DEPARTMENT OF SURGERY

Division of Surgery Research

ANNUAL REPORT
7/1/00 – 6/30/01

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Office of Surgical Research

Annual Report (Summary)

July 1, 2000-June 30, 2001

The Office of Surgical Research was created in 1998 to manage all aspects of sponsored research, both federal and non-federal, within the Department of Surgery. Research in the Department of Surgery was conducted, in this fiscal year, by 38 Faculty (Instructor-Professor), 33 Postdoctoral Research Fellows, 26 Research Associates and Assistants, 1 Visiting Professor, and 15 students from the Divisions of Cardiothoracic, General, Neuro-, Plastic and Reconstructive, Transplantation, Urology, and Vascular Surgery. Research in the Department of Surgery occupied approximately 30,000 sq. ft. of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, shared equipment rooms), and research offices. Surgery Research space included 7,300 sq. ft. at HIM, 11,300 sq. ft. on the 8th floor of Dana/Research West, 2300 sq. ft. in the basement and 900 sq. ft. on the 3rd floor of the Slosberg-Landy Building, 2, 000 sq. ft. at 21-27 Burlington Avenue, and 6, 200 sq. ft. at Research North.

The Office of Surgical Research supports sponsored research in four areas. 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. 4) Faculty career development. The Office of Surgical Research was headed, within the time frame of this annual report, by Karl S. Matlin, Ph.D., Associate Professor of Surgery and Vice Chairman for Research in the Department of Surgery. Since Dr. Matlin left the BIDMC in late August, Susan J. Hagen, Ph.D., fills this position on an interim basis until a new Director is appointed. Pat Odom, Administrative Coordinator, assists with issues concerning grant submission, facilities, and strategic planning. The Office for Surgical Research works closely with Gary Smith, Research Manager, Karen Osborne, Research Administrator and Shannon Joyce, Research Administrator. Gary Smith, Karen Osborne, and Shannon Joyce have a 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 Office 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 the Director for Research before obtaining institutional approval. Upon submission, investigators must file a final copy of the application with the Office of Surgical Research. These applications are held in our database until a funding decision has been made. Upon funding, the application is transferred to Gary Smith and Karen Osborne, 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. More than 60% of funding was from federal sources, primarily from the National Institutes

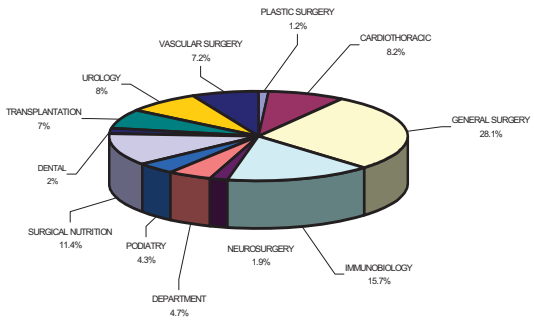
of Health (NIH). In this fiscal year, funding from a new category, non-federal sources, was added to our overall research activity.

Table 1. *Summary of all research awards and expenditures in the Department of Surgery from 7/01/00-6/30/01*

Sponsor	Direct Awarded	Indirect Awarded	Total Awarded	Direct Expended	Indirect Expended	Total Expended
NIH	4,226,869	2,367,408	6,594,277	3,682,224	2,184,576	5,866,799
Other Federal	196,010	11,490	307,500	4,006	641	4,647
SOM*	140,021	0	140,021	188,548	0	188,548
Other Sponsors	3,669,886	439,668	4,109,554	3,388,784	141,422	3,560,207
TOTAL	8,232,786	2,918,566	11,151,352	7,263,562	2,356,639	9,620,201

*State of Massachusetts

FIGURE 1.
00-01 DIRECT EXPENDITURES BY DIVISION



Funding for research in the Department of Surgery increased by 18% from $9,135,090 in fiscal year 99/01 to $11,151,352 in this fiscal year (Table 1). Funding was from the NIH (50.7%), the State of Massachusetts (2.6%), and from Other Sponsors (46.7%). Research activity was distributed widely among Divisions, where General Surgery, the largest Division, accounted for 28.1% and Transplantation (Immunobiology) accounted for 15.7% of direct expenditures (Figure 1). Significant activity occurred in Cardiothoracic Surgery, Vascular Surgery, Surgical Nutrition, Podiatry 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, and Urology 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 laboratories are located at the Burlington Avenue building.

During the last year, renovation of both the S-L basement laboratories and Dana 807/809 were completed. Dr. Ganguly's laboratory of Cancer Biology (General Surgery) was moved from Burlington Ave. into approximately one-half (1,000 sq. ft.) of the S-L space

and the other half (1,000 sq. ft.) remains unoccupied. Dr. Karl Matlin moved his laboratory into the newly renovated space on Dana 8 (Dana 807/809). Drs. Richard Hodin and Jeffrey Matthews relocated and their space was cleaned and assigned to new occupants.

Research Development and Strategic Planning

Initiatives in the past fiscal year were begun to improve communication between the diverse research groups in the Department. First, to obtain a program project grant. The grant application was submitted but was not funded. Second, to list all research personnel on the Department's web page. This initiative is still in development. Third, to hire new faculty in epithelial biology. This goal was aborted due to lack of funding. Lastly, to increase corporate funding. This was done by working with Dr. Alfred Handler to interface between biotechnology companies and researchers in Surgery. No corporate contracts were forthcoming so Dr. Handler's association with Surgery was terminated.

The Office of Surgical Research offered a seminar series with presentations from both Department investigators and from other departments and local institutions. A summary of seminars that were presented from 07/01/00-06/30/01 are listed in Table 2.

Table 2. *Seminars sponsored by the Office of Surgical Research from 07/01/00-06/30/01*

8.1.00	The Ideological Basis of the Research Publication: Deconstructing an Artifact: P.K. Rangachari, McMaster University, Hamilton, Ontario
10.13.00	Defining the Role of NF*k*B in Acute Pancreatitis: Craig Logsdon, University of Michigan
11.14.00	Potential Role of Fatty Acids in the Pathogenesis and Treatment of Cystic Fibrosis: Juan Alvarez, Department of OB/GYN, BIDMC
12.20.00	Pathophysiology of Ischemic Acute Renal Failure: Joseph Bonventre, Massachusetts General Hospital
1.23.01	Pathogenesis of Acute Pancreatitis: Role of Heat Shock Proteins, Cytokines and Other Culprits: Ashok Saluja, Department of Surgery, BIDMC
2.12.01	EFG Receptor Family Members in Mammary Epithelial Morphogenesis and Transformation: Senthil K. Muthuswamy, Harvard Medical School
2.13.01	Novel Mediators of Tumor Metastasis in Prostate Cancer: Bruce Zeter, Children's Hospital
2.23.01	Exit Strategies from the ER: Fred Gorelick, Yale University
3.20.01	Hyperbaric Oxygen Attenuates Cell Adhesion Molecule Expression in Ischemia-Reperfusion Injury: John Buras, Department of Emergency Medicine, BIDMC
3.19.01	Actin Regulatory Proteins as Signal Transducers: Examples from Epithelial Cells: Seema Khurana, Johns Hopkins University
4.24.01	Cell-Cell Interactions in vessel Development and Stability: Patricia A. D'Amore, Children's Hospital
5.3.01	Esophageal Epithelial Cells: Differentiation and Oncogenesis: Anil K. Rustgi, University of Pennsylvania

6.5.01	Protective Genes: A Regulatory Response to Injury: Christiane Ferran, Department of Surgery, BIDMC
6.12.01	Mechano-activation Programs in Vascular Endothelium: Guillermo Garcia-Cardena, Brigham and Women's Hospital
6.19.01	Mucosal Responses to Hypoxia: Sean Colgan, Brigham and Women's Hospital
6.21.01	Oxidant Modulation of Potassium Channels in Colonic Smooth Muscle: Madhu Prasad, Oregon Health Sciences University

Faculty Career Development

No information is available to include in this category.

Faculty Accomplishments

Many new grant applications were funded in this fiscal year. New funding was obtained by Archer, Blackburn, Ganguly, Gaston, Parengi, Saluja, Sellke and Veves. Funding sources were from the NIH, State of Massachusetts and from corporate sponsors. At the national level, accomplishments included working with the Program Committee at the AAS (Archer), appointment to NIH study section (Blackburn and Hagen), and invited lectureships at programs and universities across the country (Blackburn, Ferran, Gaston, Hagen, Kiessling, LoGerfo, Steer, Saluja). At the international level, many surgery researchers were invited speakers at meetings (Archer, Blackburn, Ferran, Gaston, Polombo, Steer, Saluja, Zuk). Four investigators in Surgery submitted patent application (Ganguly, Hagen, LoGerfo, Polombo) and Dr. Hagen went on a "mini-sabbatical". This year, Dr Fritz Bach received the "Pioneers in Transplantation" award from the American Society for Transplantation.

Researchers in Surgery continue a strong commitment to teaching. This includes acting as mentors in the NIH in-service teacher program, SHURP, MIT Bioengineering Undergraduate Research Program, Project Success and the Biomedical Science Careers Program. At HMS, many investigators teach in various courses, including "The Body" (Hagen and Zuk) and "Integrated Human Physiology"(Gaston and 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	Instructor in Surgery
Kahn, Tanveer	Research Fellow
Ruel, Marc	Research Fellow
Li, Jianyi	Research Assistant
Plum, Joe M., Jr.	Student
Levitsky, Sidney	**Professor of Surgery**
McCully, James	**Associate Professor of Surgery**
Wakiyama, Hidetaka	Surgical Fellow
Chai, Jianyuan	Research Associate
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**
Ma, Qing	Research Assistant
Mun, Edward	**Assistant Professor of Surgery**
Navina, Sarah	Research Fellow
Um, Jun Won	Research Fellow
Parangi, Sareh	**Instructor in Surgery**
Zi, Tong	Research Technician
Pancreas Group	
Steer, Michael	**Professor of Surgery**
Saluja, Ashok	**Associate Professor of Surgery**
Bhagat, Lakshmi	Instructor in Surgery
Charania, Munira	Research Fellow
Singh, Vijay	Research Fellow
Zuk, Anna	**Assistant Professor of Surgery**
Laboratory of Cancer Biology	
Ganguly, Aniruddha	**Assistant Professor of Surgery**
Castro, Christine	Research Assistant
Robbins, Jonathan	Research Assistant
Chakrabarti, Anindita	Student
Guarino, Elisia	Student
Hwang, Sharon	Student
Newton, Marissa	Student

Pories, Susan	**Assistant Professor of Surgery**
Lotz, Margaret	Instructor in Surgery
Hagen, Susan J.	**Assistant Professor of Surgery**
Nakamura, Eiji	Postdoctoral Fellow
Tashima, Kimihito	Postdoctoral Fellow
Wu, Tong	Research Assistant
Sheppard, Barbara	Research Associate
Cho, Howard	Student (MIT)
Berger, Urs	Instructor in Surgery
Brown, Daniel	Senior Research Associate
White, Suzanne	Histotechnologist

Surgical Nutrition

Blackburn, George L.	**Professor of Surgery**
Zhou, Jin-Rong	**Assistant Professor of Surgery**
Khaodhiar, Lalita	Junior Faculty
Pan, Weijun	Research Fellow
Greene, Pennie	Research Fellow
Maykel, Justin	Research Fellow
Yu, Lunyin	Research Fellow
Copeland, Trisha	Research Associate
Hirsch, Wanda	Research Associate
Karun, Pam	Research Associate
McNamara, Anne	Research Associate
Sherwood, Michelle	Research Associate
Zhong, Ying	Research Technician
Lin, Min	Student (unpaid intern)

Surgical Metabolism/Nutrition

Palombo, John D.	**Assistant Professor**
Boyce, Patricia	Student (volunteer)
Stratton, Tom	Student (volunteer)

Division of Neurosurgery

Wu, Julian K.	**Associate Professor of Surgery**
	Chief, Division of Neurosurgery
Perides, George	Assistant Professor of Surgery
Zhuge, Yuzheng	Post Doctoral Fellow
Wang, Yu	Technician (part-time)
Park, Aric	MD Student (Tufts Medical School)

Malek, Adel	**Instructor in Surgery**

Division of Ophthalmology

Division of Otolaryngology

Division of Plastic and Reconstructive Surgery

Division of Podiatry

Veves, Aristidis	**Assistant Professor of Surgery**
Dinh, Thanh T.	Junior Faculty
Pham, Hau T.	Junior Faculty
Caselli, Antonella	Research Fellow
Economides, Panayiotis	Research Fellow
Sparks, Caitlin	Research Technician
Tiani, Elizabeth	Research Technician

Division of Transplantation

Immunobiology Research Center

Bach. Fritz H.	**Louis Thomas Professor and Director**
Soares, Miguel P.	Junior Faculty
Tobiach, Edda M.	Junior Faculty
Berberat, Pascal	Research Fellow
Gunther, Lukas	Research Fellow
Wang, Ning	Research Fellow
Yamashita, Kenichiro	Research Fellow
Csizmadia, Vilmosne Eva	Research Technician
Ferran, Christiane	**Associate Professor of Surgery**
Grey, Shane T.	Assistant Professor of Surgery
Arvelo, Maria B.	Post-doctoral Fellow
Daniel, Soizic	Post-doctoral Fellow
Mahiou, Jerome	Post-doctoral Fellow
Longo, Christopher	Surgical Resident
Patel, Virendra I.	Surgical Resident
Kunter, Uta	Visiting Research Fellow
Monaco, Anthony	**Peter Medawar Professor of Surgery**
Maki, Takashi	**Associate Professor of Surgery**
Kanamoto, Akira	Research Fellow
Ogawa, Norihiko	Research Fellow
Gottschalk, Rita	Research Technician
Zenitani, Taira	Summer Student

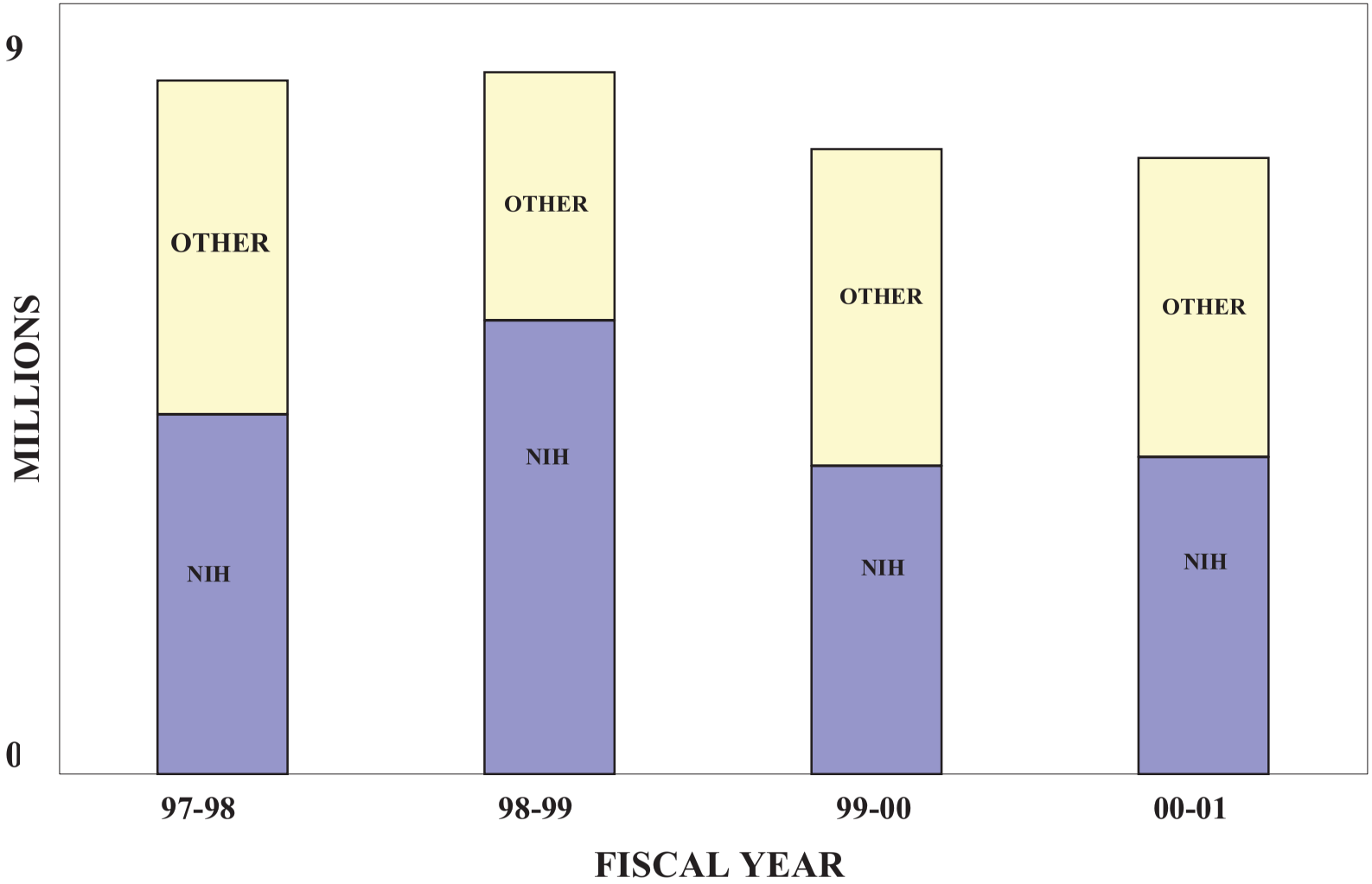
Division of Urology (Research)

Urologic Research Laboratories

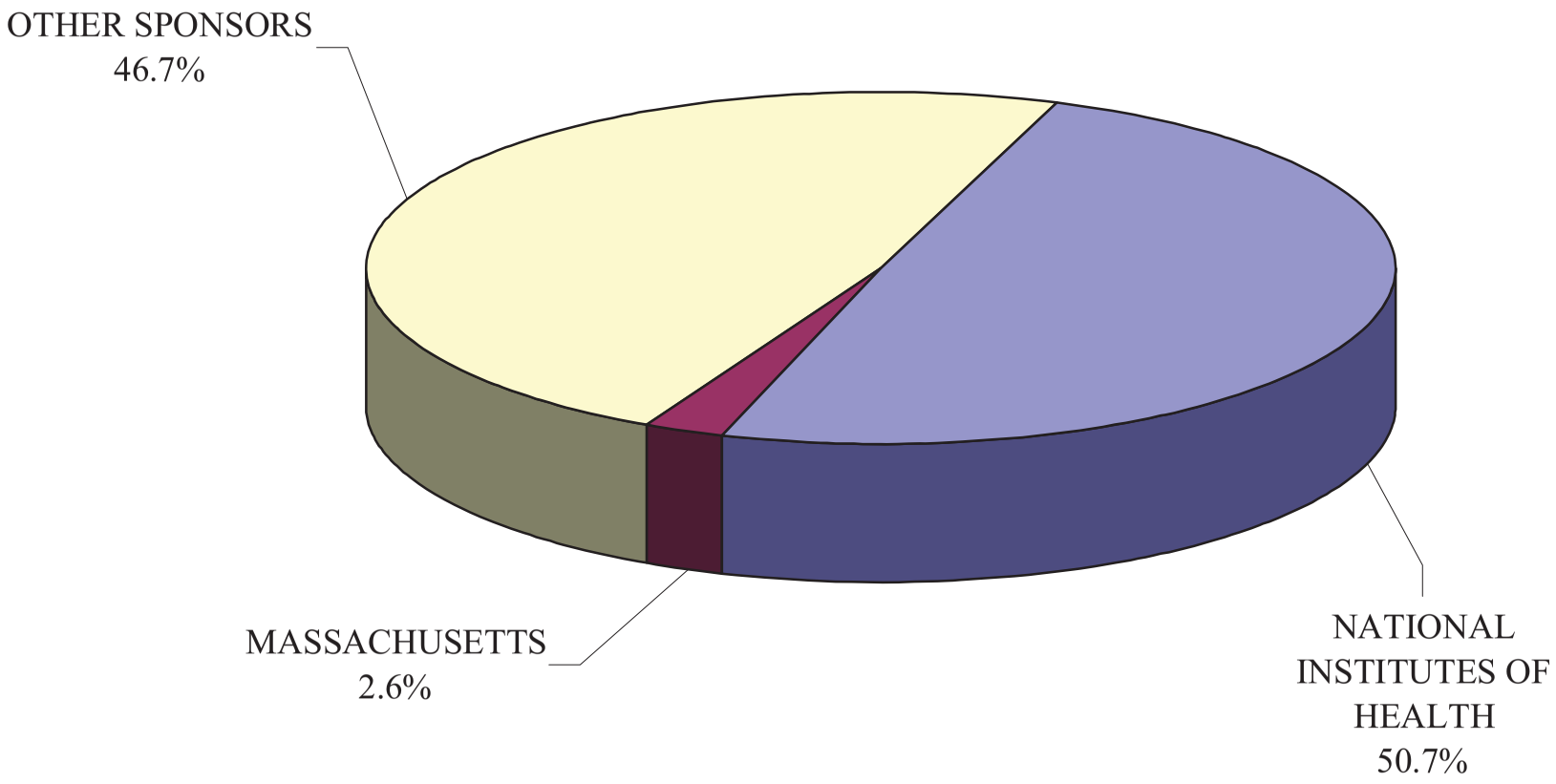
DeWolf, William	**Professor of Surgery**
	Chief, Division of Urology
Schopperle, William	Postdoctoral Fellow
Olumi, Aria	**Instructor in Surgery and Medical Science Director**
San Francisco, Ignacio	Reseach Fellow
Xiao, Yingwen	Research Technician
Gaston, Sandra	**Instructor in Surgery and Basic Science Director**
Kim, Seanna	Research Technician
Mathew, Lynn	Research Technician
Vu, Dang	Research Assistant
Das, Chandan	Student
Goldner, Dana	Student

