

# WORDS FROM THE CHAIRMAN



**Josef E. Fischer, MD**

I am delighted to welcome you to review this report, which highlights research activities in the Department of Surgery at the Beth Israel Deaconess Medical Center from 7/1/02-6/30/03. This is, by definition, an academic department. A true academic Department of Surgery not only has a commitment to clinical excellence, but also to research excellence, at the laboratory bench in molecular biology and physiology, and in clinical research, as well. Well-trained and productive investigators in basic and clinical research are essential to the mission of this department and also serve as part of the departmental infrastructure to entice surgical residents into the laboratory for a two-year elective in which they develop research skills to pursue a career in academic surgery.

Building of the research component of the Department of Surgery represents a sustained academic effort to which we are committed. While the initial effort in building the Department of Surgery was clinical, with emphasis on clinical volume in order to improve the financial situation of the Beth Israel Deaconess Medical Center, we always stated openly that even if the first recruits were clinical, the next recruits had to have some academic component. In general, as we have recruited partners for the initial clinical individuals, we have stressed that they must have a significant research component, either through bench research or outcome related research. This has certainly occurred, with an increase in total funding this year for research of 22 percent, which gives the Department about \$11 million dollars per year of research funding. As we continue to recruit faculty, we anticipate a very significant increase again next year in not only clinical research funds, but also in NIH funds. With regards to NIH funding,

the Department of Surgery at BIDMC is among the top 10 in the country, and our goal is to be in the top 5. Then, and only then, will the Department live up to its full potential.

I would like to thank the Division Chiefs and all members of the Department of Surgery, both Faculty and Staff, for their continued superb efforts on behalf of making the Department of Surgery at the Beth Israel Deaconess Medical Center a true academic Department of Surgery. Keep up the good work!

*Josef E. Fischer, M.D.  
Professor and Chairman  
Department of Surgery*

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# SURGICAL RESEARCH



Per-Olof Hasselgren, MD, PhD

## Division Members

Per-Olof Hasselgren, MD, PhD  
Susan J. Hagen, PhD  
Pat Odom-Andrews

Vice-Chairman for Research  
Associate Director  
Administrative Coordinator

The mission of the Division of Surgical Research is to help create an environment in the Department of Surgery that supports both basic and clinical research. Although it may be debated how the success and progress of a research program should be monitored, external funding and publications are tangible measures of the vitality of research. Based on those criteria, research programs in the Department continue to be successful. In this section of the Annual Report we provide an overall description of the goals and responsibilities of the Division, a summary of funding and publications generated by researchers in the Department of Surgery, and other aspects of research

within the Department. More detailed accounts are found for individual members of the different Divisions in subsequent sections of the Report.

The Division of Surgical Research has the following responsibilities. 1) Pre- and post- award management of all grants submitted by and awarded to investigators working in the Department of Surgery. Our responsibilities include assisting in the process of submission of grant applications and interaction with the BIDMC Office of Sponsored Programs. 2) Management of research space, including laboratory and office space, and shared research equipment. For this, we oversee the allocation of research space within the Department and represent the Department at ReAc space sub-committee meetings. 3) Monthly Surgical Research and Administrative seminars. 4) Preparing the Department of Surgery Annual Research Report. 5) Organize laboratory and shared equipment maintenance and telecommunications. 6) Support and Mentor junior faculty in the establishment of research laboratories. 7) Interact with and provide information to Surgical Residents who plan to spend time in the research laboratory. 8) Make recommendations concerning research faculty appointments and reappointments in Surgery. 9) Assist with the development of existing and new research areas within the Department of Surgery, including both short- and long-term strategic planning and recruitment.



**Susan J. Hagen, PhD**

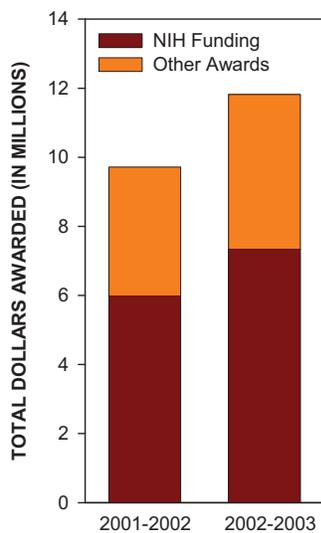
The Division of Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, who is the Vice Chairman for Research in the Department of Surgery. Susan J. Hagen, PhD, is Associate Director and is responsible for the day-to-day administration of Surgical Research. Pat Odom-Andrews provides administrative support for the Division, under the supervision of Dr. Hagen. The Division of Surgical Research works closely with Research Administration (Team 5), headed by Jennifer Sabbagh, Research Administrative Director. Shannon Joyce, Jennifer Clark, and Jonathon Lyon, Sr. Research Administrator and Research Administrators, respectively, are responsible for grant management, research-related purchases, staff payroll, and the management of new hires for research in Surgery.

### **Research Activity for 2002-2003**

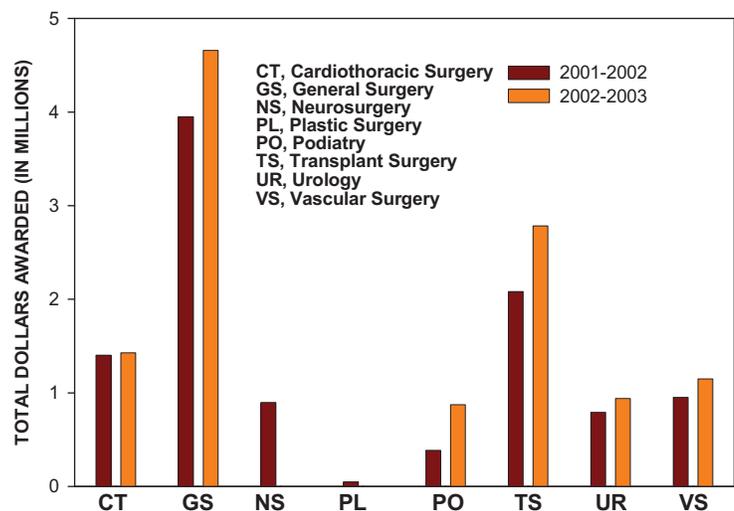
External research funding in the Department of Surgery increased by 21.8% from \$9,714,965 in fiscal year 2001-2002 to \$11,831,596 in this fiscal year (Figure 1). The increase in research funding this year is due to a general increase in funding per Division, with the most significant increases in funding seen in General Surgery, Podiatry, and Transplant Surgery (Figure 2). Approximately 66% of the awarded funding was from federal sources, primarily from the NIH, and 34% from Other Sponsors (Table 1).

**Table 1. Summary of all research awards and expenditures in the Department of Surgery from 7/01/02-6/30/03**

| Sponsor        | Direct Awarded   | Indirect Awarded | Total Awarded     | Direct Expended  | Indirect Expended | Total Expended    |
|----------------|------------------|------------------|-------------------|------------------|-------------------|-------------------|
| NIH            | 4,807,678        | 2,544,853        | 7,352,531         | 4,521,157        | 2,501,138         | 7,022,294         |
| Other Federal  | 215,204          | 141,644          | 356,848           | 110,460          | 63,533            | 173,993           |
| Other Sponsors | 3,690,654        | 419,003          | 4,109,657         | 4,384,060        | 251,249           | 4,635,309         |
| <b>TOTAL</b>   | <b>8,713,536</b> | <b>3,105,500</b> | <b>11,819,036</b> | <b>9,015,676</b> | <b>2,815,920</b>  | <b>11,831,596</b> |



**Figure 1. Total research dollars awarded to Surgery from 2001-2003.**



**Figure 2. Total research dollars per Division awarded from 2001-2003.**

## **Research Facilities and Space**

This year, research in the Department of Surgery occupied approximately 33,000 square feet of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Surgery (basic) research space included (in square feet) 5,870 at HIM, 12,273 in Dana/Research West, 917 in Slosberg-Landy, 1,706 at 21-27 Burlington Avenue, and 6,125 at Research North. Clinical research in Surgery included (in square feet) 605 in Palmer and 4,272 in Finard/Rabb. The greatest concentration of researchers are found on the 7<sup>th</sup> and 8<sup>th</sup> floors of the Dana/Research West building on the East Campus, where General Surgery, Cardiothoracic Surgery, Neurosurgery, and Urology research laboratories are located. Vascular Surgery, Cardiothoracic Surgery, and Urology laboratories are located on the 1<sup>st</sup> floor of the Harvard Institutes of Medicine. Research related to Transplantation/Immunobiology is located on the 3<sup>rd</sup> floor of Research North. Finally, Surgical Nutrition research laboratories are located at the Burlington Avenue building. New space was recently renovated for the Clinical Nutrition laboratories on Feldberg 8,

so Dr. Blackburn moved his clinical research effort from Finard/Rabb to that space in the middle of the year. Podiatry's clinical research effort remains in Palmer.

## **Research Seminars**

The Division of Surgical Research offered a seminar series with presentations from investigators within the Department of Surgery, from other Departments at BIDMC, and from other local institutions. Seminars were designed this year with a programmatic theme, with 2 seminars each from Vascular/Cardiovascular, Transplant, Muscle Wasting and Metabolism, Epithelial Biology, and Urology. We also had 3 administrative seminars this year, covering topics of interest to both faculty and staff. A summary of seminars that were presented from 07/01/02-06/30/03 are listed in Table 2.

**Table 2. Seminars sponsored by the Division of Surgical Research from 07/01/02-06/30/03**

|                 |  |
|-----------------|--|
| <b>09.9.02</b>  | Molecular Regulation of Muscle Wasting: Per-Olof Hasselgren, Department of Surgery, BIDMC  |
| <b>09.23.02</b> | Town Hall Meeting: Division of Surgical Research – Mission, Goals, Structure: Per-Olof Hasselgren, Department of Surgery, BIDMC                  |
| <b>10.07.02</b> | Cholesterol and Prostate Cancer Cell Survival: Michael R. Freeman, Children's Hospital, Boston   |
| <b>10.21.02</b> | Legal Implications for H1B and J1 Visas: Dan Hassenfeld, Legal, BIDMC  |
| <b>11.04.02</b> | Leptin in Body Weight Regulation: Jeffrey S. Flier, BIDMC  |
| <b>11.18.02</b> | Grant Compliance: Gretchen Brodnicki, Office of Business Conduct, BIDMC  |
| <b>12.02.02</b> | Xenotransplantation: Fritz H. Bach, Department of Surgery, BIDMC   |
| <b>01.06.03</b> | <i>Helicobacter pylori</i> and Gastric Cancer: Tim Wang, University of Massachusetts Medical School, Worcester, MA.                              |
| <b>01.14.03</b> | Muscle Atrophy: A Tale of Two Protease Systems, S. Russ Price, Emory University, Atlanta, Georgia  |
| <b>02.03.03</b> | Differentiation of Islets from Pancreatic Ducts: A Potential Source for Beta Cell Replacement, Susan Bonner-Weir, Joslin Diabetes Center, Boston |
| <b>03.03.03</b> | Myocardial Hypertrophy and Heart Failure: The Role of Angiogenesis: Pedro del Nido, Children's Hospital, Boston                                  |
| <b>04.07.03</b> | Dissecting ER Stress Pathway by Cellular and Chemical Biological Approaches: Junying Yuan, Harvard Medical School, Boston                        |
| <b>05.05.03</b> | Novel Estrogenic Compounds In Prostate Cancer Therapy: Shuk-Mei Ho, University of Massachusetts Medical School, Worcester, MA                    |
| <b>06.02.03</b> | Temporal and Spatial Regulation of Endothelial Cell Phenotypes: William C. Aird, BIDMC   |

## **Faculty Accomplishments**

During 2002-2003, research in the Department of Surgery was conducted by 45 Faculty members, 29 Postdoctoral Research Fellows, 6 Surgical Residents, 25 Research Associates and Assistants, 4 Visiting Scientists, and 14 undergraduate, medical school and graduate students from the Divisions of Cardiothoracic, General, Neuro, Plastics Podiatry, Transplant, Urology, and Vascular Surgery. Numerous research coordinators, administrative assistants, and administrative coordinators provided support for research-related effort.



**Pat Odom-Andrews**

Many new grant applications were funded in this fiscal year. New (NIH) R01 funding was obtained by Drs. Sellke, Hasselgren, and Ferran. New non-federal grants were obtained by Drs. Archer, Blackburn, Gaston, LoGerfo, Maki, Sellke, Veves, and Zhou. Dr. Rosseau, with mentorship from Dr. McCully, obtained an American Heart Postdoctoral Fellowship. At the national level, Dr. Archer continued service as Councillor on the Executive Committee of the Association for Academic Surgery and Dr. Jones was appointed to the Board of Governors of the Society of American Gastrointestinal Endoscopic Surgeons. Dr. DeWolf served as Past President of the National Urologic Forum, member of the AUA Program Committee for Basic Research, and was a member of the Medical Advisory Board of

the Boston Prostate Cancer walk. Several faculty in Surgery were appointed to NIH study section or grant review committees including Drs. Blackburn, Zhou, Hasselgren, Veves, and Olumi. In addition, most faculty in Surgery were invited speakers at programs and universities across the country. At the international level, Surgery faculty were invited speakers at meetings around the world from Hawaii to Paris to China. Two investigators in Surgery submitted patent applications (Drs. Ferran and LoGerfo), and Drs. Jones and Kiessling authored or edited textbooks. This year, Dr. Blackburn received the “Distinguished Alumni Award” from the University of Kansas and Dr. Ferran received the Mary Jane Kugel Award from the Juvenile Diabetes Foundation. The American Society of Transplantation selected Dr. Bach as one of the “Pioneers in Transplantation”.

Researchers in Surgery continue a strong commitment to teaching. This includes acting as mentors in the NIH in-service teacher program, Summer Honors Undergraduate Research Program, MIT Bioengineering Undergraduate Research Program, Project Success, Biomedical Science Careers Program, Undergraduate Research Opportunities Program, The American Cancer Association Fuller Fellowship Program, Howard Hughes Summer Research Fellowship Program, and the Biomedical Science Careers Program. At Harvard Medical School, many investigators teach in various courses, including “The Body”, “Chemistry and Biology of the Cell”, “Integrated Human Physiology”, and “Pharmacology”.

## **Bibliography (7/1/02-6/30/03)**

A total of 86 original articles were published by faculty members in the department of Surgery between the period of 7/1/02 and 6/30/03. This represents a 15 % increase in published original articles when compared to the previous year. The number of publications in other categories, including Proceedings of Meetings, Reviews, Chapters, Editorials, Books, Monographs, Textbooks, Clinical Communications, Educational Materials, Nonprint Materials, and Abstracts also increased from last year.

### **Listing of articles published by researchers in the Department of Surgery from 7/1/02-6/30/03 (in alphabetical order).**

#### **Original Articles**

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25. **Villegas L**, Kondraske G, Napper C, Cadeddu J, **Jones DB**. Laparoscopic skills: do good hands beget laparoscopic ability? *Surg Endosc* 2002;16:S322.
26. Vuletic V, Hutchinson L, **DeWolf WC, Gaston SM**, Zetter BR. The urinary proteome in prostate cancer diagnosis: Tumor markers and protein signatures. *Proc Am Assoc Cancer Research* 2003;44:1078.
27. Wang D, **Perides G**, Liu A, Feldman R, Liu YF. Emotional stress induces activation of MKK4 in glutamatergic neurons. *Neurosci* 2002;397:3A.
28. **Yang H, Evenson A, Menconi M, Fischer JE, Hasselgren PO**. Dexamethasone upregulates the gene expression of C/EBP $\beta$  and atrogen-1 through different mechanisms in cultured myotubes. *J Am Coll Surg* 2003;197:S35.

## List of Faculty and Staff by Division

| <u>Personnel</u>                                 | <u>Title</u>   |
|--|--|
| <b><u>Division of Cardiothoracic Surgery</u></b> |  |
| <b>Sellke, Frank</b>                             | <b>Chief, Division of Cardiovascular Surgery</b>     |
| Bianchi, Cesario                                 | <b>Johnson and Johnson Professor of Surgery</b>      |
| Feng, Jun  | Assistant Professor of Surgery                       |
| Kahn, Tanveer                                    | Instructor in Surgery                                |
| Voisine, Pierre                                  | Surgical Resident                                    |
| Malik, Tamer                                     | Postdoctoral Fellow                                  |
| Li, Jianyi                                       | Postdoctoral Fellow                                  |
| Xu, Shu Hua                                      | Research Assistant                                   |
| Michael, Keith                                   | Research Assistant                                   |
|  | 2nd year Medical Student                             |
| <b>Levitsky, Sidney</b>                          | <b>Professor of Surgery</b>                          |
| <b>McCully, James</b>                            | <b>Associate Professor of Surgery</b>                |
| Rousou, Anthony                                  | Postdoctoral Fellow                                  |
| Hsieh, Yng-Ju                                    | Research Associate                                   |
| <b>Ellis, Henry</b>                              | <b>Clinical Professor of Surgery, Emeritus</b>       |
| Loda, Massino                                    | Associate Professor of Pathology (DFCI)              |
| Xu, Xiangjun                                     | Postdoctoral Fellow                                  |
| Lechpammer, Mirna                                | Postdoctoral Fellow                                  |
| <b><u>Division of General Surgery</u></b>        |  |
| <b>Callery, Mark</b>                             | <b>Chief, Division of General Surgery</b>            |
| Bai, Jirong                                      | <b>Associate Professor of Surgery</b>                |
| Enos, Benjamin                                   | Research Associate in Surgery                        |
|  | Technician, part-time                                |
| <b>Archer, Sonia</b>                             | <b>Assistant Professor of Surgery</b>                |
| <b>Blackburn, George</b>                         | <b>Chief, Section of Surgical Nutrition</b>          |
|  | <b>S. Daniel Abraham Chair in Nutrition Medicine</b> |
| <b>Zhou, Jin-Rong</b>                            | <b>Associate Professor of Surgery</b>                |
| Khaodhiar, Lalita                                | <b>Assistant Professor of Surgery</b>                |
| Pan, Weijun                                      | Instructor in Medicine                               |
| Mai, Zhiming                                     | Visiting Scientist                                   |
| McNamara, Anne                                   | Senior Postdoctoral Fellow                           |
| Copeland, Trisha                                 | Research Associate                                   |
| Karun, Pam                                       | Research Associate                                   |
| Hirsch, Wanda                                    | Research Associate                                   |
| Sherwood, Michelle                               | Research Associate                                   |
| McCormick, Heather                               | Research Associate                                   |
| Lin, Min   | Research Assistant                                   |

Li, Xin  
Singh, Aijita  
Wu, Lei  
Wu, Zhanggui  
Zhao, Yi  
Ainsley, Barbara  
Sidell, Susan

Research Associate  
Postdoctoral Fellow  
Visiting Associate Professor  
Research Associate  
Postdoctoral Fellow  
Administrative Assistant  
Administrative Coordinator

**Fischer, Josef**

**Chairman, Department of Surgery  
Mallinckrodt Professor of Surgery**

**Hagen, Susan**

**Associate Director for Research  
Director, Morphology Core Facilities**

Tashima, Kimihito  
Muvaffak, Asli  
Brown, Daniel  
Li, Suqian  
White, Suzanne

Postdoctoral Fellow  
Postdoctoral Fellow  
Sr. Research Associate  
Research Technician  
Histotechnologist

**Hasselgren, Per-Olof**

**Vice-Chairman for Research  
Chief, Section of Endocrine Surgery**

Menconi, Michael  
Fareed, Moin  
Cahill, Catherine  
Yang, Hongmei  
Wei, Wei  
Evenson, Amy

Assistant Professor of Surgery  
Instructor in Surgery  
Instructor in Surgery  
Postdoctoral Fellow  
Postdoctoral Fellow  
Surgical Resident

**Jones, Daniel B.**

**Chief, Section of Minimally Invasive Surgery  
Visiting Associate Professor of Surgery**

Sanchez, Vivian  
Villegas, Leonardo  
Goodspeed, Eleanor

MIS Clinical Fellow  
Skills Lab Coordinator  
Administrator

**Mun, Edward**

**Assistant Professor of Surgery**

Lin, Hsi-Chiang  
Choe, Jae Won  
Davis, Kyrah

Instructor in Surgery  
Postdoctoral Fellow  
Technician

**Parangi, Sareh**

**Instructor in Surgery**

Galardi, Eric  
Zhang, Xue Feng

Research Technician  
Postdoctoral Fellow

**Tawa, Nicholas E.**

**Assistant Professor of Surgery**

Mitchell, Jamie

Surgical Resident

## **Division of Neurosurgery**

**Wu, Julian**

Tam, Angela

**Malek, Adel**

Younis, Hesham

Sur, Gargi

**Chief, Division of Neurosurgery**

**Associate Professor of Surgery**

Research Technician

**Instructor in Surgery**

Postdoctoral Fellow

Research Technician

## **Division of Plastic and Reconstructive Surgery**

**Slavin, Sumner**

Borud, Loren J.

Contreras, Mauricio A.

Goldwyn, Robert M.

Brahmer, Geoffrey

**Chief, Division of Plastic and Reconstructive Surgery**

Instructor in Surgery

Instructor in Surgery

Clinical Professor of Surgery

Educational Coordinator

## **Division of Podiatry**

**Veves, Aristidis**

Khaodhiar, Lalita

Dinh, Thanh

Lyons, Thomas

Porramatikul, Sriurai

Lima, Christina

Longoria, Lydia

**Assistant Professor of Surgery**

Instructor in Medicine

Junior Faculty

Junior Faculty

Postdoctoral Fellow

Research Coordinator

Research Coordinator

## **Division of Transplantation**

**Hanto, Douglas W.**

Pavlakis, Martha

Johnson, Scott R.

Khwaja, Khalid

Curry, Michael P.

Wong, Michael A.

Riemer, Louise

Seminara, Tina

**Chief, Division of Transplant Surgery**

**Lewis Thomas Professor of Surgery**

Assistant Professor of Medicine

Instructor in Surgery

Instructor in Surgery

Instructor in Medicine

Assistant Professor of Medicine

Transplant Coordinator

Transplant Coordinator

**Bach, Fritz H.**

Soares, Miguel

Tyagi, Shivraj

Yamashita, Kenichiro

Wang, Hongjun

McDaid, James

Oellinger, Robert

Graca-Souza, Aurelio

Biblan, Martin

Csizmadia, Vilmosne Eva

Lee, Soo

**Louis Thomas Professor of Surgery**

Instructor in Surgery

Instructor in Surgery

Instructor in Surgery

Instructor in Surgery

Postdoctoral Fellow

Postdoctoral Fellow

Postdoctoral Fellow

Postdoctoral Fellow

Research Assistant III

Research Assistant II

**Ferran, Christiane**

Arvelo, Maria  
Daniel, Soizic  
Patel, Virendra I.  
Shrikande, Gautam  
Sun, David  
Shukri, Tala  
Alegria, Judy D. Cueva

**Monaco, Anthony**

**Maki, Takashi**

Ogawa, Norihiko  
Minamimura, Keisuke  
Paranjape, Charudutt  
Gottschalk, Rita

**Division of Urology**

**DeWolf, William**

Schopperle, William

**Olumi, Aria**

San Francisco, Ignacio  
Zhang, Xiaoping

**Gaston, Sandra**

Soares, Marc  
Brice, Mark  
Lee, Jung  
Vu, Dang  
Gutierrez, Efren  
Goldner, Dana  
Mukhpadhyay, Piali  
Rogg, Jonathan  
Kim, Tae Wan  
Ford, Catherine  
Kolenik, Becky  
Nichols, Aislinn

**Kiessling, Ann**

Desmarais, Bryan  
Neville, Nathan

**Division of Vascular Surgery**

**LoGerfo, Frank**

**Associate Professor of Surgery**

Postdoctoral Fellow  
Instructor in Surgery  
Surgical Resident  
Surgical Resident  
Postdoctoral Fellow  
Research Assistant  
Research Assistant

**Peter Medawar Professor of Surgery**

**Associate Professor of Surgery**

Postdoctoral Fellow  
Postdoctoral Fellow  
Visiting Fellow  
Research Technician

**Chief, Division of Urology**

**Professor of Surgery**

Postdoctoral Fellow

**Medical Science Director for Urology**

**Instructor in Surgery**

Research Fellow  
Research Fellow

**Basic Science Director for Urology**

**Instructor in Surgery and**

Research Technician  
Research Technician  
Research Technician  
Research Technician  
Harvard Medical Student  
Student  
Student  
Student  
Student  
Student  
Student  
Student

**Associate Professor of Surgery**

Research Technician  
Student

**Chief, Division of Vascular Surgery**

**William V. McDermott Professor of Surgery**

**Hamdan, Allan**

Aggarwal, Puja

Gross, Barry

Kalish, Jeffrey A.

Lambert, Jennifer

Monahan, Thomas S.

Panossian, Haig

Patel, Vaishali B.

Phaneuf, Matthew

Shah, Amish A.

Sousa, Kery

**Assistant Professor of Surgery**

Undergraduate Student

IS Development

Research Fellow

Clinical Trials Research Administrator

Research Fellow

Undergraduate Student

Administrative Assistant

Assistant Laboratory Director

Graduate Student

Undergraduate Student

**Division of Surgical Research**

**Hasselgren, Per-Olof**

**Hagen, Susan**

Odom-Andrews, Patricia

**Vice Chair for Research**

**Associate Director of Research**

Administrative Coordinator

**Research Administration**

**Sabbagh, Jennifer**

Clark, Jennifer

Joyce, Shannon

Lyon, Jonathon

**Director, Research Administration, Team 5**

Research Administrator

Sr. Research Administrator

Research Administrator

# CARDIOTHORACIC SURGERY



Frank W. Sellke, M.D., Chief

## Division Members

Simon K. Ashiku Jr., M.D.

Cesario F. Bianchi, M.D., Ph.D.

William E. Cohn, M.D.

Ralph de la Torre, M.D.

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

Sidney Levitsky, M.D.

John R. Liddicoat, M.D.

James D. McCully, Ph.D.

John Sapirstein, M.D.

Robert L. Thurer, M.D.

John D. Urschel, M.D.

Ronald M. Weintraub, M.D.

This year has been very productive for the Division of Cardiothoracic Surgery in terms of research. Frank Sellke has been awarded a T-32 training grant and Ralph Delatorre was awarded a multiyear grant from the Abiomed Corporation to investigate the total artificial heart device (Abiocor). Drs Levitsky and McCully continue to examine mechanisms of ischemic preconditioning and myocardial protection. Drs Sellke and Bianchi investigate changes in vascular function and signal transduction during cardiac surgery and myocardial ischemia, and therapeutic angiogenesis using protein growth factors in the setting of hypercholesterolemia. Dr. Ellis is looking at the changes in molecular characteristics in the GE junction leading to malignant transformation and Drs. William Cohn and Liddicoat examine minimally invasive techniques for valve repair. The division continues to be one of the best- funded divisions of cardiothoracic surgery in the country in terms of NIH grants.

## **F. Henry Ellis Jr., M.D., Ph.D**

### **Division of Cardiothoracic Surgery**

#### **I. Narrative Report**

p27 is a tumor suppressor gene that controls cell cycle progression by inactivating cyclin-dependent kinases (cdks) that are required for cell cycle progression at the G1/s transition. These include cdk 4 and 6 (cyclin D) as well as cdk2 (cyclin E). We previously showed that lack of p27 in esophagogastrectomy specimens from patients with Barrett's associated adenocarcinoma (BAA) is a negative prognostic marker for this disease. Influenced by these findings, we produced a model of BAA by performing an esophagojejunostomy and administering a carcinogen. Subsequently we showed that malignant transformation of the esophageal mucosa is greatly enhanced in p27 knock out mice, leading to studies using Flavopiridol as a cdk inhibitor in p27 knock out mice. Our studies are done in collaboration with Massimo Loda, MD, from the Dana Farber Cancer Institute.

#### **II. List of Current Employees**

- |                                  |                 |
|----------------------------------|-----------------|
| 1. Xiangun Xu, M.D., Ph.D.       | Research Fellow |
| 2. Mirna Lechpammer, M.D., Ph.D. | Research Fellow |

#### **III. List of Current Funding**

1. Thelma and Jerry Stergios Fund for Thoracic Surgical Education and Research

#### **IV. Division Accomplishments Over the Past Year**

1. The effect of Flavopiridol, a cdk inhibitor, on carcinogenesis using the p27 knock out mouse model of BAA was the subject of last year's experiments. One hundred and twenty one p27 knock out mice were used. Seventy one underwent esophagojejunostomy and were treated with Flavopiridol (5 mg/kg/day), while 50 control mice had a similar operation and carcinogen but were treated with a placebo. Flavopiridol reduced the prevalence of Barrett's esophagus (BE) in contrast to control animals (7% vs. 26%,  $p=0.0079$ ). Flavopiridol also reduced the prevalence of BAA (11% vs. 32%,  $p=0.0098$ ) as well as the overall cancer rate (15% vs. 60%,  $p<0.0001$ ). The effect of Flavopiridol was also evaluated at the cellular level by immunohistochemistry.
2. Dr. Ellis attended the annual meeting of the American Surgical Association in Washington D.C. April 24-26, 2003, and the annual meeting of the American Association for Thoracic Surgery in Boston, M.A. May 4-7, 2003.

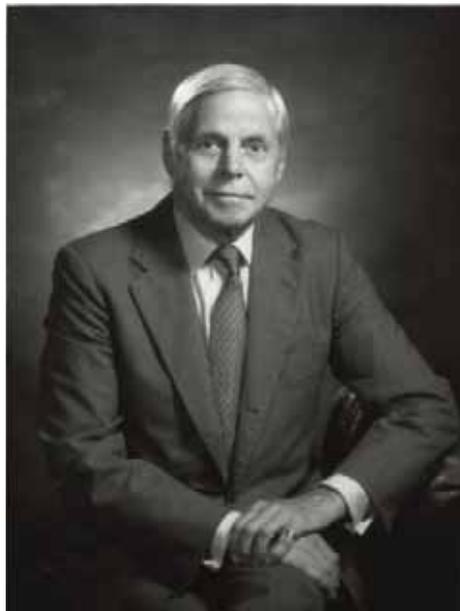
#### **V. Report of Teaching**

1. Dr. Ellis was invited to give a talk at the 7<sup>th</sup> triannual meeting of O.E.S.O. in Paris, France Aug. 31- Sept. 5, 2003 on the compared rate of development of

BAA after experimental DGER and GER. He also participated in a “topic forum” on the subject of Genetic Aspects of BAA at the same meeting.

## VI. Plans for the Coming Year

1. Having shown that it is possible to prevent the high rate of carcinogenesis in p27 knock out mice, we are currently studying ways to treat experimental carcinogenesis in p27 knock out mice after it has developed. Thus p27 knock out mice will undergo esophagojejunostomy plus administration of a carcinogen, which will be discontinued after 16 to 18 weeks when 60% to 80% are predicted to have developed cancer. Half of the mice will then be treated with a combination of Flavopiridol and Gemcitabine while the other half will receive a placebo. After a month, mice will be killed and pathologic studies performed.



**Dr. F. Henry Ellis, Jr.**

## VII. Bibliography

### Original Articles (in press)

1. **Lechpammer M, Xiangjun Xu, Ellis FH Jr., et al.** Flavopiridol, a cyclin-dependent kinase inhibitor, reduces malignant transformation of esophageal mucosa in p27 knockout mice. *Nature Medicine* (in press).

### Proceedings of Meetings

1. **Ellis FH Jr.** Is preexisting gastroesophageal reflux necessary for the development of Barrett's Esophagus in Achalasia? In: Giuli R, editor. O.E.S.O. London: John Libby Eurotext Ltd; 2003. p. 274-8.
2. Streitz JM, **Ellis FH Jr.** What can be concluded from 24-hour pH studies in patients with achalasia? In: Giuli R, editor. O.E.S.O. London: John Libby Eurotext Ltd; 2003. p. 278-82.

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

## Division of Cardiothoracic Surgery

### I. Narrative Report

#### Basic Research

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



Current research areas involve identification of mitochondrial changes in morphology, function, respiration, volume in association with intrinsic and extrinsic apoptotic and necrotic myocardial cell death following ischemia and reperfusion; the identification of mitochondrial ATP-sensitive potassium channel regulation of apoptosis and necrosis in the blood perfused pig heart model of acute myocardial infarction; and the role of STAT1/STAT2 signal transduction in myocardial preservation. These studies include comparison between mature and aged populations and differential gender response.

### I. Current List of Employees

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

## **II. List of Current Funding**

1. "Myocardial Protection: Reperfusion Injury Amelioration "  
National Institutes of Health, RO1 HL 59542  
Project period: 2000-2005  
Principal Investigator: Sidney Levitsky, M.D.  
Collaborating Investigator: James D. McCully, Ph.D.
2. "Mechanisms of Surgically Induced Ischemia/Reperfusion Injury in the Aged Heart:  
Role of apoptosis and necrosis."  
American Heart Association, Post-Doctoral Fellowship (0225661T)  
Project period: 2002-2004  
Fellowship Mentor: James D. McCully, Ph.D.

## **III. Applications Submitted and Pending Review/Funding**

1. Myocardial Protection: Reperfusion Injury Amelioration "  
National Institutes of Health, RO1 HL 59542  
Principal Investigator: Sidney Levitsky, M.D.  
Collaborating Investigator: James D. McCully, Ph.
2. Surgical Cardioprotection for the Mature and Aged Heart  
National Institutes of Health, National Heart Lung and Blood Institutes,  
Public Health Service Grant: Dr. J. D. McCully

## **IV. Divisional Accomplishments over the Past Year**

### Grants Submitted

1. "Pig and Rabbit Microarray Construction"  
National Institutes of Health,  
Comparative Medicine  
Resource-Related Research Project Grant  
R24
2. Myocardial Protection: Reperfusion Injury Amelioration "  
National Institutes of Health, RO1 HL 59542  
Principal Investigator: Sidney Levitsky, M.D.  
Collaborating Investigator: James D. McCully, Ph.
3. Surgical Cardioprotection for the Mature and Aged Heart  
National Institutes of Health, National Heart Lung and Blood Institutes,  
Public Health Service Grant: Dr. J. D. McCully

### Individual Accomplishments

1. Sidney Levitsky, M.D. was elected Second Vice-President and is President-Elect of The Society of Thoracic Surgeons.

### National Presentations

1. **Wakiyama H, McCully JD, Levitsky S.** (2002). Contribution of RNA and protein dependent mechanisms to enhanced cardioprotection with diazoxide supplemented cardioplegia. American College of Surgeons, 88<sup>th</sup> Clinical Congress, October 6-10, 2002, San Francisco, CA.
2. **McCully JD, Wakiyama H, Jones, M, Levitsky, S.** (2002). Role of necrosis and apoptosis in the evolution of surgical ischemia/reperfusion injury. American Heart Association, Scientific Sessions 2002, November 17-20, 2002, Chicago, IL. Circulation 106 (19), 2002.
3. **McCully JD, Wakiyama H, Jones, M, Levitsky, S.** (2002). Diazoxide supplemented cardioplegia provides enhanced cardioprotection through RNA and protein dependent mechanisms. American Heart Association, Scientific Sessions 2002, November 17-20, 2002, Chicago, IL. Circulation, 106 (19), 2002 .
4. **Levitsky S, Laurikka J, Stewart RD, Campos CT, Lahey SJ, McCully JD.** (2003). Mitochondrial DNA deletions in coronary artery bypass grafting patients. 38<sup>th</sup> Congress of the European Society for Surgical Research. Ghent, Belgium, May 28-31,2003.
5. **Levitsky, S.** Problems with myocardial protection in the “oldest old”. International Society Of Heart research, June 29, 2003, Mystic, Connecticut.

## **VI. Report of Teaching**

### Invited Presentations (local, national and international)

1. Levitsky S “Myocardial Protection in the Senescent Heart” BIDMC Surgical Research Seminar Series.

## **VII. Plans for the Coming Academic Year**

### Staff Changes

1. Addition of new technician for microarray studies.

## Research

1. Submission of 2 RO1 grant application (November 1, 2003).

## **VIII. Bibliography (7/01/2002-6/30/2003)**

### Original Articles

1. **Bianchi C, Wakiyama H, Faro R, Khan T, McCully JD, Levitsky S, Szabo C, Sellke FW.** A novel peroxyxynitrite decomposer catalyst (FP-15) reduces myocardial infarct size in an in vivo peroxyxynitrite decomposer and acute ischemia-reperfusion in pigs. *Ann Thorac Surg* 2002;74(4):1201-1207.
2. **McCully JD, Wakiyama H, Cowan DB, Federman M, Levitsky S.** Diazoxide amelioration of myocardial injury and mitochondrial damage during cardiac surgery. *Ann Thorac Surg* 2002;74:2138-2146.

### Original Articles (in press)

1. **Levitsky S, Laurikka J, Stewart RD, Campos CT, Lahey SJ, McCully JD.** Mitochondrial DNA deletions in coronary artery bypass grafting patients. *Eur J Cardiothorac Surg*; in press.
2. **McCully JD, Levitsky S.** Mitochondrial ATP-sensitive potassium channels in surgical cardioprotection. *Arch Biochem Biophys*; in press.

### Proceedings of Meetings

1. **Levitsky S, Laurikka J, Stewart RD, Campos CT, Lahey SJ, McCully JD.** Mitochondrial DNA deletions in coronary artery bypass grafting patients. Proceedings of the European Society for Surgical Research International; 2003. pp. 49-153.

### Reviews, Chapters, and Editorials

1. **McCully JD, Levitsky S.** Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *CT Digest* 2002;4(5).
2. **McCully JD, Levitsky S.** Effects of acute reduction of temperature on ventricular fibrillation activation patterns. *CT Digest* 2003
3. **McCully JD, Levitsky S.** Exercise improves postischemic cardiac function in males but not females: Consequences of a novel sex-specific heat shock protein 70 response. *CT Digest* 2002;4(7).

4. **McCully JD, Levitsky S.** Sildenafil (Viagra) induces powerful cardioprotective effect via opening of mitochondrial  $K_{ATP}$  channels in rabbits. *CT Digest* 2002;4(10).
5. **McCully JD, Levitsky S.** The mitochondrial  $K_{ATP}$  channel and cardioprotection. *Ann Thorac Surg* 2003;75:S667-S673.
6. **McCully JD.** Oxygenated multidosed delivery of crystalloid esmolol cardioplegia as an alternative to high potassium cardioplegia. *J Thorac Cardiovasc Surg* 2002 124(2):219-220.

#### Clinical Communications

1. Dusek JA, Sherwood JB, Friedman R, Myers P, Bethea CF, **Levitsky S**, Hill DC, Jain MK, Koprosky SL, Mueller PS, Benson H, Hibberd PL. Study of the therapeutic effects of intercessory prayer (STEP): Study design and research methods. *Am Heart J* 2002; 143:577-584.

#### Abstracts

1. **McCully JD, Wakiyama H, Jones M, Levitsky S.** Role of necrosis and apoptosis in the evolution of surgical ischemia/reperfusion injury. *Circulation* 2002;106A.
2. **McCully JD, Wakiyama H, Jones M, Levitsky S.** Diazoxide supplemented cardioplegia provides enhanced cardioprotection through RNA and protein dependent mechanisms. *Circulation* 2002;106A .

