Madison, Wisconsin, July 2002.
2. Thimmarayappa J, Karathanasis E, **Wilson TE**. Roles of Pol4 and Mre11 in microhomology searching and end-processing during nonhomologous end-joining. Presented at the Genetics Society of America conference "Yeast Genetics and Molecular Biology", Madison, Wisconsin, July 2002.

SECTION REPORTS

ANATOMIC PATHOLOGY

DIVISION OF ANATOMIC PATHOLOGY

DEPARTMENT OF PATHOLOGY

ANNUAL REPORT

1 JULY 2001 - 30 JUNE 2002

The Division of Anatomic Pathology continues to enjoy a strong national and international academic reputation while providing a breadth of expertise in support of the clinical and educational programs of the University of Michigan Health System, Medical School, and University. This past year two new faculty joined the Division, Drs. Barbara McKenna and Yiran Dai. These faculty bring additional expertise in general surgical pathology as well as sub-specialty expertise in cytology.

Faculty research programs and extramural support continues to increase especially in programmatic areas associated with the Cancer Center, GI pathology and SPORes in Urologic Disease and Head and Neck Disease. There continues to be expansion of core research facilities directed by faculty in the division including; tissue microarrays, laser capture microdissection, histology/immunoperoxidase/FISH, and tissue procurement. Several faculty continue collaborations with biomedical research companies including Genetech (Calif.), Eli Lilly (Ind.) and Pfizer (Mich.).

Three senior residents completed surgical pathology fellowships. Five additional house officers completed fellowship training in blood bank/transfusion medicine, cytopathology, urologic pathology, and hematopathology. All found excellent positions in sub-specialty (4) fellowships, private practice (2), and academic faculty positions (2). One fellow was awarded a prestigious Robert Wood Johnson Award.

Overall, the in-house clinical activity in surgical pathology and cytopathology increased by approximately 5%. The dermatopathology service realized a 9% increase in cases. Design of new space for support of cytopathology will allow the department to support activity associated with this service. The efforts of Kathy Smiezney (Anatomic Pathology Laboratory Supervisor), Kris Kern (Cytology Laboratory Supervisor) and all laboratory staff continue to be instrumental in successfully implementing the UMHS Cost Efficiency Program (CEP) and maintaining the high quality of our Anatomic Pathology laboratory services.

With continued expansion of clinical services and academic programs as well as recent faculty departures, it will be necessary in the next three years to recruit additional faculty especially in areas of general surgical pathology, urologic pathology, head and neck pathology and cytopathology. These are times of opportunity for the division, department and medical school and we are well positioned to continue as one of the pre-eminent academic divisions and departments in the country.

AUTOPSY SERVICE

**DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. Timely Completion of Autopsy Reports:

The autopsy service continues to emphasize timely completion all our autopsy reports. This has required active management of the autopsy late list and individually contacting both house officers and faculty when their cases are older than 30 days. Additionally, with the new incoming house officers we have made a strong statement that autopsies should be completed within 30 days. The table below lists the autopsy completion time for different years.

Time Interval	% completed in 60 days	% completed in 90 days	# of Autopsies
1995-96	40	58	541
1996- 97	64	89	565
1998-99	96	100	350
1999-2000	91	100	295
2000-2001	84	99	295
2001-2002	85	99	293

II. Autopsy percentage:

We continue to determine the autopsy rate by clinical service in the hospital. The total number of deaths, number of cases and autopsy percentage for the 2001-02 year are listed below. This information as they shared with both the clinical chairs as well as the residency program directors of the University of Michigan.

	# of deaths	# of cases	% of deaths
Medicine	487	101	21%
Surgery	293	49	17%
Pediatrics	133	42	32%
Other services	36	10	28%
Total Hospital	949	202	21%

Hospital total 21%

III Conferences:

We continue to present our cases at several different conferences. Pathology regularly participates in the weekly Death and Complications conference in the Department of Surgery. We also make presentations at the monthly Morbidity and Mortality conference in the Department of Internal Medicine. A new, monthly conference has been initiated in the Department of Internal Medicine where 4 autopsies are presented each month. In contrast to the usual M&M conference where most of the presentation deals with the clinical story, the emphasis for this conference is on the autopsy findings and histopathology. This conferences run primarily

by the first year pathology residents who have completed their autopsies. At the request of the Department of Emergency Medicine, we also making presentations twice a year to their house officers.

IV Medical Examiner Cases:

The Department of Pathology continues to have a presence in Medical Examiner issues in the State of Michigan and Washtenaw County. However, the Department of Pathology no longer provides medical examiner investigators to be on call for the Washtenaw County Medical Examiners office. The Medical Examiners office now provides staffing for investigators to be on call to investigate medical examiner deaths that arise at the University of Michigan. This has resulted in a cost saving to the department since we are no longer providing on call pay.

V Statistics:

This covers the time period July 1, 2001 to June 30, 2002.

Total number of autopsies performed	278
Hospital autopsies	229
Medical examiner autopsies	49

Daniel G. Remick, M.D.
Director, Autopsy Service

CYTOPATHOLOGY LABORATORY

**DEPARTMENT OF PATHOLOGY
ANNUAL REPORT
1 JULY 2001 – 30 JUNE 2002**

Total gynecologic specimens for the year were 48,183. Non-gynecologic specimens numbered 6,266; a 2.5% increase from last year. Fine needle aspirations totaled 1,412 for the current year. Of these aspirates, the cytopathologists have performed or attended a total of 749 aspirates. The laboratory continued to achieve the turnaround time for non-gynecologic specimens within 24-48 hours, and the turnaround time for the Papanicolaou smears have been markedly improved to the current 5-7 working days.

Effective August 2001, one of the cytotechnology positions was switched to an evening shift, and, in September 2001, Susan Clozza joined our laboratory as the new cytotechnologist. Jenise Falan was appointed Co-President of the Michigan Society of Cytology, and Brian Smola was reappointed as Web Chairman of the Michigan Society of Cytology and also serves on the Public Information Committee of the American Society of Cytology.

The department continues its moving forwards towards implementation of ThinPrep. All staff has received ThinPrep training. The T3000 processor is scheduled for installation on July 24th and 25th, 2002. Gradual conversion will occur after the processor is up and running, and the interface with Cerner system is established. The number of ThinPrep paps in the current year increased to 7.4% (3.4% in 2000-01).

Our fellowship program continued to be highly successful. Dr. Yiran Dai and Dr. Christine Sturm completed their training with distinction. Dr. Barbara McKenna and Dr. Yiran Dai were successfully recruited to join our faculty in cytopathology effective July 1, 2002.

The Cytopathology Section had excellent representation at national and international meetings with several workshops and posters presented by the cytology faculty and residents.

Ms. Kristine Kern continued the development, testing and troubleshooting of the Millennium System for Cytopathology and Surgical Pathology.

**Claire W. Michael, M.D.
Director, Cytopathology Laboratory**

DERMATOPATHOLOGY SERVICE
DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 – 30 JUNE 2002

The Dermatopathology Service receives diagnostic case material from six different sources: (1) UMMC (ID) cases; (2) outside contractual (MD) cases; (3) personal consultation cases (DP); (4) outside slides reviewed for referred patients (TD) cases; (5) miscellaneous intramural referrals (IE, IF, IS, MU) cases; (6) and informal consultations (intramural and VAH).

The clinical service volume has continued to increase and is as follows:

	1999-2000	2000-2001	2001-2002
ID	6,246	6,947	7,205
MD	6,153	6,381	7,248
TD	1,275	1,486	1,691
DP	796	876	1,244
MISC		87	126
TOTAL	14,470	15,777	17,514

Once again, the Dermatopathology Service has seen a significant increase in volume. Overall, there has been a 13.5% increase in MD cases, a 3.7% increase in ID cases, a 13.8% increase in TD cases, and an impressive 42% increase in consultation cases. The total number of cases for 2001-2002 was 17,514, an 11% increase when compared to the previous year, and a 45% increase over the past three years. The clinical service load seen by each faculty member of the Dermatopathology Service, Dr. Su, Dr. Fullen, and Dr. Lowe, is substantial and exceeds any other surgical pathologist in the Department. In addition, we have continued to be highly productive in scholarly activities and academic pursuits. Dr. Fullen's administrative responsibilities are significant, as he has assumed the position of Director of the Histology Laboratory.

The Dermatopathology Service continues its extensive involvement with residency and medical student education in the Department of Dermatology. Teaching activities include weekly formal didactic sessions, weekly diagnostic conference, instruction at the microscope during signout, and active participation in the MSII Dermatology Sequence and Dermatopathology Laboratory. Dr. Fullen was the recipient of the William B. Taylor Award for excellence in residency teaching from the Department of Dermatology in June, 2002. Dr. Lyndon Su and Dr. Douglas Fullen also actively participate in formal dermatopathology didactic sessions for our pathology residents.

We continue our active involvement in the University of Michigan Multidisciplinary Melanoma Clinic (MDMC) and Tumor Board (bi-weekly). This remains the largest melanoma program in the United States. Accordingly, the volume of difficult pigmented lesions seen by our service is substantial, as are the numbers of wide local excisions, biopsies, and sentinel lymph node biopsies generated by this busy clinic, all of which directly impact on Dermatopathology. Importantly, there is a 25% significant change in diagnosis for all patients referred to the MDMC after review by our service.

Lori Lowe, M.D.
 Director, Dermatopathology Service

NEUROPATHOLOGY SERVICE
DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001– 30 JUNE 2002

Dr. Mila Blaivas, Ms. Constance J. D'Amato, Dr. Andrew Lieberman and Dr. Paul E. McKeever contributed to the Neuropathology Service. Ms. D'Amato is active emeritus.

I. CLINICAL ACTIVITIES:

1. There were over 1200 neurosurgical cases examined this year. There were many personal consult cases. (M.B. = 105)
2. The Diagnostic Unit of the Neuropathology Core Laboratory of the MADRC processed 76 dementia brain cases. Of these 76 brains, 59 were MADRC cases, 12 were neurology hospital patients, and 5 were from the Michigan Dementia Postmortem Network Program.
3. There were 364 muscle biopsies, 30% with electron microscopy. There were 102 peripheral nerve biopsies. There were 11-teased fiber preparations and 100 with electron microscopy. 12 skin or non-muscle/nerve tissue examined with electron microscopy. 21 muscle biopsies were examined with 10 anti-dystrophy antibodies in the IPOX laboratory.
4. There were over 300 University Hospital brains examined.
5. The Brain Tumor Board of the University of Michigan Cancer Center and Hospitals, supported weekly by a neuropathologist, reviewed neuropathology and clinical aspects of more than 150 difficult neuro-oncology cases.

II. TEACHING ACTIVITIES:

1. Medical Students: This year the neuropathology faculty taught in the eight week Neuroscience Sequence for our second year medical school curriculum. There were fourteen hours of neuropathology taught: six hours of lecture and eight hours in the laboratory.
2. Dental Students: 4 lectures.
3. House Officers, Graduate Students, Postgraduate and other students and faculty: These include the following Continuing Medical Education accredited conferences: periodic conferences for Neurology; monthly Rheumatology Pathology Grand Rounds and occasional CPC conferences; monthly conferences where all biopsies are presented and interpreted; a weekly conference where abnormal brains are examined (including two or three weeks per month for dementia cases) with all clinicians invited; weekly nerve and muscle conferences; monthly nerve and muscle biopsy conferences. We provided individual instruction on autopsies and biopsy material; Neuropathology 858, an 8-hour laboratory course; bi-monthly conferences with Neuroradiology, Neurosurgery and Neuroradiology House Staff and every third month a microscopic conference for dementia brain cases. Weekly seminars are provided to neurological and neurosurgical house staff on clinico-pathological correlations.
4. Neuropathology 858, an evening course, given in the Fall, is taught by Ms. D'Amato.

5. Electives: Pathology, Neurosurgery, and Neurology Residents chose elective rotations in the Neuropathology Section.
6. A Pathology Fellow from Stanford University Medical School spent a month on the Neuropathology service.

