DEPARTMENT OF SURGERY

Division of Surgical Research

ANNUAL REPORT
7/1/01-6/30/02

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Division of Surgical Research

Annual Report (Summary)

July 1, 2001-June 30, 2002

During 2001-2002, research in the Department of Surgery was conducted by 42 Faculty (Instructor-Professor), 31 Postdoctoral Research Fellows, 3 residents, 27 Research Associates and Assistants, 3 Visiting Professors, and 16 students from the Divisions of Cardiothoracic, General, Neuro-, Plastics and Reconstructive, Transplantation, Urology, and Vascular Surgery. Research in the Department of Surgery occupied approximately 36,500 square feet of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Surgery (basic) research space included (in square feet) 5,870 at HIM, 11,935 in Dana/Research West, 3,081 in Slosberg-Landy, 2,314 at 21-27 Burlington Avenue, and 6, 568 at Research North. Clinical research in Surgery included (in square feet) 639 in Palmer and 6,165 in Finard/Rabb.

The Division of Surgical Research has three major responsibilities. 1) Pre- and post-award financial and scientific management of all grants submitted by and awarded to investigators working in the Department of Surgery. 2) Management of research space, including laboratory and office space, and shared research equipment. 3) Development of existing and new research areas within the Department of Surgery, including both short- and long-term strategic planning. The Division of Surgical Research is also responsible for making recommendations concerning faculty appointments and re-appointments. The Division of Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, who is the (Director) Vice Chairman for Research in the Department of Surgery. Susan J. Hagen, PhD, is Associate Director and Pat Odom-Andrews provides administrative support for the Division. The Division of Surgical Research works closely with Stephanie Wasserman, Research Manager, and with Karen Osborne and Shannon Joyce, Research Administrators. Stephanie Wasserman, Karen Osborne, and Shannon Joyce, formally part of Research Administration (Team 5), have the major responsibility for grant management, research-related purchases, staff payroll and benefits, and the management of new hires for research in the Department of Surgery.

Pre- and Post-Awards Grants Management

The Division of Surgical Research is responsible for maintaining a formalized process for all grant submissions in the Department of Surgery whereby all new and competing grant applications must be signed by either the Director or Associate Director before obtaining institutional approval. Prior to submission, investigators must file a final copy of the application with the Division of Surgical Research. These applications are held in our database until a funding decision is made. Upon funding, the application is transferred to Research Administration (Team 5), where it is used for financial management of the project.

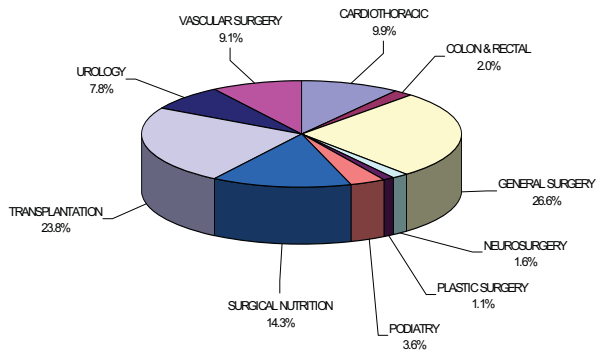
Research activity, defined as the amount of direct and indirect funds awarded and expended in the Department of Surgery (Table 1), decreased slightly from last fiscal year. Approximately 50% of funding was from federal sources, primarily from the NIH, and 50% from Other Sponsors (Table 1).

Table 1. *Summary of all research awards and expenditures in the Department of Surgery from 7/01/01-6/30/02*

Sponsor	Direct Awarded	Indirect Awarded	Total Awarded	Direct Expended	Indirect Expended	Total Expended
NIH	3,890,305	2,115,135	6,005,440	3,791,788	2,257,122	6,048,910
Other Federal	117,430	71,494	188,924	90,192	55,433	145,624
SOM*	0	0	0	54,661	0	54,661
Other Sponsors	3,219,693	300,909	3,520,602	4,006,695	271,724	4,278,419
TOTAL	7,227,427	2,487,538	9,714,965	7,943,336	2,584,278	10,527,614

*State of Massachusetts

FIGURE 1
01-02 DIRECT EXPENDITURES BY DIVISION



Funding for research in the Department of Surgery decreased by 13% from $11,151,352 in fiscal year 2001 to $9,714,965 in this fiscal year (Table 1). Although declining in this fiscal year, total awards are still increased by 6% from those in fiscal year 2000. Decline in funding this fiscal year is due to the departure of a number of well-funded investigators, including Drs. Matthews, Hodin and Matlin. In addition, grants were approved for funding from the State of Massachusetts, but no awards were made in this fiscal year due to cuts in the State budget. Research activity was distributed widely among Divisions where General Surgery, the largest Division, accounted for 26.6% and Transplantation accounted for 23.8% of direct expenditures (Figure 1). Significant activity occurred in Cardiothoracic Surgery, Surgical Nutrition, Vascular Surgery, and Urology (Figure 1).

Research Facilities

Departmental research laboratories are distributed among 4 different sites at the Beth Israel Deaconess Medical Center. The greatest concentration of researchers are found on the 8th floor of the Dana/Research West and the basement of the Slosberg-Landy (S-L) buildings on the East Campus, where General Surgery, Cardiothoracic Surgery, Colon and Rectal Surgery, Neurosurgery, and Urology research laboratories are located. Vascular Surgery, Cardiothoracic Surgery, and Urology laboratories are located on the 1st floor of the Harvard Institutes of Medicine. Research related to Transplantation/Immunobiology is located on the 3rd floor of Research North. Finally, Surgical Nutrition research laboratories are located at the Burlington Avenue building. New space was designed and renovated for the Clinical Nutrition laboratories in the vacated ER in Finard/Rabb and Dr. Blackburn recently moved his clinical research effort into that space.

During the last year, Dr. Per-Olof Hasselgren relocated his laboratory from Cincinnati to Dana 8 and Drs. Richard Hodin, Jeffrey Matthews, and Karl Matlin, relocated to different institutions.

Research Seminars

The Division of Surgical Research offered a seminar series with presentations from both Department investigators and from other departments and local institutions. Dr. Sandra Gaston (Urology) organized the entire seminar series this year and obtained external funding so that an honorarium could be offered to outside speakers. A summary of seminars that were presented from 07/01/01-06/30/02 are listed in Table 2. Please note that seminars were not held in the summer months of July and August.

Table 2. *Seminars sponsored by the Division of Surgical Research from 07/01/01-06/30/02*

09.10.01	Neutraceuticals in Prevention and Treatment of Cancer: From Clinical to Molecular Biology: George Blackburn and Jin-Rong Zhou, Department of Surgery, BIDMC
09.24.01	Tissue Engineering, Stem Cells and Cloning: Current Concepts and Changing Trends: Anthony Atala, Children's Hospital, Boston
10.15.01	*C. elegans* Proteomics to Help Understanding Human Cancer: Marc Vidal, Dana Farber Cancer Institute, Boston
11.05.01	Antiangiogenic Therapy in a Mouse Model of Pancreatic Cancer: Sareh Parangi, Department of Surgery, BIDMC
11.18.01	Matrix Metalloproteinases: Positive and Negative Regulators of Angiogenesis and Tumor Progression: Marsha Moses, Children's Hospital, Boston
12.03.01	Mechanical Regulation of Chondrocyte Gene Expression and Biosynthesis: Relevance to Cartilage Degeneration and Repair: Alan Grodzinsky, Massachusetts Institute of Technology
12.17.01	Coping With Radicals: Cellular Defenses and Gene Control: Bruce Demple, Harvard School of Public Health
01.28.01	High Throughput Screen for Key Proteins in Cancer Cell Invasion: Daniel Jay, Tufts University School of Medicine
02.04.01	Effects of c-Src Overexpression and EGF Stimulation on Breast Carcinoma Invasion: Susan Pories, Department of Surgery, BIDMC
02.18.01	Beyond PI 3-Kinase: Phospho-binding Modules as Integrators of Cell Signaling Pathways: Michael Yaffe, Massachusetts Institute of Technology
03.04.01	Protective Genes: A Regulatory Response to Injury: Christiane Ferran, Department of Surgery, BIDMC
03.18.01	Translational Proteomics: Spatial-Molecular Mapping of Tumor Markers in Surgical Tissue Specimens: Sandra Gaston, Department of Surgery, BIDMC
04.04.01	Development of Conditionally Replicating Herpes Vectors for Cancer Therapy: Robert Martuza, Massachusetts General Hospital
04.08.01	Putting Medicant Ion to the Acid Test: Genetics and Regulation of Chloride/Bicarbonate Exchangers: Seth Alper, Department of Medicine, BIDMC

04.29.01	Protein-Kinase Activities During Cardiopulmonary Bypass: Cesario Bianchi, Department of Surgery, BIDMC
05.06.01	Glutamine and Mucosal Protection in the *H. pylori* Infected Stomach: Susan Hagen, Department of Surgery, BIDMC
05.20.01	Molecular, Anatomic and Functional Dissection of Tumors Using Intravital Microscopy: Rakesh Main, Massachusetts General Hospital
06.03.01	Macrophages in Tumorigenesis: Aniruddha Ganguly, Department of Surgery, BIDMC

Faculty Development Workshop

04.17.02 "Criteria for Promotion at Harvard Medical School"
Rosemary Duda, MD
Associate Professor of Surgery
Director, Center for Faculty Development (BIDMC)

"Preparation of the CV and Educator's Portfolio
Jennifer Doyle, MS
Director, Educational Development and Evaluation

Faculty Accomplishments

Many new grant applications were funded in this fiscal year. New funding was obtained by Drs. Archer, Bach, Blackburn, Callery, Contreras, Ferran, Gentilello, Gaston, LoGerfo, Quist, Maki, Parengi, Perides, Veves, Zhou, and Zuk. Funding sources were from the NIH, State of Massachusetts and from corporate sponsors. At the national level, accomplishments included appointment to the Executive Committee of the Association for Academic Surgery (Dr. Archer), President of the National Urologic Forum (Dr. DeWolf), appointment to NIH study section (Drs. Blackburn, Hagen, and Sellke) or an NIH site-visit team for evaluation of NCI Intramural Urologic Oncology programs (Dr. DeWolf), and to the Grant Review Committee for the Juvenile Diabetes Foundation (Dr. Veves). In addition, many faculty in Surgery were invited speakers at programs and universities across the country (Drs. Blackburn, Borud, Ferran, Ganguly, Gaston, Hagen, Hasselgren, Kiessling, LoGerfo, Mun, Sellke, Slavin, Veves, and Zhou). At the international level, many faculty in Surgery were invited speakers at meetings (Drs. Blackburn, Ferran, Ganguly, Hagen, Hasselgren, Levitsky, McCully, Veves, and Zhou). Two investigators in Surgery submitted patent application (Drs. Hagen and LoGerfo). This year, Dr. Fritz Bach received the "Pioneers in Transplantation" award from the American Society for Transplantation and Dr. Aristidis Veves received the Mary Jane Kugel Award from the Juvenile Diabetes Foundation.

Researchers in Surgery continue a strong commitment to teaching. This includes acting as mentors in the NIH in-service teacher program, Summer Honors Undergraduate Research Program, MIT Bioengineering Undergraduate Research Program, Project Success, Biomedical Science Careers Program, Undergraduate Research Opportunities Program, The American Cancer Association Fuller Fellowship Program, Howard Hughes Summer Research Fellowship Program, and the Biomedical Science Careers Program. At HMS, many investigators teach in various courses, including "The Body" (Drs. Bianchi, Hagen, and Zuk), "Chemistry and Biology of the Cell" (Drs. Bianchi and Gaston), "Integrated Human Physiology" (Dr. Bianchi), and "Pharmacology" (Dr. Bianchi). Clinical teaching responsibilities will be listed under the clinical division report.

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List of Faculty by Division

Personnel	Title
Division of Cardiothoracic Surgery	
Sellke, Frank	**Professor of Surgery** **Chief, Division of Cardiovascular Surgery**
Bianchi, Cesario	Assistant Professor of Surgery
Feng, Jun	Instructor in Surgery
Kahn, Tanveer	Research Fellow
Voisine, Pierre	Research Fellow
Li, Jianyi	Research Assistant
Xu, Shu Hua	Research Assistant
Levitsky, Sidney	**Professor of Surgery**
McCully, James	**Associate Professor of Surgery**
Rousou, Anthony	Research Fellow
Hsieh, Yng-Ju	Research Associate
Ellis, Henry	**Clinical Professor of Surgery, Emeritius**
Loda, Massino	Associate Professor of Pathology (DFCI)
Xu, Xiangjun	Research Fellow
Lechpammer, Mirna	Research Fellow
Division of General Surgery	
Callery, Mark	**Associate Professor of Surgery** **Chief, Division of General Surgery**
Canete, Jonathan	Research Fellow
Chandler, Nicole	Research Fellow
Archer, Sonia	**Assistant Professor of Surgery**
Mou, Huizhong	Research Assistant
Surgical Nutrition	
Blackburn, George	**Associate Professor of Surgery** **S. Daniel Abraham Chair in Nutrition Medicine**
Zhou, Jin-Rong	**Assistant Professor of Surgery**
Khaodhiar, Lalita	Instructor in Medicine
Pan, Weijun	Visiting Scientist
Mai, Zhi Ming	Sr. Research Fellow
Greene, Pennie	Research Fellow
Copeland, Trisha	Research Associate
Hirsch, Wanda	Research Associate
Karun, Pam	Research Associate
McNamara, Anne	Research Associate
Sherwood, Michelle	Research Associate
McCormick, Heather	Research Associate
Lin, Min	Research Assistant

Ainsley, Barbara	Administrative Assistant
Presscott, Jessica	Administrative Assistant
Sidell, Susan	Administrative Assistant
Fischer, Josef	**Mallinckrodt Professor of Surgery** **Chairman, Department of Surgery**
Ganguly, Aniruddha	**Assistant Professor of Surgery**
Robbins, Jonathan	Research Assistant
Newton, Marissa	Research Assistant
Yeung, Helen	Student
Opelka, Erin	Student
Chakrabarti, Anindita	Student
Opelka, Frank Andrew	Student
Nguyen, Kimberly	Student

Trauma and Critical Care

Gentilello, Larry	**Visiting Associate Professor of Surgery** **Chief, Trauma and Critical Care**
Hagen, Susan	**Assistant Professor of Surgery**
Tashima, Kimihito	Research Fellow
Muvaffak, Asli	Research Fellow
Smith, Marianne	Sr. Research Associate
Brown, Daniel	Sr. Research Associate
White, Suzanne	Histotechnologist
Li, Suqian	Research Assistant
Hasselgren, Per-Olof	**Visiting Professor of Surgery** **Chief, Endocrine Surgery**
Menconi, Michael	Assistant Professor of Surgery
Yang, Hongmei	Research Fellow
Wei, Wei	Research Fellow
Mun, Edward	**Assistant Professor of Surgery**
Parangi, Sareh	**Instructor in Surgery**
Zi, Tong	Research Assistant
Zuk, Anna	**Assistant Professor of Surgery**

Division of Neurosurgery

Wu, Julian	**Associate Professor of Surgery** **Chief, Division of Neurosurgery**
Joshi, Sangeeta	Research Fellow
Malek, Adel	**Instructor in Surgery**

Division of Plastic and Reconstructive Surgery

Slavin, Sumner	**Associate Clinical Professor of Surgery** **Chief, Division of Plastic and Reconstructive Surgery**
Borud, Loren	Instructor in Surgery
Contreras, Mauricio	Instructor in Surgery
Brahmer, Geoffrey	Research Coordinator

Division of Podiatry

Veves, Aristidis	**Assistant Professor of Surgery**
Khaodhiar, Lalita	Instructor in Medicine
Dinh, Thanh	Junior Faculty
Caselli, Antonella	Research Fellow
Economides, Panayiotis	Research Fellow
Rich, Jeremy	Resident
Brady, Jane	Resident
Sparks, Caitlin	Research Coordinator
Tiani, Elizabeth	Research Coordinator

Division of Transplantation

Immunobiology Research Center

Bach. Fritz H.	**Louis Thomas Professor of Surgery**
Soares, Miguel	Instructor in Surgery
Tyagi, Shivraj	Instructor in Surgery
Yamashita, Kenichiro	Research Fellow
McDaid, James	Research Fellow
Wang, Hongjun	Research Fellow
Csizmadia, Vilmosne Eva	Research Assistant
Lee, Soo	Research Assistant
Ferran, Christiane	**Associate Professor of Surgery**
Grey, Shane	Assistant Professor of Surgery
Arvelo, Maria	Research Fellow
Daniel, Soizic	Research Fellow
Patel, Virendra I.	Surgical Resident
Monaco, Anthony	**Peter Medawar Professor of Surgery**
Maki, Takashi	**Associate Professor of Surgery**
Ogawa, Norihiko	Research Fellow
Kanamoto, Akira	Research Fellow
Gottschalk, Rita	Research Assistant
Thaxton, Jessica	Research Assistant

Division of Urology

DeWolf, William	**Professor of Surgery** **Chief, Division of Urology**
Schopperle, William	Research Fellow

Olumi, Aria	**Instructor in Surgery and Medical Science Director for Urology**
San Francisco, Ignacio	Reseach Fellow
Zhang, Xiaoping	Research Fellow
Gaston, Sandra	**Instructor in Surgery and Basic Science Director for Urology**
Mathew, Lynn	Research Assistant
Brice, Mark	Research Assistant
Hsiao, Rusan	Research Assistant
Vu, Dang	Research Assistant (part-time)
Soares, Marc	Student
Shih, Jennifer	Student
Corin, Karolina	Student
Chang, Jennifer	Student
Kim, Tae Wan	Student
Chow, Stephanie	Student
Khan, Ilana	Student
Chilton, Sven	Student
Goldner, Dana	Student
Cherella, Elizabeth	Student
Kiessling, Ann	**Associate Professor of Surgery**
Fleischman, Julian	Visiting Associate Professor
Yin, Hui-Zhong	Senior Research Fellow
Desmarais, Bryan	Research Assistant
Neville, Nathan	Student

Division of Vascular Surgery

LoGerfo, Frank	**William V. McDermott Professor of Surgery Chief, Division of Vascular Surgery**
Quist, William	**Associate Professor of Pathology**
Hamdan, Allan	**Assistant Professor of Surgery**
Contreras, Mauricio	Instructor in Surgery
Phaneuf, Matthew	Assistant Laboratory Director
Aggarwal, Puja	Research Fellow
Deutsch, Evan	Research Fellow
McArthur, Claudie	Research Fellow
Willis, David	Research Fellow
Sousa, Kery	Research Fellow
Hile, Chantel	Surgical Research Fellow
Gross, Barry	IS Development
Patel, Vaishali	Administrative Assistant
Veraldi, Jennifer	Research Assistant

Division of Surgical Research

Hasselgren, Per-Olof	**Vice Chair for Research**
Hagen, Susan	**Associate Director of Research**
Patricia Odom-Andrews	Administrative Coordinator

Research Administration

Wasserman, Stephanie	**Director, Research Administration, Team 5**
Osborne, Karen	Research Administrator

INDIVIDUAL INVESTIGATOR NARRATIVES

Sonia Archer, M.D.

Division of General Surgery

I. Narrative Report

Basic Research

My group is interested in understanding the molecular mechanisms involved in butyrate's (and fiber's) protection against colon carcinogenesis. Our long-term goal is to translate findings we make in the research laboratory into diagnostic and therapeutic strategies against colon cancer.

II. List of Current Employees

1. Huizhong Mou, B.S. Research Assistant

III. List of Current Funding

1. "Regulation of p21 by butyrate in intestinal epithelia"
   NIH, Physician Scientist Award (R-O3, supplement to K-O8)
   Project Period: 09/25/00 - 6/30/03
   Principal Investigator: Dr. Sonia Archer

2. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"
   Robert Wood Johnson Award, Minority Medical Faculty Development Award
   Project Period: 07/01/02 – 06/30/06
   Principal Investigator: Dr. Sonia Archer

3. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"
   Harvard Medical School, Minority Medical Faculty Development Bridge Award
   Project Period: 06/01/02 – 05/31/03
   Principal Investigator: Dr. Sonia Archer

IV. Divisional Accomplishments Over Past Year

1. Over the past year, I have successfully competed for and obtained a Robert Wood Johnson Minority Medical Faculty Development Award to study the molecular mechanisms underlying the regulation of cyclin B1 gene expression by butyrate in colon cancer cells. I have published a review article on the p21 gene in the book, Encyclopedia of Molecular Medicine. I have authored a paper: "American ginseng transcriptionally activates p21 mRNA in breast cancer cell lines" which was published in the Journal of Korean Medical Sciences.

2. At the national level, I was voted in by national poll as a councillor on the executive committee of the Association for Academic Surgery. I also conducted a workshop on grantsmanship in the Fundamentals of Surgical Research Course offered by the

Association for Academic Surgery. I have presented well-received abstracts at the American Gastroenterological Association meetings in 2002, and at the Clinical Congress of the American College of Surgeons and the Association for Academic Surgery in 2001.

Congress of the American College of Surgeons

Archer SY, Tang R, Kim HJ, Ma Q, Hodin RA. VX-563: A novel butyrate prodrug induces differentiation and the program of cell cycle inhibition in colon cancer cells.

Association for Academic Surgery

Archer SY, Johnson JJ, Kim HJ, Hodin RA. A novel function of Sp1 transcription factor: repression of p21 gene expression in human colon cancer.

3. I have continued to serve as advisor and mentor for minority students in the Biomedical Science Careers Student Project.

V. Plans For The Coming Year

1. I will continue to work towards attaining independence in research through the acquisition of an NIH-RO1 award. Further funding will allow the recruitment of much needed additional experienced laboratory personnel, e.g. a postdoctoral fellow, who will be able to accelerate the progress of our research, which has the exciting possibility of imminent clinical translation.

VI. Bibliography (07/01/2001-06/30/2002)

Original Reports

1. Duda RB, Kang S-S, **Archer SY**, Meng S, Hodin RA. American ginseng transcriptionally activates p21 mRNA in breast cancer cell lines. *J Korean Med Sci* 2001;16:S54-S60.

Reviews, Chapters, and Editorials

1. **Archer SY**, Hodin RA. P21. In: Encyclopedia of Molecular Medicine. Creighton TE, ed, John Wiley & Sons, New York, N.Y. 2002;4:2359-2361.

Abstracts

1. **Archer SY**, Ma Q, Hodin RA. Intestinal ischemia: alterations in cell cycle regulators and differentiation. *Gastroenterology* 2002;375A.

Fritz H. Bach, M.D.

Division of Transplantation

I. Narrative Report

Basic Research

Organ grafts can contribute to their own survival by expressing a series of protective genes in their endothelial and smooth muscle cells. Protective genes have two characteristics: they are anti-apoptotic and anti-inflammatory. The protective gene of interest to us is heme oxygenase-1 (HO-1) and two of the products of HO-1 action on heme: carbon monoxide (CO) and biliverdin/bilirubin. We have shown that CO can mediate most of the protective effects of HO-1. However, we now find that in two situations CO cannot substitute for HO-1 while biliverdin/bilirubin can. In a model of inflammatory bowel disease, in which dextran sulfate is administered to mice, as well as in a heart transplant model in mice, we find that administration of biliverdin suppresses the disease/results in long-term survival, while CO (at least at the doses we give) does not. We are able to induce HO-1 expression by treatment with cobalt protoporphyrin (CoPP); CO can be administered via the lungs, and biliverdin can be given i.p. We plan to optimize the use of HO-1, CO and biliverdin to promote organ and tissue graft survivals as well as to treat various disorders.

II. List of Current Employees

1.	Miguel P. Soares, Ph.D.	Instructor in Surgery
2.	Shivraj Tyagi, Ph.D	Instructor in Surgery
3.	KenichiroYamashita, M.D., Ph.D.	Postdoctoral Fellow
4.	James McDaid, M.D.	Postdoctoral Fellow
5.	Hongjun Wang, Ph.D.	Postdoctoral Fellow
6.	Vilmosne Eva Csizmadia	Research Technician
7.	Soo Lee	Research Technician

III. List of Current Funding

1. "Xenotransplantation for Islet Protection"
   JDF International/HMS
   Project Period: 09/01/2001 - 08/31/2002
   Principal Investigator: Fritz Bach, M.D.

2. "Protection of Islets for Transplantation"
   Riva Foundation

Project Period: 09/01/2002 - 08/31/2003
Principal Investigator: Fritz Bach, M.D.

3. "Xenotransplants: Genetically Engineered Endothelial Cells"
National Institutes of Health, NHLBI 1RO1HL58688-02
Project Period: 09/01/1998 - 08/31/2002
Principal Investigator: Fritz Bach, M.D.

4. "Islet Xenotransplantation: Genetic Approaches to the Problem"
Joslin Diabetes Center: 1PO1DK53087 NIDDK
Project Period: 12/01/2001 - 11/30/2002
Principal Investigator: Gordon Weir-Program Director
Project Principal Investigator: Fritz H. Bach, M.D.

5. "Studies in Transplantation"
Novartis (Sandoz) Pharma/BI Deaconess Medical Center
Project Period: 01/01/2000-
Principal Investigator: Fritz Bach, M.D.

IV. Divisional Accomplishments over the Past Year

Research Accomplishments

1. We have elucidated signaling pathways used by cells treated with HO-1 and CO. In some cells, such as pancreatic islets, cGMP is the most important pathway; in other cells, such as endothelial cells, it is the p38MapKinase pathway. In smooth muscle cells, both cGMP and p38 are involved and p38 activation depends on cGMP for its activation.

2. We have shown that pre-treatment of pancreatic islets with CO for 2 hours will markedly improve their function when transplanted to diabetic mice.We have also shown that inducing the expression of HO-1 in islets, including treating the recipient with CoPP, which induces HO-1, results in long-term survival of the islets in about 50% of cases. Preliminary data show that giving biliverdin may have the same effect as inducing HO-1.

3. We have demonstrated that treatment of a rat receiving an aortic transplant with CO for the entire 56 days of the experiment results in a very highly significant reduction in the degree of post-transplant arteriosclerosis that develops.

4. We have demonstrated that expression of ferritin in endothelial cells is anti-apoptotic, and that the anti-apoptotic effect is mediated in part through p38.

5. I have shown that Th2 cytokines are involved in eliciting the expression of protective genes in endothelial cells.

Personal Accomplishments

1. I was selected as one of the Pioneers of Transplantation at a meeting of the American Society of Transplantation in Chicago in an event sponsored by Roche.

V. Plans for the Coming Year

Staff Changes/Recruitments

1. I will search for a molecular biologist and a senior laboratory manager will be recruited. Also, substitutes for the post-docs who are leaving will be recruited.

Plans for Research

1. An application to further the work with diabetic islets and CO is being submitted.

VI. Bibliography (07/01/01-6/30/02)

Original Articles

1. Brouard S, Berberat PO, Tobiasch E, Seldon MP, **Bach FH**, Soares MP. Heme oxygenase-1-derived carbon monoxide requires the activation of transcription factor NF-kappa B to protect endothelial cells from tumor necrosis factor-alpha-mediated apoptosis. *J Biol Chem* 2002;227(20):17950-17961.

2. Gunther L, Berberat PO, Haga M, Brouard S, Smith RN, Soares MP, **Bach FH**, Tobiasch E. Carbon monoxide protects pancreatic beta-cells from apoptosis and improves islet function/survival after transplantation. *Diabetes* 2002;51(4):994-999.

3. Pileggi A, Molano RD, Berney T, Cattan P, Vizzardelli C, Oliver R, Fraker C, Ricordi C, Pastori RL, **Bach FH**, Inverardi L. Heme oxygenase-1 induction in islet cells results in protection from apoptosis and improved in vivo function after transplantation. *Diabetes* 2001;50(9):1983-1991.

4. Tobiasch E, Gunther L, **Bach FH**. Heme oxygenase1 protets pancreatic beta cells from apoptosis caused by various stimuli. *J Investig Med* 2001;49(6):566-571.

Reviews and Book Chapters

1. **Bach FH**, Ivinson AJ. A shrewd and ethical approach to xenotransplantation. *Trends Biotechnol* 2002;20(3):129-131.

2. **Bach FH**, Ivinson AJ, Weeramantry C. Ethical and legal issues in technology: xenotransplantation. *Am J Law Med* 2001;27(2-3):283-300.

3. Horvath I, MacNee W, Kelly FJ, Dekhuijzen PN, Phillips M, Doring G, Choi AM, Yamaya M, **Bach FH**, Willis D, Donnelly LE, Chung KF, Barnes PJ. "Haemoxygenase-1 induction and exhaled markers of oxidative stress in lung diseases", summary of the ERS Research Seminar in Budapest, Hungary, September, 1999. *Eur Respir J* 2001;18(2):420-430.

4. Ivinson AJ, **Bach FH**. The xenotransplantation question: public consultation is an important part of the answer. *CMAJ* 2002;167(1):42-43.

5. Soares MP, Brouard S, Smith RN, **Bach FH**. Heme oxygenase-1, a protective gene that prevents the rejection of transplanted organs. *Immunol Rev* 2001;184:275-285.

6. Soares MP, Brouard S, Smith RN, Otterbein L, Choi AM and **FH Bach**. Expression of heme oxygenase-1 by endothelial cells: a protective response to injury in transplantation. *Emerging Therapeutic Targets* 2000;4(1):11-27.

7. Soares MP, Usheva A, Brouard S, Berberat PO, Gunther L, Tobiasch E, **Bach FH**. Heme oxygenase-1, a protective gene that prevents the rejection of transplanted organs. *Immunol Rev* 2001;184:275-285.