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

**Division of Cardiothoracic Surgery**

**I. Narrative Report**

Basic Research

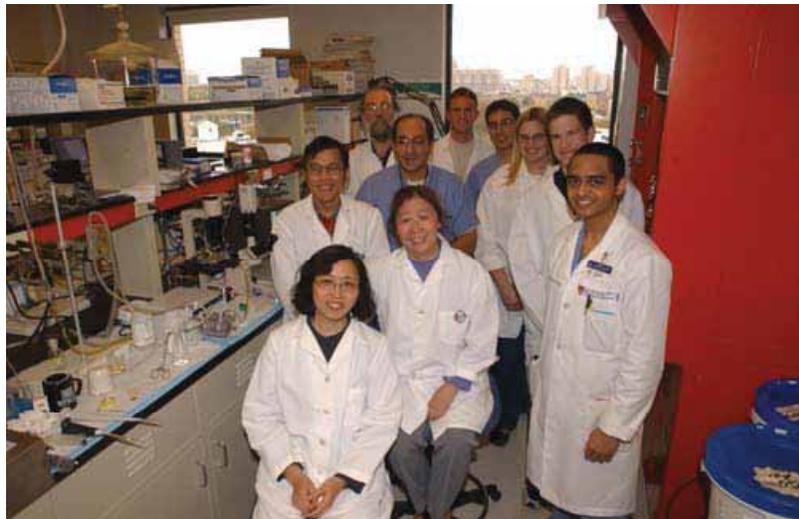
The goal of our research efforts is twofold. 1) To examine changes in coronary and peripheral microvascular reactivity and permeability and identify the respective cellular and molecular mechanisms of change, which occur as a consequence of cardiopulmonary bypass and cardioplegia in a porcine model.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

**II. List of Current Employees**

- |                       |                                      |
|-----------------------|--------------------------------------|
| 1. Jun Feng, MD, PhD  | Instructor in Surgery                |
| 2. Tanveer A Khan, MD | Surgical Resident                    |
| 3. Pierre Voisine, MD | Research Fellow                      |
| 4. Tamer Malik, MD    | Research Fellow                      |
| 5. Jiannyi Li, MB     | Research Assistant                   |
| 6. Shu Hua Xu, PhD    | Research Assistant                   |
| 7. Keith Michael, BS  | 2 <sup>nd</sup> Year Medical Student |



Dr. Frank Sellke



Dr. Sellke's Research Group

**III. List of Current Funding**

1. "Cardioplegia and Coronary Microvascular Reactivity"

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

2. "Surgical Intramyocardial Angiogenesis in a Swine model of Endothelial Dysfunction"  
RO1 HL-69024  
Project period: 07/01/2002-06/30/2007  
Principal Investigator: Dr. Frank W. Sellke
3. "NHLBI Administrative Supplements for Microarray Applications and Analyses"  
NOT-HL-02-003  
Project period: 09/01/2002-08/31/2003  
Principal Investigator: Dr. Frank W. Sellke
4. "BIDMC-Cardiothoracic Surgery Discretionary Fund"  
Principal Investigator: Dr. Frank Sellke
5. "Effect of PARS Inhibitor in Myocardial Ischemia"  
National Institutes of Health/NHLBI, R43 HL65863  
Project Period: 07/31/2001–12/31/2002  
Principal Investigator: Dr. Frank W. Sellke  
Subcontract with Dr. C. Csaba from Inotek Corporation
6. "HMG CoA Reductase Inhibitors and Cardiopulmonary Bypass"  
NIH Individual National Research Service Award F32 HL69651  
National Institutes of Health/NHLBI  
Project period: 2001-2003  
Principal Investigator: Dr. Tanveer Khan  
Sponsor: Dr. Frank W. Sellke
7. "Anti-inflammatory and Thrombotic Effects of Aprotinin"  
Bayer Corporation  
Principal Investigator: Dr. Frank W. Sellke
8. "Double-Blind Multi-Center Study of the Safety and Efficacy of Parecoxib Followed by Valdecoxib Compared to Placebo for Treatment of Post-Surgical Pain in Patients who have Coronary Bypass Graft Via Median Sternotomy".  
Pharmacia  
Principal Investigator: Dr. Frank W. Sellke

#### **IV. Applications Submitted and Pending Review/Funding**

##### Pending Grants (resubmission)

1. "Cardiovascular Surgery Research Training Grant"  
National Research Service Award T32

Project period: 03/31/2004-3/31/2009  
Program Director: Frank W. Sellke  
(score: 170)

## **V. Report of Teaching**

### Undergraduate and Medical School Courses

1. Dr. Cesario Bianchi continues as a member of the Teaching Faculty for Harvard Medical School, tutoring first year Harvard Medical / Dental Students (Human Body, Cell Biology).
2. The laboratory sponsors 1 or 2 high school students from Project Success, Harvard Medical School Office for Diversity and Community Partnership. Each student spends 10 weeks in the laboratory doing a research project.

### Graduate School and Graduate Medical Courses

1. Dr. Frank W Sellke does daily teaching rounds, instruction and assisting at surgery (cardiac and thoracic).
2. Dr. Sellke is Director of the Cardiothoracic Surgery Residency Training Program, where he is responsible for the organization and administration of conferences and training programs. He has 1 junior (PGY-6) and 1 senior (PGY-7) resident per year.

### Invited Presentations (local, national, international)

#### Dr. Frank W. Sellke

1. "Therapeutic Angiogenesis for Inoperable Coronary Artery Disease". The Northeast Cardiothoracic Surgical Society, Effingham, NH, Oct 2002.
2. Organizer and Moderator: Harvard Combined Cardiothoracic Surgical Conference. BIDMC, March 26, 2003.
3. BIDMC Vascular Biology Lecture Series, "Therapeutic Angiogenesis using Protein Growth Factors: Can we enhance the Response", June 2003.
4. Invited Lecturer: "Surgical Angiogenesis for the Treatment of Coronary Artery Disease", Dartmouth Medical School, Hanover NH. June 2003
5. Invited Lecturer: "The future of Cardiac Surgery: Panic or Opportunity", Society of University Surgeons, Honolulu, Hawaii. Feb 2002
6. Moderator: Cardiac Surgery Forum Session, American Association for Thoracic Surgery Meeting, Washington DC.

7. Invited Lecturer: Third International Symposium: Myocardial Protection from Surgical Ischemia Reperfusion Injury "Treatment of the Unrevascularizable Myocardial Segment: Angiogenesis", Asheville, NC.
8. Moderator: Third International Symposium: Myocardial Protection from Surgical Ischemia Reperfusion Injury, "Use of Molecular and Cellular Therapy in Myocardial and Vascular Protection: What is clinically applicable?" Asheville, NC.
9. Invited Lecturer: Therapeutic Coronary Angiogenesis using FGF-2 Protein. 8<sup>th</sup> World Congress on Heart Failure. Washington DC.
10. Invited Lecturer: Therapeutic Coronary Angiogenesis: Does it have a future? American College of Surgery, Surgery Biology Club I, San Francisco CA. Oct 2002
11. Moderator: Surgical Forum, American College of Surgeons, Cardiothoracic Surgery I: Ventricular Remodeling/Myocardial Protection.
12. Moderator: Novel approaches to surgical myocardial revascularization. American Heart Association Scientific Sessions. Chicago, IL.
13. Moderator: Novel methods of myocardial revascularization. American Heart Association Scientific Sessions. Chicago, IL.
14. Invited Discussant: Special Session XII: Late-breaking clinical trials. American Heart Association Scientific Sessions. Chicago, IL.
15. Invited speaker: Thoracic Surgery Directors Association Meeting, San Diego, CA.
16. Invited Lecturer: Ottawa Heart Institute, Ottawa, Ontario, Canada.
17. Invited Lecturer: "The Peer Review Process in Medical Publishing-a Reviewer's Perspective". AATS Symposium "Developing the Academic Thoracic Surgeon".
18. Invited Lecturer: "Vascular Protection after cardiac Surgery: Does it Matter?" International Society for Heart Research, Mystic CT, June 2003.
19. Invited Lecturer: "Therapeutic Angiogenesis using Protein Growth Factors" International Society for Heart Research, Mystic CT, June 2003.
20. Invited Speaker: International Symposium of Cardiovascular Research, Sendai, Japan.

## VI. Plans for the Coming Academic Year

### Staff Change

1. Dr. Tanveer Khan, MD returned to the BIDMC Clinical Surgery Residency Program.
2. Dr. Yasunari Nakai, MD from Osaka Medical College will join our laboratory as a Research Fellow, in November 2003.
3. Jennifer Sandmeyer, BS, a 2<sup>nd</sup> year Harvard Medical School student will join our laboratory in September 2003.

## VII. Bibliography (07/01/02-06/30/03)

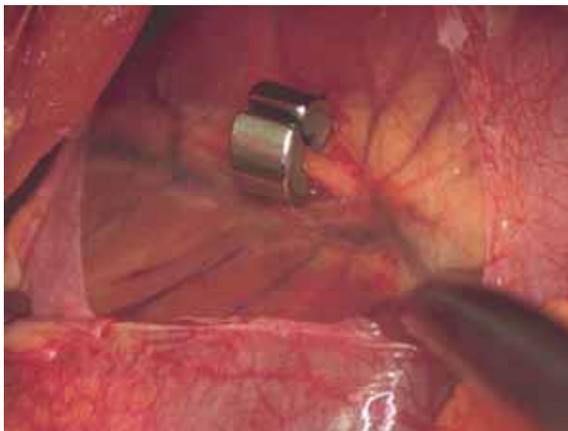
### Original Articles

1. **Bianchi C, Wakiyama H, Faro R, Khan T, McCully JD, Levitsky S, Szabo C, Sellke FW.** A novel peroxy nitrite decomposer catalyst (FP-15) reduces myocardial infarct size in an in vivo model of acute ischemia/reperfusion in pigs. *Ann Thorac Surg* 2002;74:1201-1207.
2. **Khan TA, Bianchi C, Aurajo EG, Ruel M, Voisine P, Li JY, Liddicoat JR, Sellke FW.** Cardiopulmonary bypass reduces peripheral microvascular function by inhibition of nitrogen activated protein kinase activity. *Surgery* 2003;247-254.
3. **Khan TA, Ruel M, Bianchi C, Voisine P,** Komjati K, Szabo C, **Sellke FW.** Poly (ADP-ribose) Polymerase inhibition improves postischemic myocardial function after cardiopulmonary bypass. *J Am Coll Surg* 2003;247-254.
4. Laham RJ, **Li J, Tofukuji M,** Post M, Simons M, **Sellke FW.** Spatial heterogeneity in VEGF-induced vasodilation: VEGF dilates microvessels but not epicardial and systemic arteries and veins. *Ann Vasc Surg* 2003;245-252.
5. Li J, Parovian C, **Li Jianyi, Hampton TG, Metais C,** Tkachenko E, **Sellke FW,** Simons M. Modulation of microvascular signaling by heparin sulfate matrix: studies in syndecan-4 transgenic mice. *Microvascular Research* 2002;64:38-46.
6. Maynard SE, Min J-Y, Merchan J, Lim K-H, **Li JY,** Mondal S, Libermann T, Morgan JP, **Sellke FW,** Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental sFLT-1 contributes to endothelial dysfunction, hypertension and proteinuria of pre-eclampsia. *J Clin Invest* 2003;649-658.

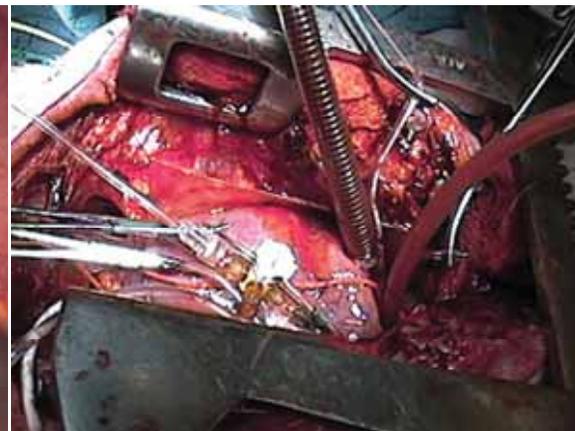
7. **Ruel M, Sellke FW, Bianchi C, Khan TA, Faro R, Zhang J-P, Cohn WE.** Endogenous myocardial angiogenesis and revascularization using a gastric submucosal patch. *Ann Thorac Surg* 2003;1443-9.
8. Zhang Y, **Li JY, Sellke FW**, Simons M. Syndecan 4 modulates basic fibroblast growth factor (FGF2) signaling in vivo. *Am J Physiol Heart and Circulatory Physiol* 2003;H2078-H2082.



The laboratory uses two large animal operating rooms for survival (left) and non-survival (right) experimental protocols. Around 500 surgeries were performed between July 2002 and June 2003.



Ameroid Placement



Cardiopulmonary Bypass

Original Articles (in press)

1. **Cohn WE, Ruel M, Zhang JP, Sellke FW, Johnson RG.** Internal thoracic artery flow competition: Studies in a canine H-graft. *European Journal of Cardiovascular Surgery*; in press.
2. **Feng J, Bianchi C, Li JY, Sellke FW.** Improved profile of bad phosphorylation and caspase 3 activation after blood versus crystalloid cardioplegia. *Ann Thorac Surg*; in press.

3. **Khan TA, Bianchi C, Ruel M, Voisine P, Li JY, Liddicoat JR, Sellke FW.** Mitogen-activated protein kinase inhibition and cardioplegia-cardiopulmonary bypass reduce coronary myogenic tone. *Circulation*; in press.
4. Laham RJ, Rezaee M, Post M, **Xu X, Sellke FW.** Intrapericardial administration of basic fibroblast growth factor: Myocardial and tissue distribution and comparison with intracoronary and intravenous administration. *Catheterization and cardiovascular interventions*; 2003; in press.
5. **Ruel M, Bianchi C, Khan TA, Xu S, Liddicoat JR, Araujo E, Voisine P,** Lyon H, Kohane I, Libermann TA, **Sellke FW.** Gene expression profile after cardiopulmonary bypass and cardioplegic arrest. *J Thorac Cardiovasc Surg*; in press.
6. **Ruel M, Fu G, Khan TA, Voisine P, Bianchi C, Li J, Li J, Laham R, Sellke FW.** Inhibition of the cardiac angiogenic response to surgical FGF-2 therapy in a swine endothelial dysfunction model. *Circulation*; in press.
7. Wu G, Mannam, AP, Kirbis, S, Wu, J, Laham, RJ, **Sellke, FW,** Li, J. Hypoxia induces myocyte-dependent COX-2 gene regulation in human vascular endothelial cells. *Am J Physiol*; in press.

#### Reviews, Chapters, and Editorials

1. Harrison DG, Doughan A, **Sellke FW.** Physiology of the coronary circulation. In: *Surgery of the Chest. Seventh Edition*, ed. Sellke FW, Swanson S, Del Nido P. Harcourt Health Sciences, Philadelphia PA., in press.
2. **Khan TA, Sellke FW,** Laham RJ. Gene therapy progress and prospects: therapeutic angiogenesis for limb and myocardial ischemia. *Gene Therapy* 2003;10:285.
3. **Khan TA, Sellke FW,** Laham RJ. Therapeutic angiogenesis: Protein-based therapy for coronary artery disease. *Expert Opinion on Pharmacotherapy* 2003;4:219-226.
4. **Ruel M, Sellke FW.** Coronary artery bypass grafting. In: *Surgery of the Chest. Seventh Edition*, ed. Sellke FW, Swanson S, Del Nido P. Harcourt Health Sciences, Philadelphia PA.
5. **Ruel M, Sellke FW.** Therapeutic coronary angiogenesis. In: *Surgery of the Chest. Seventh Edition*, ed. Sellke FW, Swanson S, Del Nido P. Harcourt Health Sciences, Philadelphia PA.

6. **Sellke FW.** Gene therapy in cardiac surgery: Is there a role? *J Thorac Cardiovasc Surg* 2003;125:994-997.
7. **Sellke FW.** Invited commentary. *Ann Thorac Surg* 2003;75: 773-774.
8. **Sellke FW, Ruel M.** Vascular growth factors and angiogenesis in cardiac surgery. *Ann Thorac Surg* 2003;75:S685-690.
9. Urschel **JD, Ashiku S, Thurer R, Sellke FW.** Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer- A review. *Dis Esophagus* 2003;60-65.
10. Urschel **JD, Sellke FW.** Complications of salvage esophagectomy. *Med Sci Monit* 2003;RA173-180.

Reviews, Chapters, and Editorials (in press)

1. **Frank W Sellke.** Editor in Chief: *Surgery of the Chest*. Seventh Edition, Harcourt Health Sciences, Philadelphia PA; in press.
2. **Ruel M, Sellke FW.** Protein angiogenic therapy. *Seminars in Thoracic and Cardiovascular Surgery*; in press.
3. **Ruel M, Song J, Sellke FW.** Protein-, gene-, and cell-based therapeutic angiogenesis for the treatment of myocardial ischemia. *Journal of molecular and cellular biochemistry*; in press.
4. **Sellke, FW.** The peer-review process in medical publishing: A reviewer's perspective. *Journal of Thoracic and Cardiovascular Surgery*; in press.
5. **Sellke FW, Delatorre R.** Aortic dissection. In: *Textbook of Critical Care Medicine*, 5th edition. Edited by Abraham, Vincent, Kochanek, Fink. McGraw-Hill; in press.
6. **Sellke FW, Ruel M, Laham R, Simons M.** Therapeutic coronary angiogenesis using FGF-2 protein. In: *Proceedings of the 8<sup>th</sup> World Congress on Heart Failure*. ISI, Philadelphia; in press.

Nonprint Materials

1. **Sellke FW.** Invited internet review (*Annals of Thoracic Surgery*): Duraflon II heparin bonding does not attenuate cytokine release or improve pulmonary function. *Internet Cardiothoracic Digest*. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
2. **Sellke FW.** Invited internet review (*Annals of Thoracic Surgery*): Therapeutic angiogenesis induced by local autologous bone marrow cell

- implantation. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
3. **Sellke FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): Does off-pump coronary surgery reduce morbidity and mortality? Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
  4. **Sellke FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): Normothermia does not improve postoperative hemostasis nor does it reduce inflammatory activation in patients undergoing primary isolated coronary artery bypass. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
  5. **Sellke FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): The early clinical and angiographic outcome of sequential coronary artery bypass grafting with the off-pump technique. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
  6. **Sellke FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): The Insulin Cardioplegia Trial: Myocardial protection for urgent coronary artery bypass grafting. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2002: ctdigest.com.
  7. **Sellke, FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): Therapeutic angiogenesis in the ischemic canine heart induced by myocardial injection of naked complementary DNA plasmid encoding hepatocyte growth factor. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2003: ctdigest.com.
  8. **Sellke, FW.** Invited internet review (Journal of Thoracic and Cardiovascular Surgery): Vacuum-assisted closure as a treatment modality for infections after cardiac surgery. Internet Cardiothoracic Digest. CME Network, Southampton, NY, L Cohn, Ed. 2003: ctdigest.com.

### Abstracts

1. Khan T, **Bianchi C, Ruel M, Sellke FW.** Mitogen-activated protein kinase activation and vasomotor dysfunction after cardiopulmonary bypass. Presented at the Canadian Cardiovascular Congress 2002 of the Canadian Cardiovascular Society. Edmonton, Alberta, Canada. 2002.
2. **Khan T, Ruel M, Bianchi C, Szabo C, Sellke FW.** Inhibition of poly ADP-ribose synthetase improves postischemic myocardial function after cardiopulmonary bypass. Presented at the Canadian Cardiovascular Congress 2002 of the Canadian Cardiovascular Society. Edmonton, Alberta, Canada. 2002.

3. **Khan TA, Bianchi C, Aurajo EG, Ruel M, Voisine P, Li J, Liddicoat JR, Sellke FW.** Cardiopulmonary bypass reduces peripheral microvascular function by inhibition of mitogen-activated protein kinase activity. Accepted for presentation at the Society of University Surgeons Annual Meeting. Houston, TX. 2003.
4. **Khan TA, Bianchi C, Faro R, Ruel M, Sellke FW.** Activation of pulmonary mitogen-activated protein kinases during cardiopulmonary bypass. Presented at the Annual Meeting of the Association of Academic Surgery. Boston, MA. 2002.
5. **Khan TA, Bianchi C, Ruel M, Liddicoat JR, Li J, Sellke FW.** Mitogen-activated protein kinase inhibition and cardiopulmonary bypass reduce coronary myogenic tone. Presented at the Scientific Sessions 2002 of the American Heart Association. Chicago, IL. 2002.
6. **Khan TA, Bianchi C, Ruel M, Voisine P, Araujo E, Li J, Liddicoat JR, Sellke FW.** Mitogen-activated protein kinase inhibition and cardiopulmonary bypass reduce coronary myogenic tone. Presented at the Beth Israel Deaconess Medical Center Research Forum. Boston, MA 2002.
7. **Khan TA, Ruel M, Bianchi C, Szabo C, Sellke FW.** Poly ADP-ribose synthetase inhibition improves postischemic myocardial function after cardiopulmonary bypass. Presented at the 88<sup>th</sup> Annual Clinical Congress of the American College of Surgeons. San Francisco, CA. 2002.
8. **Khan TA, Ruel M, Bianchi C, Voisine P, Li J, Xu S, Laham RJ, Sellke FW.** Chronic myocardial ischemia increases syndecan-4 expression and alters coronary microvascular function. Accepted for presentation at the Society of University Surgeons Annual Meeting. Houston, TX. 2003.
9. **Ruel M, Bianchi C, Khan TA, Xu S, Cohn WE, Liddicoat JR, Lyon H, Liberman T, Kohane I, Sellke FW.** Genomic expression profile of the clinical response to cardiopulmonary bypass. Presented at the Scientific Sessions 2002 of the American Heart Association. Chicago, IL. 2002.
10. **Ruel M, Bianchi C, Khan TA, Xu S, Liddicoat JR, Cohn WE, Liberman T, Lyon H, Kohane I, Sellke FW.** Genomic expression profile of the clinical response to cardiopulmonary bypass. Presented at the Canadian Cardiovascular Congress 2002 of the Canadian Cardiovascular Society. Edmonton, Alberta, Canada. 2002.
11. **Ruel M, Wu GF, Khan TA, Bianchi C, Cohn WE, Laham RJ, Li J, Sellke FW.** Surgical angiogenesis with FGF-2 is impaired by endothelial dysfunction. Presented at the Canadian Cardiovascular Congress 2002 of the Canadian Cardiovascular Society. Edmonton, Alberta, Canada. 2002.

12. **Ruel M**, Wu GF, **Khan TA**, **Bianchi C**, **Cohn WE**, **Li J**, Laham RJ, **Sellke FW**. Inhibited angiogenic response to surgical FGF-2 protein therapy in a swine model of endothelial dysfunction. Presented at the Scientific Sessions 2002 of the American Heart Association. Chicago, IL. 2002.
13. **Sellke FW**. Vascular protection during cardiac surgery: Does it make a difference? Presented at the 25th Annual Meeting of the International Society for Heart Research. Mystic CT. Journal of Molecular and Cellular Cardiology 2003;35:A7.

# GENERAL SURGERY



Mark Callery, M.D., Chief

## Division Members

|                                  |                                   |
|----------------------------------|-----------------------------------|
| Sonia Y. Archer, M.D.            | Clinton Koufman, M.D.             |
| Chris G. Boyd, M.D.              | Donald W. Moorman, M.D.           |
| George L. Blackburn, M.D., Ph.D. | Peter M. Mowschenson, M.B.        |
| Michael J. Cahalane, M.D.        | Edward C. Mun, M.D.               |
| Jonathan F. Critchlow, M.D.      | Sareh Parangi, M.D.               |
| Rosemary B. Duda, M.D.           | Nicholas E. Tawa Jr., M.D., Ph.D. |
| Josef E. Fischer, M.D.           | Susan L. Troyan, M.D.             |
| Dana K. Fugelso, M.D.            | Benjamin E. Schneider, M.D.       |
| Susan J. Hagen, Ph.D.            | Charles Vollmer, M.D.             |
| Per-Olof Hasselgren, M.D., Ph.D. | Jin-Rong Zhou, Ph.D.              |
| Mary Jane Houlihan, M.D.         | Clinton Koufman, M.D.             |
| Daniel B. Jones, M.D.            |                                   |

**Sonia Archer, M.D.**

**Division of General Surgery**

**I. Narrative Report**

My research focuses on deciphering mechanisms involved in the beneficial effects of fiber on colon cancer. This work is of significant clinical and societal importance since colon cancer is the third most common cancer, and the second leading cause of cancer deaths in the United States. Although both environmental and genetic factors play a role in its genesis, environmental factors appear to predominate in importance.

Butyrate, a product of fiber fermentation in the colon, is known to inhibit colon carcinogenesis and colon cancer cell growth both *in vivo* and *in vitro*. Cell growth occurs through cell cycle progression, which is controlled by a variety of protein cyclins and their associated kinases. Cell cycle inhibitors, such as p21, block the association of cyclins and kinases, resulting in growth arrest. Our laboratory has shown that butyrate inhibits colon cancer cell growth *in vitro* by transcriptional induction of p21. We have further defined molecular mechanisms that are involved in transcriptional induction of p21 by butyrate, both *in vitro* and *in vivo*. In addition, we have expanded the scope of this work to include examination of other cell cycle regulators, such as cyclin B1, a cell cycle promoter that is increased in colon cancer cells. We are now actively involved in studies to address the regulation and importance of the cyclin B1 gene product in colon cancer cell growth, as well as its regulation by butyrate.

Our long-term goal is to continue to advance the understanding of molecular mechanisms involved in butyrate's (and fiber's) protection against colon carcinogenesis. My expectation is that we will eventually be able to translate these findings into diagnostic and therapeutic strategies against colon cancer.

**II. List of Current Employees**

1. Search in progress Postdoctoral Fellow

**III. List of Current Funding**

1. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"  
Robert Wood Johnson, Minority Medical Faculty Development Award  
Project period: 07/01/2002-06/30/2006  
Principal Investigator: Sonia Archer, M.D.
2. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"  
HMS, Minority Medical Faculty Development Bridge Award  
Project Period: 07/01/03-06/30/04  
Principal Investigator: Sonia Archer, M.D.

#### IV. Applications Submitted and Pending Review/ Funding

1. “Molecular mechanisms underlying butyrate-mediated growth inhibition in colon cancer cells *in vivo* – importance of the p21 gene and histone hyperacetylation”  
Dana Farber/ Harvard Cancer Center G.I. Cancer SPORE - Colorectal Adenoma  
Developmental Projects Program, National Institutes of Health.



**Dr. Sonia Archer**

#### V. Divisional Accomplishments Over Past Year

Over the past year, with the acquisition of a new research technician, I have successfully begun studies in the molecular mechanisms underlying the regulation of cyclin B1 gene expression by butyrate in colon cancer cells. This interesting work has attracted students to come to the laboratory to participate. I have also authored two papers: “The effects of

short-chain fatty acids on human colon cancer cell phenotype are associated with histone hyperacetylation” published in *Journal of Nutrition*, and “Enterocyte response to ischemia is dependent on differentiation state” published in the *Journal of Gastrointestinal Surgery*. I have contributed a grant proposal in the Dana Farber/ Harvard Cancer Center G.I. Cancer SPORE Developmental Projects Program, National Institutes of Health. The proposed project will examine the importance of the p21 gene in butyrate-mediated inhibition of colon cancer cell growth and the molecular mechanisms involved in p21 gene regulation, *in vivo*.

At the national level, I continue active service as a councillor on the executive committee of the Association for Academic Surgery. I will again teach in the Fundamentals of Surgical Research Course offered by the Association for Academic Surgery in November.

I have continued to serve as advisor and mentor for minority students in the Biomedical Science Careers Student Project, as well as students who work in my laboratory.

## V1. Report of Teaching

### Undergraduate and medical school courses:

1. Focused Discussion on Colon Cancer Genetics, Colon Cancer, and Polyps in G.I. Pathophysiology Course for 2<sup>nd</sup> year Harvard Medical School Students.
2. I continue to serve as advisor and mentor for minority students in the Biomedical Science Careers Student Project, as well as students who work in my laboratory.

### Graduate school and graduate medical school course:

1. I continue to teach surgical residents in our General Surgery program on a regular basis.

## VII. Plans For The Coming Year

### Plans for research:

1. We will continue our work on the regulation of cyclin B1 by butyrate, both in *in vivo* and *in vitro* models. Our work has produced exciting data which will soon be submitted for publication. With the acquisition of additional grant funding, our long-term goal will be 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.

### Plans for educational programs:

1. I will continue to teach the HMS G.I. Pathophysiology and Surgical Core Clerkship courses, and other courses as needed. I will be giving a CME lecture at Winchester Hospital in December.

## VIII. Bibliography (07/01/2002-06/30/2003)

### Original Reports

1. **Hinnebusch BF**, Ma Q, Henderson JW, Siddique A, **Archer SY**, Hodin RA. Enterocyte response to ischemia is dependent on differentiation state. *J Gastrointest Surgery* 2002;6:403-09.
2. **Hinnebusch BF**, Meng S, Wu JT, **Archer SY**, Hodin RA. The effects of short-chain fatty acids on human colon cancer cell phenotype are associated with histone hyperacetylation. *J Nutr* 2002;132:1012-17.

**George L. Blackburn, M.D., Ph.D.**  
**Jin-Rong Zhou, Ph.D.**

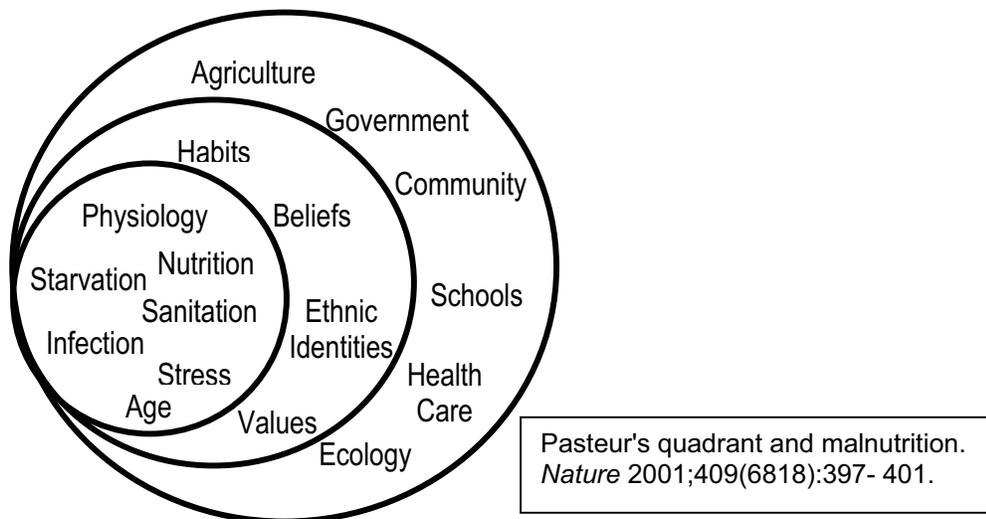
**Division of General Surgery**  
Section of Surgical Nutrition  
Center for the Study of Nutrition Medicine (CSNM)  
Nutrition Metabolism Laboratory (NML)

## **I. Narrative Report**

### Clinical Research

Our group focuses on the framework for determinants of malnutrition and intervention strategies. Our current NIH sponsored research is concerned with prevention, diagnosis, and treatment of malnutrition. The aim of our program is on new technologies in food and nutrition science, food delivery systems, and changes in social, political and ecological systems.

### **Framework for Determinants of Malnutrition and Intervention Strategies**



Current investigations address areas such as breast cancer, prostate cancer, hypertension, diabetes and obesity. CSNM provides sophisticated, scientific nutrition interventions that are utilized to support research, training and patient care in these areas. In line with the medical center's "bench-to-bedside" mission, CSNM actively utilizes the data gleaned from research in the future treatment of patients. In collaboration with OB/GYN, we also study alternatives to hormone replacement therapy in post-menopausal women. We are investigating the effect of the novel daidzein-rich isoflavone-aglycone extract from soy germ fermentation on the severity and frequency of hot flashes in postmenopausal women. We are responsible for analyses of biomarkers in the blood and urine samples. The laboratory is equipped with two state-of-art HPLC systems to determine soy isoflavones and catecholamines for the proposed clinical study.

## Basic Research

The Nutrition Metabolism Laboratory studies the effects of plant components, such as soy phytochemicals, tea polyphenols and other dietary/herbal supplements, on the prevention and treatment of cancer and obesity, and to elucidate the underlying molecular and cellular mechanisms. We are particularly interested in the in vivo evaluation of preventive activities of bioactive components in soy, tea and other plant compounds by application of clinically relevant orthotopic tumor models. We are studying the molecular mechanisms by which dietary bioactive components modulate cell proliferation and apoptosis and tumor angiogenesis. We are investigating the effect of a novel daidzein-rich isoflavone-aglycone extract from soy germ fermentation with Koji fungus (*Aspergillus awamori*) on the prevention of obesity. We are further isolating and identifying other bioactive components in soy and tea that may also be responsible for their cancer prevention activity. Collaborative research with the investigators inside and outside the BIDMC involves studies in the effects of plant phytochemicals on hormonal modulation (Dr. Sandra Gaston, Department of Surgery, BIDMC), in the effect of nutritional treatment on early prevention of prostate cancer by using an established transgenic animal model (Dr. Steve Balk, Department of Medicine, BIDMC), in the modulation of gene expression by nutritional manipulations in prostate and breast cancer (Dr. Towia Libermann, Department of Medicine, BIDMC), in the effect of plant components on prostate cancer prevention by inhibition of DNA topoisomerase (Dr. David Lee, McLean Hospital/HMS), and in the effect of cholesterol on prostate cancer (Dr. Michael Freeman, Children's Hospital). Our long-term goal of research is to identify the effective components in nature for prevention of cancer and obesity.

## **II. List of Current Employees**

- |     |   |                            |
|-----|---|----------------------------|
| 1.  | Lalita Khaodhiar, M.D.  | Instructor in Medicine     |
| 2.  | Weijun Pan, MD, PhD.  | Visiting Scientist         |
| 3.  | Zhiming Mai, Ph.D.  | Senior Postdoctoral Fellow |
| 4.  | Anne McNamara RN  | Research Associate         |
| 5.  | Trisha Copeland, MS, RD   | Research Associate         |
| 6.  | Pam Karun, MS   | Research Associate         |
| 7.  | Wanda Hirsch, RD  | Research Associate         |
| 8.  | Michelle Sherwood, RD   | Research Associate         |
| 9.  | Heather McCormick, RD   | Research Associate         |
| 10. | Min Lin, BA   | Research Assistant         |
| 11. | Xin Li, MD  | Research Associate         |
| 12. | Aijita Singh, Ph.D.   | Postdoctoral Fellow        |
| 13. | Lei Wu, MD  | Visiting Scientist         |
| 14. | Zhanggui Wu, Ph.D.  | Research Associate         |
| 15. | Yi Zhao, Ph.D.  | Postdoctoral Fellow        |
| 16. | Barbara Ainsley, DTR  | Administrative Assistant   |
| 17. | Susan Sidell  | Administrative Coordinator |
| 18. | Edward C. Mun, M.D., Assistant Professor of Surgery, also works closely with our group. |                            |



Dr. Zhou (back row, 2<sup>nd</sup> from the left) and the Nutrition Metabolism Group

## II. List of Current Funding

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

1. The Study of Health Outcomes of Weight Loss  
NIDDK DK57154-03  
Project period: 09/01/01-08/31/03  
PI: David Nathan, M.D.  
Co-Investigator: George Blackburn, M.D., Ph.D.
2. Low-Fat Diet in Stage II Breast Cancer: Outcome Trial  
AHF/NCI 5R01-CA45504-11  
Project period: 01/01/97 – 12/30/04  
PI: Daniel Nixon, M.D.  
Co-Investigator/Committee Chair: George Blackburn, M.D., Ph.D.
3. Effects of Soy Isoflavones on Menopausal Hot Flashes  
Nichimo  
Project period: 6/03/02 – 6/03/05  
PI: Hope Ricciotti, M.D.  
Co-PI: George Blackburn, M.D., Ph.D.
4. “Interaction between dietary soy components and tamoxifen on breast cancer progression”

NCCAM/NIH RO1 AT00863  
Project Period: 09/12/2001-05/31/2004  
PI: Jinrong Zhou, Ph.D.  
Co-Investigator: George Blackburn, M.D., Ph.D.

5. "Chemoprevention of Bladder Cancer by Soybean bioactive components"  
RO1 CA92546-01  
Project Period: 06/01/2003-05/31/2007  
PI: Jinrong Zhou, Ph.D.  
Co-Investigator: George Blackburn, M.D., Ph.D.
6. The Boston Obesity Nutrition Research Center (BONRC)  
NIDDK/NIH P30DK46200  
Project Period: 9/30/98-3/31/03 4/01/03-4/01/08  
PI: Barbara Corkey, Ph.D.  
Associate Director: George Blackburn, M.D., Ph.D.
7. Liver Chemistry Monitoring Program as Follow-Up to An Eight-Week, Parallel Group, Double-Blind, Randomized, Placebo and Active-Controlled, Multicenter Study to Evaluate the Efficiency, Safety and Tolerability of Two Formulations of GI181771X, Each a Two Different Doses in Obese Subjects.  
GlaxoSmithKlein  
Project Period: 9/03 –11/03  
PI: George Blackburn, M.D., Ph.D.

Jin-Rong Zhou, Ph.D.

1. "Interaction between dietary soy components and tamoxifen on breast cancer progression"  
National Institutes of Health, RO1 AT00863  
Project period: 09/12/2001-05/31/2004  
PI: Jin-Rong Zhou, Ph.D.  
Co-Investigator: George Blackburn, M.D., Ph.D.
2. "Chemoprevention of Bladder Cancer by Soybean"  
National Institutes of Health, RO1 CA92546  
Project period: 06/01/2003-05/31/2007  
PI: Jin-Rong Zhou, Ph.D.  
Co-Investigator: George Blackburn, M.D., Ph.D.
3. "Genes modulated by soy in prostate cancer progression"  
National Institutes of Health, RO3 CA101041  
Project period: 05/01/2003-04/30/2005  
PI: Jin-Rong Zhou, Ph.D.
4. "Combined effects of soy and tea bioactive components on breast cancer progression".  
Susan Komen Breast Cancer Foundation

Project period: 10/01/2000-09/30/2003  
PI: Jin-Rong Zhou, Ph.D.

5. "Effects of AglyMax on the prevention and treatment of obesity and prostate cancer"  
Nichimo Company, Japan  
Project period: 03/01/2001-05/30/2003  
PI: Jin-Rong Zhou, Ph.D.
6. "Trace elements and the development of prostate cancer"  
Department of Defense  
Project period: 01/01/2002-12/31/2004  
PI: Arthur Sytkowski, M.D.  
Co-Investigator: Jin-Rong Zhou, Ph.D.
7. "Functional erythropoietin receptors expressed by human prostate cancer cells"  
Department of Defense  
Project period: 04/01/2003-03/28/2006  
PI: Arthur Sytkowski, M.D.  
Co-Investigator: Jin-Rong Zhou, Ph.D.

### **III. Applications Pending Review and Funding**

George L. Blackburn, MD, Ph.D.

1. "Safety, efficacy of high protein, low carbohydrate diet".  
NIDDK/NIH  
Project Period: 4/01/03 – 3/31/09  
PI: George L. Blackburn, M.D., Ph.D.
2. Exercise and Weight Loss for Breast Cancer Prevention  
Department of Defense  
Project Period: 1/01/04 – 12/31/0  
PI: Anne McTiernan  
Co-Investigator: George L. Blackburn, M.D., Ph.D.

Jin-Rong Zhou, Ph.D.

1. "Black tea and prostate cancer prevention"  
National Institutes of Health, RO1 AT001623  
Project period: 12/01/2003-11/30/2008  
PI: Jin-Rong Zhou, Ph.D.
2. "Androgen modulation by genistein in prostate cancer"  
National Institutes of Health, RO1 CA101011  
Project period: 04/01/2004-03/31/2009  
PI: Jin-Rong Zhou, Ph.D.

3. "Effects of soy products on estrogen insufficiency-induced tamoxifen-nonresponsive breast cancer"  
Susan Komen Breast Cancer Foundation  
Project period: 05/01/2004-04/30/2006  
PI: Jin-Rong Zhou, Ph.D.
4. "Soy and tea combination on prostate cancer prevention"  
American Cancer Society  
Project period: 01/01/2004-12/31/2007  
PI: Jin-Rong Zhou, Ph.D.

