Beth Israel Deaconess Medical Center

DEPARTMENT OF SURGERY
ANNUAL RESEARCH REPORT 2004

Per-Olof Hasselgren, MD, PhD
Vice-Chairman for Research

Susan J. Hagen, PhD
Associate Director for Research

WORDS FROM THE CHAIRMAN

Josef E. Fischer, MD

Welcome to the Annual Research Report for the Department of Surgery at the Beth Israel Deaconess Medical Center. This Research Report Summary covers the period from January 1, 2004 through January 31, 2004.

As I have stated previously, a truly academic department of surgery not only has a commitment to clinical excellence and the teaching of residents, medical students, and progression in the skills of the faculty, but also has a commitment to laboratory bench work in molecular biology, physiology, as well as in clinical research. These components are essential if we are to produce an academic product, such as residents that go on to be the leaders in their respective specialties. These components are also crucial for residents who go into the laboratory for two years, something which I personally believe is essential for residents, not only to their mental well-being, but to increase their understanding of their clinical skills and prepare them for an academic career.

Drs. Hasselgren and Hagen continue to do an excellent job in documenting the growth of this academic department. What is contained herein represents the documentation of a sustained academic effort to which we are committed. The initial effort was to build a clinical entity for the benefit of the hospital as well as the Department, given the depletion of the clinical ranks of the Department. However, as you can tell by the increase in external funding, this commitment has not been carried out to the exclusion or detriment of the academic and research component of the Department.

In most divisions, we stated that if the initial recruitment of, for example, the division chief entail more clinical criteria, then the next recruitment had to be based upon research and academic criteria as well as clinical. In general, as we have continued to recruit younger members of the faculty to fill out divisions, we have stressed that they must have a truly significant research component, either bench research or outcome related in clinical research.

This approach has certainly aided in an increase in total funding for this year, which we estimate at $12.5 million. This increase from $11.8 million last year is 6% as opposed to the 22% increase that we experienced last year when we had a large influx of new research-oriented surgical faculty. With the addition of new junior faculty that have a research component and the continued growth of existing research groups, we hope to continue these steady gains in funding each year.

Most departments of surgery are medical school based, so the NIH methodology for calculating departmental rank is limited to medical schools and not hospitals. Although the Beth Israel Deaconess Medical Center is third in the country in NIH-funding for hospitals, no such ranking exists for departments of surgery that are part of hospitals exclusively like the ones in the Harvard hospitals. We will have to be content with an estimate. We continue to strive to be in the top five departments of surgery in terms of NIH funding, but I think more realistically we are likely to be sixth or seventh in the country and will continue to strive to achieve our goal.

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

This introduction would not be complete without my thanking the Administration of the Beth Israel Deaconess Medical Center, Mr. Paul Levy, President and Chief Executive Officer, Dr. Michael Epstein, Executive Vice President and Chief Operating Officer, and Dianne Anderson, M.S., R.N., Senior Vice President for Clinical Operations, for their strong support. I would also like to provide a special thanks to Dr. Jeffrey Flier, the Chief Academic Officer, whose cooperation in our effort to build the department is so valuable and without which I believe we would not have been as successful.

Josef E. Fischer, M.D.
Chairman, Department of Surgery
Surgeon-in-Chief
Mallinckrodt Professor of Surgery
Harvard Medical School

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Per-Olof Hasselgren, M.D., Ph.D.

Division Members

Per-Olof Hasselgren, M.D., Ph.D.	Vice-Chairman for Research
Susan J. Hagen, Ph.D.	Associate Director for Research
T. Andrew French, B.A.	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- award approval of all grants submitted by investigators 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 seminars. 4) Preparing the Department of Surgery Annual Research Report. 5) Organizing laboratory and shared equipment maintenance and telecommunications. 6) Supporting and Mentoring junior faculty in the establishment of research laboratories. 7) Interacting with and providing information to Surgical Residents who plan to spend time in the research laboratory. 8) Obtaining visas for foreign scholars in Research and in preparing application for HMS appointments (Research Fellow-Instructor) to Harvard Medical School. 9) Making recommendations concerning research faculty appointments (Assistant-Full Professor) and reappointments in Surgery. 10) Assisting 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. In 2004, Jessica Figueroa provided administrative support for the Division, under the supervision of Dr. Hagen. The Division of Surgical Research worked closely with Research Administration (Team 5), headed by Jennifer Sabbagh, Research Administrative Director, Shannon Joyce, Ruth Coburn, Jennifer Clark-Croes, and Lani Radford, Sr. Research Administrators and Research Administrators, respectively. Team 5 is responsible for post-award grant management, research-related purchases, compliance, staff payroll, and the management of new hires for research in Surgery.

Research Activity for Fiscal Year 2004

External research funding in the Department of Surgery increased by 6.1% from $11,831,596 in fiscal year 2003 to $12,553,220 in this fiscal year (Figure 1). The increase in research funding this year is due to a general increase in NIH funding per Division, with the most significant increases in Podiatry, Transplantation, and Urology (Figure 2). Approximately 68% of the awarded funding was from federal sources, primarily from the NIH, and 32% from Other Sponsors (Table 1). Documented for the first time this year, there were numerous awards for clinical trials in fiscal year 2004. The dollar amount indicated is for funds received in this fiscal year and not for awarded funds, due to the long recruitment process for patients in clinical trials.

Table 1. ***Summary of Research Awards in the Department of Surgery in Fiscal Year 2004***

Sponsor	Direct Awarded	Indirect Awarded	Total Awarded
NIH	5,675,172	2,815,756	8,490,928
Other Sponsors	2,200,529	731,159	2,931,688
Clinical* Trials	972,088	158,516	1,130,604
TOTAL	8,847,789	3,705,431	12,553,219

*Funds received rather than total funds awarded.

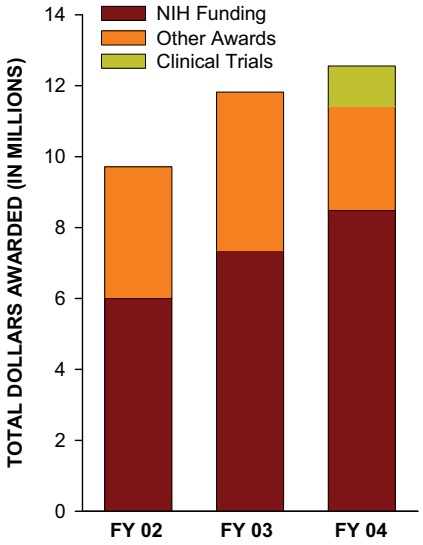

Figure 1. Total research dollars awarded to Surgery in fiscal years 2002-2004.