Kim, Tae Won	Student
Powley, Nicholas	Student
Shih, Jennifer	Student
Soares, Marc	Student
Kiessling, Ann A.	**Associate Professor of Surgery**
Yin, Hui-Zhong	Senior Research Fellow
Desmarais, Bryan	Research Technician
Fleischman, Julian	Visiting Associate Professor
Division of Vascular Surgery	
LoGerfo, Frank W.	**William V. McDermott Professor of Surgery** **Chief, Division of Vascular Surgery**
Quist, William C.	Assistant Professor of Pathology
Phaneuf, Matthew D.	Assistant Laboratory Director
Contreras, Mauricio	Instructor in Surgery
Sivamurthy, Nayan	T32 Research Fellow
Stone, David	T32 Research Fellow
Patel, Vaishali	Administrative Assistant
Division of Surgical Research	
Hagen, Susan J.	**Interim Chief**
Patricia Odom	Administrative Coordinator
Research Administration	
Smith, Gary	**Director, Research Administration, Team 5**
Osborne, Karen	Research Administrator

DIRECT EXPENDITURES BY FISCAL YEAR



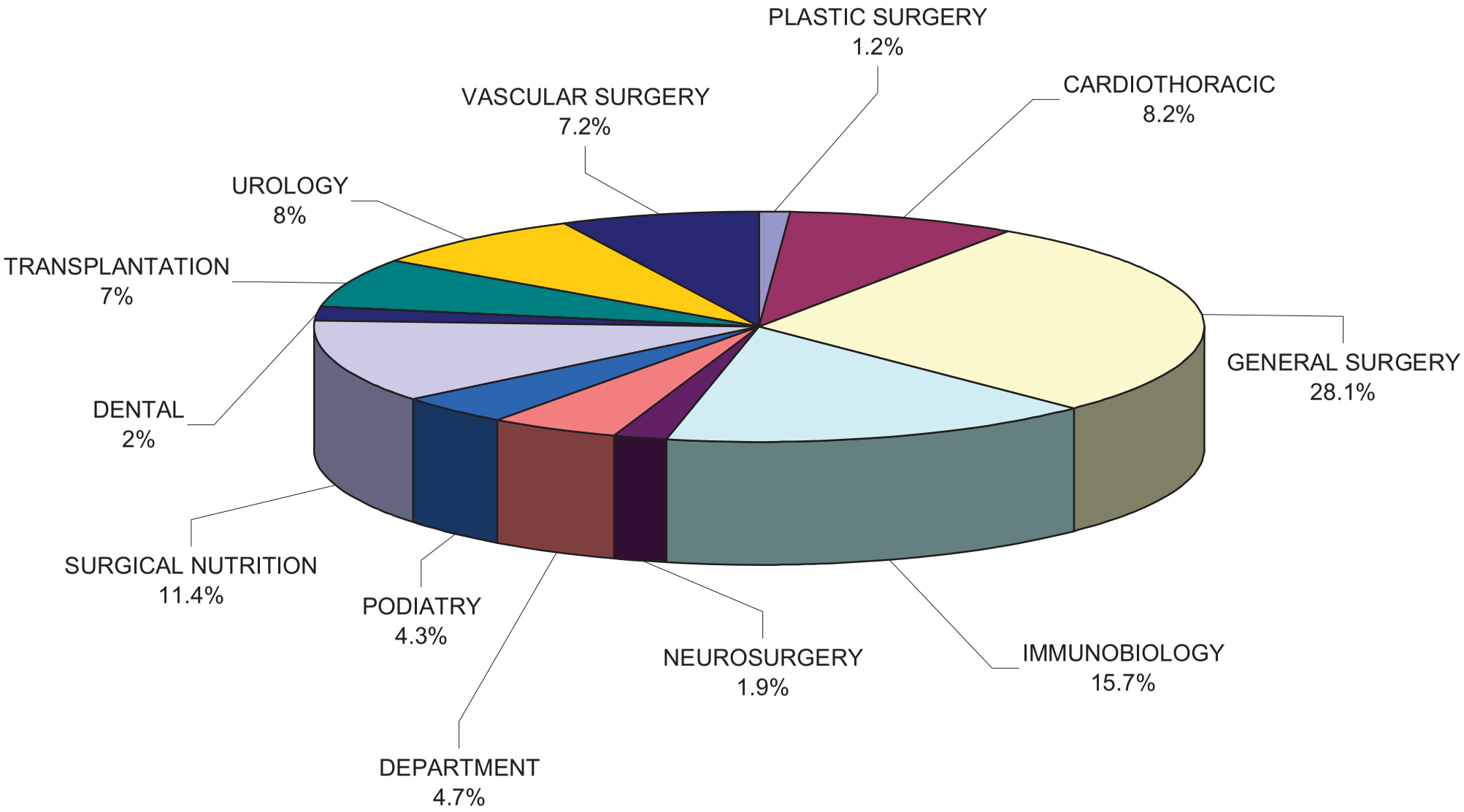
00-01 DIRECT EXPENDITURES BY SPONSOR



BETH ISRAEL DEACONESS MEDICAL CENTER
DEPARTMENT OF SURGERY
RESEARCH ACCOUNT AWARDS AND EXPENDITURES
TOTALS BY SPONSOR
10/1/00 - 9/30/01

SPONSOR	DIRECT AWARDED	INDIRECT AWARDED	TOTAL AWARDED	DIRECT EXPENDED	INDIRECT EXPENDED	TOTAL EXPENDED
NATIONAL INSTITUTES OF HEALTH	4,226,869	2,367,408	6,594,277	3,682,224	2,184,576	5,866,799
OTHER FEDERAL	196,010	111,490	307,500	4,006	641	4,647
STATE OF MASSACHUSETTS	140,021	0	140,021	188,548	0	188,548
OTHER SPONSORS	3,669,886	439,668	4,109,554	3,388,784	171,422	3,560,207
TOTAL	**8,232,786**	**2,918,566**	**11,151,352**	**7,263,562**	**2,356,639**	**9,620,201**

00-01 DIRECT EXPENDITURES BY DIVISION



BETH ISRAEL DEACONESS MEDICAL CENTER
DEPARTMENT OF SURGERY
RESEARCH ACCOUNT AWARDS AND EXPENDITURES
TOTALS BY DIVISION
10/1/00- 9/30/01

DIVISION	DIRECT AWARDED	INDIRECT AWARDED	TOTAL AWARDED	DIRECT EXPENDED	INDIRECT EXPENDED	TOTAL EXPENDED
CANCER BIOLOGY	1,660	(1,660)	0	14,238	(13,935)	304
CARDIOTHORACIC	615,245	260,825	876,069	596,709	256,286	852,996
DENTAL SURGERY	185,291	0	185,291	144,805	0	144,805
DEPARTMENT	42,136	0	42,136	342,585	0	342,585
GENERAL SURGERY	2,322,073	1,008,697	3,330,770	2,040,999	839,622	2,880,621
IMMUNOBIOLOGY	1,279,333	527,416	1,806,749	1,140,902	392,225	1,533,126
NEUROSURGERY	182,900	5,000	187,900	134,531	2,771	137,302
OPHTHALMOLOGY	0	0	0	6,636	0	6,636
OTOLARYNGOLOGY	920	0	920	1,708	0	1,708
PLASTIC SURGERY	59,929	0	59,929	85,584	291	85,874
PODIATRY	309,874	10,734	320,608	311,162	38,284	349,446
SURGICAL NUTRITION	1,350,765	511,756	1,862,522	830,364	332,644	1,163,008
TRANSPLANTATION	313,218	169,612	482,830	508,411	153,477	661,888
UROLOGY	675,783	166,974	842,757	580,690	151,995	732,685
VASCULAR SURGERY	893,659	259,213	1,152,873	524,239	202,979	727,219
TOTAL	**8,232,786**	**2,918,566**	**11,151,352**	**7,263,562**	**2,356,639**	**9,620,201**

Individual Investigator Narratives

Sonia Archer, M.D.

Division of General Surgery

I. Narrative Report

Basic Research

My goal is to obtain independence as an academic researcher with the acquisition of an NIH RO1 award, and to continue to advance the understanding of the molecular mechanisms involved in butyrate's (and fiber's) protection against colon carcinogenesis. My expectation is that this will eventually be able to translate the findings into diagnostic and therapeutic strategies against colon cancer.

II. List of Current Employees

1. Qing MA, M.D. Research Technician

III. List of Current Funding

1. " Mechanisms underlying the regulation of p21 $^{(CIP1/WAF1)}$ during enterocyte differentiation"
   NIH, Physician Scientist Award (K-08)
   PI: Dr. Sonia Archer
   1997-2002

2. "Importance of the p21 gene and histone hyperacetylation in butyrate-mediated growth inhibition in colon cancer cells"
   PI. Dr. Sonia Archer
   Beth Israel Deaconess Medical Center Junior Investigator Award
   1998-2000

3. "Regulation of p21 by butyrate in intestinal epithelia"
   NIH, Physician Scientist Award (R-O3, supplement to K-O8)
   PI: Dr. Sonia Archer
   2000-2002

IV. Applications Submitted and Pending Review/Funding

1. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"
   Robert Wood Johnson Award, Minority Medical Faculty Development Award
   PI: Dr. Sonia Archer
   2002-2006

V. Divisional Accomplishments Over Past Year

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 first-authored two papers: "Transient vs. prolonged histone hyperacetylation: effects on colon cancer cell growth, differentiation, and

apoptosis" published in the American Journal of Physiology, and "p21 gene regulation during enterocyte differentiation" published in the Journal of Surgical Research. Both of these articles have received national and international recognition, and I have received correspondence from around the world regarding them. In addition, I have published a chapter entitled "Intestinal regeneration and adaptation models" in the textbook Surgical Research, edited by Drs. Souba and Wilmore. Finally, I am awaiting publication of a review article on the p21 gene in the book, Encyclopedia of Molecular Medicine.

At the national level, I continue to participate as a member of the program committee of the Association for Academic Surgery, and moderated a scientific program at the November, 2000 meeting. I have presented well-received abstracts at the American Gastroenterological Association meetings of 2000 and 2001, and the Association for Academic Surgery in 2000.

At the international level, based on my work and my review article on "Histone acetylation and cancer" published in the 1999 issue of Curr Opin Genet Dev, I have been invited to present a scientific contribution at the "Predictive Oncology & Intervention Strategies" international symposium at the Pasteur Institute in Paris France, next year.

I have participated in the NIH sponsored In-Service Teacher Program as advisor/ mentor to a Boston public school teacher who obtained training in basic science research in our laboratory last summer and I have continued to serve as advisor and mentor for minority students in the Biomedical Science Careers Student Project.

VI. Plans For The Coming Year

I will continue to work towards the attainment of 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. postdoctorate fellows, who will be able to accelerate the progress of our research, which has the exciting possibility of imminent clinical translation.

VII. Bibliography (07/01/2000-06/30/2001)

Original Reports

1. Wu JT*, **Archer SY***, Hinnebusch B, Meng S, Hodin RA. Transient vs. prolonged histone hyperacetylation: effects on colon cancer cell growth, differentiation, and apoptosis. *Am J Physio.* (Gastrointest Liver Physiol.) 2001; 280:G482-90. * equal contribution of authors.

2. **Archer SY**, Johnson JJ, Kim H-J, Hodin RA. p21 gene regulation during enterocyte differentiation. *J Surg. Res.* 2001; 98:4-8.

Proceedings of Meetings

None Listed

Reviews, Chapters, and Editorials

1. **Archer SY**, Hodin RA. P21. In: Creighton T, ed. Encyclopedia of Molecular Medicine. Creighton TE et. al., editors. John Wiley & Sons, New York, N.Y. In Press.

2. **Archer SY**, Hodin RA. Intestinal regeneration and adaptation models. In: Surgical Research. Souba WW and Wilmore DW, editors. Academic Press, San Diego, California, 2001, 557-571.

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts

1. **Archer SY**, Johnson JJ, Hodin RA. p21 gene regulation during enterocyte differentiation: identification of activator and repressor elements. Association for Academic Surgery, November, 2000.

2. **Archer SY**, Kim HJ, Johnson JJ, Hodin RA. Cyclin B1 transcriptional repression in colon cancer cells: dual pathways of regulation. Gastroenterology 2001; 120(5): A292.

3. Hinnebusch BF, **Archer SY**, Wing MA, Hodin RA. Enterocyte response to ischemia is dependent on differentiation state. Gastroenterology 2001; 120(5):A62.

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 one of the products of HO-1 action on heme: carbon monoxide (CO). We have shown that CO can mediate most, if not all, of the protective effects of HO-1. We are able to induce HO-1 expression by treatment with cobalt protoporphyrin (CoPP); CO can be administered via the lungs. We plan to optimize the use of HO-1 and CO to promote organ and tissue graft survivals.

II. List of Current Employees

Junior Faculty

1. Miguel P. Soares, Ph.D.
2. Edda M. Tobiach, Ph.D.

Research Fellows

1. Kenichiro Yamashita, M.D., Ph.D.
2. Ning Wang, M.D.
3. Lukas Gunther, M.D.
4. Pascal Berberat, M.D.

Research Technicians

1. Vilmosne Eva Csizmadia

III. List of Current Funding

1. JDF International/HMS (Auchincloss/Bach)
   9/1/01-8/31/02 "Xenotransplantation of Protected Porcine Islets"

   The major goals of this project are to test whether expression of heme oxygense-1 (HO-1) or the one or more of the products of HO-1 action on heme will benefit islet survival and function after transplantation.

2. NHLBI 1RO1HL58688-02 (Fritz H. Bach)
   Cells"

   The long term project of this grant is to achieve long term acceptance of vascularized organs in a small animal xenotransplantation model.

3. 1PO1DK53087 NIDDK/Joslin Diabetes Center
   "Islet Xenotransplantation: Genetic Approaches to the Problem"

12/1/01-11/30/02

4. "Studies in Transplantation"
   Novartis (Sandoz) Pharma/BI Deaconess Medical Center B
   PI: Dr. Bach
   1/1/00-

   The major goals of this project are to develop a knowledge base of the factors that are involved in rejection of a xenograft, and to devise therapeutic approaches to overcoming these factors. Special emphasis is on the use of genetic engineering strategies for this purpose.

IV. Applications Submitted and Pending Review

None

V. Divisional Accomplishments

Research accomplishments

1. I 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, t is the p38MapKinase pathway. In smooth muscle cells, both cGMP and p38 are involved and p38 activation depends on cGMP for its activation.

2. I have shown that pre-treatment of pancreatic islets with CO for 2 hours will markedly improve their function when transplanted to diabetic mice.

3. I 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.

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

4. 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.

VI. 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 2.

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

VII. Bibliography (07/01/00-6/30/01)

Original Articles

1. Brouard S, Otterbein LE, Anrather J, Tobiasch E, Bach FH, Choi AM, Soares MP. Carbon monoxide generated by heme oxygenase-1 suppresses endothelial cell apoptosis. *J. Exp. Med*. 2000;192 (7):1015-26.

2. Imai M, Takigami K, Guckelberger O, Kaczmarek,E, Csizmadia E, Bach FH, Robson SC. Recombinant adenoviral mediated CD39 gene transfer prolongs cardiac xenograft survival. *Transplantation* 2000; 70(6):864-70.

3. Lin Y, Soares MP, Sato K, Czismadia E, Robson SC, Smith N, Bach FH. Long-term survival of hamster hearts in pre-sensitized rats. *J. Immunol.* 2000; 164(9):4883-92.

4. Otterbein LE, Bach FH, Alam J, Soares M, Tao Lu H, Wysk M, Davis RJ, Flavell RA, Choi AM. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. *Nature Med.* 2000; 6(4):422-8.

5. Sato L, Balla J, Otterbein L, Smith RN, Brouard S, Lin Y, Csizmadia E, Sevigny J, Robson SC, Vercelliotti G, Choi Am, Bach FH, Soares MP. Carbon monoxide generated by heme oxygenase srppresses the rejection of mouse-to rat cardiac transplants. *J. Immunol*. 2001; 166(6):4185-94.

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Reviews and Book Chapters

1. Soares, MP, S Brouard, RN Smith, L Otterbein, AM Choi 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.

Abstracts

1. Grey ST, Lock J, Bach FH, Ferran C. Adenovirus-mediated gene transfer of A20 in murine islets inhibits Fas-induced apoptosis. *Transplant Proc.* 2001;33(1-2):577-8.

2. Imai M, Takigami K, Guckelberger O, Lin Y, Sevigny J, Kaczmarek E, Goepfert C, Enjyoji K, Bach FH, Rosenberg RD, Robson SC. CD39/vascular ATP diphosphohydrolase modulates xenograft survival. *Transplant Proc.* 2000;32(5):969.

3. Pileggi A, Cattan P, Berney T, Molano RD, Vizzardelli C, Ricordi C, Bach FH. HO-1 upregulation protects the pancreatic cell line betaTC3 from cytokines and Fas-induced apoptosis. *Transplant Proc.* 2001;33(1-2):266-7.

4. Wang N, Lee JM, Soares MP, Csizmadia E, Robson SC, Smith N, Bach FH, Lin Y. Long-term survival of hamster hearts in presensitized rats. *Transplant Proc.* 2001;33(1-2):747-8.

5. Wang N, Lee JM, Soares MP, Csizmadia E, Xu D, Liew FY, Smith N, Bach FH, Lin. TH2 cytokines regulate gene expression and proinflammatory responses in xenografts. *Transplant Proc*. 2001 Feb-Mar;33(1-2):776-7.

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 provides nutrition research and clinical interventions. Current studies address areas such as breast cancer, prostate cancer, hypertension, diabetes and obesity. Various nutrition interventions are utilized to support research 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

Nutrition Metabolism Laboratory (NML) .The major research goals in the Nutrition Metabolism Laboratory are to determine the effects of nutraceutical 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.

II. List of Current Employees

1. Edward C. Mun, M.D.	Assistant Professor of Surgery
2. Lalita Khaodhiar, M.D.	Junior Faculty
3. Jin-Rong Zhou, Ph.D.	Assistant Professor of Surgery
4. Weijun Pan, MD, PhD.	Research Fellow
5. Lunyin Yu, MD.	Research Fellow
6. Pennie Greene, Ph.D.	Research Fellow
7. Justin Maykel, M.D.	Research Fellow
8. Anne McNamara RN	Research Associate
9. Trisha Copeland, MS, RD	Research Associate
10. Pam Karun, MS	Research Associate
11. Wanda Hirsch, RD	Research Associate
12. Michelle Sherwood, RD	Research Associate
13. Ying Zhong	Research Technician
14. Min Lin	Student (unpaid intern)

III. List of Current Funding

1. (NIH) The Study of Health Outcomes of Weight Loss (Blackburn) 09/01/01-08/31/02

The major goals of this project are to 1) determine whether intensive therapies directed at achieving and maintaining weight loss in moderately overweight persons with Type 2 diabetes affect a variety of long-term outcomes known to be sensitive to obesity when compared with a control group that is managed according to community standards.

2. (NCI) Low-Fat Diet in Stage II Breast Cancer: Outcome Trial (Blackburn) 01/01/97-12/30/04
   The major goal of the project is to test that low fat diet will reduce disease recurrence and increase patient survival for post-menopausal women with localized breast cancer.

3. Atkins Foundation (Blackburn)
   06/01/01-05/30/02
   Comparison of weight loss dietary strategies: low carbohydrate ketogenic diets compared with low fat diet

4. Aventis Pharma (Blackburn-PI) 05/01/01-05/01/02
   Pharmacodynamics, safety, and tolerability of HMR 1426 for the treatment of obesity

5. NCI/NIH (1RO1 CA78521) (Zhou) 06/01/1999-05/31/2002
   Dietary Soybean Components Affect Prostate Cancer Progression

6. American Institute for Cancer Research (Zhou) 01/31/1999-05/31/2001
   "Soy Isoflavone as a Radiation Sensitizer in Prostate Cancer"

7. Massachusetts Department of Public Health (Zhou) 01/01/99-05/31/01
   Dietary soy isoflavone as radiation sensitizer in treating breast cancer.

8. Susan Komen's Breast Cancer Research Foundation (Zhou)
   10/01/2000 – 09/30/2002
   Combined effects of soy and tea bioactive components on breast cancer progression

9. Massachusetts Department of Public Health (Zhou) 01/01/2001 – 12/30/2003
   Combined effect of soybean and tea bioactive components on delaying the development of androgen-independent prostate cancer

11. Nichimo Co. (Zhou)03/01/2001-02/28/2003
    Effects of Isoflavone-aglycones on the prevention and treatment of ovarian deficiency (menopause), obesity and prostate cancer

IV. Applications Submitted and Pending Review/Funding

1. NCCAM/NIH (1RO1 AT00863-01) (Zhou)09/12/2001-05/31/2004

Interactions between dietary soy components and tamoxifen on breast cancer progression.