Abstracts

1. **Bach FH**. A 50-year retrospective: cell-mediated immunity and the major histocompatibility complex. *Transplant Proc* 2002;34(4):1071-1072.

George L. Blackburn, M.D., Ph.D.

Division of Surgical Nutrition

I. Narrative Report

Clinical Research

The Center for the Study of Nutrition Medicine (CSNM) at Beth Israel Deaconess Medical Center, which I direct, provides medical nutrition research, consultation, early phase clinical-trials, interventions, education and training. Current investigations address areas such as breast cancer, prostate cancer, hypertension, diabetes and obesity. CSNM provides sophisticated, scientific nutrition interventions that are utilized to support research, training and patient care in these areas. Support of these studies ranges from government grants to industry sponsored clinical research. The goal of the center is to continue to provide study participants with ethical protocols offering nutritional treatment options for varied diseases. The CSNM works to provide the best possible care to patients both in research as well as in a clinical setting. In line with the medical center's "bench-to-bedside" mission, CSNM actively utilities the data gleaned from research in the future treatment of patients. Transversely, it also uses clinical outcomes to develop research that would advance either therapeutics or novel approaches to care.

Basic Research

The Nutrition Metabolism Laboratory (NML), which I direct, studies the effects of plant phytonutrients components, such as soy phytochemicals, tea polyphenols and other dietary/herbal supplements, on the prevention and treatment of cancer, and to elucidate the underlying molecular and cellular mechanisms. Collaborative research with other department of surgery divisions involve studies in the gastrointestinal track and OB/GYN study of alternatives to hormone replacement therapy in post menopausal women.

II. List of Current Employees

1.	Edward C. Mun, M.D.	Assistant Professor of Surgery
2.	Lalita Khaodhiar, M.D.	Instructor in Medicine
3.	Jin-Rong Zhou, Ph.D.	Assistant Professor of Surgery
4.	Weijun Pan, MD, PhD.	Visiting Scientist
5.	Zhi Ming Mai, Ph.D.	Senior Postdoctoral Fellow
6.	Pennie Greene, Ph.D.	Postdoctoral Fellow
7.	Anne McNamara RN	Research Associate
8.	Trisha Copeland, MS, RD	Research Associate
9.	Pam Karun, MS	Research Associate
10.	Wanda Hirsch, RD	Research Associate
11.	Michelle Sherwood, RD	Research Associate
12.	Heather McCormick, RD	Research Associate
13.	Min Lin	Research Technician
14.	Barbara Ainsley	Administrative Assistant

15. Jessica Prescott — Administrative Assistant
16. Susan Sidell — Administrative Coordinator

III. List of Current Funding

1. "The Study of Health Outcomes of Weight Loss"
   NIH/NIDDK 5U01 DK57154-03
   Project period: 09/01/2002 - 08/31/2003
   Principal Investigator: Dr. George Blackburn

2. "Low-Fat Diet in Stage II Breast Cancer: Outcome Trial"
   NIH/NCI 5R01 CA45504-11
   Project period: 01/01/1997 - 12/30/2004
   Principal Investigator: Dr. George Blackburn

3. "Comparison of Weight Loss Dietary Strategies: Low Carbohydrate Ketogenic Diets Compared with Low Fat Diet"
   Atkins Foundation
   Project period: 06/01/2001 - 05/30/2003
   Principal Investigator: Dr. George Blackburn

4. "Dietary Soybean Components Affect Prostate Cancer Progression"
   NIH/NCI, RO1 CA 78521
   Project period: 06/01/1999 - 11/31/2002
   Principal Investigator: Dr. Jin-Rong Zhou
   Co-Investigator: Dr. George Blackburn

5. "Soy Isoflavone as a Radiation Sensitizer in Prostate Cancer"
   American Institute for Cancer Research"
   Project period: 01/31/1999 - 11/31/2001
   Principal Investigator: Dr. Jin-Rong Zhou
   Co-Investigator: Dr. George Blackburn

6. "Dietary Soy Isoflavone as Radiation Sensitizer in Treating Breast Cancer"
   Massachusetts Department of Public Health
   Project period: 01/01/1999 - 11/31/2001
   Principal Investigator: Dr. Jin-Rong Zhou
   Co-Investigator: Dr. George Blackburn

7. "Combined Effects of Soy and Tea Bioactive Components on Breast Cancer Progression"
   Susan Komen's Breast Cancer Research Foundation
   Project period: 10/01/2000 – 09/30/2002
   Principal Investigator: Dr. Jin-Rong Zhou
   Co-Investigator: Dr. George Blackburn

8. "Combined Effect of Soybean and Tea Bioactive Components on

Delaying the Development of Androgen-Independent Prostate Cancer"
Massachusetts Department of Public Health
Project period: 01/01/2001 – 12/30/2003
Principal Investigator: Dr. Jin-Rong Zhou
Co-Investigator: Dr. George Blackburn

9. "Effects of Isoflavone-aglycones on the Prevention and Treatment of Ovarian Deficiency (menopause), Obesity and Prostate Cancer"
Nichimo Company
Project period: 03/01/2001 - 02/28/2003
Principal Investigator: Dr. Jin-Rong Zhou
Co-Investigator: Dr. George Blackburn

10. "An Eight-Week, Parallel Group, Double-Blind Randomized, Placebo and Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Two Formulations of GI181771X, Each of Two Different Doses in Obese Subjects"
GlaxoSmithKlein
Project period: 06/03/02 - 06/03/03
Principal Investigator: Dr. George Blackburn

11. " Interactions Between Dietary Soy Components and Tamoxifen on Breast Cancer Progression"
NIH(NCCAM) RO1 AT00863
Project period: 09/12/2001 - 05/31/2004
Principal Investigator: Dr. Jin-Rong Zhou
Co-Investigator: Dr. George Blackburn

IV. Applications Submitted and Pending Review/Funding

1. Nichimo (Blackburn/Ricciotti)
Effects of Soy Isoflavones on Menopausal Hot Flashes

2. NCI/NIH (1RO1CA80011-01A1) (Zhou), 12/01/2002-11/30/2006
Effects of soybean components on growth and metastasis of bladder cancer

3. NCI/NIH (1RO1 CA101011-01) (Zhou) 07/01/2003-06/30/2007
Androgen modulation by genistein in prostate cancer

4. NCI/NIH (1RO3 CA101041-01) (Zhou) 01/01/2003-12/31/2004
Genes modulated by soy in prostate cancer progression

V. Divisional Accomplishments over the Past Year

Research Accomplishments

1. 2001 NIH NIDDK Special Emphasis Panel (Blackburn)

2. NIH Boston Obesity Nutrition Research Center (BONRC)
   Associate Director (Blackburn)

New grants in the past year

1. NCCAM/NIH (1RO1 AT00863-01) (Zhou) 09/12/2001-05/31/2004
   Interactions between dietary soy components and tamoxifen on breast cancer progression.

2. GlaxoSmithKlein (Blackburn) 6/03/02-6/03/03
   An eight-week, parallel group, double-blind randomized, placebo and active-controlled, multicenter study to evaluate the efficacy, safety and tolerability of two formulations of GI181771X, each of two different doses in obese subjects.

Educational Accomplishments

1. The Centers for Obesity Research and Education (CORE) is one of eight nutrition research centers collaborating to develop practical workshops to educate physicians and allied health professionals in managing overweight and obesity in their patients, and to provide the latest scientific literature on the assessment, treatment and monitoring of obesity. This year a new workshop on the diagnosis and treatment of the Metabolic Syndrome was developed.

2. HMS, Department of Continuing Medical Education, Hyperalimentation Course, Enhancing the Safety of Parenteral and Enteral Nutrition. Dr. Blackburn delivered a lecture entitled "Critical Opportunity for Metabolic Support of the Seriously Ill Patient". Cambridge, MA. Dr. Blackburn was the course director.

3. HMS, Department of Continuing Medical Education, " Practical Approaches to the Treatment of Obesity" Cambridge, MA. Dr. Blackburn was the course director.

4. Harvard Medical School, Division of Nutrition Annual Meeting, Nutrition and Women's Health Symposium. Dr. Blackburn delivered a lecture entitled " Diet and Breast Cancer".

5. Harvard Medical School Teacher Institute Fall Breakout Session. Dr. Blackburn delivered a lecture entitled "Dietary Patterns in Health and Disease".

Individual Accomplishments – Invited Presentations
Dr. Blackburn

1. *Current Research and Future Possibilities,* Commission on Dietetic Registration, Certificate of Training in Adult Weight Management Program, Cambridge, MA, August 9,

2. *Fats; the good, the bad, the trans*, *Chairman*, 17th International Congress of Nutrition, "Functional Indicators of Nutritional Status", Vienna, Austria, August 27-31, 2001

3. *Advances in the Management of Over and Under Nutrition in the 21st Century*, Gastroenterology Update 2001: The Intergration of Medicine, Surgery and Radiology in Improved Patient Management, Richmond, VA, September 8, 2001

4. *Neutraceuticals in Pevention and Treatment of Cancer, From Clinical to Molecular Biology, (Blackburn and Zhou),* Surgical Research Seminar, Boston, MA, September 10, 2001

5. *Importance of Nutrition Research*, Presentation to Dietetic Interns, Boston, MA, October 1, 2001

6. Surgical Therapy for Severe Obesity, BIDMC, Department of Surgery Dinner Presentation, Newton, MA, October 18, 2001

7. The Metabolic Syndrome: Treating Obesity and Dyslipidemia, Marina Del Ray, November 9-10, 2001

8. *Cardiovasular Risk Reduction in Patients with Obesity,* America Heart Association, Ingenix Symposium, Anaheim, CA, November 14, 2001

9. ROSS Pediatric Obesity Panel, Columbus, OH, January 17-28, 2002

10. *Nutrition in the Elderly,* 18th Annual Review of Geriatric Medicine, Harvard Medical School Continuing Medical Education Course, Boston, MA, March 1, 2002

11. *Obesity is a complex disease,* Dietetic Intern Class on Obesity, Beth Israel Deaconess Medical Center, Boston, MA, March 11, 2002

12. *Management of Obesity in Adults, and Determining Appropriate Clinical Treatment,* University of Vermont Residency Program, Vermont, April 5, 2002

13. *Childhood Obesity/Improving Meal Quality,* FRAC, America's Second Harvest, National CACFP Forum, Washington, D.C., April 7-8, 2002

14. *A potential solution for a public health epidemic*, Uniliever Health Institute Symposium "Trends in Weight Management: Science, Technology and Public Health" and Slim.Fast Satellite Symposium, Netherlands, April 18, 2002

15. *Managing Metabolic Syndrome: Weighing the Risk for Obese Patients,* Medical Education Systems, Obesity Webcast, Los Angeles, CA, May 14-15, 2002

16. *Management of Obesity in Adults*, St.Elizabeth's Hospital-Endocrine Grand Rounds, Boston, MA, May 23, 2002

17. *A Practical Guide for the Diagnosis and Treatment of Metabolic Syndrome*, AAPA's 30th Annual PA Conference, Boston, MA, May 29, 2002

18. *Obesity Risk Factors, and Open Remarks,* AHA Annual Meeting "Stayin' Alive" Stuart, FL, June 7-8, 2002

Dr. Zhou

1. Invited presentation, Symposium on Diet and Prevention of Gender Cancers, American Chemical Society annual meeting, Chicago, IL, Aug. 2001.

2. Invited presentation, 2nd International Conference on Nutraceuticals and Functional Foods, "Nutraceutical Components in Soy and Tea for Prevention of Prostate Cancer", Portland, Oregon, Nov. 2001.

3. 4th International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, "Prevention of Human Prostate Tumor Growth in Mice by Combination of Soy and Tea Bioactive Components", San Diego, CA, November 2001.

4. Attended and presented at Nutrition Week, " Soy and Tea as Functional Foods in Prevention of Prostate Cancer Progression", San Diego, CA, February 2002.

5. Attended and presented at the International Scientific Conference on Complementary, Alternative and Integrative Medical Research, "PC-SPES inhibits growth and metastasis of androgen-sensitive human prostate tumors in mice", Boston, MA, April 2002.

6. AACR annual meeting, San Francisco, CA, April 2002.

7. Experimental Biology annual meeting, New Orleans, LA, April 2002.

8. Jin-Rong Zhou, Lunyin Yu, & George L. Blackburn: Only Whole Black Tea Significantly Inhibits the Progression of Androgen-Independent Human Prostate Tumor in an Orthotopic Tumor Model. Late-Breaking Abstract, 65 (abst.#LB334), New Orleans, LA, 2002.

9. Invited speaker, Institute of Molecular Medicine, Nanjing University, Nanjing, P. R. China, May 2002.

VI. Plans for the Coming Academic Year

CSNM

1. Encourage and support Junior Faculty in Nutritional Research
2. Collaborate with Endocrinology and Joslin in clinical trials
3. Continue to actively pursue new clinical trials

4. Recruit qualified staff in order to manage clinical trials efficiently
5. Associate Director of Clinical Affairs for NIH Boston Obesity Nutrition Research Center (BONRC) will develop a series of courses to train scientists working in Obesity treatment in various areas i.e. assessment, genetics, biomarkers, psychometrics

Nutrition/Metabolism Lab.

1. To recruit 2-3 postdoctoral fellows and accept one Visiting Associate Professor

2. To submit 2-3 RO1 grants

3. To be involved in Nutrition curriculum development at HMS

4. To further establish tools for proteomics (2D system and image analysis) and alternative/complementary medicine (plant compound extraction and fractionation, and bioassays) research

V11. Bibliography (07/01/01-06/30/02)

Original Articles (Blackburn)

1. **Blackburn GL**. The American obesity epidemic is getting worse. *Food Technology* 2002;56:148.

2. **Blackburn GL**. The public health implications of the Dietary Approaches to Stop Hypertension Trial. *Am J Clin Nutr* 2001;74(1):1-2.

3. **Blackburn GL**. Treatment approaches: food first for weight management and health. *Obes Res* 2001;9:223S-227S.

4. Burger AJ, Charlamb MJ, Singh S, Notarianni M, **Blackburn GL**, Sherman HB. Low risk of significant echocardiographic valvulopathy in patients threated with anorectic drugs. *Int J Cardiol* 2001;79:159-65.

5. Khaodhiar L, **Blackburn GL**. Results of expert meetings: Obesity and cardiovascular disease. Obesity assessment. *Am Heart J* 2001;142:1095-1101.

Original Articles (Zhou)

1. Jones JL, Daley BJ, Enderson BL, **Zhou J-R,** Karlstad MD: Genistein inhibits tamoxifen effects on cell proliferation and cell cycle arrest in T47D breast cancer cells. *Am Surg* 2002;68(6):575-577.

Original Articles (in press)

1. **Zhou J-R**, Yu L, Zhong Y, Nassr RL, Franke AA, **Gaston SM, Blackburn GL:** Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. *Prostate 2002;* in press.

Reviews, Chapters, and Editorials

1. **Blackburn GL**. Introduction – Dietary patterns for weight management and health. Guest Editors Blackburn, GL, Heymsfield, SB, Saris WHM. *Obes Res* 2001;9:217S-218S.

2. **Blackburn GL**. Managing obesity in America: an overview. *John Hopkins Advanced Studies in Medicine* 2002;2:40-49.

3. **Blackburn GL**, Bevis LC. The obesity epidemic: prevention and treatment of the metabolic syndrome. Medscape Nurses Clinical Update. September 18, 2002. Available at http://www.medscape.com/viewprogram/2015.

4. **Blackburn GL**, Phillips JCC, Morreale S. Physician's guide to popular low-carbohydrate weight-loss diets. *Cleveland Clinic J of Med* 2001;68:761-774.

5. Butchko HH, Stargel WW, Comer CP, Mayhew DA, Benninger C, **Blackburn GL**, de Sonneville LM, et al. Aspartame: review of safety. Regul *Toxicol Pharmacol* 2002;35:S1-93.

6. Melanson KJ, McInnis KJ, Rippe JM, **Blackburn G,** Wilson PF. Obesity and cardiovascular disease risk: research update. *Cardiology in review* 2001;9:202-207.

7. **Blackburn GL**. Weight Loss and Risk Factors. In: Brownell KD, Fairburn CG, ed. Eating Disorders and Obesity 2nd edition, The Guilford Publications Inc., 2001, NY, London.

8. Khaodhiar L, **Blackburn GL**. Health Benefits and Risks of Weight Loss. In: Bjorntorp P, ed. International Textbook of Obesity. John Wiley & Sons, Ltd., 2001, West Sussex, UK.

9. Polyxeni KD, Apovian CM, **Blackburn GB**. In: Principles and Practice of Palliative Care and Supportive Oncology, Second Edition, Edited: Berger AM, Portenoy RK, Weissman DE. Lippincott Williams & Wilkins, 2002;68:933-955.

Abstracts

1. Mai Z, **Blackburn GL, Zhou J-R.** Genistein and tamoxifen combination has synergistic effect on growth inhibition of estrogen-independent human breast cancer cells but has antagonistic effect on growth inhibition of estrogen-dependent human breast cancer cells *in vitro*. *FASEB J 2002;*16:1006A.

2. Pan W, Takebe M, **Blackburn GL, Zhou JR.** Effects of isoflavone aglycone on the prevention of obesity in a diet-induced obese mouse model. *FASEB J* 2002;16:1013A.

3. Yu L, **Zhou J-R.** Development of a new animal model for androgen-independent prostate tumor from androgen-sensitive prostate tumor and elucidation of molecular mechanisms in the progression. *Proc AACR* 2002;43:640.

4. **Zhou JR.** Yu L, Zhong Y, **Blackburn GL.** Tea polyphenols potentiate anti-prostate cancer activity of the herbal supplement PC-SPES. *FASEB J* 16:611A.

Mark P. Callery, M.D.

Division of General Surgery

I. Narrative Report

Our laboratory focuses on defeating chemoresistance in pancreatic cancer. We believe this depends on over-activation of Nuclear Factor kappa-B (NF-kB), a small molecule that regulates key processes in apoptosis and cell cycle progression. While chemoradiation therapy can induce apoptosis in pancreatic cancer cells, it can also activate a NF-kB "salvage pathway" which limits the degree of apoptosis. We currently are measuring how 26S proteasome inhibition of NF-kB and overexpression of p21Cip1 (an important cell cycle regulator) potentiate established chemotherapy agents. By targeting both apoptotic and cell cycle checkpoints, we expect this NF-kB-dependent chemoresistance to be overcome. Once the current *in vitro* work in completed, future work will be translated to an established *in vivo* mouse xenograft model of pancreatic cancer.

II. List of Current Employees

1. Jonathan J. Canete, MD, MPH — Postdoctoral Fellow
2. Nicole M. Chandler, MD — Postdoctoral Fellow

III. List of Current Funding

1. "Mechanisms of Chemoresistance in Human Pancreatic Cancer"
   National Pancreas Foundation
   Project Period: 10/01/01 – 9/30/02
   PI: Mark P. Callery, M.D.

2. "Overcoming Chemoresistance in Human Pancreatic Cancer"
   American Hepato-Pancreato-Biliary Association
   Project Period: 7/01/00 – 6/30/03
   PI: Nicole M. Chandler, M.D.

3. "Research Support"
   Beth Israel Hospital Foundation
   Project Period: 9/24/01 – 9/30/02
   PI: Mark P. Callery, M.D.

IV. Plans for the Coming Academic Year

Staff Changes / Recruitments

1. Recruitment is underway for a full-time laboratory Co-Director.

V. Bibliography (07/01/01-06/30/02)

Original Articles

1. Shah SA, Potter MW, Hedeshian MH, Kim RD, Chari RS, **Callery MP**. PI-3' kinase and NF-kappaB cross-signaling in human pancreatic cancer cells. *J Gastrointest Surg* 2001; 5(6):603-612.

2. Ricciardi R, Foley DP, Quarfordt SH, Donohue SE, Wheeler SM, **Callery MP**, Meyers WC. Donor hepatic function: a factor in postreprefusion syndrome. *J Gastrointest Surg* 2002; 6(2): 248-254.

3. Ricciardi R, Foley DP, Quarfordt SH, Kim RD, Donohue SE, Wheeler SM, Chari RS, **Callery MP**, Meyers WC. Alterations in intrahepatic hemodynamics of the harvested porcine liver. *J Gastrointest Surg* 2001;5(5):490-498.

4. Ricciardi R, Anwaruddin S, Schaffer BK, Quarfordt SH, Donohue SE, Wheeler SM, Gallagher KA, **Callery MP**, Litwin DE, Meyers WC. Elevated intrahepatic pressures and decreased hepatic tissue blood flow prevent gas embolus during limited laparoscopic liver resections. *Surg Endosc* 2001;15(7):729-733.

5. Ricciardi R, Schaffer BK, Kim RD, Shah SA, Donohue SE, Wheeler SM, Quarfordt SH, **Callery MP**, Meyers WC, Chari RS. Protective effects of ischemic preconditioning on the cold-preserved liver are tyrosine-kinase dependent. *Transplantation* 2001;72(3):406-412.

Original Articles (in press)

1. Ricciardi R, Shah SA, Wheeler SM, Quarfordt SH, **Callery MP**, Meyers WC, Chari RS. Regulation of NF-kappaB in hepatic ischemic preconditioning. *J Am Coll Surg* 2002; 195(3): 319-326.

2. **Chandler NM, Canete JJ**, Stuart KE, **Callery MP**. Preoperative chemoradiation in resectable pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2002, in press.

Reviews, Chapters, and Editorials

1. Shah SA, Potter MW, **Callery MP**. Ubiquitin proteasome pathway: implications and advances in cancer therapy. *Surg Oncol* 2001;10:43-52.

2. Shah SA, Potter MW, **Callery MP**. Ubiquitin proteasome inhibition and cancer therapy. *Surgery* 2002;131(6):595-600.

Reviews, Chapters, and Editorials (in press)

1. **Canete JJ, Chandler NM, Callery MP**. Laparoscopy Ultrasonography In: Laparascopic Surgery: Principles and Procedures, Jones DB, Wu JS, Soper NJ, eds. WB Saunders Company. 2002; in press.

William C. DeWolf, M.D.

Division of Urology

I. Narrative Report

Basic Research

Basic research within the Division of Urology is directed by three principal investigators, Drs. William DeWolf, Aria Olumi, and Sandra Gaston. The main interest of the laboratory is centered around cancer biology with regard to diseases of the genitourinary system. Investigations are performed with all of the latest techniques in biochemistry and molecular genetics. Current active projects involving my input (among others), include 1) characterization of Gp200 as a testis tumor marker for clinical and histopathologic use; 2)investigation of a new "tissue printing" technique for use in identifying positive margins and studying molecules associated with invasiveness and 3) investigation of RNA inhibition on ion channels in prostate cancer. This is a new initiative and will study phenotypic loss of calcium channels in prostate cancer cell lines.

Clinical Research

Clinical research within the Division of Urology is very active. Included is an analysis of a ten year experience of patients who have undergone radical prostatectomy. Their case histories with data have been put into a computerized retrieval system for data analysis. Thus far, four manuscripts have been generated and/or submitted for publication.

II. List of Current Employees

1. W. Michael Schopperle, Ph.D. Postdoctoral Fellow

III. List of Current Funding

1. Intramural

2. "Matrix Metaloproteinase 9: Tumor Marker or Risk Factor for Prostate Cancer"
   Massachusetts Department of Public Health
   Project period: 01/01/2001 – 12/30/2004
   Principal Investigator: Sandra Gaston, Ph.D.
   Co-Investigator: William C. DeWolf, M.D.

IV. Applications Submitted and Pending Review/Funding

1. "Characterization of Podocalyxin/glucose 3 Transporter in Human Testis Cancer"
   American Foundation for Urologic Disease
   Project period: 07/01/03 – 06/30/05
   PI: W. Michael Schopperle, Ph.D.
   Mentor: William DeWolf, M.D.

2. "Characterization of Podocalyxin/glucose 3 Transporter in Human Testis Cancer"
   American Cancer Society
   Project Period: 07/01/03 – 06/30/05
   PI: W. Michael Schopperle, Ph.D.
   Mentor: William DeWolf, M.D.

V. Divisional Accomplishments over the Past Year

Research Accomplishments

We have completed another phase of work on Gp200 which is a sialomucin expressed on embryonal carcinoma cells. This next installment of work has identified and sequenced the Gp200 protein which has been identified as podocalyxin. To our surprise and delight, we have discovered that glut-3 (which is a glucose transporter isoform found in human testis and brain), co-purifies with podocalyxin; thus, podocalyxin and glut-3 transporter form a stable complex in EC cells. The basis for this interaction is not known, however, podocalyxin has a PDZ-binding site in its intracellular domain that may play a role in forming protein-protein complexes. Further work is now planned looking at the molecular mechanisms underlying the formation of podocalyxin and glut-3 complex and provide some insight into why a glucose transporter is interacting with a sialomucin in cancer cells. Another basic/translational project that has been completed is the "tissue printing" project. This involves a conceptually simple way of using molecular technology to "visualize" the entire surface of an organ by wrapping it in nitrocellulose paper to capture surface molecules. The nitrocellulose is then processed in one of several ways to determine if there are malignant cells on its surface. Using this technology, positive margin assessment is made. Furthermore, this technology allows for recapture of those malignant cells at the surface for further molecular analysis to help investigate causes and changes responsible for its invasive character. These "add-on" studies may involve polyacrylamide gel electrophoresis, Western Blotting, zymography, and mass spectroscopy analysis (or related technology). Thus far, we have been able to identify unique collagen fragments and PSA at the surface of prostate glands with positive or near-positive margins as determined by whole mount pathologic analysis.

Clinical research projects have been very productive with special regard to use of our prostate cancer data base. Manuscripts regarding biopsy technique and results as well as clinical outcome and predictors of recurrence have been submitted and accepted (see Bibliography).

Individual Accomplishments

1. Member of the NIH Site Visit Team for evaluation of NCI Intramural Urologic Oncology Branch Programs.

2. AUA Program Committee for Basic Research: Prostate Cancer.

3. President, National Urologic Forum.

4. Member of Medical Advisory Board, Boston Prostate Cancer Walk.

VI. Report of Teaching

Undergraduate and Medical School Courses

Undergraduate Research Opportunities Program. This is an MIT-based teaching program in which 3-5 undergraduates rotate through our laboratory on a 6-12 month basis science projects and gain experience in biological research. This is particularly important because it is the only undergraduate course with opportunity to view surgical operations as part of the curriculum. Additional medical school teaching includes SU518M.1 which is a general course in urologic science for medical students. The course includes a 1 month rotation on the urology service and involves clinical and didactic experience relating to urologic disease.

CMR Courses

"Cell cycle regulators: Guardian of the Genome. Urologic Cancer Course, Harvard Medical School, Department of Continuing Education. Boston. 10/2002

VII. Plans for the Coming Academic Year

Staff Changes/Recruitments

1. Over the next year, the division has significant changes in mind for recruitment and specialty supplementation. Additions are being sought in the subspecialties of urodynamics, female incontinence, bladder cancer (for both basic and clinical work) and endourology/urinary stone disease. Recruitment is already underway with prime candidates already identified for each area. Each of the individuals will be starting a new program in either basic and/or clinical research as they arrive over the next one year.

Plans for Research

1. There will be one new research project starting by Dr. Schopperle involving suppression of ion channels in prostate cancer by RNA interference. Prostate cancer cell lines express tissue-specific calcium channels that may have fundamental roles in the growth and survival of the cancer cell. In an effort to gain insight into the importance of these ion channels and prostate cancer, we will use RNA interference to eliminate protein expression levels in the cell lines and determine the phenotypic effects of loss of calcium channels on the prostate cancer cell lines.

VIII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Gollob JA, Upton MP, **DeWolf WC,** Atkins MB. Long term remission on a patient with metastatic collecting duct carcinoma treated with taxol/carboplatin and surgery. *Urology* 2001;58(6):1058.

2. Kerfoot BP, **DeWolf WC.** Does the outpatient setting provide the best environment for medical students learning of urology? *J Urol* 2002;167:1797-1799.

3. O'Donnell MA, Krohn J, **DeWolf WC.** Salvage intravesical therapy with interferon alpha2B plus low dose Bacillus Calmette-Guerin is effective in patients with superficial bladder cancer in whom BCG alone previously failed. *J Urol* 2001;166:1300-1305.

4. Yin Y, Stahl BC, **DeWolf WC,** Morgentaler A. p53 and Fas are sequential mechanisms of testicular germ cell apoptosis. *J Androl* 2002;23:64-70.

Original Articles (in press)

1. Bubley G, Balk S, Regan M, Duggan S, Morrissey M, **DeWolf WC,** Salgaami E, Mantzoros C. Serum IGF-1 and IGF-1 binding proteins after radical prostatectomy. *J Urol* 2002; in press.

2. SanFrancisco I, **DeWolf WC,** Rosen S, Upton M, Olumi A. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. *J Urol* 2001; in press.

3. Ung J, SanFrancisco I, Regan M, **DeWolf WC,** Olumi A. The relationship of prostate gland volume to extended needle biopsy on prostate cancer detection. *J Urol* 2002; in press.

4. Zhang PL, Bubley G, Upton M, Morgentaler A, **DeWolf WC,** Rosen S. Pathologic features of occult prostate carcinoma in hypogonadal men. *Prostate* 2002; in press.