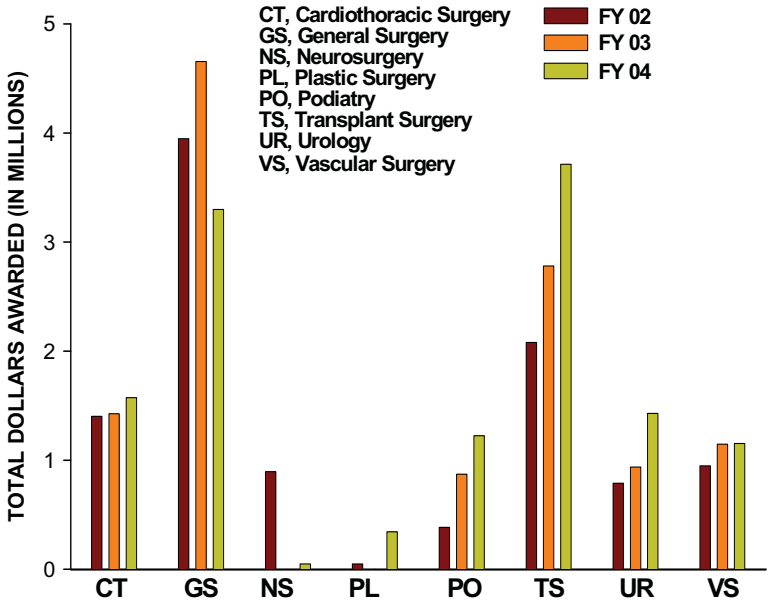

Figure 2. Total research dollars per Division awarded in fiscal years 2002-2004.

Research Facilities and Space

This year, research in the Department of Surgery occupied approximately 31,000 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) 8,350 at HIM, 12,610 in Dana/Research West, 917 in Slosberg-Landy, 1,601 at 21-27 Burlington Avenue, and 4,452 at Research North. Clinical research in Surgery included (in square feet) 605 in Palmer and 2,163 in Feldberg. The greatest numbers of researchers were found on the 7th and 8th 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 1st and 10th floors of the Harvard Institutes of Medicine. Research related to Transplantation/ Immunobiology is located on the 3rd floor of Research North and 10th floor of the Harvard Institutes of Medicine. 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. 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. Again this year, seminars were designed with a programmatic theme, with seminars each from Vascular/Cardiovascular, Transplant, Muscle Wasting and Metabolism, Epithelial Biology, and Urology. A summary of seminars that were presented in 2004 are listed in Table 2.

Table 2. ***Seminars Sponsored by the Division of Surgical Research in 2004***

5-Jan-04	Raghu Kalluri, Ph.D.	Associate Professor of Medicine Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Genetic Control of Angiogenic Balance in Tumors"
2-Feb-04	Daniel Goodenough, Ph.D.	Takeda Professor of Cell Biology Department of Cell Biology Harvard Medical School	"Paracellular Channels in Tight Junctions"
1-Mar-04	Megan Sykes, M.D.	Professor of Surgery Harvard Medical School Massachusetts General Hospital	"Transplantation Tollerance through Mixed Chimerism"
5-Apr-04	Daniel Tenen, M.D.	Professor of Medicine Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Transcription Factors, Differentiation, and Cancer"
4-May-04	Sean P. Colgan, Ph.D.	Associate Professor of Anesthesia Harvard Medical School Brigham and Women's Hospital	"Contribution of Hypoxia to the Development of Colitis"
7-June-04	Richard N. Mitchell, M.D., Ph.D.	Associate Professor of Pathology Harvard Medical School Brigham and Women's Hospital	"How About Allograft Arteriopathy: Learning from Rejection"

13-Sept-04	Martin G. Sanda, M.D.	Visiting Assoc. Prof. of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Refining Prostate Concer Care through Outcomes and Translational Research"
4-Oct-04	David H. Sachs, M.D.	Paul S. Russel/Warner Lambert Professor of Surgery Harvard Medical School Massachusetts General Hospital	"Tolerance in Allogenetic Xenogenic Trans-plantation"
1-Nov-04	George Blackburn, M.D., Ph.D.	S. Daniel Abraham Associate Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Outcome of the Women's Intervention Nutrition Study"
6-Dec-04	Leo E. Otterbein, Ph.D.	Visiting Associate Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Carbon Monoxide: Toxic Molecule or Novel Therapeutic for Inflammatory-Proliferative Disorders?"

In addition to our regular seminar series, Surgical Research started a new series that highlights the research effort of Junior Faculty within the Department. Below is a listing of the Junior Faculty Seminars that were held in 2004, starting 9/04.

Table 3. ***Junior Faculty Seminars Sponsored by the Division of Surgical Research in 2004***

20-Sept-04	Susan J. Hagen, Ph.D.	Associate Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Rules, Rules, Rules: Procedural Guidelines to Help you Navigate the BIDMC"
18-Oct-04	Nicholas E. Tawa, M.D., Ph.D.	Assistant Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Metabolic Adaptions to Dietary Protein Deficiency"
29-Nov-04	Sandra M. Gaston, Ph.D.	Assistant Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr	"Real Patients, Real Tumors: Molecular Profiles of Prostate Cancers in Radical Prostatectomy Specimens"
20-Dec-04	Cesario Bianchi, M.D., Ph.D.	Assistant Professor of Surgery Harvard Medical School Beth Israel Deaconess Med. Ctr.	"Signal Transduction in Cardiopulmonary Bypass"

Residents' Research Competition

In 2004, we started what we hope will become a tradition – an annual Residents' Research Competition. All surgical residents who are or have recently been in a research laboratory or who are involved in a clinical research project were invited to submit a research abstract. Among the contributions, four finalists are selected to present their work at a Surgical Grand Rounds in early June. The finalists and the winner were selected by a committee consisting of faculty involved in research.

The four finalists in 2004 were:

Tenveer Khan: "Aprotinin Reduces Myocardial Reperfusion Injury after Regional Ischemia and Cardioplegic Arrest". Research Sponsor: Dr. Frank Sellke, Cardiothoracic Surgery.

Christopher Longo: "A20 Confers a Proliferative Advantage to Hepatocytes and Promotes Liver Regeneration". Research Sponsor: Dr. Christiane Ferran, Vascular and Endovascular Surgery.

Shishir Maithel: "Mechanisms of Weight Loss after Roux-en-Y Gastric Bypass". Research Sponsor: Dr. Dan Jones, General Surgery (Minimally Invasive Surgery).

Thomas Monahan: "Preoperative Cardiac Evaluation does not Improve or Predict Perioperative or Late Survival in Asymptomatic Diabetic Patients Undergoing Elective Lower Extremity Arterial Reconstruction". Research Sponsor: Dr. Frank LoGerfo, Vascular and Endovascular Surgery.

The winner of the 2004 Residents' Research Competition was **Tenveer Khan.**

Faculty Accomplishments

During fiscal year 2004, research in the Department of Surgery was conducted by 55 faculty, 27 postdoctoral research fellows, 7 surgical residents, 34 research associates and assistants, 2 visiting scientists, and 23 undergraduate, graduate, and medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provided important administrative support for research-related efforts. In all, these figures represent a significant increase in overall research staff when compared to last year, mostly due to new recruitments in Urology and Transplantation.