III. RESEARCH ACTIVITIES:

1. Dr. Andrew Lieberman and Ms. D'Amato provided neuropathology support for MADRC. Dr. Lieberman was co-director of the Neuropathology core of MADRC.
2. Dr. Blaivas is working on the histology of animal models and human application in genetic treatment of rheumatoid arthritis with the Arthritis and Rheumatology Section with Blake Roessler; Neurology, Neuro-oncology, Genetics and Pulmonary/Internal medicine on various projects.
3. Dr. McKeever and associates were determining the extent and cause of differences in gene product expression in brain tumors. They assessed the predictive value of markers in brain tumor specimens. He was principal investigator on a NIH funded project studying the prognostic potential of MIB-1 proliferation marker on brain tumors. He is the study pathologist for a multi-institutional study of treatments of low-grade astrocytoma for the Children's Cancer Group.
4. Dr. Lieberman's laboratory studies the mechanisms of neurodegeneration in Kennedy's disease, a disorder affecting motor neurons of the brain stem and spinal cord. He is using cell culture and animal models to determine how the causative mutation leads to neuronal dysfunction and death. He is the principal investigator on grants from the NIH, Muscular Dystrophy Association, and MADRC that support his work.
5. University of Michigan Cancer Center faculty and staff with clinical research interests in brain tumors met and generated a number of project considerations with Pathology, Neurosurgery, Nuclear Medicine, Neuropathology, Neurology and Neuroradiology collaborations.
6. Collaboration with Neurology, Michigan State University, The Alzheimer's Association, Spectrum Health, and Wayne State University has established a registry for Alzheimer's disease and other dementias and degenerative diseases.

**SPECIAL STUDIES LABORATORY
(CLINICAL IMMUNOHISTOCHEMISTRY, IMMUNOFLUORESCENCE
AND NEURAL AND MUSCULAR STUDIES)**

**DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

INTRODUCTION

Immunoperoxidase has continued as an active clinical service with the addition of 17 new antibodies in the past year. New antibodies have also been added to the frozen section panel of antibodies for the diagnosis of muscular dystrophies. Muscle histochemistry continues to grow steadily and the laboratory has continued to take on new muscle clients. This is reflected in the 11% increase in caseload. Immunofluorescence remains busy with a small increase for the skin and heart specimens.

CLINICAL IMMUNOHISTOCHEMISTRY

Year-end figures show that the average number of slides stained per day has increased from 128.5 slides/day to 131 slides/day representing a 2% increase over last year. Fourteen new antibodies have been added to the menu of antibody stains including CD2, CD4, CD7, CD8, Dysferlin, BerEP4, Complement Component C9, Calponin, Calretinin, Galectin-3, Hepatocyte, p63, Cocktail of p63&K903 and TIA1. Additionally, our lab supported and helped the research immunohistochemistry laboratory between 7/2000 and 9/2000. During this period 1327 slides were processed and stained in our laboratory.

With the loss of one FTE in August 2000 and the ever-increasing workload efficiency is the top priority. All antibodies have successfully been automated as of this year and several eliminated. An additional FTE, from another laboratory (Electron Microscopy Lab) was assigned to help our laboratory (2 days/week), she helps in immunofluorescence staining, preparing the slides, and helps other staff to compete their work. Despite these efforts, the demand for new antibodies and utilization is will necessitate recruitment of additional laboratory staff. As in the past, we have continued to score 100% on the biannual Immunohistochemistry CAP testing.

IMMUNOFLUORESCENCE

Under the direction of Drs. Killen, Johnson and Gordon this laboratory continues to stain skin, heart and renal biopsies using the automated Ventana ES immunostainer. The caseload has remained steady in all areas. There were over 424 renal biopsies and 192 skin and heart biopsies. This is comparable to last year (447 and 210 respectively).

NEURAL AND MUSCULAR STUDIES

This service under the direction of Dr. Blaivas has developed many new diagnostic tools this year. A panel of 11 frozen section antibodies has been added for the diagnosis of muscular dystrophies. Three new special stains that were obtained from the Mayo Clinic have been added for muscular disease diagnosis. All of these new tests have increased our recognition as a lab and this is evident by the number of new clients that have been added recently. The case load for this service has increased from 307 muscles last year to 364 this year (18.6%).

CONCLUSION

The clinical load in all services continues to increase in the year 2001. Our future goals are the establishment of In Situ hybridization in the lab and continuing with quality improvement and increased efficiency.

CLINICAL PATHOLOGY

DIVISION OF CLINICAL PATHOLOGY

**DEPARTMENT OF PATHOLOGY
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The Clinical Laboratories have continued to provide excellent, full-spectrum service (more than 800 different laboratory analyses) as the UMHS has expanded both its volume and scope in ambulatory care activities and experienced growth in several major clinical programs. Substantial effort has been directed towards aggressive laboratory utilization control, the improvement of test ordering, laboratory logistics, achievement of compliance with HCFA-mandated rules on documentation of test-ordering indications, and achievement of compliance with federal rules related to FDA approval of testing methods. Superimposed upon these efforts has been further development of computer links with M-Labs clients and ongoing software conversion to the Cerner Millennium product. In 2000-01 the Clinical Laboratories again performed more than 3 million billable analyses (5 million individual measurements), supported a wide array of clinical and research programs, and added or replaced more than 30 testing methods. The maintenance of high quality services by the Clinical Laboratories, in the face of increasing complexity of demands, is testimony to the professionalism of the staff and the management capabilities of the laboratory directors and senior laboratory personnel. The Clinical Laboratories successfully completed the biannual College of American Pathologists onsite in May, 2001. Maintenance of the delicate balance among quality service, cost effective testing, utilization control, and the research and development which characterizes an academic institution, will be a continuing challenge.

A major initiative was achievement of a more aggressive utilization management program. More than \$850,000 in direct laboratory cost avoidance and test utilization control was realized in 2000-01. This was made possible through educational meetings with each clinical department chairman, a series of extra-departmental educational presentations, publication of on-line (CareWeb) cost data, and, most effectively, direct utilization control policies and interventions.

Finally, the Clinical Laboratories have continued to respond to the change in scope and organization of UMHS patient care activities. In contrast to the early 1990s when 70% of laboratory testing volume came from inpatient services and 30% from ambulatory patients, the split is now 40:60 in the opposite directions. The laboratories currently support more than 30 UMHS-owned regional satellite facilities as well as many more patients who are M-Care subscribers. These shifts have substantially increased our focus to informatics, logistics, and cost-containment.

Faculty and laboratory staff participated in a wide variety of intramural and extramural educational programs during 2000-01. For instance, the 28th annual Blood Bank/Transfusion Medicine course and the ASMCL course were again well attended, making them among the most visible courses of their kinds in the United States. The May AIMCL course brought together leaders from a variety of institutions and laboratory information technology fields to discuss the future of clinical pathology practice. These programs, along with the M-Labs educational programs, are prominent examples of educational outreach activities. The revised clinical pathology residency training format (July, 1993), which organizes pathology residents into teams that rotate through three blocks of clinical laboratories

that are grouped according to “relatedness of discipline”, was again updated in 2000-01. In keeping with a thematic approach, the 2000-01 version solidified the four rotation blocks and places greater emphasis on molecular diagnostics, coagulation, informatics, statistics, and management. The continued high quality of trainees in the Hematopathology Fellowship program has enhanced the service, educational, and academic missions of the Hematopathology group and the Department. The Department added a second slot in the Hematopathology Fellowship program and added a Blood Bank/Transfusion Medicine fellow. Outstanding new faculty were recruited in Cytogenetics (Diane Roulston, Ph.D.) and Blood Bank/Transfusion Medicine (Laura Cooling, M.D.).

The academic achievements of faculty members within the Clinical Pathology Division have been outstanding. As a group, the CP faculty had approximately 100 articles published in peer-reviewed journals. Most faculty members played highly visible leadership roles in national organizations, courses, symposia, as well as on editorial boards, examining committees, and research review study sections; an illustration of their high levels of recognition throughout the United States (see individual reports). Numerous faculty members received extramural funding that supported a variety of scholarly activities (see individual reports).

The Clinical Pathology Division will continue to face new challenges. In addition to its ongoing academic enterprises, educational issues, leadership and development in quality assurance, and laboratory resource utilization in the context of the hospital cost efficiency program, the Division plans to continue its attention to informatics and the clinical molecular diagnostics program. Achievement of these objectives will require the continued commitment, professionalism, and hard work of the faculty, laboratory staff, administration, and house officers.

Jeffrey S. Warren, M.D.
Director, Clinical Pathology Division

**UNIVERSITY HOSPITALS BLOOD BANK
AND TRANSFUSION SERVICE**

**DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
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PATIENT CARE:

Blood component utilization decreased relative to the previous year with approximately 100,000 total components dispensed. Red Blood Cell utilization approximated 32,000 units with the majority being used in surgery. Platelet Concentrate utilization was approximately 49,000, representing a decrease of about 10% from the previous year. The decline in blood usage occurs despite an increase in clinical activity in high blood usage area. This reflects the successful efforts of the medical staff to control costs.

Hematopoietic progenitor cell processing activity was comparable to the previous year with 550 total units processed. Fewer peripheral blood progenitor cell collections were performed as a result of improvement in collection efficiency. The procedure to patient ratio is now 1.5 with 68% of patients reaching the collection target in one apheresis procedure. In addition, this has resulted in a higher CD34 cell dose and earlier platelet engraftment.

The transfusion and apheresis activity was also similar to the previous year with approximately 2,000 patient encounters. The proportion of progenitor cell collections and therapeutic apheresis procedures has remained steady. There continues to be significant activity in the areas of vascular heart transplant rejection, post-transplant recurrence of focal segmental glomerulosclerosis, and cryoglobulinemia. Approval was obtained to implement a new procedure, low density lipoprotein apheresis, for the treatment of refractory hypercholesterolemia. We anticipate treating the first such patient in 2002.

The utilization of prestorage leukocyte reduced blood components increased significantly. This has resulted in fewer febrile reactions and possibility in a reduction of other complications of transfusion.

A new contract with the American Red Cross for the provision of blood components was concluded. This contract ensures continued supply and limits price increases for the next year. An agreement with Indiana Blood Center was concluded that supplemented the supply of platelet concentrates and fresh frozen plasma.

EDUCATIONAL ACTIVITIES:

Members of the Blood Bank medical and technical staffs participated in Pathology house officer teaching, Hematology fellow teaching, M2 and M4 medical students teaching, the transfusion component of nursing orientation, and many interdepartmental conferences.

The 29th annual postgraduate course, "Current Topics in Blood Banking", was held on June 5-7, 2002. The course, under the direction of Mr. Judd, attracted over 100 technologists and physicians from throughout the United States. It continues to be one of the most popular postgraduate courses in the

country devoted to blood bank topics, and was the first to be presented by a medical center rather than by a national blood program. The Blood Bank and Transfusion Service medical and technical staff were instrumental in planning, organizing and presenting this program.

Educational activities of blood bank faculty members are documented in individual faculty reports. In addition, Dr. Afenyi-Annan participated in programs of the Michigan Association of Blood Banks. Members of the technical staff also participated in state and national educational activities. Ms. Butch was particularly active in this regard.

PROFESSIONAL ACTIVITIES:

Members of the Blood Bank and Transfusion Service medical and technical staffs were active at the regional and national levels. Ms. Butch served on committees of the American Association of Blood Banks, the Michigan Association of Blood Banks, ICCBBA, the American Society for Clinical Laboratory Science, the Michigan Society for Clinical Laboratory Science, and the National Certifying Agency of Clinical Laboratory Personnel. Ms. Dake was a member of the AABB Immunohematology Reference Laboratories Accreditation Program Unit Committee, and presented at programs of the Michigan Association of Blood Banks and the Immunohematology Reference Laboratory Conference. Dr. Davenport served the American Association of Blood Banks on the Scientific Section Coordinating Committee, the Editorial Board of TRANSFUSION, and the Annual Meeting Program Planning Committee. Ms. Butch and Ms. Stoe served as Assessors for the American Association of Blood Banks. Ms. Stoe served on the Executive Board of the Michigan Association of Blood Banks.