#### **IV. Divisional Accomplishments**

##### **Research accomplishments: New grants in the past year (Dr. Zhou)**

1. "Interaction between dietary soy components and tamoxifen on breast cancer progression"  
NIH/NCCAM (RO1 AT00863)  
Project period: 09/12/2001-05/31/2004  
PI: Jin-Rong Zhou, Ph.D.  
Co-Invest: George L. Blackburn, M.D., Ph.D.
2. "Chemoprevention of Bladder Cancer by Soybean"  
NIH/NCI (RO1 CA92546)  
Project period: 06/01/2003-05/31/2007  
PI: Jin-Rong Zhou, Ph.D.  
Co-Invest: George L. Blackburn, M.D., Ph.D.
3. "Genes modulated by soy in prostate cancer progression"  
NIH/NCI (RO3 CA101041)  
Project period: 05/01/2003-04/30/2005  
PI: Jin-Rong Zhou, Ph.D.
4. "Combined effects of soy and tea bioactive components on breast cancer progression"  
Susan Komen Breast Cancer Foundation  
Project period: 10/01/2000-09/30/2003  
PI: Jin-Rong Zhou, Ph.D.
5. "Effects of AglyMax on the prevention and treatment of obesity and prostate cancer"  
Nichimo Company, Japan  
Project period: 03/01/2001-05/30/2004  
PI: Jin-Rong Zhou, Ph.D.  
Co-Invest: George L. Blackburn, M.D., Ph.D.
6. "Trace elements and the development of prostate cancer"  
Department of Defense  
Project period: 01/01/2002-12/31/2004

PI: Arthur Sytkowski, M.D.  
Co-Invest: Jin-Rong Zhou, Ph.D.

7. "Functional erythropoietin receptors expressed by human prostate cancer cells"  
Department of Defense  
Project period: 04/01/2003-03/28/2006  
PI: Arthur Sytkowski, M.D.  
Co-Invest: Jin-Rong Zhou, Ph.D.
8. "Effects of Soy Isoflavones on Menopausal Hot Flashes"  
Nichimo Company, Japan  
Project period: 06/03/2002-06/03/2005  
PI: Hope Ricciotti, M.D.  
Co-PI: George L. Blackburn, M.D., Ph.D.  
Co-Invest.: Jin-Rong Zhou, Ph.D.

Individual Accomplishments: (George L. Blackburn, M.D., Ph.D.)

1. Distinguished Alumni Award, University of Kansas Medical Center.
2. Invited Guest: Federal Trade Commission Press Conference on Weight Loss Advertising.
3. NIDDK Special Emphasis Panel Loan Repayment Study Section 2003

Individual Accomplishments (Dr. Zhou)

1. NIH/NCI Special Emphasis Panel "Cancer Prevention on Research and Epidemiology", 2002-2003.
2. NIH/NCI Special Emphasis Panel "Chemoprevention of ER-Negative Breast Cancer", 2002.
3. Nutrition Curriculum Committee, Division of Nutrition, Harvard Medical School, 2002-2003.

**V1. Report of Teaching**

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

Undergraduate and Medical School Courses

1. Surgery Core Clerkship SU600M.5. Third year Harvard medical students. Nutrition didactic lecture – Lecturer Approx. 25 students 1 hour lecture and syllabus 1/yr.
2. Preventive Medicine & Nutrition course number PM711.0; Second year HMS Tutor.

## CME Courses

1. The Centers for Obesity Research and Education (CORE) is one of eight nutrition research centers collaborating to develop practical workshops to educate physicians and allied health professionals in managing overweight and obesity in their patients, and to provide the latest scientific literature on the assessment, treatment and monitoring of obesity. This year a new workshop on the diagnosis and treatment of the Metabolic Syndrome was developed.
2. HMS, Department of Continuing Medical Education, Hyperalimentation Course, Enhancing the Safety of Parenteral and Enteral Nutrition. Dr. Blackburn delivered a lecture entitled "Critical Opportunity for Metabolic Support of the Seriously Ill Patient". Cambridge, MA. Dr. Blackburn was the course director.
3. HMS, Department of Continuing Medical Education, " Practical Approaches to the Treatment of Obesity" Cambridge, MA. Dr. Blackburn was the course director.
4. Division of Nutrition/HMS Annual Nutrition Conference " Nutrition and Gene Regulation" Obesity Chair and moderator, Boston, MA March 13-14, 2003

## Invited Presentations local, national, international

1. National Obesity Consultant Forum, Aspen, CO August 16-17, 2002.
2. CORE Workshop – Boston University Medical Center, Obesity Surgery, September 10, 2002.
3. American Society for Bariatric Physicians Annual Meeting, Boston, MA "Drug Induced Weight Gain" September 19, 2002.
4. National Diabetes Initiative, Boston, MA "Surgical Approaches to Obesity and Diabetes Prevention Strategies" October 5, 2002.
5. Pharmacy Medical Update, Philadelphia, PA " Drug Induced Weight Gain", October 19, 2002.
6. Blue Cross Blue Shield/Boston University Medical Center Continuing Medical Education, Dedham, MA "Obesity and the Metabolic Syndrome" October 26, 2002.
7. Providence Hospital Endocrinology Grand Rounds, Providence, RI "Surgical Approaches to Obesity and Diabetes Prevention Strategies" October 30, 2002.

8. Harvard Medical School CME Enhancing the Safety of Parenteral and Enteral Nutrition, Boston, MA “Enteral vs. Parenteral Nutrition” November 3, 2002.
9. Nurse Practitioners Annual Meeting, Boston, MA CORE Workshop on Obesity and the Metabolic Syndrome, November 13, 2002.
10. Museum of Science, Boston, MA “Low Fat or Low Carbohydrate: Are you what you eat?” Lecture and Panel discussion for the public, November 13, 2002.
11. Visiting Professor Groff Lecture Series, UMDNJ School of Osteopathic Medicine, NJ “Nutrition Support of the ICU Patient”, November 16, 2002.
12. Harvard Business School, Cambridge, MA PAPSAC Meeting – Public Policy Presentation “Obesity”, November 18, 2002.
13. Federal Trade Commission, Washington, D.C., Science Panel, November 19, 2002.
14. Unilever Health Institute, Bangkok, Thailand, Treatment of Obesity, Diabetes and the Metabolic Syndrome, and Structured Diet Plan using Meal Replacement, December 3-4, 2002.
15. Humane Medicine Program, Philadelphia, PA “Food First for Weight Management and Health, December 14, 2002.
16. Nutrition Week, San Antonio, TX “Metabolic Syndrome, January 19, 2003.
17. Cytokines and Obesity, January 21, 2003.
18. Surgical Grand Rounds, St. Lukes Hospital, New Bedford, MA, “Nutrition in the ICU Patient” February 8, 2003.
19. Emory Annual Nutrition Symposium, Atlanta, GA “Making good decisions about Diet Therapy” February 13, 2003.
20. Surgical Grand Rounds, Mt. Auburn Hospital, Cambridge, MA, “Nutrition Support of the Surgical Patient” February 25, 2003.
21. Division of Nutrition/HMS Annual Nutrition Conference” Nutrition and Gene Regulation” Obesity Chair and moderator, Boston, MA March 13-14, 2003.
22. HMS Core Clerkship, Boston, MA “Nutrition Support of the Hospitalized Patient” April 5, 2003.
23. Boston Area Dietetic Interns, Obesity Day, Boston, MA “Practical Guide to Medical Nutrition Therapy – Obesity Treatment” April 7, 2003.

24. University of New England College of Osteopathic Medicine, Portland, ME "Drug Induced Weight Gain" April 11, 2003.
25. Experimental Biology 2003, San Diego, CA "Obesity and Infection" April 13, 2003.
26. Oklahoma Heart Institute, Tulsa, OK "The Obesity Epidemic: What can we do for our patients" May 2, 2003.
27. American Diabetes Association Annual Meeting, New Orleans, LA "Do we know about the Metabolic Syndrome to treat it?" June 16, 2003.
28. HMS/CME "Practical Approach to the Treatment of Obesity" Cambridge, MA Director, moderator and speaker, June 19 –21, 2003

Invited Presentations local, national and international (Dr. Zhou)

1. Frontiers in Cancer Prevention Research, International meeting, "Tea components delayed progression to androgen-independent prostate tumor in an orthotopic prostate tumor model", Boston, MA, October 14-18, 2002.
2. Invited Speaker, China and International Soy Conference and Exhibition, "Effects of Daidzein-rich isoflavone aglycones on the prevention of obesity in an ovariectomized mouse model"; "Soybean bioactive components inhibit orthotopic growth and metastasis of human prostate tumor in mice", Beijing, China, November 6-9, 2002
3. Invited speaker, 3<sup>rd</sup> International Scientific Symposium on Tea and Human Health: Role of Flavonoids in the Diet, "Tea bioactive components in prevention of prostate cancer growth and progression", Washington, DC, September 23-24, 2002.
4. Invited speaker, 3<sup>rd</sup> International Conference and Exhibition on Nutraceuticals and Functional Foods: From Laboratory to the Real World and the Marketplace, "Nutraceutical components in soy and tea synergistically inhibit growth of estrogen-dependent MCF-7 human breast carcinoma in mice", San Diego, CA, November 17-20, 2002.

**VII. Plans for the Coming Academic Year**

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

Plans for research (new grants/programs)

1. Collaborate with Forsyth Dental School
2. Collaborate with National Dairy Council



Dr. Jin-Rong Zhou

Plans for Educational Programs (courses given/participated in – from Medical School through CME).

1. Continue with HMS/CME on Obesity and TPN/Enteral Nutrition
2. Evaluate On-line CME Programs

Jin-Rong Zhou, Ph.D.

1. To recruit 1-2 postdoctoral fellows if the pending grants are funded.
2. To submit 2 new RO1's.
3. To expand research on natural products and cancer prevention.
4. To expand collaborations within BIDMC, Dr. Steve Balk and Dr. Towia Libermann on prostate cancer and breast cancer research.
5. To expand collaborations with Dr. David Lee in McLean Hospital/HMS on natural products and prostate cancer research, and with Michael Freeman in Children's Hospital on prostate cancer research.
6. To be a tutor in the course of Preventive Medicine for the 2<sup>nd</sup> year Medical Students, HMS, during the spring semester, 2004.

7. To present as an invited speaker in The Global Soy Forum in Brazil, Feb. 29 – March 5, 2004.
8. To attend several scientific meetings, such as the 2<sup>nd</sup> International meeting “The Frontiers in Cancer Prevention Research” (Oct 2003), annual AACR meeting (March, 2004), and annual Experimental Biology meeting (April, 2004)

## VIII. Bibliography (07/01/02 – 6/30/03)

### Original Articles

1. Merrigan KA, Bistrain B, **Blackburn G**, Dwyer JT, Juma C, Mackey M, Rosenberg IH, Young VR. Agricultural biotechnology: the road to improved nutrition and increased production? *Nutr Rev* 2003; 61:S95-S100.
2. Yu L, **Blackburn GL**, **Zhou J-R**. Geistein and daidzein down-regulate androgen-regulated transcript-1 (PART-1) gene expression induced by 5 $\alpha$ -dihydrotestosterone in human prostate LNCaP cancer cells. *J Nutr* 2003; 133: 389-92.
3. **Zhou JR**, Yu L, Zhong Y, **Blackburn GL**. Soy phytochemicals and tea bioactive components synergistically inhibit androgen-sensitive human prostate tumors in mice. *J Nutr* 2003; 133: 516-21.
4. **Zhou JR**, Yu L, Zhong Y, Nassr RL, Franke AA, **Gaston SM**, **Blackburn GL**. Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. *Prostate* 2002; 53:143-53.

### Original Articles (in press)

1. Winters BL, Mitchell DC, Wright H, Grosvenor M, Liu W, **Blackburn GL**. Dietary patterns in women treated for breast cancer who successfully reduced fat intake: The Women’s Intervention Nutrition Study (WINS). *J Am Diet Assoc* 2003; in press.
2. **Zhou J-R**, Yu L, Mai Z, **Blackburn GL**: Combined inhibition of estrogen-dependent human breast carcinoma by soy and tea bioactive components in mice. *Int J Cancer* 2003; in press.

### Reviews, Chapters, and Editorials

1. **Blackburn GL**. Making good decisions about diet: weight loss is not weight maintenance. *Cleveland Clinic J of Med* 2002; 69:864-865.
2. **Blackburn GL**, Copeland T, Khaodhiar L, Buckley R. Diet and Breast Cancer. *J Women’s Health* 2003; 12(2): 183-92.

3. **Blackburn GL.** National health and nutrition examination survey: where nutrition meets medicine for the benefit of health. *Am J Clin Nutr* 2003; 78:197-8.
4. Maithel SK, **Blackburn GL.** Feeding the critically ill patient. *JPEN* 2003; 27: 383-4.
5. Pratt JSA, **Blackburn GL.** Surgical approaches to the treatment of obesity: a practical guide for the covering physician. In: Bray GA, editor. Office Management of Obesity, 1<sup>st</sup> edition. Philadelphia: Elsevier Inc.; 2003. p 275-298.

#### Clinical Communications

1. **Blackburn, GL.** HealthNews-Physician's Perspective.
2. **Blackburn, GL.** How long before scheduled surgery do I have to stop eating and drinking? HealthNews, 2002; July; 8(7):12.
3. **Blackburn, GL.** Menu and workout makeovers. HealthNews, 2002; November 8(11):1-2.
4. **Blackburn, GL.** Salt Shakedown. HealthNews, 2002; December 8(12):5.
5. **Blackburn, GL.** Sugar's Not-So-Sweet Revenge. HealthNews, 2003; May 9(5):3.
6. **Blackburn, GL.** The Skinny on Obesity and Cancer. HealthNews, 2003; June 9(6):3

#### Educational Materials

1. **Blackburn, GL.** Centers for Obesity Research and Education (CORE) Workshop on the Metabolic Syndrome

#### Nonprint materials

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

#### Abstracts

1. **Khaodhiar L,** Ling P, **Blackburn GL,** Bistrrian BR. Inflammatory Markers in Morbidly Obese Individuals: C-Reactive Protein (CRP), but not IL-6 or STNF-II is independently correlated to BMI in Morbid Obesity. *Obesity Surgery* 2003;13:223-24.

2. **Zhou J-R, Mai Z, Blackburn GL.** Soy phytochemicals potentiate the efficacy of tamoxifen treatment to tamoxifen-nonresponsive, ER-positive human breast tumor in a mouse model. *FASEB J* 2003;17: 872.7A.
3. **Zhou JR, Pan W,** Takebe M, **Blackburn GL.** Effects of daidzein-rich isoflavone aglycones on inhibition of hormone-sensitive human breast and prostate cancer cell lines in vivo. *Proc Am Assoc Cancer Res* 2003; 44(3):3918A.

Abstracts (in press)

1. **Blackburn GL,** Nixon D, Chlebowski R, Elashoff R, Hoy MK, **Copeland T,** Grosvenor MB, Mitchell DC, Smiciklas-Wright H, Liu W, Winters B. Interim results reflect changes in fat intake and weight in the Women's Intervention Nutrition Study (WINS). American Association for Cancer Research, 2003; in press.
2. **Blackburn GL, Copeland T,** Grosvenor MB, Hoy MK, Mitchell D, Smiciklas-Wright H, Liu W, Winters BL. Dietary recall response rate across 5 years in a long-term nutrition intervention (WINS). *FASEB J* 2003; in press.
3. **Blackburn GL, Copeland T,** Grosvenor MB, Hoy MK, Mitchell D, Smiciklas-Wright H, Liu W, Winters BL. Dietary recall response rate across 5 years in a long-term nutrition intervention (WINS). *FASEB J* 2003; in press.
4. Hoy MK, Winters BL, Lubin M, Liu W, Lillington L, **Blackburn GL,** Nixon D. Psychosocial factors differentiating stage of change in the Women's Intervention Nutrition Study using a motivational action plan. *FASEB J* 2003; in press.
5. **Khaodhiar L,** Nixon D, Hoy MK, Chlebowski RT, Elashoff R, **Blackburn GL.** Insulin Resistance in postmenopausal women with breast cancer. American Association for Cancer Research 2003; in press.

## Mark P. Callery, MD, FACS

### Division of General Surgery

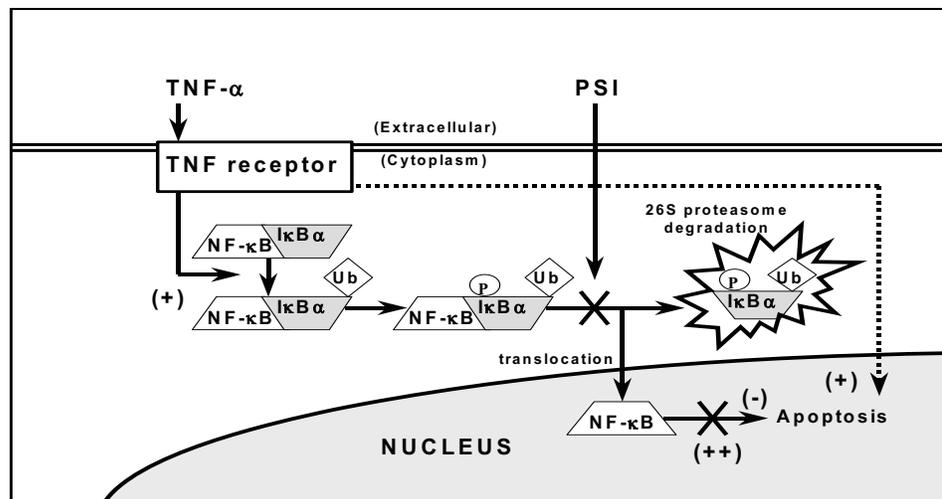
#### I. Narrative Report

Apoptosis is a natural genetically determined mechanism for cell death that can regulate tumor growth in cancer. The **global objective** of my research program is to determine whether we can enhance apoptosis and promote tumor regression in pancreatic cancer. Chemoradiation and cytokines, like TNF- $\alpha$ , can induce apoptosis in pancreatic cancer cells. However, these agents also activate a NF- $\kappa$ B "salvage pathway" which limits the degree to which apoptosis occurs. Our **particular objective** is to overcome NF- $\kappa$ B-dependent chemoresistance in pancreatic cancer. Our strategies, once clarified *in vitro*, are next tested in an *in vivo* mouse xenograft model of human pancreatic cancer. Using biochemical and molecular biology tools applied to both models, we attempt to confirm or exclude the following:

- 1. Resistance to chemoradiation therapy in human pancreatic cancer is regulated by NF- $\kappa$ B-dependent mechanisms.**
- 2. Both apoptosis and cell cycle progression control mechanisms are affected.**
- 3. Blockade of the NF- $\kappa$ B salvage pathway allows chemoradiation-induced apoptosis to occur unopposed and limit cancer cell proliferation.**
- 4. Blockade of the NF- $\kappa$ B salvage pathway, in living animals, will promote apoptosis and, as a direct result, prevent tumor growth.**

My laboratory recently demonstrated, for the first time in pancreatic cancer, that 26S proteasome inhibition induces apoptosis and overcomes chemoresistance (*J. Cell. Biochem.* 82: 110, 2001). These data have provided the experimental framework for current studies examining NF- $\kappa$ B regulated transcription of specific anti-apoptotic genes, and defects in cell cycle control from altered p21<sup>Cip1-Waf-1</sup> activity.

Schematic for NF- $\kappa$ B salvage pathway and hypothesized site of action of proteasome inhibition with PSI. Note that for activation of the NF- $\kappa$ B pathway, the I $\kappa$ B- $\alpha$  repressor protein must first be ubiquitinated, and then phosphorylated, marking it for degradation by the 26S proteasome. Until I $\kappa$ B- $\alpha$  is degraded by the proteasome, nuclear translocation of NF- $\kappa$ B is impossible.



#### II. List of Current Employees

1. Jirong Bai, Ph.D. Research Associate in Surgery
2. Benjamin Enos Technician, part-time

### III. List of Current Funding

1. "Research Support"  
Beth Israel Hospital Foundation  
Project Period: 7/1/02 – 6/30/03  
PI: Mark P. Callery, MD

### IV. Report of Teaching

#### Invited presentations, local, national, and international

1. **Canete JJ, Chandler NM, Callery MP.** P21<sup>Cip1</sup> gene transfer potentiates gemcitabine efficacy in pancreatic cancer. Association for Academic Surgery Annual Meeting, November 7-9, 2002, Boston, MA.
2. **Chandler NM, Canete JJ, Callery MP.** Increased expression of NF-kB subunits in human pancreatic cancer. Association for Academic Surgery 36<sup>th</sup> Annual Meeting, November 7-9, 2002, Boston, MA.
3. **Canete JJ, Chandler NM, Callery MP.** P21<sup>Cip1</sup> gene transfer potentiates apoptosis in gemcitabine-treated pancreatic cancer. Society of University Surgeons Annual Meeting, Residents' Conference, February 13, 2002, Houston, TX.
4. **Chandler NM, Canete JJ, Callery MP.** p21<sup>WAF1/Cip1</sup> increases with cell cycle arrest in pancreatic cancer cells treated with gemcitabine. Society of University Surgeons Annual Meeting, Houston, Texas, February 12-15, 2003
5. **Chandler NM, Canete JJ, Callery MP.** Caspase-3 induces apoptosis in pancreatic cancer cells after treatment with gemcitabine. American Hepato-Pancreato-Biliary Association 4<sup>th</sup> Annual Americas Congress, March 1, 2003, Miami, FL.
6. **Canete JJ, Chandler NM, Callery MP.** Cyclooxygenase-2 inhibitors suppress growth proliferation primarily via independent pathways in cyclooxygenase-depleted pancreatic cancer cells. American Hepato-Pancreato-Biliary Association 4<sup>th</sup> Annual Americas Congress, March 1, 2003, Miami, FL.

### V. Plans for the Coming Academic Year

We have no new staff changes planned for this year. We have part-time technical assistance with Benjamin Enos, an area undergraduate student. Dr. Nicole Chandler and Dr. Jonathan Canete left the laboratory as research fellows in June 2003, returning to complete their General Surgery Residency training at the University of Massachusetts, Worcester, MA.

## VI. Bibliography (07/01/02-06/30/03)

### Original Articles (in press)

1. **Chandler NM, Canete JJ, Callery MP.** Increased expression of NF- $\kappa$ B p65 correlates with increased nuclear activity in pancreatic cancer cells. *J Surg Res* 2003; in press.

### Reviews, Chapters, and Editorials (in press)

1. **Canete JJ, Chandler NM, Callery MP.** Laparoscopy ultrasonography In: *Laparoscopic Surgery: Principles and Procedures*. Jones DB, Wu JS, Soper NJ, eds. WB Saunders Company. 2003; in press.
2. **Chandler NM, Canete JJ, Stuart KE, Callery MP.** Preoperative chemoradiation in resectable pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2003; 10(1): in press.

**Josef E. Fischer, M.D.**  
Chairman, Department of Surgery  
Mallinckrodt Professor of Surgery

## **Division of General Surgery**

### **I. Narrative Report**

Our current research involves the elucidation of certain metabolic processes in sepsis, including the areas of proteolysis, the contribution of the gut (which appears to be an active participant in the septic process, not, as previously thought, a victim), the elucidation of transcription factors and heat-shock proteins in the elaboration and release of certain interleukins in the gut which affect the liver's response to sepsis. In the area of proteolysis, we have helped elucidate the role of the ubiquitin-proteasome system as well as calpains in the destruction of muscle. Similar studies have begun in cancer, which is metabolically quite similar to sepsis.

In the area of cancer anorexia and cachexia, we have attempted to define some of the metabolic abnormalities in experimental animals and patients with cancer which result in deranged neurotransmitters, particularly some of the pancreatic peptide family in the hypothalamus, as the etiology for cancer anorexia.

Finally, of late, we have turned our attention to some of the membrane transport activities and the production of lactate. The concept that hyperlactatemia always means inadequate perfusion or hypoxia may be deleterious to patients, as patients may be over-resuscitated, has been challenged by our finding that epinephrine stimulates both glycolysis, which is linked in turn to aerobic glycolysis, to supply energy for the sodium-potassium ATPase. This has resulted in a controversy in intensive care as well as other areas concerning hyperlactatemia, and has been used by others as proof of the approach of metabolic control analysis rather than rate-limiting enzymes in the control of certain aspects of metabolism.

The laboratory currently deals with four areas:

1. Changes in metabolism during sepsis. Sepsis is a major killer in surgical patients. We have focused primarily on the areas of the muscle and increased proteolysis in trying to determine the mechanisms of muscle proteolysis. This has involved a description of the reasons for the increased activity of the ubiquitin-proteasome pathway as well as the influence of calpain on the structure of muscle with destruction of the myofibrils and their metabolism.
2. The gut, rather than being a victim, turns out to be an active and willing participant in the septic process.

3. In the area of membrane transport, we have ascertained that the reason for hyper-lactatemia following sepsis is increased epinephrine, which stimulates glycolysis and is linked to aerobic glycolysis in its support of the sodium-potassium ATPase.
4. The anorexia and cachexia which complicate cancer, notably involving hyperthalamic pathways including peptide neurotransmitters, particularly NPY and PYY, whose metabolism is abnormal in animals with large cancer burdens and anorexia.

## II. List of Current Funding

Funded by the NIH, with few minor interruptions, since 1971.

1. "C/EBP and IL-6 Production in Mucosa and Enterocytes"  
NIH, R01 DK060546-01  
Project period: 5/1/2003-2/28/2007  
PI: Per-Olof Hasselgren, M.D., Ph.D.  
Co-Investigator: Josef Fischer, M.D.
2. "Muscle Lactate Production in Sepsis"  
NIH, 2 R01 GM54775-04  
PI: JH James, Ph.D. (University of Cincinnati Medical School)  
Co-Investigator: Josef Fischer, M.D.  
Project Period 12/1/2001-3/31/2005

## III. Report of Teaching

Invited Presentations (local, national, and international)

1. Edward Peirson Richardson Memorial Lectureship: Massachusetts General Hospital, Boston, MA.
2. Seligman Lecture: Department of Surgery, Mount Sinai Hospital / Johns Hopkins University School of Medicine, Baltimore; 13 April, 2003.
3. Presidential Address: Society for Surgery of the Alimentary Tract; "Abandoned." Orlando, Florida; May 20, 2003.

## IV. Bibliography (07/01/02-06/30/03)

Original Articles

1. Pritts TA, Wang Q, Sun X, Fischer DR, Hungness ES, **Fischer JE**, Wong HR, **Hasselgren PO**. The stress response decreases NF-kappaB activation in liver of endotoxemic mice. *Shock* 2002;18(1):33-37.

#### Reviews, Chapters, and Editorials

1. **Fischer JE.** Socio-economic activism in a changing medical workplace. *Am J Surg* 2003;185(1):6-9.
2. **Fischer JE:** Colonel Pete. *Surgery* 2003;133(5):589-591.
3. **Fischer JE.** “Whither goest?”: A look at Britain’s national health service. *Bull ACS.* 2003;88(2):21-24.
4. **Fischer JE.** They will sell you the rope. *Surgery* 2003;133(4):356-357.
5. **Fischer JE.** Unresectable liver metastases. *J Am Coll Sur* 2002;195(3):359-360.

#### Reviews, Chapters, and Editorials (in press)

1. **Fischer JE.** Enterocutaneous fistula. In: Norton, LW, Stiegmann G, Eiseman B, editors. *Surgical Decision Making*, 5<sup>th</sup> edition. W.B Saunders; 2003; *in press*.
2. **Fischer JE.** Current management of intestinal fistulas. In: Cameron, JL, editor. *Advances in Surgery*, volume 37. Mosby; 2003; *in press*.
3. **Fischer JE.** The surgical workforce crisis: rising to the challenge of caring for an aging America. In: L.T. Dvali, LT, et. al., editors. *Plastic and Reconstructive Surgery*, 2003; *in press*.

#### Books, Monographs, and Text Books

1. Maykel JA, **Fischer JE.** Current management of intestinal fistulas. In: J. Cameron, et. al., editors, *Adv Surg Volume 37*. Philadelphia: Mosby, Inc.; 2003;283-299.

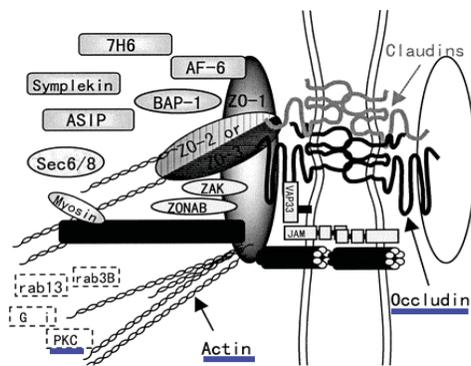
## Susan J. Hagen, PhD

Division of General Surgery  
Division of Surgical Research

### I. Narrative Report

My group focuses on the physiological and cell biological mechanisms that regulate cell function and death in the stomach. Our current NIH sponsored research is concerned with mechanisms that regulate gastric barrier function during health and disease, including tight junction permeability and gastric mucosal restitution after injury. Although we are particularly interested in the regulation of barrier function during *H. pylori* infection and how defects in the gastric barrier result in mucosal damage and gastric atrophy during infection, such studies are also pertinent to understanding gastric ulceration and stress-induced mucosal damage under surgical conditions and other critical illnesses including trauma and sepsis, where inflammation and hypoxia impact mucosal permeability, restitution and epithelial cell death.

#### Tight junction Permeability



from Mitic, et al, *Am J Physiol* 279: G250, 2002

Although the structure of tight junctions is well-defined (inset), whether this generic organization is the same and how it relates to barrier properties of the gastric mucosa is unknown. In recent studies, we have shown that gastric surface and chief cells in culture have a different transepithelial resistance (TER) and that these differences in TER can be attributed, in part, to occludin, one of two proteins that seal the paracellular space. Gastric surface epithelial cells in culture have virtually no TER, occludin is in very low concentration, and is localized to the cytoplasm. In contrast, occludin is localized to the tight junction in cultured chief cells,

which have a very high TER that is maintained by growth factors such as HGF. The cell and molecular regulation of occludin in gastric surface and chief cells, and how infection with *H. pylori* alters occludin localization and mucosal permeability are studies currently underway in the laboratory.

#### Gastric Mucosal Restitution after Injury

We are also interested in mechanisms that regulate restitution, or rapid epithelial repair after injury, in the stomach. Our current focus concerns mechanisms by which intracellular pH is regulated and how this regulation affects restitution and subsequent repair of barrier function after injury. Our results indicate that blood bicarbonate ( $\text{HCO}_3^-$ ) acts as a buffer to neutralize gastric luminal pH during restitution so that intracellular pH is maintained in migrating surface epithelial cells. Furthermore, we are actively pursuing the novel idea that  $\text{H}^+$ /lactate export, via the monocarboxylate transporter 1 (MCT1), may be essential for pH regulation during restitution by exporting lactate that is generated by glycolysis, a process we recently showed to be the main energy source for restitution after injury in the stomach.

## II. List of Current Employees

### Research Laboratory

Kimihito Tashima, PhD

Postdoctoral Fellow

Asli Muvaffak, PhD

Postdoctoral Fellow

### Core Facilities

#### Imaging

Dan Brown, MS

Sr. Research Associate

Siqian Li, MD

Research Technician

#### Histology

Suzanne White, BS

Histotechnologist

### Surgical Research

Pat Odom-Andrews

Administrative Coordinator



Dr. Hagen with her Laboratory and Core Group

*Back row, from left: Kimihito Tashima, Susan Hagen, Pat Odom-Andrews, Suzanne White, and Dan Brown*

*Front row, from left: Asli Muvaffak, Suqian Lu*

## III. List of Current Funding

1. "GI Mucosal Barrier in Health and Surgical Disease"  
National Institutes of Health, 3R01 DK 15681  
Project period: 07/01/2003 - 06/31/2008  
PI: Susan J. Hagen, Ph.D.

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

### **III. Divisional Accomplishments over the Past Year**

#### Research Accomplishments

1. My R01 grant was successfully renewed for 5 years.
2. Dr. Nakamura's paper, "Role of glutamine and arginase in protection against ammonia-induced cell death in gastric epithelial cells" was 4<sup>th</sup> of the 20 most accessed papers in mucosal biology (Am J Physiol) in 2002.

#### Administrative Accomplishments

1. I applied for- and was accepted to the Leadership Development Course for Junior Faculty. This was supported by the Carl J. Shapiro Institute for Education and Research at the BIDMC and was held at the Harvard Club, Cambridge, MA in October of 2002.
2. I assumed the position of Associate Director for Research and continued to provide administrative support for Research in Surgery.
3. I continued to direct the Morphology Core Facilities and Confocal Microscopy Facility and to provide oversight and consultation for imaging experiments in the hospital and for members of the Harvard Digestive Diseases Center.

### **IV. Report of Teaching**

#### Undergraduate and Medical School Courses

1. I participated in the Body Block at Harvard Medical School from 9/01/2002 10/31/2002 as co-director of the histology laboratory. In addition, I chaired a committee to write the midterm and final exams.

#### Summer and Medical Students

1. I was a mentor for Ms. La Toya Perry from the SHURP (Summer Honors Undergraduate Research Program) at Harvard Medical School. LaToya was in the laboratory for 10 weeks from June-August of 2002.
2. Mr. Anupam Verma did a research rotation in my laboratory for 6 weeks in March and April of 2003. Mr. Verma is a 4<sup>th</sup> year medical student at the University of Leicester, UK.

3. Ms. Ivy Kuofie, a 2<sup>nd</sup> year medical student from the University of Michigan, did a summer research rotation in my laboratory from June-August of 2003.
4. Ms. Farah Khachab was in the laboratory for 6 weeks from June 27-July 31 of 2003. Ms. Khachab, a high school student from Lebanon, was accepted to the Research Science Institute (due to her SAT scores of 1600) and hosted by the Massachusetts Institute of Technology.

#### Invited Presentations (local, national, and international)

1. Invited Speaker-“Ammonia and Gastric Acid Secretion: A Key to Understanding Activity and Regulation of the H<sup>+</sup>,K<sup>+</sup>-ATPase”. International Meeting of the IUPHAR GI section, Advances in GI Pharmacology: From Acid Secretion to Mucosal Protection. Honolulu, Hawaii. July 2002.
2. Moderator-Neuronal System in the GI Tract. International Meeting of the IUPHAR GI section, Advances in GI Pharmacology: From Acid Secretion to Mucosal Protection. Honolulu, Hawaii. July 2002.
3. “New Insights into the Regulation of Gastric Acid Secretion” Surgical Grand Rounds, Beth Israel Deaconess Medical Center, September 2002.
4. “Overview of Surgery Research”. Resident’s Research Orientation: Opportunities in Surgery Research. September 20, 2002.
5. “Glutamine Protects against *Helicobacter pylori*-induced Mucosal Damage”. Invited Speaker for the George H.A. Clowes Visiting Professor in Surgical Research, November 2002.
6. I presented a poster at Digestive Diseases Week in May of 2003 concerning our recent work with MCT-1 and restitution.

#### **V. Plans for the Coming Academic Year**

##### Plans for Research

1. I plan to write another R01 application for either the February or June deadline. This application will be to study mechanisms of cell death in gastric epithelial cells—an important area related to atrophy and progression to gastric cancer during *H. pylori* infection.
2. To finish many other manuscripts which need to be published.

##### Educational Plans

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

## VI. Bibliography (7/01/02-6/30/03)

### Original Articles

1. **Nakamura E, Hagen SJ.** Role of glutamine and arginase in protection against ammonia-induced cell death in gastric epithelial cells. *Am J Physiol (Gastrointest Liver Physiol)* 2002;283: G1264-75.

### Original Articles (in press)

1. **Hagen SJ, Morrison SW, Law CS, Yang DX.** Restitution of the bullfrog gastric mucosa is dependent on a DIDS-inhibitable pathway not related to HCO<sub>3</sub><sup>-</sup> ion transport. *Am J Physiol (Gastrointest Liver Physiol)* 2003: in press.

### Reviews, Chapters, and Editorials

1. **Hagen SJ, Hasselgren P-O, Odom-Andrews P.** Annual Report, Department of Surgery, BIDMC. Minuteman Press, December 2002.
2. **Hagen SJ.** Ammonia and gastric acid secretion: a key to understanding activity and regulation of the H, K-ATPase. *Inflammopharmacol* 2002; 10(4-6) 471-81.

### Abstracts

1. **Hagen SJ, Zuk A, Nakamura E, Smith M.** Activity of the monocarboxylate transporter 1 (MCT-1) may be required for cell migration after injury in gastric surface cells. *Gastroenterology* 124:447A.



Kimihito Tashima, PhD



Asli Muvaffak, PhD

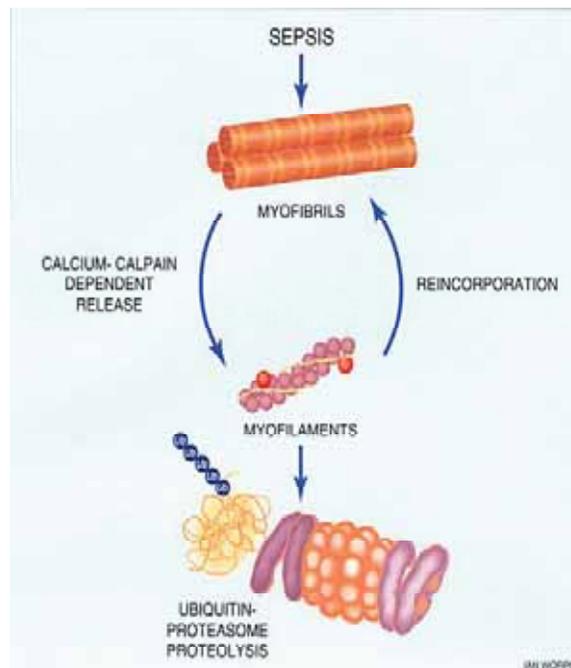
## Per-Olof Hasselgren, MD, PhD

Division of General Surgery  
Division of Surgical Research

### I. Narrative Report

The research efforts are focused on the metabolic and inflammatory responses to injury and sepsis in skeletal muscle and intestinal mucosa. Sepsis and severe injury are associated with a catabolic response in skeletal muscle. Studies in our laboratory have provided evidence that muscle wasting during sepsis and after burn injury mainly reflects degradation of myofibrillar proteins.

Our research supports a model in which myofilaments are released from the sarcomere through a calcium/calpain-dependent mechanism. The myofilaments (actin and myosin) are then ubiquitinated and degraded by the 26S proteasome (Figure). The gene expression of calpains and several components in the ubiquitin-proteasome pathway is upregulated in atrophying muscle, supporting the concept that increased gene transcription is an integral part of muscle wasting mechanisms. Currently, the transcriptional regulation of genes in the ubiquitin-proteasome pathway is studied. In particular, experiments are conducted to examine the role of the transcription factors C/EBP $\beta$  and  $\delta$  and the nuclear coactivator p300 in the regulation of the newly described ubiquitin ligases MuRF1 and atrogin-1.