V. Divisional Accomplishments

Research Accomplishments

1. NIH Grant Review Study Section. Nutritional Modification of Genetic Pathways, Washington DC May 14, 2001 (Blackburn)

New grants in the past year

1. Susan Komen's Breast Cancer Research Foundation (Zhou)
   10/01/2000 – 09/30/2002
   Combined effects of soy and tea bioactive components on breast cancer progression

2. Massachusetts Department of Public Health (Zhou) 01/01/2001 – 12/30/2003
   Combined effect of soybean and tea bioactive components on delaying the development of androgen-independent prostate cancer

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

4. Nichimo Co. (Zhou) 03/01/2001-02/28/2003
   Effects of AglyMax on the prevention and treatment of obesity and prostate cancer

5. Atkins Foundation (Blackburn) 06/01/01-05/30/02
   Comparison of weight loss dietary strategies: low carbohydrate ketogenic diets compared with low fat diet

6. Aventis Pharma (Blackburn-PI) 05/01/01-05/01/02
   Pharmacodynamics, safety, and tolerability of HMR 1426 for the treatment of obesity

Educational Accomplishments

1. HMS, Faculty Development and Diversity, NSF Consultant and preceptor for Native American Pre-Medicine Student, August 2000

2. HMS, Invited Lecture to Native American Health Services of DHHS, "Native American Indians: Facing the Obesity Epidemic" Boston, MA April 4, 2001

3. HMS, Department of Continuing Medical Education "Enhancing the Safety of Parenteral and Enteral Nutrition, Boston, MA November 5-7, 2000 (speaker and director)

4. HMS, Department of Continuing Medical Education "Practical Approaches to the Treatment of Obesity, Boston, MA June 21-23, 2001 (speaker and director)

5. HMS, Division of Nutrition "Nutrition and Disease Prevention Symposium" Boston, MA June 22-23, 2001 (moderator and organizer)

6. NIH Boston Obesity Nutrition Research Center (BONRC) Executive Committee
   Chairperson, Food Patterns in Weight Management and Health "Obesity, the Major Health Issue of the 21st Century", Dallas, TX April 26-29, 2001 (Proceedings, Nov. 2001 *Obesity Res*)

7. Annual Scientific Program, July 16, 2001

8. Centers for Obesity Research and Education (CORE) 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.

Individual accomplishments
Dr. Blackburn

1. American Association of Lifestyle Counselors, "Overweight and Obesity Prevalence Cost Strategies" Dallas, Texas August 24, 2001

2. Mexican Endocrine Society and NAASO, "Goals of Treatment of Obesity, Definitions of Success, and Health Benefits of Weight Loss" Mexico City, Mexico August 24, 2000

3. Mid-Hudson Health Continuing Medical Education, GI Teaching Day, "Nutritional Support of the Patient with Inflammatory Bowel Disease" and "Obesity" Poughkeepsie, NY September 27, 2000

4. National Dairy Council Grant Review, Chicago, IL October 2-3, 2000

5. Society for Women's Health Research, "Dieting: Health Hazard ~ Health Strategy" Washington DC October 4, 2000

6. American Dietetic Association "Tomorrow's Answer: Obesity prevention and Treatment", Denver, CO October 16, 2000

7. Boston University Medical Center OB/GYN Women's Health Conference, lecture on "Obesity", Natick, MA November 4, 2000

8. Latin American Nutrition Society, "Fat: The Good, The Bad, The Trans" Buenos Aires, Argentina November 12-17, 2000

9. Massachusetts Biotechnology Council, Health Writers Symposium, "The Evolution of Obesity" Boston, MA December 6, 2000

10. American College of Preventative Medicine, "Tools in the Prevention and Treatment of Obesity" Miami, FL February 24, 2001

11. Medical Staff Presentation "Bariatric Surgery", Melrose-Wakefield Hospital April 25, 2001

12. Lowell General Grand Rounds "Diet and Weight Control: Practical Approaches" May 9, 2001

13. 11th European Congress on Obesity, Vienna, Austria May 30- June 3, 2001

14. National Dairy Research Forum, "Obesity: Where are we now and where are we heading?" Chicago, IL June 5-6, 2001.

15. Jones JL, Zhou JR, **Blackburn GL**. Genistein enhances radiation sensitivity of human MCF-7 breast cancer cells in vivo. 34th Annual Meeting Association for Academic Surgery, Tampa, FL, November 2-4, 2000.

Dr. Zhou

1. March, 2001 Plenary presentation
   American Association of Nutritional Sciences, Experimental Biology 2001

2. May 2001 Visiting Professorship
   Institute of Molecular Medicine, Nanjing University, Nanjing, P. R. China

3. May 2001 Invited lecture
   The 2nd Military Medical University, Shanghai, P. R. China

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

5. Zhou JR. Prevention of orthotopic growth of estrogen-dependent human breast tumor in mice by dietary soy phytochemicals. 222nd ACS National Meeting, #AGFD0121, 2001.

6. Jones JL, Zhou JR, **Blackburn GL**. Genistein enhances radiation sensitivity of human MCF-7 breast cancer cells in vivo. 34th Annual Meeting Association for Academic Surgery, Tampa, FL, November 2-4, 2000.

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 Laboratory

1. To recruit two postdoctoral fellows
2. To submit two RO1 grants (one for competing renewal and another new one)
3. To be involved in Nutrition curriculum development at HMS

VII. Bibliography (07/01/00-06/30/01)

Original articles (Blackburn)

1. **Blackburn, GL**. Weight gain and antipsychotic medication. *J Clin Psychiatry* 2000;61 (8 S):36-42.

2. Copeland T, Grosvenor M, Mitchell DC, Smiciklas-Wright H, Marsoobian V, **Blackburn GL**,Winters BL. Designing a quality control system for dietary data in a multi-center clinical trial: women's intervention nutrition study. *JADA*, 2000;100:1186-90.

4. **Blackburn GL**. Pasteur's quadrant and malnutrition. *Nature* 2001; 409:397-401.

5. **Blackburn GL**. Feeding 9 billion people- a job for food technologists. *Food Technology* 2001;55:106.

Original articles (Zhou)

1. Williams AW, Boileau TW, **Zhou JR**, Clinton SK, Erdman JW. Beta-carotene modulates human prostate cancer cell growth and may undergo intracellular metabolism to retinol. *J. Nutr*. 2000;130(4):728-32.

Reviews, Chapters, and Editorials

1. **Blackburn, GL**. (Letter) Blockade of pancreatic lipase. *Am J Clin Nutr* 2000;71:845.

2. **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.

3. 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.

4. Khaodhiar L, Maloo MJ, **Blackburn GL**. Parenteral and Enteral Nutrition. In:Altals of Clinical Endocrinology. Vol. V Human Nutrition and Obesity Edited: Korenman SG, Heber D. Current Medicine, Philadelphia, 2000, 14:199-214.

5. Melanson KJ, McInnis KJ, Rippe JM, Blackburn G, Wilson PF. Obesity and cardiovascular disease risk: research update. *Cardiol Rev*. 2001;9(4):202-7.

6. McCowen KC, Chan S, **Blackburn GL**. Diet—Calories In:Hypertension a companion to Brenner and Rector's The Kidney. Edited: Oparil S, Weber MA. W.B. Saunders Company, Philadelphia, 2000, 48: 460-5.

7. McCowen KC, **Blackburn GL**. Obesity, Weight Controll, and Cardiovascular Disease In: Preventive Cardiology. Edited: Wong ND, Black HR, Gardin JM. McGraw-Hill, New York, 2000, 10:251-267.

8. Mun EC, **Blackburn GL**, Matthews JB. Current status of medical and surgical therapy for obesity. Gastroenterology 2001;120:669-681.

Books, Monographs, and Text Books

1. Khaodhiar L, McCowen KC, **Blackburn GL**. Obesity and its comorbid conditions. In: Clinical Cornerstone, Obesity. Excerpta Medica, Inc. Belle Mead, NJ, 2000.

Clinical Communications

1. HealthNews-Physician's Perspective (Blackburn)
2. Reduced-Fat Fallacy. HealthNews, 2000;November 6:11.
3. Surgery for Obesity. HealthNews, 2000; December 6: 12.
4. Heart-Wise Dietary Guidelines Overhauled. Heart Watch, 2000; December 4:11
5. Honing Type 2 Diabetes Treatment. HealthNews, 2001; January 7:1.
6. You Can Prevent Type 2 Diabetes, 2001; June 7:6
7. Reckoning with Cholesterol, 2001; July 7:7

Abstracts

1. Yu L, Zhong Y, **Blackburn GL, Zhou JR.** Effects of dietary soy bioactive components on the modulation of molecular biomarkers in LNCaP human

prostate tumor grown orthotopically in mice. Experimental Biology annual meeting, *FASEB J.* 2001;15:A631.

2. Zhong Y, Yu L, **Blackburn GL**, **Zhou JR**. Combined effects of soy phytochemicals and radiation treatment on the growth of DU 145 human prostate carcinoma in mice. *FASEB J.* 2001;15:A616.

3. **Zhou JR**, Yu L, Zhong Y, **Blackburn GL**. Soybean bioactive components inhibit the orthotopic growth of human bladder carcinoma in mice. *FASEB J.* 2001;15:A61.

William DeWolfe, M.D.

No Annual Report submitted

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 and acute fulminant hepatitis. 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 and hepatitis. This interest is based on our original finding that these genes serve a broad cytoprotective function in endothelial cells. Expression of A20, A1, Bcl-2 and Bcl-x_L in endothelial cells not only protects the cells from apoptosis but also serve a broad anti-inflammatory purpose.

II. LIST OF CURRENT EMPLOYEES

1. Shane T. Grey, Ph.D. — Assistant Professor of Surgery
2. Maria B. Arvelo, M.D. — Post-doctoral fellow
3. Jerome Mahiou, Ph.D. — Post-doctoral fellow
4. Soizic Daniel, Ph.D. — Post-doctoral fellow
5. Christopher Longo, M.D. — Surgical Resident at the Beth Israel Deaconess Medical Center. Recipient of a fellowship training grant from the Longwood vascular biology training program, a NIH training program headed by Dr. F. LoGerfo (T32).
6. Uta Kunter M.D. — Visiting Research fellow from the University of Aachen, Germany. Currently finishing her residency at the University of Aachen.
7. Virendra I. Patel, M.D. — Surgical Resident at the Beth Israel Deaconess Medical Center. Recipient of a fellowship training grant from the Longwood vascular biology training program, a NIH training program headed by Dr. F. LoGerfo. (T32).

III. LIST OF CURRENT FUNDING

1. "Modulation of Endothelial Cell Response by A20"
   NIH RO1 Grant # HL57791
   PI: Dr. C. Ferran
   01/1998-12/2001

2. "Genetic Engineering of Xenogeneic Islets with Anti-apoptotic Genes and Cytokine Inhibitors".
   NIH PO1 # DK53087
   Principal Investigator: Dr. C. Ferran
   Program Director: Dr. Gordon Weir, Joslin Clinic.
   12/1997- 11/2002

3. "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.
   PI: Dr. C. Ferran
   Program Head: Dr. Hugh Auchincloss Jr.
   09/1998-08/2003

4. "Xenotransplants: Genetically engineered endothelial cells".
   NIH RO1 # HL58688-01
   PI: Dr. Fritz H. Bach
   Co-investigator: Dr. C.Ferran
   09/1998- 08/2002

5. The Longwood Vascular Biology Training Grant
   NIH T32.
   PI: Dr. C. Ferran
   Program director: Dr. Grank W. LoGerfo

IV. APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

1. Roche Organ Transplantation Research Foundation
   PI: Dr. C. Ferran
   Title: "Protective effect of A20 against Translant-Associated Vasculopathy"
   We received the notification of funding this October 1, 2001
   Grant funding is for 3 years.

3. NIH RO1 Grant # HL67058
   Principal Investigator: C. Ferran
   Title: "Anti-atherogenic Function of A20 in Smooth Muscle Cells"

3. NIH RO1 Grant # DK61648
   Principal Investigator: Dr. C. Ferran
   Title: "Modulation of Hepatocyte Apoptosis and Proliferation by A20"

V. DIVISIONAL ACCOMPLISHMENTS

Educational activities

1. Boston University Medical School, Boston, MA.
   I was a lecturer at the Immunology Training Program Seminars on the protective regulatory response of EC and SMC to injury.

2. Beth Israel/Deaconess Medical Center, Harvard Medical School.
   I was a lecturer at the weekly Endocrinology Seminars
   Title: "Role of the protective gene A20 in the protection of islet transplantation and type I diabetes".

3. 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 vascular Injury".

4. I was a lecturer at a transplantation course organized by the Brazilian Society of Transplantation on the topics of vascular biology and transplantation and gene therapy in organ transplantation. March 21-24, 2000, Buzios, Brazil.

<u>International Presentations</u>

1. I was an invited Lecturer at the 96th American Thoracic Society on the role of Bcl-2 genes in apoptosis, May 5-10, 2000, Toronto, Canada.

2. I was the moderator of a Workshop on gene therapy in organ transplantation, at The Transplant 2000 meeting of the ASTS and AST, May 13-17, 2000, Chicago, IL, USA.

3. I was a lecturer at the VIIth International congress of the Middle Eastern Society of Organ Transplantation on the topics of gene therapy in organ transplantation and xenotransplantation,. June 8-11, 2000 Beirut, Lebanon.

4. I was Chairman at the XVIIIth International meeting of the Transplantation Society, August 27, Sep 1 2000, Rome Italy.

5. I was a lecturer at the European Symposium for diabetes. August 11-14, 2000, Keble College. Oxford. United Kingdom.
   Title: "Protective genes in islet transplantation and autoimmunity".

6. I was a lecturer at the Transplantation Grand Rounds on the topic of genetic engineering of organ transplant. October 2000, University of Cincinnati, OH.

7. I was a lecturer at the 6th International Conference on Tolerance Induction. Topic: "Gene therapy in tolerance induction". Tucson, Arizona, January 21-24, 2001.

8. I was Chairman and a lecturer at the Basic Science Symposium of the Transplantation Society. Topic: "Protective Genes and Tolerance Induction". Thun, Switzerland, August 21-26, 2001.

9. Dr. Daniel gave an oral presentation at the the XVII International Congress of the Transplantation Society. Roma, Italy (August 29- Sep2nd 2000) "Overexpression of A20 in endothelial cells of vascularized grafts creates a protective barrier against TNF- and FAS-mediated apoptosis".

10. Dr. Grey gave an oral presentation at the the XVII International Congress of the Transplantation Society. Roma, Italy (August 29- Sep 2nd 2000). "Adenovirus-mediated gene transfer of A20 in murine islets inhibits Fas-induced apoptosis".

11. Dr. Ferran gave an oral presentation at the the XVII International Congress of the Transplantation Society. Roma, Italy (August 29- Sep 2nd 2000). "A20 and Bcl proteins exert a broad and complementary cytoprotective effect in endothelial cells via blockade NF-κB and NFAT".

12. Dr. Rocha gave an oral presentation at the XVII International Congress of the Transplantation Society , Roma, Italy (August 29 –Sept 2nd 2000). "The Bh4 domain of A1, an anti-apoptotic bcl family gene, is necessary and sufficient for its anti-inflammatory function in endothelial cells".

13. Dr. Grey gave 2 oral presentations at the Islets and Pancreas International Transplantation Association (IPITA) Meeting in Innsbruck, Austria in June 2001. "Recombinant adenoviral mediated gene transfer of A20 in islets inhibits Fas induced apoptosis at the level of the death initiating signaling complex (DISC)" and "Genetic engineering of rodent islets with A20 overcomes primary non-function".

VI. PLANS FOR THE COMING ACADEMIC YEAR

Staff changes

1. Christopher Longo, M.D. will finish his research fellowship in July 2002 and will be departing.

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

Grant applications to be submitted

1.Response to NIH RFA on gene therapy for islet transplantation: to be submitted December 12, 2001.

2.Protective role of A20 against diabetic vasculopathy. To be submitted Feb 1st 2002 to NIH and possibly concomitantly to the JDFI.

3.Possible renewal of the PPG: "Genetic Engineering of Xenogeneic Islets with Anti-apoptotic Genes and Cytokine Inhibitors".

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 lecturer 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.

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

4. 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.

5. Invited lecturer at the 2002 FASEB summer Research Conference on Transplantation Immunology. Topic: Endothelial cell cytoprotection in Transplantation". The Vermont Acadamy in Saxtons River, Vermont. June 15-20, 2002.

6. Invited lecturer at the XIX International Congress of the Transplantation Society. Speaker of the state-of-the-art Symposium " Endothelial Cell Activation". Buenos Aires, Argentina. August 18-23, 2002.

VII. BIBLIOGRAPHY (7/01/00-6/30/01)

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* 2001, in press.

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* 2001, in press.

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* 2001, in press.

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* 2001, in press.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Text Books
1. **Ferran C**. and Bach FH. Xenotransplantation: Hopes and Goals in Transplantation Surgery, Editors Nadey Hakim and Gabriel Danovitch (Springer, Verlag, Eds) 2001, Chapter 15, p.343-353.

Clinical communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
1. Badrichani AZ, **Ferran C.** A20 and BCL proteins exert a broad and complementary cytoprotective effect in endothelial cells via blockade of NF-kappaB and NFAT. *Transplant Proc.* 2001;33:450.

2. Daniel S, Arvelo M, **Ferran C.** Overexpression of A20 in endothelial cells of vascularized grafts creates a protective barrier against TNF- and FAS-mediated apoptosis. *Transplant Proc.* 2001;33:225.

3. Grey ST, Lock J, Bach FH, **Ferran C.** Adenovirus-mediated gene transfer of A20 in murine islets inhibits Fas-induced apoptosis. *Transplant Proc.* 2001;33:577-8.

4. Rocha E, Mahiou J, Badrichani AZ, Stroka DM, **Ferran C.** The BH4 domain of A1, an anti-apoptotic bcl family gene, is necessary and sufficient for its antiinflammatory function in endothelial cells. *Transplant Proc.* 2001;33:314.

Aniruddha Ganguly, Ph.D.

Division of General Surgery
Laboratory of Cancer Biology

I. Narrative Report

Basic Research

I 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 some other diseases. An understanding of the mechanisms of tumorigenesis relative to expression of the macrophage protein is needed for effective management and ultimately for development of therapeutic approaches to control and prevent disease.

We also 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 Technician
2	Christine Castro, BA	Research Technician
3.	Marissa Newton	Student
4.	Sharon Hwang	Student
5.	Anindita Chakrabarti	Student
6.	Elisia Guarino	Student

III. List of Current Funding

1. "A macrophage protein in colon tumorgenesis"
   NIH R01 CA87678-01
   PI: Dr. Ganguly
   7/01/01-6/30/06

2. The Charlotte Geyer Foundation, Principal Investigator.
3. Wendy Will Case Cancer Fund, Inc., Principal Investigator.
4. Corporate Funding, Principal Investigator.
5. Aids for cancer Research, Principal Investigator.
6. Gift Account, Principal Investigator.

IV. Applications Submitted and Pending Review/Funding

None

IV. Divisional Accomplishments

Research accomplishments (including new grants/programs)

1. I recently obtained federal (NCI/NIH), non-federal and corporate funding. A laboratory space is assigned to me at end of June 2001. We have been able to begin our studies and obtained preliminary results that emphasize physiological relevance of the new macrophage protein (discovered by me) in tumorigenesis. Some of the research accomplishments are listed in the bibliography section.

Educational activities

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

V. Plans for the Coming Academic Year

staff changes/recruitments

Undecided

plans for research (new grants/programs)

1. Continue with the same program.

plans for educational programs

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

VI. Bibliography (7/01/00-6/30/01)

Original Articles

1. Lise M, Belluco C, Perera SP, Patel R, Thomas P, **Ganguly A**. Clinical correlations of 2,6-sialyltransferase expression in colorectal cancer patients. *Hybridoma* 2000; 19 (4):281-6.

2. Palombo JD, **Ganguly A**, Bistrian BR, and 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* (In press), 2001.

Proceedings of Meetings

None Listed

Reviews, Chapters, and Editorials

None Listed

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.

Clinical Communications
None Listed

Educational Materials
None Listed

Abstracts
None Listed

Sandra M. Gaston, Ph.D.

Division of Urology
Basic Science Director
Urological Research Laboratory

I. Narrative Report

Basic research

Our primary research interests focus on the molecular biology of the 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.