RESEARCH ACTIVITIES:

Faculty research activities are documented in individual reports of Dr. Davenport, Dr. Cooling, and Mr. Judd. The Transfusion and Apheresis Service provided crucial support in leukocyte collection for General Clinical Research Center clinical research protocols.

Robertson D. Davenport, M.D.
Medical Director,
Blood Bank and Transfusion Service

CLINICAL CYTOGENETICS LABORATORY

DEPARTMENT OF PATHOLOGY ANNUAL DEPARTMENTAL REPORT 1 JULY 2001 - 30 JUNE 2002

Overview

The laboratory maintained nearly the same sample volume this year compared to last fiscal year, with a total of 2555 cytogenetics and/or FISH studies performed. A slight decrease in samples for cytogenetics (N=2309, -4.8%) was offset by an increase in the number of FISH tests (N=223, +39%) and tissue culture procedures for fibroblasts for send-out biochemical or DNA testing.

Thomas Glover, Ph.D. (Professor, Department of Human Genetics) continued to provide invaluable expertise and sign-out coverage of constitutional genetics cases. Analysis and sign-out of a fraction of the bone marrow samples were covered by another consultant, Dr. Ramesh Babu of Penrose-St. Francis Hospital, Colorado Springs, CO. We hired Lisa R. Smith, Ph.D. to serve as Assistant Director; she will begin work in September 2002. Dr. Smith recently completed her fellowship training in Clinical Cytogenetics at the Indiana University School of Medicine. We also hired and trained 2 very well qualified technologists to replace one departure and to fill one new position.

Clinical Services

Although the overall sample volume remained steady, there were some fluctuations for different sample types. Decreases in the number of bone marrow samples (N=1121, -14% over last year), which are the most labor-intensive samples to analyze, allowed us to decrease the number of samples sent to Penrose. The decline in bone marrow samples over the year, first noted in the fall of 2001, was due to loss of some Mlabs business that went to a commercial laboratory. Fetal tissue samples also decreased (N=83, -30%). These decreases were offset by increases in the number of peripheral blood samples for constitutional studies (N=624, +13%), and samples for prenatal diagnosis (N=449, +8.2%). As mentioned above, more FISH testing was performed, both constitutional (N=167, +15%) and oncology studies (N=56, +273%). The increase in oncology FISH testing was due to the increasing use of BCR/ABL FISH to monitor the remission status of patients with CML treated with Gleevec, and testing for deletions of 13q for patients with multiple myeloma, which has been associated with a poor prognosis. Subtelomeric FISH procedures were developed and are being tested for clinical implementation.

Education

Residents and fellows from several departments came to the laboratory for rotations. Six residents and fellows from Pathology, one fellow from Clinical Genetics, and one fellow from Hematology/Oncology rotated through the laboratory. The Pathology and Genetics residents and fellows gave brief talks for the technologists in areas relevant to the case work in the laboratory, and made significant contributions to continuing education. Four students from the genetic counseling Master's degree program visited and watched procedures. This year four cytogenetics technologists drove together to the Association for Genetics Technologists annual meeting and presented a poster on a familial deletion of 4p ascertained by

the laboratory, in collaboration with Dr. Susan Dagenais from the Glover laboratory who has performed FISH studies to map the deletion in order to determine what genes may produce the phenotype.

Future Plans

Upon Dr. Smith's arrival, we will be able to complete all of our cases in-house and improve turn-around times. Due to space constraints and the labor-intensive nature of cytogenetics studies, we have reached the limit for the number of samples that can be processed and analyzed, given the current configuration of the laboratory.

Diane Roulston, Ph.D.
Assistant Professor
Director, Clinical Cytogenetics

**COMBINED HEMATOLOGY LABORATORY
(HEMATOLOGY, BONE MARROW, FLOW CYTOMETRY, COAGULATION)**

**DEPARTMENT OF PATHOLOGY
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The combined hematopathology laboratories completed another successful year in FY 2002, and our stated goals for the laboratories over the past year have largely been fulfilled. Following is a summary of developments, achievements, and current status:

I. Laboratory Operations

Although consolidation of the laboratories occurred over four years ago, we continue to make strides in integrating and streamlining our services. Through the outstanding efforts of our technologist staff, we have successfully cross-trained several technologists who are now capable of covering services in the main hematology, flow cytometry, and bone marrow laboratories. We also undertook additional cross training between the special coagulation and main hematology laboratories. The physical space within the bone marrow and flow cytometry laboratories was reorganized to optimize day-to-day operations and to make way for necessary upgrades to the adjacent cytopathology laboratory, and to accommodate newly rotating medical technology students from Ferris State University (See "Research and Teaching" below). The fact that the labs operated with at least one unfilled full-time position all year is a testament to the labs' productivity and dedication. Section-specific reports are as follows:

A. Coagulation Laboratory

The routine coagulation section is now fully integrated with the staff of the main hematology laboratory. On average 2.0 FTEs perform special coagulation laboratory studies during weekdays. 1.5 FTE individuals are performing routine coagulation studies during weekdays (PT, APTT, fibrinogen, D-Dimer). Afternoon shift, weekends and night shifts have about 1 FTE performing routine coagulation testing.

Several new programs have been established in the Coagulation Laboratory. Behring BCS coagulation equipment was established in the routine and specialized coagulation areas. The laboratory went live with the BCS equipment on 08/28/01. Four instruments were set-up and standardized: two for routine coagulation testing and two for specialized testing. The entire specialized coagulation staff has been trained on the Behring BCS coagulation equipment.

As part of establishing the BCS in the Coagulation Laboratory for routine coagulation lab testing, a new APTT reagent had to be evaluated. This effort was instituted after the initial "go live" date because reproducibility and reliability of the APTT values were not confirmed until such time as several months experience of patient data were obtained. Presently, the values for the APTT appear to have reliable 95% confidence intervals.

The anti-factor Xa assay has been established on the BCS for the routine unfractionated heparin assay presently available in our institution. The thrombin clotting time (TCT) to monitor standard heparin therapy has been abolished because the manufacturer of the reagent for that assay stopped producing it. A thrombin clotting time diagnostic (TCTD) is still available for the diagnosis of dysfibrinogenemias. The anti-factor Xa assay for unfractionated heparin is available 24 h/day, 7 days a week, 365 days per year. Likewise, the anti-factor Xa assay for low molecular weight heparin also is available 24/7/365 days per year.

The advanced D-Dimer assay was set-up and established in the routine coagulation laboratory as planned and in response to the needs of our clinical colleagues to develop a more discriminatory assay for the diagnosis of DVT and PE. Normal values have been established for coagulation testing, but discriminatory values for the diagnosis of DVT and PE await efforts by our clinical colleagues.

The Director of the Coagulation laboratory has implemented electronic records of the interpretations of the specialized coagulation laboratory reports. These reports now appear regularly on CareWeb. Efforts have been made to improve the timeliness of reporting of these results.

B. Hematology and Bone Marrow Laboratories

In FY 2002, we formally transferred administration of the Taubman Center laboratory to the phlebotomy section, completing the planned closure of the Taubman laboratory. Service is now provided to the Taubman outpatient clinics via the main hematology laboratory, with certain waived tests (e.g. macroscopic urinalysis) performed by the phlebotomy service in the Taubman Center.

This year saw a major restructuring of our manual review policies for complete blood counts (CBCs). Reflex manual differential leukocyte counts based solely upon instrument flags have been eliminated. Instead, each flagged results is manually scanned, and manual differentials are then only performed if the discovery of findings not reported by the automated method result in additional clinical value for a manual differential. The result has been an approximately 70% decrease in the performance of manual differentials. This optimization of resources has also enhanced patient care by increasing the application of the far more precise automated differential counting method over the relatively imprecise manual method. New policies on the reporting of red cell morphology with CBCs has increased clinical utility by establishing quantitative reporting guidelines designed to decrease interobserver variability.

C. Flow Cytometry Laboratory

The Clinical Flow Cytometry Laboratory continues to play a leading role in the optimum utilization of clinical laboratory resources. Attending staff continue to triage all requests for leukemia/lymphoma immunophenotyping, with cancellation of unwarranted requests. Of the 2443 specimens submitted for leukemia/lymphoma immunophenotyping, pathologist review lead to cancellation of 787 (32%) of these requests. Leukemia and lymphoma profiles are the most

labor-intensive tests offered by the laboratory, and these test volumes continue to show substantial growth.

A new initiative in the section this year has been validation of flow cytometric panel reactive antibody beads, a collaborative effort in conjunction with the tissue typing laboratory. In addition, one medical technologist began training in flow cytometry and two experienced flow cytometry technologists began cross-training in the bone marrow area.

We have streamlined verification procedures for immunodeficiency monitoring and CD34 stem counts (together accounting for a majority of test volume in the laboratory). Operations were further optimized by a switch from microfilm-based report archiving to a system of computer imaging of previous reports and data. This system permits attending faculty to readily access prior flow cytometry data from an internal secured computer server, allowing rapid comparison of previous data for enhanced patient care.

II. Laboratory Growth

A. Coagulation Laboratory

Overall, there was an 8.99% increase in coagulation laboratory activity in fiscal year '01 to fiscal year '02. The high volume assays PT and APTT had a 6.5% and 13.6% increase in assays requested, respectively. The largest increase in specialized coagulation laboratory testing was in performance of assays for lupus anticoagulants. There was a 420% increase in the number of DRVVT assays from 575 last year to 2417 this year. Likewise, there was a 88% increase in the number of tissue thromboplastin inhibition assays from 865 last year to 1630 this year. There were large increases in specific coagulation factor assays: factor IX (205 assays), a 36.6% increase; factor V (733 assays), a 45% increase; and factor VIII (790 assays), a 25% increase. There was a 16.3% increase in the number of HIT assays (391) performed.

Alternatively, there was decreased use of the following assays: the template bleeding time (446 assays); activated protein C resistance (204 assays); fibrinogen antigen (175 assays); D-Dimer assay (4487 assays); and plasminogen activity (134 assays) and antigen (115 assays).

B. Hematology and Bone Marrow Laboratories

Overall test volumes continued to increase in FY 2002. Complete blood counts (with or without automated differential counts) increased by 3.8% to 348,123, while reticulocyte count orders remained almost unchanged. Our concerted effort to restructure the approach to manual differential counts resulted in a decrease in manual differential count orders of over 46%, to 22,710. Urinalysis orders increased by 6.5% to 52,913. Body fluid cell counts/fluid differential counts increased by 2.7% to 6,416. Erythrocyte sedimentation rate orders rose by almost 19% to 18,980. Additional special testing (osmotic fragility, Heinz body, G6PD screen, inulin screen, etc.), continues to grow, with 3,292 such tests performed. Bone marrow aspirates and biopsies decreased by about 16% each, to 1,443 and 1,491, respectively. In addition, our faculty reviewed over 1,300 bone marrow and lymph node biopsies from patients transferred from outside

hospitals, and over 500 cases sent in consultation from outside pathologists. We also continue to interpret thousands of in-house blood smears, body fluid preparation, lymph node biopsies, and tissue biopsies each year for work-up of possible hematologic disorders.

C. Flow Cytometry Laboratory

The Clinical Flow Cytometry Laboratory processed about 5600 specimens in FY 2002, an overall volume decrease of 8% from FY 2001. This was due to decreases in immunodeficiency monitoring and CD34 stem cell counts (decreases of 4% and 34%, respectively). Chronic leukemia/lymphoma immunophenotyping orders remained unchanged, while acute leukemia immunophenotyping orders increased by 17%. Finally, T-cell subset monitoring in organ transplant recipients increased by 12%. Of note, the greatest growth in test orders has been in the most labor-intensive area (leukemia and lymphoma immunophenotyping).