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

## II. List of Current Employees

- |                            |                                |
|----------------------------|--------------------------------|
| 1. Michael Menconi, Ph.D.  | Assistant Professor of Surgery |
| 2. Moin Fareed, Ph.D.      | Instructor in Surgery          |
| 3. Catherine Cahill, Ph.D. | Instructor in Surgery          |
| 4. Hongmei Yang, Ph.D.     | Postdoctoral Fellow            |
| 5. Wei Wei, Ph.D.          | Postdoctoral Fellow            |
| 6. Amy Evenson, M.D.       | Surgical Resident              |



*Dr. Hasselgren with his lab group (from left sitting): Hongmei Yang, Ph.D. (post doc fellow), Wei Wei, Ph.D. (post doc fellow) Amy Evenson, M.D. (surgical resident), (standing) Michael Menconi, Ph.D. (Assistant Professor, Lab Supervisor), Per-Olof Hasselgren, M.D., Ph.D., Moin Fareed, Ph.D. (Instructor), Nick Tawa, M.D., Ph.D. (in the process of establishing his own laboratory in the field of muscle wasting). Missing from the picture, Catherine Cahill, Ph.D. (Instructor), Jamie Mitchell, M.D. (surgical resident)*

## III. List of Current Funding

1. "Muscle protein turnover and amino acid uptake in sepsis"  
National Institutes of Health, RO1 DK 37908-15  
Project period: 08/01/2000-07/31/2004  
PI: Hasselgren

2. "C/EBP and IL-6 production in mucosa and enterocytes"  
National Institutes of Health, RO1 DK60546-01  
Project period: 05/01/2003 – 02/28/2007  
PI: Hasselgren

#### **IV. Applications Submitted and Pending Review/Funding**

1. "C/EBP, atrogen-1, and muscle wasting"  
National Institutes of Health, RO1 NR008545-01  
Project Period: Pending  
PI: Hasselgren  
Priority Score: 187, Percentile 16.2
2. "C/EBP, p300, and atrogen-1 in muscle wasting"  
National Institutes of Health, F32 DK066964-01  
Individual National Research Service Award  
Period: Pending  
PI: Evenson  
Sponsor: Hasselgren  
Priority Score: 149, Percentile: 8.9



**Mike Menconi, Ph.D.**



**Amy Evenson, M.D.**

#### **V. Narrative of Divisional Accomplishments over the Past Year**

##### Research Accomplishments

1. Paper belonging to "the ten most-frequently-read authors" in November 2002 issue of the American Journal of Physiology (Am J Physiol 2002;283:R1140-R1148).
2. Paper belonging to "the ten most-frequently-read authors" in the May 2003 issue of the American Journal of Physiology (Am J Physiol 2003; 284:R1249-R1254)
3. One new RO1 grant, RO1 DK60546.

## Individual Accomplishments

1. Invited speaker: "Surgery in Sweden at the time of Halsted". Halsted Society, September 2002
2. Invited speaker: "Molecular biology of muscle wasting". Research Day, BIDMC, October 2002
3. Invited speaker: "Enhancing the safety of parenteral and enteral Nutrition". Harvard Medical School, November 2002.
4. Invited speaker : "C/EBP and other transcription factors in muscle wasting- Potential links to the ubiquitin-proteasome pathway". Fifth International Workshop on Proteasomes, Clermont-Ferrand, France, April 2003.
5. NIH Study Section, Special Emphasis Panel.

## **VI. Report of Teaching**

1. Surgical clerkship, medical students: Endocrine Surgery – Thyroid/Parathyroid

## **VII. Plans for the Coming Academic Year**

### Staff Changes/Recruitments

1. Hire Investigator for Faculty position to be part of Muscle Wasting Program.

### Plans for Research

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

## **VIII. Bibliography (07/01/02-6/30/03)**

### Original Articles

1. Fang CH, Li BG, Wray CJ, **Hasselgren PO**. IGF-1 inhibits lysosomal and proteasome-dependent proteolysis in skeletal muscle after burn injury. *J Burn Care Rehab* 2002; 23:318-325.
2. Hershko D, Robb BW, Hungness ES, Luo G, Guo X, **Hasselgren PO**. Arsenite inhibits IL-6 production by downregulating NF- $\kappa$ B activity in IL-1 $\beta$ -stimulated intestinal epithelial cells. *Clin Sci* 2002;103:381-390.

3. Hershko DD, Robb BW, Luo G, Paxton JH, **Hasselgren PO**. Interleukin-6 induces thermotolerance in cultured Caco-2 cells independent of the heat shock response. *Cytokine* 2003;21:1-9.
4. Hershko DD, Robb BW, Luo GJ, **Hasselgren PO**. Multiple transcription factors regulating the IL-6 gene are activated by cAMP in cultured Caco-2 cells. *Am J Physiol* 2002;283;R1140-R1148.
5. Hungness ES, Luo G, Pritts TA, Sun X, Robb BW, Hershko D, **Hasselgren PO**. The transcription factors C/EBP- $\beta$  and  $\delta$  regulate IL-6 production in IL-1 $\beta$ -stimulated human enterocytes. *J Cell Physiol* 2002;192: 64-70.
6. Hungness ES, Robb BW, Luo GJ, Hershko DD, **Hasselgren PO**. Hyperthermia-induced heat shock activates the transcription factor C/EBP- $\beta$  and augments IL-6 production in human intestinal epithelial cells. *J Am Coll Surg* 2002;195:619-626.
7. Luo GJ, Hershko DD, Robb BW, Wray CJ, **Hasselgren PO**. IL-1 $\beta$  stimulates IL-6 production in cultured skeletal muscle cells through activation of MAP kinase signaling pathway and NF $\kappa$ B. *Am J Physiol* 2003;284: R1249-R1254.
8. Pritts TA, Wang Q, Sun X, Fischer D, Hungness ES, Fischer JE, Wong HR, **Hasselgren PO**. The stress response decreases NF- $\kappa$ B activation in liver of endotoxemic mice. *Shock* 2002;18:33-37.
9. Robb BW, Hershko DD, Paxton JH, Luo GJ, **Hasselgren PO**: Interleukin-10 activates the transcription factor C/EBP and the interleukin-6 gene promoter in human intestinal epithelial cells. *Surgery* 2002; 132:226-231.
10. Wray CJ, Mammen JMV, Hershko D, **Hasselgren PO**. Sepsis upregulates the gene expression of multiple ubiquitin ligases in skeletal muscle. *Int J Biochem Cell Biol* 2003; 35:698-705.
11. Wray CJ, Tomkinson B, Robb BW, **Hasselgren PO**. Tripeptidyl peptidase II expression and activity are increased in skeletal muscle during sepsis. *Biochem Biophys Res Commun* 2002;296:41-47.

Original Articles (in press)

1. **Hasselgren PO**. Surgery in Sweden at the time of Halsted. *Arch Surg* 2003; in press.
2. Hershko DD, Robb BW, Luo GJ, Hungness ES, **Hasselgren PO**. Sodium arsenite downregulates transcriptional activity of AP-1 and CRE binding proteins in IL-1 $\beta$ -treated Caco-2 cells by increasing the expression of the transcriptional repressor CREM $\beta$ . *J Cell Biochem* 2003; in press.

## Reviews, Chapters, and Editorials

1. **Hasselgren PO.** Molecular regulation of muscle wasting. *Science and Medicine* 2002;8:230-239.
2. Wray CJ, Mammen JMV, **Hasselgren PO.** The catabolic response to stress and potential benefits of nutritional support. *Nutrition* 2002;18:971-977.

## **VI. Abstracts**

1. **Yang H, Evenson A, Menconi M, Fischer JE, Hasselgren PO.** Dexamethasone upregulates the gene expression of C/EBP $\beta$  and atrogin-1 through different mechanisms in cultured myotubes. *J Am Coll Surg* 2003;197:S35.



**Wei Wei, Ph.D.**



**Moin Fareed, Ph.D.**

**Daniel B. Jones, M.D., F.A.C.S.**

**Division of General Surgery**

Section for Minimally Invasive Surgery

Harvard Center for Minimally Invasive Surgery (HCMIS)

Teleconferencing, Simulation and Technical Skills Lab

**I. Narrative Report**

Our group integrates clinical activity and teaching into innovation and education research. We have focused on advanced minimally invasive surgery, bariatric surgery, and technical skill acquisition. Bench-top work has led to a better understanding of tumor implantation during pneumoperitonium, accuracy of laparoscopic radiofrequency ablation, and technical advances of new operations such as endoscopic parathyroidectomy, laparoscopic aorta surgery, laparoscopic Heller myotomy, and laparoscopic gastric bypass. HCMIS has had the privilege to train several talented medical students, research fellows, and clinical fellows. We have also developed mini-fellowships for community surgeons and extended educational commitment from monthly CME courses to laparoscopic proctorships and preceptorships. At Harvard Medical School, our group has been invited into the Harvard Bariatric Surgery Consortium and Boston Obesity Nutrition Research Center. We have worked clinically with colleagues, hospital, investigators, and insurance companies to introduce the laparoscopic adjustable band to Boston.

Education research is focused on establishing a technical skills laboratory validating new teaching tools and instituting curriculums for medical students and residents. At Harvard Medical School, we have established the Teleconferencing, Simulation & Technical Skills Lab at the Carl J. Shapiro Education and Research Center and hope to be involved in issues of learning and patient safety. Teaching is a top priority and we strive to be innovative and enthusiastic at all levels of training. Medical students and residents also receive individual teaching at the bedside, clinic, and operating room. In collaboration with Chemical Engineering at MIT, we are studying alginate and collagen as materials, which can be modified to synthesize an injectable mesh. The goal is to develop a biodegradable liquid that will solidify upon injection into the hernia defect. Availability of an injectable liquid mesh can not only make the hernia operation less invasive but also potentially eliminate the need for incisions. The project is currently funded through a grant from Center for the Integration of Medicine and Innovative Technology (CIMIT), a research consortium of Harvard hospitals and the MIT.

**I. List of Current Employees**

- |    |                    |                        |
|----|--------------------|------------------------|
| 1. | Vivian Sanchez, MD | MIS Clinical Fellow    |
| 2. | Leo Villegas, MD   | Skills Lab Coordinator |
| 3. | Eleanor Goodspeed  | Administrator          |

### Collaborators

- |                           |                         |
|---------------------------|-------------------------|
| 1. Jonathan Critchlow, MD | Surgery, BIDMC          |
| 2. Ed Mun, MD             | Surgery, BIDMC          |
| 3. Ben Schneider, MD      | Surgery, BIDMC          |
| 4. Lee Kaplan, MD         | Weight Loss Center, MGH |
| 5. David Brooks, MD       | Surgery, BWH            |
| 6. David Rattner, MD      | Surgery, MGH            |
| 7. George Blackburn, MD   | Surgery, BIDMC          |

## **II. List of Current Funding**

1. "Liquid Inguinal Hernia Repair"  
Center for the Integration of Medicine and Innovative Technology (CIMIT)  
Project period: 6/01/2003-06/30/2004  
PI: Ashish Patel, MD  
Mentor: Daniel Jones, MD
2. "Educational Training Grant"  
Ethicon Endosurgery  
Project period: 01/01/03-07/01/03  
PI: Ben Schneider, MD
3. "Educational Training Grant, HCMIS"  
United States Surgical/Tyco  
PI: Daniel Jones, MD
4. "Task performance using head mounted display vs two dimensional monitor system"  
Stryker Endoscopy  
PI: Shishir Maithel, MD  
Mentor: Daniel Jones, MD

## **III. Applications Submitted and Pending Review/Funding**

1. Endoplicator vs laparoscopic fundoplication: RPT
2. Laparoscopic ventral hernia repair: RPT

## **IV. Narrative of Divisional Accomplishments over the Past Year**

I was appointed to the Board of Governors, Society of American Gastrointestinal Endoscopic Surgeons (SAGES) and later served as Chair, Appropriateness conference: Surgical management of morbid obesity, SAGES, Los Angeles, CA, March 13, 2003 which lead to a consensus statement paper. Furthermore as Chair, SAGES TOP 14 Videos, I organized a leading educational video collection for resident training. I taught courses for the American Society Bariatric Surgery concerning laparoscopic gastric bypass and organized programs for teaching laparoscopic adjustable band. My teaching has extended to directing the annual MIS Fellows National Laparoscopic Gastric Bypass Course. Current educational

activities focus as Co-Chair on the preparation of Learning Center, Annual Meeting Society of American Gastrointestinal Endoscopic Surgeons.

## V. Report of Teaching

### Graduate School and Graduate Medical Courses

1. I provided mentoring for the following faculty and residents who are spending time in the research laboratory:  

|                     |                         |
|---------------------|-------------------------|
| Ben Schneider, MD   | Clinical MIS Fellow     |
| Vivian Sanchez, MD  | Clinical MIS Fellow     |
| Ashish Patel, MD    | Resident, BIDMC Surgery |
| Shishir Maithel, MD | Resident, BIDMC Surgery |
2. I was Course Director for the CMR courses *Laparoscopic Adjustable Band*, Beth Israel Deaconess Medical Center

### Invited Presentations (local, national and international)

1. Yoo M, **Jones DB**: Basic ultrasound curriculum for medical students: validation of content and phantom. 42 Annual meeting of the North Texas Chapter of the American College of Surgeons, Dallas, Texas. 2002; 21 February.
2. **Jones DB**. Minimally invasive surgery: frontier, Department of Surgery Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA, June 2002.
3. **Jones DB**. Training in advanced laparoscopic HPB. Boston Massachusetts, December 7, 2003.
4. **Jones DB**. Avoiding complications in obesity surgery. Laparoscopic Bariatric Surgery, Dallas, Texas, January 24, 2003.
5. **Jones DB**. Laparoscopic adjustable band. Laparoscopic Bariatric Surgery, Dallas, Texas, January 24, 2003.
6. **Jones DB**. Faculty: Laparoscopic colon resection: moderator live surgery. ASCRS Laparoscopic Colon , Dallas, Texas, February 1, 2003.
7. **Jones DB**. Laparoscopic obesity surgery, Beth Israel Deaconess/Glover Hospital Grand Rounds, Needham, MA, March 26, 2003.
8. **Jones DB**. Laparoscopic obesity surgery, St. Luke's Hospital Grand Rounds, New Bedford, MA, March 29, 2003
9. **Jones DB**. Laparoscopic obesity surgery, North Shore Medical Center Union Hospital Grand Rounds, Lynn, MA, April 22, 2003.

10. **Jones DB.** Trends in skills training. Leadership conference. Beth Israel Deaconess Medical Center, May 22, 2003.
11. **Jones DB.** Laparoscopic adjustable band in the elderly. Laparoscopic Adjustable Band, Boston, Massachusetts, June 16, 2003.
12. **Jones DB.** Surgical education: BIDMC, Boston & beyond. Board of Trustees, Beth Israel Deaconess Medical Center, Boston, MA, July 24, 2003.
13. **Jones DB.** Minimally invasive surgery: frontier. Grand Rounds. Harvard University Medical School, Boston, MA, June 2002.
14. **Jones DB.** Provost D. Telecast of live laparoscopic gastric bypass surgery. American Society of Bariatric Surgery, Las Vegas, NV, 28 June 2002.
15. **Jones DB.** Laparoscopic obesity surgery. Emory University, Atlanta, Georgia, August 2002.
16. **Jones DB:** Teaching curriculum using a TEP laparoscopic hernia simulator, Texas Surgical Society, Austin, Texas, September, 2002.
17. **Jones DB.** Videotrainers, simulators and virtual reality. Weil Medical College of Cornell University, NYC, NY Oct 21, 2002.
18. **Jones DB.** Routine intra-operative ultrasound during laparoscopic gastric bypass. Association of Academic Surgeons, Boston, Massachusetts, November 7, 2002.
19. **Jones DB.** Laparoscopic gastric bypass for MIS fellows. Norwalk, Connecticut, December 4, 2003.
20. **Jones DB.** Training in advanced laparoscopic HPB. HPB, Boston Massachusetts, December 7, 2003.
21. **Jones DB.** Avoiding complications in obesity surgery. Laparoscopic Bariatric Surgery, Dallas, Texas, January 24, 2003.
22. **Jones DB.** Laparoscopic adjustable band. Laparoscopic Bariatric Surgery, Dallas, Texas, January 24, 2003.
23. **Jones DB.** Faculty: Laparoscopic colon resection: moderator live surgery. ASCRS Laparoscopic Colon , Dallas, Texas, February 1, 2003.
24. **Jones DB.** Laparoscopic gastric bypass using transabdominal circular stapler. Minimally Invasive Surgery for Morid Obesity and GERD. University of Pittsburgh, Lake Tahoe, California, February 18, 2003.

25. **Jones DB.** Chair: Appropriateness Conference on Surgical Management of Morbid Obesity, SAGES, Los Angeles, California, March 12-15, 2003.
26. **Jones DB.** Evolution of obesity surgery: Appropriateness Conference on Surgical Management of Morbid Obesity, SAGES, Los Angeles, California, March 12-15, 2003.
27. **Jones DB.** Panel Moderator: Obesity Surgery: Universal coverage vs medical exclusion. SAGES, Los Angeles, California, March 12-15, 2003.
28. **Jones DB.** Laparoscopic gastric bypass techniques. SAGES, Los Angeles, California, March 12-15, 2003.
29. Yoo M, **Jones DB.** Basic ultrasound curriculum for medical students: validation of content and phantom SAGES, Los Angeles, California, March 14, 2003.
30. **Jones DB.** Perioperative management of the bariatric patient, University of Pittsburgh, Pittsburgh, PA, March 21, 2003.
31. **Jones DB.** Gastrojejunostomy using a circular stapler technique. University of Pittsburgh, Pittsburgh, PA, March 21, 2003.
32. **Jones DB.** Leaks. University of Pittsburgh, Pittsburgh, PA, March 22, 2003.
33. **Jones DB.** Current challenges in bariatric surgery. University of Pittsburgh, Pittsburgh, PA, March 22, 2003.
34. **Jones DB.** Faculty, Laparoscopic gastric bypass and band placement animal lab, University of Pittsburgh, Pittsburgh, PA, March 22, 2003.
35. **Jones DB.** Laparoscopic Roux-en-Y gastric bypass. Lone Star Update on Minimally Invasive Surgery. San Antonio, Texas, May 9, 2003.
36. **Jones, DB.** Bariatric program development: the mature practice. Lone Star Update on Minimally Invasive Surgery. San Antonio, Texas, May 9, 2003.
37. **Jones DB.** Laparoscopic gastric bypass. SSAT, Orlando, Florida, May 18, 2003.
38. **Jones DB.** Techniques for gastrojejunostomy durg laparoscopic gastric bypass. Medical College of Virginia, Richmond VA , June 9, 2003.
39. **Jones DB.** Expert moderator, laparoscopic gastric bypass telebroadcast. Medical College of Virginia, Richmond VA , June 9, 2003.
40. **Jones DB.** Faculty, Laparoscopic gastric bypass porcine lab. Medical College of Virginia, Richmond VA , June 10, 2003.

41. **Jones DB.** Telebroadcast live surgery: laparoscopic adjustable band, Boston, Massachusetts, June 16, 2003.
42. **Jones DB.** Laparoscopic adjustable band in the elderly. Laparoscopic Adjustable Band, Boston, Massachusetts, June 16, 2003.
43. **Jones DB.** Construction of gastrojejunostomy: circular stapler, transabdominal. American Society for Bariatric Surgery, Advanced Bariatrics Course, Boston, MA, June 18, 2003.
44. Blackburn GL, **Jones DB.** Difficult case studies in the evaluation & treatment of obesity. Practical Approaches to the Treatment of Obesity. Boston Obesity Research Nutrition Center, HMS, Cambridge, MA, June 20, 2003.
45. Villegas L, Provost D, **Jones DB.** Is routine cholecystectomy required during laparoscopic gastric bypass? American Society for Bariatric Surgery, Advances Bariatrics Course, Boston, MA, June 20, 2003.
46. **Jones DB.** Laparoscopic gastric bypass cadaver course. American Society for Bariatric Surgery, Tufts-New England Medical Center, Boston, MA, June 21, 2003.
47. **Jones DB.** Laparoscopic colon surgeon wannabe. SSAT Symposium, Annual Meeting of the American Society Colon and Rectal Surgeons, New Orleans, Louisiana, June 26, 2003.

#### Presented Abstracts

1. Jones SB, Coloma M, White PF, **Jones DB.** Comparison of the acustimulation relief band device to ondansetron for treatment of postoperative nausea and vomiting after laparoscopy. Surgical Endoscopy, March 2002.
2. Sims T, Hamilton E, **Jones DB,** Provost DA. Modified Stoppa/Wanantz hernia repair in obese patients. Obesity Surgery, Los Vegas, NV, 25 June 2002. (2002 Outstanding Poster Award).
3. Hamilton EC, **Jones DB,** Provost DA. Outcomes after Roux-en-Y gastric bypass inpatients over 500 pounds. Obesity Surgery, Las Vegas, NV, 25 June 2002.
4. **Villegas L,** Fleming J, Chang C, Tesfay T, **Jones DB.** Laparoscopic hepaticojejunostomy using PTFE-covered biliary stent. Surgical Endoscopy, 2003.
5. **Villegas L,** Rege RV, Tesfay S, **Jones DB.** Development of a laparoscopic common bile duct exploration model for resident training. Surgical Endoscopy, 2003.

6. Levitan D, Buedick S, **Schneider B**, Provost D, **Jones DB**, Balloon dilatation for the treatment of gastrojejunal anastomotic stricture after laparoscopic Roux-en-Y gastric bypass. *Surgical Endoscopy*, 2003.
7. **Schneider B**, **Villegas L**, Recard A, Hamza M, White P, **Jones DB**. Humidified and warmed carbon dioxide insufflation during laparoscopic gastric bypass for morbid obesity surgery. *Surgical Endoscopy*, Los Angeles, CA, March 2003.
8. **Schneider BE**, Provost DA, **Jones DB**. Band prolapse: complication following laparoscopic adjustable gastric band. *Southwestern Surgical*, Orlando, FL May 2003.
9. **Schneider BE**, Provost DA, **Villegas L**, **Jones DB**. Improvement of glaucoma following gastric bypass. *Obesity Surgery*, American Society for Bariatric Surgery, Boston, MA June 17, 2003.

## VI. Plans for the Coming Academic Year

### Basic Science

In collaboration with MGH Weight Loss Program, we plan to develop a rodent model to study roux-en-y gastric bypass with band procedure. Studies will look at central gut neuroendocrine changes after surgery, specifically the ghrelin, POMC pathway, PYY 3-3.

### Applied Research

Projects include the Self-Centering Colonoscope. More than 200,000 Americans die every year due to colon cancer. Prevention of this disease requires routine colonoscopies for every American over the age of fifty. Currently used colonoscope technology requires the surgeon to manually guide the colonoscope through the rectum into the colon and up to the cecum. The procedure is uncomfortable and is responsible for vast patient non-compliance. We are currently developing new scope technology that will make colonoscopy faster and safer. The new scope will have intelligent software, which will analyze continuous stream of images from the scope and control motors which will guide the tip of the scope towards the lumen. This will enable the surgeon to guide the scope faster while keeping all judgment under his or her control. In the future the software can be optimized to recognize abnormalities and assist in procedures.

### Clinical Research

Heller Myotomy. We have established a database of 100 patients who have undergone a heller myotomy for the treatment of achalasia at our medical center. We have reviewed the effects of fundoplication technique on patient outcome. Current work is focused on collecting data on postoperative reflux and patient satisfaction.

Pre-operative testing for Gastric bypass. Gastric bypass patients undergo extensive pre-operative laboratory testing at many medical centers. We are cataloging our 500 gastric bypass patients to assess the need for such testing. Initial results indicate that routine panels of pre-operative laboratory tests for gastric bypass patients do not predict outcome and can be avoided.

### Educational Research

Plans for educational programs are to formally train third year Harvard medical students and general surgery residents weekly with novel curricula established at Beth Israel Deaconess Medical Center. Urology, gastroenterology, and gynecology have also joined the teaching excitement of the Skills Lab. MIS video lecture series and plans to host a monthly grand rounds using teleconferencing to other institutions. Teleproctoring links to three BIDMC operating suites will help standardize MIS procedures by junior faculty and clinical fellows, and will be the focus of continuing research to evaluate error in the practice of MIS. Of significant achievement to Harvard Medical School, HCMIS has expanded and embraced the teaching programs at the Massachusetts General Hospital and Brigham and Women's Hospital, and Tufts' Saint Elizabeth Hospital into all educational endeavors. We will expand upon curriculum development and seek NIH grants addressing patient safety and error using teleproctoring technology.

The Harvard Center for Minimally Invasive Surgery plans CME courses: MIS Nursing, MIS Bariatrics for Nurses, Laparoscopic Ventral Hernia, Laparoscopic Colon, Laparoscopic Band, Laparoscopic Gastric Bypass, Laparoscopic Hernia Repair, Laparoscopic GYN, Laparoscopic CT Surgery.

## **VII. Bibliography (07/01/02-06/30/03)**

1. Coloma M, White PF, Ogunnaike BO, Markowitz SD, Brown PM, Lee AQ, Berrisford SB, Wakefield CA, Jones SB, **Jones DB**. Comparison of acustimulation and ondansetron for the treatment of established postoperative nausea and vomiting. *Anesthesiology*; 2002; 97(6):1387-1392.
2. Douglas JM, Young WN, **Jones DB**. Lichtenstein inguinal herniorrhaphy using sutures versus tacks. *Hernia* 2002;6(3):99-101.
3. Gettman MT, Kondraske GV, Traxer O, Ogan K, Napper C, **Jones DB**, Pearle MS, Cadeddu JA. Assessment of basic human performance resources predicts operative performance of laparoscopic surgery. *J Am Coll Surg* 2003;197(3):489-96.
4. Hamilton EC, Scott DJ, Fleming JB, Rege RV, Laycock R, Bergen PC, Tesfay ST, **Jones DB**. Comparison of video trainer and virtual reality training on acquisition of laparoscopic skills. *Surg Endosc* 2002;16: 406-11.

5. Hamilton EC, Sims TL, Hamilton TT, Mullican MA, **Jones DB**, Provost DA. Clinical predictors of leak after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Surg Endosc* 2003; 17:679-84.
6. Kondraske GV, Hamilton EC, Scott DJ, Fischer CA, Tesfay ST, Taneja R, Brown RJ, **Jones DB**. Surgeon workload and motion efficiency with robot and human laparoscopic camera control. *Surg Endosc* 2002;16:1523-27.
7. Scott DJ, Fleming J, Watumull LM, Lindberg G, Tesfay ST, **Jones DB**. Effect of hepatic inflow occlusion on laparoscopic radiofrequency ablation using simulated tumors. *Surg Endosc* 2002; 16(9):1286-91.
8. Sims TL, Mullican MA, Hamilton EC, Provost DA, **Jones DB**. Routine upper gastrointestinal Gastrografin swallow after laparoscopic Roux-en-Y gastric bypass. *Obesity Surgery* 2003;13(1):66-72.
9. **Schneider BE**, Castillo JM, **Villegas L**, Scott DJ, **Jones DB**. Laparoscopic totally extraperitoneal versus Lichtenstein herniorrhapy: cost comparison at teaching hospitals. *Surg Laparosc Endosc Percutan Tech* 2003;13(4):261-67.
10. **Villegas L**, Rege RV, **Jones DB**. Laparoscopic Heller myotomy with bolstering partial posterior fundoplication for achalasia. *J Laparoendosc Adv Surg Tech* 2003;13(1):1-4.

#### Original Articles (in press)

1. Scott DJ, **Villegas L**, Sims TL, Hamilton EC, Provost DA, **Jones DB**. Intraoperative ultrasound and prophylactic ursodiol for gallstone prevention following laparoscopic gastric bypass. *Surg Endosc* 2003; in press.
2. **Villegas L**, **Schneider B**, Chang C, Scott D, Sims T, Hill L, Provost D, **Jones D**: Is routine cholecystectomy required during laparoscopic gastric bypass? *Obesity Surgery*, in press.
3. Wilkiemeyer MB, Bieligm SC, Asnfaq R, **Jones DB**, Rege RV, Fleming JB. Laparoscopy alone is superior to peritoneal cytology in staging of gastric and esophageal carcinoma. *Surg Endosc* 2003; in press.

#### Reviews, Chapters, and Editorials

1. **Jones DB**, Nguyen N, Lopez JA, O'Brien P, Provost D. Gastric bypass and adjustable-band surgery for obesity. *Contemporary Surgery* 2003; 59(9):403-10.
2. Ogunnaike BO, Jones SB, **Jones DB**, Provost D, Whitten C. Anesthetic considerations for bariatric surgery. *Anesth Analg* 2002;95(6):1793-1805.

3. **Schneider B, Villegas L, Blackburn GL, Mun EC, Critchlow JF, Jones DB.** Laparoscopic gastric bypass surgery: outcomes. *J Laparosc Adv Surg Tech* 2003; 13(4):247-55.

Reviews, Chapters, and Editorials (in press)

1. **Villegas L, Schneider B, Callery MP, Jones DB.** Laparoscopic skills training. *Surg Endosc* 2003; in press.

Books, Monographs, and Textbooks

1. Diaz S, Soper NJ, **Jones DB:** Suturing and knot tying. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> Edition. New York: Marcel Dekker, Inc.; 2003, in press.
2. **Jones DB,** Rege RV. Operations for peptic ulcer and their complications. In: Feldman M, Friedman LS, Sleisenger MH, editors. *Sleisenger and Fordtan's Gastrointestinal and Liver Disease* 7<sup>th</sup> Edition. New York: W.B. Saunders; 2002, p.797-809.
3. Rege RV, **Jones DB:** Asymptomatic cholelithiasis. In: Bland KI, editor. *The Practice of General Surgery*. New York: W.B. Saunders; 2002. p. 663-6.
4. Scott DJ, **Jones DB.** Hernias and abdominal wall defects. In: Norton JA, Bollinger RR, Chang AE, Lowry SF, Mulvihill SJ, Pass HI, Thompson RW, editors. *Essential Practice of Surgery: basic Science and Clinical Evidence*. New York: Springer-Verlag; 2003, pp335-55.

Books, Monographs, and Textbooks (in press)

1. **Critchlow J,** Carter SL, **Jones DB.** Complications of laparoscopic surgery. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> Edition. New York: Marcel Dekker, Inc. 2003; in press.
2. Desai K, **Jones DB,** Soper NJ. Nissen fundoplication. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
3. Hamilton EC, **Jones DB.** Cholecystectomy. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
4. Hamilton EC, **Jones DB.** Common bile duct stones. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
5. Hamilton EC, **Jones DB.** Laparoscopic common bile duct exploration. In: Van Heerden J, Farley DR, editors. *Operative Techniques in General Surgery*. Philadelphia: W.B. Saunders 2003; in press.

6. Jones SB, **Jones DB**. Preoperative evaluation of the healthy laparoscopic patient. In: Whelan RL, Fleshman J, editors. *The SAGES Manual of Perioperative Management in Minimally Invasive Surgery*. New York: Springer-Verlag. 2003; in press.
7. **Maithel S, Jones DB**. Access and port placement. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
8. **Mun E, Jones DB**. Postoperative assessment, documentation and follow-up. In: Schauer PR, editor. *Laparoscopic Obesity Surgery*. New York; Springer-Verlag. 2003; in press.
9. **Schneider BE, Jones DB**. Transabdominal transgastric gastrojejunoscopy. In: Schauer PR, editor. *Laparoscopic Obesity Surgery*. New York; Springer-Verlag. 2003; in press.
10. **Schneider BE, Provost DA, Jones DB**. Obesity surgery. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
11. Scott DJ, **Jones DB**. Inguinal hernias. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
12. Scott DJ, **Jones DB**. Skills training. In: Jones DB, Wu JS, Soper NJ, editors. *Laparoscopic Surgery: Principles and Procedures*, 2<sup>nd</sup> edition. New York: Marcel Dekker, Inc. 2003; in press.
13. Scott DJ, **Jones DB**. Virtual reality training and teaching tools. In: Eubanks S, Soper NJ editors. *Mastery of Endoscopic and Laparoscopic Surgery*. Lippincott, Williams, and Wilkins. 2003; in press.

### Abstracts

1. Scott DJ, **Villegas L**, Sims T, Hamilton EC, Provost DA, **Jones DB**. Intraoperative ultrasound and prophylactic ursodiol therapy for gallstone prevention following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc* 2002;16:S191.
2. **Villegas L**, Bieligg S, Fleming JB, **Jones DB**, Loggie B. Laparoscopic intraperitoneal hyperthermic chemotherapy for malignant ascites in peritoneal carcinomatosis. *Surg Endosc* 2002;16:S332.
3. **Villegas L**, Kondraske G, Napper C, Cadeddu J, **Jones DB**. Laparoscopic skills: do good hands beget laparoscopic ability? *Surg Endosc* 2002;16:S322.

**Edward C. Mun, M.D.**

**Division of General Surgery**

**I. Narrative Report**

Basic Research

The NIH-funded project “Intestinal Transport during Metabolic Stress” investigates 1) whether metabolic stress induces epithelial Cl<sup>-</sup> secretory response in native human intestinal mucosa via purinergic signaling pathways, and 2) whether the regulatory mechanism of ischemia-elicited secretion involves modulation of basolateral K<sup>+</sup> channel activity. More recent focus of basic science research is in the effects of inflammatory mediators such as IL-6 and TNF on insulin sensitivity and fatty acid oxidation mediated by adiponectin in muscle tissues. Regulation of adiponectin receptor (AdipoR1 and AdipoR2) gene expression in various tissues (muscle and liver) is also being investigated.

Clinical Research

IRB-approved Laparoscopic omentectomy is currently performed on a selected patient cohort with type II diabetes and CT-confirmed visceral obesity to investigate the effects of such surgical visceral fat reduction on insulin sensitivity and glucose tolerance.

**II. List of Current Employees**

- |    |                       |                       |
|----|-----------------------|-----------------------|
| 1. | Hsi-Chiang Lin, PhD   | Instructor in Surgery |
| 2. | Jae Won Choe, MD, PhD | Research Fellow       |
| 3. | Kyrah Davis, BA       | Technician            |

**III. Current List of Funding**

1. “Intestinal Transport during Metabolic Stress”  
NIH/NIDDK K08 DK 02604  
Project period: 12/01/1998 - 11/30/2003  
Principal Investigator: Dr. Edward C. Mun
2. BIDMC Special Research Discretionary Fund

**IV. Narrative of Divisional Accomplishments**

Research Accomplishments

1. The NIH K08 DK 02604 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. The main focus of the basic science research has shifted to investigation of effects of protein adiponectin on muscle metabolism and insulin sensitivity.

2. The clinical research project "Surgical visceral fat reduction by omentectomy as treatment for obesity-related type II diabetes" is a pilot study with a goal of 6 completed cases. This project investigates the effects of visceral fat reduction in the regulation of serum glucose by insulin. So far 4 cases have been successfully completed without perioperative complications. The early results are quite promising and the results will be written up when 2 more cases are completed.

## **V. Report of Teaching**

### Undergraduate and Medical School Courses

1. I participate in the Core Clerkship in Surgery for third year HMS students. During a 2 week rotation on my service, each student receives didactic teaching sessions in the clinical office, during ward rounds, and in the operating room. I additionally participate in the Saturday lecture series and have given clinical talks on various subjects including "Gastrointestinal Bleeding".

### Graduate School and Graduate Medical Courses

1. As an attending surgeon on the general surgery service, I teach rotating residents (4-5 per month) on the ward, during rounds, as well as in the operating room, totaling approximately 15-20 hours a week. I moderated several teaching rounds and Chief's rounds covering a broad range of general surgical subjects including surgery for reflux disease, gastric bypass, and small bowel obstruction.

### Invited Presentations Local, National and International:

1. "Bariatric Surgery Outcomes", Surgical Grand Rounds, Beth Israel Deaconess Medical Center, 2002
2. "Current Status of Obesity Surgery", Grand Rounds, South Shore Hospital, 2003
3. "Practical Approaches to the Treatment of Obesity", Harvard MED-CME, Royal Sonesta Hotel, Cambridge, 2003
4. "Complications of Gastric Bypass Surgery", Radiology Rounds, Beth Israel Deaconess Medical Center, 2003

## VI. Plans for the Coming Academic Year

### Plans for Research

1. Continue current basic and clinical science research projects by conducting and supervising experiments in the laboratory. Keep in close contact with Dr. Per-Olof Hasselgren, who functions as a mentor in research, and Dr. Christos Mantzoros, who functions as an advisor and co-investigator. Bi-weekly meetings are on-going with these investigators. Publish original articles from our current data. Continue with presentations at the national scientific meetings. Join additional academic research societies. Establish a non-clinical, dedicated research day each week to accommodate research needs. Broaden joint research endeavors with the Joslin Diabetes Center in basic and clinical research. Plan for an RO1 application within the next 1-2 years.

### Plans for Educational Programs

1. Plan to continue with student/resident teachings by participating in various ward teachings, OR education, didactic conferences, and lecture series. Also plan to participate in various Harvard CME courses covering obesity management and minimally invasive surgery techniques including telesurgery conferences.

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

### Original Articles

1. Mayol JM, Alarma-Estrany P, O'Brien TC, Song JC, Prasad M, Adame-Navarrete Y, Fernandez-Represa JA, **Mun EC**, Matthews JB. Electrogenic ion transport in mammalian colon involves an ammonia-sensitive apical membrane K<sup>+</sup> conductance. *Dig Dis Sci* 2003;48 (1):116-25.
2. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, **Mun E**, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proc Natl Acad Sci U S A* 2003;100(14):8466-71.

### Educational Materials

1. "Bariatric Surgery at BIDMC". This publication is a patient guide.

## **Sareh Parangi, M.D.**

### **Division of General Surgery**

#### **I. Narrative Report**

The main focus of my research centers on the analysis of angiogenesis during tumor progression 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 the use of a transgenic insulinoma model as well as orthotopic models to test novel antiangiogenic therapies. Animals are monitored by doppler ultrasound and magnetic resonance imaging during antiangiogenic therapy to look specifically at tumor vasculature. Gene therapy with antiangiogenic agents is also used to affect tumor progression. Using the above techniques and models, the topics currently under investigation in the laboratory are as follows:

1. Angiogenesis and pancreatic tumor progression.
2. Use of antiangiogenic drugs in combination to treat tumors.
3. Antiangiogenic gene therapy.
4. Effects of Thrombospondin on endothelial cells *in vivo* and *in vitro*.

#### **II. List of Current Employees**

- |                        |                     |
|------------------------|---------------------|
| 1. Eric Galardi        | Research Technician |
| 2. Xue Feng Zhang, PhD | Postdoctoral Fellow |

#### **III. List of Current Funding**

1. "Antiangiogenic gene therapy in a mouse model of pancreatic cancer"  
American College of Surgeons Faculty Research Fellowship  
PI: Dr. S. Parangi  
2001-2003
2. "Role of IGF-1 in pancreatic cancer"  
American Cancer Society  
Co-investigator: Dr. Parangi  
2001-2004
3. "Temporal and Spatial Regulation of Angiogenesis"  
Project 3: "Inhibition of Angiogenesis by Thrombospondin –1".  
National Cancer Institute P01, NCI- Program Project Grant  
Co-investigator, Dr. Parangi  
2002-2007
4. "Antiangiogenic therapy of pancreatic cancer"  
National Cancer Institute  
K08 CA88965-01  
PI: Dr. Parangi  
2002-2007

#### IV. Divisional Accomplishments over the Past Year

1. I hired a postdoctoral fellow in the last year.

#### V. Report of Teaching

##### Invited presentations local, national, and international

1. **Parangi S.**, Kaustubh D, Zeng,H, and Mukhopadhyay. "Requirement of Insulin Like Growth Factor –I for Autocrine-induced Proliferation, Invasion and VPF/VEGF Expression in Pancreatic carcinoma" *Surgical Forum American College of Surgeons, San Francisco, CA October 2002*

#### VI. Plans for the Coming Academic Year

1. Initiate collaboration with endocrinologist regarding novel antiangiogenic treatments aimed at endocrine tumors, develop an orthotopic model of thyroid cancer in mice.
2. Submit Research papers
3. Look at the role of PET/CT scanning in patients with thyroid nodules.
4. Look at the role of fine needle aspiration under ultrasound guidance in patients with incidentally detected thyroid nodules under 8 mm and write an IRB Protocol for this project.
5. Create data base for analysis of thyroid patients at BIDMC.
6. Collaborate with cytopathology on IRB approved study on fine needle aspiration of follicular thyroid lesions for molecular differentiation of follicular thyroid cancer from follicular adenoma.

#### VII. Bibliography (7/1/02-6/30/03)

##### Original Articles

1. Saurborn DP, Kruskal JB, Stillman IE, **Parangi S.** Paranganglioma of the organs of Zuckerkandl. *Radiographics* 2003;23:1279-86.
2. Zeng H, Datta K, Neid M, Li J, **Parangi S**, Mukhopadhyay D. Requirement of different signaling pathways mediated by insulin-like growth factor-I receptor for proliferation, invasion, and VPF/VEGF expression in a pancreatic carcinoma cell line. *Biochem Biophys Res Commun* 2003; 302(1):46-55.