II. List of Current Employees

1. Lynn Mathew — Research Technician
2. Seanna Kim — Research Technician
3. Dang Vu — Research Assistant
5. Marc Soares — Student
6. Dana Goldner — Student
7. Jennifer Shih — Student
8. Nicholas Powley — Student
9. Chandan Das — Student
10. Tae Won Kim — Student

III. List of Current Funding

1. "Androgen Receptor Biochips: Prostate Cancer Management"
   National Institutes of Health CA86365
   PI: Ian Hunter Ph.D. (MIT)
   Role on Project: Sandra M. Gaston Ph.D. is PI on the BIDMC Subcontract

   This project was funded under the NIH Innovative Molecular Analysis Technologies Program (IMAT). We have successfully completed the R21 phase of this grant, and the BIDMC subcontract has been awarded the full R33 budget requested. We have been invited to submit an application for substantial supplemental funding for this project, which will be submitted in November 2001. The major objective of this project is development of a yeast based biochip ("living chip") and other instrumentation necessary to support automated yeast-based bioassays of androgens and related compounds in sera and other complex biological fluids.

2. "Prostate Cancer Biomakers in Urine"
   National Institutes of Health
   PI: Bruce Zetter, Ph.D. (Children's Hospital)
   Role on Project: Sandra M. Gaston PhD is the BIDMC PI
   Project period: 07/01/01 – 06/30/02
   The major objective of this project is to evaluate a series of beta thymosins as urinary biomarkers for prostate cancer.

3. "Y- Chromosome Micro-Deletions Test on Sperm DNA"
   Repromedix Industry Supported Research
   PI: Sandra M. Gaston PhD
   Project period: June-Dec 2001 (pilot phase)

   A genetic test based on the analysis of DNA from somatic cells cannot preclude the presence of deletions or mutations in the germ line, and mutations which produce profound male infertility can and do arise during spermatogenesis. The major objective of this project is to adapt a PCR-based test for Y-chromosome deletions associated with male infertility for direct analysis of sperm DNA from men with one or more sub-normal semen parameters.

4. "Matrix Metalloprotease 9: Tumor Marker or Risk Factor for Prostate Cancer?"
   Massachusetts Department of Public Health
   Role on Project: Sandra M. Gaston Ph.D., PI
   Project period: 01/01/2001-12/30/04

   The major objective of this project is to characterize the role of constitutive MMP9 expression in prostate cancer risk and progression.

5. "Translational Development of New Methods for Monitoring Nutritional Management in the Treatment of Prostate Cancer: Microscale Bioassays for Androgen"
   CaP CURE Research Award Funding
   PI: Sandra M. Gaston Ph.D.
   Project period: 01/01/2000

   The major objective of this project is the development of yeast based biochips that can monitor changes in bioactive serum androgens and estrogens in response to dietary management and "over the counter" nutritional supplements.

IV. Applications Submitted and Pending Review/Funding

1. Hershey Family Foundation Grant (submitted 9/15/01)
   Title: Spatial-Molecular Mapping of Molecular Markers of Capsular Invasion: Coupling Prostate Tissue-Printing to High Throughput Protein Mass Spectrometry
   Role on Project: Sandra M. Gaston PhD, PI

V. Divisional Accomplishments

Research Accomplishments

1. I have established a research bank of frozen semen samples 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).

New Grants and Programs

1. We have been invited to apply for a supplemental NIH grant to our R33 CA86365. This supplemental funding, if approved, will be used to extend our micro-bioassay system for the analysis of tissue and serum samples from breast cancer patients and to expedite the development of a novel tissue sampling system

that allows simultaneous micro-bioassay of steroid ligands and micro-array mRNA analysis. Dr. Stuart Schnitt, senior BIDMC breast pathologist, has agreed to join this phase of the project as a collaborator.

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

Educational Accomplishments

1. Sponsor/Research Mentor for first year Harvard Medical School Student, Lani Chun (School of Dental Medicine), Summer 2000.

2. Sponsor/Research Mentor for American Cancer Society Fuller Fellowship Student, Rena Nassr, Summer 2000.

3. Sponsor/Research Mentor for twelve MIT undergraduate students, including three who were awarded Howard Hughes summer research fellowships and three who were awarded MIT Bioengineering Undergraduate Research Fellowships.

4. Teaching Faculty, Harvard Medical School Integrated Human Physiology Course for first year medical students.

Individual Accomplishments

1. I became Basic Science Director or the Urological Research Laboratories at BIDMC.

2. I became director of the Molecular Urology Training Program at the BIDMC.

3. I received a CaPCURE Research Award..

4. I received a Massachusetts Department of Public Health Prostate Cancer Research Grant (with an additional post-award supplement).

5. I received a grant from the National Cancer Institute, CA86365. I also successfully completed all R21 milestones, allowing transition to the R33 phase of the grant.

Invited Presentations (National)

1. Kanigan T, **Gaston S.M.** and Hunter I. Androgen Receptor Bio-Chips: Novel Micro-Bioassays for Androgens and Androgen Mimics in the Sera and Tissues of Men with Prostate Cancer. NCI Principal Investigators Meeting, Innovative Molecular Analysis Technologies Programs, July 2000.

2. **Gaston, S.M.,** Hess S., Aminipour S, Cusano N, Tung, S-F, **Dewolf WC**, **Perides G**. Matrix Metalloprotease 9: Tumor Marker Or Risk Factor For Prostate Cancer? Society for Basic Urological Research, November 2000.

3. **Gaston S.M.**, Hunter I.W. 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.

4. **Gaston S.M**., Soares M., Siddiqui M.M., **Perides G.** and **DeWolf W.C**. Spatial-Molecular Mapping of Prostate Cancer Invasion: Print-Phoresis Profiles of Capsular Penetration.CaPCURE Research Retreat, September 2001.

Invited Presentations (Local)

1. **Gaston S.M.** and Hunter I. MicroArray Technology for Biological Applications. MIT Center for Bio-Medical Engineering Industrial Advisory Board Meeting, October 30, 2000.

2. **Gaston S.M**. New Methods to Assess Tumor Invasion in Human Prostate Cancer. BIDMC In Vivo Cellular and Molecular Imaging Center, November 6, 2000

3. **Gaston S.M**. Molecular Mapping for Clean Margins at Prostatectomy. Countway Urology Rounds, March 14, 2001

4. **Gaston S.M.** Prostate Cancer Invasion – Markers and Mechanisms. Pfizer site visit to BIDMC, April 10, 2001.

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

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

7**. Gaston S.M.** Yeast Based Micro-bioassays for Prostate Cancer Management: Bioactive AR Ligands in Sera. Dana Farber Cancer Institute (Vidal Laboratory), August 2, 2001.

VI. Plans for the Coming Academic Year

Staff Changes/Recruitments

1. My laboratory will add a new, full time research fellow or technician to the micro-bioassay project in the fall of 2001.

Plans for Research (new grants/programs)

1. CaP CURE Research Award (due 10/12/01)
   Title: Spatial-Molecular Mapping of Prostate Cancer Invasion
   Role on Project: Sandra M. Gaston PhD, PI

2. National Institute of Health (NCI) (due 11/15/01)
   Title: Androgen Receptor Biochips: Prostate Cancer Management (Invited Supplemental Application to Grant CA86365)
   Role on Project: Sandra M. Gaston PhD, BIDMC subcontract PI

3. National Institute of Health (IMAT Program) (due 11/21/01)

Tumor Print-phoresis Technology: Spatial-Molecular Maps
Role on Project: Sandra M. Gaston PhD, PI

New Research collaborations

1. With Dr Peter Juhasz at Applied Biosystems (Framingham MA), we will couple our prostate tissue-print and print-phoresis technology to a state-of-the-art high throughput protein mass spectrometry analysis. This collaboration will allow us to obtain a detailed profile of the proteins that cluster at sites of tumor erosion of the prostate capsule.

2. Dr. Rittenhouse at Hybritech-Beckman (San Diego CA) is sending us an important, newly developed set of monoclonal antibodies to specific prostate tumor antigen isoforms. 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.

Plans for Educational Programs/Activities

1. 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 five 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.

2. I will continue to teach first year Harvard Medical Students, in the Chemistry and Biology of the Cell Course.

VII. Bibliography (07/01/2000-06/30/2001). BIDMC Faculty are shown in bold type.

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 of Heparin-binding EGF-like Growth Factor: A Unique Role for proHB-EGF in Cell Survival Regulation. *J. Biol. Chem*. 2001;276:30127-32.

Proceedings of Meetings

None Listed

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: 113-20.

2. **DeWolf WC, Gaston SM.** Failure to achieve castrate levels of testosterone during LHRH agonist therapy. *Urology Times* (Editorial) 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* (Editorial) 2001;166:131-2.

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
1. **Gaston SM**, Siddiqui M, **O'Donnell M** and **DeWolf WC.** New Methods for Rapid Assessment of Tumor Invasion of Tumor Invasion of the Prostate Capsule: Tissue Prints and Marker Maps. 95th Annual Meeting of the American Urological Association*, J. Urology* 2000;163 (4): 183.

2. **Gaston SM**, 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 Research* 2001;42: 948.

Susan J. Hagen, Ph.D.

Division of Surgery 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 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 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. Eiji Nakamura, PhD	Postdoctoral Fellow
2. Kimihito Tashima, PhD	Postdoctoral Fellow
3. Tong Wu, MS	Research Assistant
4. Barbara Sheppard, DVM	Research Associate
5. Howard Cho	Student (MIT)

Core Facility

1. Urs Berger, PhD	Instructor in Surgery
2. Daniel Brown, MS	Sr. Research Associate
3. Suzanne White, BS	Histotechnologist

Division of Surgical Research

1. Pat Odom	Administrative Coordinator

III. List of Current Funding

1. "GI Mucosal Barrier in Health and Surgical Disease"
   National Institutes of Health, R01 DK 15681
   Project period: 01/01/1999-12/31/2002
   PI: Susan J. Hagen, Ph.D.

2. "Biology of Alimentary Epithelia in Health and Disease"
   National Institutes of Health, P30 DK34854
   Project period: 1999-04
   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

None

V. Divisional Accomplishments over the Past Year

Research accomplishments

1. I established a new fee-for-service core facility at the BIDMC, which will support research projects relating to *in situ* hybridization techniques. I recruited Dr. Urs Berger, a neuroanatomist, to supervise the facility.

2. The BIDMC submitted, on my behalf, a provisional patent application, #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.

3. I went on a "mini-sabbatical" to the University of California at Irvine. I learned molecular biology in the laboratory of Dr. Andre Ouellette.

Educational activities

1. I participated in the Body Block at HMS as a tutor, gross anatomy instructor, and co-director of the histology laboratory.

2. I participated in the Summer Honors Undergraduate Research Program at HMS by acting as a mentor. I hosted the research of Ms. Ivy Kuofie from Washington University in St. Louis.

3. I organized a symposium for the Harvard Digestive Diseases Center "Imaging Techniques for the New Millennium". I invited 3 speakers to discuss new imaging techniques and vendors with equipment to do hands-on demonstrations.

4. I organized a visiting professor, Dr. Marshall Montrose, for the Harvard Digestive Diseases Center. Dr. Montrose gave a seminar on "Confocal Microscopy Techniques" and visited member laboratories for 2 days.

5. I was asked to be a member of the ZRG1-SS1(02) study section at the NIH which met in September, 2000. This study section reviews applications for shared instrumentation concerning confocal, 2-photon, LCM, and general fluorescence microscopy applications.

Individual accomplishments
Invited speaker (Local)

1. "Life and Death of Gastric Epithelial Cells: Implications for Parietal and Chief Cell Deletion during Infection with *Helicobacter pylori*"
   GI Division, Massachusetts General Hospital
   July 2000

VI. Plans for the Coming Academic Year

Staff changes/recruitments

1. Ms. Peartree will leave the lab and I will hire Ms. Tong Wu as a research assistant.

2. Dr. Barbara Sheppard, a veterinary pathologist at MIT, will join my laboratory 2 days per week to study intestinal metaplasia during *H. pylori* disease.

3. Mr. Howard Chou, a sophomore at MIT, will join my laboratory as a student. Mr. Chou will study intestinal metaplasia during *H. pylori* disease.

Plans for research

1. The competitive renewal of my current RO1 is due on March 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.

Educational plans

1. I plan to attend a workshop from March 9-13, 2002 on FRET microscopy techniques. The workshop is at the W.M. Kneck Center for Cellular Imaging at the University of Virginia.

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

VII. Bibliography (07/01/00-06/30/01)

Original Articles

1. Esteves MI, Schrenzel MD, Marini RP, Taylor NS, Xu S, **Hagen SJ**, Feng Y, Shen Z, Fox JG. *Helicobacter pylori* gastritis in cats with long term natural infection as a model for human disease. *Am. J. Pathol*. 2000;156:709-21.

2. He D, **Hagen SJ**, Pothoulakis C, Chen M, Medina ND, Warny M, LaMont JT. *Clostridium difficile* toxin A causes early damage to mitochondria in cultured cells. *Gastroenterology* 2000;119:139-50.

3. **Hagen SJ**, Wu H, Morrison SW. NH_4Cl inhibition of acid secretion: possible involvement of an apical K^+-channel in bullfrog oxyntic cells. *Am. J. Physiol*. (*Gastrointest. Liver Physiology*) 2000;279:G400-10.

4. Ouellette AJ, Satchell DP, Hsieh MM, **Hagen SJ**, Selsted ME. Characterization of luminal paneth cell α-defensins in mouse small intestine:

Attenuated antimicrobial activities of peptides with truncated amino termini. *J. Biol. Chem*. 2000;275(43): 33969-73.

5. Saubermann LJ, Beck P, DeJong YP, Pitman RS, Ryan M, Exley M, Snapper S, Balk SP, Knauchi O, Motoki K, **Hagen SJ**, Terhorst C, Padolsky DK, Koezuka Y, Blumberg RS. Natural killer-T cell activation by α-galactosylceramide in the presence of CD1d provides protection against colitis in a mouse model. *Gastroenterology* 2000;119: 119-28.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Textbooks
None Listed

Clinical communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts

1. Ayabe T, Satchell DP, Tanabe H, **Hagen SJ**, Wilson CL, Ouellette AJ. Processing and activation of α-defensins in mouse paneth cells. 2001, *Gastroenterology* 120(5): 968A

2. **Hagen SJ**, Ouellette AJ, Yang DX. Identification of inwardly rectifying K+-channels at the apical surface of rat parietal cells: implications for the regulation of gastric acid secretion. 2001, *Gastroenterology* 120(5): 823A.

3. He D, Pothoulakis C, **Hagen SJ**, LaMont JT. Mitochondrial generation of reactive oxygen species (ROS) is necessary for IL-8 release from colonocytes exposed to *Clostridium difficile* toxin A. 2001, *Gastroenterology* 120(5): 1668A.

4. Nakamura E, **Hagen SJ**. Glutamine protects gastric mucosal cells against ammonia-induced cell death: implications for the reduction of mucosal injury during infection with H. pylori. 2001, *Gastroenterology* 120(5): 788.

5. Nakamura E, **Hagen SJ**. Gastric mucosal repair after injury: inhibition of wound repair and restitution by isothiocyanate. 2001, *Gastroenterology* 120(5): 784A.

Ann A. Kiessling, PhD

Division of Urology

I. Narrative Report

Basic research

The long-term goals of my laboratory 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. Hui-Zhong Yin, MD	Senior Research Fellow
2. Bryan Desmarais	Research Technician
3. Julian Fleischman, PhD	Visiting Associate Professor

III. List of Current Funding

1. "Role of the Male Genital Tract in HIV Disease"
   NIH RO1 DK52761
   PI: Dr. Kiessling
   Project Period: 09/01/2000-08/30/2005

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

IV. Applications Submitted and Pending Review/Funding

None

V. Divisional Accomplishments

Research accomplishments

1. The longitudinal genetic and phylogenetic analyses of HIV genes have required both new equipment and new lab approaches. This has taken approximately a year to establish. The work is now proceeding rapidly and we will seek a grant supplement in Jan. 02 in order to add two more HIV genes to our analyses. The first four years of data are currently being analyzed and the results to date indicate targeting male GU tract organs may be essential to adequately control HIV disease in men.

2. Using new methods for tissue fixation, we have identified a novel class of macrophages in male mouse and human tissues that 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.

Educational activities

1. 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. It is sponsored by the Assisted Reproduction Foundation, a non-profit organization founded in Boston.

Individual accomplishments

1. I was recruited to serve on the Ethics Advisory Board for Advanced Cell Technology, the Worcester based company seeking to derive human stem cells. I chair a subcommittee charged with developing guidelines for human egg donation for research purposes. The guidelines were reviewed by the Boston Globe, the Washington Post and the Wall Street Journal in July, 2001.

2. Invited lectures
   Invited Speaker, National Institutes of Health, Laboratory of Dr. Tony Fauci, "HIV infection in the male genital tract"

   Invited Speaker, 2000 TALA National Meeting, "Reproductive Challenges and Options for Couples Living with HIV Disease" Boca Raton, FL

   Invited Speaker, Department of Biology, Boston University, "Biology of Human Immunodeficiency Virus and Risks of Sexual Transmission"

   Invited Speaker, Brandeis University, Department of Biology "Reproductive concerns and sexually transmitted diseases."

   Invited Speaker, New England Medical Center, Division of Reproductive Endocrinology, "Reproductive Options for Couples Living with HIV Disease"

3. Abstracts presented at National or International Meetings
   American Urologic Association annual meeting:
   a) Yakamoto M, Mullins T, Byrn R, Eyre R, Church P, Kiessling A. Seminal plasma, but not seminal vesicle fluid, induces apoptosis in stimulated peripheral blood leukocytes.

   b) Eyre RC, Zheng G, Byrn R, Fitzgerald L, Kiessling A. Evidence for a distinct, isolated reservoir of HIV in semen.

   American Society for Reproductive Medicine annual meeting:
   a) Kiessling AA, Markoulaki S. Inhibiting phosphodiesterase activity to maintain germinal vesicle stage arrest inhibits DNA strand breaks in germinal vesicle stage mouse oocytes.
   b) Kiessling AA, Mullen TE, Kiessling RL, Eyre SJ, Eyre RC. Detection in mice and

men of a novel class of leukocyte/macrophages essential for normal development of reproductive tract tissues.

c) Kiessling AA, Eyre RC, Yin H-Z, Mullen TE, Desmarias B. The burden of human immunodeficiency virus in semen is highly variable and independent of antiviral therapy.

3. Frontiers in Reproduction (NIH sponsored, Boston)
   a) Serta R, Kiessling A. Developmental potential of mouse oocytes matured in serum-free culture.
   b) Markoulaki S, Kiessling AA. Evidence for DNA strand breaks in mouse oocytes mediated by topoisomerase II.

IV. Plans for the Coming Year

Staff changes/recruitments

1. Two additional lab staff will be recruited in Jan '01 to replace two who recently departed.

Plans for research

1. Two grant applications will be submitted:
   a) 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 bio-statistical expertise. Dr. Wei will fill this need.

   b) We will revise our application to the DOD for funds to support work designed to further understand the immunology of the prostate. The original application was criticized for a lack of pilot studies, which we have now nearly completed. Dr. Fleischman will assist with this application and will participate in reviewing information available on the immunology of the seminal vesicles and prostate.

VII. Bibliography (07/01/00-06/30/01)

Original articles

1. Eyre RC, Zheng G and AA **Kiessling**. Multiple drug resistance mutations in human immunodeficiency virus in semen but not blood of a man on antiretroviral therapy. *Urology*. 2000: 55: 591-4.

2. **Kiessling** AA, Markoulaki S. Interaction of gametes with exogenous genes: possible opportunities for incorporation into embryonic genome. *Molecular Reproduction and Development.* 2000;56: 271-4.

3. Yakamoto M, Mullins T, Byrn R, Eyre R, Church P, **Kiessling A**. Seminal plasma induces programmed cell death in peripheral blood mononuclear cells. *AIDS and Human Retroviruses* 2001; in press.

Proceedings of Meetings: none

Reviews, Chapters, and Editorials

1. Kiessling AA. Should Assisted Reproductive Technology be used to aid HIV infected men have children? Contemporary OB/Gyn, July, 2000.

Books, monographs and textbooks: none

Clinical Communications: none

Educational materials: none

Non print materials:

1. **Two forms of embryonic cleavage revealed by time lapse microscopy.** Scott C. Anderson and Ann A. Kiessling. Computer enhanced rendering of time lapse recordings of embryonic cleavages.

Abstracts: none

Sidney Levitsky, M.D.
James 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 with specific concentration on the discriminant and/or coordinate contribution of the two morphologically distinct pathways, namely necrosis and apoptosis, utilizing models of stunning and ischemia/reperfusion injury in the isolated Langendorff perfused rabbit and the *in situ* blood perfused pig heart and determination as to 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 using rabbit heart and pig heart cDNA libraries constructed in our laboratory and using non-redundant cDNA's isolated, sequenced and putatively identified by our laboratory for microarray analysis.

II. Current List of Employees

1. Hidetaka Wakiyama, M.D. — Surgical Fellow, Dept. Of Cardiothoracic Surgery, Kobe University School of Medicine, Kobe, Japan
2. Jianyuan Chai, Ph.D. — Research Associate

III. List of Current Funding

1. "Myocardial Protection: Reperfusion Injury Amelioration "
   NIH RO1 HL 59542
   Collaborating Investigator: Dr. J. McCully
   2000-2005

2. "Myocardial Mitochondrial DNA Deletions In Cardiac Surgery "
   NIH RO1 HL 59542
   PI: Dr. J. McCully
   1998-2001

IV. Applications Submitted and Pending Review/Funding

1. Pig and Rabbit Microarray Construction
   NIH R24PI: Dr. J. McCully

V. Divisional Accomplishments

1. Grant Awarded**:** National Institutes of Health,
   National Heart Lung and Blood Institutes, Public Health Service Grant
   RO1 (HL 59542)
   Myocardial Protection: Reperfusion Injury Amelioration

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

VI. Plans for the Coming Academic Year

1. Staff Changes: Addition of new technician for microarray studies.

2. Research: Submission of R24 grant application for microarray studies (October 1,2001).
   Submission of RO1 grant application for myocardial injury (February 1, 2002)

VII. Bibliography (7/01/2000-6/30/2001)

Original Articles

Faculty Members in Bold Type, Residents and Fellows in Plain Type.