Many new grant applications were funded in this fiscal year. New NIH grants, in the R01, R03, and R21 categories were awarded to Drs. Blackburn, Zhou, Hasselgren, and Veves. Dr. Karp received a K08 grant from the NIH and a Faculty Development Award from the American College of Surgeons. Dr. Evenson was awarded a postdoctoral research fellowship from the NIH and Dr. Sellke was awarded a T32 training grant from the NIH for residents interested in research in cardiovascular surgery. New research grants from other sources were awarded to Drs. Blackburn, Zhou, Jones, Parangi, Malek, and Olumi. Drs. Sellke and Slavin both obtained large awards from private donors to support research by residents and fellows.

Faculty in Surgery continued to be active at the national and international levels. Dr. Archer continued service this year as Councillor on the Executive Committee of the Association for Academic Surgery and joined the nominating committee of the Association for Academic Surgery. Dr. Levitsky was President-elect for the Society of Thoracic Surgeons. Several faculty in Surgery were appointed to NIH study sections including Drs. Blackburn, Zhou, Hagen, Hasselgren, Gaston, Kiessling, Ferran, and Otterbein. Dr. Veves also reviewed grant applications for the Juvenile Diabetes Foundation and for the American Diabetes Association. In the International arena, Surgery faculty were invited speakers around the world.

Many honors were also given to faculty in Surgery this year. Dr. Levitsky received the 2004 Surgery Mentoring Award from the American Heart Association. Dr. Slavin received the Jubilee Metal from the Swedish Medical Society and Dr. Veves was the Roger Pecoraro Lecturer for the American Diabetes Association. The Transplantation Division was featured this year at the BIDMC Research Day and Drs. Bach and Maki gave Plenary presentations.

Researchers in Surgery also continued a strong commitment to teaching. This includes acting as mentors in the NIH in-service teacher program, MIT Bioengineering Undergraduate Research Program, Biomedical Science Careers Program, Project Success, Undergraduate Research Opportunities Program, and Research Scholars Institute Summer Program. The Vascular and Endovascular Surgery Division continues to be actively involved in the William J von Leibig research training program for both medical and postdoctoral students. At Harvard Medical School, many investigators in Surgery teach in the Body, Cell Biology, Pharmacology, and/or GI Pathophysiology courses and nearly all of the Surgeons participate in the surgical clerkships. Dr. Jones is Course Director for the MIS course series and laboratory.

Bibliography (1/1/04-12/31/04)

A total of 69 original articles were published and 30 articles were accepted for publication by faculty members in the Department of Surgery in 2004. This represents a 15 % increase when compared to the previous year. The number of Reviews, Chapters, and Editorials more than doubled, from 35 in 2003 to 77 in 2004. Contributions to Books, Monographs, and Textbooks, as well as Clinical Communications, Educational and Non-Print Materials, and Abstracts also increased from last year.

Below is a listing, in alphabetical order, of articles published by researchers in the Department of Surgery in 2004. **Bold** represents research Faculty in Surgery at BIDMC.

Original Articles

1. Aldhahi W, **Mun E**, Goldfine AB. Portal and peripheral cortisol levels in obese humans. *Diabetologia* 2004; 47(5):833-6.

2. Akamatsu Y, Haga M, Tyagi S, Yamashita K, Graca-Souza AV, Ollinger R, Czismadia E, May GA, Ifedigbo E, **Otterbein LE**, **Bach FH**, Soares MP. Heme

oxygenase-1-derived carbon monoxide protects hearts from transplant associated ischemia reperfusion injury. *FASEB J* 2004;18:771-2.

3. Aulivola B, **Hamdan AD**, Hile CN, Sheahan MG, **Skillman JJ**, **Campbell DR**, **Scovell SD**, **LoGerfo FW, Pomposelli FB**. Major lower extremity amputation: Outcome of a modern series. *Arch Surg* 2004;139(4):395-9.

4. Aulivola B, **Hamdan AD**, Hile CN, Sheahan MG, **Skillman JJ**, **Campbell DR**, **Scovell SD**, **LoGerfo FW**, **Pomposelli FB**. Popliteal artery aneurysms: a comparison of outcomes in elective versus emergent repair. *J Vasc Surg* 2004;39(6):1171-7.

5. Brown RS, Rush SH, Rosen HR, Langnas AN, Klintmalm GB, **Hanto DW**, Punch JD. SRTR report on the state of transplantation. Liver and intestine transplantation. *Am J Transplant* 2004;4:81-92.

6. Cai D, Frantz JD, **Tawa NE**, Melendez PA, Oh BC, Lidov HGW, **Hasselgren PO**, Frontera WR, Lee J, Glass DJ, Shoelson SE. Ikkbeta/NF-kB activation causes severe muscle wasting in mice. *Cell* 2004;119:285-98.

7. Chandler NM, Canete JJ, **Callery MP**. Caspase-3 drives apoptosis in pancreatic cancer cells after treatment with gemcitabine. *J Gastrointest Surg* 2004;8(8):1072-8.

8. Chandler NM, Canete JJ, **Callery MP**. Increased expression of NF-kappa B subunits in human pancreatic cancer cells. *J Surg Res* 2004;118(1):9-14.

9. Choi H, Bide MJ, Phaneuf MD, **Quist WC**, **LoGerfo FW**. Antibiotic treatment of silk to produce novel infection-resistant biomaterial. *Textile Res J* 2004;74(4):333.

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11. Dash A, Dunn RL, Resh J, Wei JT, Montie JE, **Sanda MG**. Patient, surgeon, and treatment characteristics associated with homologous blood transfusion requirement during radical retropubic prostatectomy: multivariate nomogram to assist patient counseling. *Urol* 2004; 64(1):117-22.

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15. Fondevila C, Shen XD, Tsuchiyashi S, Yamashita K, Csizmadia E, Lassman C, Busuttil RW, Kupiec-Weglinski JW, **Bach FH**. Biliverdin therapy protects rat livers from ischemia and reperfusion injury. *Hepatology* 2004; 40(6):1333-41.

16. George DJ, Regan MM, Oh WK, Tay MH, Manola J, DeCalo N, Duggan S, **DeWolf W,** Kantoff P, Bubley GJ. Radical prostatectomy lowers plasma vascular endothelial growth factor (VEGF) levels in patients with prostate cancer. *Urology* 2004;63:327-32.

17. Gremmels JM, Kruskal JB, **Parangi S,** Kane RA. Hemorrhagic cholecystitis simulating gallbladder carcinoma *J Ultrasound Med* 2004;23(7):993-5.

18. **Hagen SJ**, Morrison SW, Law CS, Yang DX. Restitution of the bullfrog gastric mucosa is dependent on a DIDS-inhibable pathway not related to HCO_3^- ion transport. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: G596-605.

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5. **Paranji S.** A DVD of "Thyroid surgery and recurrent laryngeal nerve monitoring" for teaching of Harvard Medical Students, February 2005, Skills Lab, Beth Israel Deaconess Medical Center

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5. **Jones DB** (ed): SAGES Top 14 Videos, 2nd edition, Cine-Med; 2004.