III. Research and Teaching Activities

The academic productivity of the hematopathology group remains solid. Despite increasing clinical service loads, members of our group published numerous papers in peer-reviewed scientific journals, and we continue to be active regionally, nationally, and internationally in hematopathology through invited lectures, participation in educational courses and workshops, and editorial activities with several hematology, hemostasis, flow cytometry, and pathology journals. Members of our group are also involved nationally in setting and maintaining standards for hematopathology practice through involvements in oversight bodies such as the American Society of Clinical Pathology CheckPath planning committee and expert panel in hematopathology, the ASCP matrix committee, the College of American Pathologists hematology and clinical microscopy resource committee, and the executive committees of the Society for Hematopathology and the North American Specialized Coagulation Laboratory Association (NASCOLA).

We currently maintain two ACGME-accredited hematopathology fellowship positions, with provisional approval for a third position. Our group is quite active in the teaching of pathology residents, including participation in formal rotations and several lecturers in the Clinical Pathology Grand Rounds series.

We are also quite active in teaching medical and dental students through involvement in first year histopathology and host-defense sequences, the second year hematology sequence (directed by Dr. Schmaier and co-directed by Dr. Stoolman) and the general pathology course for second year dental students (directed by Dr. Stoolman). In addition, Dr. Stoolman served on two Dean's committees involved in the evaluation and redesign of the Medical School Curriculum (Curriculum Redesign Committee and the Abnormal Organ Systems Task Force).

This year we began an affiliation with the medical technology program at Ferris State University. To date this new affiliation has been quite successful. We have received excellent feedback from the students rotating through the laboratories, and this new program has enhanced our recruiting efforts during a time of critical shortage of medical technologists.

We have also focused on providing a regular schedule of continuing education (“in service”) lectures for the laboratory staff. Dr. Ric Valdez has successfully coordinated this series which features talks given by pathology residents and faculty.

IV. Future Goals for the Combined Hematopathology Laboratories

We continue to monitor and update the technology in the laboratories. We plan to acquire new hematology analyzers with expanded automated analytical capabilities by the end of calendar 2003. We will automate the preparation of flow cytometry samples with the acquisition of robotic prep stations in the next few months, and we also plan to acquire new flow cytometers by 2004. All of these planned upgrades will continue our past trend toward significantly increased productivity despite consistent increases in clinical testing volume.

We also plan to develop and refine our testing menus to meet clinical demand. In the coagulation laboratory, our goals include development of a chromogenic assay for prekallikrein (the success of this effort may depend on the availability of a commercial source for an *in vitro* prekallikrein activator), completion of on-going re-analysis of platelet function testing with the addition of new agonists (arachidonic acid, thrombin), development of the ecarin clotting time assay to monitor hirudin and argatroban anticoagulant therapy, and development of new antigen assays for total and free Protein S. In the hematology laboratory, we will continue trying to optimize our automated and manual differential count policies, including the probable implementation of automated absolute neutrophil counts as a stand-alone order. Additional new test offerings in the hematology laboratory (including the possibility of extended automated differential counts) may depend upon the planned eventual implementation of new automated analyzers. Likewise, our flow cytometry service will likely be greatly enhanced by the eventual acquisition of new instruments.

We also plan to continue and enhance our educational mission with the training of three hematopathology fellows, continued integration of pathology residents and fellows into the operation of the combined laboratories, and to hopefully recruit a post-doctoral fellow in Clinical Pathology to educate in clinical and research coagulation testing.

William G. Finn, M.D.
Director, Hematopathology

Bertram Schnitzer, M.D.
Director, Hematopathology Fellowship Program

Charles W. Ross, M.D.
Director, Flow Cytometry

Lloyd M. Stoolman, M.D.
Co-Director, Flow Cytometry

Alvin Schmaier, M.D.
Director, Coagulation Laboratory

HISTOCOMPATIBILITY AND IMMUNOGENETICS LABORATORY

**DEPARTMENT OF PATHOLOGY
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CLINICAL ACTIVITIES:

Clinical activity of the Histocompatibility Laboratory remains stable, making the Laboratory one of the ten busiest in the United States.

DNA-based typing is the primary technique used for the determination of class I HLA and class II HLA alleles. The extent of Class I and Class II HLA antibody screening continues to increase as does the number of recipient/donor crossmatches performed annually. The laboratory has begun the process of validating flow cytometry technology for HLA Class I and Class II antibody screening. Dr. Riccardo Valdez continues to devote a portion of his professional effort in the area of histocompatibility and immunogenetics, working toward ASHI certification as a laboratory director

TEACHING ACTIVITIES:

Ms. Cynthia Schall, the Laboratory Supervisor, and other members of the Laboratory were involved in the teaching activities of the Laboratory and were effective in their work. Laboratory personnel were involved in the instruction of pathology residents, allergy fellows, renal fellows, and postdoctoral candidates from the Department of Hematology. Dr. Baker has continued to serve as a consultant and plays an active role in ASHI. Cynthia Schall was again involved in teaching review courses at ASHI, Henry Ford Hospital, and the University of Michigan. She also oversaw the teaching activities for residents in the Laboratory. Dr. Valdez initiated a monthly journal club/literature review for the Laboratory staff and residents.

NEW GOALS:

The goal for the Laboratory is to continue address the demand for more complex services from the transplant programs which have become more active in their clinical and basic research activities. Dr. Valdez will continue to develop his expertise in tissue typing and will participate in the teaching programs.

Jeffrey S. Warren, M.D.
Director, Division of Clinical Pathology

Riccardo Valdez, M.D.
Clinical Assistant Professor

CLINICAL IMMUNOPATHOLOGY LABORATORY

DEPARTMENT OF PATHOLOGY ANNUAL REPORT

1 JULY 2001- 30 JUNE 2002

I. OVERVIEW:

The Immunopathology Laboratory performed more than 65,000 analyses in 2001-02. Anthony A. Killeen, M.D., Ph.D. and John Lowe, M.D. provided invaluable service to the laboratory in the interpretation of protein electrophoresis studies. Kent Johnson, M.D., Paul Killen, M.D., Ph.D., and Dr. Killeen also provided coverage of anti-neutrophil cytoplasmic antibody (ANCA) and anti-GBM studies.

II. CLINICAL SERVICES:

Integration of clinical immunopathology testing into the Chemistry Section continued to progress. New procedures were implemented in the protein electrophoresis area, in the analysis of antibodies to extractable unclear antigens, and in the measurement of several individual analytes previously measured by nephelometry.

III. RESEARCH AND DEVELOPMENT:

The Laboratory supported clinical studies of the effects of cytotoxic/immunosuppressive drugs on IgG, IgA and IgM as well as IgG subclass concentrations in lupus patients and in serum banking in conjunction with Dr. Joseph McCune (Department of Medicine, University of Michigan). Several commercially-financed methods and instrument evaluations were also carried out. These studies involved a new method for detection of antibodies to extractable nuclear antigens and antineutrophil cytoplasmic antibodies.

IV. QUALITY ASSURANCE:

The laboratory actively participated in the Division-wide utilization management program.

V. TEACHING/PROFESSIONAL:

Residents, M4 medical students, and medical technology students from Eastern Michigan University rotated through the laboratory. Clinical Pathology Grand Rounds included immunopathology presentations by Dr. David Keren (Warde Medical Laboratory, Ann Arbor), and Dr. Warren (see individual faculty report). Drs. Warren and Keren continued a weekly series of didactic sessions entitled "Current Topics in Immunopathology". Other professional activities of faculty and staff in the laboratory are summarized under individual reports.

Jeffrey S. Warren, M.D.
Director, Clinical Immunopathology Laboratory

GENERAL PATHOLOGY

**ELECTRON MICROSCOPY SERVICE
DEPARTMENT OF PATHOLOGY - ANNUAL REPORT
1 JULY 2001 - 30 JUNE 2002**

In the past 8 years there has been a 57% increase in the number of cases processed by the electron microscopy lab (an additional 305 cases per year compared to 1994-95). Despite this increase there has been no increase in the number of staff assigned to the electron microscopy service, and a decrease in the commodity cost since we are no longer producing photographic prints. This highlights the wise investment by the Department in the new electron microscope with its state-of-the-art digital technology.

The table below indicates the volume of cases processed by the electron microscopy service during the past academic year. The % increase is relative to the 1994-95 year. As can be observed, both the renal cases as well as the nerve and muscle cases had a significant increase. It is also informative to compare the workload per FTE for the electron microscopy service at the University of Michigan compared to other academic institutions. A recent survey of 12 other academic institutions indicates that the average workload is 252 cases per FTE, while the University of Michigan's workload is 522 per FTE. These numbers are even more remarkable since several of these other institutions have the pathologist perform the work on the electron microscope, while at the University of Michigan all this work is performed by the technical staff.

	94-95	97-98	98-99	99-00	00-01	01-02	% increase
Nerve/Muscle	252	258	275	290	323	397	58%
Renal	256	320	349	379	372	390	52%
Other	23	55	100	105	66	49	113%
Total	531	669	724	774	761	836	57%

The table below displays a breakdown of the cases. Inside cases are from University Hospital patients while outside cases are from hospitals and laboratories outside the hospital. The held cases represent those cases where it was decided not to proceed with additional processing. Thin sections indicate that the tissue was processed completely and the digital images submitted for diagnosis to the pathologist.

CASE TYPE	TOTAL		HELD		THICK		THIN	
	Inside	Outside	Inside	Outside	Inside	Outside	Inside	Outside
RENAL	180	216	39	30	138	189	121	173
NEURO	191	199	115	119	79	78	78	71
OTHER	37	13	14	3	23	9	12	8
RESEARCH	0	0	0	0	0	0	0	0
TOTALS	408	428	168	152	240	276	211	252

The electron microscopy lab also assists with nerve teasing. This is a labor-intensive effort that frequently requires 8 hours of time. Nerve teasing is done in order to prepare the tissue for optimal examination by the neuropathologist. Additionally, the technical personnel from the electron microscopy suite spend 2 days per week assisting in the immunohistochemistry lab. This reassignment of personnel has resulted in overtime in order to complete the workload of the electron microscopy service.

Daniel G. Remick, M.D.
Director, Electron Microscopy Service

M-LABS

**DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002**

I. MISSION:

MLabs is the University of Michigan Health System's reference laboratory program, established in 1985. MLabs offers the high quality reference laboratory services and other resources of the Department of Pathology laboratories to hospitals, clinics, other institutions, and physician offices. MLabs mission is to ensure that the Department of Pathology laboratories: (1) remain financially strong, (2) receive sufficient laboratory specimens for teaching, training and research programs, and (3) to encourage increased productivity of the laboratory staff.

II. CURRENT STATUS

Since its origin, the MLabs program has experienced continuous growth, most notably since 1994 at which time the University Hospital chose to increase resources devoted to it. Gross billings have increased fourfold in the last four years.

MLabs currently provides full anatomic pathology coverage and esoteric clinical laboratory services to one hospital and to the University of Michigan Health Service. MLabs is the primary reference laboratory and provides full esoteric laboratory testing to another 13 hospitals in Michigan and northern Ohio. MLabs does esoteric testing for a regional medical laboratory and a local pharmaceutical firm. MLabs also now provides daily courier service and receives laboratory testing from approximately 100 physician offices/clinics and a nearby correctional facility.

III. GOALS:

1. To generate increased revenue and decreased unit operating cost of the University of Michigan Hospitals Clinical Laboratory System by outreach testing for:
 - Reference laboratory services to hospitals.
 - Group Practices.
 - Physicians offices.
 - Managed care organizations.
 - Specific esoteric services such as renal biopsies, molecular diagnostics, cytogenetics, and flow cytometry, and other "centers of excellence".
2. Develop and participate in hospital laboratory networks to:
 - Compete effectively for managed care laboratory testing.
 - Reduce costs through test sharing and consolidation.