1. Matsuda H, **McCully JD, Levitsky S**. Inhibition of RNA transcription modulates Magnesium Supplemented Potassium Cardioplegia Protection. *Annals of Thoracic Surgery* 2000;70:2107-12.

2. **McCully JD,** Toyoda Y, Ueumatsu M, Stewart RD, **Levitsky S**. Adenosine-enhanced ischemic preconditioning: adenosine receptor involvement during ischemia and reperfusion. *Am. J. Physiol. (Heart Circ. Physiol.)* 2001;280:H591-H602.

3. Sasaki S, Yasuda K, **McCully JD, Palombo JD, LoCicero J.** Perfusion with lipopolysaccharide negative blood eliminates lipopolysaccharide induced lung injury. *Asaio Journal* 2001;47: 45-9.

4. 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. *Annals of Thoracic Surgery* 2001;72:555-63.

5. Toyoda Y, Di Gregorio V, **Parker RA, Levitsky S, McCully JD**. Anti-stunning and anti-infarct effects of adenosine enhanced ischemic preconditioning. *Circulation* 2000;102: 326-31.

6. Toyoda Y, Friehs I, **Parker RA**, **Levitsky S, McCully JD**. Differential role of sarcolemmal and mitochondrial K_{ATP} channels in adenosine enhanced ischemic preconditioning. *Am. J. Phyiol.(Heart Circ. Physiol.)* 2000;279:H2694-H2703.

7. Toyoda Y, **Levitsky S, McCully JD**. Opening of mitochondrial ATP-sensitive potassium channels enhances cardioplegic protection. *Annals of Thoracic Surgery* 2001;71:1281-9.

8. Toyoda Y, Khan S, Weimen Chen, **Parker, RA, Levitsky S, McCully JD**. Effects of NHE-1 Inhibition on Cardioprotection and Impact on Protection by K/Mg Cardioplegia. *Annals of Thoracic Surgery* 2001;72:836-43.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials

1. **McCully JD, Levitsky S.** Mechanism and Selectivity of the Effects of Halothane on Gap Junction Channel Function. *CT Digest* 2000;2(7).

2. **McCully JD, Levitsky S.** Vascular Endothelial Growth Factor 165 Gene Transfer Augments Circulating Endothelial Progenitor Cells in Human Subjects. *CT Digest* 2000; 2(10).

3. **McCully JD, Levitsky S**. A Novel Angiotensin-Converting Enzyme–Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *CT Digest* 2000; 2 (10).

4. **McCully JD, Levitsky S**. Myocardial Ischemia/Reperfusion Injury in NADPH Oxidase–Deficient Mice. *CT Digest* 2000; 2 (12).

5. **McCully JD, Levitsky S**. Reduction of $[Ca^{2+}]_i$ Restores Uncoupled ß-Adrenergic Signaling in Isolated Perfused Transgenic Mouse Hearts**.** *CT Digest* 2001; 3(2).

6. **McCully JD, Levitsky S**. Oxidative DNA Damage and Repair in Experimental Atherosclerosis Are Reversed by Dietary Lipid Lowering. *CT Digest* 2001; 3(6).

7. **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)

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
1. Toyoda Y, **Levitsky S, McCully JD**. Evidence for the modulation of infarct size by mitochondrial K_{ATP} channels during ischemia with cardioplegic protection. *Surgical Forum* 2000;51:108-10.

Frank W. LoGerfo, M.D.

Division of Vascular Surgery

I. Narrative Report

Basic Research

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. Based on these promising foundation studies, the specific objectives of this study are to: 1) determine differential gene expression at prosthetic graft/arterial wall anastomoses compared to quiescent arteries at 2 and 7 day time intervals using cDNA Microarray Technology, 2) complete differential display and Northern blot confirmation of 14 and 30 day graft explants, 3) evaluate the mechanism(s) by which gene or gene products yielded from differential display/cDNA Microarray technology effect the development of AIH, 4) examine the presence of gamma interferon stimulated proteins in hyperplastic tissue, 5) elucidate the role of the proteasome in AIH formation by assessing the effects of specific proteasome inhibitors using cultured vascular smooth muscle and endothelial cells, 6) assess proteasome inhibition on intimal hyperplasia formation in vivo and 7) determine the effects of apolipoprotein J on HUVEC and VSMC migration, proliferation and gene expression in the presence of extracellular matrix. Completion of these specific objectives will result in identification of altered gene expression from acute (48 hours) to delayed (30 days) time periods post-grafting. Additionally, the mechanism(s) by which identified up or down regulated genes alter in vitro vascular smooth muscle and endothelial cell function will be elucidated. Having identified genes such as interferon gamma upregulated protein, apolipoprotein J, osteopontin and human retinoblastoma susceptibility as novel to AIH as well other known genes such as type III collagen, the mechanism(s) by which these genes and gene products are regulated will be determined. Lastly, initial in vivo assessment of inhibition of these gene products (i.e. PA28) will be performed. Thus, 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.

II. List of Current Employees

Name	Title
Frank W. LoGerfo, M.D.	Chief, Division of Vascular Surgery
William C. Quist, M.D., Ph.D.	Assistant Professor of Pathology, Laboratory Director
Matthew D. Phaneuf, B.S.	Assistant Laboratory Director
Mauricio Contreras, M.D.	Instructor in Surgery

Nayan Sivamurthy, M.D.	T32 Research Fellow
David Stone, M.D	T32 Research Fellow
Vaishali Patel, B.S.	Administrative Assistant

III. List of Current Funding

1. "Mechanisms of Prosthetic Arterial Graft Failure"
   NIH R01 HL21796
   PI: Frank W. LoGerfo, M.D.
   Project period: 1978 - 2003
2. Harvard-Longwood Research Training Program in Vascular Surgery (T32)
   N.I.H. - Heart, Lung and Blood Institute
   PI: Frank W. LoGerfo, M.D.
   Project period: 1993 - 2003

3. William J. von Liebig Research Training in Vascular Surgery
   William J. von Liebig Foundation
   PI's: Drs. LoGerfo and Quist
   Project period: 2000-2001

4. Infection-Resistant Polyurethane Biomaterials
   N.I.H. - Small Business Technology Transfer Research Grant (Phase I/II)
   PI: Frank W. LoGerfo, M.D.
   Project period: 2000-2001

5. Infection-Resistant Prosthetic Heart Valve Sewing Cuffs
   N.I.H. - Small Business Innovative Research Grant (Phase I)
   PI: William C. Quist, M.D., Ph.D.
   Project period: 2001

IV. Applications Submitted and Pending Review/Funding

1. "Development of a Biologically-Active Prosthetic Graft" (Phase II Pending)
   N.I.H. - Small Business Technology Transfer Research Grant (Phase I)
   PI: Frank W. LoGerfo, M.D.
   Project period: 2000-2001.

2. Development of a Titanium Surface with Antithrombin Properties (Phase II Pending)
   N.I.H. - Small Business Innovative Research Grant (Phase I)
   PI: William C. Quist, M.D., Ph.D.
   Project period: 2000-2001.

3. "Nanofiber Technology in Small-Diameter Vascular Grafts"
   N.I.H.- Small Business Technology Transfer Research Grant (Phase I)
   PI: William C. Quist, M.D., Ph.D.
   Project period: 2001.

V. Divisional Accomplishments

Research accomplishments

1. *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).

   Current Personnel
   Matthew D. Phaneuf, B.S.

2. *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.

   Current Personnel
   Matthew D. Phaneuf, B.S.

3. *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.

Current Personnel
Matthew D. Phaneuf, B.S.

4. *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.

   Current Personnel
   Matthew D. Phaneuf, B.S.

<u>Patent Disclosures</u>

1. Growth-Promoting Biocompatible Substances and Methods of Use Thereof (09/139,507)

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

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

4. Development of Infection-Resistant Biomedical Materials Using Textile Dye/Material Interactions (09,876,604)

5. Bioactive Surface for Titanium Implants (Provisional Patent)

6. A Novel Small-Diameter Prosthetic Vascular Graft (In Process)

7. Development of a Bifunctionalized Dacron Surface (In Process)

Educational activities

1. *Harvard-Longwood Research Training Program in Vascular Surgery*
   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*
Christopher Longo, M.D.	Beth Israel Deaconess Medical Center
Kurt Rhynhart, M.D.	Brigham and Women's Hospital
Nayan Sivamurthy, M.D	University of Rochester
David H. Stone, M.D.	New York University

2. *William J. von Liebig Research Training in Vascular Surgery for Medical Students*
   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.

Personnel – Summer 2000	*Medical School*	*Lab Assignment*
Daniel Catenacci, B.S. (BWH)	Wayne State	Michael Conte, M.D.
Matthew Doane, B.A. (BIDMC)	University of Rochester	Frank LoGerfo, M.D.
Matthew Heinz, B.A. Ph.D. (CHMC)	Wayne State	Richard Mulligan,
Monet France, B.A. Ph.D., M.D. (BIDMC)	New Jersey Medical School	Christiane Ferran,

Individual accomplishments

1. Invited presentations

Sivamurthy N, Rohan DI, Stone DH, Quist WC, LoGerfo FW. Inhibition of vascular smooth muscle and endothelial cell migration by apolipoprotein J. *Owen H. Wangensteen Surgical Forum, American College of Surgeons*, Chicago, IL, October 2000.

Sivamurthy N, Stone DH, LoGerfo FW, Quist WC. Apolipoprotein J, a protein expressed during intimal hyperplasia, influences cell-matrix interactions. *American Heart Association*, New Orleans, LA, November 2000.

Stone DH, Sivamurthy N, Fitzgerald LM, LoGerfo FW, and Quist WC. Diminished ubiquitin/proteasome expression in anastomotic intimal hyperplasia. *Society of University Surgeons*, Chicago, IL, February 2001.

Sivamurthy N, Stone DH, LoGerfo FW, Quist WC. Apolipoprotein J inhibits the migration and adhesion of endothelial cells in intimal hyperplasia. *Society of University Surgeons*, Chicago, IL, February 2001.

Stone DH, Sivamurthy N, Fitzgerald LM, Quist WC, and LoGerfo FW. Diminished ubiquitin/proteasome expression in anastomotic intimal hyperplasia. *Association of International Vascular Surgeons.* Sestriere, Italy, March 2001.

Sivamurthy N, Stone DH, LoGerfo FW, Quist WC. Apolipoprotein J inhibits the migration and adhesion of endothelial cells in intimal hyperplasia. *United States and Canadian Academy of Pathology*, Atlanta, GA, March 2001.

Stone DH, Sivamurthy N, Fitzgerald LM, LoGerfo FW, Quist WC. 48-hour differential gene expression in anastomotic intimal hyperplasia. *United States and Canadian Academy of Pathology.* Atlanta, GA, March 2001.

Stone DH, Sivamurthy N, Contreras M, Quist WC, LoGerfo FW. Decreased ubiquitin/proteasome expression in anastomotic intimal hyperplasia. *American Heart Association*, Arlington, VA, May 2001.

Stone DH, Sivamurthy N, Contreras M, Quist WC, LoGerfo FW. Sustained decreased expression of the ubiquitin pathway in two distinct time intervals in anastomotic intimal hyperplasia. *Eastern Vascular Society,* Washington, D.C., May 2001.

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, June 2001.

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., May 2001.

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 (ASAIO Fellowship Award).

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, August 2001.

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, August 2001.

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 Biology*, June 2001.

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*, June 2001.

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, Sept 2001.

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

VII. Bibliography (07/01/00-06/30/01)

Original articles

1. Contreras, MA, Quist WC, LoGerfo FW. Porosity versus no-porosity in small arterial ePTFE grafts and its influence on patency and healing. *Microsurg* 2000;20:15.

2. Dempsey DJ, Phaneuf MD, Bide MJ, Quist WC, LoGerfo FW. Optimizing sealing technique for Dacron vascular grafts using an ionic polyurethane: Potential use as a hemodialysis access graft. *Colloids and Surfaces B:Biointerfaces.* 2001; submitted.

3. Faries PL, LoGerfo FW, Hook SC, Pulling MC, Akbari CM, Campbell DR, Pomposelli FB. The impact of diabetes on arterial reconstructions for multilevel arterial occlusive disease. *Am. J. Surg*. 2001;181(3) 251-5.

4. Faries PL, Rohan DI, Takahara H, Wyers MC, Contreras, MA, Quist Wc, King GL, LoGerfo FW. Human vascular smooth muscle cells of diabetic origin exhibit increased proliferation, adhesion, and migration. *J. Vasc. Surg*, 2001;33(3):601-7.

5. Faries PL, Brophy D, LoGerfo FW, Akbari CM, Campbell DR, Spence LD, Hook SC, Pomposelli FB. Combined iliac angioplasyt and infainguinal revasculatization surgery are effective in diabetic patients with multilevel arterial d9isease. *Ann. Vasc. Surg*. 2001; 15(1):67-72.

6. Faries PL, LoGerfo FW, Arora S, Hook S, Pulling MC, Akbari CM, Campbell DR, Pomposelli FB. A comparative study of alternative conduits for lower extremity revascularization: all autogeneous conduit versus prosthetic grafts. *J. Vasc.Surg* 2000;32(6): 1080-90.

7. Hamdy O, Abou-Elenin K, LoGerfo FW, Horton ES, Veves A. Contribution of nerve-axon reflex-related vasodialation to the total skin vasodialation in diabetic patients with and without neuropathy. Diabetes Care 2001; 24(2):344-9.

8. 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;22:463-9.

9. 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; in press.

10. Sivamurthy N, Stone DH, Quist WC, LoGerfo FW. Apolipoprotein J, a protein expressed during intimal hyperplasia, influences cell matrix interactions. *Circulation* 2000;102(18, supplement):3585.

11. Sivamurthy N, Rohan DI, Stone DH, Quist WC, LoGerfo FW. Inhibition of vascular smooth muscle and endothelial cell migration by apolipoprotein *J. Surg. Forum* 2000;LI:367.

12. Sivamurthy N, Rohan DI, Stone DH, Quist WC, LoGerfo FW. Inhibition of vascular smooth muscle and endothelial cell migration by apolipoprotein J. *JACS* 2000;191(4,supplement):S2.

13. Sivamurthy N, Stone DH, LoGerfo FW, Quist WC. Apolipoprotein J inhibits the migration and adhesion of endothelial cells in intimal hyperplasia. *Surgery* 2001;130:204-9.

14. 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;in press.

15. Sivamurthy N, Stone DH, LoGerfo FW, Quist WC. The retinoblastoma gene product is reduced in the formation of anastomotic intimal hyperplasia. *J. Surg Forum.* 2001; in press.

16. Stone DH, Phaneuf MD, Rohan DI, Sivamurthy N, Quist WC, and LoGerfo FW. *In vitro* study of vascular endothelial growth factor in tissue culture for designing improved prosthetic vascular grafts. *Current Surg* 2000; 57(5):506.

17. Stone DH, Sivamurthy N, Contreras M, Fitzgerald L, LoGerfo FW, Quist WC. Sustained decreased ubiquitin/proteasome expression in anastomotic intimal hyperplasia. *J Vasc Surg.* 2001; in press.

18. Stone DH, Phaneuf MD, Rohan DI, Sivamurthy N, Quist WC, LoGerfo FW. Bioengineering improved prosthetic vascular grafts using vascular endothelial growth factor. *J Biomed Mater Res.* 2001; in press.

Proceedings of Meetings
None listed

Reviews, Chapter, and Editorials
None listed

Clinical Communications
None listed

Educational Material
None listed

Nonprint Materials
None Listed

Books, Monographs, and Text Books

1. Bide MJ, Phaneuf MD, Quist WC, LoGerfo FW, Szycher M. Arterial Grafts as Biomedical Textiles. In Bioactive Fibers and Polymers, eds Edwards JV and Vigo TL, American Chemical Society, Washington, D.C.

2. Phaneuf MD, Bide MJ, Quist WC, LoGerfo FW. Merging of biomedical and textile technologies in order to create infection-resistant prosthetic vascular grafts. In Anti-microbial/Anti-infective Materials; Principles, Applications and Devices, eds Sawan SP and Manivannan G, Technomic Publishing, Lancaster, PA.

Abstracts
None listed

Margaret M. Lotz, Ph.D.

Division of General Surgery

I. Narrative Report

Basic Research

My research goal is to determine the mechanism by which c-src and epidermal growth factor receptor work together to regulate matrix metalloproteinase activity and the ensuing invasion of breast cancer cells into the surrounding tissue.

II. List of Current Employees

I collaborate with Dr. Susan Pories

III. List of Current Funding

Present funding is from departmental support.

IV. Applications Submitted and Pending Review/Funding

None identified.

V. Divisional Accomplishments

None identified.

VI. Plans for the Coming Academic Year

1. My plans include submitting grant proposals to the Pardee Foundation and the Department of Defense. These proposals will focus on describing the regulation of breast cancer cell invasion by c-src and epidermal growth factor receptor.

VII. Bibliography (7/1/00-6/30/01)

Original Articles

None Listed

Proceedings of Meetings

None Listed

Reviews, Chapters, and Editorials

None Listed

Books, Monographs, and Text Books

None Listed

Clinical Communications

None Listed

Educational materials

None Listed

Nonprint materials
None Listed

Abstracts
1. Lotz MM, Song CJ and Matthews JB. The role of PKC isoforms in gut epithelial wound healing *in vitro*. *Gastroenterology* 2001;120(5):702A.

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

Transplant Center and
Transplantation and Cellular Immunology Laboratory

I. Narrative Report

Basic Research

Induction of transplantation tolerance with the use of donor bone marrow is studied in a mouse skin allograft model. Two protocols are employed; a) a non-radiation-based regimen with transient immunosuppression by anti-lymphocyte serum and rapamycin and postgraft donor bone marrow injection, and b) a radiation-based regimen consisting of total body irradiation and bone marrow transplantation. Current research focuses on elucidation of the mechanisms underlying tolerance.

Immunotherapy of autoimmune diabetes for induction of disease remission is studied using an NOD mouse model. Treatment of diabetes with islet transplantation is also studied in NOD mice and non-human primates.

II. List of Current Employees

1.	Norihiko Ogawa, M.D.	Research Fellow
2.	Akira Kanamoto, M.D.	Research Fellow
3.	Rita Gottschalk	Research Technician
4.	Taira Zenitani	Summer Student

III. List of Current Funding

1. "Induction of unresponsiveness to allografts"
   NIH 2 RO1 AI14551-19
   PI: Anthony P. Monaco
   07/01/97 - 06/30/02

2. “Induction of tolerance to islet allografts”
   Juvenile Diabetes Research Foundation Center for Islet Transplantation at Harvard Medical School, Project 46
   P.I.: Takashi Maki
   09/01/00 – 08/31/02

3. "A novel diffusion-type bioartificial organ"
   1R21 HL62337
   PI: Takashi Maki
   09/21/98 - 08/31/00

4. "Development of a new diffusion-type bioartificial pancreas"
   Juvenile Diabetes Research Foundation International
   PI: Takashi Maki
   09/01/98 - 08/31/00

IV. Applications Submitted and Pending Review/Funding

1. Juvenile diabetes Research Foundation Center for Islet Transplantation at Harvard Medical School (Takashi Maki)

2. "Treatment of overtly diabetic NOD mice" (Priority Score: 1.84, 18 percentile)
   PI: Takashi Maki
   12/01/01 - 11/30/06

3. "Allograft tolerance after bone marrow transplantation"
   PI: Takashi Maki
   04/01/02 - 03/31/07

4. "Induction of tolerance to allografts in non-human primates" (RFA, Non-human Primate Immune Tolerance Cooperative Study Group)
   PIs: Anthony P. Monaco and Takashi Maki
   04/01/02 - 03/31/07

V. Divisional Accomplishments over the Past Year

Educational activities

1. Takashi Maki gave a course in Harvard Medical School continuing medical education programs entitled "Converging Therapies: The Role of Mixed Chimerism in Transplantation Tolerance and in the Treatment of Hematologic Malignancies" March 18 - 19, 2001, Boston, MA

2. Takashi Maki chaired a scientific session on "Basic Science - Tolerance III" at the joint meeting of the American Society of Transplant Surgeons and American Society of Transplantation, Transplant 2001, May 11 - 16. 2001.

VI. Plans for the Coming Academic Year

Staff changes:

1. Possible addition of research fellows

VII. Bibliography (7/01/00-6/30/01)

Dr. Takashi Maki

Original Articles

1. Hale DA, Gottschalk R, Umemura A, Maki T, Monaco AP. Establishment of stable multilineage hematopoietic chimerism and donor-specific tolerance without irradiation: A unique role for sirolimus. *Transplantation* 2000;69:1242-51.