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2. Alexopoulos S, Sanchez-Fueyo A, **Hanto D**, Zheng X, Strom TB. Regulatory T-cell proliferation and gene expression in response to alloantigen stimulation. *Am J Transplant* 2004;4 Suppl 8:263.

3. Evenson A, Fareed M, **Hasselgren PO**. Sepsis-induced muscle proteolysis is blocked by glycogen synthase kinase (GSK)-3 beta inhibitors. *J Am Coll Surg* 2004;199:S37-8.

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5. Evenson AR, Mitchell JC, Menconi MJ, **Hasselgren PO**. Glycogen synthase kinase 3-beta (GSK3-beta) inhibitors decrease protein degradation in L6 myotubes. *J Surg Res* 2004;121:314-5.

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9. **Gaston S**, Vu D, Brice M, Goldner D, Rogg J, Lee J, Genega E, **DeWolf WC**. Tissue print profiling of prostate needle biopsy: Obtaining comprehensive tissue sampling for molecular marker analysis without compromising microscopic evaluation of the biopsy cores. *J Urol* 2004;171:A309.

10. **Gaston SM,** Rogg JG, Lee JM, Vu D, Goldner DL, Brice MJ, Genega EM, Lenkinski RL**, DeWolf WC**. Gene Expression profiles that underlie biological events visualized by magnetic resonance spectra (MRS) of human prostate cancer: choline kinase. *Proc Amer Assoc for Cancer Res* 2004; 45: A213.

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14. Kauffman HM, Cherikh WS, Cheng Y, **Hanto DW**, Kahan BD. Maintenance of immunosuppression with TOR inhibitors is associated with a reduced incidence of *de novo* malignancies *Am J Transplant* 2004;4 suppl 8:297.

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16. **McCully JD**, Cowan DB, Federman M, **Levitsky S**. Induction of anoïkis occurs independent of caspase induction following ischemia/reperfusion and is associated with myocardial dysfunction. *Circulation* 2004; 110 (17): A54.

17. Mai Z, **Blackburn GL, Zhou JR**. Synergistic inhibitory effect of genistein in combination with tamoxifen on HER-2-overexpressing BT-474 human breast cancer cell growth. *FASEB J* 2004; 18:A1111.

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21. San Francisco I, **DeWolf WC**, Peehl M, **Olumi AF.** Expression of transforming growth factor – B1 and growth in soft agar differentiate prostate carcinoma-associated fibroblasts from normal prostate fibroblasts. *Proc Am Assoc Cancer Res* 2004;45:A382.

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23. Stylopoulos N, *Maithel SH*, **Jones DB**, Rattner DW, Kaplan L. Increased energy expenditure accounts for a substantial portion of the weight loss after Roux-en-Y gastric bypass in rats. *Gastroenterology*. 2004;126(4):A90.

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28. **Zhou JR**, Mai Z, Lin M, **Blackburn GL**. Soy isoflavone genistein potentiates the efficacy of tamoxifen treatment to estrogen-dependent human breast tumor in a mouse model. *FASEB J* 2004; 18:A1110.

29. **Zhou JR**, Mai Z, **Blackburn GL**. Soy isoflavone genistein synergistically enhances the preventive effect of tamoxifen on the growth of estrogen-dependent MCF-7 human breast cancer cells in vitro and in vivo. *Cancer Epidemiol Biomarkers Prev* 2004; 13(11): A119.

30. **Zhou JR**,Mai Z, **Blackburn GL**. Genistein and tamoxifen combination synergistically inhibits the growth of HER2-overexpressing BT-474 human breast cancer cells via apoptosis induction and down-regulation of survivin expression. *Cancer Epidemiol Biomarkers Prev* 2004; 13(11): A122.

LIST OF FACULTY AND STAFF BY DIVISION

Personnel	Title
DIVISION OF CARDIOTHORACIC SURGERY	
Sellke, Frank	**Chief, Division of Cardiovascular Surgery** **Johnson & Johnson Professor of Surgery**
Bianchi, Cesario	**Assistant Professor of Surgery**
Feng, Jun	Instructor in Surgery
Boodhwani, Munir	Research Fellow
Shigetoshi, Mieno	Research Fellow
Nakai, Yasunari	Research Fellow
Ramlawi, Basel	Research Fellow
Malik, Tamer	Research Fellow
Xu, Shu Hua	Research Associate
Li, Jianyi M.B.	Research Assistant
Michael, Keith	2nd year Medical Student
Levitsky, Sidney	**Cheever Professor of Surgery**
McCully, James	**Associate Professor of Surgery**
Illigans, Ben	Research Fellow Surgical Resident
Ellis, Henry	**Clinical Professor of Surgery, Emeritius**
Xu, Xiangjun	Research Fellow
DIVISION OF GENERAL SURGERY	
Callery, Mark	**Chief, Division of General Surgery** **Associate Professsor of Surgery**
Bai, Jirong	Instructor in Surgery
Demirjian, Aram	Research Fellow Surgical Resident
Archer, Sonia	**Assistant Professor of Surgery**
Song, Qinhui	Instructor in Surgery
Blackburn, George	**S. Daniel Abraham Chair in Nutrition Medicine** **Associate Professor of Surgery** **Director of Surgical Nutrition**
Zhou, Jin-Rong	**Assistant Professor of Surgery**
Khaodhiar,Lalita	Instructor in Medicine
Pan, Weijun	Visiting Scientist
Wu, Lei	Visiting Scientist
Mai, Zhiming	Sr. Research Fellow

Wang, Fengfei	Research Fellow
Singh, Aijita	Research Fellow
McNamara, Anne	Research Associate
Sherwood, Michelle	Research Associate
Li, Xin	Research Associate
Wu, Zhanggui	Research Associate
Lin, Min	Research Assistant
Waltman, Belinda	Research Assistant
Buckley,Rita	Medical Writer
Ainsley, Barbara	Administrative Assistant
Sidell, Susan	Administrative Coordinator
Fischer, Josef	**Chairman, Department of Surgery** **Mallinckrodt Professor of Surgery**
Hagen, Susan	**Associate Professor of Surgery** **Associate Director for Research** **Director, Morphlogy Core Facilities**
Tashima, Kimihito	Research Fellow
Muvafak, Asli	Research Fellow
Brown, Daniel	Sr. Research Associate
White, Suzanne	Histotechnologist
Curley, Justine	Research Assistant
Yanaka, Saeko	Student, Tokyo University
Sanders, Jacob	Student, Harvard University
Hasselgren, Per-Olof	**George H. A. Clowes Professor of Surgery** **Vice-Chairman for Research** **Director of Endocrine Surgery**
Menconi, Michael	Assistant Professor of Surgery
Fareed, Moin	Instructor in Surgery
Cahill, Catherine	Instructor in Surgery
Yang, Hongmei	Research Fellow
Wei Wei	Research Fellow
Evenson, Amy	Research Fellow Surgical Resident
Reilly, Natasha	Research Assistant
Gwin, Sally	Administrative Coordinator
Jones, Daniel B.	**Director of Minimally Invasive Surgery** **Visiting Associate Professor of Surgery**
Villegas, Leo	Skills Lab Coordinator
Walsh, Angi	Nurse Educator
Zoll, Deb	Administrative Assistant
Mun, Edward	**Assistant Professor of Surgery**