5. Zhang PL, Rosen S, Veeramadianeni R, Kao J, **DeWolf WC,** Bubley G. The association between prostate cancer and serum testosterone levels. *Prostate 2002;* in press.

Reviews, Chapters, and Editorials

1. **DeWolf WC.** Best of AUA: Renal cell carcinoma. *Urology Times* 2001;29:31-37.

2. **DeWolf WC.** Take home message: Renal cell carcinoma. *AUA News* 2001;6:12-16.

3. **DeWolf WC, Gaston SM.** Failure to achieve castrate levels of testosterone during LHRH agonist therapy. *Urol Times* (Editorial) 2001;28:43.

4. **DeWolf WC, Gaston SM.** PSA kinetics at tumor recurrence following radical prostatectomy do not suggest a worse disease prognosis in African-American men. *J Urol* (Editorial) 2001;166:1331-1332.

5. **DeWolf WC, Gaston SM.** The role of cell cycle regulators in cancer: An overview for urologists. *Aktuel Urol* 2001;32:113-120.

Proceedings of Meetings

1. **Gaston S,** Hess S, Shah S, Cusano N, Tung S, **DeWolf WC,** Perides G. Matrix metalloprotease 9: Tumor marker or risk factor for prostate cancer. *Proc Am Assoc Cancer Res* 2001;42:948.

Abstracts

1. **Gaston S,** Siddiqui M, Soares M, Perides G, Upton M, **DeWolf WC.** Development of molecular markers for prostate cancer local T staging. Capsular penetration positive, margin negative disease in associated with matrix metalloproteinase and collagen fragments on the external surface of the prostate gland. *J Urol* 2002;167:224A.

2. **Olumi A,** Xiao Y, SanFrancisco I, Peehl D, **DeWolf WC.** Retroviral transfection of human telomerase gene move commonly promotes senescence than expansion of life span in prostate fibroblasts. *J Urol* 2002; 167:210A.

3. SanFrancisco I, **Olumi A,** Kao J, Rosen S, **DeWolf WC.** The natural history of prostatic intraepithelial macroplasia as defined by extended biopsy. *J Urol* 2002;167:70A.

4. Ung J, SanFrancisco I, Regan M, **DeWolf WC, Olumi A.** Lower prostate cancer detection rate in large prostate glands is not associated with biopsy sampling error. *J Urol* 2002;167:333A.

F. Henry Ellis, Jr., M.D., Ph.D.
Massino Loda, M.D.

Division of Cardiothoracic Surgery
Department of Adult Oncology, Dana Farber Cancer Institute

I. Narrative Report

We have previously shown that lack of p27 in esophagogastrectomy specimens is associated with aggressive behavior of Barrett's Associated Adenocarcinoma (BAA). We have recently established an animal model to induce both Barrett's Esophagus and BAA in mice, and subsequently have shown that the rate of cancer development is greatly enhanced in p27 KO mice. Current studies, to be completed in December 2002, are designed to determine whether use of flavopiridol, an inhibitor of CDKs, including CDK-2, can reduce this high cancer rate in p27 KO mice.

II. List of Current Employees

1. Xiangjun Xu, M.D., Ph.D. Postdoctoral Fellow
2. Mirna Lechpammer, M.D., Ph.D. Postdoctoral Fellow

III. List of Current Funding

1. Thelma and Jerry Stergios Fund for Thoracic Surgical Education and Research.
2. Allen Jarabeck Esophageal Cancer Research Fund.

IV. Applications Submitted and Pending Review/Funding

1. Application to Damon Runyon Cancer Research Foundation for a Fellowship Award for Mirna Lechpammer has been submitted for review.

V. Divisional Accomplishments over the Past Year

1. Dr. Ellis attended the annual meeting of American Association for Thoracic Surgery. Washington D.C., May 5-8, 2002.

VI. Plans for the Coming Academic Year

1. Projected studies will employ novel CDK2 specific inhibitors in p27 KO mice. In order to determine the specific molecular targeting of tested CDK inhibitors, anti-Rb phosphospecific antibodies will be studied by immunohistochemistry of the tumors of treated and untreated animals.

VII. Bibliography (07/01/01-06/30/02)

Original Articles

1. **Ellis FH Jr,** Xu X, Kulke MH, Locicero J III, Loda M. Malignant transformation of the esophageal mucosa is enhanced in p27 knock out mice. *J Thor Cardiov Surgery* 2001;122:809-814.

Review, Chapters and Editorials:

1. **Ellis FH Jr.** Vagotomy, antrectomy, and Roux-en-y diversion: In: Esophageal Surgery. Pearson FG et al editors. Philadelphia, PA: Churchill Livingston 2nd ed. 2002;pp.443-8.

2. **Ellis FH Jr.** Open Nissen fundoplication: In: Esophageal Surgery. Pearson FG et al editors. Philadelphia, PA: Churchill Livingston 2nd ed. 2002;pp.319-26.

Christiane Ferran, M.D., Ph.D.

Division of Transplantation

I. Narrative Report

Basic research

Most of my time effort, i.e. eighty five per cent, is devoted to Research. My major research interests are in the field of vascular biology, transplantation including xenotransplantation and islet transplantation as well as autoimmune diabetes, acute liver failure and liver regeneration. More specifically, the work in my laboratory is focused on the understanding of the function (s) of the anti-apoptotic genes A20, Bcl-2, Bcl-x_L and A1 in different cell types, their relationship to the pathophysiology of diseases and their potential therapeutic use in organ transplantation, diabetes, atherosclerosis, hepatitis and liver regenration. This interest is based on our original finding that these genes, mainly A20 serve a broad cytoprotective function in endothelial cells, islets and hepatocytes and an atheroprotective function in smooth muscle cells. Expression of A20 in endothelial cells, islets and hepatocytes not only protects the cells from apoptosis but also serve a broad anti-inflammatory purpose by blocking NF-κB activation. Expression of A20 in smooth muscle cells inhibit their proliferation and sensitizes them to apoptosis hence significantly protects from atherosclerosis and transplant associated vasculopathy.

II. List of Current

1.	Shane T. Grey, Ph.D.	Assistant Professor of Surgery
2.	Maria B. Arvelo, M.D.	Post-doctoral fellow
3.	Soizic Daniel, Ph.D.	Post-doctoral fellow
4.	Virendra I. Patel, M.D.	Surgical Resident

III. List of Current Funding

1. "Genetic Engineering of Xenogeneic Islets with Anti-apoptotic Genes and Cytokine Inhibitors".
   National Institutes of Health, PO1 # DK53087
   Project period: 12/1997- 11/2002
   Principal Investigator: Dr. Christiane Ferran
   Program Director: Dr. Gordon Weir, Joslin Clinic

2. "Role of the anti-apoptotic gene A20 in prevention of auto-immune diabetes in NOD mice".
   Harvard Institute for the cure of juvenile diabetes, funded by the Juvenile Diabetes Foundation.
   Project period: 09/1998-08/2003
   PI: Dr. Christiane Ferran
   Program Head: Dr. Hugh Auchincloss Jr.

3. "Protective effect of A20 against Transplant-Associated Vasculopathy"
   Roche Organ Transplantation Research Foundation
   Project period: 11/2001-10/2004
   PI: Dr. Christiane Ferran

4. " Gene transplantation with A20 to improve islet transplantation
   National Institutes of Health, 1R21 # DK62601
   09/2002-08/2004
   PI: Dr. Christiane Ferran

5. The Longwood Vascular Biology Training Grant
   National Institutes of Health, T32.
   PI: Dr. Christiane Ferran
   Program Director: Dr. Grank W. LoGerfo

IV. Applications Submitted and Pending Review/Funding

1. "Improved liver function and regeneration with A20"
   National Institutes of Health, RO1 Grant # DK063275
   Title: Reviewed June 2002
   Priority Score: 172, Percentile: 7.3
   Expected to be funded for 5 years starting 12/2002
   PI: Dr. Christiane Ferran

V. Divisional Accomplishments

Educational activities

1. Beth Israel/Deaconess Medical Center, Harvard Medical School.
   I was a lecturer at the weekly Seminars of the Transplantation division
   Title: "A20 protects from transplant associated vasculopathy".

2. Beth Israel/Deaconess Medical Center, Harvard Medical School.

I was a lecturer at the Research Seminar of the Department of Surgery
Title: “Cytoprotective genes and regulation of inflammatory responses”.

3. Beth Israel/Deaconess Medical Center, Harvard Medical School.
I was a lecturer at the Surgery grand rounds
Title: " The graft unveils it secrets: Cytoprotective genes and graft rejection".

International Presentations

1. I gave a lecture at the Transplantation Grand Rounds, University of Pennsylvania Medical Center, school of Medicine, Philadelphia, Pennsylvania. Topic: “Protective strategies to overcome allograft rejection”. February 4-5, 2002.

2. Dr. Longo gave a poster presentation at the American Heart Association 2001 meeting, November 10-14 2001 Anaheim, CA. “A20 protects from CD40-CD40 ligand mediated endothelial cell activation and apoptosis”.

3. Dr. Kunter gave a poster presentation at the 2001 American Society of Nephrology/ International Society of Nephrology World Congress, October 12-17 2001, San Francisco, CA. " Differential effects of the cytoprotective proteins A1 and A20 in renal proximal tubular cells".

4. Dr. Kunter gave a poster presentation at the 2001 American Society of Nephrology/ International Society of Nephrology World Congress, October 12-17 2001, San Francisco, CA. " Expression of A20 in the vessel wall of rat kidney allografts correlates with protection from transplant arteriosclerosis".

5. Dr. Longo gave an oral presentation at the American Transplant Congress April 26-May 1, 2002, Washington, DC. “A20 protects from lethal radical hepatectomy and promotes liver regeneration".

6. Dr. Longo gave an oral presentation at the American Transplant Congress April 26-May 1, 2002, Washington, DC. “Genetic engineering of ilsets with A20 overcomes primary non-function".

7. Dr. Longo gave an oral presentation at the American Transplant Congress April 26-May 1, 2002, Washington, DC. “A20 protects from CD40-CD40 ligand mediated endothelial cell activation and apoptosis and prevent transplant associated vasculopathy".

8. Dr. Grey replaced me for a lecture at the 2002 FASEB summer Research Conference on Transplantation Immunology. Topic: Endothelial cell cytoprotection in Transplantation". The Vermont Academy in Saxtons River, Vermont. June 15-20, 2002.

VI. Plans for the Coming Academic Year

Staff changes

1. Meis Moukkayed, PhD from Cambridge University England will join my group as a post-doctoral fellow.

2. Research Assistant to be hired.

Grant Applications to be Submitted

1. " Atheroprotective function of A20 in Smooth muscle Cells" RO1 NIH grant to be submitted February 1st 2003.

2. "Protective role of A20 against diabetic vasculopathy". To be submitted June 1st 2003 to NIH as an RO1 and possibly concomitantly to the JDFI.

Regional, National and International Invitations

1. Invited speaker at the 2ND International Congress on Immunosuppresion. Plenary session, topic: " Strategies to overcome chronic rejection". San Diego, California. December 5-8, 2001.

2. Invited Speaker at annual meeting of the Royal Society of Medicine. Topic: Xenotransplantation". London, UK. March 20, 2002.

3. Invited Speaker and chairman at the annual meeting of the Transplantation Society of Australia and New Zealand. Topic: "Protective strategies to overcome organ rejection". Canberra, Australia. April 10-12th, 2002.

4. Invited Speaker at the weekly meetings of the Harvard/Longwood Vascular Biology Seminars, Children's Hospital, Boston, MA. March 7 2003. Topic: " Vasculoprotective function of A20" .

VIII. BIBLIOGRAPHY (7/01/01-6/30/02)

Original Articles

1. Arvelo MB, Cooper JT, Longo C, Daniel S, Grey S, Mahiou J, Csizmadia E, Abbujawdeh G, **Ferran C.** A20 protects mice from D-galactosamine/ lipolysaccharide acute toxic lethal hepatitis. *Hepatology* 2002;35:535-543.

2. Avihingsanon, Y, Ma N, Csizmadia E, Wang C, Pavlakis M, Strom TB, Soares M and **Ferran C.** Expression of protective genes in human renal allografts: a regulatory response to injury associated with graft rejection. *Transplantation* 2002;73:1079-1085.

3. Laybutt DR, Kaneto H, Hasenkamp W, Grey S, Jonas JC, Groff A, **Ferran C**, Bonner-Weir S, Sharma A, Weir GC. Increased expression of antioxidant and anti-apoptotic genes in islets that may contribute to beta-cell survival during chronic hyperglycemia. *Diabetes* 2002;51:413-423.

4. Millan MT, Natkunam Y, Clarke-Katzenberg R., Desai D, Prapong W, So SK Esquivel CO, **Ferran C** and Martinez O. EBV infection is associated with endothelial bcl-2 expression in transplant liver allografts. *Transplantation* 2002;73:465-469.

Original Articles (in press)

1. Kunter U, Floege J, von Jurgenson AS, Stojanovic T, Merkel S, Grone HJ, **Ferran C.** Expression of A20 in the vessel wall of rat kidney allografts correlates with protection from transplant arteriosclerosis. *Transplantation* 2002; in press.

Proceedings of Meetings

1. Longo CR; Arvelo MB, Grey ST, Daniel S, Mahiou J, Patel VI, **Ferran C.** "A20 protects from CD40-CD40 ligand mediated endothelial cell activation and apoptosis". *Circulation* 2001;104(2):171A.

Reviews Chapters, and Editorials

1. **Ferran C.** The graft unveils its secrets: Provocative therapeutic leads to protect vascularized organs. *Transplant Immunol* 2002;9(2-4):135-136.

Josef E. Fischer, M.D.

Division of General Surgery
Chairman, Department of Surgery

I. Bibliography (07/01/01-06/30/02)

Original Articles

1. McCarter FD, James JH, Luchette FA, Wang L, Friend LA, King JK, Evans JM, George MA, **Fischer JE**. Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. *J Surg Res* 2001;99:235-244.

2. McCarter FD, Nierman SR, James JH, Wang L, King JK, Friend LA, **Fischer JE**. Role of skeletal muscle Na^+-K^+ ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci* 2002;70:1875-88.

3. Pritts TA, Hungness ES, Hershko DD, Robb BW, Sun X, Luo GJ, **Fischer JE**, Wong HR, **Hasselgren PO**. Proteasome inhibitors induce heat shock response and increase IL-6 expression in human intestinal epithelial cells. *Am J Physiol Regul Integr Comp Physiol* 2002;282:R1016-R1026.

Original Articles (in press)

1. Pritts TA, Wang Q, Sun X, Fischer DR, Hungness ES, **Fischer JE**, Wong HR, **Hasselgren PO**. The stress response decreases NF-kappaB activation in liver of endotoxemic mice. *Shock* 2002; in press.

Reviews, Chapters, and Editorials

1. Fischer DR, Pritts TA and **Fischer JE**. Perioperative management and nutrition in patients with liver and biliary tract disease. In: *Shackelford's Surgery of the Alimentary Tract*, 5th edition (Zuidema GD and Yeo CJ, eds). Philadelphia: W.B. Saunders, 2001;321-333.

2. **Fischer JE.** Central splenorenal shunts. In: *Mastery of Surgery*, 4th Edition (Baker RJ and **Fischer JE**, editors). Philadelphia: Lippincott, Williams & Wilkins, 2001;1367-1373.

3. **Fischer JE**. Funding strategies and agencies. Academic-industrial relationships; intellectual property. In: Souba WW, Wilmore DW, editors. *Surgical research*. San Diego: Academic Press; 2001;63-9.

4. **Fischer JE**. Gastrointestinal-cutaneous fistulas. In: *Mastery of Surgery*, 4th Edition (Baker RJ and **Fischer JE**, editors). Philadelphia: Lippincott, Williams & Wilkins, 2001;1435-1441.

5. **Fischer JE**. Invited commentary on Radiofrequency Ablation of Unresectable Primary Liver Cancer. *J Am Coll Surg* 2002;194:828.

6. **Fischer JE**. Metabolism in surgical patients: Protein, carbohydrate, and fat utilization by oral and parenteral routes. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, editors. *Sabiston textbook of surgery: the biological basis of modern surgical practice,16th ed.* Philadelphia: W.B. Saunders, 2001;90-130.

7. **Fischer JE**. Segmental resection for diverticulitis. In: *Mastery of Surgery,* 4th Edition (Baker RJ and **Fischer JE**, editors). Philadelphia: Lippincott, Williams & Wilkins, 2001;1524-1537.

8. **Fischer JE**. Socio-economic activism in a changing medical workplace. *Am J Surg* 2002; in press.

9. **Fischer JE**. Unresectable liver metastases. *J Am Coll Surg* 2002;195:359-360.

10. Gang G and **Fischer JE**. Nutritional support in the surgical patient. In: *Current Surgical Therapy*, 7th edition (Cameron JL, ed). St. Louis: Mosby, 2001;1258-1262.

11. Pritts TA, Fischer DR, **Fischer JE**. Postoperative enterocutaneous fistula. In: Holzheimer RG, Mannick JA, editors. *Surgical treatment – evidence-based and problem- oriented.* Bern/Wien/New York: W. Zuckschwerdt Verlag München; 2001;134-9.

Clinical Communications

1. Luchette FA, James JH, **Fischer JE**. Does epinephrine explain hyperlactatemia in cardiogenic shock? *Crit Care Med* 2001;29:1848.

2. Luchette FA, Jenkins WA, Friend LA, Su C, **Fischer JE**, James JH. Hypoxia is not the sole cause of lactate production during shock. *J Trauma* 2002;52:415-419.

3. Stern LE, Nussbaum MS, Quinlan JG, **Fischer JE**. Long-term evaluation of extended thymectomy with anterior mediastinal dissection for myasthenia gravis. *Surgery* 2001;130:774-780.

Aniruddha Ganguly, Ph.D.

Division of Colon and Rectal Surgery
Laboratory of Cancer Biology

I. Narrative Report

Basic and Clinical Research

My laboratory focuses on elucidating some molecular mechanisms involved in tumor development and metastasis. Studies are aimed at understanding the interaction of tumor cell, macrophages and endothelial cells in tumorigenesis (particularly colon and breast tumorigenesis). We are also examining the interaction of macrophages and epithelial cells in inflammatory bowel disease.

In this regard, we recently discovered a novel protein on human macrophages that binds to a tumor-derived glycoprotein. Upon activation of this protein following binding with the tumor-derived glycoprotein, macrophages release a series of biological response modifiers. These substances initiate a cascade of molecular interactions in the tumor microenvironment involving macrophages, tumor cells and endothelial cells. This has implications in tumor development. We will therefore biochemically characterize the protein, clone the gene of interest and design experiments both *in vitro* and *in vivo* to understand its role in tumorigenesis and in other diseases. An understanding of the mechanisms of tumorigenesis relative to expression of the macrophage protein is needed for effective management and ultimately in the development of therapeutic approaches to control and prevent the disease.

Another focus is to study the role of a patented compound in colorectal tumor development and metastasis in the liver. The compound is an inhibitor of carbohydrate processing enzymes and therefore interferes with glycoprotein synthesis by the tumor cells. Since glycoproteins play a significant role in tumor development and metastasis, we want to examine how differential glycosylation or interference in the expression of branched carbohydrates by the tumor cells affects tumor development and metastasis.

II. List of Current Employees

1.	Jonathan Robbins, BA	Research Assistant
2.	Marissa Newton, BS	Research Assistant
3.	Helen Yeung	Student
4.	Erin Opelka	Student
5.	Anindita Chakrabarti	Student
6.	Frank Andrew Opelka	Student
7.	Kimberly Nguyen	Student

III. List of Current Funding

1. "A Macrophage Protein in Colon Tumorgenesis"

NIH R01 CA87678-01
Project period: 07/01/01 - 06/30/03
Principal Investigator: Dr. Aniruddha Ganguly

2. Wendy Will Case Cancer Fund, Inc.
Principal Investigator: Dr. Aniruddha Ganguly

3. Corporate Funding
Principal Investigator: Dr. Aniruddha Ganguly

4. Aids for Cancer Research
Principal Investigator: Dr. Aniruddha Ganguly

5. Gift Account
Principal Investigator: Dr. Aniruddha Ganguly

IV. Applications Submitted and Pending Review/Funding

1. "A Macrophage Protein in Colon Tumorgenesis"
NIH R01 CA87678
Project period: 04/01/03 – 03/31/08
Principal Investigator: Dr. Aniruddha Ganguly

V. Divisional Accomplishments

Research accomplishments (including new grants/programs)

1. We were able to begin studies and obtain preliminary results that emphasize the physiological relevance of a new macrophage protein (discovered by me) in tumorigenesis. Some of the research accomplishments are listed in the bibliography section.

2. We initiated a collaboration with Dr. Frank Opelka (Chief, Colon and Rectal Surgery) on research concerning mechanisms of colorectal tumor development and metastasis. We will examine protein/gene expressions from primary tumors and liver metastasis from colorectal cancer. We will also examine serum samples for identification of a few key marker proteins in colorectal cancer patients.

Individual Accomplishment

1. I was the Chairperson, Residents Research Orientation Committee. I was responsible for organizing an orientation program for residents in the Department of Surgery. For the program, I prepared a brochure, organized talks concerning research in Surgery, and organized a pizza dinner .

VI. Report of Teaching

Undergraduate and medical school courses

1. Teaching Faculty, Harvard Medical School (HMS), Boston, MA. Course: Integrated Human Physiology.

Invited presentation (local, national and international)

1. "A Macrophage Protein in Tumor Development". Division of General Thoracic Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, 2001.

2. "Macrophages in Tumorigenesis". Surgical Research Seminar Series, Department of Surgery, Beth Israel Deaconess Medical Center, 2002.

3. "Mechanisms of Tumorigenesis". School of Life Sciences, Jawaharlal Nehru University, New Delhi, India, 2002.

4. "Interaction of Macrophages in Colorectal Tumor Development". Department of Biophysics, University of Delhi South Campus, New Delhi, India, 2002.

5. "Interaction of Macrophages in Tumor Development". Surgical Grant Rounds, Department of Surgery, Beth Israel Deaconess Medical Center, 2002

VII. Plans for the Coming Academic Year

Staff changes/recruitments

1. Undecided

Plans for research (new grants/programs)

1. Continue with the same program. Planning to submit new grants

Plans for educational programs

1. Continue with the same course as mentioned above. In addition, I am interested in teaching/training surgical fellows interested in cancer research.

VIII. Bibliography (7/01/01-6/30/02)

Original Articles

1. Palombo JD, **Ganguly A**, Bistrian BR, Menard MP. The antiproliferative effects of biologically active isomers and a metabolite of conjugated linoleic acid on human colorectal and prostatic cancer cells. *Cancer Letters* 2002;177:163-172.

Books, Monographs, and Text Books:

1. Thomas P, Bajenova O, Zimmer R, Hayashi H, Forse RA, and **Ganguly A**. Kupffer Cell Carcinoembryonic Antigen (CEA) Interactions. A Mechanism to Enhance Liver Metastasis from CEA Producing Cancers. In: Cells of the Hepatic Sinusoid. Rijswijk, The Netherlands: The Kupffer Cell Foundation 2001;8:155-8.

Abstracts

1. **Ganguly A**, Pannell Jr R, Argos M. Analysis of a new macrophage protein in colon tumor development. *Proc Am Assoc Cancer Res* 2002;43:1136.

Sandra M. Gaston, Ph.D.

Division of Urology

I. Narrative Report

Our primary research interests focus on the molecular biology of urological cancers, and specifically on the molecular changes that underlie malignant progression in prostate and bladder cancers. One of the major goals of my research program is the development of more informative prognostic molecular markers for early prostatic malignancies, with priority effort given to the identification and characterization of potential targets for therapeutic intervention. We are also developing a new line of research that is focused on the molecular basis of male infertility.

At present, there are three major prostate cancer projects underway in my laboratory:

1. With NIH and CaPCURE support, we are developing a battery of micro-scale bioassays that can be used to monitor androgen receptor ligands in complex biological fluids including sera and tissue extracts.

2. With Massachusetts Department of Public Health Support, we are characterizing the role of constitutive matrix metalloproteinase 9 (MMP9) expression in prostate cancer risk and progression.

3. With corporate research support, we have developed a novel strategy for identifying molecular markers of tumor invasion of the prostate capsule. This "tissue printing" technology detects macromolecules blotted directly from the surface of a fresh tissue specimen onto a nitrocellulose membrane, and results in a two-dimensional molecular map of the surface of the tissue.

II. List of Current Employees

1.	Lynn Mathew	Research Technician
2.	Mark Brice	Research Technician
3.	Rusan Hsiao	Research Technician
4.	Dang Vu	Student
5.	Marc Soares	Student
6.	Jennifer Shih	Student
7.	Karolina Corin	Student
8.	Jennifer Chang	Student
9.	Tae Wan Kim	Student
10.	Stephanie Chow	Student
11.	Ilana Kahn	Student
12.	Sven Chilton	Student
13.	Dana Goldner	Student
14.	Elizabeth Cherella	Student

III. List of Current Funding

1. " Androgen Receptor Biochips: Prostate Cancer Management"
   National Institutes of Health, NCI R/R33 CA86365
   Principal Investigator: Ian Hunter Ph.D., MIT
   Principal Investigator: Sandra M. Gaston, Ph.D., BIDMC Subcontract

2. "Prostate Cancer Biomakers in Urine"
   GMP Companies, Inc.
   Project period: 07/01/2001 - 07/31/2003
   Principal Investigator: Bruce Zetter, Ph.D., Children's Hospital
   Principal Investigator: Sandra M. Gaston, Ph.D., BIDMC Subcontract

3. "Matrix Metalloprotease 9: Tumor Marker or Risk Factor for Prostate Cancer?"
   Massachusetts Department of Public Health
   Project period: 01/01/2001 - 12/30/2004
   Principal Investigator: Sandra M. Gaston, Ph.D.
   Co-Investigator: William C. DeWolf, M.D.

4. "3T Magnetic Resonance and Spectroscopy of Prostate Cancer"
   General Electric Industry Sponsored Research
   Project period: 01/01/2002 - 12/31/2002
   Principal Investigator: Robert Lenkinski, Ph.D. (BIDMC Radiology)
   Co-Investigator: Sandra M. Gaston, Ph.D.

5. "Y- Chromosome Micro-Deletions Test on Sperm DNA"
   Repromedix Industry Supported Research
   Project period: 06/01/2001 - present (pilot phase)
   Principal Investigator: Sandra M. Gaston, Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "Molecular Mapping of Prostate Cancer Invasion: Rapid Assessment of Capsular Invasion and Surgical Margin Status"
   Department of Defense Prostate Cancer Research Program (submitted May 2002)
   Principal Investigator: Sandra M. Gaston, Ph.D.

2. "Spatial-Molecular Mapping of Molecular Markers of Tumor Invasion of the Prostate Capsule"
   Dana Farber/Harvard Cancer Center Prostate Cancer SPORE Developmental Grant (submitted September 2002)
   Principal Investigator: Sandra M. Gaston, Ph.D.

3. "New Technologies for Monitoring Nutritional Management in the Treatment of Prostate and Breast Cancer: Microscale Bioassay of Hormonal Responses to Dietary Soy Phytochemicals"
   Osher Institute Pilot Study Grant (to be submitted October 2002)
   Principal Investigator: Sandra M. Gaston, Ph.D.

4. "Are the Margins Positive? Translating Molecular Technologies into Intra-operative Tools for Assessment of Surgical Margins During Partial Mastectomy
Komen Breast Cancer Research Grant (submitted October 2002)
Principal Investigator: Sandra M. Gaston, Ph.D.

5. National Institute of Health PAR 01-01-106 R21/R33 Applications of Innovative Technologies for the Molecular Analysis of Cancer: Phased Technology Application Award (to be submitted February 2003)
Principal Investigator: Sandra M. Gaston, Ph.D.

V. Divisional Accomplishments

Accomplishments: BIDMC Andrology Laboratory

1. We had successful re-accreditation of the BIDMC Andrology Laboratory by the College of American Pathology (CAP). The Andrology Lab currently provides services to approximately 40 patients per month (approximately 400-450 per year). Patients are referred to the laboratory for testing by BIDMC affiliated and staff physicians, primarily urologists, obstetrician-gynecologists and primary care physicians.

2. We obtained continued industry sponsorship for the clinical Andrology research study "Y- Chromosome Micro-Deletions Test on Sperm DNA" (Sponsored by Repromedix, Woburn MA, see Current Research Grants and Contracts).

3. We continued to accrue samples to a research bank of frozen semen samples used as a resource for the study of secreted prostate biomarkers and biomarkers of male fertility. This bank captures approximately 30 new samples per month and provides an important source of control samples for our prostate cancer studies (IRB: W-00-0427-EX).

Research Accomplishments

At present, there are three major prostate cancer projects underway in my laboratory :

1. With NIH and CaPCURE support, we are developing a battery of micro-scale bioassays that can be used to monitor AR ligands in complex biological fluids, including sera and tissue extracts. These include a series of yeast-based bioassays formatted on a "living chip" platform that allows us to perform the analysis using significantly smaller sample volumes (less than 0.1 microliter per test point) than is possible with conventional bioassays, a significant advantage when the analysis involves unique clinical specimens. In contrast to the immunoassays currently used in clinical settings, our yeast based bioassays measure the net AR response to all of the receptor-available ligands in a sample of serum or tissue extract. Our recently published studies with these bioassays indicate that, in an animal model, serum bioassay measurements of AR ligand are a better predictor of prostate tumor response to soy dietary supplements than either total serum testosterone or total

serum estrogen (Zhou et al. 2002, see Original Research Articles below). We are now expanding our battery of assays to include a series of functional AR mutations identified in human prostate cancers and to incorporate co-activator and co-repressor interactions. We have also begun to incorporate additional steroid hormone receptors into our micro-bioassay system, with the goal of obtaining more complete profiles of the hormonal micro-environment of target tissues and tumors. The grant supplement awarded this year will allow us to begin pilot studies to extend the microbioassay technology for breast cancer applications and to begin development of a microscale real time PCR system which, in parallel with the bioassay, will permit analysis of both receptor expression and ligand concentrations in microbiopsy tissue samples.