3. Through our outreach efforts, to build bridges to other institutions that will facilitate working arrangements between these institutions and other branches of the University of Michigan Health System.
4. To support the mission of the University of Michigan Hospital System by providing for outpatient laboratory services to M-Care through a network or networks of hospital laboratories which will be potential M-Labs clients.

IV. GROWTH

- In FY2002, MLabs added 13 new physician offices and specialty service practices to our client list. The majority of these were related to our contract to provide coverage to M-Care patients. Some were for specialty services, and a few were UMHS acquired practices.
- Two new hospital full reference laboratory accounts, one a hospital in northern Ohio, the other, a health alliance composed of several small hospitals in southeastern Michigan.
- Two contracts for services were terminated, one because of closure of the hospital.
- MLabs submitted one proposal to a prospective new client during FY2002 which was rejected.
- One business opportunity was rejected by MLabs because the Department of Pathology could not provide the services which were requested.

V. BILLING ACTIVITY:

- Gross billings for anatomic pathology increased by 17% and those for clinical pathology increased by 5%. Total combined expected revenue from billing increased by 12% from last year.

VI. MANAGED CARE ACTIVITIES:

In the last four years, MLabs has contracted with M-Care for provision of outpatient lab services, first to its Medicare members, and later for members enrolled in M Care's commercial and Medicaid products. MLabs subcontracted much of the work to M Care's provider hospital labs with benefits to hospitals and patients. These contracts are capitated, which will result in considerable savings to M-Care over its previous fee for service contracts for these lab services.

We have successfully implemented our renegotiated contract of 4/1/01 with M Care to provide outpatient laboratory services for all groups and products for M Care's commercial and Medicaid products. M Labs prepares quarterly QA reports on lab services for M Care's QA department and have conducted a Physician Satisfaction Survey for M Labs subcontracted providers and reported the results to M Care. We assist M Care with resolution of laboratory service issues. We are actively engaged in contracting for delivery of HEDIS data for M Care to assist them in meeting requirements of NCQA and other certifying entities.

VII. NETWORK ACTIVITY:

In the past several years, hospitals throughout the country have been forming networks in order to cope with the evolving demands of a changing health care system including intense cost cutting by third party payors, reduction in inpatient laboratory testing, competition from commercial laboratories, and carve out of outpatient laboratory services (to large independent labs) from managed care contracts. The formation of laboratory networks gives hospital labs the geographic coverage which allows them to successfully compete in a managed care environment as well as to decrease unit costs and increase revenue streams through outreach activities.

MLabs has been positioning itself to deal with an increase in managed care testing by playing a key role in two laboratory networks. Great Lakes Laboratory Network (GLN) consists of 28 hospital laboratories, predominantly in the western and northern parts of Michigan; Joint Venture Hospital Laboratories (JVHL) has grown to include 9 equity members including UMHS, and 72 participating member laboratories located in Michigan. JVHL has contracts with 14 managed care organizations including Blue Care Network. M Labs is represented on the Executive Committee.

VIII. PROSPECTS:

Looking ahead, we foresee an increasingly competitive market for outreach and esoteric laboratory testing. We are already experiencing fierce competition in the hospital reference laboratory market from increasingly consolidated large independent laboratories with a national presence who offer a broad range of esoteric testing at extremely competitive prices. Purchasing agreements among groups of hospitals and affiliations/consolidations among groups of hospitals may also dictate their use of reference laboratories other than MLabs.

In the next few years, MLabs will focus its efforts on maintaining and increasing its existing hospital client base. This will require some reduction in our pricing, some broadening of our test menu, and continued efforts to interface the Department of Pathology's information system with client hospital information systems. We may also enter into arrangements with client hospitals where we would provide some management of their outreach programs.

Our recently much increased physician office client base will require efforts to continue to make our services run smoothly. In addition to the managed care work contracted to MLabs, we will focus our efforts on obtaining the discretionary (pull-through) laboratory work from these physician clients.

MLabs plans to increase our efforts significantly in marketing specialty (niche) areas such as dermatopathology, renal pathology, cytogenetics, molecular diagnostics, neuropathology, hematopathology, and flow cytometry. We will continue our efforts to try to obtain esoteric laboratory testing from the two hospital laboratory networks (JVHL and GLM) to which we belong. Other areas of potential growth are laboratory work from clinical trials.

IX. IMPEDIMENTS:

As other hospital labs develop increasingly complex testing capabilities, the University of Michigan Clinical Laboratories must be increasingly innovative to bring more complex testing in-house in order to have a sufficient menu of complex testing to successfully compete in the hospital reference laboratory market. Investment in additional resources, personnel and space will be necessary if M Labs

is to be able to accommodate the increased demand for esoteric testing where we have special expertise. So far, recently, additional resources have not been made available stifling growth in these areas. In addition, cost constraints have worked to reduce the scope and frequency of esoteric testing. If this trend continues, it would produce a downward spiral of reduction in volume leading to increased unit costs, leading and reduction in volume, etc.

Prepared by Eugene M. Silverman, M.D.

PATHOLOGY RESEARCH MICROARRAY LABORATORY**DEPARTMENT OF PATHOLOGY
ANNUAL REPORT****1 JULY 2001- 30 JUNE 2002****I. OVERVIEW:**

The Pathology Research Microarray Laboratory was established in 1999-2000 as part of the larger Microarray Network at the University of Michigan Medical School. This array facility is in addition to the one in the Cancer Center which is largely devoted to genetic analysis of solid tumors from humans. DNA microarray analysis is a powerful, emerging technology allowing for detailed gene expression studies of cell lines, animal models, and tissues (including pathologic specimens). With the recent sequencing of the entire human genome, it may soon be possible to monitor gene expression on a comprehensive, global scale as opposed to focusing on one gene at a time. Not only will this technology have an obvious application in the basic sciences, it has the potential of impacting the treatment and diagnosis of patients. As Pathology is a discipline comprised of both scientific investigation and clinical diagnosis, it is imperative that the Department play a role in the use and development of this technology. Clinical Pathology, in particular, has the opportunity of utilizing microarray technology to develop novel diagnostic and prognostic biomarkers.

The Pathology Research Microarray Laboratory functions to support the current and future research activities of the Department as well as Interdepartmental Programs. The primary focus of this facility is in three areas important in the study of human pathology including 1) inflammation, 2) apoptosis/cell death and 3) cancer. These studies are accomplished using characterized animal models as well as with human specimens and cell lines.

II. RESEARCH AND DEVELOPMENT:

While DNA microarray analysis is a potent technique to explore complex and interlocking systems, it is clear that this technology is in its infancy and that there are formidable problems in dealing with the multitude of data generated. Dr. Arul Chinnaiyan has carefully developed our Research Microarray Laboratory, beginning 2 years ago when he visited the Brown and Botstein laboratories at Stanford in order to talk with experts and determine the best microarray system to meet our needs. Our microarray methodology is based primarily on techniques learned at the 1999 Cold Spring Harbor Workshop on DNA Microarrays attended by Dr. Chinnaiyan and taught by Drs. Joseph DeRisi (UCSF), Michael Eisen (Stanford), and Patrick Brown (Stanford), all of whom are renowned experts in the field.

Beginning October of 1999, the Lab has been assembling the equipment, clone sets, and supplies necessary to produce high-density cDNA microarrays including a robotic arrayer, microarray scanner, PCR machines, and liquid handling instrumentation. The Lab has successfully generated a 20K human cDNA chip, 10K rat cDNA chip and a 5K mouse cDNA

chip. All cDNA microarrays have undergone validation and quality control and are currently being functionally tested using samples obtained from various labs including those of Dr. Peter Ward (Pathology), Dr. Sem Phan (Pathology), Dr. N. Inohara (Pathology), Dr. Dan Remick (Pathology, protein microarrays), Dr. William Finn (Pathology), Dr. Kenneth Pienta (Internal Medicine), Dr. Marc Lippman (Internal Medicine), Dr. Andrew Lieberman (Pathology), Dr. Evan Keller (Pathology), Dr. Mark Rubin (Pathology) and Dr. Chinnaiyan (Pathology). DNA microarray projects currently underway involve profiling global gene expression in apoptosis, inflammation, sepsis, prostate cancer, and breast cancer.

In addition to establishing DNA microarrays in the laboratory, a large effort has also been placed on devising a system to monitor protein levels and activity in a high-throughput fashion. While various genome scale methodologies to identify variations in DNA and RNA exist, an analogous “biochip” to explore protein function has been difficult to implement for various reasons. In this Lab we plan to establish a platform for the massively parallel analysis of protein levels, interactions, and function. One area for which we will implement both DNA and protein microarray technology is the development of novel cancer and inflammation biomarkers. Dr. Dan Remick and Dr. Kent Johnson are both working with the Microarray Lab in order to fabricate and test protein/antibody microarrays for their respective areas of interest.

The following manuscripts include data made possible by the Microarray Lab:

1. Chinnaiyan, A. M.*, Huber-Lang, M., Kumar, C., Barrette, T.R., Shankar, S. Sarma, V.J., Ward, P.A. (2001). Molecular Signatures of Sepsis: Multiorgan Gene Expression Profiles of Systemic Inflammation. *American Journal of Pathology* 159, 1199-1209. * Corresponding author.
2. Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, Pienta, K., Rubin, MA, Chinnaiyan, A.M. (2001) Delineation of prognostic biomarkers in prostate cancer. *Nature* 412(6849):822-6.
3. Sreekumar, A., Nyati, M.K., Varambally, S., Barrette, T.R., Ghosh, D., Lawrence, T.S., Chinnaiyan, A.M. (2001) Profiling of Cancer Cells Using Protein Microarrays: Discovery of Novel Radiation-Regulated Proteins, *Cancer Research*, 61, 7585-7593.
4. Ghosh D., Chinnaiyan, A.M. (2002) Model-based Clustering of Gene Expression Data from Microarray Experiments, *Bioinformatics*, 18(2):275-286.
5. Kumar-Sinha C, Varambally S, Sreekumar A, Chinnaiyan AM. (2002). Molecular cross-talk between the TRAIL and interferon signaling pathways. *J Biol Chem* 277:575-585.
6. Rhodes, D.R., Barrette, T.R., Rubin, M.A., Ghosh, D., Chinnaiyan, A.M. (2002). Meta-analysis of Microarrays: Interstudy Validation of Gene Expression Profiles Reveals Pathway Dyregulation in Prostate Cancer. *Cancer Research*, 62: 4427-33.
7. Chay, C.H., Cooper, C.R., Gendernalik, J.D., Dhanasekaran, S.M., Chinnaiyan, A.M., Rubin, M.A., Pienta, K.J. (2002) A functional thrombin receptor (PAR1) is expressed on bone-derived prostate cancer cell lines. *Urology*, In Press.
8. Xin, W., Rhodes, D.R., Ingold, C., Chinnaiyan, A.M., Rubin, M.A. (2002) Dysregulation of the Annexin Protein Family is Associated with Prostate Cancer Progression. *American Journal of Pathology*, In Press.

9. Dash, A. Maine, I., Dhanasekaran, S.M., Barrette, T.R., Chinnaiyan, A.M., Rubin, M.A. (2002) Changes in Differential Gene Expression Due to Warm Ischemia Time of Radical Prostatectomy Specimens. *American Journal of Pathology*. In Press.
10. Varambally S., Dhanasekaran, S.M., Barrette, T.R., Sanda, M.G., Ghosh, D., Pienta, K.J., Sewalt, R.G.A.B., Otte, A.P., Rubin, M.A., Chinnaiyan, A.M. (2002). The Polycomb Group Protein EZH2 is Involved in Prostate Cancer Progression. *Nature*, In Press.