Parangi, Sareh	**Assistant Professor of Surgery**
Zhang, Xue Feng	Research Fellow
Zhu, Shao-Jun	Research Fellow
Galardi, Eric	Research Assistant
Ladha, Shabber	Pre-Med Student (Summer 2004)
Olumi, Shireen	Undergrad Student (Summer 2004)
Tawa, Nicholas E	**Assistant Professor of Surgery**
Mitchell, Jamie	Research Fellow
	Surgical Resident

DIVISION OF NEUROSURGERY

Wu, Julian	**Chief, Division of Neurosurgery** **Associate Professor of Surgery**
Lee, Diana	Research Assistant
Malek, Adel M.	Assistant Professor of Surgery
Hoit, Daniel	Research Fellow
	Surgical Resident
Edward Kim	Research Assistant

DIVISION OF PLASTIC and RECONSTRUCTIVE SURGERY

Slavin, Sumner	**Chief, Division of Plastic and Reconstructive Surgery** **Associate Professor of Surgery**
Upton, Joseph	Associate Clinical Professor of Surgery
Borud, Loren J	Instructor in Surgery
Contreras, Mauricio A	Instructor in Surgery
Lee, Bernard	Instructor in Surgery
Tobias, Adam	Instructor in Surgery
Brahmer, Geoffrey	Educational Coordinator
Forgione, Jennifer	Administrative Coordinator

DIVISION OF PODIATRY

Giurini, John M.	**Chief, Division of Podiatry** **Associate Clinical Professor of Surgery**
Veves, Aristidis	**Associate Professor of Surgery**
Khaodhiar, Lalita	Instructor in Medicine
Dinh, Thanh T	Instructor in Surgery
Lyons, Thomas	Instructor in Surgery
Lima, Christina	Research Coordinator
Longoria, Lydia	Research Coordinator
Marc, Christina	Research Coordinator

DIVISION OF TRANSPLANTATION

Hanto, Douglas W.	**Chief, Division of Transplantation** **Lewis Thomas Professor of Surgery**
Bach, Fritz H.	**Lewis Thomas Distinguished Professor of Surgery**
Sakihama, Hideyasu	Instructor in Surgery
Wang, Hongjun .	Instructor in Surgery
Wegiel, Barbara	Exchange Student/Research Fellow
Czismadia, Eva	Research Assistant
Lee, Soo	Research Assistant
Carty, Julienne	Administrative Assistant
Monaco, Anthony	**Peter Medawar Professor of Surgery**
Maki, Takashi	**Associate Professor of Surgery**
Minamimura, Keisuke	Research Fellow
Tetsuo, Kodaka	Research Fellow
Gottschalk, Rita	Research Assistant
Otterbein, Leo E	**Visiting Assistant Professor of Surgery**
Chin, Beek Yoke	Instructor in Surgery
Scott, Jeffery	Research Fellow
Gallo, David	Research Associate/HMS Associate
May, Aaron	Research Assistant
Karp, Seth J.	**Visiting Assistant Professor of Surgery**
Nesbitt, Nicole	Research Assistant

DIVISION OF UROLOGY

DeWolf, William	**Chief, Division of Urology** **Professor of Surgery**
Schopperle, W. Michael	Research Fellow
Olumi, Aria	**Assistant Professor of Surgery**
Zhang, Liang	Research Fellow
Zhang, Xiaoping	Research Fellow
Huang, Xu .	Research Fellow
Li, Wenhua	Research Fellow
Gaston, Sandra	**Instructor in Surgery**
Goldner, Dana	Research Assistant
Vu, Dang	Research Student
Rogg, Jonathan	Research Student
Klaips, Courtney	Research Student
Chizana, Tendai	Research Student

Su, Albert	Research Student
Fu, Ting Ting	Research Student
Gutierruz, Efren	Harvard Medical Student
Kiessling, Ann	**Associate Professor of Surgery**
Desmarais, Bryan	Research Assistant
Lyon, Jonathan	Research Assistant
Neville, Nathan	Research Assistant
Eyre, Stephen	Research Assistant
Chiavatago, David	MS Biotechnology Student
Laverde, Joe	MS Biotechnology Student
Purohit, Anil	Harvard Medical Student
Sanda, Martin G	**Visiting Associate Professor of Surgery** **Director, BIDMC Prostate Cancer Center**
Chen, Daohong	Research Fellow
Eljanne, Mariam	Research Associate
Haram, Kyrsten	Research Assistant
Probst, Corey	Clinical Research Assistant
Gatewood, Renee	Administrative Assistant

DIVISION OF VASCULAR and ENDOVASCULAR SURGERY

LoGerfo, Frank	**Chief, Division of Vascular and Endovascular Surgery** **William V. McDermott Professor of Surgery**
Contreras, Mauricio A.	Instructor in Surgery
Phaneuf, Matthew D.	Assistant Laboratory Director
Gross, Barry A.	Information Systems Development
Monahan, Thomas S.	Research Fellow
Popescu-Vladimir, Alexandra	Research Associate
Anderson, Nicholas D.	Graduate Student
Aggarwal, Puja	Undergraduate Student
Jain, Monica	Undergraduate Student
Panossian, Haig	Undergraduate Student
Sousa, Kerry A.	Undergraduate Student
Patel, Vaishali	Administrative Assistant
Ferran, Christiane	**Associate Professor of Surgery**
Soizic, Daniel	Instructor in Surgery
Scali, Salvatore T.	Research Fellow (T-32 Trainee)
Shrikhande,Gautam	Research Fellow (T-32 Trainee)
Kim, Peter Min	Research Fellow
Senani,Sowmya	Student
Patel, Himani	UndergraduateStudent
Arjoon, Roy	Undergraduate Student
Hamdan, Allan	**Assistant Professor of Surgery**

DIVISION OF SURGICAL RESEARCH

Hasselgren, Per-Olof	Vice-Chair for Research
Hagen, Susan	Associate Director of Research
French, T. Andrew	Administrative Coordinator

RESEARCH ADMINISTRATION (TEAM 5)

Sabbagh, Jennifer	**Director, Team 5**
Clark-Croes, Jennifer	Research Administrator
Coburn, Ruth	Sr. Research Administrator
Joyce, Shannon	Sr. Research Administrator
Radford, Lani	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.
Kamal Khabbaz, 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.
Jun Feng, MD. PhD
Robert L. Thurer, M.D.
Malcolm DeCamp, M.D.
Ronald M. Weintraub, M.D.