##### Original Articles (in press)

1. Mitchell J, **Parangi, S.** Laparoscopic adrenalectomy for pheochromocytoma. *Current Surgery.* 2003; in press.

Reviews, Chapters, and Editorials (in press)

1. **Parangi S**, Pories S. Surgical Problems in the Pregnant Patient. In: Gastrointestinal Disorders during Pregnancy. American College of Gastroenterology, 2003, in press.

Nonprint Materials

1. **Parangi S**. Updated and maintained a web site for the Thyroid Center at Beth Israel Deaconess Medical Center [www.bidmc.harvard.edu/thyroidcenter](http://www.bidmc.harvard.edu/thyroidcenter).

## **Nicholas E. Tawa Jr, MD, PhD**

### **Division of General Surgery**

#### **I. Narrative Report**

In the past 6 months, I returned to the basic science laboratory after an approximate 5 year absence, during which time I engaged in a variety of clinical research projects. My research interest and past work has focused largely on strategies by which proteolysis in muscle can be suppressed, which in turn may have potential therapeutic applications for reducing muscle wasting in disease. Specifically, mechanisms by which dietary protein deficiency reduces muscle proteolysis and the interaction of nutrients and hormones in regulating this process are of special interest. With encouragement from Dr. P. O. Hasselgren, we are currently involved in studies concerning the physiological regulation of intracellular protein breakdown in skeletal muscle, where initial experiments have shown that the amino acid leucine appears to block the induction of proteolysis by glucocorticoids in cultured muscle cells. We are actively working to define molecular mechanisms responsible for this interaction. The therapeutic potential of pharmacologic inhibitors of the ATP- ubiquitin- proteasome pathway for reducing muscle wasting and the use of such compounds as anti-neoplastic agents are also under study.

#### **II. List of Current Employees**

1. Jamie Mitchell, MD Surgical Resident

#### **III. List of Current Funding**

1. Departmental discretionary fund for the support of research with sources including the Beth Israel Deaconess Surgical Group Foundation, Boston, MA.
2. Transkaryotic Therapies Inc., Cambridge, MA  
Baxter Pharmaceutical Products Inc, New Providence, NJ

#### **IV. Report of Teaching**

##### **Invited Presentations, Local, National and International**

1. Surgical Grand Rounds (Melanoma), Beth Israel Deaconess Medical Center, Boston, MA, 2003
2. Medical Grand Rounds (Nutrition), Deaconess- Glover Hospital, Needham, MA, 2003.
3. Surgical Grand Rounds (Melanoma), Mount Auburn Hospital, Cambridge, MA, 2003.

### Undergraduate and Medical School Courses

- 2003 Lectured on topics of trauma management, nutrition, and surgical oncology to HMS surgical clerkship students and to residents in training.
- 2004 Led weekly didactic nutrition conference for hospital dietitians, nurses, and related personnel.

### CMR Courses

1. Lectured on "Long-term intravenous nutrition" in HMS CME course "Enhancing the Safety of Parenteral and Enteral Nutrition", Harvard Medical School, Boston, MA.

## **V. Plans for the Coming Academic Year**

### Staff Changes/Recruitments

1. I hope to attract a PhD- trained research associate within the next 6 months.

### Plans for Research (new grants/programs)

Our group will pursue studies in several areas, some of which represent the continuation of earlier work, which has been recently submitted for publication;

1. The regulation of ATP-dependent proteolysis in skeletal muscle by thyroid hormones.
2. The influence of dietary protein deficiency and prolonged fasting on thyroid and adrenal status and on the release of gut-derived hormones, which may be relevant to signaling the suppression of muscle proteolysis which occurs in these conditions. In this context, the ability of certain amino acids to mimic dietary protein deficiency (e.g., leucine withdrawal) will be explored.
3. The mechanisms by which dietary protein deficiency suppresses muscle atrophy caused by fasting or denervation.
4. The biochemical basis for the activation of intracellular protein breakdown in skeletal muscle by nitric oxide and oxygen free radicals.

## **VI. Bibliography (07/01/02-06/30/03)**

### Original Articles

1. **Khaodhiar L**, Keane-Ellison M, **Tawa NE**, Thibault A, Burke PA, Bistrain BR. Iron deficiency anemia in patients receiving home total parenteral nutrition. *J Parenter Enteral Nutr* 2002;26:114-9.

2. Ling PR, Ollero M, **Khaodhiar L**, McCowen K, Keane-Ellison M, Thibault A, **Tawa N**, Bistrain BR. Disturbances in essential fatty acid metabolism in patients receiving long-term home parenteral nutrition. *Dig Dis Sci* 2002;47:1679-85.

#### Reviews, Chapters, and Editorials (in press)

1. Jagoe T, **Tawa NE Jr**, Goldberg AL. Protein and amino acid metabolism in muscle. In: Engel, AG, Franzini-Armstrong, C, eds. *Myology*. Third edition. New York: McGraw-Hill, 2003; in press.
2. **Tawa NE Jr**, **Maykel JA**, **Fischer JE**. Metabolism in Surgical Patients. In: Townsend, CM, ed. *Sabiston Textbook of Surgery*. 17<sup>th</sup> Edition. WB Saunders, 2003; in press.

#### Books, Monographs, and Textbooks

1. **Tawa NE Jr**. Reoperative surgery for melanoma. In: Callery, M, ed. *Problems in General Surgery: Reoperative Surgery*. Lippincott Williams and Wilkins, 2003; in press.

#### Abstract

1. Roth DA, **Tawa NE**, Proper J, Treco DA, Schuetz T, Selden RF. Implantation of non-viral ex vivo genetically modified autologous dermal fibroblasts that express B-domain deleted human factor VIII in 12 severe hemophilia A study subjects. *Blood* 2002;100:116A.

# NEUROSURGERY

Julian K. Wu, M.D., Chief

## Division Members

Edwin G. Fischer, M.D.

Ihab John Ibrahim, M.B.

Adel M. Malek, M.D., Ph.D.

Thorkild Norregaard, M.D.

Efstathios (Steve) Papavassiliou, M.D.

Simcha J. Weller, M.D.

**Julian K. Wu, M.D.**

**Division of Neurosurgery**

Neurosurgery Brain Tumor Laboratory

**I. Narrative Report**

The Neurosurgery Brain Tumor Laboratory is designed to provide an integrated environment for clinicians, medical students and basic research scientists to study the molecular and cellular mechanisms of neurologic diseases including brain tumor formation, invasion and metastasis. Our laboratory concentrates on 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. Tumor Tissue Bank

**II. List of Current Employees**

1. Angela Tam Research Technician

**III. List of Current Funding**

1. Beth Israel Deaconess Medical Center  
Project period: 11/01/99-9/30/2003  
PI: Julian K. Wu, MD

**IV. Report on Teaching**

1. Undergraduate and Medical School Courses

During this summer we had the opportunity to introduce students from the University of Massachusetts 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.

**Angela Tam** (University of Massachusetts). Transfected brain tumor cells with epidermal growth factor receptor to study its role in matrix metalloproteinase expression.

2. Graduate School and graduate medical courses

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 and the second year covers current topics that are selected based on recent publications and discussed in conjunction with basic neuroscience.

## V. Plans for the Coming Academic Year

1. During the next academic year we plan to continue our research activities, teaching and training responsibilities and administrative duties as outlined in the first section. We will maintain the same personnel, publish our results and we will pursue additional funding to support our research.

## VI. Bibliography (7/01/02-6/30/03)

### Original Articles

1. Cucchiarini M, Ren X, **Perides G**, Terwilliger E. Selective gene expression in brain microglia mediated via recombinant adeno-associated virus vectors. *Gene Ther* 2003;10(8):657-67.
2. Song C, Wang C, **Perides G**, Liu YF. Expression of mutant beta-amyloid precursor protein or presenilin-1 causes formation of actin stress fibers through p38 mitogen-activated protein kinase. *J Neurochem* 2002;83(4):828-36.

### Original Articles (in press)

1. Westling J, Cockburn A, Thompson VP, **Perides G**, Zimmermann DR, Gottschall P, Sandy J. ADAMTS4 (aggrecanase-1) cleaves human brain versican V0/V2 at glu405-gln406 to generate glial hyaluronate binding protein (GHAP). *Biochem J* 2003; (in press).

### Reviews, Chapters, and Editorials (in press)

1. **Perides G, Wu JK**. Molecular markers of metastatic disease In: Black PM, Loeffler A, editors. *Cancer of the Nervous System*, Philadelphia: Lippincott Williams & Wilkins. 2003; (in press).

### Abstracts

1. Wang D, **Perides G**, Liu A, Feldman R, Liu YF. Emotional stress induces activation of MKK4 in glutamatergic neurons. *Neurosci* 2002;397:3A.
2. **Zhuge Y, Patel P, Wu JK**, Stins M, **Perides G**. The role of the fibrinolytic system in systemic tumors crossing the blood brain barrier. *Neuro-Oncology* 2002;74A.

Adel M. Malek, M.D., Ph.D.

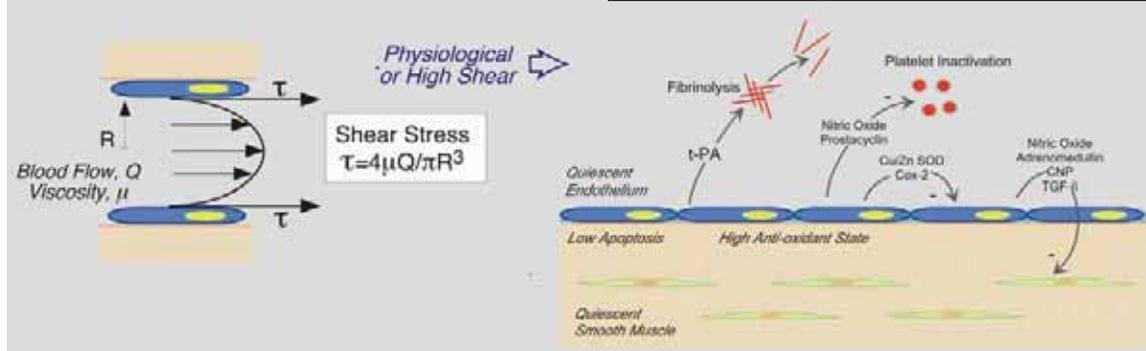
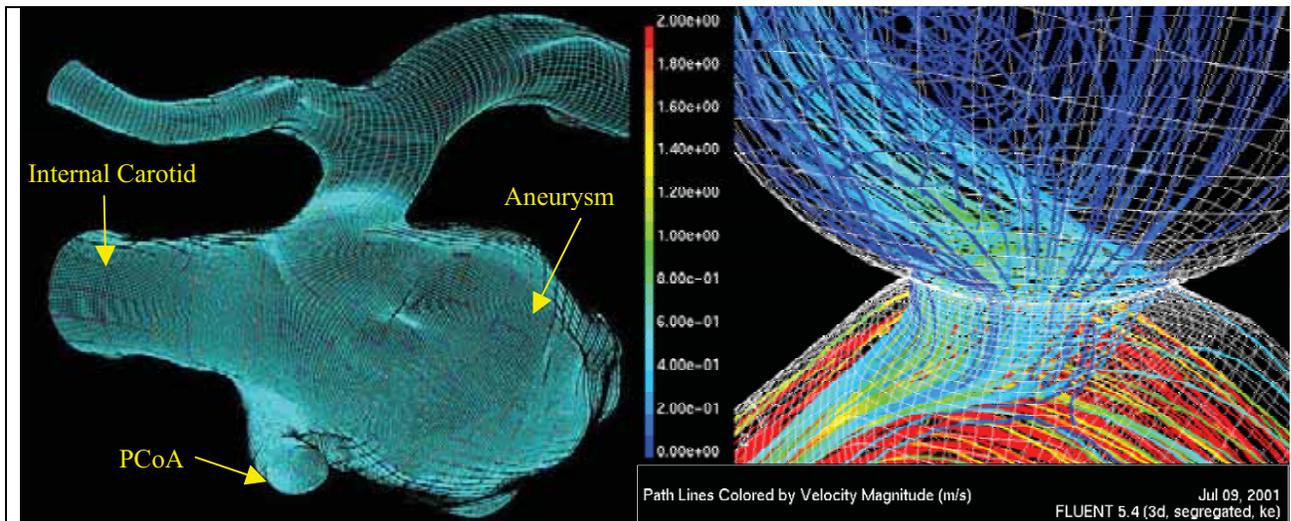
**Division of Neurosurgery**  
Molecular and Cellular Hemodynamics

## I. Narrative Report

Our group is interested in understanding the role of hemodynamic forces in determining vascular architecture in pathophysiological states, such as cerebral aneurysms and bifurcation atherosclerosis, through its modulation of endothelial and smooth muscle cellular and molecular function.

### Computational Fluid Dynamic (CFD) Modeling of the Cerebral Vasculature

We are using computational fluid dynamic (CFD) techniques to understand the shear stress and hydrostatic pressures in and around the area of interest. This is arrived at through the use of high-resolution 3D rotational angiography, which provides sub-millimeter spatial resolution and enables the construction of high-resolution hexahedral meshes. These are then used to solve the CFD problem using steady-state and time-varying parameters derive from *in vivo* hemodynamic measurements. The spatial and temporal profiles and gradients of wall shear stress and hydrostatic pressure enable us to design appropriate experiments to mimic these parameters *in vitro* and begin the molecular dissection of the endothelial and smooth muscle phenotype in these regions.



## **II. List of Current Employees**

1. Hesham Younis, Ph.D. Postdoctoral Fellow
2. Gargi Sur, M.S. Research Technician

## **III. List of Current Funding**

1. "Molecular Biology of Cerebral Aneurysm Development"  
BIDMC, Seed Fund  
Project period: 07/01/2003-06/30/2008  
PI: Adel M. Malek, MD, PhD
2. "Endothelial Flow Response Characterization using Micromachined Channel MEMS Technology"  
Draper Laboratory  
Project period: 01/01/2004-01/01/2005  
PI: Adel M. Malek, MD, PhD

## **IV. Narrative of Divisional Accomplishments over the Past Year**

### Research accomplishments

The laboratory has been focused on setting the computational infrastructure required to study the computational fluid dynamics in and around intracranial cerebral aneurysms and around atherosclerotic lesions. Using high-fidelity hexahedral meshing applied to high-resolution 3D geometry obtained from rotational digital subtraction angiography, we are applying computational fluid dynamics (CFD) techniques to understand the hemodynamic forces that may play a role in intracranial aneurysm growth and rupture.

## **V. Plans for the Coming Academic Year**

The laboratory is in the process of recruiting a post-doctoral fellow for the study of the molecular response of endothelial cells to fluid mechanical forces. In addition, the laboratory is starting a collaborative exploration of the use of micromachined surfaces and channels (MEMS technology) for the study of endothelial cell response to mechanical forces in collaboration with the Draper Laboratory.

# PLASTIC SURGERY



Sumner Slavin, M.D., Chief

## Division Members

Loren J. Borud, M.D.

Mauricio A. Contreras, M.D.

Bernard T. Lee, M.D.

Joseph Upton, M.D.

Donald J. Morris, M.D.

Michael Tantillo, M.D.

The Division of Plastic Surgery at Beth Israel Deaconess Medical Center is an integral part of the Harvard Plastic Surgery Residency Program. All plastic surgery residents rotate at Beth Israel Deaconess Medical Center during the last three years of a six- year program.

Clinical education in the Division of Plastic Surgery comprises reconstruction of all anatomical areas, hand surgery, care of the trauma patient, cancer ablation and reconstruction, and cosmetic surgery. Research focuses on clinical areas including breast reconstruction, hand surgery, and the treatment of lymphedema. Current basic science research efforts are directed at the pathophysiology of lymphatic endothelial tissues.

The Reconstructive Plastic Surgery Research Center is currently working on several projects that include both Basic Science as well as Clinical research. The primary goal of our research group is to have a better understanding of the mechanisms involved in the pathophysiology of lymphedema and lymphangiogenesis in an attempt to devise new strategies or possible treatments for this disease, which has continued to be neglected in the U.S. despite that it has now become an acceptable diagnosis.

In Basic Science Research we are currently involved in a project to promote lymphangiogenesis by stimulating lymphatic endothelial cell (LEC) proliferation and migration. Another project involves the use of laser capture microdissection to isolate lymphatic endothelial cells from human lymphedematous and normal adipose tissue samples in an attempt to elucidate at the molecular level the mechanisms involved in the pathophysiology of lymphedema.

Recently, a Lymphedema Clinic was established at Beth Israel Deaconess to treat swelling of the upper and lower extremities at both acquired and congenital causes. At the clinic, we are also involved in resident education, introducing both residents and medical students to the mechanisms and structures of the lymphatic system and the unique challenges of treating patients with both primary and secondary lymphedema. Our group has established collaborative endeavors with surgical specialists in Europe, including Dr. Rudeiger Baumeister, Chief of Plastic Surgery, University of Munich, and Dr. Håkan Brorson, a surgical investigator from Malmo, Sweden. Through such collaboration, we have established a process for collecting lymph for molecular research; we have also started to incorporate surgical techniques from Europe, particularly the Brorson liposuctioning technique for patients with lymphedema.

Finally, our research group is also involved in advocating for legislation to mandate treatment coverage for lymphedema, Senate Bill 848. In our efforts, we work closely with patients, family advocates, legislators, and the government relations office at BIDMC. Throughout the year, we have testified at special hearings at the State House, and we were also instrumental in obtaining an amendment to include coverage for “surgical treatment” as part of the bill.

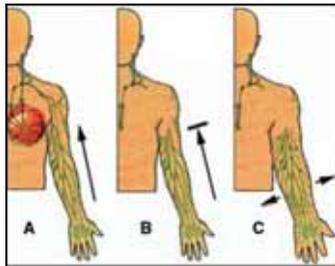
**Sumner A. Slavin, M.D.**

**Division of Plastic and Reconstructive Surgery**  
Plastic Surgery Research Center

**I. Narrative Report**

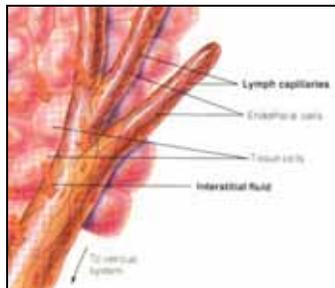
**Basic Research**

Lymphedema occurs after breast cancer treatment because lymphatic vessels are destroyed during removal of axillary lymph nodes and/or subsequent radiation therapy. This impairs lymph drainage from the arm and results in an abnormal collection of fluid and proteins within the interstitial space (Figure 1). Treatment options for this debilitating condition include drug therapy, physical therapy, and surgical approaches that have yielded limited success. Unfortunately, treatment options for lymphedema are palliative and no permanent cure is available.



**Figure 1.** Secondary lymphedema develops after breast cancer treatment (A), when lymphatic flow is interrupted (B). The arm swells (C) because fluid accumulates in the interstitial space.

Our interest is to restore lymphatic flow by promoting the development of new lymphatic vessels (or lymphangiogenesis) by using specific growth factors incorporated into an alginate biodegradable hydrogel (Figure 2). The delivery rate in alginate gels can be determined and local, rather than systemic administration can be of great advantage. We have successfully completed *in vitro* proliferation and migration studies using specific lymphatic endothelial cell growth factors, such as vascular endothelium growth factor-C and angiopoietin-2, which were incorporated into alginate gels. We are now conducting *in vivo* experiments using these biodegradable gels to determine efficacy in a mouse-tail lymphedema model.



**Figure 2.** Fluid and protein uptake occurs by the lymphatic system in the connective tissue. By restoring lymphatic flow in breast cancer patients, we hope to improve lymphodema in these patients.

**Clinical Research**

Over the past year, Drs. Sumner Slavin and Loren Borud have continued their effort to develop a *Lymphedema Treatment Center*. They opened the first

BIDMC Lymphedema Clinic in October of 2002, a first of its kind in Boston and New England. The Clinic is open on the first Friday afternoon of each month. Since it's opening, more than 50 patients, some of whom are from other parts of the country, have been evaluated and treated.

The Clinic also serves as a focal point for much needed residency education in the area of the diagnosis, treatment, and management of lymphedema. No other medical institution in Boston (and few in the United States) provides residency education in this medical area.

Drs. Slavin and Borud have also pioneered the use of aggressive suction lipectomy followed by compression therapy in the United States. Håkan Brorson, M.D., in Sweden, first established this procedure, which has had impressive results.

## **II. List of Current Employees**

- |                                |                               |
|--------------------------------|-------------------------------|
| 1. Loren J. Borud, M.D.        | Instructor in Surgery         |
| 2. Mauricio A. Contreras, M.D. | Instructor in Surgery         |
| 3. Robert M. Goldwyn, M.D.     | Clinical Professor of Surgery |
| 4. Geoffrey Brahmer            | Educational Coordinator       |

## **III. List of Current Funding**

1. "Lymphatic Regeneration within porous VEGF-C Hydrogels for Secondary Lymphedema"  
Department of Defense, BC000413  
Project Period: 07/01/2001 - 06/30/2004  
PI: Mauricio A. Contreras, MD

## **IV. Applications Submitted and Pending Review / Funding**

1. "Transplantation of Progenitor Cells and Lymphatic Regeneration in Lymphedema"  
Department of Defense, BC032122  
Project Period: 07/01/04-06/30/2007  
PI: Mauricio A. Contreras, MD

## **V. Divisional Accomplishments over the past Year**

1. Our (R01) NIH grant submission, "*Gene Expression in Lymphedematous Adipose Tissue*" received a generally favorable review but was not within the funding range. This grant application will, therefore, be re-submitted March 1<sup>st</sup>, 2004.
2. The Lymphedema treatment program has become a reality, opening a clinic in the Fall of 2002. More than 50 patients have been seen and treated since the clinic opened. Dr. Sumner Slavin serves as the Director of the

Program. Dr. Loren Borud, serving as the Co-Director, is in charge of scheduling patients, promoting and marketing the program, performing the surgery, and following the patients throughout their course of treatment.

3. A scientific collaboration continues to take place with Dr. Rudeiger Baumeister, Professor of Plastic Surgery, and Chief of Plastic Surgery, University of Munich, and Dr. Håkan Brorson, M.D., a surgical investigator in Malmo, Sweden, for the collection of lymphedematous adipose samples. Already, this collaboration has resulted in the collection of optimal samples, which are currently being used for ongoing research and grant applications. In April of 2003, Dr. Brorson spoke on the surgical treatment of lymphedema at the citywide Harvard Plastic Surgery Grand Rounds. He also was a speaker at the BIDMC Plastic Surgery Division Rounds.
4. In the past year and a half, the *first three Brorson procedures* for the surgical treatment of lymphedema in the United States were performed at BIDMC.
5. A collection process for obtaining and maintaining lymphedema tissue specimens has been established for basic molecular study.
6. Through a private donation obtained by Dr. Sumner Slavin, BIDMC obtained a surgical Coleman Lipostructure set for BIDMC. These surgical instruments are for obtaining and injecting autologous fat.
7. The entire team continues to work with lymphedema patients, family advocates, and legislators in the passage of legislation in Massachusetts to mandate insurance coverage for lymphedema. The team's efforts also led to an amendment to the legislation to include coverage for the "surgical treatment" of lymphedema.

#### Individual Accomplishments

1. Dr. Sumner Slavin continues to be active in moving the Lymphedema Project forward nationally and internationally, as well as locally, within the BIDMC community, with the Harvard Plastic Surgery Program (and with the residents), with private donors, the legislature, and with the media. Dr. Slavin serves on a National Lymphedema Think Tank associated with NIH. He is also currently working with BIDMC media services to obtain TV coverage on lymphedema. As Director of the BIDMC Lymphedema Project, Dr. Slavin works closely with Dr. Loren Borud, Co-Director, in patient care and in residency education in the Lymphedema Clinic. He also oversees the various research, clinical, educational, and activities of the Lymphedema Project at BIDMC.

In April, 2003, Dr. Slavin and the Division of Plastic Surgery hosted Håkan Brorson, M.D., a surgical investigator from in Sweden. Dr. Brorson presented a talk, on his research and on the surgical management of lymphedema at the Combined Harvard Plastic Surgery Grand Rounds. He

also attended the lymphedema clinic, a lymphedema planning meeting, observed surgeries, and participated in Division Rounds at BIDMC.

2. Dr. Loren Borud has personally seen and treated 50 patients with lymphedema, has performed multiple Brorson procedures for the surgical treatment of lymphedema, and also (through resection procedures) collected tissue specimens from patients for basic molecular study. Dr. Borud is currently developing a clinical series of patients as well as a tissue bank for molecular study. Since July of 2002, Dr. Borud has given multiple presentations on the treatment of lymphedema.
3. Dr. Mauricio Contreras presented his research work at the FASEB, Experimental Biology 2003 in San Diego, CA (April 11-15). He gave an oral presentation entitled: "Promoting Lymphangiogenesis *in vitro* utilizing Alginate Gels with Angiopoietin-2 and Vascular Endothelial Cell Growth Factor-C". In addition, Dr. Contreras has a human lymphatic endothelial cell line that will be used for multiple *in vitro* studies on lymphangiogenesis. In addition to his research effort, Dr. Contreras also continues to train surgical residents in the T-32 program in microvascular techniques in an animal model (mouse, rat, rabbit) for their research projects.
4. Geoffrey Brahmer continues to work with lymphedema support groups, and legislators to advocate for the passage of legislation to mandate insurance coverage for lymphedema. Most recently, he testified, on behalf of the team, at the Massachusetts State House, before the Joint Insurance Committee in support of the Senate bill, Senate No. 848. It is expected that the bill will be reported favorable out of this Committee, moving forward in the legislative process. Geoffrey is working closely with Mary Beth Heffernan, Director of BIDMC Government Relations, in this process.
5. Dr. Robert Goldwyn continues to meet with and consult with the group as an advisor.

## **VI. Report of Teaching**

### Undergraduate and Medical School Courses:

Medical students were introduced to the diagnosis, treatment, and management of lymphedema at the lymphedema clinic. From this experience, one medical student prepared a presentation on lymphedema.

### Graduate School and Graduate Medical Courses

1. The Division continued effort to train surgical residents in the T-32 program in microvascular techniques in animal models (mice, rats, rabbits).
2. Surgical interns and plastic surgery residents were introduced to the special challenges and approaches in treating patients with lymphedema.

## Invited Presentations, Local, National and International

### Dr. Borud

1. “*Surgical Treatment of Lymphedema*” at the Harvard Plastic Surgery Grand Rounds, Massachusetts General Hospital, December 2002.
2. Keynote address: “*Current Treatment of Lymphedema*” at the Institute for Health Professionals, Massachusetts General Hospital, May 2003.

## **VII. Plans for the Coming Academic Year**

### Clinical Lymphedema Program

Dr. Sumner Slavin and Dr. Loren Borud will continue to maintain and expand the work at the BIDMC lymphedema clinic, both as it relates to patient care and medical education of students and residents.

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

### Basic Science Studies in Lymphedema

The group intends to submit two grant proposals to the NIH in the coming year:

1. Dr. Slavin and Dr. Contreras plan to re-submit an RO1 grant application (March 1<sup>st</sup> 2004) entitled: “*Gene Expression in Lymphedematous Adipose Tissue.*”
2. Dr. Mauricio Contreras plans to submit a K08 NIH Grant application (February 1<sup>st</sup> 2004) entitled: “*Peripheral Progenitor Endothelial Cells and Lymphoangiogenesis as a New Therapy for Secondary Lymphedema* “. Dr. Slavin will serve as a mentor on this project.
3. A second research project we intend to establish in our group involves the use of laser capture microdissection to isolate lymphatic endothelial cells from human lymphedematous and normal adipose tissue samples, to isolate mRNA, and evaluate differential gene expression using Affymetrix gene-chip arrays. The purpose of this project is to analyze and study genes that play an essential role in lymphoangiogenesis. For this, Drs. Borud plans to submit an NIH grant application (K-08). Dr. Borud has collected a library of tissues to support this work and is currently developing a rodent model of lymphedema to provide an additional tool for molecular study. Dr. Slavin will serve as a mentor on this project.

### Staff Changes/Recruitments

1. A PhD will be recruited to support work in the area of gene expression in lymphedematous adipose tissue, as well as in other molecular and clinical aspects of the lymphatic system and lymphedema research we do in our group.

## **VIII. Bibliography**

### Nonprint Materials

1. **Contreras MA.** Videotape: Microvascular dissection of the neck in a mouse model. This videotape was used for teaching Surgical Residents and NIH-T32 Trainees.

### Abstracts

1. **Contreras MA, Slavin SA.** Promoting lymphangiogenesis *in vitro* utilizing alginate gels with angiopoietin-2 and vascular endothelial cell growth factor-C. *FASEB J* 2003; 514(12):A803.

# PODIATRY

John M. Giurini, M.D., Chief

## Division Members

Philip Basile, D.P.M.

Thanh L. Dinh, D.P.M.

Michael K. Gavigan, D.P.M.

Thomas E. Lyons, D.P.M.

Barry I. Rosenblum, D.P.M.

Aristidis Veves, M.D., D.SC.

## **Aristidis Veves, M.D.**

### **Division of Podiatry**

Joslin-Beth Israel Deaconess Foot Center and Microcirculation Lab

#### **I. Narrative Report**

##### **Basic Research**

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

In addition to the above, I am interested in the relationship between functional changes in the vascular reactivity and structural changes of the skin. In collaboration with other labs we are currently involved in the study of changes in protein expression, such as eNOS and RAGE and PARP activation in the endothelial cells of the skin vasculature and their association to the endothelium dependent vasodilation.

My group is also interested in the etiology of diabetic foot problems and the pathophysiology of wound healing in diabetes. We are currently conducting a larger prospective study that will evaluate the role of microvascular dysfunction in foot ulceration and wound healing failure.

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

#### **II. List of Current Employees**

- |                              |                        |
|------------------------------|------------------------|
| 1. Lalita Khaodhiar, M.D.    | Instructor in Medicine |
| 2. Thanh T Dinh, DPM         | Junior Faculty         |
| 3. Thomas Lyons, DPM         | Junior Faculty         |
| 4. Sriurai Porramatikul, MD. | Postdoctoral Fellow    |
| 5. Christina Lima            | Research Coordinator   |
| 6. Lydia Longoria            | Research Coordinator   |

### III. List of Current Funding

1. "Vascular and Metabolic Changes in the Diabetic Foot"  
National Institutes of Health, R01 HL-75678  
Project period: 9/25/03-08/31/06  
Principal Investigator: Dr. Aristidis Veves
2. "The Effect of Vitamin E on the Left Ventricular Function and the Endothelial Function of the Micro- and Macro-Circulation of Type1 and 2 Diabetic Patients"  
Juvenile Diabetes Foundation International, JDFI 1-1999-817  
Project period: 10/1/99-9/30/04  
Principal Investigator: Dr. Aristidis Veves
3. "A Phase IV Study of AQUACEL Ag versus Saline-Moistened Gauze in the Management of Diabetic Foot ulcers"  
ConvaTec, Princeton NJ, CW-0130-00-A509  
Project period: 4/1/03-12/31/2004  
Principal Investigator: Dr. Aristidis Veves
4. "Pilot & Feasibility Program in Diabetes, Endocrinology & Metabolism"  
National Institutes of Health, RO1 PA-99-036  
Project period: 07/01/02-6/30/04  
Principal Investigator: Dr. Robert Greenman
5. "Effect of Valsartan in Ventricular Function and Aortic Elasticity"  
Novartis Pharma Inc  
Project period: 09/01/02-08/31/04  
Principal Investigator: Dr. Aristidis Veves
6. "Effect of Valsartan In Endothelial Function"  
Novartis Pharma Inc  
Project period: 09/01/02-08/31/04  
Principal Investigator: Dr. Aristidis Veves
7. "PARP activation as a marker of diabetic vascular dysfunction"  
National Institutes of Health, 1R01HL/DK71215-01  
Project period: 10/1/02-30/9/05  
Principal Investigator: Dr. Csaba Szabo  
Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves
8. "Imaging early markers of diabetic microvascular complications in peripheral tissue"  
National Institutes of Health, RFA-DK-02-001  
Project period: 10/01/02-09/30/04

Principal Investigator: Dr. George L. King  
Principal Investigator on the BIDMC subcontract: Dr. Aristidis Veves

9. "A Phase 1 / 2 Study of Safety and Efficacy Topical Administration of Recombinant Human Lactoferrin in Patients with Diabetic Neuropathic Foot Ulcers"  
Agennix Inc  
Project period: 2/01/03-1/31/05  
Principal Investigator: Dr. Aristidis Veves
10. "Micro- and Macrovascular Abnormalities and Diabetic Foot Ulceration" American Diabetes Association  
Project period: 2/01/03-1/31/06  
Principal Investigator: Dr. Aristidis Veves
11. "A Multicenter, Double-blind Study to Evaluate the Effect of Pre-treatment With a Daily Dose of Viagra® (sildenafil citrate) on the PRN Efficacy of Viagra in Men With Erectile Dysfunction and Type 2 Diabetes"  
Pfizer Inc  
Project period: 2/01/03-10/31/04  
Principal Investigator: Dr Richard Sparks

#### **IV. Applications Submitted and Pending Review/Funding**

1. "Natural History of Small Fiber Diabetic Neuropathy"  
National Institutes of Health  
Project period: 2/1/04-1/31/09  
Principle Investigator: Dr. Aristidis Veves

#### **V. Divisional Accomplishments over the Past Year**

##### Research

During the last academic year we continued two investigator-initiated clinical studies that are related to vascular dysfunction in diabetes and were funded by Novartis Pharma Inc. In addition, we initiated two more clinical trials that are examining the efficacy of new treatments in healing foot ulcers. I was also awarded a three-year clinical research grant from the American Diabetes association. The main aim is to study the relationship between vascular abnormalities and diabetic foot ulceration. Finally, I was just awarded a three-year NIH grant. The main aim of this grant is to further investigate muscle and skin metabolic changes in the lower extremity of the subjects who will participate in the study that was funded by the ADA.

### Individual Accomplishments

1. I was invited to give the Prof. M. Viswanathan Lecture: "Diabetic Foot Problems". Chennai, India.
1. As a member of the Medical Science Review Committee of the Juvenile Diabetes Research Foundation International, I participated in the spring and fall grant reviews.
2. I was invited to review grants for the American Diabetes Association. I started reviewing grants during the spring review in April 2003
3. I continue to serve as an Associate Editor for the journal: *Wounds: A Compendium of Clinical Research and Practice (2000-)*.
4. I was asked to act as a peer reviewer for the journals: *Diabetes, Diabetologia, Diabetes Care Diabetic Medicine, Journal of Diabetes and its Complication,s and Circulation.*

### Awards and Honors

I was awarded the Chennai Diabetes Research Center Gold Medal Oration Award

## **IV. Report of Teaching**

### Educational Activities

I was involved in the training of the podiatry residents. More specifically, I am responsible lecturing them about the principles of clinical research and supervise them when they write a research proposal. Finally, I am helping them in reviewing the important papers that are published and are relevant to diabetic foot problems.

Chantel Hile, MD, a surgical resident who was doing research this academic year, participated in one of our studies. She also worked with me and wrote one chapter and one review article.

In collaboration with the Medical School of University of Rochester we have established the Robert L. Caldwell Vascular Research Internship and every year a first year medical student does a summer internship in my lab. This year, Matthew Hubbard spent two months in our unit.

### Professional and Educational Leadership

1. I was a member of the Planning Committee for the Consensus Development Conference on PVD in Diabetes, organized by the American Diabetes Association

2. I was a member of the Organizing Committee, Wound Healing: Science and Industry. St. Thomas, VI.

#### Invited Presentations (local, national, and international)

1. Invited Speaker: "Diabetes Related Changes in the Skin Microcirculation: Implications for Wound Healing". New Frontiers in the Treatment of Type 1 Diabetes and its Complications. 7<sup>th</sup> Oxford Diabetes Workshop jointly organized by the European Association for the Study of Diabetes (EASD) and the Juvenile Diabetes Research Foundation International (JDRF). Keble College, Oxford, UK.
2. Keynote Speaker: "Pathogenesis of Diabetic Foot Ulceration" At Saitama Diabetic Complication Workshop 2002. "Learn from Overseas Diabetic Treatment", Saitama, Japan.
3. Keynote Speaker: "Pathogenesis of Diabetic Foot Ulceration" At Chiba Diabetic Complication Workshop 2002. "Learn from Overseas Diabetic Treatment", Chiba, Japan.
4. Invited Speaker: "New Insights into the Pathogenesis of Atherosclerosis". Contemporary Issues In Atherosclerosis: Focus On The Science. Organized by Pfizer Inc.
5. Invited Speaker: "Emerging Technologies in Wound Care". Diabetic Foot Management course organized by Harvard Medical School, Boston, MA.
6. Invited Speaker: "Microcirculation Abnormalities in Diabetes". Wound Healing: Science and Industry. St. Thomas, VI.
7. Invited Speaker: "Endothelial Dysfunction and the Microcirculation". *Consensus Development Conference on PVD in Diabetes*, organized by the American Diabetes Association.
8. Invited Speaker: "Diabetes and Cardiovascular Disease". *At Renal Division Seminar Conferences,, Medical Center of University of Vermont*.
9. Invited Speaker: "Neuropathy and Microvascular Disease". Symposium on Advanced Wound Care. Las Vegas, Nevada.

#### Presented Abstracts

1. Buras JA, Reenstra WR, Orlow D, Horton ES, Veves A. Effect of troglitazone on the expression of RAGE and PPAR $\gamma$  in type 2

diabetic patients. American Diabetes Association, 63<sup>rd</sup> Scientific Sessions, June 2003, New Orleans, Louisiana, Poster Presentation.

2. Economides PA, Caselli A, Khaodhiar L, Horton ES, Veves A. Endothelium independent vasodilation is impaired in type 2 diabetes. American Diabetes Association, 63<sup>rd</sup> Scientific Sessions, June 2003, New Orleans, Louisiana, Poster Presentation.
3. Economides PA, Caselli A, Khaodhiar L, Horton ES, Veves A. The effects of atorvastatin on the endothelial function in diabetic patients and subjects at risk for diabetes. American Diabetes Association 63<sup>rd</sup> Scientific Sessions, June 2003, New Orleans, Louisiana, Poster Presentation.
4. Thanh L. Dinh, John M. Giurini, Thomas E. Lyons, Lawrence A. Lavery, Aristidis Veves. The Influence of Gender on the Development of Diabetic Foot Ulcers. American Diabetes Association 63<sup>rd</sup> Scientific Sessions, June 2003, New Orleans, Louisiana, Poster Presentation.
5. Lalita Khaodhiar, Stacey Stefansky, Chantel Hile, Robert Greenman, Aristidis Veves. Use of Magnetic Resonance Spectroscopy To Identify Neuroischemic Changes at the Diabetic Foot. American Diabetes Association 63<sup>rd</sup> Scientific Sessions, June 2003, New Orleans, Louisiana, Poster Presentation.

## **VII. Plans for the Coming Academic Year**

1. My plans for the next year are to successfully organize the conduction of the ADA and NIH studies that prospectively examine risk factors for the foot ulceration. Furthermore, we plan to finish the other clinical trials that are currently under conduction in our unit.
2. In addition to the above, in collaboration with Cardiology and Radiology I plan to continue my efforts to examine the ability of new MRI techniques to be used for clinical and research purposes in the field of Diabetes.
3. Finally, in collaboration with local biotech companies, I am trying to develop new local treatments that will improve skin microcirculation of the diabetic foot.

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

### Original Articles

1. Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor K, **LoGerfo FW**, Horton ES, **Veves A**. The effects of troglitazone, an insulin sensitizing agent, on the endothelial function in early and late type 2

diabetes. A placebo-controlled, randomized, clinical trial. *Metabolism* 2003;52:173-180.