2. With Massachusetts Department of Public Health support, we are characterizing the role of constitutive matrix metalloproteinase 9 (MMP9) expression in prostate cancer risk and progression. Increased MMP expression and activation is associated with tumor invasion in many different cancers, including prostate cancer, but the impact of constitutive MMP expression on tumor behavior has not previously been addressed. We have found that the constitutive expression of one of the major (MMP-9) is widely variable in the prostate tissue of healthy males, and that the observed pattern of prostatic MMP-9 variability is consistent with the hypothesis of a constitutive genetic "set point". We are currently analyzing MMP-9 promoter and enhancer sequences in men with high and low constitutive MMP-9 levels, in order to identify essential regulatory elements for normal MMP-9 expression in the prostate gland. We are also comparing the clinical presentation of prostate cancers in men from the high and low constitutive MMP-9 expression groups.

3. We have developed a novel strategy for identifying molecular markers of tumor invasion of the prostate capsule. This "tissue printing" technology detects macromolecules blotted directly from the surface of a fresh tissue specimen onto a nitrocellulose membrane, and results in a two-dimensional molecular map of the surface of the tissue. Tissue prints are then further analyzed by "print-phoresis," a method by which proteins on the tissue-print image are submitted to systematic electrophoresis and characterized by specific immunoblotting techniques or by detection of endogenous protein activity (ie by zymography). We have found that tissue printing techniques provide a robust, non-destructive method for collecting protein markers from human surgical specimens, one that preserves the pattern of tumor heterogeneity and tumor-tissue interfaces. We are now coupling our tissue printing efforts with high throughput protein mass spectrometry analysis to obtain a comprehensive spatial-molecular profile of the proteins on the tissue-prints. In our analysis of tumor breaches of the prostate capsule, we anticipate that mass spec analysis of the proteins that map to the external surface of the capsule at points of tumor invasion will yield a cluster that can be mined for molecular markers that are predictive of a specific, clinically important tumor behavior. We further anticipate that the proteins which cluster at sites of tumor invasion will include markers of value for prostate cancer staging and new targets for drugs designed to inhibit metastasis. In addition, one or more protein markers associated with tumor invasion of the prostate capsule will be utilized in a rapid-print protocol, allowing

intra-operative assessment of surgical margins for residual tumor. Dr. William DeWolf, BIDMC Surgery, Dr. Melissa Upton, Dr. Elizabeth Genega and Dr. Seymour Rosen, BIDMC Pathology and Dr. Robert Lenkinski BIDMC Radiology, are important collaborators on this project.

Individual Accomplishments

1. NCI Grant CA86365 *Androgen Receptor Biochips: Prostate Cancer Management* successfully completed R21 milestones, allowing transition to R33 phase of the grant.

2. A supplement was awarded to the R33 phase of our NCI Grant CA86365 *Androgen Receptor Biochips: Prostate Cancer Management* .

3. I was a Massachusetts Prostate Cancer Research Award Recipient (Massachusetts Department of Public Health), FY 2002.

4. I was asked to be a peer reviewer for the Journal of Urology and Andrology.

Invited Presentations (National)

1. **Gaston SM.** The Molecular Biology of Male Infertility: New Insights and Interventions. University of Arizona, November 28, 2001.

2. **Gaston SM**, Hunter IW and Kanigan T. Androgen Receptor Bio-Chips: Yeast Based Micro. Bioassays for Serum Androgens in Men with Prostate Cancer. NCI Principal Investigators Meeting, Innovative Molecular Analysis Technologies Programs, July 2001.

3. **Gaston SM,** Nassr RL, Zhong Y, Kim S, **Zhou J-R.** How Do We Best Utilize Soy Dietary Supplements in Prostate Cancer Management? Bioassay Serum Androgen vs Total. Serum Testosterone as Bio-Markers of Tumor Response. Modeling Human Prostate Cancer in Mice (conference), The Jackson Laboratory, October 2001.

4. **Gaston SM**, Siddiqui M, Soares M, **Perides G, Upton M**, **DeWolf WC**. Development of Molecular Markers of Prostate Cancer Staging: Capsular Invasion with Negative Margins is Associated with Matrix Metalloproteinase and Collagen Fragments on the External Surface of the Prostate Gland. Society for Basic Urological Research, November 2001.

Invited Presentations (Local)

1. **Gaston SM.** Androgen Receptor BioChips: Experimental and Potential Clinical Applications of the Yeast Based AR Micro-Bioassay. BioTrove Inc, February 21, 2002.

2. **Gaston SM.** Development of Molecular Markers for Prostate Cancer Local T Staging. BIDMC GU Radiology Conference, May 8, 2002.

3. **Gaston SM.** Matrix Metalloproteinase 9: Tumor Marker or Risk Factor for Prostate Cancer? 5th Annual Massachusetts Prostate Cancer Symposium, May 21, 2002.

4. **Gaston SM.** Molecular Analysis of Prostate Cancer: Marker Maps and Micro-Bioassays. Amgen site visit to BIDMC, July 13, 2001.

5. **Gaston SM.** Spatial-Molecular Mapping of Tumor Invasion: Prostate Print-Phoresis. Applied Biosystems, July 31, 2001.

6. **Gaston SM.** Prostate Cancer: New Technologies for Monitoring Biological Variables in Human Patients. Northeastern University, Department of Chemistry and Biomedical Science, March 28, 2002.
7. **Gaston SM.** Translational Proteomics: Spatial-Molecular Mapping of Tumor Markers in Surgical Tissue Specimens. BIDMC Surgical Research Seminar Series, March 18, 2002.

8. **Gaston SM.** Yeast Based Micro-bioassays for Prostate Cancer Management: Bioactive AR. Ligands in Sera Vidal Laboratory, Dana Farber Cancer Institute, August 2001.

BIDMC Surgical Research Seminar Series

As the Surgical Research Seminar Committee chair for 2001-2002, I recruited nineteen faculty investigators to present their research to the BIDMC Department of Surgery. These speakers came both from the BIDMC Department of Surgery and from outside research institutions. I also secured Amgen as the corporate co-sponsor for the 2001-2002 BIDMC Surgical Research Seminar Series, which allowed the Department of Surgery to offer an honorarium to each of the speakers from outside BIDMC.

Educational Activities (July 2001-June 2002)

To facilitate ongoing research and training efforts in the Division of Urology, the BIDMC Molecular Urology Training Program was initiated in the spring of 2000, with Sandra M. Gaston Ph.D. as Program Director. In this last year, ten MIT undergraduates, one Simmons college undergraduate and one Providence College undergraduate have participated in this program. In addition, I am part of the Harvard Medical School Teaching Faculty, teaching first year medical students.

1. Sponsor/Research Mentor for American Cancer Society Fuller Fellowship Student, Elizabeth Cherella, Summer 2002.

2. Sponsor/Research Mentor for ten MIT undergraduate students, including three who were awarded Howard Hughes summer research fellowships, one who was awarded

MIT Bioengineering Undergraduate Research Fellowships and two who were received American Association for Cancer Research Science Education Awards.

3. Teaching Faculty, Harvard Medical School Chemistry and Biology of the Cell Course for first year medical students (Fall 2001)

VI. Plans for the Coming Academic Year

Clinical

In the coming year, the Andrology Laboratory will be better integrated into the BIDMC Clinical Laboratory Services, with Andrology Laboratory Test results scheduled to be available through the BIDMC Clinical Computing System (OMR) in the fall of 2001. This is a much anticipated improvement in the delivery of our laboratory services,

Research

New Research Initiatives

1. With the supplement to our NIH grant R33 CA86365, we will extend our micro-bioassay system, originally developed for the analysis of tissue and serum samples from prostate cancer patients, to permit analysis of samples from breast cancer patients. Dr. Timothy Jacobs, senior BIDMC breast pathologist, has agreed to join this phase of the project as a collaborator.

2. We have undertaken a pilot study to determine if tissue print technology can be used to detect tumor positive margins in partial mastectomy surgical specimens. Initial results indicate that we have at least one set of informative markers, and we will be aggressively expanding our tissue-print profiling of breast cancer surgical specimens during this next year.

3. We look forward this year to several important new research collaborations. These include:

   Dr. Rittenhouse at Hybritech-Beckman (San Diego CA) has developed a set of monoclonal antibodies to specific prostate tumor antigen isoforms, including one post-translational isoform that appears to be more specific for tumor than the fully processed peptide. We will use these antibodies to profile normal and tumor-eroded prostate capsules, using our tissue print and print-phoresis techniques. This is an exceptional research opportunity, and may develop into a new industry sponsored phase of our prostate tissue printing project.

   Dr. Roy Ax at the University of Arizona (Tucson AZ), an expert in veterinary Andrology, has identified a well-characterized fertility factor in bovine seminal plasma as TIMP2 (tissue inhibitor of matrix metalloproteinase 2). Our initial collaborations with his laboratory indicate that the bovine sub-fertility resulting from TIMP2 deficiency may be informative about the

consequences of variable prostatic MMP-9 expression (see Research Interests above) on human reproduction.

4. In the next year, I will continue an aggressive program of generating funding to support and expand the major research efforts of my laboratory. Some of the major pending grant applications are listed in Section II B (above).

Educational Activities

One of my major goals, as a member of both the Harvard Medical School (HMS) faculty and as a Visiting Scientist in the MIT Center for Biomedical Engineering, is to continue to develop the network of MIT-BIDMC student trainees through the MIT undergraduate research program (UROP). This last year, I recruited MIT UROP students to work in three different BIDMC Surgical Research laboratories, including students with funding from MIT Bioengineering and Health, the Howard Hughes Foundation and the American Cancer Society. This next year, I will continue to recruit from this highly talented pool of students and to expand the extramural support for this effort. I will also continue to recruit HMS students to my laboratory.

For the last three years, I have been a member of the Teaching Faculty for Harvard Medical School. This year I will continue to teach first year Harvard Medical Students, in the Chemistry and Biology of the Cell Course.

VIII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Lin J, Hutchinson L, **Gaston SM**, Raab G, Freeman MR. BAG-1 is a novel cytoplasmic binding partner of the membrane form h-binding EGF-like growth Factor: A unique role for proHB-EGF in cell survival regulation. *J Biol Chem* 276:30127-30132.

Original Articles (in press)

1. **Zhou J-R**, Yu L, Zhong Y, Nassr RL , Franke AA, **Gaston SM, Blackburn GL**. Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. *Prostate* 2002; in press.

Reviews, Chapters and Editorials

1. **DeWolf WC, Gaston SM.** The Role of Cell Cycle Regulators in Cancer: An Overview for Urologists. *Aktvelle Urologie* 2001;32:113-120.

2. **DeWolf WC, Gaston SM.** Failure to achieve castrate levels of testosterone during LHRH agonist therapy. *Urology Times* 2001;28:43.

3. **DeWolf WC, Gaston SM.** PSA kinetics at tumor recurrence following radical prostatectomy do not suggest a worse disease prognosis in African-American men. *J Urol* 2001;166:131-1332.

Abstracts

1. **Gaston SM**, Soares M, Siddiqui MM, Kim TWB, Perides G, Upton M, DeWolf **WC**. Spatial-Molecular Mapping of Tumor Invasion of the Prostate Capsule: Matrix Metalloproteinase and Collagen Fragment Profiles at Sites of Capsular Infiltration. *Proc Am Assoc Cancer Research* 2002;43:3626.

2. **Gaston SM**, Siddiqui MM, Soares M, Perides G, Upton M, DeWolf WC. Development of molecular markers for prostate cancer local T staging: Capsular penetration positive, margin negative disease is associated with matrix metalloproteinases and collagen fragments on the external surface of the prostate gland. *J Urol* 2002;167(4):903.

3. Hutchinson LM, Kim S, Ushiyama N, Becker CM, Chang EL, **Gaston SM**, DeWolf WC, Zetter BR. Thymosin beta 15 levels in patient urine as a prognostic marker for human prostate cancer. *Proc Am Assoc Cancer Research* 2002;43:3176.

Larry M. Gentilello, M.D.

Division of General Surgery
Trauma and Critical Care

I. Narrative Report

I have 2 clinical-based research projects that are currently underway in my research program. First, we assess the cost-effectiveness of alcohol interventions in the emergency department (ED) and trauma center setting to determine the relevance to substance abuse and mental health insurance parity. This study was initiated because 45% of patients admitted to trauma centers are alcohol intoxicated, have a 25-44% readmission rate, and a trauma mortality rate of 20%. In addition, 77% of deaths in the trauma setting are related to continued substance abuse in a population that is (mean) 32 years of age. We found that brief interventions for alcohol and drug abuse in the ED or trauma center setting reduces 1) overall alcohol consumption, 2) drinking and driving, 3) alcohol/drug-related hospital readmission, 4) traffic violations, and 5) arrests for driving under the influence. We continue studies to assess the cost-effectiveness and perform outcome analyses of brief interventions in the ED or trauma center setting to justify health care financing of such interventions. Second, we assess the effect of repealing the uniform accident and sickness policy provision law (UPPL) on alcohol and other drug screening. We are interested in this topic because insurance companies (in 38 states) can deny payment for medical expenses incurred after a motor vehicle collision if the patient is under the influence. Studies show that 45% of trauma patients are alcohol intoxicated and 70% screen positive for alcohol or other drugs. Thus, under the UPPL, many EDs or trauma centers do not screen for substance abuse for fear that they will not be reimbursed for care. My group is interested in collecting data to determine if drug screening increases after repeal of the UPPL. We are also working with state legislators, insurance commissioners, industry representatives, and consumer advocates to either amend or repeal the UPPL.

II. List of Current Funding

1. "Assessing the cost-Effectiveness of Alcohol Interventions in the Emergency Department and Trauma Center Setting: Relevance to Substance Abuse and Mental Health Insurance Parity"
   Robert Wood Johnson Foundation
   Project Period: 6/2001 - 12/2002
   P.I. Larry M. Gentilello, M.D.

2. "The Effect of Repealing the Uniform Accident and Sickness Policy Provision Law on Substance Abuse Screening in Trauma Centers"
   Robert Wood Johnson Foundation

Project Period: 9/2002-8/2005
PI: Larry M. Gentilello, M.D.

III. Individual Accomplishments

1. Innovators Combating Substance Abuse Award.

2. Elected to American College of Surgeons Committee on Trauma.

3. American Association for Surgery of Trauma - Elected to membership on Legislature and Public Health Affairs Committee

4. Center for Disease Control Steering Committee - Alcohol and other Drugs in Trauma patients: Setting a Research Agenda to reduce complications, mortality and Trauma Recidivism.

5. Named as Technical Advisor to DAWN – Drug Abuse Warning Network Westat Health and Human Services.

6. Elected to committee to develop guidelines for substance abuse treatment in trauma patients, Center for Substance Abuse Treatment Center (CSAT) DHHS, Washington D.C.

IV. Report of Teaching

Undergraduate and Medical School Courses:
Surgery Clerkship lectures 2002

CMR courses
Harvard Medical School Department of Continuing Medical Education
Conference: "Enhancing the Safety of Parenteral & Enteral Nutrition"

V. Plans for the Coming Academic Year

Staff changes/recruitments
Ram Nirula, M. D. - 8/2002

VI. Bibliography (07/01/01-06/30/02)

Original articles

1. **Gentilello LM**. Alcohol Interventions in Trauma Centers. *J Anasth Intensivbehand* 2001;3:S105-S107.

2. **Gentilello LM**, Sanzone A, Wang L, Liu PY, Robinson L. Near infrared spectroscopy versus compartment pressure measurements for the diagnosis of lower extremity compartment syndrome using EMG determined measurements of neuromuscular function. *J Trauma* 2001;51(1):1-9.

Original Articles (in press)

1. McDonough KH, Giaimo ME, Miller HI, **Gentilello LM**. Low-dose ethanol alters the cardiovascular, metabolic, and respiratory compensation for severe blood loss. *J Trauma* 2002;53(3):in press.

2. Janczyk RJ, Park DY, Howells GA, Bair HA, Jonik AM, McFall RE, Bendick PJ, **Gentilello LM**. High-flow venovenous rewarming for the correction of hypothermia in a canine model of hypovolemic shock. *J Trauma* 2002;53(4):in press.

3. Zatzick DF, Jurkovich GJ, **Gentilello LM**, Wisner P, Rivara FP. Posttraumatic Stress, Problem Drinking, and Functional Outcomes after Injury. *Arc Surgery* 2002:137(2):in press.

Reviews, Chapters, and Editorials

1. **Gentilello, LM**. Alcohol interventions in trauma centers. In: Identification of Alcohol Problems and Brief Intervention; A Transatlantic Exchange. International Federation for Emergency Medicine, 2002. International Conference of Emergency Medicine.

Books, Monographs, and Textbooks

1. **Gentilello LM**. Surgical intensive care unit. In: Controversies in Surgery, 4th Edition. Schein M, Wise L, eds. Springer-Verlag, Heidelberg. 2001;pp. 243-248.

Books, Monographs, and Textbooks (in press)

1. **Gentilello, LM**. Temperature-associated injuries. In: Trauma Handbook, 4th edition. Mattox KL, ed. McGraw-Hill, New York. 2002, in press.

2. Reed, RL II, **Gentilello LM**. "Temperature-associated injuries and syndromes." In: Trauma, 5th Edition. Mattox KL, Moore EE, Feliciano DV, eds. McGraw-Hill, New York. 2002; in press.

3. **Gentilello LM**. Alcohol and drugs. In: Trauma, 5th ed. Mattox KL, Moore EE, Feliciano DV, eds. McGraw-Hill, New York. 2002; in press.

Susan J. Hagen, Ph.D.

Division of General Surgery
Division of Surgical Research

I. Narrative Report

My group focuses on the physiological and cell biological mechanisms that regulate cell function and death in the stomach. Three general areas of research are presently being pursued: 1) cytoskeletal regulation of gastric acid secretion, 2) mechanisms by which gastric epithelial cells regulate cell death and survival during infection with *H. pylori* bacteria, and 3) mechanisms that regulate rapid repair (restitution) of the gastric epithelium after injury. Our studies on the cytoskeletal regulation of acid secretion deal with the way in which actin participates in acid secretion. Our current work suggests that the stimulus-coupled polymerization of apical actin filaments facilitate the formation of a macromolecular assembly of K^+-channels and accessory proteins that are involved in K^+ recycling during acid secretion. Our studies on cell death and survival during *H. pylori* infection are concerned with how cells die and/or protect themselves against injury during infection. We have found that dietary glutamine is protective against the death of gastric epithelial cells during *H. pylori* infection. In addition, we found that chief cells play a significant role in mucosal protection during infection. For restitution, we study the way in which actin filaments regulate cell migration after injury. Our results suggest that, in addition to their participation in formation of the leading edge, actin filaments are required for cell migration because they organize glycolytic enzymes that are essential for energy production.

II. List of Current Employees

Research laboratory

1. Kimihito Tashima, PhD	Postdoctoral Fellow
2. Asli Muvaffak, PhD	Postdoctoral Fellow
3. Marianne Smith, MS	Sr. Research Associate

Core Facilities
Imaging

4. Daniel Brown, MS	Sr. Research Associate
5. Suqian Li, MS	Research Associate

Histology

6. Suzanne White, BS	Histotechnologist

Division of Surgical Research

7. Pat Odom	Administrative Coordinator

III. List of Current Funding

1. "GI Mucosal Barrier in Health and Surgical Disease"
   National Institutes of Health, 2R01 DK 15681

Project period: 01/01/1999-12/31/2003
PI: Susan J. Hagen, Ph.D.

2. "Biology of Alimentary Epithelia in Health and Disease"
National Institutes of Health, P30 DK34854
Project period: 9/1/1999-8/31/2004
PI: Dr. Marian Neutra, Children's Hospital
Subcontract: "Imaging Core Facility, Beth Israel Deaconess Medical Center"
PI: Susan J. Hagen, Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "GI Mucosal Barrier in Health and Surgical Disease"
National Institutes of Health, competitive renewal of 3R01 DK 15681
Project period: 07/01/2003-06/30/2008
PI: Susan J. Hagen, Ph.D.

2. "Role of Glutamine and Fish Oil in Protection against *Helicobacter pylori*-induced Gastric Atrophy"
Osher Institute
Project period: 02/01/2003-01/31/2004
PI: Susan J. Hagen, Ph.D.

V. Divisional Accomplishments over the Past Year

Divisional and Administrative Accomplishments

1. I spent most of my effort in the period 9/01/2001-6/30/2002 as Interim Chief, Division of Surgical Research. In that position, I outlined and began to implement my immediate goals for the Division of Surgical Research which were 1) to organize the structure of research in Surgery and 2) to advertise and increase visibility for the research programs in Surgery. I prepared the annual report for Surgery Research and helped Dr. Fischer with the space roster, IDC, and moving newly recruited faculty into the Department.

2. I continue to direct the Morphology Core Facilities and Confocal Microscopy Facility and to provide oversight and consultation for imaging experiments in the hospital.

Research Accomplishments

1. I wrote a number of unfinished manuscripts.

2. I was one of a few applicants accepted to a workshop from March 9-13, 2002 on "FRET Microscopy Techniques". The workshop was at the W.M. Kneck Center for Cellular Imaging at the University of Virginia and my attendance was supported by a grant from the Harvard Digestive Diseases Center.

Patent disclosures

1. The BIDMC submitted, on my behalf, a patent application (world-wide), #60/308,387, entitled "Regulation of Gastric Acid Secretion by Inwardly Rectifying K^+-channels". The patent application was the direct consequence of our current research concerning cytoskeletal regulation of gastric acid secretion.

Individual accomplishments

Study Section Assignment

1. I was a member of the *ad hoc* ZRG1-SS1(02) Special Emphasis Panel at the NIH which met in August, 2001. This study section reviews applications for shared instrumentation concerning confocal, 2-photon, LCM, and general fluorescence microscopy applications.

Invited presentations (local, national, and international)

1. "Life and Death of Gastric Epithelial Cells during *H. pylori* Infection"
   Division of Comparative Medicine
   Massachusetts Institute of Technology
   July 2001

2. "Regulation of Paracellular Permeability and Gastric Acid Secretion by F-actin"
   9th International Proton Transport Conference "Mechanisms and Consequences of Proton Transport"
   Mercure Resort, Blue Mountains
   Leura, Australia
   August, 2001

3. "Use of Frogs for Physiology Studies of the Gastric Mucosa"
   BIDMC Animal Facility, Beth Israel Deaconess Medical Center
   January, 2002

4. "Glutamine and Mucosal Protection in the *H. pylori* Infected Stomach"
   BIDMC Surgical Research Seminar Series, Beth Israel Deaconess Medical Center
   May, 2002

VI. Report of Teaching

Undergraduate and medical school courses

1. I participated in the Body Block at Harvard Medical School from 9/01/2001-10/31/2001 as co-director of the histology laboratory. In addition, I chaired a committee to write the midterm and final exams and I organized the preparation

of 400 histology slides (stomach and salivary gland) to add to histology slide boxes**.**

VII. Plans for the Coming Academic Year

Staff changes/recruitments

1. Dr. Asli Muvaffak will join my laboratory in January of 2003 as a postdoctoral fellow. Dr. Muvaffak comes from a PhD program that is joint with the Middle East Technical University (Ankara, Turkey) and Harvard Medical School. Dr. Muvaffak developed a crosslinked gelatin microsphere technology that we will use for drug delivery to facilitate restitution after injury. She will also work on DIDS and restitution.

2. Mr. Anupam Verma will join the laboratory for 6 weeks in March/April of 2003. Mr Verma is a 4th year medical student in Leicester, UK.

Plans for research

1. The competitive renewal of my current RO1 is due on November 1, 2002. After that application is submitted, I plan to write a 2nd R01 to fund projects concerned with the K^+-channel and acid secretion.

2. To finish the many other manuscripts that need to be published.

Educational plans

1. I plan to continue to teach histology and remain chair of the exam writing committee for the Body Block at HMS.

VIII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Al-Shaibani T, **Hagen SJ**. Regulation of acid secretion and paracellular permeability by F-actin in the bullfrog, *Rana catesbeiana*. *Am J Physiol (Gastrointest Liver Physiol*) 2002;282: G519-G526.

2. Ayabe T, Satchell DP, Pesendorfer P, Tanabe H, Wilson CL, **Hagen SJ**, Ouellette AJ. Activation of Paneth cell α-defensins mouse small intestine. *J Biol Chem* 2002;277(15):5219-5228.

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4. He D, Sougioultzis S, **Hagen SJ**, Liu J, Keates S, Keates AC, Pothoulakis C, LaMont JT. *Clostridium difficile* toxin A triggers human colonocyte IL-8 release via mitochondrial oxygen radical generation. *Gastroenterology* 2002;122(4): 1048-57.

Original Articles (in press)

1. Nakamura E, **Hagen SJ**. Role of glutamine and arginase in protection against ammonia-induced cell death in gastric epithelial cells. *Am J Physiol (Gastrointest Liver Physiol*) 2002:283: in press.

Reviews, Chapters, and Editorials

1. Hagen SJ, Smith G, Odom P. Annual Report, Department of Surgery, BIDMC.

2. **Hagen SJ**, Al-Shaibani T. Regulation of acid secretion and mucosal permeability by F-actin in the bullfrog gastric mucosa. In: Mechanisms and Consequences of Proton Transport. Urushidani T, Forte JG, Sachs G, eds. Kluwer Academic Publishers, Boston. 2002; pp. 349-360.

Reviews, Chapters, and Editorials (in press)

1. Hagen SJ. Ammonia and gastric acid secretion: a key to understanding activity and regulation of the H, K-ATPase. *Inflammopharmacol* 2002; in press.

Per-Olof Hasselgren, MD, PhD

Division of General Surgery
Division of Surgical Research

I. Narrative Report

The research efforts are focused on the metabolic and inflammatory responses to injury and sepsis in skeletal muscle and intestinal mucosa. Sepsis and severe injury are associated with a catabolic response in skeletal muscle, mainly reflecting increased degradation of myofibrillar proteins. Research in our laboratory examines the molecular mechanisms of muscle wasting. Previous studies have provided evidence that ubiquitin-proteasome-dependent proteolysis is an important mechanism of protein breakdown in catabolic muscle. Currently, the transcriptional regulation of genes in the ubiquitin-proteasome pathway is studied. In particular, experiments are conducted to examine the role of the transcription factors C/EBP-beta and delta and the nuclear coactivators p300/CBP in the regulation of the newly described ubiquitin ligases MURF 1 and MAFbx (atrogin-1).

In other studies, the regulation of IL-6 production in gut mucosa and enterocytes is examined. IL-6 is a pleiomorphic cytokine that may have both pro- and anti-inflammatory properties. In previous studies we have found that mucosal IL-6 production is increased during sepsis and endotoxemia and in cultured human enterocytes stimulated with IL-1 beta. In other experiments we have defined transcription factors (NF-kB, AP-1, and C/EBP) involved in activation of the IL-6 gene in stimulated enterocytes. Currently, we are testing means to influence the regulation of the IL-6 gene in mucosa and enterocytes. We have recently made the interesting observation that the heat shock response upregulates the expression of IL-6 in stimulated enterocytes and in intestinal mucosa. In those experiments, heat shock was induced by hyperthermia or treatment with proteasome inhibitor. Because IL-6 may exert protective effects in enterocytes/gut mucosa, treatments that augment IL-6 production may have important clinical implications.

II. List of Current Employees

1.	Michael Menconi, Ph.D.	Assistant Professor of Surgery
2.	Hongmei Yang, Ph.D.	Postdoctoral Fellow
3.	Wei Wei, Ph.D.	Postdoctoral Fellow

III. List of Current Funding

1. "Muscle protein turnover and amino acid uptake in sepsis"
   National Institutes of Health, RO1 DK 37908-13
   Project period: 08/01/2000-07/31/2004
   PI: Hasselgren

IV. Applications Submitted and Pending Review/Funding

1. "C/EBP and mucosal and enterocyte IL-6 production during sepsis and endotoxemia"
   National Institutes of Health, RO1
   Project period: Pending
   PI: Hasselgren

2. "C/EBP, atrogin-1, and muscle wasting"
   National Institutes of Health, RO1
   Project Period: Pending
   PI: Hasselgren

V. Divisional Accomplishments over the Past Year

1. Invited speaker, Society of Critical Care Annual Meeting (Hasselgren)
2. Invited speaker on Muscle Wasting, International Animal Agriculture and Food Sciences Conference (Hasselgren)
3. Visiting Professor, Department of Surgery, New Jersey Medical School, University of Medicine and Dentistry of New Jersey (Hasselgren)

VI. Report of Teaching

1. Surgical clerkship, medical students: Endocrine Surgery – Thyoroid/Parathyroid and Adrenal Glands

VII. Plans for the Coming Academic Year

Staff changes/recruitments

1. Hire one additional Post-doctoral Fellow.
2. Hire Investigator for Faculty position to be part of Muscle Wasting Program.