This year the Division of Cardiothoracic Surgery has been very productive in terms of research. Frank Sellke was awarded a grant to examine the effects of statin drugs on the angiogenic response to protein growth factors. Two new research fellowships were created to fund the laboratory work of residents, through the generosity of a grateful patient. Drs. Levitsky and McCully continued to examine the mechanisms of ischemic preconditioning and myocardial protection. Drs. Sellke and Bianchi investigated changes in vascular function and signal transduction during cardiac surgery and myocardial ischemia, as well as therapeutic angiogenesis through the use of protein growth factors in a hypercholesterolemia setting. Dr. Ellis is looking at changes in the molecular characteristics of the GE junction leading to malignant transformation. Finally, Drs. Ralph Delatorre and John Liddicoat examined minimally invasive techniques for valve repair. The division at BIDMC 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.

I. Narrative Report

A tumor suppressor gene, p27, controls progression of cells from the G1 to S phase of the cell cycle. It is reduced or absent in resected specimens from patients with Barrett's Associated Adenocarcinoma (BAA). This loss of p27 is correlated with tumors of high grade, with increased depth of invasion, greater lymph node involvement and a decreased postoperative survival rate.

These findings influenced us to develop an experimental mouse model of BAA by performing an esophagojejunostomy to promote reflux of alkaline and acid juices into the esophagus, and the administration of a carcinogen (N-methyl N-benzyl nitrosamine). Subsequently, we showed that malignant transformation of the esophageal mucosa was enhanced in p27 knockout (KO) mice, but could be reduced by administration of flavopiridol, a CDK inhibitor, as a chemopreventive agent.

II. List of Current Employees

1. Xiangjun Xu, 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 in the Past Year

1. Having shown that flavopiridol could act as a chemopreventive method to reduce the high cancer rate in p27 KO mice after esophagojejunostomy and carcinogen administration, we began studies designed to evaluate chemotherapeutic approaches to treating BAA after its development. Flavopiridol combined with gemcitabine were administered to mice four months after esophagojejunostomy and carcinogen administration. Results of these preliminary studies and plans for the future will be discussed in section VII.

2. Dr. Ellis attended the 100th Anniversary Meeting of the Society of Clinical Surgery at the Johns Hopskins Medical School in Baltimore, Maryland.

V. Report of Teaching

1. Dr. Ellis presented a talk at Surgical Grand Rounds on April 21, 2004 entitled: "p27 and Barnett's Esophageus – A review".

VI. Plans for the Coming Year

1. Having identified a chemopreventive agent (flavopiridol), which reduces the prevalence of esophageal cancer in our experimental mouse mode, our current studies are designed to identify chemotherapeutic agent or agents. In these experiments, p27 KO mice will undergo esophagojejunostomy and carcinogen administration and after 18 to 20 weeks will be treated by one or more CDK inhibitors for one month before terminating the experiment. Initial results employing a combination of flavopiridol and gemcitabine will be done.

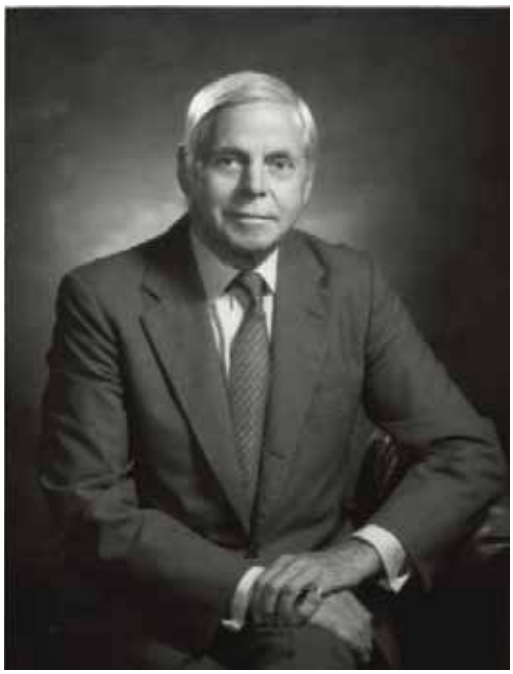
VII. Bibliography

Original Articles (in press)

1. Lechpammer M, Xu, X, **Ellis FH Jr.,** et al. Flavopiridol reduces malignant transformation of the esophageal mucosa in p27 knockout mice. *Oncogene* 2004; in press.

Reviews, Chapters and Editorials

1. **Ellis FH Jr.,** Loda M. P27 and Barrett's esophagus-a review. *Dis Esophagus* 2004; 17(2): 113-7.

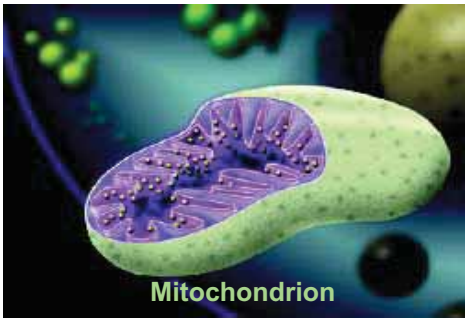


Dr. F. Henry Ellis, Jr.

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

I. Narrative Report

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. Study designs 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 and DNA integrity in association with intrinsic and extrinsic apoptotic and necrotic myocardial cell death following ischemia and reperfusion. In addition studies are underway to identify 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.

II. List of Current Employees

1. Ben Illigans, M.D. — Research Fellow, Surgical Resident

III. List of Current Funding

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

IV. 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.D.

V. Divisional Accomplishments in the Past Year

Individual Accomplishments

Sidney Levitsky, M.D.

1. President-elect- The Society Of Thoracic Surgeons
2. 2004 Surgery Mentoring Award, Council on Cardiovascular Surgery and Anesthesia, American Heart Association
3. Advisory Panel, BUSINESS BRIEFING, US Cardiology, 2004-
4. Visiting Professor- University of Massachusetts Memorial Medical Center, Worcester, MA
5. Visiting Professor-University of British Columbia, St. Paul's Hospital & Vancouver General Hospital, Vancouver, Canada

VI. Plans for the Coming Academic Year

Staff Changes
1. Addition of new surgical fellow and technician.

Research
1. Submission of an RO1 grant application (November 1, 2005)

VII. Bibliography (01/01/2004-12/31/2004)

Original Articles

1. **McCully JD**, Wakiyama H, Hsieh Y-J, Jones M, **Levitsky S**. Differential contribution of necrosis and apoptosis in myocardial ischemia/reperfusion injury. *Am J Physiol Heart Cir Physiol* 2004; 286:H1923-35.

2. **Rousou AJ**, Ericsson M, Federman M, **Levitsky S, McCully JD.** Diazoxide and cardioplegia ameliorate ischemia/reperfusion cell death through the modulation of mitochondrial volume and calcium accumulation and mitochondrial respiratory control index. *Am J Physiol Heart Circ Physiol* 2004; 287: H1967-76.

Reviews, Chapters, and Editorials

1. **Levitsky S , McCully JD**. Myocardial protection. In: Sellke FW, del Nido P, Swanson S, editors. Sabiston & Spencer Surgery of the Chest, 7th Edition. Philadelphia, PA: Elsevier Press, Chapter 66: pp 1081-1102.