The Pathology Microarray Lab has supported the following grant applications by providing preliminary gene expression analyses:

1. RO1, NIA Prostate Cancer Harbinger Genes, P.I. M. Rubin
2. ACS Beginning Investigator Grant, Molecular Classification of Prostate Cancer, P.I. A. Chinnaiyan
3. R01, Protective Effects of anti-c5a in Sepsis, P.I. P. Ward
4. R01, Lung Injury by Oxygen Metabolites, P.I. P. Ward
5. Microarray Supplement, Sepsis Profiling, P.I. P. Ward
6. U of M SPORC in Prostate Cancer, P.I. K. Pienta
7. DOD grant, Biological Differences between prostate cancer cells that metastasize to the bone versus soft tissue sites, P.I. K. Pienta
8. Breast Cancer Research Foundation, "Transcriptome Analysis of the EGFR Receptor in Breast Cancer, The Breast Cancer Foundation", PI M. Lippman
9. P01, Program Project on Prostate Cancer Bone Metastases, P.I. E. Keller
10. RO1, The Role of Polycomb Group Proteins in Prostate Cancer, P.I. Chinnaiyan
11. Glue Grant, U54 GM64351 Inflammation and the Host Response to Injury; P.I. D. Remick

The Pathology Microarray Lab can now produce 20K human cDNA arrays, 10K rat cDNA arrays, and 5K mouse cDNA arrays

A protein microarray platform is being optimized for use with clinical specimens and cell lines.

III. FUTURE GOALS:

The future goals of the Pathology Microarray Lab in the next calendar year include:

1. Continue to support the research funding applications of Pathology faculty with preliminary data and bioinformatics expertise.
2. Continue to publish data using microarray technology in peer-reviewed journals to establish the Department in the fast moving field of genomics/proteomics.
3. Expand the rat, mouse, human DNA chips to include additional cDNA clones. Ultimately, we would like to develop a chip that can monitor the entire expressed genome.
4. Develop and utilize protein microarray technology to answer biologically important questions
5. Train post-doctoral fellows and students in making and using microarrays.
6. Develop a unified bioinformatics platform for the analysis of DNA microarray, tissue microarray, protein microarray and clinical/pathology data.

7. Position our resources and expertise such that we can take advantage of opportunities in the emerging field of “clinical genomics”.

IV. TEACHING/PROFESSIONAL:

Terry Barrette, the Laboratory manager, has played an important role in setting up our microarray database and data analysis programs. Dr. Chandan Kumar, a post-doctoral fellow in the lab, was instrumental in developing our cDNA microarray system as part of his training. Arun Sreekumar, a Research Fellow, was involved in developing the protein microarray platform. Other postdoctoral fellows in the Department of Pathology that have received training in DNA or protein microarrays include: Saravana Dhanasekaran, Sooryanaryana Varambally, Ira Maine (mentored by M. Rubin), Atreya Dash (mentored by M. Rubin), Monzy Thomas (mentored by A. Lieberman), Eric Albright (mentored by P.Ward), and Thomas Neff (mentored by P. Ward). Similarly the following medical and graduate students received training in microarrays, microarray analysis and or QRT-PCR: Dan Rhodes (1st year medical student), Scott Tomlins (MSTP), Qi Cao (Pathology), Jianjun Yu (Bioinformatics), Chad Creighton (Bioinformatics), Patrick Lester (Pathology), and Srikanth Kidambi (Chemistry). The Microarray Lab hosted two international visiting scholars to train in microarray technology including Utpal Tatu (Indian Institute of Sciences) and Tanuja Teni (Cancer Research Institute).

Arul M. Chinnaiyan, M.D., Ph.D.
Director, Pathology Research Microarray Laboratory

PATHOLOGY DATA SYSTEMS
DEPARTMENT OF PATHOLOGY
ANNUAL DEPARTMENTAL REPORT
1 JULY 2001 - 30 JUNE 2002

The following is a list of some of the major accomplishments of Pathology Data Systems (PDS) personnel during the past academic year, July 1999 through June 2000:

Conversion of Cerner PathNet Classic to the Millennium system

- Continuing and vigorous efforts throughout the year on the part of PDS personnel as well as personnel in all of the laboratories to add final functionality to the software and test the system such that it can be installed in late 2002 or early 2003

Hardware/PC installation

- Installation of a SAN which is a networked storage facility for the Millennium system; it is currently running the Millennium live-feed and, when the Millennium system goes live, will provide all of the mass storage for the system; drives are being shared with Radiation Oncology which will also act as a backup facility
- Implemented a contemporary data purge strategy; conversion from a 9-track to DLT storage media
- Planned, purchased, and initialized laptop computers with wireless access to the Internet for all Pathology house offices
- Working with MCIT, implemented a SAN storage system for the DataGate interface engine

Software upgrades/new projects

- VMS upgrade (the operation system for PathNet)
- Installation of IceCap/BlackIce which is computer security software
- Final testing phase of a "future orders" applications development, web-based, for our healthcare centers
- Working with MCIT, implemented a fail-over strategy for the DataGate interface engine
- Developed a POCT application using RALS software to support point of care testing, including an ADT interface to the servers
- Validated the pathology results portion of the CareWeb/CDR II project

Network issues

- Ongoing progress on the migration of the Novell tree

Physical renovation

- Renovation of the front office space of PDS
- Renovation of the air-conditioning unit in the PDS machine room

Educational Activities

- Planned and supported the twentieth annual Symposium on Automated Information Management in The Clinical Laboratory (AIMCL) was presented at the Towsley Center on May 22-24, 2002, in the Towsley Center..

Bruce A. Friedman, M.D.
Laboratory Director

**UNIVERSITY OF MICHIGAN/PFIZER
JOINT COLLABORATIVE RESEARCH PROGRAM**

**ANNUAL REPORT
1 JULY 2001 – 30 JUNE 2002**

I. Introduction

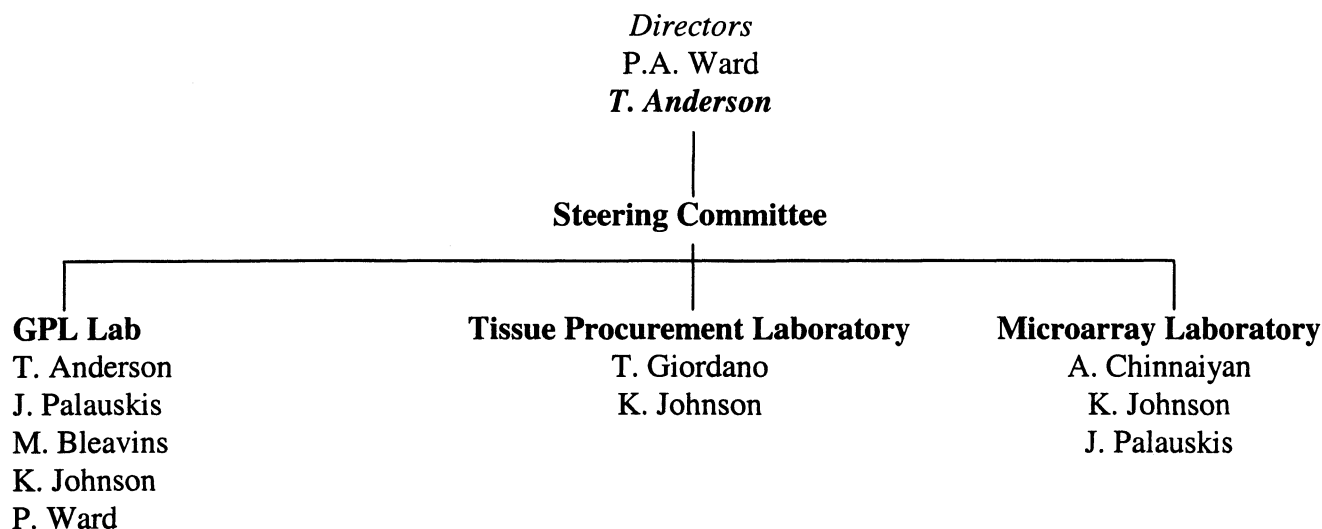
The Genomic Pathology Laboratory (GPL) was established to apply state-of-the-art molecular biology techniques and genomic information to the understanding of molecular mechanisms of disease pathogenesis and drug toxicity and metabolism, and the role of molecular approaches in the drug discovery process. The operation of this laboratory, located on the University of Michigan Medical Campus, was initiated in September 1998 and represented a scientific joint venture between the Department of Pathology and Experimental Toxicology at the former Parke-Davis and the Department of Pathology of the University of Michigan Medical School.

An agreement with Pfizer to continue and expand the focus of this interaction was put into place in 2000. The chief scientific mission of this interaction is to enhance scientific activities that benefit both Pfizer and the University of Michigan.

As shown in Figure 1 besides continuing support for the GPL laboratory, the new agreement also provides Pfizer scientists with access to the University of Michigan Tissue Procurement Facility that has allowed Pfizer scientists globally to have access to human tissues and biofluids from normal and disease states. This access is linked to access to anonymized relevant clinical data as well as to clinical scientists at the University of Michigan with research interests in these disease processes. Thus, this agreement also allows for collaborations between scientists at Pfizer with clinical and basic science researchers at the University of Michigan.

Figure 1

Components of the University of Michigan – Pfizer Collaborative Research project and principal scientists



Finally, this new agreement allows Pfizer scientists access to new technologies in the Department of Pathology at the University of Michigan. Specifically, as detailed below this includes access to custom RNA and protein microarray technologies currently in place in the department as well as access to Pathview software developed in the department which allows for the analysis of large amounts of data from array platforms which can be linked to an Oracle database. In conjunction with this microarray laboratory a proteomic facility has been added to the functions of the GPL laboratory. Utilizing state of the art SELDI-TOF protein expression profiling in conjunction with the RNA and protein expression technologies currently in place in the Department of Pathology will allow for precise characterization of proteins upregulated in disease processes in animals and humans. Details on collaborations on all three components of the agreement are detailed below.

II. Staff

Co-directors: Peter A. Ward, M.D.
Tim Anderson, D.V.M, Ph.D.

Steering Committee: Peter A. Ward, M.D.
Tim Anderson, D.V.M, Ph.D.
Michael R. Bleavins, Ph.D.
Kent J. Johnson, M.D.
Anthony Killeen, M.D., Ph.D.
Vidya Sarma, Ph.D.
Pamela Heard, Ph.D.
Thomas Giordano, M.D.
Joseph D. Paulauskis, Ph.D.

Additional Scientists: Steven K. Duddy, Ph.D.
 Tage Carlson, Ph.D.
 Marielle Delnomdedieu, Ph.D.
 Birong Liao, Ph.D.
 Douglas F. Gibbs, Ph.D.
 Richard Lieberman, M.D.
 Arul Chinnaiyan, M.D., Ph.D.
 Xianxian Zheng, Ph.D.
 Roscoe Warner, Ph.D.
 Ren-Feng Guo, M.D.

Postdoctoral Fellows: Eric Albrecht, Ph.D.
 Rabih Slim, Ph.D.
 Jayne Reuben, Ph.D.
 Eric Olle, Ph.D.

Graduate Student: Tommy Hlaing (Ph.D. completed in May 2002)

New Scientist positions: As part of this expanded agreement two staff positions were approved by Pfizer for studies dealing with the study of vasculitis in animal models and humans. The first position is that of a postdoctoral fellow. This position was recently filled by the recruitment of Dr. Eric Olle from Michigan State University. Dr. Olle has extensive experience with RNA and protein expression technologies and will work with Drs. Johnson and Paulauskis on developing the RNA and protein expression methods in the affected vessels in the animal models. The second position approved for funding is that of a research scientist position in the GPL laboratory. This scientist position will be occupied by Dr. Ren-Feng Guo, M.D. who is currently a research scientist in the Department of Pathology. Dr. Guo has extensive experience in animal models and RNA expression of inflammatory mediators from affected tissues. For this project Dr. Guo will link the animal models of vasculitis with the human vasculitis biopsies and will compare the RNA and protein expression from the affected vessels. He will also work with Dr. Johnson is coordinating these tissue finding with microarray and proteomic studies from blood and urine samples from vasculitis patients and animals.