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* 2001;(in press).

3. Umemura A, Monaco AP, Maki T. Donor MHC class II antigen is essential for induction of tolerance by bone marrow cells. *J Immunol* 2000;164:4452-7.

4. Umemura A, Monaco AP, Maki T. Donor T cells are not required for induction of allograft tolerance in mice treated with antilymphocyte serum, rapamycin, and donor bone marrow cells. *Transplantation* 2000;70:1005-9.

Proceedings of Meetings

1. Monaco AP, Maki T, Hale D, Umemura A, Morita H. The enigma of tolerance and chimerism: Variable role of T cells and chimerism in induction of tolerance with bone marrow. *Trans Proc* 2001;(in press).

2. Umemura A, Monaco AP, Maki T. Essential role of MHC class II antigens in tolerance induction in allogeneic radiation chimera. *Transplant Proc* 2001;33:112.

3. Umemura A, Monaco AP, Maki T. Expression of MHC class II antigen is essential in tolerance induction by donor bone marrow cells in antilymphocyte serum-treated and rapamycin-treated mice. *Transplant Proc* 2000;33:148.

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Textbooks
None Listed

Clinical communications
None Listed

Educational Material (course syllabus)

1. Maki T. Tolerance induction with stem cell transplantation in animal model. in "Converging Therapies: The Role of Mixed Chimerism in Transplantation Tolerance and in the Treatment of Hematologic Malignancies", March 18 - 19, 2001, Boston, MA

Nonprint materials
None Listed

Abstracts

1. Maki T. A novel ultrathin diffusion-type bioartificial pancreas. 18th International Congress of the Transplantation Society, August 27-September 1, 2000, Rome, Italy

Dr. Anthony P. Monaco

Original Articles

1. Gohh RY, Morrissey PE, Madras PN, Monaco AP. Controversies in organ donation: the altruistic living donor. *Nephrol. Dial. Transplant*. 2001;16(3):619-21.

2. Hale DA, Gottschalk R, Umemura A, Maki T, Monaco AP. Establishment of stable multilineage hematopoietic chimerism and donor-specific tolerance without irradiation. *Transplantation* 2000;69:1242-51.

3. 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* 2001;(in press).

4. Monaco AP. Transplantation of the larynx –A case report that speaks for itself. Editorial Comment. *N Engl J Med* 2001;344(22):1712-4.

5. Morrissey PE, Madras PN, Gohh RY, Monaco AP. Laparoscopic versus open donor nephrectomy. *Kidney Int*. 2000;58(6):2596-7.

6. Umemura A, Monaco AP, Maki T. Donor MHC class II antigen is essential for induction of transplantation tolerance by bone marrow cells. *J Immunol* 2000;164:4452-7.

7. Umemura A, Monaco AP, Maki T. Donor T cells are not required for induction of allograft tolerance in mice treated with antilymphocyte serum, rapamycin and donor bone marrow cells. *Transplantation* 2000;70(7):1005-9.

8. Umemura A, Morita H, Monaco AP, Maki T. Dissociation of stable haematopoietic chimerism and allograft tolerance after allogeneic bone marrow transplantation. *J. Immunol* 2001;167(6): 3043-8.

Proceedings of Meetings

1. Monaco AP. Strategies for induction of clinical tolerance. *Trans Proc* 2001;33(1-2):51-2.

2. Monaco AP, Maki T, Hale D, Umemura A, Morita H. The enigma of tolerance and chimerism: Variable role of T cells and chimerism in induction of tolerance with bone marrow. *Trans Proc* 2001;(in press).

3. Umemura A, Monaco AP. Essential role of MHC class II antigens in tolerance induction in allogeneic radiation chimera. *Trans Proc* 2001;33(1-2):112.

4. Umemura A, Monaco AP, Maki T. Expression of MHC class II antigen is essential in tolerance induction by donor bone marrow cell in antilymphocyte serum-treated and rapamycin-treated mice. *Trans Proc* 2001;33(1-2):148.

5. Vincenti F, Monaco A, Grinyo J, Kinkhabwala M, Neylan J, Rosa A, Somberg K. Rapid steroid withdrawal versus standard steroid therapy in patients treated with basiliximab, cyclosporine and mycophenolate mofetil for the prevention of a rejection in renal transplantation. *Trans Proc* 2001;33(1-2):1011-2.

Reviews, Chapters, and Editorials

None Listed

Books, Monographs, and Textbooks
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
None Listed

Edward C. Mun, M.D.

Division of General Surgery

I. Narrative Report

Basic research

My main research effort is currently focused 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 the function of the basolateral K^+ channels. A new area of research interest includes a surgical treatment of type II diabetes in patients with visceral obesity by laparoscopic omentectomy. A proposal outlining this clinical research has been submitted to the IRB committee and the Scientific Advisory committee pending reviews. To pursue both these research interests, my current time is heavily allocated to research activities (75%), and the majority spent in the laboratory. Major efforts are made to summarize and publish our current data from the "Ischemia" project.

II. List of Current Employees

1. Sarah Navina, MD — Research Fellow
2. Jun W. Um, MD — Research Fellow

III. Current List of Funding

1. NIH K08DK02604, #42982
2. BIDMC Discretionary Fund, #38180

IV. Divisional Accomplishments over the Past Year

Educational Activities

1. Undergraduate Courses:
   A. Suture Sessions: for Third Year HMS students, approximately 25 students, 3 hour sessions, twice during the academic year, as an instructor

   B. Introduction to Clinical Medicine (Patient-Doctor II): two HMS students, six to eight 3 hour sessions, preceptor for physical diagnoses, history taking, and oral presentations

   C. Core Clerkship in Surgery: for third year HMS students, total of 8 students, 2 week blocks each, 4-8 hours per week as a preceptor in office, ward rounds, and operating room, Saturday lecture series

2. Graduate Courses/ Residency Programs:
   A. Gold and Blue Team General Surgery Services (Currently Blue only): Five residents, 12 months per year, 20 hours of direct teaching per month including operating room, teaching as an attending surgeon, chief's rounds

3. Postgraduate Courses/ Fellowship Programs: NA
   A. Laparoscopic Gastric Bypass course, University of Pittsburgh, 2 day course

4. CME Courses/ Invited Presentations:
   "Current Status of Obesity Therapy", a presentation to local physicians, Pillar House, Newton

5. Laboratory Supervision:
   Principal Investigator, Surgical Research, 1 research assistant, 1 research fellow, two summer students (undergraduate and medical), 10 hours per week including daily didactic meetings

Research Activities

Currently working on NIH K08 DK 02604 Mentored Career Development Award, received on 12/1/98 for 5 years. The current 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.

Clinical Activities

Conducted gastrointestinal and bariatric surgeries with approximately 350 inpatient and outpatient procedures during the academic year. General surgery call 2-3 times monthly, weekend call every 5-6th weekend. Performed 90% of all obesity surgery cases from the Center for the Study of Nutrition Medicine

Administrative Activities

Gastric Bypass Program weekly meetings

VI. Plans for the Coming Academic Year

Plans for research

1. Increase time in reading the related literature and conducting and supervising experiments in the laboratory. Concentrate on publication of original articles and presentation at the national scientific meetings. Obtain memberships to additional academic research societies. Plan to establish non-clinical, dedicated research day weekly to accommodate the needs. Establish joint research endeavors with Joslin Diabetes Center in basic and clinical research.

VII. Bibliography (07/01/2000-06/30/2001)

Original Articles

1. Yoo J, Nichols A, Song JC, **Mun EC**, Matthews JB. Protein kinase epsilon dampens the secretory response of model intestinal epithelia during ischemia. *Surgery* 2001; 130 (2): 310-8.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
1. **Mun EC**, Blackburn GL, Matthews JB. Current Status of Medical and Surgical Therapy for Obesity. *Gastroenterology* 2001; 120: 669-681.

Books, Monographs, and Editorials
None Listed

Clinical Communications
1. Gastric Bypass Surgery at BIDMC, revised, Patient Information Booklet

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
1. **Mun EC**, Hanson CM, Um JW, Navina S, Yoo J, Matthews JB. PKC translocation during intestinal ischemia: Role of TNF . *Gastroenterology* 2001; 120: A195.

2. Um JW, Matthews JB, Song JC, **Mun EC**. Role of protein kinase C (PKC) in intestinal ischemic preconditioning. *Association of Academic Surgery* 2001.

Aria F. Olumi, M.D.

Division of Urology
(Hire date 9/1/00)

I. Narrative Report

Basic Research

Neoplastic progression is dependent on cellular signals that affect proliferation, cell death, differentiation, angiogenesis, invasion and metastasis. I believe that stromal cells associated with neoplastic epithelial cells play an important role in regulating tumor progression. My plan is to study the biology of stromal-epithelial interactions in both primary and metastatic epithelial tumors.

One of the limitations of working with primary human cells, as I do in my research, is the limited lifespan of primary cells in culture. In order to get past this major limitation I have devised a strategy to expand the lifespan of primary cells in culture, without significant changes to the genomic stability of the primary cells in culture. I have successfully transfected and expanded the lifespan of primary prostate fibroblasts with the over-expression of the human telomerase gene. These cells will be utilized to assess the important signal transduction pathways necessary for tumor progression between the stromal fibroblasts and epithelial cells.

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. We plan to make recommendations to the urologic community regarding the number of required core biopsies for varying prostatic sizes.

II. List of Current Employees

1. Yingewen Xiao, M.S.	Research Assistant
2. Ignacio San Francisco, M.D.	Post-doc fellow (50% effort)

III. List of Current Funding

1. Present funding is from departmental support.

IV. Applications Submitted and Pending Review/Funding

1. NIH- K08 award

2. American Cancer Society – Research Scholar Grant

3. Massachusetts Dept. of Public Health Prostate Research Award

V. Divisional Accomplishments over the Past Year

Educational Activities

1. Director of Graduate Training Program in Urology
   Prepared objectives and guidelines for interns and residents in urology.
   Monthly one-on-one evaluation with interns and residents.

2. Weekly faculty representative for the Harvard Urology Program conferences.

Courses attended

1. Hand assisted laparoscopic nephrectomy sponsored by AUA – September 2001.
2. Cryoablation in prostate and renal cancer; sponsored by Endocare Healthcare Systems, November 2001.

3. Directed an animal laparoscopy program for the Harvard Urology Program at Rhode Island Hospital, 8/01.

4. Plan another animal laparoscopy program for the Harvard Urology Program in 12/01.

5. Teach medical students on a weekly basis with a one-hour didactic session.

6. Core surgery clerkship lecturer for medical students. Topics discussed were BPH and prostate cancer (once every three months).

VI. Plans for the Coming Academic Year

staff changes

1. If one of the above grants is funded, I plan to hire an additional, full-time, post-doc.

plans for research

1. In addition to the above listed grants, I plan to apply for another Department of Defense Prostate Cancer Research Grant.

VII. Bibliography (7/01/00 to 6/30/01)

Original Articles

1. **Olumi AF**, Richie JP, D'Amico AV. Calculated volume of prostate cancer identifies patients with clinical stage T1c disease at high risk of biochemical recurrence after radical prostatectomy: a preliminary study. *Urology* 2000;56:273-7.

2. **Olumi AF**, Weidner N, Presti J Jr. p53 Immunoreactivity correlates with Ki-67 and Bcl-2 expression in renal cell carcinoma. *Urologic Oncology*, 2001;6:63-7.

3. **Olumi, AF**. A critical use of p53 as a marker for management of bladder cancer. *Urologic Clinics of North America*. 2000;27:75-82.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
None Listed

John D. Palombo, D.Sc.

Surgical Metabolism/Nutrition Laboratories

I. Narrative Report

Our current research efforts are directed toward the identification and application of unique dietary fatty acids and fatty acid mixtures that have antiproliferative properties against prostatic and colorectal cancer cells. Growth arrest and restoration of apoptotic mechanisms in prostate and colorectal cancer cells represent two clinically relevant strategies to reduce cancer proliferation. Our recent studies have shown that 18 and 20 carbon polyunsaturated fatty acid isomers with conjugated double bonds inhibit human colorectal and prostate cancer proliferation and induce programmed cell death by caspase-dependent processes. Before clinical intervention trials with conjugated fatty acids are established, a greater understanding of the molecular mechanisms promoting these effects is warranted. One goal is to identify the primary apoptotic pathway (i.e., intrinsic vs. extrinsic) and regulatory oncogenes induced by these fatty acids to promote programmed cell death. A second goal is to design, develop, test and patent an enteral and/or parenteral formulation that will optimally deliver these fatty acids and other potential anticarcinogenic nutrients to the target tissues, using novel structured triglycerides and phospholipids as the vehicles.

II. List of Current Employees

1. Tom Stratton, B.A., Student (volunteer)
2. Patricia Boyce, B.S. Student (volunteer)

III. List of Current Funding

1. PharmaNutrients, Inc., Grant-in-aid for lipid research.
2. Aid for Cancer Research, Grant for equipment and supplies.

IV. Applications Submitted and Pending Review/Funding

1. CapCure Research Award: prostate cancer grant application in review.
2. Hershey Family Funds: prostate cancer grant application in review.

V. Divisional Accomplishments

Educational activities

1. I was a tutor at Harvard Medical School in Chemistry and Biology of the Cell.

Research accomplishments

1. I filed a Patent application through BIDMC OCR: "Methods and compositions for the prevention and/or treatment of colorectal, prostatic or other cancers with conjugated linoleic acid isomers and/or metabolites".

2. I presented a poster at Research Day on 10/27/00. Palombo J.D., DeMichele S.J., Liu J-W., Bistrian B.R., Huang Y-S. Pre-clinical evaluation of the short-term biologic effects of a diet containing γ-linolenic acid (GLA) derived from transgenically modified canola plants.

Individual accomplishments

1. I was a guest professor at the University of Ulm, Germany, April 8 -20, 2001

VI. Plans for the Coming Year

1. I plan to apply for grants from the following funding agencies:
   Ross Products Division, Abbott Laboratories
   Milton Fund, Harvard University
   ConcernFoundation

2. Conduct studies of the efficacy of dietary conjugated fatty acids to inhibit cancer proliferation in vivo using athymic nude mice models.

3. Collaborate with BIDMC investigators to determine role of oncogenes and other regulatory proteins in programmed death of cancer cells exposed to CLA isomers.

4. Acquire additional equipment/funds to continue research efforts.

5. Hire a postdoctoral fellow to implement new research technologies.

VII. Bibliography (07/01/2000-06/30/2001)

Original Articles

1. **Palombo JD**, DeMichele SJ, Liu J-W, Bistrian BR, Huang Y-S. Comparison of growth and fatty acid metabolism in rats fed diets containing equal levels of g-linolenic acid from high g-linolenic acid-canola oil or borage oil. *Lipids* 2000;35:975-81.

Proceedings of Meetings

None Listed

Reviews, Chapters, Editorials

2. **Palombo JD**, DeMichele SJ, Liu J-W, Bobik E, Hastilow C, Chuang L-T, Bistrian BR, Huang Y-S. Growth and fatty acid metabolism in rats fed diets containing high γ-linolenic acid-canola oil, borage oil, or corn oil. In:γ–Linolenic Acid: Recent Advances in Biotechnology and Clinical Applications, Huang Y-S, and Ziboh V-A., Eds. AOCS Press, Champaign, IL. 2001. Chap. 9, p. 79.

Books, Monographs, and Text Books

None Listed

Clinical Communications

None Listed

Educational materials

None Listed

Nonprint materials

None Listed

Abstracts
None Listed

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. In addition, animals are monitored by doppler ultrasound and magnetic resonance imaging during antiangiogenic therapy to look specifically at tumor vasculature.

II. List of Current Employees

1. Tong Zi Research Technician

III. List of Current Funding

1. "Antiangiogenic therapy, a novel therapy for pancreatic cancer"
   Medical Foundation/ Dolphin Trust Grant
   PI: Dr. S. Parangi
   1999-2001

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

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

IV. Applications Submitted and Pending Review/Funding

1. "Spatial and temporal regulation of angiogenesis"
   Program Project grant to the National Cancer Institute
   PI: Dr. Harold Dvorak
   Co-Investigator: Dr. Parangi (project #4)

V. Divisional Accomplishments over the Past Year

1. Became Surgical Staff, Mount Auburn Hospital

2. Named Surgical Director, BIDMC Thyroid Center

3. Named Director of Surgical Grand Rounds

4. Became member of the American Association of Endocrine Surgeons

5. Submitted application to the Society of Surgical Oncology

VI. Plans for the Coming Academic Year

1. Re-submit K08 grant

2. Re-submit Program Project if needed

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

VII. Bibliography (7/1/00-6/30/01)

Original articles

1. D'Avanzo A, **Parangi S,** Morita E, Duh QY, Siperstein AE, Clark OH. Hyperparathyroidism after thyroid surgery and autotransplantation of histologically normal parathyroid glands *J. Amer. College of Surgeons* 2000;190: 546-52.

Proceedings of Meetings

None Listed

Reviews, Chapters, and Editorials

1. **Parangi S.,** Hodin R. "Laparoscopic appendectomy". In: Bland, K, editor. The Practice of General Surgery. W.B. Saunders, 2000, in press.

2. **Parangi S.,** Hodin R. "Abdominal Cavity: Anatomy, structural Anomalies and Hernias" In: Yamada, editor "Textbook of Gastroenterology" 4th edition, Lippinocott, 2001, in press.

Books, Monographs, and Text Books

None Listed

Clinical Communications

None Listed

Educational materials

None Listed

Nonprint materials

None Listed

Abstracts

1. **Parangi S**., Delic M., Lawler J., and Terwilliger E., "Gene therapy with a recombinant adenoassociated virus (rAAV) in an orthotopic model of pancreatic cancer in SCID mice" *Surgical Forum American College of Surgeons, New Orleans, LA*, October 2001.

Susan Pories, M.D.

Division of General Surgery

I. Narrative Report

Basic Research

We are studying breast cancer cell lines in culture, specifically examining the pathways that lead to MMP release. Our hypothesis is that breast cancer progression is in part dependent upon cooperative signaling between the c-src/epidermal growth factor receptor complex (c-src/EGFR) and MMPs.

Clinical Research

We are, in collaboration with Marsha Moses PhD and Carolyn Lamb MD, evaluating the potential of urinary MMPs as a biomarker for breast cancer.

I am also the Principal Investigator for an IRB approved study at the Mount Auburn Hospital looking at Sentinel node biopsy in breast cancer patients.

II. List of Current employees

Dr. Margaret Lotz and I collaborate on all of our laboratory projects and publications.

III. List of Current Funding

1. Present funding is from departmental support.

IV. Applications Submitted and Pending Review/Funding

1. MMPS in Women with Breast Cancer

2. Harvard Medical School's Fund for Women's Health

3. Arimidex For Breast Cancer Risk Reduction, AstraZeneca Pharmaceutical

4. Metalloproteinases as Markers and Determinants of Breast Cancer Progression, Cancer Research Foundation of America

5. Determinants of Breast Cancer Progression, NIH R21

V. Divisional Accomplishments in the Last Year

Research Accomplishments

1. I established a collaboration with Melodie Domurad PhD at Matritech. We are evaluating blood samples for pre-clinical investigations of tumor markers in breast disease.

2. I established a collaboration with Marsha Moses PhD from Children's Hospital and Carolyn Lamb MD from radiation oncology at BIDMC/MAH to evaluate urine samples for tumor markers in breast cancer.

Educational Activities

1. I served as a tutor for the Harvard medical students in the Patient-Doctor III course. This course meets in groups of ten students two hours weekly for six months every year, focusing on ethical and social issues of clinical medicine.

2. I participated in the Core Clerkship course in Surgery for third year Harvard medical students, rotating through the Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, giving a series of 3 hour long lectures on breast disease 6 times a year and 30 medical students each session.

3. I acted as an oral examiner at HMS. This entailed 30 minutes of examination time per student, 5 medical students each exam period, 4 times a year.

4. I was Co-Director of the month-long Tumor Biology course for fourth year HMS students and completely re-designed this course since assuming this position.

5. I was Director of the month long Surgical Oncology elective for fourth year Harvard Medical Students.

6. I supervised medical students and residents in the General Surgery Division. I supervise students and residents in the clinics, wards and operating room at Beth Israel Deaconess Medical Center and Mount Auburn Hospital.

Individual Accomplishments

1. Chair, Professional Advisory Board, The Wellness Community, Newton, Ma

2. Chair, Professional Advisory Board, The Wellness Community, Newton, Ma

3. Co-editor, Resident's Corner, Current Surgery

4. Institute Education Scholar, Shapiro Institute for Education and Research, Harvard Medical School and Beth Israel Deaconess Medical Center

5. Who's Who in America

6. Mentor, Research Science Institute, Center for Excellence in Education

7. Professional Advisory Board, The Virginia Thurston Healing Garden, Harvard, Ma

8. Nominating Committee, Mount Auburn Cambridge Independent Practice Association.

9. I gave an oral presentation at the Society of Surgical Oncology (2001) entitled

"Src Inhibitor PP2 Suppresses Cell Invasion".

10. I gave an oral presentation at the Society of Surgical Oncology (2001) entitled "Invasive Behavior In Breast Cancer Cells".