Plans for research

1. Work towards the establishment of a Program for Studies in Muscle Wasting by establishing collaboration with other researchers within the field and at the BIDMC and other institutions. Several world renowned researchers in the field of muscle wasting are at the BIDMC and Harvard Medical School and we have already started collaboration with some of them.

VIII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Al-Ahmadie H, **Hasselgren PO,** Yassin R, Mutema G. Co-localized granular cell tumor and infiltrating ductal carcinoma of the breast: a case report and review of the literature. *Arch Pathol Lab Med* 2002;126:731-733.

2. **Hasselgren PO.** Molecular regulation of muscle wasting. *Sci Med* 2002;8:230-239.

3. **Hasselgren PO.** Stress and muscle cachexia. *J Anim Sci* 2002;80(E.Supp1.2):E50-E55.

4. **Hasselgren PO,** Azizkhan RG, Bower RH, Hurst JM, McDonough JJ, Neale HW, Warden DG. Festschrift for Josef E Fischer. *Am J Surg* 2002;183:325-328.

5. **Hasselgren PO,** Wray C, Mammen J. Molecular regulation of muscle cachexia – it may be more than the proteasome. *Biochem Biophys Res Commun* 2002;290:1-10.

6. Hershko DD, Robb BW, Hungness ES, Luo G, **Hasselgren PO.** Arsenite stabilizes IkBalpha and prevents NF-kB activation in IL-1 beta-stimulated Caco-2 cells independent of the heat shock response. *J Cell Biochem* 2002;84:687-698.

7. Hungness ES, Luo G, Robb BW, Hershko DD, **Hasselgren PO.** Heat shock activates C/EBP beta and augments IL-6 production in IL-1 beta-treated human enterocytes. *Surg Forum* 2001:52:135-137.

8. Hungness ES, Pritts TA, Luo GJ, Hershko DD, Robb BW, **Hasselgren PO.** IL-1 beta activates C/EBP-beta and C/EBP-delta in human enterocytes through a mitogen-activated protein-kinase signaling pathway. *Int J Biochem Cell Biol* 2002;34:382-395.

9. Hungness ES, Robb BW, Luo GJ, Pritts TA, Hershko DD, **Hasselgren PO.** Proteasome inhibitors activate the transcription factors C/EBP-beta and C/EBP-delta in human intestinal epithelial cells. *Biochem Biophys Res Commun* 2002;290:469-474.

10. Hungness ES, RobbBW, Seeskin C, **Hasselgren PO,** Luchette FA. Early debridement for necrotizing pancreatitis – is it worthwhile? *J Am Coll Surg* 2002;194:740-745.

11. Luo GJ, Sun X, Hungness ES, **Hasselgren PO.** Heat shock protects L6 myotubes from catabolic effects of dexamethasone and prevents downregulation of NF-kB. *Am J Physiol* 2001;281:R1193-R1200.

12. O'Brien DP, Nelson LA, Kemp CJ, Williams JL, Wang Q, Erwin CR, **Hasselgren PO,** Warner BW. Intestinal permeability and bacterial translocation are uncoupled after small bowel resection. *J Pediatr Surg* 2002;37:390-394.

13. Pritts TA, Hungness ES, Hershko DD, Robb BW, Sun X, Luo GJ, Fischer JE, Wong HR, **Hasselgren PO.** Proteasome inhibitors induce heat shock response and increase IL-6 expression in human intestinal epithelial cells. *Am J Physiol* 2002;282:R1016-R1026.

14. Pritts TA, Hungness ES, Wang Q, Robb BW, Hershko D, **Hasselgren PO.** Mucosal and enterocyte IL-6 production during sepsis and endotoxemia. Role of transcription factors and regulation by the stress response. *Am J Surg* 2002;183:372-383.

15. Safal M, Lower EE, **Hasselgren PO,** Hungness ES, Gazder P, Aron B, Shaughnessy EA, Yassin R. Bilateral synchronous breast cancer and Her-2/neu overexpression. *Beast Cancer Res Treat* 2002;72:195-201.

16. Sun X, Fischer DR, Pritts TA, Wray CJ, **Hasselgren PO.** Expression and binding activity of the glucocorticoid receptor are upregulated in septic muscle. *Am J Physiol* 2002;282:R509-R518.

17. Wang Q, Fang CH, **Hasselgren PO.** Intestinal permeability is reduced and IL-10 levels are increased in septic IL-6 knock out mice. *Am J Physiol* 2001;281:R1013-R1023.

18. Wang Q, **Hasselgren PO.** Heat shock response reduces intestinal permeability in septic mice: potential role of IL-10. *Am J Physiol* 2002;282:R669-R676.

19. Wray CJ, Luo GJ, Hungness ES, **Hasselgren PO.** Genomic analysis of glucocorticoid-induced muscle cachexia. *Surg Forum* 2001;52:142-144.

20. Wray CJ, Sun X, Gang G, **Hasselgren PO.** Dantrolene downregulates the gene expression and activity of the ubiquitin-proteasome proteolytic pathway in septic skeletal muscle. *J Surg Res* 2002;104:82-87.

Original Articles (in press)

1. Hershko DD, Robb BW, Luo GJ, **Hasselgren PO.** Multiple transcription factors regulating the IL-6 gene are activated by cAMP in cultured Caco-2 cells. *Am J Physiol* 2002; in press.

2. Hungness ES, Robb BW, Luo GJ, Hershko DD, **Hasselgren PO.** Hyperthermia-induced heat shock activates the transcription factor C/EBP-

beta and augments IL-6 production in human intestinal epithelial cells. *J Am Coll Surg* 2002; in press.

3. Wray CJ, Mammen JMV, **Hasselgren PO.** The catabolic response to stress and potential benefits of nutritional support. *Nutrition* 2002; in press.

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1. **Hasselgren PO,** Fischer DR, Pritts T. Metabolic response to trauma and infection. In: Baker RJ, Fischer JE, eds. Mastery of Surgery, 4th edition. Philadelphia: Lipincott, Williams & Wilkins, 2001:3-22.

2. **Hasselgren PO,** Fischer DR, Pritts T. Models of protein metabolism. In: Souba WW, Wilmore DW, eds. Surgical Research. San Diego: Academic Press, 2001:825-844.

3. Pritts TA, Hungness ES, **Hasselgren PO.** Protein metabolism in liver and intestine during sepsis: mediators, molecular regulation, and clinical implications. In: Latifi R, Dudrick SJ, eds. The Biology and Practice of Current Nutritional Support, 2nd edition. Texas: RG Landes Bioscience Publishing Company, 2002:97-119.

Abstracts

1. Hershko D, Robb BW, Luo GJ, **Hasselgren PO.** Superinduction of IL-6 by cycloheximide is mediated by sustained activation of p38 MAP kinase and NF-kB in human enterocytes. *J Am Coll Surg* 2002;195:S90.

2. Luo GJ, Hershko DD, Robb BW, **Hasselgren PO.** IL-1 beta induces IL-6 production in cultured skeletal muscle cells through activation of the MAP kinase signaling pathway and NF-kB. *J Am Coll Surg* 2002;195:S81-S82.

3. Mammen J, Penner G, Wray CJ, **Hasselgren PO.** Transcription factor C/EBP is activated by dexamethasone is skeletal muscle. *J Am Coll Surg* 2002;195:S78.

4. Wray CJ, Mammen JMV, **Hasselgren PO.** Subtraction suppression hybridization of muscle RNA during sepsis: upregulation of MURF 1, a novel ubiquitin ligase. *J Am Coll Surg* 2002;195:S78-S79.

Ann A. Kiessling, Ph.D.
Robert C. Eyre, M.D.
Paul Church, M.D.

Division of Urology

I. Narrative Report

The long-term goals are to understand retrovirus gene expression in reproductive tract tissues and embryos. Studies of HIV infection of male GU tract tissues began in 1983 with the first measurements of viral burden in seminal plasma from men with AIDS. The immune privilege of male GU tract tissues led to the hypothesis that semen-producing organs could be an isolated sanctuary of HIV disease. Originally controversial, this concept is now broadly accepted. Current focus: (1) phylogenetic analysis of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a longitudinal study design. (2) immunology of male GU tract tissues with emphasis on the prostate and seminal vesicles.

II. List of Current Employees

1.	Julian Fleischman, PhD	Visiting Associate Professor
2.	Hui-Zhong Yin, MD	Senior Research Fellow
3.	Bryan Desmarais	Research Technician
4.	Nathan Neville	Student

III. List of Current Funding

1. "Role of the Male Genital Tract in HIV Disease"
   NIH/NIDDK 7R01 DK 52761
   Project period: 2000-2005
   Principal Investigator: Ann A. Kiessling, Ph.D.

2. Urologic Research Fund
   Provides support for the male GU tissue studies not included in the NIH funded project.

IV. Divisional Accomplishments over the Past Year

1. The longitudinal genetic and phylogenetic analyses of HIV genes have required both new equipment and new lab approaches. The work is now proceeding rapidly and we have developed methods for gene sequencing directly from PCR reactions, thus avoiding the need for cloning. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men, including those on therapy.

2. Using new methods for tissue fixation, we have identified a novel class of macrophages in male mouse and human tissues, which appear to play a fundamental role in organ function. This could have broad application to

understanding the physiology of the prostate and seminal vesicles, as well as their role as reservoirs of HIV infection. This work has been presented in abstract form and is nearly ready for publication.

3. We continue to host Egg Group, a New England area seminar series in existence for more than a decade which attracts reproductive scientists from Northeastern, Tufts, Harvard, U Mass Amherst, Boston U, and Woods Hole MBL. This seminar is sponsored by the Bedford Research Foundation, a non-profit organization founded in Boston.

Invited presentations (local, national, and international)

1. "Sanctuaries of HIV Disease"
National Hemophilia Foundation Annual Meeting
Cincinnati, Ohio 2002.

2. Eyre RC, Desmarais B, Yin H-Z, Steinberg J, **Kiessling AA.** "Polymerase Chain Reaction (PCR) detection of bacterial ribosomal RNA gene sequences in semen", New England Urology Association Annual Meeting, Boston, 2002.

3. **Kiessling AA,** Mullen TM, Kiessling RL "Presence in mice and men a novel class of leukocytes/macrophages essential for normal development of male mouse reproductive tract tissues". Third International Conference on the Epididymis, Charlottesville, VA, May, 2002.

V. Plans for the Coming Academic Year

1. We will continue to recruit staff in Jan '03 to replace two whom departed.

2. Two grant applications will be submitted:

    1. In collaboration with LJ Wei, Harvard School of Public Health, we will be submitting a request for funding a comprehensive, longitudinal analysis of HIV in all male GU tract tissues. Originally submitted in 2000, the application was not funded, primarily due to a perceived need for additional biostatistical expertise. Dr. Wei will fill this need.

    2. We will revise our application to the NIDDK for studies of the development of male genitourinary tract organs. Originally submitted in 2000, the study of gene expression in epididymis is in keeping with our general interest in male tract tissues.

VI. Bibliography (07/01/01-06/30/02)

Original Articles

1. Cibelli JB, **Kiessling AA,** Cunniff K, Richards C, Lanza RP, West MD. Somatic Cell Nuclear Transfer in Humans: Pronuclear and Early Embryonic Development. *J Regener Med* 2001;2:25-31.

2. Green RM, DeVries KO, Bernstein J, Goodman KW, Kaufmann R, **Kiessling AA,** Levin SR, Moss SL, Tauer CA. Overseeing research on therapeutic cloning: a private ethics board responds to its critics. *Hastings Center Report* 2002;32:27-33.

Original Articles (in press)

1. Mullen, T, Kiessling RL, **Kiessling AA.** Distinct Populations of Leukocytes in Semen Producing Organs of the Normal, Hemicastrated and Vasectomized Mouse. *AIDS Res Hum Retroviruses* 2002; in press.

2. Yakamoto M, Mullins T, Byrn R, Eyre R, Church P, **Kiessling AA.** Seminal plasma induces programmed cell death in peripheral blood mononuclear cells. *AIDS Res Hum Retroviruses* 2002;18:797-803.

Reviews, Chapters, and Editorials

1. **Kiessling AA.** In the stem cell debate, new concepts need new words. *Nature* 2001;413: 453.

Frank W. LoGerfo, M.D.
William C. Quist, M.D.
Allen Hamdan, M.D.

Division of Vascular Surgery Research

I. Narrative Report

Basic Research

The vascular surgery research laboratory has been extensively involved in two main areas of vascular biology research: 1) evaluating mechanisms responsible for prosthetic graft failure and 2) developing novel biomaterial surfaces. Anastomotic intimal hyperplasia (AIH) remains the most common cause of delayed prosthetic arterial graft failure, a consequence of focal, unregulated gene expression. As graft healing occurs, genes are either up- or downregulated compared to a quiescent arterial wall. We study altered gene expression that results in cellular proliferation, migration and extracellular matrix production by smooth muscle cells, leading to AIH. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting *in vivo* and to examine their role in the cellular environment *in vitro*.

As for biomaterials research, we have designed and patented a novel, biocompatible Dacron vascular graft and are evaluating a novel infection-resistant Dacron prosthetic valve sewing cuff with optimum antimicrobial properties. In addition, we are developing a novel titanium surface via covalent linkage of recombinant hirudin to silane that is bound to chemisorbed oxygen on the titanium surface, and are evaluating, *in vivo,* an infection-resistant polyurethane via application of quinolone antibiotics using textile dyeing techniques. These materials would be utilized in a wide range of implantable devices such as catheters, wound dressings and vascular grafts.

Clinical Research

Our divisional clinical projects entail both database review as well as a major clinical trial. Database review projects are based on information from our prospectively entered registry (started in 1990) that is the evaluated retrospectively and then supplemented by hospital and office chart review. The goals of these projects are both quality control for our division as well as an attempt to put in the literature our stamp on major issues. An added benefit is the training of fellows and residents in analyzing data, writing papers and presenting at national meetings.

The clinical trial is A Phase III Multi-Center Randomized, Double-Blind, Placebo-Controlled Trial of the Ex-Vivo Treatment with CGT003 of Peripheral Vein Grafts in Patients Undergoing Peripheral Arterial Bypass Graft Procedures. This involves the use of an oligonucleotide decoy for transcription factor E2F delivered into the vein graft wall at the time of bypass. The hypothesis is that shutting down E2F will limit the downstream effect of

intimal hyperplasia and decrease graft stenosis or failure. We are one of 60 centers in the trial but are currently the number one center, accounting for almost 10 % of all patients entered.

II. List of Current Employees

1.	Mauricio Contreras, M.D.	Instructor in Surgery
2.	Matthew Phaneuf, B.S.	Assistant Laboratory Director
3.	Puja Aggarwal, M.D.	Research Fellow
4.	Evan Deutsch, M.D.	Research Fellow
5.	Claudie McArthur, M.D.	Research Fellow
6.	David Willis, M.D.	Research Fellow
7.	Kery Sousa, M.D.	Research Fellow
8.	Chantel Hile, M.D.,	Research Fellow
9.	Barry Gross, B.S.	Information Systems Development
10.	Vaishali Patel, B.S.	Administrative Assistant
11.	Jennifer Veraldi, B.A.,	Research Assistant

III. List of Current Funding

1. "Mechanisms of Prosthetic Arterial Graft Failure"
   National Institutes of Health, R01 HL21796
   Project period: 1978 - 2003
   Principal Investigator: Frank W. LoGerfo, M.D.
   Co-Principal Investigator: William C. Quist, M.D., Ph.D.

2. Harvard-Longwood Research Training Program in Vascular Surgery (T32)
   National Institutes of Health - Heart, Lung and Blood Institute
   Project period: 1993 - 2003
   Principal Investigator: Frank W. LoGerfo, M.D.
   Co-Principal Investigator: William C. Quist, M.D., Ph.D.

3. William J. von Liebig Research Training in Vascular Surgery
   William J. von Liebig Foundation
   Project period: 2001 - 2002
   Principal Investigators: Drs. LoGerfo and Quist

4. "Infection-Resistant Polyurethane Biomaterials"
   National Institutes of Health - Small Business Technology Transfer Research Grant (Phase II)
   Project period: 2001 - 2002
   Principal Investigator: Frank W. LoGerfo, M.D.

5. "Infection-Resistant Prosthetic Heart Valve Sewing Cuffs"
   National Institutes of Health - Small Business Innovative Research Grant (Phase I)
   Project period: 2001
   Principal Investigator: William C. Quist, M.D., Ph.D.

6. "Development of a Biologically-Active Prosthetic Graft"
   National Institutes of Health - Small Business Technology Transfer Research Grant (Phase II)
   Project period: 2002 - 2004
   Principal Investigator: Frank W. LoGerfo, M.D.

7. "Nanofiber Technology in Small-Diameter Vascular Grafts"
   National Institutes of Health.- Small Business Technology Transfer Research Grant (Phase I)
   Project period: 2002
   Principal Investigator: William C. Quist, M.D., Ph.D.

8. "Infection-Resistant Prosthetic Heart Valve Sewing Cuffs"
   National Institutes of Health - Small Business Innovative Research Grant (Phase II)
   Project period: 2003 - 2005
   Principal Investigator: William C. Quist, M.D., Ph.D.

9. "A Phase III Multi-Center Randomized, Double-Blind, Placebo-Controlled Trial of the Ex-Vivo Treatment with CGT003 of Peripheral Vein Grafts in Patients Undergoing Peripheral Arterial Bypass Graft Procedures"
   Industry funding - Corgentech
   Study period: 03/01/02 - end of recruitment
   Principal Investigator: Allen Hamdan M.D.

IV. Applications Submitted and Pending Review/Funding

1. "Development of a Titanium Surface with Antithrombin Properties" (Phase II)
   National Institutes of Health - Small Business Innovative Research Grant
   Project period: 2002 - 2003
   Principal Investigator: William C. Quist, M.D., Ph.D.

2. "Developing Multi-Functionality in Small-Diameter Grafts"
   National Institutes of Health – National Heart, Lung and Blood (R21)
   Project period: 2002 - 2005
   Principal Investigator: William C. Quist, M.D., Ph.D.

3. "Bioactive Textiles: Inherent Antimicrobial and Antifungal Properties"
   Department of Defense
   Project period: 2002 - 2003
   Principal Investigator: William C. Quist, M.D., Ph.D.

V. Divisional Accomplishments

Research Accomplishments

1. *Mechanisms of Prosthetic Arterial Graft Failure*
Anastomotic intimal hyperplasia (AIH) remains as the most common cause of delayed prosthetic arterial graft failure, a consequence of focal, unregulated gene expression. As graft healing occurs, genes are either up- or downregulated compared to a quiescent arterial wall. Our hypothesis is that this altered gene expression results in cellular proliferation, migration and extracellular matrix production by smooth muscle cells, leading to AIH. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting *in vivo*.

   The results obtained from this study will greatly expand our knowledge related to the specific problem of AIH and will also provide new insights for either novel graft designs or potential therapeutic intervention, with the derived mechanisms having pertinence to the larger field of vascular biology.

2. *Infection-Resistant Polyurethane Biomaterials*
Infection of polymeric biomaterials is a major problem. In phase I, the antibiotic ciprofloxacin (Cipro) was applied to an ionic polyurethane (cPU) using textile dyeing technology, and the application parameters were optimized. No exogenous binding agents were involved. This "dyed"-cPU demonstrated slow release of Cipro with sustained antimicrobial activity. The goal of this phase II application is to evaluate this Cipro-dyed cPU *in vivo*. We hypothesize that dyeing the cPU with Cipro will result in sustained infection resistance *in vivo*. cPU polymer will be coated onto pre-formed indwelling catheters. Cipro will be dyed onto cPU-coated catheters using parameters from phase I. Chemical and physical characteristics of the cPU-coated catheter will be assessed pre and post-dyeing. Cipro-dyed catheters will then be evaluated for Cipro release and sustained antimicrobial activity. Catheters will be subjected to an *in vitro* flow model in order to determine antibiotic release pharmacokinetics. Optimized Cipro-dyed catheters will then be evaluated using an *in vivo* subcutaneous implant model. A successful indwelling polyurethane catheter with long-term infection resistance would generate a U.S. market greater than $300 million annually. This technology could be applied to other biomedical materials (vascular grafts, wound dressings) and commercial products (shower curtains, clothing).

3. *Development of a Titanium Surface with Antithrombin Properties*
Titanium (Ti), which has advantageous bulk and surface properties, is susceptible to surface thrombus formation in devices such as mechanical heart valves. In phase I, the potent antithrombin agent recombinant hirudin (rHir) was covalently bound to Ti surfaces (Ti-Ep-PEI-S-SMCC-rHir) using proprietary technology and maintained *in vitro* biologic activity. The goal of this phase II proposal is to assess surface antithrombin properties of Ti-Ep-PEI-S-SMCC-rHir surfaces both *ex vivo* and *in vivo*. The specific objectives are to: 1) determine surface antithrombin properties *ex vivo* using whole blood platelet aggregation, 2) develop a Ti chamber to simulate a mechanical heart valve chamber, 3) establish Ep and PEI coating methodology, 4) examine coating efficiency and amine content, 5) covalently attach ^{125}I-rHir to Ti

housing chambers, 6) evaluate surface ^{125}I-rHir stability under simulated arterial flow conditions and 7) assess *in vivo* surface antithrombin properties using a canine bilateral common iliac model. This technology, if applied only to mechanical heart valves, could have an annual market in excess of $100 million and can be applied to other Ti implants such as left ventricular assist devices, dental implants and bone replacements to which biologic agents such as growth factors or adhesion molecules could be covalently bound.

4. *Development of a Biologically-Active Prosthetic Graft*
Medium (6-8mm) and small (<5mm) internal diameter prosthetic grafts continue to have clinically unacceptable high failure rates. In phase I, an ionic polyurethane-sealed Dacron vascular graft (PEU-D) with reduced water permeation, excellent physical properties and covalently bound antithrombin (recombinant hirudin or rHir) and mitogenic (vascular endothelial growth factor or VEGF) agents was developed. These surface bound agents were determined to be biologically active**.** Our objective in this proposal is to assess blood permeation and graft patency/healing of the PEU-D graft using a canine arterial grafting model. Our hypothesis is that implantation of this novel graft will prevent blood permeation thereby obviating the need for pre-clotting and improve graft patency and healing by emulating some of the natural properties of native vessels. The specific aims are to: 1) develop a batch synthesis process for ionic polyurethane, 2) scale-up the process for sealing Dacron grafts, 3) evaluate PEU-D physical and chemical properties, 4) covalently link rHir and VEGF to PEU-D surface, 5) assess *in vivo* acute and chronic implantation periods and 6) examine macroscopically/microscopically explanted grafts. Development of a polyurethane sealant with protein binding properties would have a significant role for medical devices such as vascular grafts, catheters and artificial organs.

5. *Infection-Resistant Prosthetic Heart Valve Sewing Cuffs*
Cardiac valve replacement using prosthetic valves is indicated when progression of degenerative disease or bacterial infection of the native valve results in valvular dysfunction, thereby impacting on cardiac output. Bacterial infection is a major complication associated with implantation of these prosthetic valves. Infections are localized to the prosthesis/tissue interface at the sewing cuff leading to cuff and annular abscess formation. The goal of this phase I project is to develop an infection-resistant knitted Dacron cuff material *in vitro* with optimum antimicrobial properties via thermofixation (pad/heat) dyeing of the antibiotic ciprofloxacin (Cipro). Our hypothesis is application of quinolone antibiotics to Dacron biomaterials via dyeing technology can be optimized, resulting in slow, sustained antibiotic release without the use of exogenous binders. The specific aims of this proposal are to: optimize Cipro dyeing conditions to knitted Dacron, characterize the physical properties of Cipro-dyed Dacron, determine antibiotic release over time via spectrophotometry, examine *in vitro* antimicrobial properties and assess antibiotic release pharmacokinetics under simulated arterial flow conditions. Phase II of this project will evaluate this novel technology in an *in vivo* prosthetic valve

model. This technology, if successful, will be become the standard of care in the treatment of all forms of prosthetic endocarditis.

6. *Nanofiber Technology in Small-Diameter Vascular Grafts*
There is no small-diameter vascular prosthesis that is capable of emulating the biologic and physical properties of the normal arterial wall. The goal of this proposal is to develop a small-diameter prosthetic vascular graft using nanofiber technology. Our hypothesis is creating a nanofibrous vascular graft by electrospinning an ionic polyurethane will result in a graft that possesses properties similar to that of native artery. The potent antithrombin agent recombinant hirudin (rHir) will be covalently bound to functional groups within the polymer, resulting in an antithrombotic surface. The elastic properties of the ionic polymer will provide circumferential compliance, with longitudinal stretch and kink-resistance prevented by a thin braided Dacron mesh within the graft wall. The specific objectives are to: 1) optimize electrospinning methodology, 2) develop a Dacron inner-wall reinforcement, 3) electrospin PEU grafts containing reinforcement, 4) characterize physical and chemical properties, 5) covalently link rHir to PEU grafts, 6) characterize surface antithrombin properties, 7) evaluate blood interaction with grafts and 8) assess surface rHir stability under simulated arterial flow conditions. Phase II of this project will evaluate these PEU grafts in a canine carotid artery model. Development of a bioactive small-diameter vascular graft would have a significant impact on small vessel repair and replacement.

7. *Clinical Communications*
We presented two landmark papers, one at The New England Surgical Society and one at the national Society for Vascular Surgery meeting. The first paper (published in *Archives of Surgery*) detailed over ten years of excellent results in major vascular procedures. It was the first paper of its kind to clearly refute the preconception that diabetes is an independent risk factor for perioperative complications after vascular procedures. This paper was publicized on NPR, the *Lancet*, *The Washington Post* and *Prevention* magazine among others. The second paper (pending publication in the *Journal of Vascular Surgery*) documented the largest series in the literature of distal bypass procedures in patients with diabetes.

An exciting side effect of the clinical research has been the ability to involve the fellows and residents. Seven different residents, fellows and students have either published or presented a paper or chapter this year.

Finally, we have obtained a very large industry grant to become one of the centers studying modification of vein grafts to improve results (detailed above). In short time, we have become the largest center in North America in this multicenter trial.

Patent Disclosures

1. Application of Antibiotics to Polyurethane Biomaterials Using Textile Dyeing Technology (09/834,978)

2. Development of a Dacron Vascular Graft with an Ionic Polyurethane Sealant with Protein Binding Capabilities (60/186,154)

3. Bioactive Surface for Titanium Implants (Provisional Patent)

4. Development of a Bifunctionalized Dacron Surface (Provisional Patent)

National Presentations

1. Dempsey DJ, Phaneuf MD, Bide MJ, **LoGerfo FW, Quist WC.** Development of a novel methodology for covalent attachment to titanium implant surfaces. Surfaces in Biomaterials, Scottsdale, AZ, 2001.

2. Dempsey DJ, Phaneuf MD, **Quist WC, LoGerfo FW.** Development of a bioactive surface for titanium implant devices. Society for Biomaterials, Tampa, FL, 2002.

3. Havens J. Sun J. Narra V. Sui XX. Zeldin DC. Liao J. Conte MS. Adenoviral delivery of CYP2j2 inhibits smooth muscle cell migration and leukocyte adhesion to cytokine-stimulated endothelial cells. Research Initiatives Conference in Vascular Surgery, 2002.

4. Kansal N, Rayan S, Reddy S, Hamdan AD, Rabkin D, Pomposelli FB, **LoGerfo FW.** Endotension measurement and the effect of endoleak following endovascular aortic aneurysm repair. Presented at the Society for Clinical Vascular Surgery, 2002. Manuscript submitted: *Vascular and Endovascular* Surgery

5. Phaneuf MD, Bide MJ, Dempsey DJ, **LoGerfo FW, Quist WC.** Novel bifunctionalized Dacron biomaterial surfaces. *Society for Biomaterials*, Tampa, FL, 2002.

6. Phaneuf MD, Contreras MA, Stone DH, Bide MJ, **LoGerfo FW, Quist WC.** Assessment of *in vitro* and in vivo mitogenic properties of immobilized vascular endothelial growth factor (VEGF). *Surfaces in Biomaterials*, Scottsdale, AZ 2001.

7. Simosa HF, Blanc-Brude O, Narra V, Altieri DC, Conte MS. Survivin, an inhibitor of apoptosis, is cytoprotective in vascular smooth muscle cells and is upregulated during lesion development following balloon angioplasty. AVS/SVS Joint annual meeting, Boston, MA, 2002.

8. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Apolipoprotein J expression in intimal hyperplasia inhibits the migration, adhesion, and proliferation of vascular smooth muscle cells. 20th Annual William J. Von Liebig Foundation Award for Excellence in Vascular Surgical Research Essay Contest, *Society for Vascular Surgery*, Baltimore, MD, 2001.

9. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Apolipoprotein J inhibits the migration, adhesion, and proliferation of vascular smooth muscle cells. *Society of Vascular Medicine and Biolog,y* 2001.

10. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Attenuated retinoblastoma gene product and associated E2F/retinoblastoma imbalance in anastomotic intimal hyperplasia. *New England Society of Vascular Surgery*, Providence, RI, 2001.

11. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** The retinoblastoma gene product is reduced in the formation of anastomotic intimal hyperplasia. *American College of Surgeons Surgical Forum*, New Orleans, LA, 2001.

12. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** The retinoblastoma gene product is reduced in the formation of anastomotic intimal hyperplasia. *Society of Vascular Medicine and Biology,* 2001.

13. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** The retinoblastoma gene product is reduced in the formation of intimal hyperplasia. *Eastern Vascular Society,* Washington D.C., 2001.