III. Project Summaries for the GPL Laboratory

Introduction: The GPL laboratory has historically focused primarily on pharmacogeneomics with the laboratory having state of the art instrumentation and techniques for high-throughput genotyping, SNP validation and allele frequency determination assays. Also included in this function was the development of quantitative PCR amplification of gene expression using a TaqMan system. The laboratory has also developed expertise in laser capture microdissection (LCM) and genomic amplification of target tissues.

Finally, with support from Pfizer, the laboratory has recently added a proteomic capability. The laboratory has acquired new instrumentation such as SELDI-TOF that allows for the high-throughput analysis of protein expression in biofluids and tissues. In conjunction with such techniques as LCM this proteomic analysis will extend our ability to analyze disease processes to include protein expression in addition to gene and RNA expression. This will allow for a complete molecular characterization of a

disease process such as vasculitis. Summaries of existing projects in the GPL laboratory are detailed below.

A. *Regulation of Alanine Aminotransferase Gene Expression in Drug-induced Liver Toxicity* (P. Heard, M. Bleavins, J. Paulauskis)

The liver is sensitive to drug-induced injury because of its central role in metabolism and its physiological structure. One sensitive marker for hepatocellular damage is the elevation of serum alanine aminotransferase (ALT), which has been associated with the hepatotoxicity caused by many classes of drugs. The goal of this project is to investigate the molecular mechanisms involved in serum ALT increase during drug induced liver toxicity. Using rat and human *in vitro* models, the studies are designed to understand/determine ALT gene expression at both the transcript and protein levels. To date, data accumulated implicates translational, rather than transcriptional, control of the expression of this gene. Understanding the mechanisms involved with regulation of this gene will prove important in determining the signal transduction pathways involved in the cellular response to drugs.

B. *Polymorphisms in the Human Peroxisome Proliferator-Activated Receptor α Gene* (N. Elsis, S. Myrand, M. Shi, M. Bleavins, P. Heard, J. Paulauskis)

These studies have identified two new polymorphic sites within the protein-coding region of the PPAR α gene. Our goal is to extend these observations to a larger population in order to determine allelic frequencies by race in several human populations. PPAR α regulates genes involved in lipid metabolism and inflammation making it a candidate gene for atherosclerosis and ischemia heart disease (IHD).

C. *Microarray Analysis of Inflammation in Lung Injury and Vasculitis* (K. Johnson, R. Warner, J. Paulauskis, S. Myrand).

These studies revolve around the upregulation of inflammatory mediators in angiocentric lung injury with vasculitis. The goal is to characterize the upregulation of these mediators using a custom microarray chip for RNA expression measuring over 400 nucleotides in the mouse. This custom chip was developed jointly by Pfizer and UM scientists and has been found to be very sensitive in measuring fold increases in RNA expression of mediators in these models. These studies in the mouse will be compared with vasculitis in other sites such as the skin and ultimately compared with the expression pattern in human vasculitis.

D. *Role of Metalloproteinases in Acute Inflammation* (K. Johnson, R. Warner, J. Paulauskis)

These studies look at the role of proteases, specifically metalloproteinases in the pathogenesis of acute inflammation, specifically acute lung injury. Previous studies have identified that animals deficient in these proteases have a defect in leukocyte migration which is associated with a reduction in the subsequent lung injury. In conjunction with the GPL laboratory the studies are focusing on microarray analysis of lung tissue and alveolar macrophages to determine what differences are present in terms of the gene expression profiles between the normal wild-type animals and animals deficient in the proteases. To date we have identified several differences in gene expressions between these groups and we are verifying these findings by repeating the analysis with our custom microarray chips as well as assessing protein expression.

E. *Effects of Metalloproteinases Inhibitors on Fibroblast Proliferation* (K. Johnson, J. Varani, M. Bleavins)

Metalloproteinase inhibitors are a major focus of Pfizer for several disease processes including arthritis. A known side effect of many of these inhibitors is joint fibroplasia. These studies were undertaken to determine which of the MMP inhibitors *in vivo* would cause fibroblast proliferation and increased collagen production. Using rat, marmoset, cynomolgus monkey, and human fibroblasts we found that

some of the MMP inhibitors had the ability to induce fibroblast proliferation and increased collagen formation whereas other inhibitors were much less potent in this regard. These studies should provide valuable information when designing MMP inhibitors in order to minimize these proliferative matrix effects.

F. Molecular Mechanisms of Apoptosis (T. Hlaing, P.A. Ward, C. Vincenz).

These studies have identified a new apoptosis-promoting factor, termed DEFCAP. Advanced molecular techniques have been employed to identify the important regions of this protein involved in promotion of apoptosis. This work, which constitutes the bulk of Mr. Hlaing's doctoral thesis, is described in detail in a recent publication in the *Journal of Biological Chemistry*. At present, co-factors that interact with this protein have been identified using the two-yeast hybrid system and the chemical and functional characteristics of these associating proteins are being determined.

G. Molecular Determinants of Sepsis (R.F. Guo, M. Huber-Lang, N. Riedemann, V. Sarma, P.A. Ward and others)

These studies have identified in experimental sepsis in rodents induced by cecal ligation puncture the critical involvement of the complement activation product, C5a. Excessive production of this powerful peptide leads to premature activation of phagocytic cells, especially blood neutrophils. This leads to an inability to assemble on the cell surface the critical enzyme, NADPH oxidase, which is important for oxygen-dependent killing of bacteria by phagocytes. The signaling pathways involved in these aberrant outcomes are currently under study. In addition, reagents are being developed to measure C5a in the plasma of septic animals, the C5a receptor on neutrophils (both with respect to message and receptor protein), and to determine ways in which these events can be blocked *in vivo*.

H. Molecular Mechanisms of Endothelial Cell Activation (E. Albrecht, V. Sarma and P.A. Ward)

These studies are designed for an understanding of endothelial cell activation using cDNA microarrays. For the time being, human umbilical vein endothelial cells are used as the targets of activation, employing addition of TNF α , lipopolysaccharide, C5a or the membrane attack complex (C5b-9). Dr. Albrecht is the lead in these studies. It is anticipated that this information will provide important details regarding endothelial cell activation and predictions of proteins being produced by activated endothelial cells. In turn, we will then move to rodent endothelial cells and by the use of *in vitro* as well as *in vivo* techniques perform analogous studies. This information may be critical understanding endothelial cell activation or vasculitis developing during administration in rodents. These studies could set the stage for new understandings of mechanisms related to development of vasculitis. Dr. Albrecht is a Pfizer sponsored post-doctoral fellow.

I. Molecular Mechanisms of Ischemia/Reperfusion Injury (L. Toledo-Pereyra, V. Sarma, R.F. Guo, P.A. Ward)

These studies are directed toward an understanding of ischemia/reperfusion injury as it directly affects an organ such as liver and secondarily affects other organs, especially the lung. To date, it has been determined that direct ischemia/reperfusion injury of liver requires participation of neutrophils and the availability of all three selectins (L, P and E). These reactions are also associated with production of chemokines and cytokines that are probably involved in the recruitment of neutrophils and their activation. Recent studies involve the use of RNase protection assays to better define gene activation as it occurs in the organ directly or secondarily affected by ischemia/reperfusion. These studies will soon employ microarray analysis for more detailed information about gene activation in these models.

IV. Technologies Available in the GPL Laboratory
Equipment

Fluorescent-PCR based high-throughput genotyping analysis for single nucleotide polymorphisms (*TaqMan* protocol on the ABI 7700)

MALDI-TOF genotyping, SNP validation, and allele frequency determination assays (Sequenom, Inc.)

Real-time quantitative PCR of gene expression (*TaqMan* protocol)

Laser-capture microdissection and genome amplification of target tissues

Microarray spotting and screening / data manipulation

SELDI-TOF protein expression profiling

Hardware and software to support bioinformatic applications

Design and Installation of a New Computing Infrastructure for the Genomic Pathology Laboratory

During the past year, the entire computing infrastructure for the lab has been updated. New computers have been installed at every desktop. All workstations are now 1.7 GHz Pentium 4 or better with flat-panel displays to save bench space. The Windows 2000 operating system and applications are all installed through drive-imaging technology to facilitate updates and replacements. Conduit and Cat5e wire has been pulled where needed to provide dedicated 100 Mbps switched connections to each desktop. For file storage, a central server has been built. It runs the latest Netware operating system and has 400 GB of RAID5 protected drive space. In addition, the Pathview application (which is handling the genomics-array data) is run on 3 dedicated servers: one each for the Oracle Database, the Java Portal, and the Zoom Image server. The servers are housed in the Pathology computer room for environmental and power conditioning. All servers are 1 GHz dual processor or better. An SDLT dedicated tape backup solution has been purchased and should be installed by the middle of July. These improvements should allow for rapid processing and analysis of data collected by the laboratory.

V. Project summary for the Microarray Laboratory Collaboration

(A. Chinnaiyan, M. Rubin, J. Paulauskis, K. Johnson) Supported in part by funds/equipment from Pfizer, the Pathology Microarray Laboratory (directed by Dr. Arul M. Chinnaiyan) has developed a 20,000 element human cDNA microarray as well as a 10K rat cDNA array and a 5K mouse cDNA array. We have also assisted the Pfizer Genomics laboratory in the scanning and primary analysis of custom oligonucleotide microarrays. To handle the wealth of data generated by these genomic scale methodologies we have developed an Oracle-based bioinformatics infrastructure. Furthermore, in a project partially funded by Pfizer (Rubin and Chinnaiyan), DNA and tissue microarrays were used together to define biomarkers of prostate cancer. This work resulted in a number of manuscripts including one published recently in *Nature* (412:822) and one in *JAMA* (287:1662).

In addition to gene expression arrays, The Chinnaiyan Lab and the Pfizer Genomics Lab have been collaborating on the development of a high-throughput microarray platform to measure proteins in tissue extracts and serum. This work stems from a recent publication from the Chinnaiyan Lab (*Cancer Research* 61:7585), whereby antibody microarrays were used to measure proteins in colon cancer extracts. This collaboration will facilitate the rapid development of antibody microarrays ("micro-ELISAs") to measure 100 to over 1000 proteins simultaneously. These human and murine antibody arrays will be used to monitor inflammation- and cancer-related proteins in various animal models (e.g., vasculitis, sepsis) and tissue extracts (prostate and breast cancer). Interrogation of complete signaling pathways will be possible including associated post-translational modifications (e.g., phosphorylation, proteolytic activation). Unlike traditional 2-D gel based proteomics, this systematic approach will allow us to monitor focused pathways in a multiplex fashion.

VI. Project Summary of the Tissue Procurement Facility (K. Johnson and T. Giordano)

The tissue procurement core facility is under the guidance of Dr. Thomas Giordano and the mission is to provide tissue samples as well as biofluids to investigators at Pfizer. Over the past year over 600 blood and urine samples and 200 tissue samples have been identified for Pfizer scientists. Many of the biofluid samples have already been analyzed by scientists at Pfizer, primarily for the NMR collaborative studies. However, samples have also been supplied for proteomic analysis as well. In terms of the human tissues the majority of these samples are currently banked in the tissue facility for future use by Pfizer scientists. However, some tissues samples have already been utilized. This includes normal liver samples for molecular profiling and normal tissues for histology controls (Pfizer, Ann Arbor), ischemic heart tissue (Pfizer, Groton), and osteoarthritis and rheumatoid arthritis tissues for discovery research (Ann Arbor and Groton). Recent requests include samples of brain tissue as well as lung tumors. As part of this agreement anonymized relevant clinical data is provided to investigators. Thus the samples bank has allowed Pfizer scientists to validate emerging technologies using human tissues and biofluids and to compare these findings with animal studies. Specifically, it has provided a valuable resource to develop the NMR metabolomics, gene expression, and proteinomic research areas in PGRD.