Abstracts

1. Illigens B M-W, Hsieh Y-J, Cowan DB, McGowan FX, **Levitsky S, McCully JD**. Activation Of STAT1 increases necrosis and apoptosis following ischemia/reperfusion independent of STAT3 activation. *Circulation* 2004; 110(17):106A

2. **McCully JD**, Cowan DB, Federman M, **Levitsky S**. Induction of anoïkis occurs independent of caspase induction following ischemia/reperfusion and is associated with myocardial dysfunction. *Circulation* 2004; 110(17):54A

3. Williams M., Van Riet S., **Levitsky S**.:Comparison of mechanical valve performance in a poorly anticoagulated community. *J Cardiovasc Surg* 2004; 44 (Suppl 1):75.

Frank W. Sellke, M.D.
Cesario Bianchi, M.D., Ph.D.

I. Narrative Report

The goal of our research efforts is threefold. 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 and human atrial appendage and skeletal muscle. 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. 3) To characterize the gene expression profile of patients subjected to cardiopulmonary bypass and correlate differences in gene expression with clinical outcomes. We use cDNA microarray technology for this goal.

II. List of Current Employees

1.	Jun Feng, M.D., Ph.D.	Instructor in Surgery
2.	Munir Boodhwani, M.D.	Research Fellow
3.	Shigetoshi Mieno, M.D.	Research Fellow
4.	Yasunari Nakai, M.D.	Research Fellow
5.	Basel Ramlawi, M.D.	Research Fellow
6.	Jiannyi Li, M.B.	Research Assistant
7.	Shu Hua Xu, Ph.D.	Research Associate
8.	Keith Michael, B.Sc.	2nd Year Medical Student

III. List of Current Funding

1. "Cardioplegia and Coronary Microvascular Reactivity"
   National Institutes of Health 5R01HL046716-13
   Project Period: 08/31/2001–07/31/2005
   Principal Investigator: Frank W. Sellke M.D.

2. "Surgical Intramyocardial Angiogenesis in a Swine Model
   National Institutes of Health 5R01 HL-069024-03
   Project Period: 07/01/2002-07/31/2007
   Principal Investigator: Frank W. Sellke M.D.

3. “Cardiovascular Surgery Research Training Grant”
   NIH National Research Service Award IT32HL076130-01
   Project Period: 03/31/2004-3/31/2009
   Program Director: Frank W. Sellke M.D.

Members of the Sellke Laboratory
Back L-R: Drs. Feng, Nakai, Ramlawi, Bianchi, Sellke, Mieno, and Boodhwani.
Front *L-R*: Dr. Xu and Ms. Li

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

5. “Anti-inflammatory and Thrombotic Effects of Aprotinin”
   Bayer Corporation
   Principal Investigator: Frank W. Sellke M.D.

6. "KLF15, TGFb1, and Smooth Muscle Biology."
   RO1 HL-072952
   Project Period: 12/02/03-11/30/08
   Principal Investigator: Jain Mukesh, M.D.
   Co-Investigator: Frank W. Sellke M.D.

7. “Research Training in Vascular Surgery” Logerfo, F (PI)
   T32-HL007734-11
   Project Period: 04/01/04-03/30/09
   Principal Investigator: Frank Logerfo M.D.
   Preceptor: Frank W. Sellke, M.D.

8. “Cardiovascular Research Training Grant” Morgan, J (PI)
   NIH 5T32HL076130-02
   Project Period:04/01/04-03/31/09
   Principal Investigator: J. Morgan M.D.
   Preceptor: Frank W. Sellke, M.D.

IV. Divisional Accomplishments in the Past Year

Individual Accomplishments

1. Dr. Sellke was Editor in Chief, Surgery of the Chest. This book was published by Harcourt Health Sciences.

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. 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.

Abstracts presented at Local, National and International Meetings

1. Feng J, **Bianchi C, Sellke FW**. Bradykinin preconditioning preserves microvascular responses after cardioplegia ischemia (ISHR), Presented at the Annual Meeting of the International Society for Heart Research, 2004.

2. Nakai Y, Voisine P, **Bianchi C,** Xu, Feng J, Malik T, Rosinberg A, **Sellke FW.** Effects of L-arginine on the Endogenenous Angiogenic Response in a Model of Hypercholesterolemia. Presented at the Society of University Surgeons, 2004.

3. Voisine P, Yadlapalli N, Khan TA, Laham RJ, Roy-Chaudhury P, Kelly BS, **Bianchi C**, **Sellke FW**, Sukhatme VP. Expression of Platelet-Derived Growth factor (PDGF)-Signaling Pathway in a Porcine Model of Arterio-Venous (AV) Graft Stenosis. Presented at the Society of University Surgeons, 2004.

4. Voisine P, Ruel M, **Bianchi C,** Khan TA, Xu S, Feng J, Li J, Laham RJ, Malik T, **Sellke FW.** Inhibition of the Cardiac Angiogenic Response to Exogenous Vascular Endothelial Growth Factor (VEGF) Therapy in a Porcine Model of

Endothelial Dysfunction. Presented at the Society of University Surgeons, 2004.

VI. Plans for the Coming Academic Year

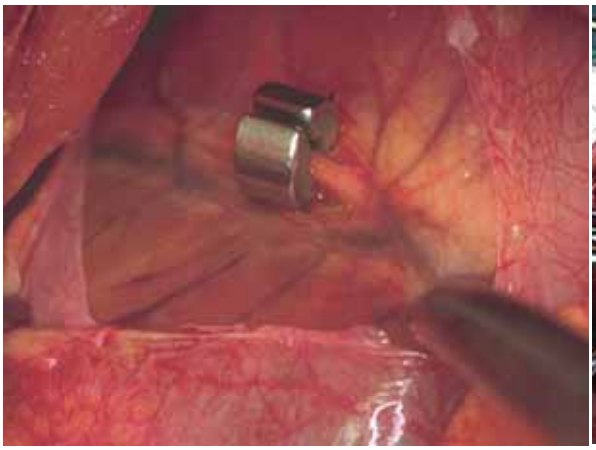
Staff Changes/Recruitments

1. Dr. T. Malik returned to his Clinical Residency Training at Brookdale Hospital in New York.

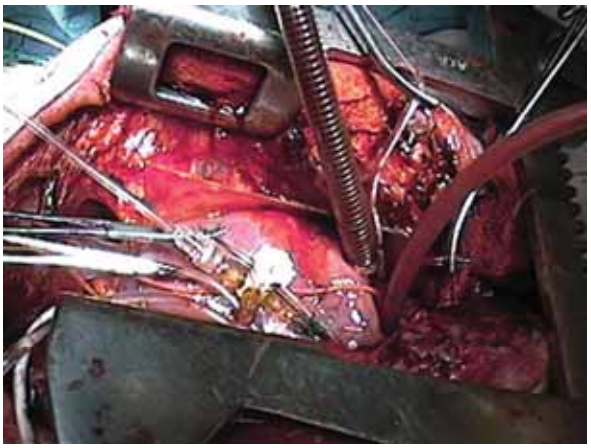
2. Dr. P. Voisine returned to Canada and joined the Cardiothoracic Faculty at Laval University in Quebec.