14. Willis D, Deutsch E, Contreras M, **LoGerfo F, and Quist W.** Downregulation of smoothelin-B at the distal anastamosis of prosthetic arterial grafts. FASEB Experimental Biology Meeting, New Orleans, LA, 2002.

15. Willis DJ, Deutsch ER, Contreras MA, **LoGerfo FW, Quist WC.** Downregulation of smoothelin-B at the distal anastomosis of prosthetic arterial grafts. FASEB, New Orleans, LA, 2002.

VI. Report of Teaching

1. T32 Training Program

Harvard-Longwood Research Training Program in Vascular Surgery (T32)
This training program is designed to provide two years of intense basic research training in vascular surgery for academic clinicians. The training program addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. Trainees will pursue a program of research activity supplemented with course work in research design, ethics, statistics and evaluation of published research in the areas of molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis. Clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis will be the main focus of these research projects. Trainees carry out their research projects under the guidance of a faculty advisor selected from 20 renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology. Upon completion of the program, trainees are capable of independent research and possess the scientific and research background needed to obtain peer-reviewed grants. Selection of trainees is based on candidate's demonstrated ability and career choice of academic practice. Applicants are resident physicians who have completed either 2/3 years of clinical post-doctoral experience (surgical residency) or 5 years of clinical training (i.e. are board eligible). Only those applicants with career goals

in academic surgery, with a keen interest in basic research in vascular surgery are compatible. Trainees in the program are not involved in any clinical activities unless research related.

	Personnel	**General Surgery Training Program**
1.	Evan Deutsch, M.D.	Saint Vincent's Hospital and Medical Center, NY
2.	Claudie McArthur, M.D.	Mount Sinai Hospital, NY
3.	Vinod Narrod, M.D.	Brigham and Women's Hospital, MA
4.	Hector Simosa, M.D.	University of Virginia, VA
5.	Virendra Patel, M.D.	Beth Israel Deaconess Medical Center, MA
6.	David Willis, M.D.	NYU Medical Center, NY

2. William J. von Liebig Research Training in Vascular Surgery for Medical Students
Program Director: William C. Quist, M.D., Ph.D.

The William von Liebig Training Fellowship in Vascular Surgery is held for 10-12 weeks during the summer months. Students receive research training in molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis, with a focus on clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis. Trainees pursue a program of intense research activity. Students carry out their research projects under the guidance of a faculty advisor, selected from renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology.

Post-Doctoral Fellow
Evan Garfein, M.D., Brigham and Women's Hospital

2001 – 2002 Summer Students

1.	Kimberly Chong, M.D.	University of Vermont
2.	Douglas Constant, M.D.	Tulane University
3.	Joan Hu, M.D.	Harvard Medical School
4.	Jonathan Kazam, M.D.	Cornell Medical School
5.	Jeffrey Link, M.D.	Southern Illinois University
6.	Matthew Milewski, M.D.	Georgetown University

VII. Plans for the Coming Academic Year

The coming year will build and amplify what we were able to accomplish in the current year. We have increased the total number of residents and fellows involved in research to eight. We already have had three papers accepted for presentation at the New England Society of Vascular surgery in early October. We have submitted two other abstracts, one to the Society of Clinical Vascular Surgery and the other to the Peripheral Vascular Surgery Society. If accepted, they will be presented by residents/fellows this year.

Finally, we have 19 other projects in various stages of completion, and we expect to submit at least 6 papers to the Society of Vascular Surgery national meeting.

In regards to funded clinical research, we are in the midst of negotiating a contract with Pfizer to be part of a multicenter trial looking at an investigational drug Zonoporide that may decrease the rate of perioperative complications in patients undergoing major vascular procedures.

VIII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Hamdan AD, Rayan SS, Hook SC, Campbell DR, Akbari CM, **LoGerfo FW,** Pomposelli FB Jr. The use of polytetrafluoroethylene in bypasses to tibial vessels. *Vasc Endovasc Surg* 2002;36(1)59-65.

2. Hamdan AD**,** Saltzberg SS, Sheahan M, Froelich J, Akbari CM, Campbell DR, **LoGerfo FW,** Pomposelli FB Jr. Lack of association of diabetes with increased postoperative mortality and cardiac morbidity: results of 6565 major vascular operations. *Arch Surg* 2002;137(4):417-21.

3. Phaneuf MD, Bide MJ, Szycher M, Gale MB, Huang H, Yang C, **LoGerfo FW, Quist WC.** Development of infection-resistant polyurethane biomaterials using textile dyeing technology. *ASAIO J* 2001;47:634-640.

4. Phaneuf MD, Dempsey DJ, Bide MJ, **Quist WC, LoGerfo FW.** Coating of Dacron vascular grafts with an ionic polyurethane: A novel sealant with protein binding properties. *Biomaterials* 2001;22:463.

5. Rayan SS, Hamdan AD**,** Campbell DR, Akbari CM, Hook SC, Skillman J, **LoGerfo FW,** Pomposelli FB Jr. Is diabetes a risk factor for patients undergoing open abdominal aortic aneurysm repair? *Vasc Endovasc Surg* 2002;36(1)33-41.

6. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Apolipoprotein J inhibits the migration, adhesion, and proliferation of vascular smooth muscle cells. *J Vasc Surg* 2001; 34(5): 716-723.

7. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Apolipoprotein J inhibits the migration and adhesion of endothelial cells in intimal hyperplasia. S*urgery* 2001;130(2):204-209.

8. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** Attenuated retinoblastoma gene product and associated E2F/retinoblastoma imbalance in anastomotic intimal hyperplasia. *J Vasc Surg* 2002;35:1233-1241.

9. Sivamurthy N, Stone DH, **LoGerfo FW, Quist WC.** The retinoblastoma gene product is reduced in the formation of anastomotic intimal hyperplasia. *Surgical Forum* 2001;52:362-363.

10. Stone DH, Phaneuf MD, Rohan DI, Sivamurthy N, **Quist WC, LoGerfo FW.** A biologically active VEGF construct *in* vitro: Implications for bioengineering-improved prosthetic vascular grafts. *J Biomed Mater Res* 2002;59:160-165.

11. Stone DH, Sivamurthy N, Contreras M, Fitzgerald L, **LoGerfo FW, Quist WC.** Altered ubiquitin/proteasome expression in anastomotic intimal hyperplasia. *J Vasc Surg* 2001;34(6):1016-1022.

Proceedings of Meetings

1. Alhilali LM, Phaneuf MD, Bide MJ, Dempsey DJ, Sousa KA, Aggarwal P, **LoGerfo FW, Quist WC.** Development of an infection resistant Dacron biomaterial. *ASAIO J* 2002;48(2):185.

2. Phaneuf MD, Bide MJ, Nelson KR, Sousa KA, Szycher M, **LoGerfo FW, Quist WC.** An infection-resistant polyurethane catheter. *ASAIO J* 2002;48(2):184.

3. Phaneuf MD, Dempsey DJ, Bide MJ, **Quist WC, LoGerfo FW.** Development of a novel hemodialysis access graft with surface antithrombin properties. *ASAIO J* 2001;47(2):172.

4. Sheahan MG, Pomposelli FB Jr., Belfield AK, Deutsch E, **LoGerfo FW,** Campbell, DR, Hamdan AD. The causes and consequences of early reoperation following infrainguinal bypass procedures.

Reviews, Chapters, and Editorials

1. Cina RA, Froelich JB, Hamdan AD. Perioperative beta blockade to reduce cardiac morbidity in noncardiac surgery. *Int Anesthesiol Clin* 2001;39(4)93-104.

2. Kansal N, Hamdan AD. Clinical features and Diagnosis of Macrovascular Disease. In: The Diabetic Foot. ed Veves A, Guirini JM, Logerfo FW. Humana Press, 2002.

3. Park K, Hamdan AD**.** Anesthesia for endovascular repair of abdominal aortic aneurysm. In: Progress in Anesthesiology. Chapter X, Volume XVI.

Books, Monographs, and Text Books

1. Phaneuf MD, Bide MJ, Quist WC, LoGerfo FW. Surface Modification of Dacron Vascular Grafts: Incorporation of Antithrombin and Mitogenic Properties. In *Polymeric Biomaterials – Second Edition*, ed Dumitriu S, Marcel Dekker, New York, NY, 2002.

Sidney Levitsky, M.D.
James D. McCully, Ph.D.

Division of Cardiothoracic Surgery

I. Narrative Report

Basic Research

The primary focus of the laboratory is to elucidate the mechanisms and subcellular localization of biochemical and molecular events contributing to myocardial cell death. In particular, we are interested in the discriminant and/or coordinate contribution of necrosis and apoptosis to myocardial cell death. We utilize models of stunning and ischemia/reperfusion injury in the isolated Langendorff perfused rabbit and the *in situ* blood perfused pig heart to determine the relative contribution of these pathways in the aged as compared to the mature cardiac surgical patient. The laboratory is also involved in the isolation and identification of genes associated with myocardial ischemia/reperfusion amelioration using differential display, selective subtraction hybridization and microarray technology. For this, we use rabbit and pig heart cDNA libraries constructed in our laboratory and non-redundant cDNA's isolated, sequenced and putatively identified by our laboratory for microarray analysis.

II. Current List of Employees

1.	Anthony Rousou, M.D	Surgical Postdoctoral Fellow
2.	Yng-Ju Hsieh, Ph.D.	Research Associate

III. List of Current Funding

1. "Myocardial Protection: Reperfusion Injury Amelioration "
   National Institutes of Health, RO1 HL 59542
   Project period: 2000-2005
   Principal Investigator: Sidney Levitsky, M.D.
   Collaborating Investigator: James D. McCully, Ph.D.

2. "Mechanisms of Surgically Induced Ischemia/reperfusion Injury in the Aged Heart: Role of apoptosis and necrosis."
   American Heart Association, Post-Doctoral Fellowship (0225661T)
   Project period: 2002-2004
   Fellowship Mentor: James D. McCully, Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. Pig and Rabbit Microarray Construction
   NIH R24
   Principal Investigator: James D. McCully, Ph.D.

2. Surgical Cardioprotection for the Mature and Aged Heart
National Institutes of Health, National Heart Lung and Blood Institutes, Public Health Service Grant: Dr. J. D. McCully

V. Divisional Accomplishments over the Past Year

Grants Submitted:

1. "Pig and Rabbit Microarray Construction"
National Institutes of Health,
Comparative Medicine
Resource-Related Research Project Grant
R24

2. "Surgical Cardioprotection for the Mature and Aged Heart"
NIH/NHLBI R01

Individual Accomplishments

National Presentations

1. Faro R, Toyoda Y, **McCully JD**, Bianchi C. (2001). Inhibition of poly ADP-ribose synthase by PJ-34 reduces pig heart infarct size and improves post-ischemic functional recovery. American Heart Association, Molecular, Integrative and Clinical Approaches to Myocardial Ischemia. Seattle WA, P80.

2. Faro R, Wakiyama H, **McCully JD**, Bianchi C. (2001). Reduction in pig heart infarct size induced by novel peroxynitrite decomposition catalyst (FP-15). American Heart Association, Molecular, Integrative and Clinical Approaches to Myocardial Ischemia. Seattle WA, P83.

3. **Levitsky S**, Wakiyama H, Toyoda Y, Federman M, Cowan DB, **McCully JD**. (2001). Selective opening of mitochondrial ATP-sensitive potassium channels during cardiopulmonary bypass decreases apoptosis and necrosis in a model of acute myocardial infarction. European Association of Cardiothoracic Surgery, Lisbon, Portugal, September 16-19.

4. **McCully JD,** Cowan DB, Wakiyama H, Toyoda Y, Chai J, Federman M, **Levitsky S.** (2002). Amelioration of myocardial injury and extracellular matrix damage during cardiac surgery via pharmacological opening of mitochondrial K_{ATP} channels. Society of Thoracic Surgeons, 2002 Annual Meeting, Fort Lauderdale, FL. January 26-29, 2002.

VI. Report of Teaching

Invited Presentations (local, national and international)

McCully JD

"The Mitochondrial K_{ATP} Channel and Cardioprotection". The 3rd International Symposium on Myocardial Protection from Surgical Ischemic Reperfusion Injury. Asheville Cardiac Surgery Symposium, June 2-5, 2002. Asheville, North Carolina.

Levitsky S

"Modalities of Blood Cardioplegia Delivery: Cold, Tepid, Miniplegia and Dilute (4:1)". The 3rd International Symposium on Myocardial Protection from Surgical Ischemic Reperfusion Injury. "Asheville Cardiac Surgery Symposium, June 2-5, 2002. Asheville, North Carolina.

VII. Plans for the Coming Academic Year

Staff Changes

1. Addition of new technician for microarray studies.

Research

1. Submission of RO1 grant application (February 1, 2003)

VIII. Bibliography (7/01/2001-6/30/2002)

Original Articles

1. Faro R, Toyoda Y, **McCully JD**, Jagtap P, Szabo E, Virag L, Bianchi C, **Levitsky S**, Szabo C, Sellke F. Protective effect on regional myocardial function and infarct size induced by PJ34: a novel potent poly(ADP-ribose) synthase inhibitor. *Ann Thorac Surg* 2002;73:575-81.

2. Stadler B, Phillips J, Toyoda Y, Federman M, **Levitsky, S, McCully JD**. Adenosine enhanced ischemic preconditioning modulates necrosis and apoptosis: Effects of stunning and ischemia/reperfusion. *Ann Thorac Surg* 2001;72:555-63.

3. Toyoda Y, Khan S, Chen W, Parker RA, **Levitsky S, McCully JD**. Effects of NHE-1 inhibition on cardioprotection and impact on protection by K/Mg ardioplegia. *Ann Thorac Surg* 2001;72:836-43.

4. Wakiyama H, Cowan DB, Toyoda Y, Federman M, **Levitsky S, McCully JD**. Selective opening of mitochondrial ATP-sensitive potassium channels during

cardiopulmonary bypass decreases apoptosis and necrosis in a model of acute myocardial infarction. *Eur J Cardiothorac Surg* 2002;21:424-33.

Reviews, Chapters, and Editorials

1. **McCully JD**. Oxygenated Multi-Dose Delivery of Crystalloid Esmolol Cardioplegia as an Alternative to High Potassium Cardioplegia. *J Thorac Cardiovasc Surg* 2002;124:219-20.

2. **McCully JD, Levitsky S**. Aging Enhances the Sensitivity of Endothelial Cells Toward Apoptotic Stimuli: Important Role of Nitric Oxide Aging Enhances the Sensitivity of Endothelial Cells Toward Apoptotic Stimuli: Important Role of Nitric Oxide. *CT Digest* 2001;3 (11).

3. **McCully JD, Levitsky S.** Cardiac Angiotensin II Formation in the Clinical Course of Heart Failure and Its Relationship With Left Ventricular Function. *CT Digest* 2001;3(8)

4. **McCully JD, Levitsky S.** Exercise improves postischemic cardiac function in males but not females: Consequences of a novel sex-specific heat shock protein 70 response. *CT Digest* 2002; 4(7).

5. **McCully JD, Levitsky S**. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *CT Digest* 2002;4(5).

6. **McCully JD, Levitsky S.** Maternal Hypercholesterolemia and Treatment During Pregnancy Influence the Long-Term Progression of Atherosclerosis in Offspring of Rabbits. *CT Digest* 2002; 4 (2).

7. **McCully JD, Levitsky S**. Reduced Cardiovagal Baroreflex Gain in Visceral Obesity: Implications for the Metabolic Syndrome. *CT Digest* 2002; 4(4).

Clinical Communications

1. Dusek JA, Sherwood JB, Friedman R, Myers P, Bethea CF, **Levitsky S,** Hill DC, Jain MK, Koproky SL, Mueller PS, Benson H, Hibberd PL. Study of the therapeutic effects of intercessory prayer (STEP): Study design and research methods. *Am Heart J* 2002;143:577-84.

Abstracts

1. **McCully JD**, Cowan DB, Chai J, Wakiyama H, Toyoda Y, Federman M, **Levitsky S**. Enhanced cardioprotection through pharmacological opening of mitochondrial K_{ATP} channels in acute myocardial infarction: Evidence for the modulation of apoptosis and preservation of mitochondrial integrity. *Circulation*

2001;104(17):522A.

2. Wakiyama H, Toyoda Y, **Levitsky S, McCully JD**. The pharmacological opening of mitochondrial K_{ATP} channels provides enhanced cardioprotection with cold blood cardioplegia in an *in situ* pig heart model of acute myocardial infarction. *Circulation* 2001;104(17):686A.

Anthony P. Monaco, M.D.
Takashi Maki, M.D., Ph.D.

Division of Transplant Center and
Transplantation and Cellular Immunology Laboratory

I. Narrative Report

Basic Research

1. Induction of tolerance to allografts. The major goal of this project is to study the allograft tolerance induced by donor bone marrow cell infusion combined with immunosuppression by antilymphocyte serum and rapamycin in a mouse skin allograft model.

2. Treatment of overtly diabetic NOD mice. The major goals of this project are to study the effectiveness of ALS and exendin-4 in inducing disease remission in autoimmune diabetic NOD mice and to study the effectiveness of allogeneic islet transplantation under the tolerance induction protocol using donor bone marrow infusion to treat autoimmune diabetes.

3. Induction of tolerance to islet allografts in non-human primates. The major goal of this project is to study the induction of tolerance to islet allografts in non-human primates using anti-thymocyte globulin, rapamycin and donor bone marrow cells.

4. Role of chimerism in allograft tolerance. The major goal of this project is to study the role of chimerism in allograft tolerance induced by mixed chimeric bone marrow transplantation in mice.

II. List of Current Employees

1.	Norihiko Ogawa, M.D.	Postdoctoral Fellow
2.	Akira Kanamoto, M.D.	Postdoctoral Fellow
3.	Rita Gottschalk	Research Technician
4.	Jessica Thaxton	Research Technician

III. List of Current Funding

1. "Induction of unresponsiveness to allografts"
   NIH 2 RO1 AI14551-19
   Project period: 07/01/97 - 06/30/07
   Principal Investigator: Anthony P. Monaco, M.D.

2. “Induction of tolerance to islet allografts”
   Juvenile Diabetes Research Foundation Center for Islet Transplantation at Harvard Medical School, Project 46

Project period: 09/01/00 - 08/31/02
Principal Investigator: Takashi Maki, M.D., Ph.D.

3. "Treatment of overtly diabetic NOD mice"
National Institutes of Health, 1R01 DK60721-01
Project period: 12/01/01 - 11/30/06
Principal Investigator: Takashi Maki, M.D., Ph.D.

5. "Induction of tolerance to allografts in non-human primates" (RFA, Non-human Primate Immune Tolerance Cooperative Study Group)
Project period: 09/15/02 - 06/30/07
Principal Investigator: Anthony P. Monaco, M.D.
Co-Principal Investigator: Takashi Maki, M.D., Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. Juvenile diabetes Research Foundation Center for Islet Transplantation at Harvard Medical School
Project period: 09/01/02 - 08/31/03
Principal Investigator: Takashi Maki, M.D., Ph.D.

2. "Role of chimerism in allograft tolerance"
National Institutes of Health
Project period: 04/01/02 - 03/31/07
Principal Investigator: Takashi Maki, M.D., Ph.D.

V. Divisional Accomplishments over the Past Year

Educational Activities

1. Takashi Maki organized and chair a weekly Beth Israel Deaconess Medical Center Transplantation Research Group Work-in-Progress Seminars (05/02 - present)

VI. Bibliography (7/01/01-6/30/02)

Takashi Maki, M.D., Ph.D.

Original Articles (in press)

1. Hale DA, Gottschalk R, Umemura A, **Maki T, Monaco AP.** Immunological mechanisms in tolerance produced in mice with non-radiation based lymphoablation and donor specific bone marrow. *Transplantation* 2002; in press.

2. **Maki T,** Gottschalk R, **Monaco AP.** Prevention of autoimmune diabetes by FTY720 in NOD mice. *Transplantation 2002;* in press.

Dr. Anthony Moncaco

Original Articles (in press)

1. Akoad M, Giraldo M, **Monaco AP,** Hanto DW, Uknis M.E. Case Report: Enteric drainage of a pancreas allograft is safe for patients with celiac sprue. *Clin Transplant* 2002; in press.

2. Hale DA, Gottschalk R., Umemura A, **Maki T, Monaco AP.** Immunological mechanisms in tolerance produced in mice with non-radiation based lymphoablation and donor specific bone marrow. *Transplantation* 2002; in press.

3. **Maki T,** Gottschalk R, **Monaco AP.** Prevention of autoimmune diabetes by FTY720 in NOD mice. *Transplantation;* in press.

4. Morrissey PE, Ramirez PJ, Gohh RJ, Yango AY, Kestin A, Madras PN, **Monaco AP.** Management of thrombophilia in renal transplant recipients. *Am J Transplant* 2:2002; in press.

5. Ramirez PJ, Gohh R, Kestin A, **Monaco AP**, Morrissey PE. Renal allograft loss due to proximal extension of ileofemoral deep venous thrombosis. *Clin Transplant* 16:2002; in press.

6. Vincenti F, **Monaco A**, Grinyo J, Kinkhabwala M, Roza A. A multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. *Am J of Transplant* 2002; in press.

7. Yango A, Morrissey P, Gohh R, Wahbeh A, **Monaco A,** Beaulieu A. Donor transmitted parvovirus infection in a kidney transplant recipient presenting as pancytopenia and allograft dysfunction. *Transplant Infectious Disease* 2002; in press.

8. Yango A, Morrissey P, **Monaco A,** Butera J, Gohh RY. Successful treatment of tacrolimus-associated thrombotic microangiopathy with sirolimus conversion and plasma exchange. *Clinical Nephrology* 2002;57; in press.

Proceedings of Meetings (in press)

1. **Monaco AP.** Chimerism in organ transplantation. Conflicting experiments and clinical effects. *Trans Proc* 2002; in press.

2. **Monaco AP.** Tolerance and chimerism: Separate and unequal concepts. *Trans. Proc* 2002; in press.

Reviews, Chapters, and Editorials

1. Morrissey P, **Monaco AP.** Polyclonal Antilymphocyte Therapy. In: Current and Future Immunosuppressive Therapies Following Transplantation. Sayegh, M.H., Remuzzi, G. eds, Kluwer Acadmic Publishers, Hingham, MA, 2002.

2. Morrissey PE, Gohh RY, **Monaco AP.** Allorecognition and Tissue Typing in Organ Transplantation. In: Immunology for Surgeons. Zbar, A.P., Guillou, P.J., Bland, K.I, Syrigos, K.N., eds., Springer-Verlag, London, UK, 2002.

3. Morrissey PE, Madras PN, **Monaco AP.** History of Solid Organ Transplantation. In: Clinical Management of the Transplant Patient. Kuo, P.C., Schroeder, R.A., Johnson, L.B. eds, Arnold Publishers, London, UK, 2001.

Edward C. Mun, M.D.

Division of General Surgery

I. Narrative Report

Basic Research

The focus of my laboratory is on the NIH-funded project "Intestinal Transport during Metabolic Stress" which investigates 1) whether metabolic stress (in the form of ischemia and hypoxia) induces epithelial Cl^- secretory response in native human intestine via purinergic signaling pathways, and 2) whether the regulatory mechanism of ischemia-elicited secretion involves modulation of basolateral K^+ channel activity. A new area of research interest includes the surgical treatment of type II diabetes in patients with visceral obesity by laparoscopic omentectomy.

II. Current List of Funding

1. "Intestinal Transport during Metabolic Stress"
   NIH/NIDDK K08 DK 02604
   Project period: 12/01/1998 - 11/30/2003
   Principal Investigator: Dr. Ed Mun

2. BIDMC Special Research Discretionary Fund

III. Divisional Accomplishments

Educational Activities

1. I participate in the Core Clerkship in Surgery for third year HMS students. I am responsible for 8 students in 2 week blocks each. I commit 4-8 hours per week as a preceptor in the office, ward rounds, and operating room. In addition, I participate in the Saturday lecture series.

2. I am a member of the "Purple Team", General Surgery Service, which includes working with 4-5 residents for 12 months per year. I spend 20 hours of direct teaching per month including operating room, teaching as an attending surgeon, and chief's rounds.

Invited Presentations (Local)

1. "Diabetes and Endocrinology: Critical Issues"
   Harvard MED-CME, Joslin Diabetes Center
   Nov 2001, Boston Marriott Copley Place

2. "Practical Approaches to the Treatment of Obesity"
   Harvard MED-CME, Beth Israel Deaconess Medical Center

Jun 2002, Royal Sonesta, Boston

Research Accomplishments

1. I currently work on NIH K08 DK 02604 Mentored Career Development Award, received on 12/1/98 for 5 years. The grant "Intestinal Transport during Metabolic Stress" focuses on examination of the regulation of intestinal secretion during epithelial metabolic stress, with a particular emphasis on the role of purinergic compounds and their surface receptor gene expression in the epithelial response to hypoxic and ischemic insults.

2. A clinical research project "Surgical visceral fat reduction by omentectomy as treatment for obesity-related type II diabetes" is now underway. This project investigates the effects of visceral fat reduction in the regulation of serum glucose by insulin.

Administrative Activities

As the Gastric Bypass Program Director, I held weekly business meetings.

VI. Plans for the Coming Academic Year

Teaching

I plan to continue with current level of undergraduate and graduate teaching responsibilities. Continue resident teaching in weekly Gastric Bypass Surgery clinic. Establish and moderate monthly clinical/basic science conference in obesity and type II diabetes in conjunction with Joslin Diabetes Center. Conduct monthly resident/student teaching rounds in obesity surgery. Increase participation in Tuesday resident teaching rounds and Friday Chief's rounds.

Research

I plan to continue current basic and clinical science research projects by conducting and supervising experiments in the laboratory. Publish original articles using the accumulated data. Continue with presentations at the national scientific meetings. Obtain memberships to additional academic research societies. Establish non-clinical, dedicated research day weekly to accommodate research need. Broaden joint research endeavors with Joslin Diabetes Center in basic and clinical research.

Clinical Activities

I plan to continue as the director of the bariatric Surgery Service, increase other major general surgery practices (i.e., gastric, esophageal, colo-rectal). My goal for next year is to increase efficiency and the number of laparoscopic gastric bypass procedures I do in the clinic each week.

VII. Bibliography (07/01/2001-06/30/2002)

Clinical Communications

1. Patient information booklet entitled “A Guide to Gastric Bypass Surgery at the Beth Israel Deaconess Medical Center”.

Aria F. Olumi, M.D.

Division of Urology

I. Narrative Report

Basic Research

My laboratory studies two areas of biology related to prostate hyperplasia and cancer. First, we study the biology of stromal-epithelial interactions in benign prostatic hyperplasia (BPH). Second, we study Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) and are interested in whether the anti-apoptotic factor, c-FLIP, has a critical role in protecting prostate tumor cells from TRAIL-induced apoptosis. Because development, growth and tumorigenesis in the prostate is closely regulated by stromal-epithelial interactions, identifying signal transduction pathways in prostatic epithelial cells that are activated by surrounding stromal cells will allow a better understand of the normal and abnormal biology in prostatic diseases. I hypothesize that the expression of specific genes (in stromal cells) regulates changes in prostatic epithelial cells leading to BPH in adulthood. Thus, current studies in the laboratory concern how paracrine signals from stromal cells activate Jun-family signaling proteins in epithelial cells to regulate epithelial proliferation, cell death and differentiation. As for TRAIL and c-FLIP, these studies will allow a better understanding of the role of c-FLIP in evasion of prostate carcinomas from TRAIL-induced apoptosis and will allow the design of rational therapeutic targets that can be used in combination with TRAIL for effective treatment of prostate tumors.

Clinical Research

Prostate cancer is usually diagnosed by ultrasound guided needle biopsy. The standard of care is to perform six core biopsies from different regions of the prostate. However, recent studies suggest that six core biopsies may not be adequate enough for proper cancer detection. In fact, larger prostates may require more biopsies in order to achieve similar cancer detection rates as smaller prostate. This discrepancy between large and small prostates is most likely secondary to a higher sampling error associated with larger prostate. There is no consensus on the appropriate number of prostate biopsies required for varying prostatic sizes. In order to standardize the number of prostate biopsies required for varying prostatic sizes we are reviewing the prostate biopsies of over 1000 patients at BIDMC who have had extended (more than 10 core) biopsies.

II. List of Current Employees

1.	Xiaoping Zhang, M.D., Ph.D.	Research Fellow
2.	Ignacio San Francisco, M.D.	Research Fellow

III. List of Current Funding

1. "Stromal Epithelial Interactions in Benign and Malignant Prostatic Disease"
   Beth Israel Deaconess Medical Center
   Project Period: 09/01/00 - 8/31/03
   Principal Investigator: Aria Olumi, MD

IV. Applications Submitted and Pending Review/Funding

1. "The Role of Anti-apoptotic Factors in Evasion of Prostate Tumors from TRAIL-Induced Apoptosis"
   NIH/Harvard Prostate SPORE
   Project Period: 11/01/02-10/31/05 (FUNDED)
   Principal Investigator: Aria Olumi, M.D.

2. "Role of Stromal-Epithelial Interactions in BPH"
   NIH/NIDDK K-08 (Priority score 150 at review 10/02)
   Project period: 01/01/03-12/31/07
   Principal Investigator: Aria Olumi, M.D.
   Mentors: Steven Balk, M.D., Ph.D. and Glen Bubley, M.D.