VI. Plans for the Coming Academic Year

1. Obtain grant funding
2. Continue with teaching activities.

VII. Bibliography (7/1/00-6/30/01)

Original Articles

1. Abner A, Kaufman M, **Pories SE**, Gauvin G. Unusual Presentations of Malignancy, Case 1. Male Inflammatory (?) breast cancer. *J. Clin. Oncology* 2001;19: 3288-93

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational Materials

1. Rechtschaffen L, **Pories, SE.** Psychiatry Curriculum outline. In: Cox, S.S., Pories, W.J.: Surgical Resident Curriculum, 3rd ed. Assoc. of Program Directors in Gen. Surgery., Arlington, VA (1999).

2. The Case of Rosalie Kiley, a teaching case of lung cancer for the Tumor Biology Course.

3. The Case of Andrew Robertson, a teaching case of colon cancer for the Tumor Biology Course.

Non-print Materials (Internet site development)

1. **Pories, S.E.:** Breast Pain, onhealth.com internet site (2000).

2. **Pories, S.E.:** Nipple Discharge, onhealth.com internet site (2000).

3. **Pories, S.E.:** Breast Implant problems, onhealth.com internet site (2000).

4. **Pories, S.E.:** Surgical menopause, onhealth.com internet site (2000).

5. **Pories, S.E.:** When nipple discharge and a breast lump are found together (2000).

Abstracts
None Listed

Frank W. Sellke, MD
Principal Investigator
Cesario Bianchi, MD, PhD
Co-Investigator

Division of Cardiothoracic Surgery
Cardiothoracic Research Laboratories

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 occurs as a consequence of cardiopulmonary bypass and cardioplegia in a porcine model. We use both in vivo and in vitro techniques of isolated microvessels (50-150 μm). 2) To examine the use of therapeutic angiogenesis for the treatment of coronary artery disease (CAD). We propose to define the effects of exogenous growth factor therapy (implantation of a sustained-release devices containing bFGF and/or VEGF) in a hypercholesterolemic porcine model with similarities to human CAD.

II. List of Current Employees

1. Cesario Bianchi, MD, PhD	Instructor in Surgery
2. Tanveer Khan, MD	Research Fellow
3. Marc Ruel, MD	Research Fellow
4. Jiannyi Li, MB	Research Technician
5. Joe M Plum Jr.	Student

III. List of Current Funding

1. "Cardioplegia and Coronary Microvascular Reactivity"
   Agency: NIH/NHLBI
   Type: RO1 HL-46716 Period: 2001-2005
   Principal Investigator: Dr. Sellke

2. "BIDMC-Cardiothoracic Surgery Discretionary Fund"
   P.I.: Dr. Sellke

3. "Angiogenesis in Myocardial Ischemia"
   Agency: NIH/NHLBI
   Type: RO1 HL-53793 Period: 1995-2004
   Principal Investigator: Dr. Michael Simons
   Co-investigator: Dr. Sellke

4. "Stimulation of coronary collaterals in the coronary circulation of human patients"
   Agency: NIH/NHLBI
   Type: P50 HL-56993 SCOR Period: 1997-2002

Principal Investigator: Lewis C. Cantley
Co-investigator: Dr. Sellke

5. "Syndecan function in endothelial cells"
   Agency: NIH/NHLBI
   Type: RO1 HL-62289 Period: 1999-2003
   Principal Investigator: Michael Simons
   Co-Investigator: Dr. Sellke

6. "Effect of PARS inhibitor in myocardial ischemia"
   Agency: NIH/NHLBI Period: 2000-2001
   P.I. 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
   Agency: NIH/NHLBI Period: 2001-2003
   P.I.: Dr. Tanveer Khan, Sponsor: Dr. Sellke

IV. Applications Submitted and Pending Review/Funding

Pending grants (new and resubmission)

1. "Surgical Intramyocardial Angiogenesis in a Swine model of Endothelial Dysfunction" (Priority Score 227, 37.2 Percentile)
   P.I.: Frank W. Sellke
   Resubmit by November 1, 2001.

2. "Cardiopulmonary Bypass and Vascular Permeability"
   P.I.: Frank W. Sellke
   Submit by February 1, 2002.

V. Divisional Accomplishments over the Past Year

New Grants/financial support:

1. Dr. Frank W Sellke R01: "Cardioplegia and Coronary Microvascular Reactivity" was renewed for 4 additional years.

2. Dr. Tanveer Khan will receive a 2-year fellowship from NIH.

3. Dr. Eugenio G. Araujo, DVM, PhD obtained a Ph D in Molecular Biology from the University of Brasilia / Brazil for the work done in the division.
   He received financial support from CAPES/Brazil sponsored by our division.

4. Dr. Renato Faro received financial support through a fellowship from FAPESP / Brazil during his postdoctoral training in our division.

Educational Activities:

1. Dr. Cesario Bianchi has been member of the Teaching Faculty for Harvard Medical School, tutoring first year Harvard Medical / Dental Students (Integrated Human Physiology and Human Body).

VI. Plans for the coming academic year:

Staff changes

1. We are currently recruiting an additional research assistant and a postdoctoral research fellow. We are also actively interviewing students from MIT and Harvard Medical/ Dental Schools.

VII. Bibliography (7/01/00-6/30-01)

Original Articles (BIDMC faculty are shown in bold)

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: 182-91.

2. Araujo EG, **Bianchi C**, Sato K, Faro R, Li XA, **Sellke FW**. Inactivation of the MEK/ERK pathway in the myocardium during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2001; 121: 773-81.

3. Araujo EG, **Bianchi C**, Sato K, **Sellke FW**. Changes in activities of 44/42 MAP kinases by cardiopulmonary bypass. *Surgical Forum* 2000; LI: 142-44.

4. **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-I24.

5. **Bianchi C, Sellke FW**. COS cells expression cloning of tyrosine-phosphorylated proteins by immunocytochemistry. *J Histochem Cytochem* 2000; 48: 1097-102.

6. **Cohn WE, Weintraub RM, Sellke FW**. Innovative Minimally Invasive Surgical Approaches to Coronary Revascularization in the High Risk Patient. *Heart Surg Forum* 2000; 3: 185-8.

7. Dessy C, Matsuda N, Hulvershorn J, Sougnez CL, **Sellke FW, Morgan KG**. Evidence for involvement of the PKC-alpha isoform in myogenic contractions of the coronary microcirculation. *Am J Physiol Heart Circ Physiol* 2000; 279: H916-23.

8. **Laham RJ, Post M, Sellke FW, Simons M**. Therapeutic Angiogenesis Using Local Perivascular and Pericardial Delivery. *Curr Interv Cardiol Rep* 2000; 2: 213-7.

9. **Laham RJ**, Rezaee M, **Post M**, Novicki D, **Sellke FW, Pearlman JD, Simons M**, Hung D. Intrapericardial delivery of fibroblast growth factor-2 induces neovascularization in a porcine model of chronic myocardial ischemia. *J Pharmacol Exp Ther* 2000; 292: 795-802.

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

11.**Li J, Post M**, Volk R, Gao Y, Li M, Metais C, Sato K, Tsai J, **Aird W, Rosenberg RD, Hampton TG, Sellke F,** Carmeliet P, **Simons M**. PR39, a peptide regulator of angiogenesis. *Nat Med* 2000; 6: 49-55.

12.Matsuda N, **Morgan KG, Sellke FW**. Effects of pinacidil on coronary $Ca(^{2+})$-myosin phosphorylation in cold potassium cardioplegia model. *Am J Physiol Heart Circ Physiol* 2000; 279: H882-8.

13.Matsuda N, **Sellke FW**. Regulation of coronary myoplasmic Ca(2+)-myosin light chain phosphorylation pathway and vasomotor tone: hyperpolarizing versus depolarizing cardioplegia. *Surgery* 2000; 128: 185-91.

14.Metais C, **Bianchi C, Li J, Simons M, Sellke FW**. Serotonin-induced human coronary microvascular contraction during acute myocardial ischemia is blocked by COX-2 inhibition. *Basic Res Cardiol* 2001; 96: 59-67.

15.**Park KW**, Dai HB, Comunale ME, Gopal A, **Sellke FW**. Dilation by isoflurane of preconstricted, very small arterioles from human right atrium is mediated in part by $K(^{+})$-ATP channel opening. *Anesth Analg* 2000; 91: 76-81.

16.**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: 990-6.

17.**Park KW**, Sato K, Dai HB, Comunale ME, **Sellke FW**. Epithelium-dependent bronchodilatory activity is preserved in pig bronchioles after normothermic cardiopulmonary bypass. *Anesth Analg* 2000; 90: 778-83.

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

19.Sato K, **Laham RJ, Pearlman JD**, Novicki D, **Sellke FW, Simons M, Post MJ**. Efficacy of intracoronary versus intravenous FGF-2 in a pig model of chronic myocardial ischemia. *Ann Thorac Surg* 2000; 70: 2113-8.

20.Sato K, Li J, Metais C, **Bianchi C, Sellke F**. Increased pulmonary vascular contraction to serotonin after cardiopulmonary bypass: role of cyclooxygenase. *J Surg Res* 2000; 90: 138-43.

21. Sato K, Wu T**, Laham RJ**, Johnson RB, **Douglas P, Li J, Sellke FW**, Bunting S, **Simons M, Post MJ**. Efficacy of intracoronary or intravenous

VEGF165 in a pig model of chronic myocardial ischemia. *J Am Coll Cardiol* 2001; 37: 616-23.

22. Schermerhorn ML, Tofukuji M, Khoury PR, Phillips L, Hickey PR, **Sellke FW**, Mayer JE, Jr., Nelson DP. Sialyl lewis oligosaccharide preserves cardiopulmonary and endothelial function after hypothermic circulatory arrest in lambs. *J Thorac Cardiovasc Surg* 2000; 120: 230-7.

23. **Simons M**, Bonow RO, Chronos NA, **Cohen DJ**, Giordano FJ, Hammond HK, **Laham RJ**, Li W, Pike M, **Sellke FW**, Stegmann TJ, Udelson JE, Rosengart TK. Clinical trials in coronary angiogenesis: issues, problems, consensus: An expert panel summary. *Circulation* 2000; 102: E73-86.

24. Tofukuji M, Stahl GL, Metais C, Tomita M, Agah A, **Bianchi C, Fink MP, Sellke FW**. Mesenteric dysfunction after cardiopulmonary bypass: role of complement C5a. *Ann Thorac Surg* 2000; 69: 799-807.

25. 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: 735-42.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Clinical Communications
None Listed

Educational Materials
None Listed

Nonprint Materials
None Listed

Abstracts
None Listed

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

THE PANCREAS GROUP
Division of General Surgery

I. Narrative Report

Our group's work focuses on the exocrine pancreas. Two general areas of investigation are being pursued -- stimulus-secretion coupling in the exocrine pancreas and the cellular events which underlie the development and govern the severity of acute pancreatitis. Our studies on pancreatitis deal with both the early and the late events involved in that disease. The early events that we are exploring include receptor-mediated events involved in supra-maximal secretagogue stimulation as well as a number of other events including activation of phosphoinositide-3-kinase (PI3K), mis-directed intracellular trafficking of exportable and lysosomal enzymes, and the acinar cell generation of a variety of cytokines/chemokines. The late events of pancreatitis that we are exploring primarily involve those which couple acute pancreatitis to the development of pancreatitis-associated lung injury—i.e. the generation and role of inflammatory mediators including cytokines, chemokines, and adhesion molecules. In addition, we are examining the role of inflammatory cells (primarily neutrophils) and of cyclo-oxygenase 2 in this process.

II. List of Current Employees

1. Michael Steer MD	Professor of Surgery
2. Ashok Saluja PhD	Associate Professor of Surgery
3. Lakshmi Bhagat PhD	Instructor in Surgery
4. Vijay Singh MD	Research Fellow
5. Munira Sarania MD	Research Fellow

III. List of Current Funding

1. R01 DK 31396 (NIH): Acute Pancreatitis
2. RO1 DK58694 (NIH) Heat Shock Proteins and Pancreatitis
3. Industry grant (Bayer): The role of Alpha-2 Macroglobulin in Pancreatitis

IV. Applications Submitted and Pending Review

None

V. Divisional Accomplishments over the Past Year

Dr. Steer

1. Keynote Speaker, Lovelace Conference on Lung Diseases, Santa Fe, New Mexico
2. Visiting Professor, Department of Surgery, University of Bergan, Norway
3. Keynote Speaker, Gastro2000, Lapland, Finland
4. Visiting Professor, Department of Surgery, University of Helsinki,

Finland
5. Visiting Professor, Department of Internal Medicine, Korea University Medical Center, Seoul, Korea.
6. Signal Division, Celgene Pharmaceuticals Symposium on Signal Transduction and inflammation, San Diego, CA
7. Course Faculty, Postgraduate Course, SSAT, 2001.
8. Keynote Speaker, 250th Anniversary of the Death of Abraham Wirsung, Wittenberg, Germany.
9. keynote Speaker: Japanese Pancreatic Society meeting, Fukuka, Japan

Dr. Saluja

1. Invited Presentation during European Pancreatic Club Meeting in Kiel, Germany, entitled, " Heat shock Proteins and Pancreatitis"

2. Organized and Moderated a focus group on NIH funding in pancreatic research during American Pancreatic Association Meeting in Chicago, IL

3. State of the Art Presentation at Indian Society of Gastroenterologists, New Delhi, India, entitled, "Pathophysiology of Acute Pancreatitis"

4. Invited Presentation during the Japan Pancreas Society meeting in Kitakyushu, Japan, entitled, " Recent Progress in the mechanism of Acute Pancreatitis"

5. Seminars in Medicine, "Mechanisms of Onset of Acute Pancreatitis- the Role of Calcium, Cytokines, Heat Shock Proteins and other Culprits" Muenster, Germany

6. Medical Seminars, " Pathogenesis of Acute Pancreatitis", Christian medical College, Ludhiana, India

7. Research Seminar, "Some Recent Insights into Pancreatitis", Torrent Research Center, Ahemdabad, India

8. Surgical Grand Rounds, "Pathogenesis of Acute Pancreatitis", Sapporo, Japan

V. Plans for coming year:

Continue as previously.

VII. Bibliography (07/01/2000-06/30/2001)

Original Articles

1. Bhagat L, Singh VP, Hietaranta AJ, Agrawal S, Steer ML, Saluja AK. Heat shock protein 70 prevents secretagogue-induced cell injury in pancreas by preventing intracellular trypsinogen activation. *J Clin Invest.* 2000;106:81-9.

2. Bhatia M, Saluja AK, Singh VP, Frossard JL, Lee HS, Bhagat L, Gerard C, Steer ML. Complement factor C5A plays an anti-inflammatory role in pancreatitis and pancreatitis-associated lung injury. *Am J. Physiol.* 2001;280:G974-78.

3. Gao Y, Lecker S, Post MJ, Hietaranta AJ, Li J, Volk R, Li M, Sato K, Saluja AK, Steer ML, Goldberg AL, Simons M. Inhibition of ubiquitin-proteasome pathway-mediated IkBa degradation by a naturally occurring antibacterial peptide. *J Clin Invest*. 2000;106:439-48.

4. Hietaranta AJ, Saluja AK, Bhagat L, Singh VP, Song AM, Steer ML. Relationship between NF-kappa B and trypsinogen activation in rat pancreas after supramaximal caerulein stimulation. *Biochem Biophys Res Comm.* 2001;280:388-95.

5. Hietaranta AJ, Singh VP, Bhagat L, van Acker GJD, Song AM, Mykoniatis A, Steer ML, Saluja AK. Water immersion stress prevents caerulein-induced pancreatic acinar cell NFkB activation by attenuating caerulein-induced intracellular Ca2+ changes. *J Biol Chem*. 2001;276:1874-7.

6. Lee HS, Bhagat L, Frossard JL, Hietaranta AJ, Singh VP, Steer ML, Saluja AK. Water immersion stress induces heat shock protein 60 expression and protects against pancreatitis in rats. *Gastroenterology* 2000;119: 220-9.

7. Sing VP, Saluja AK, Bhagat L, Hietaranta AJ, Song A, Mykoniatis A, van Acker GJD, Steer ML. Serine protease inhibitor causes F-actin redistribution and inhibition of calcium-mediated secretion in pancreatic acini. *Gastroenterology* 2001;120: 1818-27.

8. Singh VP, Saluja AK, Bhagat L, van Acker GJD, Song AM, Soltoff SP, Cantley LC, Steer ML. Phosphatidylinositol-3-kinase plays a critical role in mediating intrapancreatic activation of trypsinogen and regulating the severity of pancreatitis. *J. Clin Invest*. 2001;In press.

<u>Proceedings of meetings</u>

1. Steer ML. Relationship between pancreatitis and lung diseases. Respiration Physiology in press 2001.

<u>Reviews, chapters, editorials</u>

1. Moon MR, Luchette FA, Steer ML. Acute Pancreatitis. Manual of Intensive Care Medicine 3rd edition, Rippe, Cerra and Irwin eds, 2000.

2. Steer ML. Experimental Models of Pancreatitis in Surgical Research, Souba and Wilmore (eds), 2001.

3. Steer ML, Saluja AK. The role of pro-inflammatory factors in

pancreatitis and associated lung injury. In Cytokines and Cell Homeostasis in the Gastrointestinal Tract. Andus A et al eds, Kluher 2000 p 372-78.

Non-print materials

1. Steer ML. Cystic lesions of the pancreas. Up To Date in Gastroenterology. S. Chopra and T Lamont eds, Vol 8 #2, 2000.

2. Steer ML, Pathology of pancreatic cancer. Up To Date In Gastroenterology. S. Chopra and T Lamont eds, Vol 8 #2, 2000.

3. Steer ML. Clinical manifestations and diagnosis of exocrine pancreatic cancer. Up To Date in Gastroenterology S. Chopra and T Lamont eds, Vol 8 #2, 2000.

4. Steer ML, Management and prognosis of exocrine pancreatic cancers. Up To Date in Gastroenterology. S Chopra and T Lamont eds, Vol 8 #2, 2000.

Abstracts

1. Bhagat L, Hietaranta AJ, Singh VP, Song AM, Mykoniatis A, van Acker GJD, Pan A, Steer ML, Saluja AK. Water immersion stress prevents trypsinogen activation in the caerulein model of pancreatitis by altering intracellular calcium. *Pancreas* 2000;21: A432.

2. Bhagat L, Saluja AK, Singh VP., Song AM, van Acker G, Mykoniatis A, Steer Ml. Role of actin cytoskeleton in caerulein-induced intra-acinar cell activation of trypsinogen in an in vitro model of pancreatitis. *Gastroenterology* 2001;120: A236.

3. Bhagat L, Agrawal S, Singh VP, Song AM, van Acker G, Mykoniatis A, Steer ML, Saluja AK. HSP 70 antisense oligonucleotide administration prevents the thermal stress-induced expression of HSP70 in rat pancreas and abolishes the thermal stress-induced protection against caerulein-induced pancreatitis. *Gastroenterology* 2001;120: A537.

4. Bhagat L, Saluja AK, van Acker G, Singh VP,. Song A, Mykoniatis A, Steer ML. Lysosomal hydrolase/digestive zymogen co-localization and intra-acinar cell activation of trypsinogen: which is the horse and which is the cart? *Gastroenterology* 2001;120: A540.

5. Hietaranta AJ, Bhagat L, Singh VP. Song A, Mykoniatis A, van Acker GJD, Steer ML, Saluja AK. Prior water immersion stress prevents caerulein-induced NFkB activation in pancreatic acinar cells by altering calcium dependent signalling. *Pancreas* 2000;21: A437.

6. Singh VP, Ghagat L, Hietaranta AJ, Song AM, Pan A van Acker GJD, Mykoniatis A, Steer AM, Saluja AK. NFkB independent upregulation of Mob-1 mRNA expression in rat pancreas following supramaximal stimulation with caerulein. *Pancreas* 2000;21: A480.

7. Singh VP,. Saluja AK, Bhagat L, Hietaranta AJ, Song AM. Pan A, van Acker GJD, Mykoniatis A, Steer ML. Serine protease inhibition causes apical F-actin redistribution and inhibition of Ca2+ mediated secretion in rat pancreatic acinar cells. *Pancreas* 2000;21: A480.

8. Singh VP, Saluja AK, Bhagat L, Mykoniatis A, van Acker G, Song A, Steer ML. Regulation of CXC-ELR chemokine expression in mouse pancreatic acini after supramaximal stimulation with caerulein. *Gastroenterology* 2001;120:A132.

9. Singh VP, Saluja AK, Bhagat L, van Acker G, Song A, Mykoniatis A, Steer ML. Secretagogue (caerulein)-induced intrapancreatic activation of trypsinogen is mediated by protein kinase C (PKC), phosphoinositide-3-kinase (PI3K) and tyrosine kinases (TKs). *Gastroenterology* 2001;120:A337.

10. Singh VP, Saluja AK, van Acker G, Bhagat L, Song A, Mykoniatis A, Steer ML. Inhibition of phosphoinositide-3-kinase (PI3K) protects against both caerulein-induced and taurocholate-induced acute experimental pancreatitis. *Gastroenterology* 2001;120: A540.