2. Caselli A, Singh Bedi D, O'Connor C, Shah C, **Veves A**. Assessment of laser perfusion imager's in vivo reliability: can it be used for a prospective analysis? *J Laser Appl* 2002;14:198-202.
3. Caselli A, Rich J, Hanane T, Uccioli L, **Veves A**. Role of c-nociceptive fibers in the impairment of nerve axon reflex-related vasodilation in diabetes. *Neurology* 2003;60:297-300.
4. Caselli A, Hanane T, Brady J, Carter S. **Khaodhiar L, Veves A**. Methyl Nicotinate-Induced Skin Vasodilation In Diabetic Neuropathy. *J Diabetes Complications* 2003;17:205-210.
5. Sheehan P, Jones P, Caselli A, **Giurini JM, Veves A**. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;26:1879-1882.
6. Szabó C, Zanchi A, Komjáti K, Pacher P, Krolewski AS, **Quist WC, LoGerfo FW, Horton ES, Veves A**. Poly (ADP-Ribose) polymerase is activated in subjects at risk of developing type 2 diabetes and is associated with impaired vascular reactivity. *Circulation* 2002;106:2680-2686.
7. Varo N, Vicent D, Libby P, Nuzzo R, Calle-Pascual AL, Bernal MR, Fernández-Cruz A, **Veves A**, Jarolim P, Varo JJ, Goldfine A, Horton ES, Schönbeck U. Elevated plasma levels of the atherogenic mediator sCD40L in diabetic patients: a novel target of thiazolidinediones? *Circulation* 2003;107:2664-2669.

#### Original Articles (in press)

1. Caselli A, Uccioli L, Khaodhiar L, **Veves A**. Local anesthesia reduces the maximal skin vasodilation during iontophoresis of sodium nitroprusside and heating. *Microcirculation Research* 2003;66; in press.
2. Economides PA, Caselli A, Zuo CS, Khaodhiar L, Sparks C, Katsilambros N, Horton ES, **Veves A**. Kidney oxygenation during water diuresis and endothelial function in patients with type 2 diabetes and subjects at risk to develop diabetes. *Metabolism* 2003; in press.
3. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, Moussa A, Ceselli A, Caballero AE, Economides PA, **Veves A**, Horton ES. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. *Diabetes Care* 2003; 26; in press.

4. **Khaodhiar L, Niemi JB, Harry LD, Earnest R, Lima C, Veves A.** Enhancing sensation in diabetic neuropathic foot with mechanical noise. *Diabetes Care* 2003; in press.

Reviews, Chapters, and Editorials (in press)

1. **Hile C, Veves A.** Diabetic Neuropathy and Microcirculation. *Current Diabetes Reports*. 2003; in press.
2. **Veves A, T Dinh.** The Diabetic Foot. In: DeFronzo RA, Ferrannini E, Keen H, Zimmet P. *International Textbook of Diabetes Mellitus*. 2003; in press.
3. **Hile C, Veves A.** Microcirculation of the Diabetic Foot. In: Johnstone MT, Veves A: *Diabetes and Cardiovascular Disease* (second edition). Humana Press, Totowa, NJ; in press.
4. **Khaodhiar L, Veves A.** Therapeutic Interventions to Improve Endothelial Function in Diabetes. In: Johnstone MT, Veves A: *Diabetes and Cardiovascular Disease* (second edition). Humana Press, Totowa, NJ. 2003; in press.



Dr. Veves in his office at the BIDMC.



Dr. Veves (center) with his research team.

# TRANSPLANT SURGERY



Douglas W. Hanto, M.D., Ph.D., Chief

## Division Members

Fritz H. Bach, M.D.

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

Scott R. Johnson, M.D.

Khalid Khwaja, M.D.

Peter N. Madras, M.D.

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

Anthony P. Monaco, M.D.

Anthony Sahyoun, M.D.

The Division of Transplantation has active clinical, translational, and basic research programs that continue to expand. The research laboratory of Fritz H. Bach, M.D. continues investigations into the ability of anti-apoptotic and anti-inflammatory protective genes to promote organ and tissue graft survival. His laboratory has shown, among other things, that heme oxygenase-1 (HO-1) expression or administration of either carbon monoxide (CO) or biliverdin/bilirubin leads to improved survival of heart and islet cell allografts in mice and suppressed T cell responses. Dr. Bach was selected by the American Society of Transplant Surgeons as one of the Pioneers of Transplantation at its recent Annual Meeting. Leo E. Otterbein, Ph.D., an expert on the effects of HO-1, CO, and biliverdin in several animal models of transplantation and arteriosclerosis, will join Dr. Bach's laboratory and the Division of Transplantation in 2004.

The laboratory of Christiane Ferran, M.D., Ph.D. is focused on investigating the functions of anti-apoptotic genes A20, Bcl-2, Bcl-x<sub>L</sub>, and A1 in models of organ and cellular transplantation, diabetes, atherosclerosis, hepatitis, and liver regeneration. Her laboratory has found that expression of A20 in endothelial cells, islets, and hepatocytes protects the cells from apoptosis and has anti-inflammatory properties by blocking activation of the transcription factor NF- $\kappa$ B. This prevents damage from atherosclerosis, diabetic vasculopathy, and transplant-associated vasculopathy. In addition her laboratory has shown that expression of A20 improves engraftment of minimal islet cell mass. Dr. Ferran received the Mary Jane Kugel Award from the Juvenile Diabetes Foundation International for her research contributions. Several surgical residents including Christopher Longo, M.D., Virendra I. Patel, M.D., and Gautam Shrikande, M.D. have had productive research fellowships in her laboratory.

The laboratories of Anthony P. Monaco, M.D. and Takashi Maki, M.D., Ph.D. are focused on inducing tolerance to organ allografts utilizing donor bone marrow cell infusion combined with immunosuppression by polyclonal anti-T cell antibody and rapamycin. This work has been extended into non-human primates with the awarding of a new five-year grant from the National Institutes of Health to examine tolerance induction. Their laboratories are also studying the effectiveness of polyclonal anti-T cell antibodies and exendin-4, an agent that stimulates beta cell neogenesis, in inducing disease remission in autoimmune diabetic NOD mice and have demonstrated a synergistic effect between these agents in achieving permanent remission.

The clinical research activities of Douglas W. Hanto, M.D., Ph.D., Scott R. Johnson, M.D., and Khalid Khwaja, M.D., focus on the development of malignancies after organ transplantation, new immunosuppressive protocols to improve efficacy and reduce toxicity, ABO incompatible transplantation, and kidney and liver transplantation in HIV+ patients. We have shown that the risk of post-transplant lymphoproliferative diseases (PTLD) is lowest in kidney transplant recipients receiving anti-IL2 R monoclonal antibody induction and is associated with improved patient and graft survival. Monoclonal antibody induction is associated with a higher risk of developing PTLD. We have shown that quadruple immunosuppression, plasmapheresis, and splenectomy can prevent antibody mediated rejection in ABO incompatible liver transplantation and may be evidence of accommodation caused by upregulation of protective genes. The Division of Transplantation will be participating in an NIH sponsored 5-year trial examining the role of transplantation in HIV+ patients. A number of other clinical studies are ongoing.

As one can see from this brief overview, and the details provided in this report from each of the individual investigators, the research programs in the Division of Transplantation are vibrant, innovative, and growing. We anticipate the recruitment of an additional transplant surgeon in the next year with a strong interest in liver regeneration. We also will be focusing significant efforts in developing translational research projects in nonhuman primate models with the ultimate goal of clinical trials. These include studies of tolerance induction using innovative therapies and studies of transcriptional profiling in a nonhuman primate model of liver transplantation in collaboration with Dr. Terry Strom and studies of protective gene upregulation in nonhuman primate models. Our goal is to translate laboratory advances that are made into clinical applications in man.

## **Fritz H. Bach, M.D.**

### **Division of Transplantation**

#### **I. Narrative Report**

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

#### **II. List of Current Employees**

- |                                     |                        |
|-------------------------------------|------------------------|
| 1. Miguel P. Soares, Ph.D.          | Instructor in Surgery  |
| 2. Shivraj Tyagi, Ph.D              | Instructor in Surgery  |
| 3. Kenichiro Yamashita, M.D., Ph.D. | Instructor in Surgery  |
| 4. Hongjun Wang, Ph.D.              | Instructor in Surgery  |
| 5. James McDaid, M.D.               | Research Fellow        |
| 6. Robert Oellinger, Ph.D           | Research Fellow        |
| 7. Aurelio Graca-Souza, PhD.        | Research Fellow        |
| 8. Martin Bilban, Ph.D.             | Research Fellow        |
| 9. Vilmosne Eva Csizmadia           | Research Assistant III |
| 10. Soo Lee                         | Research Assistant II  |

#### **III. List of Current Funding**

1. "Xenotransplantation of Protected Porcine Islets"  
Riva Foundation  
Project Period: 09/01/2003 - 08/31/2004  
Principal Investigator: Fritz Bach, M.D.
2. "CO timing and AV Graft"  
AGA Linde Healthcare

#### IV. Divisional Accomplishments over the Past Year

##### Research Accomplishments

1. We have studied the effects of heme oxygenase-1 (HO-1) expression or administration of either carbon monoxide (CO) or biliverdin/bilirubin in a number of conditions.

##### Transplantation of allogeneic hearts in mice.

- a. Administration of biliverdin to both the donor animal and the recipient leads to long-term survival of allogeneic hearts in which the donor and the recipient different for both class I and class II antigens.
- b. Recipients that carry long-term surviving hearts (>100 days) are frequently antigen-specifically tolerant.
- c. The administration of biliverdin leads to a decreased T cell proliferative response, which based on *in vitro* studies is likely caused by the suppression of the transcription factors NF- $\kappa$ B and NFAT resulting in less IL-2 production.

##### Effect of HO-1 expression on allo-immune response -- AICD.

- d. Expression of HO-1 induced with cobalt protoporphyrin IX (CoPP) leads to an initial (day 2) increased response of T cells to alloantigens followed by a later decreased response (day 6) associated with apoptosis. This is true both *in vitro* and *in vivo*.
- e. The increased response is accompanied by greater production of IL-2.
- f. This type of response (initial increase in proliferation with high IL-2 levels followed by apoptosis and therefore a decreased response is referred to as AICD (antigen-induced cell death) and is frequently found in tolerance inducing mechanisms.

##### Suppression of intimal proliferation after balloon injury.

- g. We have previously shown that administration of CO to a rat for one hour prior to balloon injury results in suppression of intimal proliferation seen without treatment on day 14.
- h. This year we focused primarily on the use of biliverdin or bilirubin to suppress post-balloon injury proliferation of smooth muscle cells (SMC).
  - i. Instilling a solution of biliverdin into the common carotid for 1 hour followed by balloon injury greatly reduces the subsequent intimal proliferation.
  - ii. Administering biliverdin or bilirubin to the recipient systemically also suppresses the intimal proliferation.
  - iii. Balloon injury in Gunn rats that constitutively have high bilirubin levels results in little if any intimal proliferation.
  - iv. Bilirubin suppresses SMC proliferation *in vitro*.

#### Treatment of TNF- $\alpha$ induced hepatitis with CO.

- i. Administration of TNF- $\alpha$  plus D-galactosamine to mice results in a rampant hepatitis that can lead to death as early as 12 hours.
- j. Pre-treatment of the mouse with CO for one hour and continual administration of CO suppresses the manifestations of hepatitis.
- k. However, the therapeutic effect of the CO is lost if NF- $\kappa$ B, iNOS or HO-1 are blocked (by using knock-out mice or by chemical inhibition). Thus, the CO therapeutic effect depends on NF- $\kappa$ B, the induction of iNOS, production of nitric oxide (NO) and the up-regulation of HO-1. The last step leads to production of more CO and the other products of HO-1: Fe<sup>++</sup> and biliverdin.

#### Prolongation of islet survival after allogeneic transplantation.

- l. We used induction of HO-1 with CoPP, administration of CO or administration of biliverdin or bilirubin to prolong survival of pancreatic islets transplanted to an allogeneic recipient rendered diabetic with streptozotocin. Both the donor and the recipient were treated in these experiments. Treatment of only the recipient produced similar results.
- m. Each of these treatments individually led to prolongation of survival and in many cases antigen-specific tolerance to the islets.
- n. Interestingly, treatment of only the donor also led to long-term survival of the islets in the untreated recipients in a high percentage of cases. Those recipients carrying long-term surviving islets became antigen-specifically tolerant. While induction of HO-1 in the donor only may carry over into the recipient, administration of CO or biliverdin or bilirubin would presumably not. These findings will be further investigated.

#### CO treatment of pigs undergoing cardiac by-pass.

- o. Together with European colleagues in Naples we showed that CO pre-treatment with CO suppressed the injury associated with the ischemia-reperfusion injury seen with by-pass and subsequent re-perfusion.
  - p. The main finding, which had not previously been shown with CO pre-treatment, was that the energetics of the heart were better maintained after re-perfusion: i.e. ATP was more efficiently generated.
  - q. This better generation of ATP likely explained the better function of the heart (evidenced by the mean number of defibrillations needed to re-start the heart after ischemia), lesser edema and lesser apoptosis.
2. We have elucidated signaling pathways used by cells treated with HO-1 and CO. In some cells, such as pancreatic islets, cGMP is the most important pathway; in other cells, such as endothelial cells, it is the p38MapKinase pathway. In smooth muscle cells, both cGMP and p38 are involved and p38 activation depends on cGMP for its activation.
  3. We have shown that pre-treatment of pancreatic islets with CO for 2 hours will markedly improve their function when transplanted to diabetic mice. We have also shown that inducing the expression of HO-1 in islets, including

treating the recipient with CoPP, which induces HO-1, results in long-term survival of the islets in about 50% of cases. Preliminary data show that giving biliverdin may have the same effect as inducing HO-1.

4. We have demonstrated that treatment of a rat receiving an aortic transplant with CO for the entire 56 days of the experiment results in a very highly significant reduction in the degree of post-transplant arteriosclerosis that develops.
5. We have demonstrated that expression of ferritin in endothelial cells is anti-apoptotic, and that the anti-apoptotic effect is mediated in part through p38.
6. I have shown that Th2 cytokines are involved in eliciting the expression of protective genes in endothelial cells.

#### Personal Accomplishments

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

### **V. Plans for the Coming Year**

#### Staff Changes/Recruitments

1. I will be recruiting an Associate Professor from the University of Pittsburgh.
2. I will search for a molecular biologist and a senior laboratory manager will be recruited. Also, substitutes for the post-docs who are leaving will be recruited.

#### Plans for Research

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

### **VI. Bibliography (07/01/02-9/30/03)**

#### Original Articles

1. Brouard S, Berberat PO, Tobiasch E, Seldon MP, **Bach FH**, Soares MP. Heme oxygenase-1-derived carbon monoxide requires the activation of transcription factor NF-kappa B to protect endothelial cells from tumor necrosis factor-alpha-mediated apoptosis. *J Biol Chem* 2002;227(20):17950-61.
2. Gunther L, Berberat PO, Haga M, Brouard S, Smith RN, Soares MP, **Bach FH**, Tobiasch E. Carbon monoxide protects pancreatic beta-cells from

apoptosis and improves islet function/survival after transplantation. *Diabetes* 2002;51(4):994-9.

3. Otterbein LE, Haga M, Zuckerbraun BZ, Liu F, Song R, Usheva A, Stachulak CH, Bodyak N, Smith RN, Cismadia E, Tyagi S, Akamatsu Y, Flavell RJ, Billiar TR, Tzeng E, **Bach FH**, Choi AM, Soares MP. Carbon monoxide suppresses arteriosclerotic lesions associated with chronic graft rejection and with balloon injury. *Nat Med* 2003; 9(2): 183-90.
4. Soares MP, Usheva A, Brouard S, Berberat OP, Gunther L, Tobiasch E, **Bach FH**. Modulation of endothelial cell apoptosis by heme oxygenase-1 derived carbon monoxide. *Antioxid Redox Signal* 2002; 4(2):321-9.
5. Wang N, Lee JM, Tobiasch E, Csizmadia E, Smith NR, Gollackes B, Robson SC, **Bach FH**, Lin Y. Induction of xenograft accommodation by modulation of elicited antibody responses 1 2. *Transplantation* 2002;74(3):334-45.

#### Original Articles (in press)

1. Soares M.P., Seldon M.P., Berberat P.O., Yu J., Vassilevskaia T., Tsui T.Y, **Bach FH**. Heme oxygenase-1 modulates the expression of adhesion molecules associated with endothelial cell activation. *J Immunol* 2003; in press.
2. Zuckerbraun BS, Billiar TR, Otterbein SL, Kim PKM, Liu F, Choi AMK, **Bach FH**, Otterbein LE. Carbon monoxide protects against liver failure via nitric oxide-induced heme oxygenase-1. *J Exp Med* 2003; in press.

#### Reviews and Book Chapters

1. **Bach FH**, Ivinson AJ. A shrewd and ethical approach to xenotransplantation. *Trends Biotechnol* 2002;20(3):129-31.
2. Ivinson AJ, **Bach FH**. The xenotransplantation question: public consultation is an important part of the answer. *CMAJ* 2002;167(1):42-3.

#### Books, Reviews, and Chapters, in press

1. Otterbein LE, Soares MP, Yamashita K, **Bach FH**. Heme oxygenase-1:unleashing the protective properties of heme. *Trends Immunol* 2003;24(8):449-55.

#### Abstracts

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

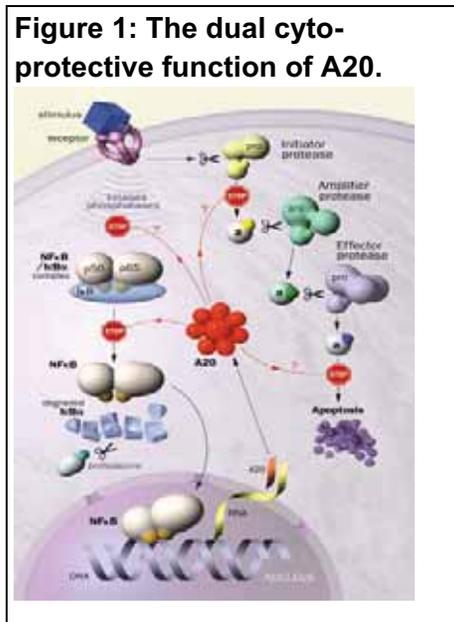
**Christiane Ferran, M.D., Ph.D.**

**Division of Transplantation  
Immunobiology Research Center**

**I. Narrative Report**

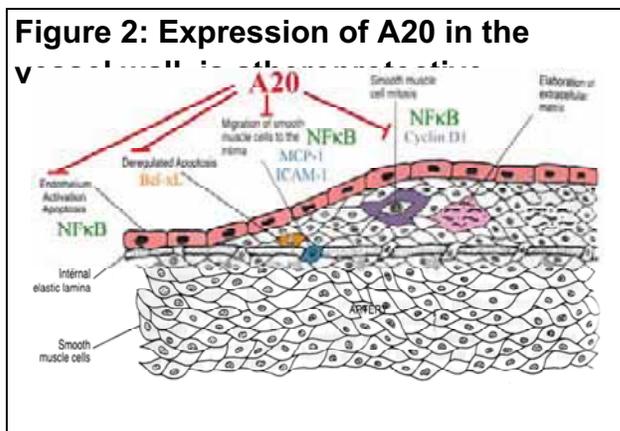
Basic Research

Most of my time effort, i.e. eighty five per cent, is devoted to research. My major research interests are in the fields of vascular biology, transplantation (including xenotransplantation and islet transplantation), autoimmune diabetes, acute liver failure, and liver regeneration. More specifically, the work in my



laboratory is focused on understanding the function (s) of anti-apoptotic genes A20, Bcl-2, Bcl-x<sub>L</sub> and A1 in different cell types, their relationship to the pathophysiology of diseases, and their potential therapeutic use in organ transplantation, diabetes, atherosclerosis, hepatitis, and liver regeneration. This interest is based on our original finding that these genes, mainly A20, serves a broad cytoprotective function in endothelial cells, islets and hepatocytes, and an atheroprotective function in smooth muscle cells. Expression of A20 in endothelial cells, islets and hepatocytes not only protects the cells from apoptosis by interrupting

activation of the caspase cascade, but also serve a broad anti-inflammatory purpose by blocking activation of the transcription factor NF-κB (Figure 1).



Expression of A20 in smooth muscle cells, on the other hand, inhibits their proliferation and sensitizes them to apoptosis hence significantly protects from athero-sclerosis, diabetic vasculopathy and transplant associated vasculopathy (Figure 2).

## II. List of Current Employees

1. Maria B. Arvelo, M.D. Research Fellow (leave of absence)
2. Soizic Daniel, Ph.D. Instructor in Surgery
3. Virendra I. Patel, M.D. Surgical Resident  
Recipient of a fellowship training grant from the Longwood Vascular Biology training program, a NIH training program (T32) headed by Dr. F. LoGerfo.
4. Gautam Shrikande MD Surgical Resident  
Recipient of a fellowship training grant from the Longwood Vascular Biology training program, a NIH training program (T32) headed by Dr. F. LoGerfo.
5. David Sun PhD Post-doctoral Fellow
6. Tala Shukri B.S. Research Assistant
7. Judy D. Cueva Alegria B.S. Research Assistant

## III. List of Current Funding

1. "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 (JDF).  
Project period: 09/1998-08/2003  
PI: Christiane Ferran MD/PhD  
Program Head: Dr. Hugh Auchincloss Jr.
2. "Protective effect of A20 against Transplant-Associated Vasculopathy"  
Roche Organ Transplantation Research Foundation  
Project period: 11/2001-10/2004  
PI: Christiane Ferran MD/PhD
3. " Gene transplantation with A20 to improve islet transplantation"  
NIH 1R21 # DK62601  
Project period: 09/2002-08/2004  
PI: Christiane Ferran MD/PhD
4. "Improved liver function and regeneration with A20"  
NIH RO1 Grant # DK063275  
Project period: 01/2003-12/2007  
PI: Christiane Ferran MD/PhD
5. The Longwood Vascular Biology Training Grant  
NIH T32.  
PI: Christiane Ferran MD/PhD

Program director: Dr. Frank W. LoGerfo

#### **IV. Applications Submitted and Pending Review/Funding**

1. "The anti-atherogenic function of A20"  
American Heart Association, Established Investigator Award  
Review date: November 2003.  
PI: Christiane Ferran MD/PhD

#### **V. Divisional Accomplishments**

##### Research Accomplishments

1. The past year, we have mainly extended our program to liver regeneration and were successful in receiving an RO1 grant for the completion of this work.
2. We have also been successful in taking our islet transplantation program in vivo and were successful in publishing a paper showing that expression of A20 allows for a good engraftment of a minimal islet mass.

##### Patent Disclosures

1. Ferran, C, inventor; No assignee.  
Use of Pro-apoptotic factors in treatment of atherosclerosis.  
US serial no 09/765,519. 2001, January 19.

##### Individual Accomplishments

1. Mary Jane Kugel Award. Juvenile Diabetes Foundation International 2002.
2. Invited lecture at the International Xenotransplantation meeting 2003, Glasgow, UK (September 30-October 4<sup>th</sup> 2003).
3. Chairman at the International Xenotransplantation meeting 2003, Glasgow, UK (September 30-October 4<sup>th</sup> 2003).

#### **VI. Report of Teaching**

##### Undergraduate and Medical School Courses

I had 3 summer students who spend between 8 and 11 weeks of work in the laboratory (June- August 2003). All benefited from bench top teaching as well as didactic teaching sessions.

1. Caroline Groft: Scholar of the Von Liebig Foundation for Vascular Biology, Medical student at Cornell University in New York.
2. Jean Choi: Summer college student, currently sophomore at MIT.
3. Nageeb Tarazi: Summer student, currently freshmen at Harvard.

#### Graduate School and Graduate Medical Courses

Weekly teaching sessions for the 2 surgical residents that are working in the laboratory. In addition to informal bench based teaching.

1. Virendra Patel, MD. Surgical Resident, BIDMC.
2. Gautam Shrikande, MD. Surgical Resident, BIDMC.

#### Invited Presentations (local, national and international)

1. 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.
2. Invited speaker at the Transplantation grand round, Lahey clinic Worcester MA. Topic: "A20 and Liver transplantation". Worcester, MA January 11<sup>th</sup> 2003.
3. Invited Lecturer at the Annual symposium in Vascular Surgery. Topic: "Atheroprotective Strategies". The Colonnade Hotel, Boston January 16<sup>th</sup> 2003
4. Invited speaker at the Harvard Seminars in Vascular Biology. Children's Hospital, Boston, MA. Help the EC live and let the SMC die, March 7<sup>th</sup> 2003.
5. Invited Lecturer at the BIDMC seminars in Vascular Biology. A20 and vascular cytoprotection. May 25<sup>th</sup> 2003.
6. Dr. Soizic Daniel PhD replaced me for a plenary session lecture at the International Xenotransplantation Meeting 2003. Topic: "Mechanisms of Vascular Cytoprotection".Glasgow, England, September 30<sup>th</sup>-October 4<sup>th</sup> 2003.
7. Dr. Soizic Daniel gave a Poster presentation at the American Transplant Congress 2003 (ATC). A20 protects the graft endothelium against death receptor (TNF and Fas) induced apoptosis, NK cytotoxicity and Complement mediated Necrosis. Wahington, DC May 2003.
8. Dr. Virendra I. Patel gave an oral presentation at at the American Transplant Congress 2003 (ATC). A20 protects from Neointimal Hyperplasia by

inhibiting smooth muscle cells (SMC) activation and proliferation and promoting SMC apoptosis. Washington, DC May 2003.

## VII. Plans for the Coming Academic Year

### Staff Changes/Recruitments

1. Salvatore Scali, MD. Surgical resident at the BIDMC. Two to 3 years of research fellowship. Start date: July 1<sup>st</sup> 2004.
2. Aram Demirjian, MD. Surgical resident at the BIDMC. Two to 3 years of research fellowship. Start date: July 1<sup>st</sup> 2004.
3. Duran Ustek, PhD. Research fellow to be hired. Tentative start date March 1<sup>st</sup> 2004.

### Plans for Research /Grant Applications to Be Submitted

1. "Atheroprotective function of A20 in Smooth muscle Cells" revision of RO1 NIH grant that was scored but not at a fundable range to be re-submitted March 1st 2004.
2. "Protective role of A20 against diabetic vasculopathy". To be submitted in 2004 to the JDFI. Submission date will depend upon progress of preliminary results.

## VIII. Bibliography (7/01/02-6/30/03)

### Original Articles

1. **Grey ST, Longo C, Shukri T, Patel V, Cszismadia E, Daniel S, Arvelo M, Tchipashvili V, Ferran C.** Genetic engineering of a suboptimal islet graft with A20 preserves  $\beta$ -cell mass and function. *J Immunol* 2003;170(12): 6250-6.
2. Kunter U, Floege J, von Jurgenson AS, Stojanovic T, Merkel S, Grone HJ, **Ferran C.** Expression of A20 in the vessel wall of rat kidney allografts correlates with protection from transplant arteriosclerosis. *Transplantation* 2003;75(1):3-9.
3. **Longo CR, Arvelo MB, Patel VI, Daniel S, Mahiou J, Grey ST, Ferran C.** A20 protects from CD40/CD40L mediated endothelial cell activation and apoptosis. *Circulation* 2003;108(9):1113-8.

### Proceedings of Meetings

1. **Daniel S, Arvelo MB, Patel VI, Longo CR, Shukri T, Mahiou J, Grey ST, Ferran C.** A20 protects the graft endothelium against death receptor (TNF and Fas) induced apoptosis, NK cytotoxicity and Complement mediated Necrosis. Proceedings of the American Transplant Congress (ATC 2003).
2. **Longo CR, Patel VI, Arvelo MB, Daniel S, Grey ST, Ferran C.** A20 Confers a Proliferative Advantage to Hepatocytes and Promotes Liver Regeneration. Proceedings of the 54<sup>th</sup> Annual meeting of the American Association for the Study of Liver Diseases.
3. **Patel VI, Arvelo MB, Longo CR, Daniel S, Shukri T, Grey ST, Ferran C.** A20 protects from Neointimal Hyperplasia by inhibiting smooth muscle cells (SMC) activation and proliferation and promoting SMC apoptosis. Proceedings of the American Transplant Congress (ATC 2003).

## **Douglas W. Hanto, M.D., Ph.D.**

### **Division of Transplantation**

#### **I. Narrative Report**

##### Basic Research

We are currently developing a nonhuman primate model of liver transplantation in order to study novel immunosuppressive regimens that have shown promise for their ability to induce tolerance in a nonhuman islet cell transplant model. An unusually potent therapeutic approach is under development in the laboratory of Dr. Terry Strom that blends his work of the role of T-cell growth factors in triggering T cell apoptotic (IL-2) and anti-apoptotic (IL-15) events in the allograft response with a long-standing interest in the design of therapeutic proteins. It will be necessary to test these protocols in nonhuman primates before proceeding to human trials. We will also use this model to examine the ability of protective genes heme oxygenase-1 (HO-1) and two of the products of HO-1 action on heme: carbon monoxide (CO) and biliverdin/bilirubin to enhance organ allograft survival and decrease the risk of rejection. This work is in collaboration with Fritz H. Bach, M.D. and Christiane Ferran, M.D., Ph.D. in the Division.

##### Clinical Research

We are engaged in a number of prospective and retrospective clinical studies involving transplantation (kidney, liver, pancreas, and islet), dialysis access, and nontransplant hepatobiliary surgery. We have had a longstanding interest in the development of malignancies after transplantation, particularly post-transplant lymphoproliferative diseases (PTLD), and also in the risk of transmission of malignancy to recipients from donors with cancer. We have also been interested in antibody mediated rejection in kidney and liver allograft recipients and the development of therapeutic strategies to permit ABO incompatible transplants and transplants in highly sensitized patients. With the introduction of several new immunosuppressive drugs over the past several years, we are examining changes in immunosuppressive protocols to minimize the side-effects of chronic corticosteroid and calcineurin inhibitor toxicity. The ability to safely transplant HIV+ patients is another significant focus of our clinical research activities as part of a multi-center NIH sponsored trial. We are beginning a clinical study in liver transplant recipients using transcriptional profiling to analyze the allograft response in patients that are likely to have predictive value for post-transplant liver function and risk of rejection with the ultimate goal of being able to individualize the degree of immunosuppression. There are many other ongoing clinical studies examining several issues including: risk of infectious complications with thymoglobulin induction in kidney transplant recipients; clinical characteristics of pancreatic schwannomas; role of portal vein embolization in facilitating radical hepatic resections; safety and efficacy of older live kidney donors; role of surgical

procedures for bleeding varices in the transplant era; results of total hepatectomy and backtable resection for hepatic malignancies; incidence and outcome of colon cancer after kidney and liver transplantation; antiviral prophylaxis in kidney transplantation; delayed steroid withdrawal utilizing anti-IL2R monoclonal antibody posttransplant; induction post-liver transplant with anti-CD52 monoclonal antibody.

## **II. List of Current Employees**

- |    |                           |                                 |
|----|---------------------------|---------------------------------|
| 1. | Martha Pavlakis, M.D.     | Assistant Professor of Medicine |
| 2. | Scott R. Johnson, M.D.    | Instructor in Surgery           |
| 3. | Khalid Khwaja, M.D.       | Instructor in Surgery           |
| 4. | Michael P. Curry, M.D.    | Instructor in Medicine          |
| 5. | Michael A. Wong, M.D.     | Assistant Professor of Medicine |
| 6. | Louise Riemer, R.N., N.P. | Transplant Coordinator          |
| 7. | Tina Seminara, R.N.       | Transplant Coordinator          |

## **III. Applications Submitted and Pending Review/Funding**

1. "Solid Organ Transplantation in HIV: Multi-site Study"  
National Institutes of Health  
Project Period: 01/01/2004–12/31/2008  
Principal Investigator: Douglas W. Hanto, M.D., Ph.D.

## **IV. Divisional Accomplishments over the Past Year (6/30/02-7/1/03)**

1. Demonstrated the efficacy of quadruple immunosuppression, plasmapheresis, and splenectomy in preventing humoral rejection in ABO incompatible liver transplantation.
2. Demonstrated that the risk of post-transplant lymphoproliferative diseases (PTLD) is lowest in kidney transplant recipients receiving anti-IL2 R monoclonal antibody induction and is associated with improved patient and graft survival. Monoclonal antibody induction is associated with a higher risk of developing PTLD.
3. Special Reviewer, Surgery, Anesthesiology, and Trauma Study Section, National Institutes of Health; Bethesda, MD, 2002.
4. Admitted to membership in The Halsted Society.

## **V. Report of Teaching**

Undergraduate and medical school courses

1. 2002 "Liver Failure and Liver Transplantation." Lecturer; 3<sup>rd</sup> Year Medical Students on Surgical Services.

#### Regional, National, and International Presentations

1. Yadlapalli N, Cherikh WS, Kauffman M, Pavlakis M, **Hanto D**. Colon cancer in solid organ recipients. Presented by Naga Yadlapalli, MD, at the American Society of Transplant Surgeons Third Winter Symposium. Miami Beach, FL, January 24-26, 2003, abstract #31.
2. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, **Hanto DW**. Is type of induction immunosuppression associated with an increased risk of PTLD? American Society of Transplant Surgeons Third Winter Symposium. Miami Beach, FL, January 24-26, 2003, abstract #51.
3. Doty TC, Merchen T, Gupta M, Hanaway M, Ahmad S, Lowy A, Matthews J, Pennington L, **Hanto DW**, Woodle ES, Buell JF. The University of Cincinnati, Cincinnati, OH. Comparison of laparoscopic and open surgical management of hepatic cysts. American Hepato-Pancreato-Biliary Association (AHPBA) Fourth Meeting. Miami Beach, FL, February 27-March 2, 2003, abstract #P55.
4. Kim J, Ahmad SA, Lowy AM, Matthews JB, Buell JF, Pennington LJ, James LE, **Hanto DW**. A comparison of the harmonic scalpel with clamp crushing technique for hepatic resection. Society for Surgery of the Alimentary Tract 44<sup>th</sup> Annual Meeting. Orlando, FL, May 18-21, 2003.
5. Kim J, Ahmad SA, Lowy AM, Matthews JB, James LE, **Hanto DW**. Biliary fistulas following hepatic resection: risk factors and treatment strategies. Society for Surgery of the Alimentary Tract 44<sup>th</sup> Annual Meeting. Orlando, FL, May 18-21, 2003.
6. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, **Hanto DW**. Is there an effect of induction immunosuppression on PTLD and graft/patient survival after kidney transplantation? American Transplant Congress 2003. Washington, DC, May 30-June 4, 2003, abstract #1623.
7. Martin J, Craycraft M, Hanaway M, **Hanto D**, Buell J, Rudich S. Induction immunosuppression in liver transplant recipients: a 14 year, single center review. International Liver Transplantation Society 9<sup>th</sup> Congress. Barcelona, Spain, June 18-21, 2003, abstract #168.

#### **VI. Plans for the Coming Academic Year**

##### Staff Changes/Recruitments

1. We are in the process of hiring an additional transplant surgeon with a research interest in liver regeneration.

2. We are actively recruiting a Clinical Research Administrator to coordinate the clinical research and translational research efforts in the Transplant Center.

#### Plans for Research

1. Establish the nonhuman primate liver transplant model and initiate studies in tolerance induction, molecular diagnostics, and protective gene studies in this model.
2. Submit a T32 Training Grant application in Transplant Immunology to the National Institutes of Health.

#### Plans for Educational Programs

1. Harvard School of Public Health, Center for Continuing Professional Education; "Leadership Development for Physicians in Academic Health Centers." November 9-21, 2003.

### **VII. Bibliography (07/01/02-06/30/03)**

#### Original Articles

1. Akoad M, Giraldo M, **Monaco AP**, **Hanto DW**, Uknis, ME. Enteric drainage of a pancreas allograft is safe for patients with celiac sprue. *Clin Transplant* 2002; 16:387-8.
2. **Hanto DW**. Reliability of voluntary and compulsory databases and registries in the United States. *Transplantation* 2003;75:2162-4.
3. **Hanto DW**, Fecteau AH, Alonso MH, Valente JF, Whiting JF. ABO incompatible liver transplantation with no immunological graft losses utilizing total plasma exchange, splenectomy, and quadruple immunosuppression: evidence for accommodation. *Liver Transpl* 2003;9:22-30.

#### Original Articles (in press)

1. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, **Hanto DW**. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. *Transplantation* 2003; in press.
2. Feng S, Buell JF, Chari RS, DiMaio M, **Hanto DW**. Tumors and Transplantation: The 2003 Third Annual ASTS State-of-the-Art Winter Symposium. *Am J Transplant* 2003; in press.

3. Guiney MJ, Kruskal JB, Sosna J, **Hanto DW**, Goldberg SN, Raptopoulos V. Multi-detector row CT of relevant vascular anatomy of the surgical plane in split liver resection. *Radiology* 2003; in press.
4. **Hanto DW**. Clinical Crossroads: A 51-year-old man with hepatitis-C cirrhosis needing liver transplantation. *JAMA* 2003; in press.
5. Kim J, Ahmad SA, Lowy AM, Buell JF, Pennington LJ, James LE, Matthews JB, **Hanto DW**. Increased biliary fistulas following liver resection with the harmonic scalpel. *Am Surg* 2003; in press.
6. Kim J, Ahmad S, Lowy AM, Matthews J, Buell J, Pennington LJ, Moulton J, **Hanto DW**. An algorithm for the accurate identification of benign liver lesions. *Am J Surg* 2003; in press.

#### Reviews, Chapters, and Editorials

1. Feng S, Buell JF, Cherikh WS, Deng MC, **Hanto DW**, Kauffman HM, Leichtman AB, Lorber MI, Maters RG, McBride MA, Metzger RA, Nolte FS, O'Connor KJ, Roth D, Terrault NA, Henry ML. Organ donors with positive viral serology or malignancy: risk of disease transmission by transplantation. *Transplantation* 2002; 74:1657-1663.
2. **Hanto DW**, Whiting JF, Valente JF. Transplantation of the liver and intestine. In: Norton JA, Bollinger RR, Chang AE, Lowry SF, Mulvihill SJ, Pass HI, and Thompson RW, editors. *Essential Practice of Surgery*. New York: Springer-Verlag Inc.; 2003:623-636.
3. Kauffman HM, McBride MA, Cherikh WS, Spain PC, **Hanto DW**, Delmonico FL. Donor related malignancies. *Transplantation Reviews* 2002;16:177-91.

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

**Division of Transplantation and**  
Transplantation and Cellular Immunology Laboratory

**I. Narrative Report**

Basic Research

1. Induction of tolerance to allografts. The major goal of this project is to study the allograft tolerance induced by donor bone marrow cell infusion combined with immunosuppression by polyclonal anti-T cell antibody (ALS) and rapamycin in a mouse skin allograft model.
2. Treatment of overtly diabetic NOD mice. The major goals of this project are to study the effectiveness of ALS and exendin-4, an agent that stimulates beta cell neogenesis, in inducing disease remission in autoimmune diabetic NOD mice. We will also study the effectiveness of allogeneic islet transplantation under the tolerance induction protocol using donor bone marrow infusion to treat autoimmune diabetes.
3. Induction of tolerance to allografts in non-human primates. The major goal of this preclinical study is to study the induction of tolerance to kidney and islet allografts in non-human primates using anti-thymocyte globulin, rapamycin and donor bone marrow cells.

**II. List of Current Employees**

- |                              |                     |
|------------------------------|---------------------|
| 1. Norihiko Ogawa, M.D.      | Postdoctoral Fellow |
| 2. Keisuke Minamimura, M.D.  | Postdoctoral Fellow |
| 3. Charudutt Paranjape, M.D. | Visiting Fellow     |
| 4. Rita Gottschalk           | Research Technician |

**III. List of Current Funding**

1. "Induction of unresponsiveness to allografts"  
NIH 2 RO1 AI14551-19  
Project period: 07/01/97 - 06/30/05  
Principal Investigator: Anthony P. Monaco, M.D.
2. "Treatment of overtly diabetic NOD mice"  
National Institutes of Health, 1R01 DK60721-01  
Project period: 12/01/01 - 11/30/05  
Principal Investigator: Takashi Maki, M.D., Ph.D.