V. Divisional Accomplishments over the Past Year

Research Accomplishments

1. I was awarded a grant from the HMS SPORE for prostate research and I received a good priority score for my K08 application such that it will, most likely, be funded for 5 years.

Presented Abstracts

1. **Olumi AF**, Xiao Y, San Francisco IF, Donna M. Peehl, DeWolf WC. Retroviral transfection of human telomerase gene more commonly leads to senescence than expansion of lifespan in prostate fibroblasts. American Urological Assoc. Annual Meeting, Orlando, FL, 2002.

   This abstract was selected as one of the top 10% of research abstracts presented at the AUA meeting.

2. Ung JO, San Francisco IF, Regan MM, DeWolf WC, **Olumi AF**. Lower prostate cancer detection rate in large prostate glands is not associated with biopsy sampling error. American Urological Assoc. Annual Meeting, Orlando, FL, 2002.

3. San Francisco IF, **Olumi AF**, Jerry Kao, Seymour Rosen, DeWolf WC. The natural history of prostatic intraepithelial neoplasia as defined by extended needle biopsies. American Urological Assoc. Annual Meeting, Orlando, FL, 2002.

VI. Report of Teaching

Educational activities

1. I was an invited speaker at the Harvard Urologic Oncology Course, October 2002. Title: "Cytoreductive Nephrectomy in Metastatic Renal Carcinoma".

2. I participated in the monthly one-on-one evaluation with interns and residents.

3. I was the weekly faculty representative for the Harvard Urology Program conferences.

4. I attended a course: "Advanced Laparoscopic Surgery", sponsored by AUA in August of 2002.

5. I directed an animal laparoscopy program for the Harvard Urology Program at Rhode Island Hospital, January 2002 and October 2002.

6. I continue to teach medical students on a weekly basis with a one-hour didactic session.

7. I was a core surgery clerkship lecturer for medical students (once every three months). I lectured on BPH and prostate cancer.

VII. Plans for the Coming Academic Year

Plans for Research-new grants/programs

1. "Mechanisms of TRAIL-Induced Apoptosis in Prostate Cancer" will be submitted to the American College of Surgeons for a Faculty Research Fellowship on 11/1/02.

2. I plan to submit a grant application to the American Cancer Society on the mechanisms of apoptosis in prostatic cancer

VIII. Bibliography (7/1/01 through 6/30/02)

Reviews, Chapters, and Editorials

1. **Olumi, AF.** Book Review-Prostate Cancer: Biology, Genetics, and the New Therapeutics. *New Engl J Med* 2002;346:1677-1678.

Sareh Parangi, M.D.

Division of General Surgery

I. Narrative Report

Basic Research

1. Angiogenesis and pancreatic tumor progression.

2. Use of antiangiogenic drugs in combination to treat tumors.

3. Imaging of angiogenic vessels during antiangiogenic therapy.

4. Antiangiogenic gene therapy.

The main focus of my research centers on the analysis of angiogenesis during tumor progresion in a variety of tumors. Focus is on development and use of models that are close to human diseases such as an orthotopic pancreatic cancer model. Projects involve use of a transgenic insulinoma model as well as orthotopic models to test novel antiangiogenic therapies. Animals are monitored by doppler ultrasound and magnetic resonance imaging during antiangiogenic therapy to look specifically at tumor vasculature. Gene therapy with antiangiogenic agents is also used to affect tumor progression

II. List of Current Employees

1. Tong Zi Research Technician

III. List of Current Funding

1. "Antiangiogenic gene therapy in a mouse model of pancreatic cancer"
   American College of Surgeons Faculty Research Fellowship
   Project period: 2001-2005
   PI: Dr. Sareh Parangi

2. "Role of IGF-1 in pancreatic cancer"
   American Cancer Society
   Project period: 2001-2004
   Co-investigator: Dr. Sareh Parangi

3. "Temporal and Spatial Regulation of Angiogenesis", Project 3: "Inhibition of Angiogenesis by Thrombospondin –1"
   National Cancer Institute, P01, NCI- Program Project Grant
   Project period: 2002-2007
   Co-investigator: Dr. Sareh Parangi

4. **"**Antiangiogenic Therapy of Pancreatic Cancer"
National Cancer Institute,1 K08 CA88965-01A1
Project period: 2002-2007
Principal Investigator: Dr. Sareh Parangi

IV. Divisional Accomplishments over the Past Year

Individual Accomplishments

1. I became member of Society of Surgical Oncology.

2. I became member of the International Association of Endocrine Surgeons.

3. I became member of the Surgical Housestaff Committee.

4. I became a member of the Subcommittee for Women, Office for Faculty Development, BIDMC.

V. Report of Teaching

1. Director of Surgical Grand Rounds, Beth Israel Deaconess Medical Center. Invite speakers to present at Surgical Grand Rounds 48 weeks per year, time commitment eight (8) hours per month, twelve (12) months per year.

2. Core Clerkship in Surgery

    1. I am a preceptor for patient care and for the operating room.

    2. I train four to six (4-6) medical students per year for 4 week blocks.

    3. I spend four to eight (4-8) hours per week in the office, ward rounds, and operating room.

3. Administration of Surgical Clerkship Examination

    1. I examine 4 medical students. The exam requires 4 hours of testing four times yearly.

4. I am a lecturer for Harvard medical students on the topic of hyperthroidism and throid cancer. There are 6 sessions per year and each session is 2 hours.

5. I participate in the Core Curriculum Conference for surgical residents I am responsible for 3 sessions on thyroid tumors, hyperparathyroidism, and adrenal tumors. Each session is 3 hours of interactive lectures and case presentations.

VI. Plans for the Coming Academic Year

Plans for Research

1. Initiate collaboration with endocrinologist regarding novel antiangiogenic treatments aimed at endocrine tumors

2. Submit research papers

VII. Bibliography (7/1/01-6/30/02)

Original Articles

1. **Parangi S**, Delic M, Lawler J, Terwilliger E. Gene therapy with a recombinant adenoassociated virus (rAAV) in an orthotopic model of pancreatic cancer in SCID mice. *Surgical Forum* 2001;52:31-32

Clinical Communications

1. "Thyroid Surgery at Beth Israel Deaconess: Information for patients and families" Prepared by me and produced and distributed by the Beth Israel Deaconess Learning Center

2. "Thyroid Surgery: Discharge Instructions" Prepared by me and produced and distributed by the Beth Israel Deaconess Learning Center

3. "Thyroid disease is More Prevalent Among Women, Thyroid nodules and Thyroiditis"

4. Prepared for Women's Health News, Published by Beth Israel Deaconess Medical Center

Nonprint Materials

1. Developed a web site for the Thyroid Center at Beth Israel Deaconess Medical Center www.bidmc.harvard.edu/thyroidcenter.

Frank W. Sellke, MD
Cesario Bianchi, MD, PhD

Division of Cardiothoracic Surgery

I. Narrative Report

Basic Research

The goal of our research efforts are twofold. 1) To examine changes in coronary and peripheral microvascular reactivity and permeability and identify the respective cellular and molecular mechanisms of change, which occur as a consequence of cardiopulmonary bypass and cardioplegia in a porcine model. We use both *in vivo* and *in vitro* techniques in isolated microvessels. 2) To examine the use of therapeutic angiogenesis for the treatment of coronary artery disease (CAD). We identify causes for the lack of effect of exogenous growth factor therapy (implantation of sustained-release devices containing bFGF and/or VEGF) in a hypercholesterolemic porcine model with similarities to human CAD.

II. List of Current Employees

1.	Jun Feng, MD, PhD	Instructor in Surgery
2.	Tanveer A Khan, MD	Research Fellow
3.	Pierre Voisine, MD	Research Fellow
4.	Jiannyi Li, MB	Research Assistant
5.	Shu Hua Xu, PhD	Research Assistant

III. List of Current Funding

1. "Cardioplegia and Coronary Microvascular Reactivity"
   National Institutes of Health/NHLBI, RO1 HL-46716
   Project period: 08/31/2001–07/30/2005
   Principal Investigator: Dr. Frank W. Sellke

2. "Surgical Intramyocardial Angiogenesis in a Swine model of Endothelial Dysfunction"
   RO1 HL-69024
   Project period: 07/01/2002-06/30/2007
   Principal Investigator: Dr. Frank W. Sellke

3. "NHLBI Administrative Supplements for Microarray Applications and Analyses"
   NOT-HL-02-003
   Project period: 09/01/2002-08/31/2003
   Principal Investigator: Dr. Frank W. Sellke

4. "BIDMC-Cardiothoracic Surgery Discretionary Fund"
   Principal Investigator: Dr. Frank Sellke

5. "Stimulation of coronary collaterals in the coronary circulation of human patients"
   National Institutes of Health/NHLBI, P50 HL-56993 SCOR
   Project period: 04/23/1997-03/31/2002
   Principal Investigator: Dr. Lewis C. Cantley
   Co-investigator: Dr. Frank Sellke

6. "Effect of PARS inhibitor in myocardial ischemia"
   National Institutes of Health/NHLBI, R43 HL65863
   Project Period: 07/31/2001–12/31/2002
   Principal Investigator: Dr. Frank W. Sellke
   Subcontract with Dr. C. Csaba from Inoteck Corporation

7. "HMG CoA Reductase Inhibitors and Cardiopulmonary Bypass"
   NIH Individual National Research Service Award F32 HL69651
   National Institutes of Health/NHLBI
   Project period: 2001-2003
   Principal Investigator: Dr. Tanveer Khan
   Sponsor: Dr. Frank W. Sellke

IV. Applications Submitted and Pending Review/Funding

Pending Grants (resubmission)

1. "Cardiopulmonary Bypass and Vascular Permeability"
   Principal Investigator: Dr. Cesario Bianchi
   Submit by October 1, 2002.

V. Divisional Accomplishments over the Past Year

New Grants/financial support:

1. Dr. Frank W Sellke was awarded a new R 01: HL-69024: "Surgical Intramyocardial Angiogenesis in a Swine model of Endothelial Dysfunction" was funded for 5 years.

2. Dr. Frank W Sellke was awarded a supplement for RO1-HL-46716: NOT-HL-02-003. "NHLBI Administrative Supplements for Microarray Applications and Analyses" was funded for 1 year.

Educational Activities:

1. Dr. Cesario Bianchi continues as a member of the Teaching Faculty for Harvard Medical School, tutoring first year Harvard Medical / Dental Students (Integrated

Human Physiology, Human Body, Cell Biology, and Pharmacology). He was nominated for "Best Tutor 2002".

Invited Presentations (Local, National, International)

1. **Bianchi C**. "Protein tyrosine kinase modulation by cardiopulmonary Bypass. Sao Paulo Heart Institute of the University of Sao Paulo, Brazil. November 2002.

2. Khan T, **Bianchi C**, Ruel M, **Sellke F**. Effects of Cardiopulmonary Bypass on Mitogen-Activated Protein Kinase Activation and Peripheral Microvascular Contractile Responses in Humans. Presented at the 51st Annual Meeting of the Scandinavian Association for Thoracic Surgery.

3. Khan TA. Vasomotor Regulation During Cardiopulmonary Bypass. Surgical Grand Rounds, Department of Surgery, Beth Israel Deaconess Medical Center. June 19, 2002.

4. Khan TA, Ruel M, **Bianchi C**, Csaba C, **Sellke FW**. Poly ADP-Ribose Synthetase Inhibition Improves Postischemic Myocardial Function After Cardiopulmonary Bypass. Presented at the 51st Annual Meeting of the Scandinavian Association for Thoracic Surgery. Aarhus, Denmark. June 13-15, 2002.

5. Ruel M, **Bianchi C**, Khan TA, Xu S, **Liberman T**, **Kohane I**, **Sellke FW**. Genomic Expression Profile of the Clinical Response to Cardiopulmonary Bypass. Presented at the Scientific Meeting of the Scandinavian Society for Thoracic Surgery, Aarhus, Denmark, June 12-15, 2002.

6. Ruel M, **Bianchi C**, Zhang JP, **Sellke FW**, **Cohn WE**. Results of myocardial revasclarization with a submucosal gastric patch. Presented at the 77th Scientific Sessions of the American Heart Association, Anaheim, CA, Nov 10-15, 2001.

7. Ruel M, **Laham RJ**, Neiman D, **Parker JA**, **Sellke FW**. Long-term nuclear perfusion imaging of patients treated with perivascular FGF-2. Presented at the 77th Scientific Sessions of the American Heart Association, Anaheim, CA, November 10-15, 2001.

8. **Sellke FW**. Invited Lecturer: Angiogenesis using protein growth factors, American Heart Association Meeting, Anaheim CA, 2001.

9. **Sellke FW**. Invited Lecturer: Mechanisms of angiogenesis and arteriogenesis, American Heart Association Meeting, Anaheim CA, 2001.

10. **Sellke FW**. Invited Lecturer: Therapeutic coronary angiogeneis using FGF-2 protein. 8th World Congress on Heart Failure. Washington DC, 2002.

11. **Sellke FW**. Invited Lecturer: Third International Symposium: Myocardial Protection from Surgical Ischemia Reperfusion Injury "Treatment of the Unrevascularizable Myocardial Segment: Angiogenesis", Asheville, NC, 2002.

12. **Sellke FW**. Moderator: Basic Science in Myocardial Protection, American Heart Association Meeting, Anaheim CA, 2001.

13. **Sellke FW**. Moderator: Cardiac Surgery Forum Session, American Association for Thoracic Surgery Meeting, Washington DC, 2002.

14. **Sellke FW**. Moderator: Third International Symposium: Myocardial Protection from Surgical Ischemia Reperfusion Injury, "Use of molecular and cellular therapy in myocardial and vascular protection: What is clinically applicable?" Asheville, NC, 2002.

15. **Sellke FW**. Organizer and Moderator: Harvard Combined Cardiothoracic Surgical Conference. BIDMC, March 13, 2002.

16. **Sellke FW**. Surgical Angiogenesis for the treatment of coronary artery disease, Dartmouth Medical School, Hanover NH, 2002.

17. **Sellke FW**. Therapeutic Coronary Angiogenesis: Fad or Real Therapy? Surgical Ground Rounds, Department of Surgery, Beth Israel Deaconess Medical Center, 2001.

18. **Sellke FW**. Visiting Professor, Carolina Heart Institute, Charlotte, NC, 2001.

19. **Sellke FW**. Visiting Professor, University of Toronto, Toronto, Ontario, 2001.

VI. Plans for the Coming Academic Year

Staff Change

1. We may recruit a research fellow for the coming year.

VII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Araujo EG, **Bianchi C**, Faro R, **Sellke FW**. Oscillation in the activities of MEK/ERK1/2 during cardiopulmonary bypass in pigs. *Surgery* 2001;130:182-191.

2. **Bianchi C,** Araujo EG, Sato K, **Sellke FW.** Biochemical and structural evidence for pig myocardium adherens junction disruption by cardiopulmonary bypass. *Circulation* 2001;104:I319-I324.

3. Faro R, Toyoda Y, **McCully JD,** Jagtap P, Zsabo E, Virag L, **Bianchi C, Levitsky S,** Szabo C, **Sellke FW.** Myocardial protection by PJ34, a novel potent poly (ADP-ribose) synthetase inhibitor. *Ann Thorac Surg* 2002;73:575-581.

4. **Park KW,** Dai HB, Metais C, Comunale ME, **Sellke FW**. Isoflurane does not further impair microvascular vasomotion in a rat model of subarachnoid hemorrhage. *Can J Anaesth* 2002;49:427-433.

5. **Park KW,** Metais C, Dai HB, Comunale ME, **Sellke FW.** Microvascular endothelial dysfunction and its mechanism in a rat model of subarachnoid hemorrhage. *Anesth Analg* 2001;92:990-996.

6. Xu X, Li **J, Simons M, Laham RJ, Sellke FW.** Expression of vascular endothelial growth factor and its receptors is increased, but microvascular relaxation is impaired in patients after acute myocardial ischemia. *J Thorac Cardiovasc Surg* 2001;121:735-742.

Original Articles (in press)

1. **Bianchi C,** Wakiyama H, Faro R, Khan T, **McCully JD, Levitsky S,** Szabo C, Sellke FW. A novel peroxinitrite decomposer catalyst (FP-15) reduces myocardial infarct size in an in vivo model of acute ischemia-reperfusion in pigs. *Ann Thorac Surg* 2002; in press.

2. Li J, Parovian C, Hampton TG, Metais C, Tkachenko E, **Sellke FW, Simons M.** Modulation of Microvascular Signaling by Heparan Sulfate Matrix: Studies in Syndecan-4 Transgenic Mice. *Microvasc Res* 2002;64:38-46.

3. Ruel M, **Laham RJ, Parker JA, Post Mj,** Ware JA, **Simons M, Sellke FW.** Long-term effects of surgical angiogenic therapy with fibroblast growth factor 2 protein. *J Thorac Cardiovasc Surg* 2002;124:28-34.

Reviews, Chapters, and Editorials

1. Khan TA, **Sellke FW**, **Laham RJ**. Therapeutic Angiogenesis for Coronary Artery Disease. *Current Treatment Options in Cardiovascular Medicine.* 2002;4(1):65-74.

2. **Laham RJ, Simons M, Sellke F**. Gene transfer for angiogenesis in coronary artery disease. *Annu Rev Med* 2001;52:485-502.

3. **Post MJ, Laham R, Sellke FW, Simons M.** Therapeutic angiogenesis in cardiology using protein formulations. *Cardiovasc Res* 2001;49:522-31.

Reviews, Chapters, and Editorials (in press)

1. Ruel M, **Kelly RA**, **Sellke FW**. Therapeutic Angiogenesis, Transmyocardial Laser Revascularization, and Cell Therapy. In Edmunds LH, Cohn LH (eds.): *Cardiac Surgery in the Adult*, 2nd ed. New York, McGraw-Hill, 2002; in press.

Non Print Materials

1. **Sellke FW**, **Cohn. WE**. Invited internet review (Annals of Thoracic Surgery): Is there a relationship between cognitive dysfunction and systemic inflammatory response after cardiopulmonary bypass*? Internet Cardiothoracic Digest.* CME Network, Southampton, NY, L Cohn, Ed. 2001;3:5.

Non-Print Materials (in press)

1. **Sellke FW**. Invited internet review (*Ann Thorac Surg*): Duraflo II heparin bonding does not attenutate cytokine release or improve pulmonary function.. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

2. **Sellke FW.** Invited internet review (*Ann Thorac Surg*): Relation of intraoperative flow measurement with postoperative quantitative angiographic assessment of coronary artery bypass grafting. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2001; in press.

3. **Sellke FW**. Invited internet review (*Ann Thorac Surg*): Therapeutic angiogenesis induced by local autologous bone marrow cell implantation. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

4. **Sellke FW**. Invited internet review (*Cardiovasc Res*): Post-ischemic PKC inhibition impairs myocardial calcium handling and increases contractile

protein calcium sensitivity. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2001;3; in press.

5. **Sellke FW**. Invited internet review (*J Thoracic Cardiovasc Surg*): The early clinical and angiographic outcome of sequential coronary artery bypass grafting with the off-pump technique. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

6. **Sellke FW**. Invited internet review (*J Thoracic Cardiovasc Surg*): The Insulin Cardioplegia Trial: Myocardial protection for urgent coronary artery bypass grafting. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

7. **Sellke FW**. Invited internet review (*J Thoracic Cardiovasc Surg*): Normothermia does not improve postoperative hemostasis nor does it reduce inflammatory activation in patients undergoing primary isolated coronary artery bypass. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

8. **Sellke FW, Cohn WE.** Invited internet review (*Ann Thorac Surg*): Does ministernotomy improve postoperative outcome in aortic valve operation: A prospective randomized study. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002; in press.

9. **Sellke FW, Cohn WE.** Invited internet review (*Ann Thorac Surg*): Influence of diabetes on mortality and morbidity: Off-pump coronary artery bypass grafting versus coronary artery bypass grafting with cardiopulmonary bypass. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2001; in press.

Abstracts

1. Ruel M, **Bianchi C**, Zhang JP, **Sellke FW**, **Cohn WE**. Myocardial revascularization with a GEA-based submucosal gastric patch. *Circulation* 2001;104(17):1926.

2. Ruel M, **Laham RJ**, Neiman D, **Sellke FW**, **Parker JA**. Late nuclear perfusion imaging follow-up after perivascular implantation of FGF-2. *Circulation* 2001;104(17):1258.

3. Ruel M, **Laham RJ**, **Parker JA**, **Simons M**, **Sellke FW**. Long-term effects of surgical angiogenic therapy with FGF-2. *Can J Cardiol* 2001;17(C):87.

4. Ruel M, **Sellke FW**, **Bianchi C**, Zhang JP, **Cohn WE**. Myocardial revascularization with a GEA-based submucosal gastric patch: a new approach to angiogenesis. *Can J Cardiol* 2001;17(C):88.

Sumner A. Slavin, M.D.

Division of Reconstructive and Plastic Surgery

I. Narrative Report

The BIDMC Lymphedema Project consists of both a basic science and clinical research components. Over the past year, our research committee has established a regular meeting schedule to study, plan, and strategize work concerning research on lymphedema, as well as clinical treatment for lymphedema. A primary goal of our committee is to integrate and utilize both the clinical and basic research components of our project.

Basic Science Research: Lymphangiogenesis

The objective of our basic science research is to promote lymphangiogenesis by stimulating lymphatic endothelial cell (LEC) proliferation and migration using an alginate-VEGF-C hydrogel. The results of *in vitro* studies indicate that an alginate biodegradable hydrogel may be an effective delivery system for VEGF-C. *In vivo* animal studies are required to evaluate alginate-VEGF-C hydrogels and their potential role in restoring the lymphatic circulation in lymphedema. Three project goals are to 1) incorporate angiopoietin-2 to alginate-VEGF-C gels to promote a more pronounced LEC response; 2) evaluate new gels *in vitro* as well as *in vivo* in a tail lymphedema rat model; evaluate gene expression of lymphedematous adipose tissue by differential gene expression using Affimatrix gene-chip arrays.

Clinical Research: Lymphedema

Over the past year, Drs. Slavin and Borud established a lymphedema clinic at BIDMC, which will utilize the techniques of aggressive suction lipectomy followed by compression therapy to reduce lymphedema in patients with lymph node resection. This procedure was first established by Håkan Brorson, M.D., a surgical investigator in Sweden. The clinic at BIDMC is the first of its kind in the United States.

II. Current Employees (Part-time)

1.	Loren J. Borud, M.D.	Instructor in Surgery
2.	Mauricio Contreras, M.D.	Instructor in Surgery
3.	Geoffrey Brahmer	Coordinator / Administration
4.	Robert M. Goldwyn, M.D.	Retired

III. List of Current Funding

1. "Lymphatic Regeneration within porous VEGF-C hydrogels for Secondary Lymphedema"
   Department of Defense / Breast Cancer / 000413
   Project Period: 06/01/01 to 05/31/04
   PI: Mauricio A. Contreras, MD

2. Friends of Beth Israel Deaconess Medical Center Grant sponsored a fundraiser entitled: "Lymphedema Treatment Program", which raised $50,000.

3. Dr. Slavin also obtained private donations in support of the Lymphedema Project.

IV. Applications Submitted and Pending Review / Funding

1. American Society for Surgery of the Hand: Outcome Studies Grant – pending review. Grant entitled "Suction-Assisted Lipectomy and Compression Treatment of Upper Extremity Lymphedema: Effectiveness and Quality of Life Assessment."

V. Divisional Accomplishments

1. A porous, biodegradable gel with alginate was produced to use as a delivery device for VEGF-C growth factor to promote lymphatic endothelial cell proliferation and migration *in vitro.* In the next phase we will incorporate Angiopoietin-1 to the VEGF-C alginate gels to enhance the proliferative and migratory response of the LEC.

2. A Rat Thoracic Duct Endothelial Cell line was created.

3. A scientific collaboration was arranged with Dr. Rudeiger Baumeister, Professor of Plastic Surgery, and Chief of Plastic Surgery, University of Munich, and Dr. Håkan Brorson, M.D., a surgical investigator in Sweden, for the collection of fat and lymph samples. Already, this collaboration has resulted in the collection of optimal fat samples, which will be used for ongoing research and grant applications.

4. In July 2002, Dr. Loren Borud performed the *first Brorson procedure* outside Sweden – the first such procedure in America. In the past year, Dr. Borud has personally seen and treated 15 patients with lymphedema, also collecting and maintaining lymphedema tissue specimens from his patients at the time of their resectional procedures – the first lymphedema tissue obtained at BIDMC for basic molecular study.

5. Drs. Slavin and Contreras submitted an Abstract to the International Meeting on Angiogenesis & Lymphangiogenesis Basic Mechanisms and Therapeutic

Implications. The abstract was accepted for a Poster presentation, and was printed in the Meeting's Publication.

6. On May 7th, Dr. Sumner Slavin was a main speaker for the first *Lymphedema Awareness Day in Massachusetts.* This event was held in the Massachusetts State House. In addition, Drs. Slavin and Loren Borud provided medical expertise for legislation to mandate insurance coverage for lymphedema in the Commonwealth of Massachusetts. In this role, they worked with legislators, grassroots lymphedema support groups, lymphedema advocates, as well as other health care professionals.

Individual Accomplishments

1. Dr. Slavin was one of a small group of scientists invited as a speaker to the Lymphedema Think Tank, sponsored by the National Institute of Health, May 2002.

2. Drs. Slavin and Contreras were invited by Dr. Stanley G. Rokson, Chief editor of the *Lymphatic Research and Biology Journal* to submit a manuscript this fall. Manuscript is currently in progress.

3. One of Dr. Slavin's Slides, obtained from Harvard Medical School, was used for the cover photo of the first *Lymphedema Journal*.

4. Since July of 2001, Dr. Borud has given multiple presentations on the treatment of lymphedema. Most notably, in October of 2001, Drs. Borud and Slavin were the keynote speakers at the annual meeting of the Maine Lymphedema Network in Bar Harbor, Maine.

Invited Presentations (local, national, and international)

1. We were invited to present our work as an Oral presentation at the Era of Hope, Breast Cancer. September 25-28, 2002 meeting. Orlando, FL.

2. Dr. Slavin presented a talk entitled, *"History and Treatment of Lymphedema,"* to the Harvard Plastic Surgery Residency Grand Rounds, July 18, 2002.

3. On March 3, 2002, BIDMC hosted a New England meeting of the National Lymphatic Research Foundation.

4. In April, Dr. Slavin and the Division of Plastic Surgery hosted Dr. Ruediger Baumeister as a Visiting Professor to Beth Israel Deaconess Medical Center. Dr. Baumeister, Chief of Plastic Surgery, University of Munich, and also a surgical specialist on lymphedema, presented a talk, *Treatment of Lymphedemas by Autogenous Lymphatic Grafts: Late Results*, at the Combined Harvard Plastic Surgery Grand Rounds. He also attended a

lymphedema planning meeting, observed surgeries, and participated in Division Rounds at BIDMC. Dr. Baumeister's visit led to a scientific collaboration on lymphedema between the University of Munich and the BIDMC.

5. Drs. Slavin and Contereras were invited to participate in the Lymphatic Continuum Conference, May 3-4, 2002, National Institutes of Health, Bethesda, Maryland. Dr. Slavin presented a talk on *"Current Surgical Management of Lymphedema."*

VI. Plans for the Coming Academic Year

Clinical Lymphedema Program

1. The Lymphedema Treatment Program is about to become a reality. Our first clinic day will be in October 2002. Dr. Slavin will serve as the Director of the Program. Dr. Borud, serving as the Co-Director, will be in charge of scheduling patients, promoting and marketing the Program, performing the surgery, and following the patients throughout their course of treatment.

2. We will continue to work for a legislative mandate to require insurance coverage for treatment of patients with lymphedema.

Basic Science Studies in Lymphedema

Two grant proposals will be submitted to the NIH in the coming year:

1. Drs. Borud and Slavin will prepare and submit an NIH grant proposal (K-08) for the study of lymphedema in the clinical, molecular biological, and animal model settings. Dr. Borud is currently developing a rodent model of lymphedema to provide an additional tool for molecular study.

2. Drs. Contreras and Slavin will prepare and submit a research proposal entitled, Plans for Research: (New Grants / Programs): RO1 / NIH Grant application under the title: " Gene expression in Lymphedematous Adipose Tissue Secondary to Breast Cancer" / March 2003.

   Both submissions will utilize tissue samples collected from patients with lymphedema (initially obtained from patients by Drs. Slavin, Borud, Baumeister, and Brorson). Dr. Ruediger Baumeister, Professor of Plastic Surgery in Munich, Germany, has agreed to collaborate and has begun to submit tissue samples from Germany for our laboratory to analyze. Dr. Mauricio Contreras will be fully active in both the collection and processing phases of these samples. It is also possible, as we move forward, that Dr. Evan Rosen, A BIDMC endocrinologist, will also be a collaborator in one (or both) of these proposals.

We will also actively seek out other funding and grant opportunities via foundations, corporations, and through private donations.

3. Staff Changes/Recruitments: A PhD is needed for work in gene expression in lymphedematous adipose tissue research, as well as in other molecular and clinical aspects of the lymphatic system and lymphedema.

VII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Chuang, DC, Ma H, **Borud LJ**, Chen HC. Surgical strategy for improving forearm and hand function in late obstetric brachial plexus palsy. *Plastic Reconstr Surg* 2002;109:1934-1946.