VII. Research Directions

A. *Molecular Mechanisms of Human and Animal Vasculitis*

Background - Vasculitis has serious health implications manifested in a variety of disease states. Unfortunately, the term "vasculitis" includes an incredibly large and diverse grouping of pathological syndromes. Classification has focused on the type of vessels affected and by the immune mechanisms involved with the inflammatory response. Most types of vasculitis are thought to be mediated by immune mechanisms, with both immune-complex and cell-mediated immune mechanisms implicated. However, the basic pathophysiologies of vasculitis are unknown in both animals and humans. Due to the serious clinical consequences of vascular disease, coupled with the lack of good diagnostics tools, drugs associated with vasculitis present significant challenges for safe development or therapy. Compounding this problem is the current inability to determine the relevance of vasculitis findings in animal models to the human risk, and the relatively poor mechanistic understanding of human vascular abnormalities. This proposed study will advance identification of vasculitis mechanisms at the molecular level in the tissues and biofluids of humans and animals, and allow us to assess the correlation between animal and human vasculitis.

Proposed Studies - The experiments outlined below combine state-of-the-art screening technologies with hypothesis-driven research. Immediate benefits include better understanding of a poorly characterized disease and identification of safety biomarkers.

1. *Global Gene Expression Profiling of Blood Vessels From Various Human and Animal Tissues.* (K. Johnson and R-F Guo) Laser-capture microdissection (LCM) will be used to precisely isolate specific cell types for mRNA extraction. Initially, protocols for fresh and frozen tissue will be developed followed by development of techniques for paraffin-embedded tissues. Global gene expression in tissue from individuals with and without vasculitis will be profiled using high-density microarrays probed with reverse-transcribed mRNA and amplified signal development. Differentially-expressed genes or gene clusters will suggest signal transduction pathways to be evaluated as well as identifying specific biomarkers of vascular inflammation. Characterization and identification of novel gene products will be performed.

2. *Characterization and Identification of Novel Proteins by Differential Mass Spectrometry and Nuclear Magnetic Resonance (NMR).* (R-F Guo, K. Johnson, and P. Heard) Tissues collected by LCM, and biofluids from individuals and animals with and without vasculitis, will be profiled by two complementary technologies currently in development. Differentially-expressed proteins will be identified using surface-enhanced laser desorption/ionization (SELDI) and by NMR. Data obtained with these technologies will be interpreted in light of microarray gene expression results. Differentially-expressed proteins may reflect signal transduction pathways operative and serve as specific biomarkers of vascular inflammation.

3. *Molecular Analysis of Endothelial Cell Cultures.* (P.A. Ward and J.V. Sarma) The Ward Laboratory is engaged in microarray analysis of gene activation patterns in endothelial cells subjected to a variety of different stimuli. Complementary gene expression work also is on-going within DSE at Pfizer. These studies can be used to establish the profile of potential gene responses within endothelial cells when perturbed. The information may identify proteins that can be searched in both *in vitro* cultures of endothelial cells, as well as *in vivo* areas of vasculitis change. It also will be possible to incubate endothelial cells with compounds of interest to determine the extent these substances cause gene activation in endothelial cells. This strategy could add significantly to understanding mechanisms of endothelial cell perturbation in the setting of vasculitis.

4. *Human and Animal Comparisons of Global Gene and Protein Expression Profiles.* (J. Paulauskis, K. Johnson). Comparison of unique gene products identified from human and animal drug/disease-induced vasculitis, as well as proinflammatory pathways operative, will allow evaluation of the animal models as surrogates for human exposure. Assessing physiologic and histologic characteristics will help identify relevant similarities and differences between the animal and human conditions.

5. *Comparison of gene and protein expression studies with NMR analysis:* (M. Delnomdedieu and K. Johnson) Dr. Marielle Delnomdedieu in collaboration with Dr. Johnson has extensively studied the NMR profile in urine and blood of humans with several disease processes including vasculitis. They have found unique profiles with NMR that differentiate not only normal versus patients with diseases but also distinct profile differences for each disease process. Given this background, we will integrate the NMR finding on patients with the gene and protein expression studies from the same patients. This "linking" of technologies has already been done with a preliminary study and shows great promise in providing specific patterns that distinguish vasculitis from other disease processes.

B. Development and Utilization of PathView Software System (J. Paulauskis, D. Gibbs, K. Johnson, A. Chinnaiyan, R. Lieberman)

University of Michigan PathView is a Web based data repository designed for storing and retrieving medial digital images. Originally developed for Web based storing and view of images generated by the practice of pathology, it has evolved into a core technology which allows integration of clinical, pathology and research data from a variety of disciplines. Backed by Oracle, PathView provides an application that can be utilized for documenting disease in the single patient (for example, digital images of pathology for tumor registry purposes), or it can be scalable to the large volume needs of high throughput research technologies such as gene chip arrays or tissue microarrays (in which a single laboratory tests can generate hundreds of tens of thousands of data points with a single slide).

What makes PathView different than any other current software technology for research purposes is the flexibility of the powerful relational database backbone and the linkage to the clinical data repository of the University of Michigan Health System. Focal points of the database architecture may be directed at a patient, a pathology tissue specimen, a research data point, an image, or diagnosis. Each of these may be worked with independently, or brought together for comparative analysis or statistical calculations. The security features of the Oracle database, along with identification keys independent of patient information, have allowed us to design this application with the utmost in privacy of patients and research data in mind. Consequently, achieving HIPPA compliance is assured.

Over the past year, the University of Michigan Department of Pathology and Pfizer have been evaluating the potential role of PathView in accelerating the collection of appropriate research tissues in our collaborative efforts. Plans are evolving for incorporating PathView into the Department's tissue procurement laboratory. Tissues procured through this facility may be catalogued in the database utilizing diagnostic and anatomic hierarchical codes, with independent links back to demographics and clinical characteristics that generated the tissue. Ultimately, this tissue inventory system would allow searches in which the viewer would direct the search, then be able to view the histologic features of the tissue samples, and select the desired samples for research. PathView will also be used to develop analytical databases for high throughput systems such as the microarray and proteomics collaborations.

C. Modulation of Coagulation/Fibrinolytic Factors during Sepsis (I. Laudes, M. Huber-Lang, R.F. Guo, N. Riedemann, V. Sarma, P.A. Ward and others) Sepsis often results in disseminated intravascular coagulation that can lead to multiple organ failure. Sepsis is also often accompanied with elevation in plasma levels of the complement activation products, especially the anaphylatoxins, C3a, C4a and C5a. Dr. Ines Laudes and others evaluated the relationship between C5a and changes in the coagulation/fibrinolytic systems during the cecal ligation and puncture model of sepsis in rats. Their studies implicate a direct role for C5a in the increased procoagulant activity found during sepsis. Treatment with anti-C5a antibodies significantly reduces changes in sepsis-induced coagulation/fibrinolytic proteins of plasma leading to improved survival in this animal model.

D. Molecular Signature of Sepsis (A. Chinnaiyan, M. Huber-Lang, V. Sarma, P.A. Ward and others). During sepsis a dysregulated system-wide response to microbial invasion is found. DNA microarray was used to explore the diverse multiorgan transcriptional programs that are activated in cecal ligation and puncture induced sepsis in rats. Although genes known to be associated with systemic inflammation were identified many genes not previously linked to the septic response were also elucidated by Dr. Chinnaiyan and others. A global perspective at the molecular level, how an organism responds to infection, may facilitate the development of enhanced detection and treatment modalities for sepsis.

E. *C5a Receptor Expression in Sepsis* (N. Riedemann, R.F. Guo, T. Neff, I. Laudes, V. Sarma, F. Zetoune, P.A. Ward and others) Excessive production of the complement activation product C5a appears to have detrimental effects during the early stages of sepsis. C5a mediates its cognate effects by binding to its receptor (C5aR) which is a G protein-linked seven transmembrane protein. Given the importance of C5a during sepsis not much is known about the regulation of C5aR. Dr. Riedemann and others show that C5aR is markedly up-regulated in the lung, liver, kidney and heart in a mouse model of sepsis by cecal ligation and puncture. This upregulation could be abrogated by the administration of anti-C5aR antibodies resulting in improved survival rates, reduction in serum levels of TNF α and IL-6 and lower organ bacterial counts. Thus, disruption of C5a-C5aR interactions may be therapeutically exploited.

F. *Protective Effects of Anti-IL-6 Treatment in Sepsis* (T. Neff, N. Riedemann, R.F. Guo, I. Laudes, V. Sarma, P.A. Ward) The glycoprotein interleukin-6 plays a key role in the regulation of the inflammatory process. It is also known that IL-6 levels in the serum are elevated during sepsis. Dr. Neff and others show that in a mouse model of sepsis treatment of animals with anti-IL-6 antibody results in significantly increased survival rates accompanied by decreased levels of serum TNF α . The suppression of IL-6 levels at the onset of sepsis may alter the acute inflammatory response with resulting beneficial effects on survival.

G. *Nitric Oxide Synthase Activity in Mouse Dermal and Lung Microvascular Endothelial Cells*. (C. Speyer, P.A. Ward and others) Nitric oxide (NO) appears to play a role in neutrophil-mediated endothelial cell injury. In endothelial cells 2 isoforms of nitric oxide synthase (NOS), iNOS and eNOS generate NO. Dr. Speyer and others determined that iNOS is the main source of NO in microvascular endothelial cells when stimulated with LPS/IFN γ . These studies suggest that the source of NO may differ between microvascular and macrovascular endothelial cells and thus modulate the inflammatory process.

H. *Identification of Single Nucleotide Polymorphism in the Human Peroxisome Proliferator-Activated Receptor Gene Family*

Peroxisome proliferator – activated receptors (PPARs) belong to the nuclear receptor superfamily and control a variety of genes in several pathways involved in lipid metabolism. Putative SNPS within the PPAR α gene have been implicated in phenotypic changes in lipid metabolism. This group used DNA sequencing technologies to identify two new single nucleotide polymorphisms within the gene that may affect the activity of this receptor.

I. *Identification and Validation of SNPs Which Regulate Function of Drug Transporters*

Peroxisome proliferator – activated receptors (PPARs) belong to the nuclear receptor superfamily and control a variety of genes in several pathways involved in lipid metabolism. Putative SNPS within the PPAR α gene have been implicated in phenotypic changes in lipid metabolism. This group used DNA sequencing technologies to identify two new single nucleotide polymorphisms within the gene that may affect the activity of this receptor.

VIII. New Collaborative Projects

Several investigators at Pfizer have requested contacts with scientists at the University of Michigan to collaborate on research and clinical projects. This includes some of the following examples.

- A. Vasculitis and Capavirine and CI-1044: Vasculitis is a concern for human clinical trials for these two drugs. Dr. Johnson works with both teams on monitoring the development of vasculitis in patients on these drugs.
- B. Cardiac Imaging: Dr. Margaret Samyn from Pfizer clinical Ann Arbor is working with radiologists at the University of Michigan on imaging studies of cardiac function for clinical trials.
- C. Ovarian tissue culture studies: Dr. John Obourn, Pfizer, Groton working with Dr. Jaram Menon from the University of Michigan on the effect of lazofloxine on ovarian epithelial proliferation.
- D. Vasculitis study in dogs: Dr. Ann Ryan, Pfizer, Groton working with Dr. Anthony Killeen from the University of Michigan on serum profiling of dogs with beagle pain syndrome.
- E. Synovial fluid analysis: Drs. Candace Bramson and Tim Wright, Pfizer, Ann Arbor working with Rheumatologists at the University of Michigan to obtain synovial fluid from patients with osteoarthritis.
- F. Serum biomarkers in Alzheimer's: Dr. David Wesche, Pfizer, Ann Arbor working with Alzheimer's group at the University of Michigan headed by Dr. Sid Gilman.
- G. Studies with MMP inhibitors and fibroblast proliferation: Dr. Michael Bleavins, Pfizer, Ann Arbor working with Drs. Varani and Johnson at the University of Michigan.

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