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

#### **IV. Applications Submitted and Pending Review/Funding**

1. Induction of tolerance to islet allografts in NHP  
National Institutes of Health  
Project period: 04/01/04 - 03/31/09  
Principal Investigator: Takashi Maki, M.D., Ph.D.

#### **V. Divisional Accomplishments over the Past Year**

##### Research Accomplishments

1. We were awarded with Non-human Primate Immune Tolerance Cooperative Study Group grant from NIH to study tolerance induction to islet allografts in non-human primates. We have presented our results in the Cooperative Study Group Steering Committee meeting.

#### **VI. Report of Teaching**

##### Graduate School and Graduate Medical Courses

1. Transplantation Research Group "Research-In-Progress" meeting For staffs, fellows, medical students and research assistants who are engaged in transplantation research at Research North

##### Invited Presentations (local, national and international)

1. **Maki T**, Kanamoto A. Chimeric donor cells are required for induction and maintenance of transplantation tolerance in a radiation-based mixed chimerism model. 2003 American Transplant Congress Meeting. May 30 - June 4, 2003, Washington, D.C.
2. Ogawa N, Thaxton JE, **Maki T**. Synergistic effect of antilymphocyte serum and exendin-4 in achieving permanent remission in overtly diabetic NOD mice. American Diabetes Association 63rd Scientific Sessions. June 13 - 17, 2003, New Orleans, LA.
3. Anthony P. Monaco, M.D. Invited Lecture, "Tolerance and chimerism". European Society for Organ Transplantation and the Turkish Transplantation Society.

## VII. Plans for the Coming Academic Year

### Plans for Research (new grants/programs)

1. Program Project Grant (PI, Terry B. Strom)  
Project 1. Barriers to allograft tolerance with lymphodepletion (PI: T. Maki)
2. Research Grant  
Juvenile Diabetes Research Foundation: Islet allotransplantation in non-human primates (PI: T. Maki)

## VIII. Bibliography (07/01/02-06/30/03)

### Original Articles

1. Akoad M, Giraldo M, **Monaco AP**, Hanto DW, Uknis ME. Enteric drainage of a pancreas allograft is safe for patients with celiac sprue. *Clin Transplant* 2002;16:387-8.
2. Morrissey PE, Ramirez PJ, Gohh RJ, Yango AY, Kestin A, Madras PN, **Monaco AP**. Management of thrombophilia in renal transplant recipients. *Am J Transplant* 2002; 2(9): 872-6.
3. Ramirez PJ, Gohh R, Kestin A, **Monaco AP**, Morrissey PE. Renal allograft loss due to proximal extension of ileofemoral deep venous thrombosis. *Clin Transplant* 2002; 16:(4)310-3.
4. Vincenti F, **Monaco A**, Grinyo J, Kinkhabwala M, Roza A. A multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. *Am J Transplant* 2002; 3(3):306-11.
5. Yango A, Morrissey P, Gohh R, Wahbeh A, **Monaco A**, Beaulieu A. Donor transmitted parvovirus infection in a kidney transplant recipient presenting as pancytopenia and allograft dysfunction. *Transpl Infect Dis* 2002; 2(9):872-6.
6. Yango A, Gohh R, Morrissey P, Centracchio J, **Monaco AP**. Renal production of hepatocyte growth factor increases after unilateral nephrectomy in man. *Trans Proc* 2002; 34(8):3128-9.
7. Yango A, Morrissey P, **Monaco A**, Butera J, Gohh RY. Successful treatment of tacrolimus-associated thrombotic microangiopathy with sirolimus conversion and plasma exchange. *Clin Nephrol* 2002; 58(1):77-8.

8. Yango A, Morrissey P, Zanabli A, Beaulieu J, Shemin D, Kworkin L, **Monaco A**, Gohh R. Comparative study of prophylactic oral Gancyclovir and valacyclovir in high risk kidney transplant recipients. *Nephrol Dial Transplant* 2003; 18(4):809-14.

#### Original Articles (in press)

1. Morrissey P, Gohh R, Yango A, Gautam A, **Monaco A**. Renal transplant survival from older donors: A single center experience. *Arch Surg* 2003 (in press).

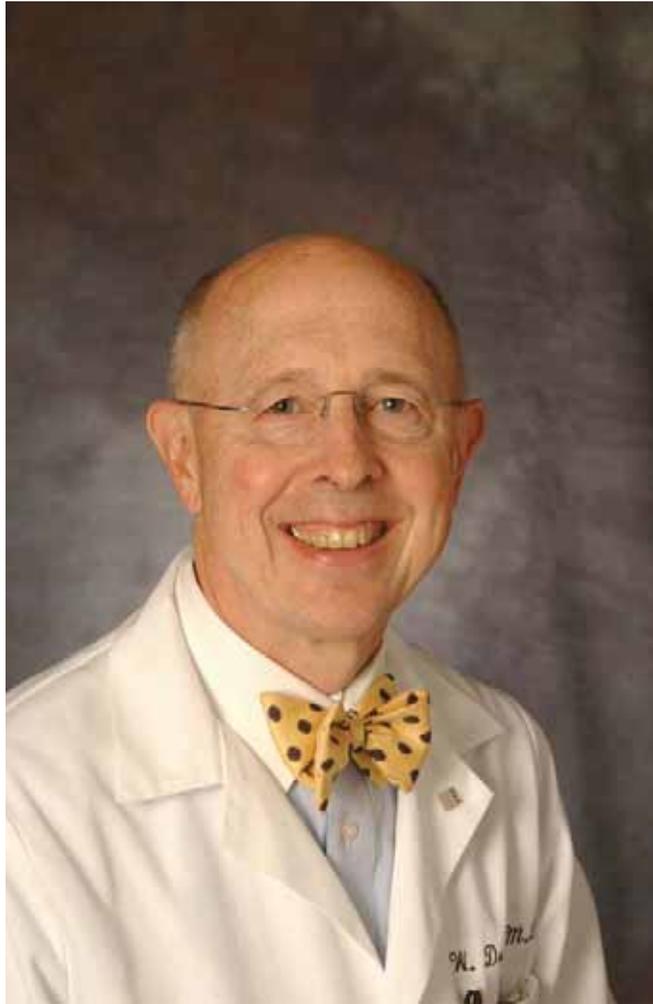
#### Proceedings of Meetings (in press)

1. **Monaco AP**. Chimerism in organ transplantation. Conflicting experiments and clinical effects. *Trans Proc* 2002; in press.
2. **Monaco AP**. Tolerance and chimerism: Separate and unequal concepts. *Trans Proc* 2002; in press.

#### Reviews, Chapters, and Editorials

1. Hale, DA, Gottschalk R., Umemura A, **Maki T**, **Monaco AP**. Immunological mechanisms in tolerance produced in mice with non-radiation based lymphoablation and donor specific bone marrow. *Transplantation* 2002;74:477-84.
2. **Maki T**, Gottschalk R, **Monaco AP**. Prevention of autoimmune diabetes by FTY720 in NOD mice. *Transplantation* 2002;74:1684-6.

# UROLOGY



William C. DeWolf, M.D., Chief

## Division Members

Paul A. Church, M.D.

Anurag (Andy) Das, M.D.

Robert C. Eyre, M.D.

Sandra M. Gaston, Ph.D.

Ann A. Kiessling, Ph.D.

Kathy Niknejad, M.D.

Abraham Morgentaler, M.D., Ph.D.

Aria F. Olumi, M.D.

Brian Saltzman, M.D.

Martin G. Sanda, M.D.

The Division of Urology has a wide-ranging research interest that incorporates both clinical and basic topics. The program touches on many aspects of this specialty including, reproduction, stem cell biology, tumor markers, stomal-epithelial interaction, virology (AIDS), neurourology and clinical outcomes analysis. The urology laboratory

community involves at least four PhD's and in addition we have at least 4-8 students from Harvard and MIT assigned to rotations thru our laboratories. Funding is continually growing and currently involves several NIH and DOD grants as well as private funding. Much of the Clinical Research is based on work from the new Continence Center focusing on aspects of neurourology as well as our busy oncology practice. We have established a database incorporating a single surgeon series of radical prostatectomies from the decade of the 1990's involving about 500 cases. This has been used to complete a series of manuscripts that now number five with more submitted.

The research work in Urology is presented at a wide range of meetings including the AUA, AACR and FASAB meetings. In addition as noted, in the following descriptions, the research work is published in a broad range of journals.

## William C. Dewolf, M.D.

### Division of Urology

#### I. Narrative Report

##### Basic Research

The basic component of my own research deals with biochemical characterization of a stem cell antigen that we originally described in 1992 (Schopperle W, Armant R, DeWolf WC: Purification of a tumor specific PNA-binding glycoprotein, gp200, from a human embryonal carcinoma cell line. Arch Biochem Biophys 1992;298: 538). We were the first to sequence the molecule and it has been found to be identical to a protein called podocalyxin (also Gp200, TRA1-60, and GCTM-2) (Schopperle WM, Kershaw DB, DeWolf WC. Human embryonal carcinoma tumor antigen Gp200/GCTM2, is Podocalyxin. Biochem Biophys Res Commun 2003; 300:295-300). This molecule is a 528 amino acid transmembrane protein that is heavily glycosylated and contains a single putative transmembrane domain. Podocalyxin has a large extracellular region containing a mucin and globular domain and a small cytoplasmic domain with a PDZ-binding motif. Podocalyxin was originally identified and cloned from podocytes, the blood-filtering cells of the body, where it has been shown to have putative function as a protein anchoring membrane protein that forms complexes with other proteins through its cytoplasmic PDZ-binding motif. This podocalyxin complex is critical for proper podocyte function. We are studying with what podocalyxin is interacting in embryonal carcinoma cells. Protein sequencing data reveal that glucose-3 transporter, the testis and brain-specific glucose transporter, copurifies with podocalyxin in purified protein fractions from embryonal carcinoma stem cells. Immuno-precipitation experiments with antiglucose-3 transporter and podocalyxin antibody confirm a stable complex exists in detergent extracted protein lysates. Podocalyxin may be functioning as an anchoring protein for this plasma membrane glucose transporter in stem cells. Current studies are underway to determine if podocalyxin and the transporter are interacting directly or if other proteins interacting through the PDZ-binding motif are tethering podocalyxin to the transporter, and to explore if there is any critical function for this complex in pleuripotent stem cells.

##### Clinical Research

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

#### II. List of Current Employees

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

### **III. List of Current Funding**

1. Intramural
2. “Matrix Metalloproteinase 9: Tumor Marker or Risk Factor for Prostate Cancer”  
Massachusetts Department of Public Health  
Project Period: 01/01/2001 – 12/30/2004  
Principal Investigator: Sandra Gaston, Ph.D.  
Co-Investigator: William C. Dewolf, M.D.

### **V. Divisional Accomplishments Over the Past Year**

#### Research Accomplishments

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

#### Individual Accomplishments

1. AUA Program Committee for Basic Research: Prostate Cancer.
2. Past President, National Urologic Forum.
3. Member of Medical Advisory Board, Boston Prostate Cancer Walk.
4. Faculty Sponsor to Dr. Price Kerfoot, AUA Scholar Award.

## VI. Report of Teaching

### Undergraduate and Medical School Courses

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

### CMR Courses

1. "Cell cycle regulators: Guardian of the Genome." Urologic Cancer Course, Harvard Medical School, Department of Continuing Education. Boston, 10/2/2002.

### Faculty Sponsored – AUA Scholar Award

1. Dr. Price Kerfoot, a recent graduate from the Harvard Program in Urology, has been awarded a two year AUA Scholar Award, which is a funded fellowship to study programs in medical student education with specific reference to implementation of new programs in urologic teaching. These awards are provided to the new graduate and a faculty sponsor/mentor who is responsible for research accomplishments and programs.

## VII. Plans for the Coming Academic Year

### Plans for Research

1. This information can be obtained from the narrative as well as research accomplishments. However, the basic thrust will be completion of our analysis of the glut-3/podocalyxin interaction and its biochemical characterization. Most of this work is completed and final completion will be in the form of a Journal of Biological Chemistry-type paper, which will form the platform and basis for a grant proposal.

## VIII. Bibliography (07/01/02-06/30/03)

### Original Articles

1. Bublely G, Balk S, Regan M, Duggan S, Morrissey M, **DeWolf WC**, Salgaami E, Mantzoros C. Serum levels of insulin-like growth factor –1 and insulin-like growth factor –1 binding proteins after radical prostatectomy. *J Urol* 2002;168:2249-2252.

2. Kerfoot P, **DeWolf WC**. Does the outpatient setting provide the best environment for medical students learning of urology? *J Urol* 2002;167:1797-1799.
3. **San Francisco I, DeWolf WC**, Rosen S, Upton M, **Olumi A**. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. *J Urol* 2003;169:136-140.
4. **San Francisco I, Olumi A**, Kao J, Rosen S, **DeWolf WC**. Clinical management of prostatic intraepithelial neoplasia as diagnosed by extended needle biopsies. *Brit J Urol* 2003;91:350-354.
5. **Schopperle WM, Kershaw DB, DeWolf WC**. Human embryonal carcinoma tumor antigen Gp200/GCTM2, is Podocalyxin. *Biochem Biophys Res Commun* 2003;300:295-300.
6. Sosna J, Rofsky N, **Gaston SM, DeWolf WC**, Lenkinski. Redetermination of prostate volume at 3-Tesla using external phased array coil: comparison to pathologic specimens. *Acad Radiol* 2003;10:846-53.
7. Spentzos D, Mantzoros C, Regan M, Morrissey M, Duggan S, Flickher-Garvey S, McCormick H, **DeWolf WC**, Balk S, Bubley G. Minimal effect of a low fat/high soy diet for asymptomatic hormonally naïve prostate cancer patients. *Clin Cancer Research* 2003;9:3282-3287.
8. Ung J, **SanFrancisco I**, Regan M, **DeWolf WC, Olumi A**. The relationship of prostate gland volume to extended needle biopsy on prostate cancer detection. *J Urol* 2003;169:130-135.
9. Yoon JH, **DeWolf WC**. Decreasing prostate specific antigen value leading to the diagnosis of pituitary adenoma. *J Urol* 2002;168:194.

Original Articles (in press)

1. George D, Regan M, Oh W, Manola J, DeCalo N, Duggan S, **DeWolf W**, Kantoff P, Bubley G. Radical prostatectomy lowers plasma vascular endothelial growth factor (VEGF) levels in patients with prostate cancer. *Urology*; in press.
2. **San Francisco I, Olumi A**, Yoon J, Regan M, **DeWolf WC**. Preoperative serum acid phosphatase and alkaline phosphatase are not predictors of pathologic stage and PSA failure after radical prostatectomy in the post PSA era. *Brit J Uro*; in press.
3. Zhang P, Rosen S, Veeramachameni R, Kao J, **DeWolf WC**, Rosen S, Bubley G. The association between prostate cancer and serum testosterone levels. *Prostate*; in press.

## Reviews (in press)

1. **DeWolf WC, Gaston S.** The cell cycle and its relevance to the urologist. *J Urol*; in press.

## Abstracts

1. **Gaston S, Siddiqui M, Soares M, Perides G, Upton M, DeWolf WC.** Development of molecular markers for prostate cancer local T staging: Capsular penetration positive, margin negative disease is associated with matrix metalloproteinase and collagen fragments on the external surface of the prostate gland. *J Urol* 2002;167:224A.
2. **Gaston S, Soares M, Brice M, Vu D, Upton M, Rosen S, Genega E, Lenkinski R, DeWolf WC.** Prostate capsule tissue prints detect a collagen fragment fingerprint that is positively correlated with the Gleason Grade of the tumor beneath the capsule. *J Urol* 2003; 169:294A.
3. Ko Y-J, **DeWolf WC, Olumi A**, et al. Neoadjuvant chemo-hormonal therapy followed by radical prostatectomy for high risk prostate cancer. *Proc Am Soc Clin Oncol* 2002; 21:2465A.
6. Ko Y-J, **DeWolf WC**, Sesterhan I, Balk S, Upton M, Bubley G. Pathologic findings after neoadjuvant chemo-hormonal therapy followed by radical prostatectomy (RP) for high risk prostate cancer (PCa). *Proc Am Assoc Cancer Res* 2003; 44:1243(a).
8. **Olumi A, Xiao Y, SanFrancisco I, Peehl D, DeWolf WC.** Retroviral transfection of human telomerase gene more commonly promotes senescence than expansion of life span in prostate fibroblasts. *J Urol* 2002;167:210A.
9. **Olumi A, Zhang X, San Francisco I, DeWolf WC**, Talquang J, Kohsravi-Far. Protein expression of C-FLIP (L) is associated with resistance to TRAIL-induced apoptosis in prostate cancer. *J Urol* 2003; 169:214A.
10. **SanFrancisco I, Olumi A**, Kao J, Rosen S, **DeWolf WC.** The natural history of prostatic intraepithelial macroplasia as defined by extended biopsy. *J Urol* 2002;167:70A.
11. Ung J, **SanFrancisco I**, Regan M, **DeWolf WC, Olumi A.** Lower prostate cancer detection rate in large prostate glands is not associated with biopsy sampling error. *J Urol* 2002;167:333A.

**Sandra M. Gaston, Ph.D.**

**Division of Urology**

**I. Narrative Report**

Our primary research interests focus on the molecular biology of urological cancers, and specifically on the molecular changes that underlie malignant progression to local invasion and metastasis. 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.

With NIH and corporate research support, we have developed a set of “tissue printing” technologies to detect macromolecules that are transferred directly from the surface of a fresh tissue specimen onto a nitrocellulose membrane. Combined with specific protein and RNA/DNA detection methods, these new techniques generate two-dimensional maps of the molecular markers in human tissue samples. Because tissue print collection does not damage the specimen, “tissue print” and “print-phoresis” serve as platform technologies that simplify the process of obtaining an adequate representation of human cancers in biopsies and surgical samples, particularly when the tissue of interest must be conserved for diagnostic evaluation. Moreover, when the molecular profile of the specimen is itself of potential diagnostic importance, such as in the evaluation of surgical margins for microscopic tumor, the tissue-printing platform can be adapted as a clinical tool to provide a “molecular section” of an extended area of the specimen. Tissue print profiles of the exterior surface of the intact prostate gland reveal clusters of protein markers that co-localize with sites of microscopic prostate cancer invasion into the prostate capsule. We have identified molecular “fingerprints” of collagen fragments that co-localize on prostate tissue print maps with high grade tumor foci. A distinct collagen fragment “fingerprint” is strongly associated ( $p < .005$ ) with tumor invasion of the prostate capsule. Recently, we extended our print-phoresis technology to the analysis of surgically resected partial mastectomy tissues and found that in breast cancer, positive surgical margins are associated with a different “fingerprint” of collagen fragments. Our working hypothesis is that collagen fragments and other products of extracellular matrix hydrolysis provide a class of markers that are particularly sensitive for actively invasive tumor foci, differentiating these more dangerous cancers from indolent disease.

With support from the Massachusetts Department of Public Health, we are characterizing the role of constitutive matrix metalloproteinase 9 (MMP9) expression in prostate cancer risk and progression. We have found that the constitutive expression of one of the major matrix metalloproteinases, MMP-9, is widely variable in the prostate tissue of healthy males, and that the observed pattern of prostatic MMP-9 variability is consistent with a constitutive genetic “set point”. Our working hypothesis is that men who have a high constitutive “set-point” for prostatic MMP-9 are at greater risk for clinically aggressive prostate

cancer than men who have a low constitutive expression of this enzyme. This year, we were awarded a pilot grant from the Susan Love Breast Cancer Foundation to extend this studies to include the evaluation of MMP-9 expression in nipple aspirate fluids (NAFs), and early results indicate that the breast ductal epithelium shows a similar variability in constitutive MMP-9 expression.

With NIH and CaPCURE support, we are developing a battery of micro-scale bioassays that can be used to monitor androgen receptor ligands in complex biological fluids including sera and tissue extracts. This last year we extended our micro-bioassay system, originally developed for the analysis of tissue and serum samples from prostate cancer patients, to permit analysis of samples from breast cancer patients. In addition, and to more completely characterize the endocrine microenvironment within solid tissues and tumors, we have begun to develop the instrumentation and protocols that will allow us to measure receptor expression in parallel with bioavailable ligand. This integrated analytical strategy, on a scale compatible with needle biopsies, will provide both a means for direct assessment of critical variables in the tissue/tumor microenvironment and a strategy for monitoring those variables in response to hormonally based therapies

We are also interested in the molecular events that result in male infertility. Currently, we are developing a protocol to evaluate the response of human spermatozoa to mycotoxins known to inhibit mitochondrial function, focusing on compounds known to inhibit sperm motility in animals. Our goal is to determine the basis of the individual differences observed in susceptibility of sperm motility to specific mycotoxins, and ultimately to translate these findings into a protocol that can be used in the clinical evaluation of sub-fertile human males.



Dr. Gaston's Laboratory

*Back row (from left): Ilana Kahn, Jon Rogg, Marc Soares, Sandra Gaston  
Front row (from left): Dana Goldner, Mark Brice, Lynn Mathew, Dang Vu*

## II. List of Current Employees

|     |                    |                         |
|-----|--------------------|-------------------------|
| 1.  | Marc Soares        | Research Technician     |
| 2.  | Mark Brice         | Research Technician     |
| 3.  | Jung Lee           | Research Technician     |
| 4.  | Dang Vu            | Research Technician     |
| 5.  | Efren Gutierrez    | Harvard Medical Student |
| 6.  | Dana Goldner       | Student                 |
| 7.  | Piali Mukhopadhyay | Student                 |
| 8.  | Jonathan Rogg      | Student                 |
| 9.  | Tae Wan Kim        | Student                 |
| 10. | Catherine Ford     | Student                 |
| 11. | Becky Kolenik      | Student                 |
| 12. | Aislinn Nichols    | Student                 |

## III. List of Current Funding

1. "Androgen Receptor Biochips: Prostate Cancer Management"  
National Institutes of Health, NCI R/R33 CA86365  
Principal Investigator: Ian Hunter Ph.D., MIT  
Principal Investigator: Sandra M. Gaston, Ph.D., BIDMC Subcontract
2. "Prostate Cancer Biomarkers in Urine"  
GMP Companies, Inc.  
Project period: 07/01/2001 - 07/31/2004  
Principal Investigator: Bruce Zetter, Ph.D., Children's Hospital  
Principal Investigator: Sandra M. Gaston, Ph.D., BIDMC Subcontract
3. "Matrix Metalloprotease 9: Tumor Marker or Risk Factor for Prostate Cancer?"  
Massachusetts Department of Public Health  
Project period: 01/01/2001 - 12/30/2004  
Principal Investigator: Sandra M. Gaston, Ph.D.  
Co-Investigator: William C. DeWolf, M.D.
4. "3T Magnetic Resonance and Spectroscopy of Prostate Cancer"  
General Electric Industry Sponsored Research  
Project period: 01/01/2002 - 12/31/2004  
Principal Investigator: Robert Lenkinski, Ph.D. (BIDMC Radiology)  
Co-Investigator: Sandra M. Gaston, Ph.D.
5. "Matrix Metalloproteinase 9 Expression and Secretion in Healthy Mammary Ducts: Risk Factor For Breast Cancer?"  
Susan Love MD Breast Cancer Research Foundation  
Project period: 05/01/2003-04/30/2004  
Principal Investigator: Sandra M. Gaston, Ph.D.

#### **IV. Applications Submitted and Pending Review/Funding**

1. "Prostate Needle Biopsies: Extending the Zone of Detection"  
National Institute of Health PAR 01-01-106 R21/R33  
Applications of Innovative Technologies for the Molecular Analysis of Cancer  
Prostate Needle Biopsies: Extending the Zone of Detection  
Submitted July 2003  
Principal Investigator: Sandra M. Gaston, Ph.D.
2. "Imaging Tumor Markers in Surgical Specimens and Biopsies"  
National Institute of Health PAR 01-01-106 R21/R33  
Innovative Technologies for the Molecular Analysis of Cancer: Phased Technology  
Submitted July 2003  
BIDMC Subcontract Principal Investigator: Sandra M. Gaston, Ph.D.
3. "Matrix Metalloproteinases as Molecular Biomarkers in Nipple Aspirate Fluids (NAFs): Establishing Clinically Relevant Baselines"  
BIDMC Clinical Research Feasibility Funds Program (CReFF)  
Submitted October 2003  
Principal Investigator: Sandra M. Gaston, Ph.D.
5. National Institute of Health RFA-CA-04-006  
Early Detection Research Network: Biomarker Development Laboratories  
To be submitted January 23, 2004  
Principal Investigator: Sandra M. Gaston, PhD

#### **V. Divisional Accomplishments**

##### Clinical Research Accomplishments (BIDMC Andrology Laboratory)

1. BIDMC Andrology was chosen to participate in a multi-institutional NIH funded study of the criteria used in the clinical assessment of sperm morphology (the "Human Sperm Morphology Standardization Project").
2. We continued to accrue samples to a research bank of frozen semen samples used as a resource for the study of secreted prostate biomarkers and biomarkers of male fertility. This bank captures approximately 30 new samples per month and provides an important source of control samples for our prostate cancer studies (IRB: W-00-0427-EX).
3. We initiated a collaboration with the leading manufacturer of automated systems for semen analysis, Hamilton-Thorne Biosciences Inc, to develop protocols for an SBIR proposal in which IVOS technologies will be modified for the detection of mitochondrial toxins that impair sperm motility (BIDMC will be subcontracted on the Hamilton-Thorne SBIR grant).

## Research Accomplishments

1. With NIH and CaPCURE support, we have developed a battery of micro-scale bioassays that can be used to monitor androgen receptor (AR) ligands in complex biological fluids, including sera and tissue extracts. These include a series of yeast-based bioassays formatted on a “living chip” platform that allows us to perform the analysis using significantly smaller sample volumes (less than 0.1 microliter per test point) than is possible with conventional bioassays, an important advantage when the analysis involves unique clinical specimens. In contrast to the immunoassays currently used in clinical settings, our yeast based bioassays measure the net AR response to all of the receptor-available ligands in a sample of serum or tissue extract.

We have continued to expand our battery of bioassays to include a series of functional AR mutations identified in human prostate cancers and to incorporate co-activator and co-repressor interactions. We are also incorporating additional steroid hormone receptors into our micro-bioassay system, with the goal of obtaining more complete profiles of the hormonal micro-environment of target tissues and tumors. The supplement awarded to our NIH grant has allowed us to begin pilot studies to extend the microbioassay technology for breast cancer applications and to begin development of a microscale real time PCR system which, in parallel with the bioassay, will permit analysis of both receptor expression and ligand concentrations in micro biopsy tissue samples.

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

4. We have developed a novel strategy for identifying and mapping molecular markers from human tissues and tumors obtained from surgical specimens. This “tissue printing” technology is used to analyze macromolecules blotted directly from the surface of a fresh tissue specimen onto a nitrocellulose membrane, and results in a two-dimensional molecular map of the surface of the tissue. Tissue prints can then further analyzed by “print-phoresis,” a method by which proteins on the tissue-print image are submitted to systematic electrophoresis and characterized by specific immunoblotting techniques or by detection of endogenous protein activity (ie by zymography). Recently, we have demonstrated that mRNA and DNA markers as well as protein makers can be quantitatively recovered from tissue prints. By combining sampling efficiency with multiple marker analysis, tissue print technologies provide a platform for the evaluation of an extended area of a tissue specimen for specific types of microscopic tumor. This strategy offers a practical new approach to the assessment of surgical margins that also preserves the specimen for standard clinical pathology and for research.

We applied our tissue print technologies to the analysis of molecular markers associated with tumor invasion of the prostate capsule, an event that is generally not apparent to the naked eye and thus may result in tumor at the surgical margins (“positive margins”) after radical prostatectomy. Prostate tissue print analysis showed that tumor breaches of the capsule were associated with focal concentrations of prostate specific antigen (PSA) on the exterior surface of the prostate gland (PSA “hot spots”); these PSA hot spots were also associated with established clinical indicators of aggressive prostate cancer, including disease recurrence. In addition, tissue print analysis revealed markers of extracellular matrix turnover on the external surface of the prostate at sites that overlie large, aggressive tumors. These matrix markers include profiles of relatively large collagen fragments (>20 kDa) that are associated with sites of histologically evident capsular invasion. These findings were included in a manuscript submitted for publication (Gaston et al. *Tissue Printing As a New Platform Technology for the Molecular Analysis of Human Surgical Specimens: Applications to Prostate Cancer.*) We anticipate that the proteins which cluster at sites of tumor invasion will include additional markers of value for prostate cancer staging, and may yield new targets for drugs designed to inhibit metastasis. In addition, one or more protein markers associated with tumor invasion of the prostate capsule will be utilized in a rapid-print protocol, allowing intra-operative assessment of surgical margins for residual tumor. Dr. William DeWolf, BIDMC Surgery, Dr. Elizabeth Genega and Dr. Seymour Rosen, BIDMC Pathology, Dr. Robert Lenkinski BIDMC Radiology and Dr. Ian Hunter, MIT (Bio-engineering) are important collaborators on this project.

5. Three of the students in the Gaston laboratory, Dana Goldner, Marc Soares and Jennifer Shih, received 2003 AACR-Thomas J. Bardos Science Education Awards (travel awards) to present the results of their work at the 94<sup>th</sup> Annual Meeting of the American Association for Cancer Research.

6. Dang Vu, a student in the Gaston laboratory, received a travel award from the American Society for Andrology to present the results of his work at the annual ASA national research conference.
7. Catherine Ford, a student in the Gaston laboratory, received a Fuller Fellowship from the New England Division of the American Cancer Society to support her summer research.

#### Individual Accomplishments

1. NCI Grant CA86365 *Androgen Receptor Biochips: Prostate Cancer Management* A funding supplement was awarded to each year of the R33 phase of this grant.
2. I was awarded a pilot research grant from the Susan Love MD Breast Cancer Research Foundation: *Matrix Metalloproteinase 9 Expression and Secretion in Healthy Mammary Ducts: Risk Factor For Breast Cancer?* .
3. I was named to the NIH National Cancer Institute Special Emphasis Panel to review grants submitted to the Innovative Technologies for the Molecular Analysis of Cancer (IMAT) program.
4. I was named to the NIH National Cancer Institute National Cancer Institute Special Emphasis Panel to review grants submitted to the Small Business Initiatives Research Topics (Molecular Analysis of Cancer).

#### Invited Presentations (national)

1. **Gaston SM.** *The Molecular Biology of Male Infertility: New Insights and Interventions.* University of Arizona, December 6, 2003.
2. **Gaston SM.** *Matrix Metalloproteinases and TIMPs in Human and Bovine Seminal Plasma.* TMI Laboratories of the Marks Institute, Tucson, Arizona, April 2, 2003.
3. **Gaston SM,** Hsiao R, Crane B, Hogan NC, Madden J, Hunter IW and Kanigan T *Androgen Receptor Bio-Chips: Yeast Based Micro-Bioassays for Serum and Tissue Androgens in Men with Prostate Cancer.* Principle Investigators Meeting, National Cancer Institute IMAT, June 16, 2003.
4. **Gaston SM.** *Tissue Printing and Print-Phoresis: A Practical Strategy for Mapping Tumor Markers in Human Surgical Specimens.* Activx Biosciences, La Jolla, CA June 18, 2003.

5. **Gaston SM** *Matrix Metalloproteinase 9 Expression and Secretion in Healthy Mammary Ducts: Risk Factor for Breast Cancer?* Love MD Breast Cancer Research Foundation 3<sup>rd</sup> Annual Santa Barbara Symposium, March 28, 2003.
6. **Gaston SM**, Soares M, Siddiqui M, Brice M, Vu D, Upton M, Rosen S, Genega E, Lenkinski RE and Dewolf WC. *Prostate Capsule Tissue Prints Detect Collagen Fragment Fingerprints Positively Correlated With Key Pathological Characteristics of the Tumor Beneath the Capsule.* American Urological Association 98<sup>th</sup> Annual Meeting, April 29, 2003 (Moderated Poster).
7. **Gaston SM**. Mathew LM, Hess S, Kahn I, Goldner D, Cherella E, Brice M, Hsiao R, Perides G, DeWolf WC *Are Genetic Polymorphisms in the Matrix Metalloprotease 9 Promoter Risk Factors for Prostate Cancer?* Society for Basic Urological Research, December 5, 2002 (Poster)
8. **Gaston SM**, Vu D, Oyarzo JN, Dawson GR, Ax RL *Activation Of Matrix Metalloproteinase-2 In Semen From Sub-Fertile Bulls.* American Society for Andrology, March 30, 2003 (Poster).
9. **Gaston SM**. Soares M, Brice MJ, Vu D, Shih J, Chow S, Chang JT, Upton M, Rosen S, Genega E, Pories S, Lenkinski R, DeWolf WC. *Tissue print analysis of surgically resected prostate and breast cancer specimens reveals collagen fragment "fingerprints" associated with tumor grade and with positive surgical margins.* American Association for Cancer Research July 12, 2003 (Poster).
10. **Gaston SM** Mathew LM, Hess S, Kahn I, Goldner D, Cherella E, Brice M, Hsiao R, Perides G, DeWolf WC *Functional genetic polymorphisms in the matrix metalloproteinase 9 promoter: risk factors for prostate cancer?* American Association for Cancer Research July 12, 2003 (Poster).

#### Invited Presentations (local)

1. **Gaston SM**. *Mapping Molecular Markers at Surgical Margins: Prostate Tissue Printing and Print-phoresis.* BIDMC GU Radiology Conference, April 16, 2003.
2. **Gaston SM**. *Tissue Print Analysis of Surgically Resected Prostate and Breast Cancer Specimens Reveals Collagen Fragment "Fingerprints" Associated with Tumor Grade and with Positive Surgical Margins.* Joint Retreat for Programs of Cell Biology, Breast Cancer and Prostate Cancer in the Dana Farber/Harvard Cancer Center, May 27, 2003.

#### Educational Activities (July 2002-June 2003)

I am part of the Harvard Medical School Teaching Faculty, teaching first year medical students.

To facilitate ongoing research and training efforts in the Division of Urology, the BIDMC Molecular Urology Training Program was initiated in the spring of 2000, with Sandra M. Gaston Ph.D. as Program Director. This last year, ten MIT undergraduates, two Simmons college undergraduate, one Georgetown University undergraduate and one first year Harvard Medical Student have participated in this program.

1. Sponsor/Research Mentor for American Cancer Society Fuller Fellowship Student, Catherine Ford, Summer 2003.
2. Sponsor/Research Mentor for ten MIT undergraduate students, including three who received American Association for Cancer Research Science Education Awards and one received an American Society of Andrology travel award.
3. Sponsor/Research Mentor for first year Harvard Medical Student, Efren Gutierrez.
4. Host for Harvard Medical School "Explorations" program for Boston middle school students.
5. Teaching Faculty, Harvard Medical School Chemistry and Biology of the Cell Course for first year medical students (Fall 2002).
6. Teaching Faculty, Harvard Medical School Principles of Pharmacology for first year medical students (Spring 2003).

## **VI. Plans for the Coming Academic Year**

### Clinical

In the coming year (November 2003), the BIDMC Andrology Laboratory is scheduled for a site visit for re-accreditation by the College of American Pathology (CAP).

### Research

#### New Research Initiatives

1. With the supplement to our NIH grant R33 CA86365, we will extend our micro-bioassay system to permit us to measure the levels of AR ligand receptor expression in parallel with bioavailable AR ligand. Our goal is to develop the instrumentation and protocols that will allow us to perform this integrated analysis on a scale compatible with needle biopsies.

2. In collaboration with Dr. Ian Hunter at MIT, we will develop a prototype of a device that will allow us to visualize specific molecular markers on tissue prints within an hour of collection, a time frame compatible with intra-operative use for detection of tumor-positive surgical margins.
3. We will undertake a pilot study to determine if tissue print technology can be used to detect tumor positive margins in partial nephrectomy surgical specimen.
4. We look forward this year to several important new research collaborations. These include:
  - A. With Dr. Stan Lilleberg of Transgenomic, Inc (Gaithersburg, MD) we will be applying the tissue print technology to the detection of low level tumor associated mutations in early (organ confined) human prostate cancers.
  - B. With Dr. Diarmaid Douglas-Hamilton at Hamilton-Thorne Biosciences, Inc (Beverly, MA), we will be developing protocols in which Hamilton-Thorne Biosciences IVOS technologies will be modified for the evaluation of mitochondrial toxins that impair sperm motility.
  - C. With Dr. Chun Li, Director of the Genetic Data Analysis Core in the Program in Human Genetics at Vanderbilt University, we will extend our analysis of MMP-9 promoter polymorphisms in order to identify the sequences that determine the constitutive MMP-9 “set point” in the prostate gland. These “set point” polymorphisms can then be used to analyze the association between constitutive MMP-9 expression and prostate cancer risk in reference populations.
  - D. In the next year, I will continue an aggressive program of generating funding to support and expand the major research efforts of my laboratory. Some of the major pending grant applications are listed in Section IV (above).

### Educational Activities

One of my major goals, as a member of both the Harvard Medical School (HMS) faculty and as a Visiting Scientist in the MIT Center for Biomedical Engineering, is to continue to develop the network of MIT-BIDMC student trainees through the MIT undergraduate research program (UROP). This next year, I will continue to recruit from this highly talented pool of students and to expand the extramural support for this effort.

This last year, for the third year, I accepted an invitation to be a research sponsor for a Fuller Fellow, a recipient of one of the undergraduate research fellowships

offered by the New England Division of the American Cancer Society. This next year, I will renew that commitment.

I will continue to sponsor Efren Guterriez, a first year Harvard Medical Student who is undertaking a study of the response of spermatozoa to mycotoxins.

My laboratory will again host middle school students from the Harvard Medical School "Explorations" program.

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

## VIII. Bibliography (07/01/02-06/30/03)

### Original Articles

1. **Zhou J-R**, Yu L, Zhong Y, Nassr RL, Franke AA, **Gaston SM**, **Blackburn GL**. Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. *Prostate* 2002;53(2):143-53.

### Original Articles (in press)

1. Sosna J, Rofsky NM, **Gaston SM**, DeWolf WC, Lenkinski RE. Determinations of prostate volume at 3-Tesla using an external phased array coil: comparison to pathologic specimens. *Acad Radiol* 2003; in press.

### Abstracts

1. **Gaston SM**, Mathew LM, Hess S, Kahn I, Goldner D, Cherella E, Brice M, Hsiao R, Perides G, DeWolf WC. Functional genetic polymorphisms in the matrix metalloproteinase 9 promoter: risk factors for prostate cancer? *Proc Am Assoc Cancer Research* 2003;44:651A.
2. **Gaston SM**, Soares M, Brice MJ, Vu D, Shih J, Chow S, Chang JT, Upton M, Rosen S, Genega E, Pories S, Lenkinski R, DeWolf WC. Tissue print analysis of surgically resected prostate and breast cancer specimens reveals collagen fragment "fingerprints" associated with tumor grade and with positive surgical margins. *Proc Am Assoc Cancer Research* 2003;44:37A.
3. Vuletic V, Hutchinson L, DeWolf WC, **Gaston SM**, Zetter BR. The urinary proteome in prostate cancer diagnosis: Tumor markers and protein signatures. *Proc Am Assoc Cancer Research* 2003;44:1078.