11. Song A, Bhagat L, Hietaranta AJ, Singh VP, Mykoniatis A, van Acker GJD, Pan A, Saluja AK, Steer ML. Macrophage migration inhibitory factor (MIF) does not have a significant effect on the severity of caerulein-induced pancreatitis and associated lung injury in mice. *Pancreas* 2000;21:A481.

12. Song AM, Bhagat L, Singh VP. Mykoniatis A, van Acker G, Saluja AK, Steer ML. Inhibition of cyclooxygenase-2 (COX-2) enzyme ameliorates the severity of caerulein-induced pancreatitis and associated lung injury in mice. *Gastroenterology* 2001;120:A537.

13. Van Acker GJD, Saluja AK, Bhagat L, Hietaranta AJ, Singh VP,. Song AM, Mykoniatis A, Pan A, Steer ML. Relationship between intrapancreatic activation of trypsinogen and intrapancreatic sequestration of neutrophils following supramaximal stimulation with caerulein in mice. *Pancreas* 2000;21:A486.

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Aristidis Veves, M.D.

Joslin-Beth Israel Deaconess Foot Center
and Microcirculation Lab

I Narrative Report

Clinical Research

My research goals are to develop a high quality research unit that will be a world leader in the fields of microvascular disease, wound healing and peripheral neuropathy in diabetes. In order to achieve this, I aim to secure research funding from government and other non-profit organizations. Furthermore, my aim is to make long-term strategic alliances with major pharmaceutical and biotech companies that will allow our unit to fully participate in the development of new products. Finally, I plan to organize educational programs that will appeal to physicians from all over the world and will help our unit to be recognized as the leading research facility worldwide.

II. List of Current Employees

Junior Faculty

Hau T Pham, DPM (employed 20% of his time for research activities).

Thanh T Dinh, DPM (employed 20% of her time for research activities).

Research Fellows

Antonella Caselli, MD. Dr Caselli is a visiting Research Fellow from Italy and is a trained endocrinologist. She is in her second (and last) year as research fellow in my unit.

Panayiotis Economides, MD. Dr Economides is a clinical fellow at Joslin and he is actively involved in all the studies I do in collaboration in Joslin. Part of his salary is coming from these projects

Two third-year podiatry (Jeremy Rich and Jane Brady) residents are receiving research training

Technicians

Caitlin Sparks and Elizabeth Tiani are research coordinators at Joslin Diabetes Center and are responsible for the projects I conduct in collaboration with Dr. Edward Horton.

III. List of Current Funding

1. American Diabetes Association, Clinical Research Grant. Principal Investigator for the BIDMC. (PI for the whole grant: E.S. Horton, Joslin diabetes Center). "*Endothelial dysfunction in subjects with glucose intolerance"*.

2. Parke-Davis. Principal Investigator. (Investigator Initiated Research Additional funding was provided by a NIH grant to Beth Israel Deaconess Clinical Research Center). "*Effect of insulin-sensitizing agent troglitazone on the endothelial function of the micro- and macro-vasculature of subjects at risk of type 2 diabetes and type 2 diabetic patients with or without vascular complications".*

3. Johnson and Johnson. Principal Investigator. *"A comparison of the UK-97-005 Dressing versus saline moistened gauze in the management of diabetic foot ulcers".*

4. Juvenile Diabetes Foundation International. Principal Investigator. "*The effect of vitamin E on the left ventricular function and the endothelial function of the micro- and macro-circulation of type 1 and 2 diabetic patients".*

5. Pfizer Inc. Principal Investigator. (Investigator Initiated Research. Additional funding was provided by a NIH grant to Beth Israel Deaconess Clinical Research Center). "*Effect of Atorvastatin on the endothelial function in Diabetes and pre-Diabetes*".

6. Pfizer Inc. Co- Investigator. Responsible for vascular reactivity tests in BIDMC. (Investigator Initiated Research. Additional funding was provided by a NIH grant to Beth Israel Deaconess Clinical Research Center). "*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".*

7. ConvaTec. Principal Investigator. "*A prospective, randomized, comparative parallel study of Hyalofill wound dressing in the management of indolent diabetic foot ulcers".*

8. Organogenesis Inc. Principal Investigator. "*Vitrix for the treatment of deep diabetic foot ulcers".*

9. Biochemics, Principal Investigator*: "Comparison of skin vascular reactivity to different vasodilatory substances in diabetic patients and healthy subjects".*

10. NIH. Co-Investigator, 5% effort. Principle Investigator: Jason D. Harry, Sensory Technologies Inc. Type: SBIR. Period: 07/01/01-12/31/01 "*Restoring diabetic tactile sense with mechanical noise".*

IV. Applications Submitted and Pending Review/Funding

1. Principle Investigator: Aristidis Veves, MD
Agency: American Diabetes Association
Period: 1/1/02-31/12/04
"*Vascular functional abnormalities and diabetic foot ulceration*".

2. Principle Investigator: Aristidis Veves
Agency: Juvenile Diabetes Research Foundation

Period:02/01/01-01/31/02
"*MRI techniques in measuring vascular function of the diabetic foot*".

3. Pilot & Feasibility Program in Diabetes, Endocrinology & Metabolism
   Principle Investigator: Robert Greenman
   Agency: NIH
   Type: RO1 PA-99-036
   Period:07/01/01-6/30/03

4. Sigma-Tau Research, Inc. Principal Investigator: "*Safety and efficacy of propionyl l-carnitine in peripheral arterial disease (intermittent claudication) as assessed by a fixed treadmill protocol in a diabetic population*". A multi-center study.

5. Welfide International Corporation. Principal Investigator. (Part of the proposal is Investigator Initiated Research.). "*A double-blind, randomized, placebo-controlled study to assess the efficacy and safety of Circulase™ for the treatment of critical leg ischemia*".

V. Divisional Accomplishments

Research accomplishments

During the last academic year we initiated five new clinical trials of a total value of $1,133,000.00. Three of these clinical trials are investigator initiated (Pfizer Atorvastatin and Quinapril and Biochemics). Additional NIH funding from the GCRC has been secured for the first two of them. Furthermore, in studies that were initiated in previous years (Parke Davis Troglitazone and Johnson and Johnson), recruitment has been successfully completed and the results have been analyzed and submitted for publication.

Educational activities

1. Lectures

2000	Diabetic Neuropathy: New Options at *Emerging Clinical Issues in Managing Diabetes.* Harvard Medical School, October 2000
2000	Emerging technologies in Wound Care at *Diabetic Foot Management*. Harvard Medical School, November 2000
2000	Endothelial function in diabetic neuropathy. Joint symposium – Neurodiab/Diabetic Foot Study Group, European Association for the Study of Diabetes. Rome, Italy, September 2000
2000	New directions in the management of diabetic foot ulcers: Advances in Diabetic Foot Care: Utilization of Bioengineered Skin. Industry sponsored symposium: New concepts in the management of diabetic foot ulcers.

	European Association for the Study of Diabetes 36th Annual Meeting. Jerusalem, Israel, September 2000.
2000	Neuropathy: New concepts in Evaluation and treatment. Joint educational program by American Diabetes Association- American Podiatric Medical Association. Orlando, FL, January 2001
2001	Diabetic Neuropathy *At: Medical Grand Round, University of Arkansas for Medical Sciences*. March 2001
2001	A comparison of a new topical treatment, Promogran® versus standard treatment in the management of diabetic foot ulcers. German Wound Healing Society. Ulm, Germany, June 2001

Courses given

I am responsible for organizing *The Joslin-Beth Israel Deaconess Foot Center Preceptorship* that is sponsored by Novartis Pharma AG. The main purpose of the preceptorship is to train physicians in the management of the diabetic foot. Three preceptorships were organized during the academic year. Nine doctors from Europe attended each preceptorship that lasted two days.

Individual accomplishments

1. I was invited to give a lecture at the Joint symposium of the Neurodiab and Diabetic Foot Study Groups of the European Association for the Study of Diabetes at Rome, Italy, September 2000.
2. 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 have also participated in five center grant applications that were hold on separate occasions.
3. I was the Chairman of the Wound Care Device Expert Meeting that was organised by Johnson and Johnson at London, UK in May 2001.
4. I was asked to chair two sessions at the American Diabetes Association 61st annual meeting at Philadelphia, June 2000.
5. My presentation was awarded the second prize for clinical studies at the Symposium on Advanced Wound Care and Medical Research Forum in Las Vegas, Nevada, May 2001.
6. I have been invited to the scientific advisory boards of Abbot Inc., Biogen, Inotek Inc, Novartis Pharma, Johnson & Johnson Medical, Parke-Davis Zenarestat Advisory Board (1999-2000) and Welfide International Corporation.
7. I have been serving as an Associate Editor in the journal: *Wounds: A Compendium of Clinical Research and Practice (2000-)*. I have been asked to act as a peer reviewer for the journals: *New England Journal of Medicine,* the

Lancet, Diabetes, Diabetologia, Diabetes Care Diabetic Medicine, Journal of Diabetes and its Complications, Archives of Physical Therapy, JAMA, Clinical Science, The Journal of Clinical Investigation and the American Journal of Hypertension.

VI. Plans for the Coming Academic Year

1. In collaboration with the divisions of Vascular Surgery (Frank LoGerfo) Podiatry (John Giurini, Hau Pham), Radiology (Neil Rofsky, Robert Greenman), Cardiology (Peter Danias) and Emergency Medicine (Jon Buras, Wendy Buras) we plan to submit two to three NIH grant applications in response to two recent RFA that are related to diabetes and microvascular disease. The deadline for these RFA's is mid-February 2002.
2. The effort of ensuring research funding from the pharmaceutical industry will continue. My priority is to ensure funds for Investigator Initiated Research. The initiation of the Welfide protocol is one of the first priorities. Additional research projects are currently negotiated with other pharmaceutical companies.
3. I plan to continue my efforts to make long-term strategic alliances with the pharmaceutical industry. Thus, I am currently in discussion with Novartis Pharma and Johnson & Johnson to develop educational programs in the area of the diabetic foot and diabetes and cardiovascular disease.
4. I also plan to continue my collaboration with small, start up companies that are involved in the development of exciting novel ideas. My collaboration with Sensory Technologies has already resulted in a SBIR Phase I NIH grant and we plan to expand the collaboration and apply for a substantially bigger new NIH grant. My collaboration with BioChemics has already results in a small ($40,000.00) grant from them and we plan to further expand the collaboration in the future. This collaboration will involve the biomechanics unit of Boston University. An NIH grant application (total budget of $2,000,000.00) is expected to be submitted by the end of September 2001. Finally, in collaboration with Sealtek, BioChemics Inc and Inotek Inc. we plan to develop a new technique that will deliver nitric oxide in the wound area. The main aim of these collaborations is to align with companies that are in their very early stages so that in case the succeed there is a substantial benefit for this unit.
5. The continuation of the educational preceptorships that attract physicians from the USA and all over the world is another of my priorities. I am also collaborating with the International Hospital of the Hospital (Antoine Kaldany) in order to expand the program.
6. I am exploring the possibility of having visiting fellows from prestigious universities outside USA who will spend one year of training in our unit in a similar way Antonella Caselli (the current Fellow) did.

7. I am member of a three-person committee that is responsible for the organization and conduction of a seminar entitled: Wound healing. Science and Industry. The main purpose of this meeting is to bring together the world-leading physicians and industries in the field of diabetes and wound healing.

VII. Bibliography (7/1/00-6/30/01)

Original articles

1. Hamdy O, Abou-Elenin K, LoGerfo FW, Horton ES, **Veves A**. Contribution of nerve-axon reflex-related vasodilation to the total skin vasodilation in diabetic patients with and without neuropathy. *Diabetes Care* 2001; 24(2):344-9.

2. Malik RA, **Veves A**, Walker D, Siddique I, Lye RH, Schady W, Boulton AJ. Sural nerve fibre pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. *Acta Neuropathol* 2001;101(4):367-74.

3. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, **Veves A**. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000;23(5):606-11.

4. Rich J, **Veves A**. Forefoot and Rearfoot Plantar Pressures in Diabetic Patients: Correlation to Foot Ulceration. *Wounds* 2000;12:82-87

5. **Veves A**, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001; 24(2):290-5.

6. **Veves A**, King GL. Can VEGF reverse diabetic neuropathy in human subjects? *J Clin Invest.* 2001; 107(10):1215-8.

Reviews, Chapters, Editorials.

1. Caballero AE, Lim SC, Horton ES, **Veves A**. Vascular abnormalities in the prediabetic stage. In: Johnstone MT, **Veves A**: Diabetes and Cardiovascular Disease. Humana Press, Totowa, NJ, 2001, pp65-80

2. Economides PA, **Veves A**. Etiopathogenesis of Foot Ulceration in Diabetes. Wounds 2000;12 (Suppl B): 1B-6B

3. Hamdy O, Abou-Elenin K, **Veves A**. Microcirculation of the diabetic foot. In: Johnstone MT, **Veves A**: Diabetes and Cardiovascular Disease. Humana Press, Totowa, NJ, 2001, pp 431-446

4. **Pham H**, Rich J, **Veves A.** Wound Healing in Diabetic Foot Ulceration**.** Wounds 2000;12: 79-82

Editorship in Supplements

1. Veves A, Falanga V. Diabetic Foot Ulcers: Prevention and Treatment. Wounds 2000;12: Supplement B

Editorship in Books

1. **Johnstone MT**, **Veves A**: Diabetes and Cardiovascular Disease. Humana Press, Totowa, NJ, April 2001
2. **Veves A, Giurini JM**, **LoGerfo FW**: The Diabetic Foot: Medical and Surgical Management. Humana Press, Totowa, NJ. (In press, estimated date of release December 2001)

Abstracts

1. Caballero E, Saouaf R, Lim SC, Hamdy O, O'Connor C, Abuelenin K, Logerfo FW, Horton ES, Veves A. The effects of troglitazone on the endothelial function of the micro- and macrocirculation in patients with early or late type 2 diabetes. *Diabetes* 2001;50 (Suppl 1):A600.
2. Caselli A, Pham H, Giurini JM, Armstrong DG, Veves A. The forefoot / rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration. *Diabetes* 2001;50 (Suppl 1):A929.
3. Pham HT, Sabolinski ML, Veves A. Healing rate measurement can predict complete wound healing rate in chronic diabetic foot ulceration. *Diabetes* 2000;49 (Suppl l):A8111.
4. Veves A, Quist WC, Caballero AE, LoGerfo FW, Horton ES. Expression of endothelial nitric oxide synthase (eNOS) in the skin microvasculature. *Diabetes* 2000;49 (Suppl l):A614.

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 brain tumor formation, invasion and metastasis. Our laboratory concentrates on 3 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. Tissue Bank

II. List of Current Employees

1. Julian K. Wu, M.D.	Chief, Neurosurgery
2. George Perides, Ph.D.	Director, Neurosurgery Brain Tumor Laboratory
3. Yuzheng Zhuge, M.D.	Postdoctoral Fellow
4. Yu Wang	Research Associate
5. Aric Park	Medical Student (Tufts Medical School)

III. List of Current Funding

1. Julian Wu Research Support
   Beth Israel Deaconess Medical Center
   11/01/99-9/30/2002

2. "Lipid-associated sialoprotein as a marker of CNS lymphoma of the brain"
   NIH: Center for AIDS Research (CFAR)
   12/1/2000-11/30/2002

3. "The role of the fibrinolytic system in development of metastasis to the brain"
   The Brain Tumor Society, Alan Goldfine Chair of Research
   11/01/2000-10/30/2002

4. "Prinomastat and tumor markers in the CSF of patients participating in the Agouron" AG3340-019 trial
   10/01/2000-9/30/2002

I. Applications Submitted and Pending Review/Funding

1. NIH: Pathogenesis of Borrelia burgdorferi induced arthritis

2. Army: Cell adhesion and brain metastasis of breast carcinomas

II. 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 Brown University, Wellesley College and Tufts Medical School 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.

   Sonia Bhangoo (Wellesley College). Studied the ability of growth factors to induce the expression of matrix metalloproteinases by human glioma and breast carcinoma cells.

   Sayumi DeSilva (Brown University). Studied the extracellular matrix in the brain of patients with primary and metastatic brain tumors.

   Aric Park (Tufts Medical School). Studied the levels of matrix metalloproteinases, vascular endothelial growth factor and lipid-associated sialoprotein in longitudinally collected cerebrospinal fluid samples from tumor patients.

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 Harvard Central Nervous System Tumors SPORE planning committee that met twice monthly during 2001 leading to the SPORE application (October 2001).

3. 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.

4. Dr. Perides served as a judge of the final oral presentations of students who attended the 2001 Research Science Institute carried out at MIT.

III. 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, Dr. Zhuge, Mr. Park and Ms. Wang.

1. During the next academic year, we plan to submit grant application to the following programs:

   NIH: Pathogenesis of Borrelia burgdorferi induced arthritis
   Army: Cell adhesion and brain metastasis of breast carcinomas
   NIH: Neuro-oncology SPORE (10/01/2001)
   NIH: Pathogenesis of Lyme neuroborreliosis (10/01/2001)
   NIH: Pathogenesis of tumor metastasis to the brain (02/01/2002)

VII. Bibliography (07/01/2000-06/30/2001)

Original Articles

1. Hu LT, Eskildsen MA, Masgala C, Steere AC, Arner EC, Pratta MA, Grodzinsky AJ, Loening A, **Perides, G.** Host metalloproteinases in Lyme arthritis. *Arthr. & Rheum*. 2001 44:1401-10.
2. Katopodis N, Glantz MJ, Kim L, Dafni U, **Wu J K, Perides G**. Lipid associated sialoprotein in the cerebrospinal fluid: association with brain malignancies. *Cancer* 2001;92:856-62.
3. Saba S, Vanderbrink BA, **Perides G,** Glickstein LJ, Link MS, Homoud MK, Bronson RT, Estes NAM, Wang PJ. Cardiac conduction abnormalities in a mouse model of Lyme borreliosis. *J. Invest. Cardiol*. 2001;5:137-43.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Textbooks
None Listed

Clinical communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts

1. Friedberg MH, Kim L, Glantz MJ, Tanner-Brown LM, **Perides G**. Serial Measurements of Metalloproteases (MMPs) in the Cerebrospinal Fluid (CSF) of Primary and Metastatic Brain Tumor Patients Correlate with the Tumor Behavior. *American Society of Clinical Oncology* 2000;19:A663.
2. **Gaston SM,** Hess S, Aminipour S, Cusano N, Tung S-F, **DeWolf** WC, **Perides G**. Matrix Metalloprotease-9: Tumor marker or risk factor for prostate cancer? *Society for Basic Urologic Research*, November 2000.
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:A261.

4. **Lin T, Zhuge Y, Wu JK, Perides G**. The role of plasminogen in melanoma metastasis to the brain. *Society for Neuro-Oncology* 2001;3:48.

Anna Zuk, Ph.D.

Division of General Surgery

I. Narrative Report

Basic Research

My research goal involves understanding the cellular and molecular mechanisms of epithelial cell injury and repair in the kidney. Specifically, I am examining the role of cell-cell and cell-extracellular matrix interactions in the pathogenesis of acute renal failure and in recovery of the kidney after injury. I have found that in response to ischemia, the major family of extracellular matrix receptors expressed on the plasma membrane of the renal epithelium reorganizes to aberrant sites as molecules of the extracellular matrix are newly expressed. These studies will facilitate the design of novel therapeutics aimed at limiting injury and/or speeding recovery in the patient population.

II. List of Current Employees

None

III. List of Current Funding

1. "Integrins in Kidney Morphogenesis"
   NIH RO1-DK46768
   PI: Dr. Karl S. Matlin
   Co-Investigator: Dr. Anna Zuk

IV. Applications Submitted and Pending Review/Funding

1. Scholars in Medicine Grant, Harvard Medical School
   P I: Dr. Anna Zuk
   "Role of the Extracellular Matrix in Renal Epithelial Injury and Repair"
   9/01-8/02

V. Divisional Accomplishments Over the Past Year

Research accomplishments

1. I have continued my research on the cellular mechanisms mediating acute renal failure. My recent work addresses the role of laminin, a major glycoprotein of the extracellular matrix, and its integrin receptors in renal injury and regeneration. I have found that one isoform of laminin, known as laminin-5, is newly expressed and that along with its integrin receptor, the $\alpha 3\beta 1$, may play a role during regeneration of the damaged epithelium.

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. In the past year, I was promoted to Assistant Professor of Surgery at Harvard Medical School.

2. I was invited to be a Moderator for an Abstract Session regarding Cell-Matrix Interactions/Integrins/Collagen for the annual meeting of the American Society of Nephrology in Toronto, Canada, October 13-17, 2000.

VI. Plans for the Coming Academic Year

Staff Changes

1. Michael Bilozur, Ph.D., Chairman of Biology at Regis College, will join my laboratory during his sabbatical leave.

New Grants

1. In the coming academic year, I will continue to apply for research funding from local and national agencies, including the NIH.

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.

VII. Bibliography (07/01/00-06/30/01)

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:F1037-53.

Proceedings of Meetings
None Listed

Reviews, Chapters, and Editorials
None Listed

Books, Monographs, and Text Books
None Listed

Clinical Communications
None Listed

Educational materials
None Listed

Nonprint materials
None Listed

Abstracts
None Listed