2. McCarthy JG, **Borud LJ**. Hemangiomas of the nasal tip. *Plastic Reconstr Surg* 2002;109:31-40.

Proceedings of Meetings

1. **Contreras MA**, **Slavin AS**. Lymphangiogenesis from porous alginate-VEGF-C-hydrogels *in vitro. Proceedings of the Department of Defense Breast Cancer Research Program.* 2002;3:46-54.

Reviews, Chapters, and Editorials

1. Patel J, **Borud LJ**, Upton J. Neuromas. In: *Manual of Pain Management.* Warfield and Fausett, eds. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 2002; pp. 357-363.

Reviews, Chapters, and Editorials (in press)

1. **Borud LJ** Upton J. Applied Embryology of the Extremities. In: *Basic Science for Surgical Specialists* Argenta L, et al, eds. Philadelphia: WB Saunders 2002; in press.

Michael L. Steer, M.D.
Ashok Saluja, Ph.D.

Division of General Surgery

I. Bibliography (07/01/01-06/30/02)

Original Articles

1. **Bhagat L**, **Singh VP**, Song AM, van Acker GJ, Agrawal S, **Steer ML**, **Saluja AK**. Thermal stress-induced HSP70 mediates protection against intrapancreatic trypsinogen activation and acute pancreatitis in rats. *Gastroenterology* 2002;122(1):156-165.

2. Frossard JL, **Bhagat L**, Lee HS, Hietaranta AJ, **Singh VP**, Song AM, **Steer ML**, **Saluja AK**. Both thermal and non-thermal stress protect against caerulein induced pancreatitis and prevent trypsinogen activation in the pancreas. *Gut* 2002;50(1):78-83.

3. **Singh VP**, **Saluja AK**, **Bhagat** L, van Acker GJ, Song AM, Soltoff SP, Cantley LC, **Steer ML**. Phosphatidylinositol 3-kinase-dependent activation of trypsinogen modulate the severity of acute pancreatitis. *J Clin Invest* 2001;108(9):1387-1395.

Original Articles (in press)

1. Song AM, **Bhagat L**, **Singh VP**, Van Acker GG, **Steer ML**, **Saluja AK**. Inhibition of cyclooxygenase-2 ameliorates the severity of pancreatitis and associated lung injury. *Am J Physiol (Gastrointest Liver Physiol)* 2002; in press.

2. Van Acker GJ, **Saluja AK**, **Bhagat L**, **Singh VP**, Song AM, **Steer ML**. Cathepsin B inhibition prevents trypsinogen activation and reduces pancreatitis severity. *Am J Physiol (Gastrointest Liver Physiol)* 2002; in press.

3. Frossard JL, **Saluja AK**, Mach N, Lee HS, **Bhagat L**, Hadenque A, Rubbia-Brandt L, Dranoff G. **Steer ML**. *In vivo* evidence for the role of GM-CSF as a mediator in acute pancreatitis-associated lung injury. *Am J Physiol (Lung Cell Mol Physiol)* 2002; in press.

Reviews, Chapters, and Editorials

1. **Steer ML**. Relationship between pancreatitis and lung diseases. *Respir Physiol* 2001;128(1):13-16.

Aristidis Veves, M.D.

Division of Podiatry

Joslin-Beth Israel Deaconess Foot Center
and Microcirculation Lab

I. Narrative Report

Basic Research

My main research interest is the vascular reactivity of micro- and macrocirculation. During the last few years, I developed the Microcirculation Lab, which tests the microvasculature in a non-invasive way. The Microcirulation Lab is equipped with an ultrasound apparatus that enables evaluation of endothelial function in the brachial artery. Our research is investigator-initiated interventional trials that examine the effects of atorvastatin, valsartan and Vitamin E on endothelial function, renal blood flow, and myocardial function.

My group is also interested in the etiology of diabetic foot problems and the pathophysiology of wound healing in diabetes. For this, we study risk factors of foot ulceration in diabetic patients. In addition, we are involved in studies that evaluate the efficacy of new products, such as artificial skin or new wound dressings, in promoting wound healing in the diabetic foot.

Finally, in collaboration with the department of Radiology, we employ a 3 Tesla (3T) magnetic resonance scanner that can access metabolic activity through measurements of the concentrations and reaction rates of the high-energy phosphorus cellular compounds in humans by employing magnetic resonance imaging and spectroscopy methods. The main advantage of this technique is that it can give a direct non-invasive assessment of muscle metabolism. As a first step, we evaluate the effect of diabetes and its complications on the leg blood flow and metabolic function.

II. List of Current Employees

1.	Lalita Khaodhiar, M.D.	Instructor in Medicine
2.	Thanh T Dinh, DPM	Junior Faculty
3.	Antonella Caselli, M.D.	Postdoctoral Fellow
4.	Panayiotis Economides, M.D.	Postdoctoral Fellow
5.	Jeremy Rich	Resident
6.	Jane Brady	Resident
8.	Caitlin Sparks	Research Coordinator
9.	Elizabeth Tiani	Research Coordinator

III. List of Current Funding

1. *"Effect of Atorvastatin on the endothelial function in Diabetes and pre-Diabetes" (investigator initiated research"*
   Parke-Davis, Pfizer, NY, 981-952-477
   Project period: 10/1/00-6/30/02
   Principal Investigator: Dr. Aristidis Veves

2. *"Effect of Angiotensin Converting Enzyme Inhibitor Quinapril on the Endothelial Function of the Micro- and Macro- Vasculature of Subjects with Impaired Glucose Tolerance and Type 2 Diabetic Patients with or without Microalbuminuria*"
   Parke-Davis, Pfizer, NY, 906-953-444
   Project period: 10/1/00-6/30/02
   Principal Investigator: Dr. Edward Horton
   Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

3. *"The Effect of Vitamin E on the Left Ventricular Function and the Endothelial Function of the Micro- and Macro-Circulation of Type1 and 2 Diabetic Patients"*
   Juvenile Diabetes Foundation International, JDFI 1-1999-817
   Project period: 10/1/99-9/30/01
   Principal Investigator: Dr. Aristidis Veves

4. *"Restoring diabetic tactile sense with mechanical noise"*
   National Institutes of Health/SBIR
   Project period: 7/1/2001-12/31/01
   Principal Investigator: Dr. Jason Harry
   Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

5. *"A prospective, randomized, comparative parallel study of Hyalofill wound dressing in the management of indolent diabetic foot ulcers"*
   ConvaTec, Princeton NJ, CW-0130-00-A509
   Project period: 2/1/01-1/31/2003
   Principal Investigator: Dr. Aristidis Veves

6. "*Vitrix for the treatment of deep diabetic foot ulcers"*
   Organogenesis Inc, Canton, MA, 00-DUS-001-VX
   Project period: 9/01/01-8/31/02
   Principal Investigator: Dr. Aristidis Veves

7. *"Comparison of skin vascular reactivity to different vasodilatory substances in diabetic patients and healthy subjects"*
   Biochemics, Beverly, MA, W-01-0249-FB
   Project period: 10/1/01-30/9/02
   Principal Investigator: Dr. Aristidis Veves

8. *"MRI techniques in measuring vascular function of the diabetic foot*"
   Juvenile Diabetes Research Foundation, JDRF 5-2002-329

Project period: 04/01/01-03/31/02
Principal Investigator: Dr. Aristidis Veves

9. *"Pilot & Feasibility Program in Diabetes, Endocrinology & Metabolism"*
National Institutes of Health, RO1 PA-99-036
Project period: 07/01/02-6/30/04
Principal Investigator: Dr. Robert Greenman
Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

10. *"Effect of Valsartan in Ventricular Function and Aortic Elasticity"*
Novartis Pharma Inc
Project period: 09/01/02-08/31/04
Principal Investigator: Dr. Aristidis Veves

11. *"Effect of Valsartan In Endothelial Function"*
Novartis Pharma Inc
Project period: 09/01/02-08/31/04
Principal Investigator: Dr. Aristidis Veves

12. *"PARP activation as a marker of diabetic vascular dysfunction*"
National Institutes of Health, 1R01HL/DK71215-01
Project period: 10/1/02-30/9/05
Principal Investigator: Dr. Csaba Szabo
Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

13. *"Imaging early markers of diabetic microvascular complications in peripheral tissue"*
National Institutes of Health, RFA-DK-02-001
Project period: 10/01/02-09/30/04
Principal Investigator: Dr. George L. King
Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

IV. Applications Submited and Pending Review/Funding

1. *"Natural History of Small Fiber Diabetic Neuropathy"*
National Institutes of Health
Project period: 10/1/02-30/9/07
Principle Investigator: Dr. Aristidis Veves

2. *"Imaging Microcirculation in Diabetic Foot Ulceratio*n"
National Institutes of Health
Project period: 10/1/02-30/9/06
Principle Investigator: Dr. Aristidis Veves

3. *"PARP Activation as a Surrogate Marker in Diabetes"*
National Institutes of Health

Period: 11/1/02-10/30/05
Principal Investigator: Csaba Szabo

4. *"Micro- and Macrovascular Abnormalities and Diabetic Foot Ulceration"*
American Diabetes Association
Period: 1/1/02-31/12/04
Principle Investigator: Aristidis Veves

5. *"Cardiovascular Effects of Air Pollution in Diabetics"*
National Institutes of Health
Period: 10/1/02-30/9/05
Principle Investigator: Dr. Joel Schwarz

6. *"Cardiac Effects of Ambient Air Pollution among Diabetics"*
Environmental Protection Agency
Project period: 10/1/02-30/9/06
Principal Investigator: Dr. Joel Schwarz

V. Accomplishments over the Past Year

Research

During the last academic year we continued five clinical trials, which totaled $1,133,000.00 in revenue for our program. Three of these clinical trials are investigator initiated (Pfizer Atorvastatin and Quinapril and Biochemics). Additional NIH funding from the GCRC has been secured for two of the trials. Furthermore, two investigator-initiated studies were funded by Novartis, for a revenue total of $433,000 to our program. I was PI on the JDRFI grant and co-investigator for two NIH funded grants. I was also the co-investigator for two more NIH grants that are pending funding.

Educational Activities

Invited Presentations (Local, National, and International)

1. **Role of Microcirculation in Wound Healing.** *Wound Healing: Science and Industry*. St. Thomas, VI.

2. **Vascular Reactivity Changes in Diabetes and Pre-Diabetes.** Joslin Diabetes Center, Boston, MA.

3. **Diabetic Neuropathy and Pain.** Pain Center, Dept. of Anesthesia, Massachusetts General Hospital.

4. **Endothelial Function in Diabetes and Pre-Diabetes.** Juvenile Diabetes Research Foundation Center on Diabetic Complications & The Center for

Vascular and Lung Pathobiology at Columbia University, Columbia Presbyterian Hospital, New York, NY.

5. **Pathogenesis of Diabetic Foot Ulceration.** Boston University NeuroMuscular Research Center, Boston, MA.

Presentations at Meetings

1. Economides PA, Caselli A, Zuo CS, Epstein FH, Sparks C, Horton ES, **Veves A.** Correlation of Renal Cortical Oxygenation and Macro- and Microvascular Reactivity in Type 2 Diabetes. Selected for Poster Presentation at the 62nd American Diabetes Association Scientific Sessions, San Francisco, 2002.

2. Economides PA, Zuo CS, Epstein FH, Sparks C, Hamdy O, **Veves A,** Horton ES. Renal Cortical Oxygenation Correlates with Fasting Plasma Glucose, Insulin, and Total Cholesterol in Type 2 Diabetes Mellitus. Accepted for publication in the 62nd American Diabetes Association Scientific Sessions Abstract Book, June 2002.

3. Caselli A, Economides PA, Spark C, Horton ES, Johnstone MT, **Veves A:** Vascular Reactivity in the Peripheral Circulation is Correlated with Measurements of Left Ventricular Function in Type 1 and 2 Diabetic Patients. Diabetes 2002. Selected for Poster Presentation at the 62nd American Diabetes Association Scientific Sessions, San Francisco, 2002.

4. Sheehan P, Caselli A, Pham HT, **Veves A**: Change in Foot Ulcer Area Over a 4-Week Period Can Predict Complete Healing in a Prospective Clinical Trial. Selected for Oral Presentation at the 62nd American Diabetes Association Scientific Sessions, San Francisco, 2002.

Professional and educational leadership

1. **Meeting Committee member of *Wound Healing: Science and Industry*. St. Thomas, VI.** This is an interdisciplinary meeting that allows opinion leaders to discuss and interact with various professionals in academics and industry, 2002.

2. American Diabetes Association Expert Committee on Foot Wound Classification, member, 2001.

Awards and Honors

1. Mary Jane Kugel Award by the Juvenile Diabetes Research Foundation for participation in the Medical Science Review Committee, 2002.

Individual Accomplishments

1. As a member of the Medical Science Review Committee of the Juvenile Diabetes Research Foundation International I have participated in the spring and fall grant reviews. I also participated in the review of five center grant applications.

2. I was invited to participate in the scientific advisory boards of Biogen, Inotek Inc, Novartis Pharma, Biochemics, ConvaTec and Johnson & Johnson Medical.

3. I was invited as the keynote speaker at the Johnson & Johnson meeting related to the USA launch of Promogran.

4. I continue to serve as an Associate Editor for the journal: *Wounds: A Compendium of Clinical Research and Practice (2000-).*

5. I was asked to act as a peer reviewer for the journals: the *Lancet, Diabetes, Diabetologia, Diabetes Care Diabetic Medicine, Journal of Diabetes and its Complications and Circulation.*

6. Our book, **Diabetes and Cardiovascular Disease**, sold more than 13,000 copies during the first year of its release and a second edition is planned.

VI. Plans for the Coming Academic Year

1. My plans for the coming academic year are to successfully finish the studies that are currently being contacted. In addition, I plan to aggressively seek funding from sources like the NIH and non-profit organizations such as the Juvenile Diabetes Research Foundation International and American Diabetes Association. As can be seen in the funding section, grants have already been submitted and I hope that this effort will be successful.

2. In addition to the above, in collaboration with Cardiology and Radiology I plan to continue my efforts to examine the ability of new MRI techniques to be used for clinical and research purposes in the field of Diabetes.

3. Finally, in collaboration with local biotech companies, I am trying to develop new local treatments that will improve skin microcirculation of the diabetic foot.

VII. Bibliography (07/01/01-06/30/02)

Original Articles

1. Arora S, Pomposelli F, LoGerfo FW, **Veves A.** Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely

after successful lower extremity revascularization. *J Vasc Surg* 2002;35:501-505.

2. Abou-Elenin A, Antonios Xydakis A, Hamdy O, Economides PA, Horton ES, **Veves A**. The effect of aspirin and various iontophoresis solution vehicles in skin microvascular reactivity. *Microvasc Res* 2002;63:91-5.

3. Epstein FH, **Veves A**, Prasad P. Effect of diabetes mellitus on renal medullary oxygenation during water diuresis. *Diabetes Care* 2002;25:575-578.

4. Caselli A, Pham Ht, Giurini JM, Armstrong DG, **Veves A**. The forefoot / rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration. *Diabetes Care* 2002;25:1066-1071.

5. Pham HT, Exelbert L, Segal-Owens AC, **Veves A.** A prospective randomized controlled double-blind study of a moisturizer containing 10% urea and 4% lactic acid versus the vehicle for xerosis of the feet in subjects with diabetes. *Ostomy Wound Manage* 2002;48:30-36.

6. Caselli A, Singh Bedi D, O'Connor C, Shah C, **Veves A**. Assessment of laser perfusion imager's in vivo reliability: Can it be used for a prospective analysis? *J Laser Applic* 2002;14:198-202.

Original Articles (in press)

1. Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor K, LoGerfo FW, Horton ES, **Veves A**. The effects of troglitazone, an insulin sensitizing agent, on the endothelial function in early and late type 2 diabetes. A placebo-controlled, randomized, clinical trial. *Metabolism,* in press.

2. Szabó C, Zanchi A, Komjáti K, Pacher P, Krolewski AS, Quist WC, LoGerfo FW, Horton ES, **Veves A.** Poly (ADP-Ribose) polymerase is activated in subjects at risk of developing type 2 diabetes and is associated with impaired vascular reactivity. *Circulation*, in press.

3. Caselli A, Rich J, Hanane T, Uccioli L, **Veves A**. Role of c-nociceptive fibers in the impairment of nerve axon reflex-related vasodilation in diabetes. *Neurology*, in press.

4. **Veves A,** Sheehan P, Pham TH. A comparison of a new topical treatment, Promogran® versus standard treatment in the management of diabetic foot ulcers. *Archives of Surgery* 2002; in press.

Reviews, Chapters, and Editorials

1. Rich J, Pham HT, **Veves A**. Living Skin Equivalents - Changing Trend for Diabetic Foot Ulceration. *Lower Limb Wounds* 2002;1:27-31.

2. Dinh D, Pham HT, **Veves A**. Emerging Treatments in Diabetic Wound Care. *Wounds* 2002;14:2-10.

3. Lyons TE, Rich J, **Veves A**. Foot pressure abnormalities in the diabetic foot. In: The Diabetic Foot: Medical and Surgical Management. **Veves A,** Giurini JM, LoGerfo FW, eds. Humana Press, Totowa, 2002;127-146.

4. Pham HT, **Veves A**. Living skin equivalents for the diabetic foot ulcer. In: The Diabetic Foot: Medical and Surgical Management. **Veves A,** Giurini JM, LoGerfo FW, eds. Humana Press, Totowa, NJ, 2002;397-410.

5. **Veves A**, Caselli A, Economides PA. New therapies for the treatment of diabetic neuropathy. In: Diabetes Annual 2002. Barnett AH, ed. Martin Dunitz, London, UK. 2002;185-207.

Reviews, Chapters, and Editorials (in press)

1. Cotter MA, **Veves A**, Tesfaye S, Cameron NE. Nerve Blood Flow. In: Diabetic Neuropathy; Gries A, Ziegler D, Low P, Cameron NE, eds., in press.

Books, Monographs, and Text Books

1. **Veves A,** Giurini JM, LoGerfo FW: The Diabetic Foot: Medical and Surgical Management. Humana Press, Totowa, NJ, 2002.

2. Johnstone MT, **Veves A**: Diabetes and Cardiovascular Disease (second edition). Humana Press, Totowa, NJ, in preparation.

Julian K. Wu, M.D.
George Perides, Ph.D.

Division of Neurosurgery
Neurosurgery Brain Tumor Laboratory

I. Narrative Report

The Neurosurgery Brain Tumor Laboratory is designed to provide an integrated environment for clinicians, medical students and basic research scientists to study the molecular and cellular mechanisms of neurologic diseases including brain tumor formation, invasion and metastasis. Our laboratory concentrates on 4 main areas of research that range from basic research to clinical trials.

1. Mechanisms of systemic tumor metastasis to the brain.
2. Markers in the cerebrospinal fluid for diagnosis and prognostication.
3. Signal transduction mechanisms in neurologic diseases
4. Tissue Bank

II. List of Current Employees

1. Sangeeta Joshi, M.D. Postdoctoral Fellow

III. List of Current Funding

1. Julian Wu Research Support
   Beth Israel Deaconess Medical Center
   Project period: 11/01/99-9/30/2003

2. "Lipid-Associated Sialoprotein as a Marker of CNS Lymphoma of the Brain"
   National Institutes of Health: Center for AIDS Research (CFAR)
   Project period: 12/1/2000-11/30/2002

3. "Pathogenesis of *Borrelia burgdorferi*-induced Arthritis
   National Institutes of Health: NIAID
   Project period: 4/1/02-3/31/03

IV. Applications Submitted and Pending Review/Funding

1. "Tumor metastasis to the brain"
   National Institutes of Health

2. "Sensitization of NMDA Receptors in Huntington's Disease"
   National Institutes of Health

3. "Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illness"
   Department of Defense

V. Divisional Accomplishments

Educational Activities

1. The Neurosurgery laboratory has developed a review course in Neuroscience for the residents in Neurosurgery. The course takes place once a month. The first year covers basic principles in neuroscience. For the second year current topics are selected based on recent publications and the subject is discussed in conjunction with basic knowledge in Neuroscience.

2. During this summer we had the opportunity to introduce students from Boston University, Wellesley College, Massachusetts Institute of Technology, University of Massachusetts and Research Science Institute to various aspects of our research and they have learned a number of laboratory techniques including molecular biology techniques, protein chemistry and cell culture and animal surgeries.

   Khuram Bajwa (Boston University). Studied the role of plasminogen in tumor metastasis to the brain using an animal model.

   Natalie Cusano (Massachusetts Institute of Technology). Studied the levels of matrix metalloproteinases, vascular endothelial growth factor and lipid-associated sialoprotein in longitudinally collected cerebrospinal fluid samples from tumor patients.

   Parmita Dalal (Research Science Institute). Studied the role of the fibrinolytic system in migration of cancer cells and *Borrelia burgdorferi* spirochetes through a blood-brain barrier model. Her presentation was selected as one in the top ten of the year.

   Grace Park (Wellesley College). Studied the role of plasminogen in tumor metastasis to the brain using an animal model.

   Angela Tam (University of Massachusetts). Transfected brain tumor cells with epidermal growth factor receptor to study its role in matrix metalloproteinase expression.

Administrtative Duties

1. Dr. Perides is a member of the Institutional Animal Care and Use Committee with monthly meetings to review animal research protocols.

2. Dr. Perides is a member of the Dana-Farber Harvard Cancer Center and hosts the monthly meeting of the Neuro-Oncology program as it rotates between MGH, BWH and BIDMC.

Presentations (Local, National and International)

1. Aboody KS, Brown A, Yang W, **Wu JK, Zhuge Y**, Black PM, **Perides G**. "Neural Stem Cells as Potential Vehicles to Target Gene Therapy to Brain Metastases". *Society for Neuro-Oncology* 2002;51A.

2. Gottschall PE, Westling J, Juan W, **Perides G**, Sandy JD. "Glial Hyaluronic Acid Binding Protein (GHAP): Identification in Human Brain as a Product of ADAMTS-4-dpendent Cleavage of Versican V2". *Society for Neuroscience* 2002;192:4A.

3. Kim L, Glantz MJ, Dafni UG, **Wu JK**, Edwards K, Katopodis N, **Perides G.** "The Level of Lipid-Associated Sialoprotein in the Cerebrospinal Fluid Correlates with the Presence and Response Status of Primary and Metastatic Brain Tumors". *American Society of Clinical Oncology* 2001;20:261A.

4. **Lin T**, **Zhuge Y**, **Wu JK**, **Perides G**. "The Role of Plasminogen in Melanoma Metastasis to the Brain". *Society for Neuro-Oncology* 2001;3:48A.

5. Wang D, **Perides G**, Liu A, Feldman R, Liu YF. "Emotional Stress Induces Activation of MKK4 in Glutamatergic Neuron". *Society for Neuroscience* 2002;397:3A.

6. **Zhuge Y**, **Patel P**, **Wu JK**, Stins M, **Perides G**. "The Role of the Fibrinolytic System in Systemic Tumors Crossing the Blood Brain Barrier". *Society for Neuro-Oncology* 2002;74A.

VI. Plans for the Coming Academic Year

During the next academic year we plan to continue our research activities, teaching and training responsibilities and administrative duties as outlined in the first section. We will maintain the same personnel, publish our results and we will pursue additional funding to support our research.

VII. Bibliography (07/01/01-6/30/02)

Original Articles

1. Song C, **Perides G**, Liu YF. Expression of full-length polyglutamine-expanded huntingtin disrupt growth factor receptor signaling in rat pheochromocytoma (PC12) cells. *J Biol Chem* 2002;277:6703-6707.

Original Articles (in press)

1. **Cucchiarini M,** Ren X, **Perides G,** Terwilliger E. Selective gene expression in brain microglia mediated via recombinant adeno-associated virus vectors. *Gene Therapy,* 2002; in press.

2. Song C, Wang C, **Perides G**, Liu YF. Expression of mutant beta-amyloid precursor protein or presenilin 1 causes formation of actin stress fibers through p38 mitogen-activated protein kinase. *J Neurochem* 2002; in press.

Anna Zuk, Ph.D.

Division of General Surgery

I. Narrative Report

Basic Research

The research in my laboratory is focused on the cell biology of the extracellular matrix, more specifically cell-cell and cell-extracellular matrix (ECM) interactions critical for morphogenesis. The emphasis is on those interactions mediated by the integrin family of adhesion receptors that signal epithelial differentiation and polarization, including dedifferentiation/depolarization. Identifying the mechanism(s) controlling epithelial differentiation will enhance our understanding of normal and abnormal development (e.g. birth defects) as well as pathologic processes (e.g. wound healing, carcinogenesis).

Currently, I am investigating integrin-ECM interactions in epithelial injury and repair, including renal ischemia. Acute renal failure induced by ischemic injury to the kidney epithelium is a major source of morbidity and mortality in the hospitalized population, the prognosis of which has not improved in over 40 years. Specifically, (1) the mechanism by which integrin families mediate tubular occlusion and epithelial regeneration is being investigated in a rodent model of acute renal failure. In particular, candidate integrins are being evaluated as mediators of cell-cell and cell-matrix adhesions in the obstructive cast, a major component of the pathophysiology of acute renal failure. In addition, interactions of specific integrins in the surviving epithelium with matrix components in the underlying basement membrane are being assessed to determine whether they specify dedifferentiation or redifferentiation. (2) The role of signaling through the integrin-linked kinase on kidney epithelial cell polarization and dedifferentiation/redifferentiation following injury in vivo and in vitro is being investigated. Phosphorylation, expression and distribution of the integrin-linked kinase are being measured as cells polarize apical and basolateral membrane markers and dedifferentiate/ redifferentiate following injury. The functional importance of this pathway to polarization and regeneration is also being defined through overexpression of sense, antisense and dominant negative constructs, as well as silencing of mRNA. (3) Lastly, the role of matrix metalloproteinases –2 and –9 in vivo in tubular occlusion and epithelial regeneration is being studied by measuring the activity and determining the expression of these enzymes in the ischemic kidney. Functional importance will then be tested in kidneys of transgenic animals deficient in MMP-2 or MMP-9 that have been made ischemic. The goal of these studies is to uncover novel therapeutic approaches to limit injury and/or speed recovery.

II. List of Current Funding

1. "Integrins in Kidney Morphogenesis"
   NIH RO1-DK46768
   Project period: until 09/01/01

Principal Investigator: Karl S. Matlin, Ph.D.
Co-Investigator: Anna Zuk, Ph.D.

2. "Role of the Extracellular Matrix in Renal Epithelial Injury and Repair"
Scholars in Medicine Grant, Harvard Medical School
Project period: 09/01/01 - 08/31/02
Principal Investigator: Anna Zuk, Ph.D.

3. "Role of the Extracellular Matrix in Renal Epithelial Cell Injury and Repair"
The William F. Milton Fund, Harvard University
Project period: 1/1/02-12/31/02
Principal Investigator: Anna Zuk, Ph.D.

III. Applications Submitted and Pending Review/Funding

1. "Role of the Extracellular Matrix in Renal Epithelial Injury and Repair
NIH/NIDDK R01 application DK 064153-01 (submitted 07/2002)
P I: Dr. Anna Zuk

IV. Divisional Accomplishments Over the Past Year

Research Accomplishments

1. I have continued my research on the cellular mechanisms mediating acute renal failure. Recent studies that are *in press* demonstrate the induction of a novel variant of the laminin family and its cognate integrin receptor, the $\alpha 3\beta 1$, in the regeneration phase following ischemic injury to the kidney. Studies are now underway to investigate signaling pathways emanating from altered cell-matrix interactions, particularly those involving the integrin-linked kinase. Because no studies to date have examined the role of matrix metalloproteinases in the injury and repair phases accompanying acute renal injury, the functional role of candidate proteolytic enzymes are being examined in transgenic animals in which the kidney has been ischemic. Preliminary data has also been collected on the appearance of plasma fibronectin and matrix metalloproteinase-2 in the urine of patients with acute renal failure; these studies will continue in order to determine whether these molecules can serve as prognostic and diagnostic indicators of renal injury in the patient population.

Educational Activities

1. I have continued by my involvement in The Human Body, the first block of classes for medical students in the New Pathway Curriculum at Harvard Medical School. I have served as Tutor (8 students) and Instructor in both Histology and Gross Anatomy (40 students each).

Individual Accomplishments

1. I received the William Silen, M.D. Fellowship from Harvard Medical School.

2. I reviewed abstracts pertaining to Cell-Matrix Interactions/Integrins/Collagen for the annual meeting of the American Society for Nephrology to be held in Philadelphia, PA, October, 2002.

V. Plans for the Coming Academic Year

Staff Changes

1. Pending funding, I plan to recruit a technician, post-doc and/or student (medical, undergraduate) to carry on the projects begun in the lab.

New Grants

1. In the coming academic year, I will continue to apply for research funding from local and national agencies.

Participation in HMS Courses

1. I will continue to participate in The Human Body at Harvard Medical School where I will serve as Tutor and Laboratory Instructor in both Histology and Gross Anatomy.

VI. Bibliography (07/01/01-06/30/02)

Original Articles

1. **Zuk A,** Bonventre JV, Matlin KS. Expression of fibronectin splice variants in the post-ischemic rat kidney. *Am J Physiol(Renal Physiol*) 2001;280:F1037-1053.

Abstracts

1. **Zuk A,** Matlin KS. Laminin-5 and its integrin receptors in the injured and regenerating kidney. *J Am Soc Nephrol* 2001;12:797A.

2. Matlin KS, **Zuk A**, Haus B, Kayas A. Characterization of the MDCK cell endogenous extracellular matrix. *J Am Soc Nephrol* 2001;12:710A.