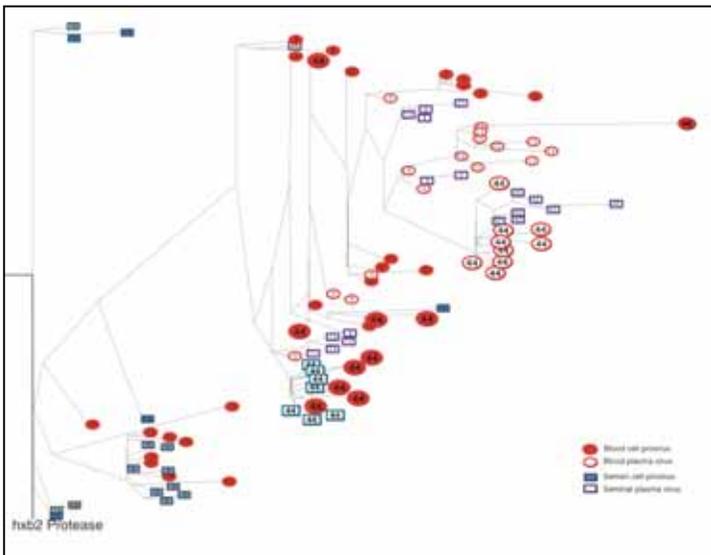
4. **Gaston SM, Soares M, Brice MJ, Vu D, Upton M, Rosen S, Genega E, Lenkinski R, DeWolf WC.** Prostate capsule tissue prints detect a collagen fragment fingerprint that is positively coordinated with the Gleason grade of the tumor beneath the capsule. *J Urol* 2003;162(4):294A.
5. **Gaston SM, Vu D, Oyarzo JN, Dawson GR, Ax RL.** Activation of matrix metalloproteinase-2 in semen from sub-fertile bulls. *J Androl* 2003;24A.

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

## Division of Urology

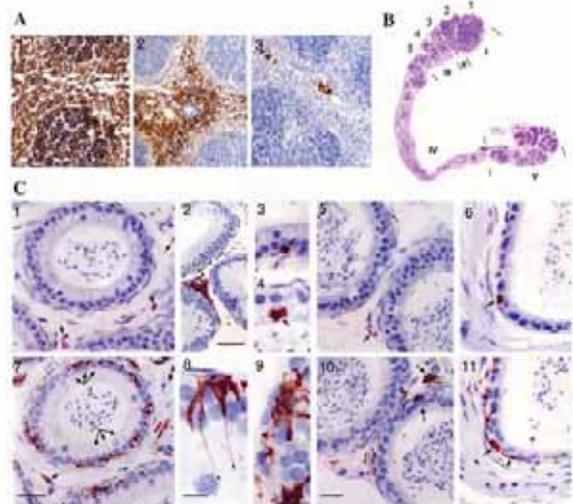
### I. Narrative Report

The long-term goals of my research lab are to understand tissue specificity and controls on 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.



**PROJECT 1:** Phylogenetic analysis of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a longitudinal study design. Maximum-Likelihood Tree at left illustrates the unique clustering pattern of HIV quasispecies isolated from paired blood and semen specimens from month 9 of study to Month 44 for one study subject. Tree shown is analysis of 97 unique, cloned HIV protease gene sequences. Similar analyses are ongoing with other study subjects.

**PROJECT 2:** Immunology of male GU tract tissues with emphasis on the prostate, seminal vesicles and epididymis. Understanding immune controls in these tissues will provide important insights into not only sexually transmitted diseases, but also specific gland pathologies, such as prostatitis and prostate cancer. The figure to the left illustrates immunostaining of spleen (A-2) and epididymis (C7-C11) for the macrophage marker F4/80 and the pan-leukocyte marker, CD45 (A-1) and (C1-6). The unusual dendritic presentation of the F4/80 positive cells in the epididymis has not been previously reported and is under investigation.



## II. List of Current Employees

- |                           |                              |
|---------------------------|------------------------------|
| 1. Julian Fleischman, PhD | Visiting Associate Professor |
| 2. Bryan Desmarais        | Research Technician          |
| 3. Nathan Neville         | Student                      |

## III. List of Current Funding

1. "Role of the Male Genital Tract in HIV Disease"  
NIH/NIDDK 7R01 DK 52761  
Project period: 2000-2005  
Principal Investigator: Ann A. Kiessling, Ph.D.
2. Urologic Research Fund  
Provides support for the male GU tissue studies not included in the NIH funded project.

## IV. Narrative of Divisional Accomplishments over the Past Year

### Research Accomplishments

1. The longitudinal genetic and phylogenetic analyses of HIV genes are now proceeding rapidly and we are using methods for gene sequencing directly from PCR reactions, thus avoiding the need for cloning. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men, including those on therapy. Moreover, we have identified several study subjects who failed their antiretroviral therapy first in semen producing organs. The drug resistant HIV species showed up in peripheral blood several weeks later.
2. We have identified a novel class of macrophages in male mouse and human tissues, which appear to play a fundamental role in organ function. This could have broad application to understanding the physiology of the prostate, seminal vesicles, and epididymis, as well as their role as reservoirs of HIV infection. The work in the mouse has now been published and the human work is ongoing.
3. We continue to host Egg Group, a New England area seminar series in existence for more than a decade, which attracts reproductive scientists from Northeastern, Tufts, Harvard, U Mass Amherst, Boston U, and Woods Hole MBL. This seminar is sponsored by the Bedford Research Foundation, a non-profit organization founded in Boston.

### Individual Accomplishments

1. Dr. Kiessling authored an introductory textbook "Human Embryonic Stem Cells: An Introduction to the Science and Therapeutic Potential" published in April, 2003, by Jones and Bartlett.

2. Dr. Church was Director of the Surgical Core Clerkship, Third Year, Lecture Series, Harvard Medical School.
3. Drs. Eyre and Church gave multiple lectures to the medical students rotating through the Surgical Core Clerkship, Third Year.
4. Dr. Eyre was a member of the American Urologic Association Investment Board.
5. Dr. Eyre was elected Treasurer of the New England Section of the American Urologic Association

## V. Report of Teaching

### Undergraduate and Medical School Courses

1. Surgical Core Clerkship Lecture Series, Third Year  
Dr. Church  
Dr. Eyre
2. Director, Senior Surgical Residency Rotation, Faulkner Hospital  
Dr. Eyre

### Invited Presentations (local, national, and international)

#### Dr. Kiessling

1. Keynote Address: "Human Embryonic Stem Cells: The Present and the Future"  
Fourth International Conference on Biotechnology,  
Shanghai, China  
November, 2002
2. "Reproductive Concerns and Sexually Transmitted Diseases"  
Invited Speaker  
Department of Biology  
Brandeis University
3. "The Future of Stem Cell Therapy"  
Invited Dinner Speaker  
Women's Health Society  
Winston-Salem, NC
4. **Kiessling AA**, Mullen TM, Kiessling RL "Presence in mice and men of a novel class of leukocytes/macrophages essential for normal development of male mouse reproductive tract tissues". Third International Conference on the Epididymis, Charlottesville, VA, May, 2002.

## VI. Plans for the Coming Academic Year

1. We have recruited one new staff member (Stephen Eyre) and will continue to recruit one more.
2. We will seek collaborators in primate research facilities, which house HIV-infected chimpanzees, to continue and refine our efforts to discover HIV host cells in male genitourinary tract tissues. This preliminary data will allow us to prepare a new NIH grant submission in 2004.
3. We will continue our efforts to gain approval from the BIDMC CCI to conduct collaborative studies with the University of Virginia of HIV genetics in paired follicular fluids and blood from an HIV infected female physicians. There has been confusion about how to structure the CCI consent for this two-center study.

## VII. Bibliography (07/01/02-06/30/03)

### Original Articles

1. Mullen T, RL Kiessling, **AA Kiessling**. Distinct populations of leukocytes in semen producing organs of the normal, hemicastrated and vasectomized mouse. *AIDS Res Hum Retroviruses* 2003;19(3):235-43.
2. Yakamoto M, Mullins T, Byrn R, Eyre R, Church P, **Kiessling AA**. Seminal plasma induces programmed cell death in peripheral blood mononuclear cells. *AIDS Res Hum Retroviruses* 2002;18(11):797-803.

### Books, Monographs and Textbooks

1. **AA Kiessling**, SC Anderson: Human Embryonic Stem Cells: An Introduction to the Science and Therapeutic Potential. Jones and Bartlett, Publishers, 2003.

## Aria F. Olumi, M.D.

### Division of Urology

#### I. Narrative Report

##### Basic Research

##### PROJECT 1: STROMAL-EPITHELIAL INTERACTIONS REGULATE DEVELOPMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH).

The long-term goal of my laboratory is to study the biology of stromal-epithelial interactions in benign prostatic hyperplasia (BPH). Because development, growth and tumorigenesis in the prostate are closely regulated by stromal-epithelial crosstalk, identifying signal transduction pathways between prostate epithelial cells and surrounding stromal cells will enable us to better understand the normal and abnormal biology in prostatic diseases. I hypothesize that expression of particular stromal genes is one component that regulates proliferation, cell death, and differentiation of prostatic epithelial cells leading to BPH in adulthood.

The Jun-family proteins, which are early transcription factor molecules, have been shown to regulate stromal-epithelial interactions via paracrine modulation. Moreover, Jun family proteins have been shown to play an important role in proper development of the genitourinary organs. One goal of my research lab is to determine if the differential expression of Jun-family proteins in the stroma regulates proliferation, survival and/or differentiation of prostatic epithelial cells. Stromal expression of Jun-family proteins is examined in relation to signal transduction pathways known to be important in prostatic stromal-epithelial interactions. These studies will improve our understanding of normal and abnormal stromal-epithelial interactions that may lead to BPH in adulthood.

##### PROJECT 2: MOLECULAR MECHANISMS OF DEVELOPING RESISTANCE TO TRAIL-INDUCED APOPTOSIS IN PROSTATE CANCER.

TRAIL is a relatively new molecule that causes cancer cell death. Since TRAIL specifically kills cancer cells and spares normal cells, its use is not associated with commonly known anti-cancer drug toxicities. This property makes TRAIL an ideal cancer therapy agent. Prostate cancer cells are responsive to the effects of TRAIL, however, some prostate cancer cells develop mechanisms of resistance to TRAIL. We have discovered specific signals within prostate cancer cells that promote or inhibit prostate cancer cell killing by TRAIL. We hypothesize that the presence or absence of these molecules in prostate cancer is responsible for determining whether a cell is sensitive or resistant to TRAIL.

In my laboratory, we plan to manipulate specific signals associated with TRAIL resistance in prostate cancer. We will determine whether manipulation of these signals can change a prostate cancer cell from being resistant to TRAIL to becoming sensitive to TRAIL.

##### Clinical Research

**PROJECT 1: SYSTEMATIC PROSTATE NEEDLE BIOPSY FOR IMPROVED DIAGNOSIS OF PROSTATE CANCER.**

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.

**PROJECT 2: HYPOGONADISM AND ASSOCIATION WITH DIAGNOSIS AND OUTCOME OF PATIENTS WITH PROSTATE CANCER.**

Androgens regulate normal prostate development and prostate cancer progression. We have previously shown a paradoxical link of serum total and Free-T(esterone) levels with prostate cancer. The purpose of this project is to validate whether hypogonadism is associated with high grade prostate cancer, to examine the relationship between Free-T, PSA, and age of diagnosis, and to determine whether Free-T levels can be used as predictors for prostate cancer recurrence after surgical therapy for prostate cancer.

**II. List of Current Employees**

1. Xiaoping Zhau, M.D., PhD. Research Fellow
2. Ignacio San Francisco, M.D. Research Fellow

**III. List of Current Funding**

1. "Stromal Epithelial Interactions in Benign and Malignant Prostatic Diseases"  
BIDMC, Department of Surgery  
Project Period: 9/01/00-8/30/03  
PI: AF Olumi
2. "The Role of Anti-Apoptotic Factors in Evasion of Prostate Tumors from TRAIL-Induced Apoptosis"  
NIH/Harvard Prostate SPORE grant  
Project period: 11/03-10/05  
PI: P. Kantoff  
Pilot Project PI: AF Olumi
3. "Stromal-epithelial Interactions in BPH"

NIH/NIDDK K08 DK64062-01  
Project period: 7/1/03-6/31/07  
PI: AF Olumi

#### **IV. Narrative of Divisional Accomplishments over the Past Year**

##### Research Accomplishments

1. Awarded grant from NIH/NIDDK—K08
2. Renewal of pilot project grant from NIH/SPORE Prostate Research grant from DFCI/HCC.

##### Individual Accomplishments

1. Invited grant reviewer for Department of Defense Prostate Cancer Program

#### **V. Report of Teaching**

##### Undergraduate and Medical School Courses

1. MIT pre-medical advisor for three undergraduate students
2. HMS: Core surgery clerkship lecturer for medical students; topics: BPH and prostate cancer (once every three months).

##### Graduate School and Graduate Medical Courses

1. Resident teaching – Harvard Program in Urology
  - b) Monthly one-on-one evaluation with interns and residents
  - c) Weekly faculty representative for the Harvard Urology Program conferences.
  - d) Directed an animal laparoscopy program for the Harvard Urology Program at Rhode Island Hospital, January 2002 and October 2002

##### Invited presentations (local, national, and international)

1. **Olumi AF, Zhang X, San Francisco IF, DeWolf WC**, Jin T, Khosravi-Far R. Protein expression of c-FLIP(L) is associated with resistance to trail-induced apoptosis in prostate cancer. American Urological Assoc. Annual Meeting, Chicago, IL, 2003.

#### **VI. Plans for the Coming Academic Year**

1. To hire a new post doctoral fellow since Dr. San Francisco, one of the present post-docs in my lab will be leaving at the end of this academic year.
2. Re-submit grants to the Dept. of Defense Prostate cancer program

## VII. Bibliography (7/1/02 through 6/30/03)

### Original Articles

1. **San Francisco IF, DeWolf WC, Rosen S, Upton M, Olumi AF.** Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy, *J Urol* 2003;169(1):136-140.
2. **San Francisco IF, Olumi AF, Kao J, Rosen S, DeWolf WC,** Clinical management of prostatic intraepithelial neoplasia as diagnosed by extended needle biopsies, *BJU Int* 2003;91(4):350-354.
3. Ung JO, **San Francisco IF, Regan MM, DeWolf WC, Olumi AF.** The relationship of prostate gland volume to extended needle biopsy on prostate cancer detection. *J Urol* 2003;169(1):130-135.

# VASCULAR SURGERY



Frank LoGerfo, M.D., Chief

## Division Members

David R. Campbell, M.D.  
Allen D. Hamdan, M.D.  
Frank B. Pomposelli, M.D.

Sherry D. Scovell, M.D.  
John J. Skillman, M.D.

**Frank W. LoGerfo, M.D.**  
**Allen D. Hamdan, M.D.**

**Division of Vascular Surgery**  
Vascular Surgery Research Laboratory

## **I. Narrative Report**

### Basic Research

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

As for biomaterials research, we have designed and patented a novel, biocompatible Dacron vascular graft with a polyurethane sealant, with this graft currently being evaluated *in vivo*. Additionally, we are evaluating *in vivo* a novel infection-resistant Dacron prosthetic valve sewing cuff with optimum antimicrobial properties. We are also developing a novel titanium surface with mitogenic properties via covalent linkage of bone morphogenic protein-2 (an osteoblast mitogen). Lastly, an infection-resistant polyurethane was developed via application of quinolone antibiotics using textile dyeing techniques, with this surface demonstrating *in vivo* activity. This biomaterial can be used to comprise a wide range of implantable devices such as catheters, wound dressings and vascular grafts.

### Clinical Research

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

The clinical trials are a Phase III multicenter randomized, double-blind, placebo-controlled trial of the ex-vivo treatment with CGT003 of peripheral vein grafts in

patients undergoing peripheral arterial bypass graft procedures - the PREVENT III Trial. This involves the use of an oligonucleotide decoy for transcription factor E2F delivered into the vein graft wall at the time of bypass. The hypothesis is that shutting down E2F will limit the downstream effect of intimal hyperplasia and decrease graft stenosis or failure. We are one of 60 centers in the trial but are currently the number one as far as numbers enrolled.

The second trial is CREST (Carotid Revascularization Endarterectomy vs Stent Trial). This is a multicenter randomized trial attempting to answer one of the most important questions in vascular surgery today: is carotid angioplasty a reasonable or better alternative than carotid endarterectomy in the treatment of symptomatic carotid stenosis? We plan to start in the fall.

## **II. List of Current Employees**

1. Puja Aggarwal Undergraduate Student.
2. Barry A. Gross, B.S. Information Systems Development
3. Jeffrey A. Kalish, M.D. Research Fellow
4. Jennifer Lambert, R.N., B.S.N. Clinical Trials Research Administrator
5. Thomas S. Monahan, M.D. Research Fellow
6. Haig Panossian Undergraduate Student
7. Vaishali B. Patel, B.S. Administrative Assistant
8. Matthew D. Phaneuf, B.S. Assistant Laboratory Director
9. Amish A. Shah, M.D., Ph.D. Graduate Student
10. Kerry A. Sousa Undergraduate Student
11. Dr. Mauricio A. Contreras, M.D., Instructor in Surgery, also collaborates with our group.

## **III. List of Current Funding**

1. Mechanisms of Prosthetic Arterial Graft Failure  
National Institutes of Health, R01 HL21796  
Project period: 1978 - 2003  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.
2. Harvard-Longwood Research Training Program in Vascular Surgery (T32)  
National Institutes of Health - Heart, Lung and Blood Institute  
Project period: 1993 - 2003  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.
3. William J. von Liebig Research Training in Vascular Surgery  
William J. von Liebig Foundation  
Project period: 2002 - 2003  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.
4. Development of a Biologically-Active Prosthetic Graft

- National Institutes of Health - Small Business Technology Transfer  
Research Grant (Phase II)  
Project period: 2002 - 2004  
Principal Investigator: Frank W. LoGerfo, M.D.
5. Nanofiber Technology in Small-Diameter Vascular Grafts  
National Institutes of Health - Small Business Technology Transfer  
Research Grant (Phase I)  
Project period: 2002 - 2003  
Principal Investigator: William C. Quist, M.D., Ph.D.
  6. Infection-Resistant Prosthetic Heart Valve Sewing Cuffs  
National Institutes of Health - Small Business Innovative Research Grant  
(Phase II)  
Project period: 2003 - 2005  
Principal Investigator: Allen D. Hamdan, M.D.
  7. Bioactive Textiles: Inherent Antimicrobial and Antifungal Properties  
Department of Defense (United States Army)  
Project period: 2003  
Principal Investigator: William C. Quist, M.D., Ph.D.
  8. A Phase III Multi-Center Randomized, Double-Blind, Placebo-Controlled Trial  
of the Ex-Vivo Treatment with CGT003 of Peripheral Vein Grafts in Patients  
Undergoing Peripheral Arterial Bypass Graft Procedures  
Industry funding - Corgentech  
Study period: 03/01/02 - end of recruitment  
Principal Investigator: Allen Hamdan M.D.

#### **IV. Applications Submitted and Pending Review/Funding**

1. Mechanisms of Prosthetic Arterial Graft Failure  
National Institutes of Health, R01 HL21796  
Project period: 2003 - 2008  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.
2. Harvard-Longwood Research Training Program in Vascular Surgery (T32)  
National Institutes of Health - Heart, Lung and Blood Institute  
Project period: 2004 - 2009  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.
3. William J. von Liebig Research Training in Vascular Surgery  
William J. von Liebig Foundation  
Project period: 2003 - 2004  
Principal Investigator: Frank W. LoGerfo, M.D.  
Co-Principal Investigator: William C. Quist, M.D., Ph.D.

4. Development of an Infection-Resistant Bioactive Surface  
National Institutes of Health - Small Business Technology Transfer  
Research Grant (Phase I)  
Project period: 2003 - 2004  
Principal Investigator: Frank W. LoGerfo, M.D.

## V. Divisional Accomplishments

### Research Accomplishments – Basic Research

1. *Mechanisms of Prosthetic Arterial Graft Failure*  
Anastomotic intimal hyperplasia (AIH) remains as the most common cause of delayed prosthetic arterial graft failure, a consequence of focal, unregulated gene expression. As graft healing occurs, genes are either up- or downregulated compared to a quiescent arterial wall. Our hypothesis is that this altered gene expression results in cellular proliferation, migration and extracellular matrix production by smooth muscle cells, leading to AIH. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting *in vivo*. Altered gene expression between normal and grafted artery is determined via several methodologies: 1) Microarray analysis to generate lists of up- and down-regulated genes, 2) qPCR to validate mRNA expression levels for the genes of interest, and 3) immunohistochemistry to qualitatively localize protein expression for the genes of interest. Over the next year, Laser-Capture Microdissection (LCM), a new technology developed by the National Institutes of Health and available at Beth Israel Deaconess Medical Center that permits selection of cells within a chosen area of tissue, will be employed to further localize alterations in gene expression.

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 such as RNA interference (RNAi), with the derived mechanisms having pertinence to the larger field of vascular biology. We are presently using small interfering RNA (siRNA) to decrease the expression of genes implicated in the pathogenesis of AIH. This technique, RNA interference (RNAi), has potential therapeutic applications with pertinence to the larger field of vascular biology.

2. *Infection-Resistant Polyurethane Biomaterials*  
Infection is a major complication associated with the use of indwelling catheters. Catheter-related infections are caused by bacteria that originate either from the skin of the patient that migrate along the external surface of the catheter or from a contaminated hub that migrate along the internal surface of the catheter. Major risk factors include duration of implant, degree of manipulation, location of implant, and the use of occlusive dressings. 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. In phase II, the Cipro was dyed onto cPU coated Chronoflex catheter segments (ChronoCide). *In vitro* evaluation of the ChronoCide catheters showed slow, sustained Cipro release as well as antimicrobial activity under washing conditions for 15 days (length of study). The ChronoCide catheter segments were then assessed *in vivo*. Segments (0.5cm) of control, a silver sulfadiazine/chlorhexidine catheter (SSC) and ChronoCide catheters were cut and implanted into subcutaneous pockets on the dorsum of rats (n=18). After sonication, both control and SSC catheters had gram-positive bacterial growth on backplating whereas ChronoCide catheter segments had no bacterial growth (7, 14 or 28 days). In the zone of inhibition studies, control segments had no antimicrobial properties after explant and the SSC had minimal to no activity. In contrast, ChronoCide catheter segments maintained significant antimicrobial activity at all time periods. 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). We are in process of disseminating the results of these promising studies to industry with our collaborators at CardioTech International and the University of Rhode Island.

3. *Development of a Titanium Surface with Mitogenic Properties*  
Titanium (Ti), which has advantageous bulk and surface properties, does not encourage osseointegration when utilized in devices such as hip joints, pins and dental implants. The potent osteoblast mitogen bone morphogenic protein-2 (BMP-2, obtained from Wyeth Laboratories) was covalently bound to Ti surfaces (Ti-Ep-PEI-S-SMCC-BMP-2) using proprietary technology and maintained *in vitro* biologic activity determined via tissue culture studies. A phase I SBIR will be submitted in December 2003 to further continue this research. The next objective for this technology is to assess surface mitogenic properties of Ti-Ep-PEI-S-SMCC-BMP-2 segments in a rat model in a dorsal subcutaneous implant (as suggested by Wyeth Laboratories). This technology could have an annual market in excess of \$100 million and could be applied to other Ti implants such as left ventricular assist devices and mechanical heart valves to which biologic agents such as antithrombin agents/growth factors could be covalently bound.
4. *Development of a Biologically-Active Prosthetic Graft*  
Medium (6-8mm) and small (<5mm) internal diameter prosthetic grafts continue to have clinically unacceptable high failure rates. In phase I, an ionic polyurethane-sealed Dacron vascular graft (PEU-D) with reduced water permeation, excellent physical properties and covalently bound antithrombin (recombinant hirudin or rHir) and mitogenic (vascular endothelial growth factor or VEGF) agents was developed. These surface bound agents were determined to be biologically active. Our objective in this proposal is to assess blood permeation and graft patency/healing of the PEU-D graft using a canine arterial grafting model. Our hypothesis is that

implantation of this novel graft will prevent blood permeation thereby obviating the need for pre-clotting and improve graft patency and healing by emulating some of the natural properties of native vessels. The specific aims are to: 1) develop a batch synthesis process for ionic polyurethane, 2) scale-up the process for sealing Dacron grafts, 3) evaluate PEU-D physical and chemical properties, 4) covalently link rHir and VEGF to PEU-D surface, 5) assess *in vivo* acute (3 and 7 day) and chronic (14 and 30 day) implantation periods and 6) examine macroscopically/microscopically explanted grafts. Development of a polyurethane sealant with protein binding properties would have a significant role for medical devices such as vascular grafts, catheters and artificial organs.

5. *Infection-Resistant Prosthetic Heart Valve Sewing Cuffs*

Cardiac valve replacement using prosthetic valves is indicated when progression of degenerative disease, annular dilatation or bacterial infection of the native valve results in valvular dysfunction, thereby impacting cardiac output. An estimated 50,000 valves are implanted annually in the United States, with this number increasing due to an aging population and, to a lesser extent, a more aggressive approach to mitral valve insufficiency. Bacterial infection is a major complication associated with implantation of these prosthetic valves (prosthetic valve endocarditis or PVE). Our phase I studies demonstrated that quinolone antibiotics can "dye" Dacron, that this uptake can be optimized and the material possessed controlled sustained antibiotic release. Additionally, Cipro was dyed onto a tubular Dacron construct and maintained antimicrobial activity under flow conditions. In this phase II proposal, Cipro will be dyed into clinically-available Dacron sewing cuffs via thermofixation using the parameters established in phase I. Antimicrobial activity Cipro-dyed Dacron sewing cuff segments will be determined over time via a zone of inhibition assay. Physical characteristics such as tensile strength and ultimate elongation of the untreated (control) and Cipro-dyed Dacron sewing cuffs will be examined to confirm no changes in Dacron properties due to dyeing. Unmodified (clinical standard) and Cipro-dyed sewing cuffs will then be implanted in a porcine heart valve infection model to determine infection-resistance. Explanted control and Cipro-dyed sewing cuffs will then be assessed via histological/microbiological techniques. Lastly, the physical properties of the Cipro-dyed sewing cuffs post-explantation will be determined. Successful development of a Dacron material with long-term infection resistance through Phase III would have application in a wide range of implanted medical devices such sewing cuffs, vascular grafts, left ventricular assist devices, wound dressings and suture. The cost of this biomaterial to the patient ("off-the-shelf" cost) will be far less than the projected \$50,000/patient cost for re-operation of an infected valve. This value does not take into account the significant morbidity and mortality rates associated with re-operation. Even conservative estimates indicate that the market for such infection-resistant valves is greater than \$25 million.

6. *Nanofiber Technology in Small-Diameter Vascular Grafts*  
There is no small-diameter vascular prosthesis that is capable of emulating the biologic and physical properties of the normal arterial wall. The goal of this proposal is to develop a small-diameter prosthetic vascular graft using nanofiber technology. Our hypothesis is creating a nanofibrous vascular graft by electrospinning an ionic polyurethane will result in a graft that possesses properties similar to that of native artery. The potent antithrombin agent recombinant hirudin (rHir) will be covalently bound to functional groups within the polymer, resulting in an antithrombotic surface. The elastic properties of the ionic polymer will provide circumferential compliance, with longitudinal stretch and kink-resistance prevented by a thin braided Dacron mesh within the graft wall. The specific objectives are to: 1) optimize electrospinning methodology, 2) develop a Dacron inner-wall reinforcement, 3) electrospin PEU grafts containing reinforcement, 4) characterize physical and chemical properties, 5) covalently link rHir to PEU grafts, 6) characterize surface antithrombin properties, 7) evaluate blood interaction with grafts and 8) assess surface rHir stability under simulated arterial flow conditions. Phase II of this project, which will be submitted in December 2003, will evaluate these PEU grafts in a canine carotid artery model. Development of a bioactive small-diameter vascular graft would have a significant impact on small vessel repair and replacement.

#### Research Accomplishments – Clinical research

1. There have been a number of exciting divisional accomplishments this year. We have presented a number of papers at diverse vascular meetings and expect all to come to publication in peer-reviewed journals. A very exciting side effect of the clinical research has been the ability to involve the fellows and residents. Seven different residents, fellows and students have either published or presented a paper or chapter this year.
2. Finally, we are the largest center in North America in a multicenter trial looking at decreasing vein graft failure after bypass. We are also about to join a large multicenter trial comparing carotid stents to angioplasty.

#### Patent Disclosures

1. Application of Antibiotics to Polyurethane Biomaterials Using Textile Dyeing Technology (09/834,978).
2. Development of a Dacron Vascular Graft with an Ionic Polyurethane Sealant with Protein Binding Capabilities (60/186,154).
3. Method for Making Infection-Resistant Fabricated Textile Articles for Biomedical Applications (09,876,604).
4. Methods for Making Infection-Resistant Fabricated Textile Articles and Devices Suitable for Non-Implantable Biomedical, Environmental, Safety and Other Protective Applications (Full Patent Submitted).

5. Bioactive Surface for Titanium Implants (Full Patent Submitted).
6. Development of a Bifunctionalized Dacron Surface (Provisional Patent).

Regional and National Presentations (07/01/02 – 06/30/03)

1. Aggarwal P, Phaneuf MD, Bide MJ, Sousa KA, Alhilali LM, **LoGerfo FW, Quist WC**. Development of an infection-resistant bifunctionalized Dacron material. *American Chemical Society*, August 2002.
2. Sousa KA, Phaneuf MD, Bide MJ, Aggarwal P, Alhilali LM, **LoGerfo FW, Quist WC**. Development of an infection-resistant anionic Dacron biomaterial using textile dyeing technology. *American Chemical Society*, August 2002.
3. **Sheahan MG, Hamdan AD, Deutsch E**, Belfield AK, **McArthur CS, Campbell DR, LoGerfo FW, Pomposelli FB**. A decade of infrainguinal bypass procedures: Predicting the natural course of lower extremity vascular disease. *New England Society of Vascular Surgery*, October 2002.
4. **Deutsch ER**, Phaneuf MD, **Willis DJ**, Bide MJ, **LoGerfo FW, Quist WC**. *In vitro* and *in vivo* assessment of novel bifunctionalized Dacron surfaces. *New England Society for Vascular Surgery*, October 2002.
5. **Willis DJ, Deutsch ER, Contreras MA, Stone DH, LoGerfo FW, Quist WC**. Temporal gene expression in anastomotic intimal hyperplasia using microarray analysis and hierarchical clustering. *New England Society for Vascular Surgery*, October 2002.
6. **Willis DJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC**. Decreased expression of Smoothelin-B in anastomotic intimal hyperplasia. *Surgical Forum*, October 2002.
7. **Deutsch ER**, Phaneuf MD, **Willis DJ**, Bide MJ, **LoGerfo FW, Quist WC**. *In vitro* and *in vivo* assessment of novel bifunctionalized Dacron surfaces. *Association for Academic Surgery*, November 2002.
8. **Sheahan MG, Aulivola B, Pomposelli FB, LoGerfo FW, Skillman JJ, Campbell DR, Scovell SD, Hamdan AD**. Amputation-free survival after lower extremity revascularization: The adverse impact of even moderate renal dysfunction. *Peripheral Vascular Surgery*, February 2003.
9. **Willis DJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC**. Allograft inflammatory factor-1 is overexpressed after prosthetic arterial bypass grafting. *United States and Canadian Academy of Pathology*, March 2003.
10. **Sheahan MG, Hamdan AD**, Veraldi JR, **McArthur CS, Skillman JJ, Campbell DR, Scovell SD, LoGerfo FW, Pomposelli FB**. The effect of

VRE and MRSA on results of lower extremity revascularization. *Society for Clinical Vascular Surgery*, March 2003.

11. **Kalish JA, Willis DJ, Link JJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Temporal gene expression in vein bypass grafts using microarray analysis. *United States and Canadian Academy of Pathology*, March 2003.
12. **Deutsch ER, Phaneuf MD, Willis DJ, Bide MJ, LoGerfo FW, Quist WC.** Covalent linkage of protein to woven Dacron modified with ethylenediamine. *Society for Biomaterials*, April 2003.
13. **Kalish JA, Willis DJ, Link JJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Application of microarrays and hierarchical clustering to assess early vein graft remodeling. *Federation of American Societies for Experimental Biology (FASEB)*, April 2003.
14. **Deutsch ER, Phaneuf MD, Willis DJ, Bide MJ, LoGerfo FW, Quist WC.** Covalent linkage of protein to woven Dacron modified with ethylenediamine. *Society for Biomaterials*, May 2003.

## VI. Report of Teaching

### Undergraduate and Medical School Courses:

1. William J. von Liebig Research Training in Vascular Surgery (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, Boston Children's Hospital, and Joslin Diabetes Institute) and the Massachusetts Institute of Technology.

#### 2003 Summer Students

Alexander Gelbard  
Caroline Groft  
Eric Kim  
Babak J. Orandi  
Timothy Peterson

Tulane University School of Medicine  
Cornell Medical School  
Vanderbilt Medical School  
Univ. of Michigan Medical School  
Washington Univ. School of Med.

## Graduate School and Graduate Medical Courses

### 1. William J. von Liebig Research Training in Vascular Surgery (Post-Doctoral)

Evan Garfein, M.D., is in his second year of this program. He works with Drs. Michael Conte and Richard Mulligan and focuses on the science of tissue engineering, which is rapidly expanding. One of the fundamental problems that remains is that of vascularizing implanted tissue constructs. Obviously, this is closely related to the angiogenesis that occurs in a variety of pathological and physiological settings. While this is a very complicated process controlled by a number of soluble and insoluble mediators as well as by mechanical forces, better understanding of how the body performs these processes will help answer the question for tissue engineers. An important first step in developing mechanisms for vascularizing tissue engineered constructs is to be able to assess them in vivo. Currently, they are developing a system by which we are able to genetically modify a tissue engineered construct, and assess its viability using an imaging modality based on the interaction of luciferin with the transgene luciferase.

### 2. T-32 Training Program

#### *Harvard-Longwood Research Training Program in Vascular Surgery (T32)*

This training program is designed to provide two years of intense basic research training in vascular surgery for academic clinicians. The training program addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. Trainees will pursue a program of research activity supplemented with course work in research design, ethics, statistics and evaluation of published research in the areas of molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis. Clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis will be the main focus of these research projects. Trainees carry out their research projects under the guidance of a faculty advisor selected from 20 renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology. Upon completion of the program, trainees are capable of independent research and possess the scientific and research background needed to obtain peer-reviewed grants. Selection of trainees is based on candidate's demonstrated ability and career choice of academic practice. Applicants are resident physicians who have completed either 2/3 years of clinical post-doctoral experience (surgical residency) or 5 years of clinical training (i.e. are board eligible). Only those applicants with career goals in academic surgery, with a keen interest in basic research in vascular surgery are compatible. Trainees in the program are not involved in any clinical activities unless research related.

|        |  |   |
|--------|--|---|
|        | <b>Trainee</b><br>Jeffrey A. Kalish, M.D.<br>Thomas S. Monahan, M.D. | <b>General Surgery Training Program</b><br>Boston University<br>Beth Israel Deaconess Medical |
| Center | Gautam Shrikhande, M.D.  | Beth Israel Deaconess Medical   |
| Center | Grace J. Wang, M.D.  | Massachusetts General Hospital  |

Invited presentations (see Section V: Divisional Accomplishments)

## VI. Plans for the Coming Academic Year

1. Establish in our laboratory, the technology for RNA interference. This will create a continuum from the identification of genetic response for arterial injury to a methodology for inhibition or control of the response.
2. Complete work on the in vivo assessment of biologically active prosthetic arterial grafts.
3. Initiate fabrication and implant studies of composite electronspun fibrous textile.
4. Initiate studies of matrix bonded biomaterials.

## VIII. Bibliography (07/01/02 – 06/30/03)

### Original Articles

1. Caballero AR, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connon C, **LoGerfo FW**, Horton ES, **Veves A**. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism* 2003;52(2):173-180.
2. **Kansal N, LoGerfo FW**, Belfield AK, **Pomposelli FB, Hamdan AD**, Angle N, **Campbell DR**, Sridhar A, Freischlag JA, Quinones-Baldrich W. A comparison of antegrade and retrograde mesenteric artery bypass. *Ann Vasc Surg* 2002;16(5):591-597.
3. **McArthur CS, Sheahan M, Pomposelli FB**, Dayko A, Belfield AK, **Campbell DR, Skillman JJ, LoGerfo FW, Hamdan AD**. Infringuinal revascularization after renal transplantation. *J Vasc Surg* 2003;37(6):1181-1185.
4. Pedrosa I, Aschkenasi C, **Hamdan AD**, and Rofsky NM. Effort –induced thrombosis: diagnosis with three dimensional MR venography. *Emergency Radiology*, 2002;9:326-328.
5. **Pomposelli FB, Kansal N, Hamdan AD**, Belfield A, **Sheahan M, Campbell DR, Skillman JJ, LoGerfo FW**. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. *J Vasc Surg* 2003;37(2):307-315.

6. **Ramdev P, Rayan SS, Sheahan M, Hamdan AD, LoGerfo FW, Akbari CM, Campbell DR, Pomposelli FB Jr.** A decade experience with infrainguinal revascularization in a dialysis-dependent patient population. *J Vasc Surg* 2002;36(5):969-974.
7. Szabo C, Zanchi A, Komjati K, Pacher P, Krolewski AS, **Quist WC, LoGerfo FW**, Horton ES, **Veves A.** Poly (ADP-Ribose) polymerase is activated in subjects at risk of developing type 2 diabetes and is associated with impaired vascular reactivity. *Circulation* 2002; 106(21):2680-2686.

#### Proceedings of Meetings

1. Aggarwal P, Phaneuf MD, Bide MJ, Sousa KA, Alhilali LM, **LoGerfo FW, Quist WC.** Development of an infection-resistant bifunctionalized Dacron material. Proceedings of the American Chemical Society; August 18-22, 2002, Boston, MA, United States of America.
2. **Deutsch ER**, Phaneuf MD, **Willis DJ**, Bide MJ, **LoGerfo FW, Quist WC.** Covalent linkage of protein to woven Dacron modified with ethylenediamine. Proceedings, Society for Biomaterials, May 1-3, 2003, Reno, NV, United States of America.
3. **Kalish JA, Willis DJ**, Link JJ, **Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Application of microarrays and hierarchical clustering to assess early vein graft remodeling. *Proceedings, Federation of American Societies for Experimental Biology*, April 11-15, 2003, San Diego, CA, United States of America. \
4. **Kalish JA, Willis DJ**, Link JJ, **Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Temporal gene expression in vein bypass grafts using microarray analysis. Proceedings, United States and Canadian Academy of Pathology, March 25-26, 2003, Washington, D.C., United States of America.
5. Sousa KA, Phaneuf MD, Bide MJ, Aggarwal P, Alhilali LM, **LoGerfo FW, Quist WC.** Development of an infection-resistant anionic Dacron biomaterial using textile dyeing technology. Proceedings of the American Chemical Society; August 18-22, 2002, Boston, MA, United States of America.
6. **Willis DJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Allograft inflammatory factor-1 is overexpressed after prosthetic arterial bypass grafting. Proceedings, United States and Canadian Academy of Pathology, March 25-26, 2003, Washington, D.C., United States of America.
7. **Willis DJ, Deutsch ER, Contreras MA, LoGerfo FW, Quist WC.** Decreased expression of smoothelin-B in anastomotic intimal hyperplasia. Proceedings from the Surgical Forum, October 6-10, 2002, San Francisco, CA, United States of America.

## Abstracts

1. Alhilali LM, Phaneuf MD, Bide MJ, Dempsey DJ, Sousa KA, Aggarwal P, **LoGerfo FW, Quist WC**. Development of an infection resistant Dacron biomaterial. *ASAIO J*, 2002; 48(2):185A.
2. Phaneuf MD, Bide MJ, Nelson KR, Sousa KA, Szycher M, **LoGerfo FW, Quist WC**. An infection-resistant polyurethane catheter. *ASAIO J*, 2002;48(2):184A.



Dr. Allan Hamdan