3. Dr. Neel R. Sodha from the BIDMC Clinical Surgery Residency Program is joining the lab for a 2-year Research Fellowship.

The laboratory uses two large animal operating rooms for survival (left) and non-survival (right) experimental protocols. Approximately 500 surgeries were performed between January 2004 and December 2004.



Ameroid Placement



Cardiopulmonary Bypass

VII. Bibliography (01/01/04-12/31/04)

Original Articles

1. 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* 2004;77(4):1384-9.

2. Khan TA, **Bianchi C**, Voisine P, Feng J, Hart M, Takahashi M, Stahl G, **Sellke FW**. Reduction of myocardial reperfusion injury by aprotonin after regional ischemia and cardioplegic arrest. *J Thorac Cardiovasc Surg* 2004;128(4):602-8.

3. Voisine P, **Bianchi C**, Ruel M, Malik T, Rosinberg A, Feng J, Khan TA, Xu SH, Sandmeyer J, Laham RJ, **Sellke FW**. Inhibition of the cardiac angiogenic response to exogenous vascular endothelial growth factor therapy in a porcine model of endothelial dysfunction. .*Surgery* 2004;136(2):407-15.

4. Voisine P, Ruel M, Khan TA, **Bianchi C**, Xu S, Kohane I, Libermann TA, Out H, Saltier AR, **Sellke FW**. Differences in gene expression profiles of diabetic and non-diabetic patients undergoing cardiopulmonary bypass and cardioplegic arrest. *Circulation* 2004;110 Suppl 1:II280-II286.

5. Wu J, Post M, **Sellke FW**, Simons M, Li J. PR39 inhibits apoptosis in hypoxic endothelial cells - Role of inhibitor apoptosis protein-2.*Circulation* 2004; 109(13):1660-7.

Proceedings of Meetings

1. **Sellke FW**, Ruel M, Laham R, Simons M. Therapeutic coronary angiogeneis using FGF-2 protein. Proceedings of the 8th World Congress on Heart Failure;2004 Philadelphia; ISI; 2004

Reviews, Chapters, and Editorials

1. Harrison DG, Doughan A, **Sellke FW**. Physiology of the coronary circulation. In: Sellke FW, Swanson S, Del Nido P, editors. Surgery of the chest. Philadelphia: Harcourt Health Sciences; 2004. p753-65.

2. Khan TA, **Bianchi C**, Ruel M, Voisine P, **Sellke FW**. Mitogen-activated protein kinase pathways and cardiac surgery. *J Thorac Cardiovasc Surg* 2004; 127(3):806-11.

3. Rosinberg A, Khan TA, **Sellke FW**, Laham RJ. Therapeutic angiogenesis for myocardial ischemia. *Expert Rev Cardiovasc Ther* 2004;2(2):271-83.

4. Ruel M, **Sellke FW**. Coronary artery bypass grafting. In: Sellke FW, Swanson S, Del Nido P, editors. Surgery of the Chest. Philadelphia: Harcourt Health Sciences; 2004. p.1459-90.

5. Ruel M, **Sellke FW**. Therapeutic coronary angiogenesis. In: Sellke FW, Swanson S, Del Nido P, editors. Surgery of the Chest. Philadelphia: Harcourt Health Sciences; 2004. p.1559-73.

6. Ruel M, Song J, **Sellke FW**. Protein-, gene-, and cell-based therapeutic angiogenesis for the treatment of myocardial ischemia. *Mol Cell Biochem* 2004;264(1-2):119-31.

7. **Sellke FW**, Delatorre R. Aortic dissection. In: Textbook of Critical Care Medicine Abraham E, Vincent J-L, Kochanek PM, Fink MP, editors. McGraw-Hill; 2004. p. 2013-19.

Clinical Communication

1. Carrozza JP Jr, **Sellke FW**. A 69-year-old woman with left main coronary artery disease. *JAMA* 2004;292(20):2506-14.

Abstracts

1. Feng J, **Bianchi C,** Sandmeyer JL, **Sellke FW.** Bradykinin preconditioning improves the profile of bad phosphorylation and caspase-3 activation after cardioplegic arrest. *Circulation* 2004; 110(17): A358.

2. Feng J, **Bianchi C,** Sandmeyer JL, **Sellke FW**. Molecular indices of apoptosis after intermittent blood and crystalloid cardioplegia. *Circulation* 2004; 110(17): A753.

3. Khan T, Voisine P, **Bianchi C,** Rosinberg A, Feng J, Malik T, **Sellke FW**. Aprotinin preserves coronary endothelial cellular junctions and reduces myocardial edema after regional ischemia and cardioplegic arrest. *Circulation* 2004; 110(17): A506.

4. Voisine P, Li J, **Bianchi C,** Khan TA, Ruel M, Xu S, Feng J, Rosinberg A, Malik T, Nakai Y, **Sellke FW**. L-Arginine supplementation improves the inhibited angiogenic response to FGF in a porcine model of myocardial ischemia with endothelial dysfunction. *Circulation* 2004;110(17): A398.

GENERAL SURGERY

Mark Callery, M.D., Chief

Division Members

Sonia Y. Archer, M.D.
Jirong Bai, Ph.D, D.V.M.
Christopher Baker, M.D.
George L. Blackburn,Ph.D., M.D.
Chris G. Boyd, M.D.
Michael J. Cahalane, M.D.
Catherine Cahill, Ph.D
Jonathan F. Critchlow, M.D.
Rosemary B. Duda, M.D.
Josef E. Fischer, M.D.
Dana K. Fugelso, M.D.
Susan J. Hagen, Ph.D.
Per-Olof Hasselgren, M.D., Ph.D.
Mary Jane Houlihan, M.D.
Daniel B. Jones, M.D.
Clinton Koufman, M.D.
Thomas McIntyre, M.D.
Michael Menconi, Ph.D.
Fareed Moin, Ph.D.
Donald W. Moorman, M.D.
Peter M. Mowschenson,M.D.
Edward C. Mun, M.D.
Sareh Parangi, M.D.
Vivian Sanchez, M.D.
Benjamin E. Schneider M.D.
Valarie Staradub, M.D.
Nicholas E. Tawa Jr., M.D., Ph.D.
Susan L. Troyan M.D.
Leonardo Villegas, M.D.
Charles Vollmer, M.D.
Jin-Rong Zhou, Ph.D.

Sonia Archer, M.D.

I. Narrative Report

My research focuses on deciphering the 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 U.S.A. Although both environmental and genetic factors play a role in its genesis, environmental factors appear to predominate in importance.

Dr. Sonia Archer

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 and cell cycle progression is controlled by a variety of protein cyclins and their associated kinases. These complexes are inhibited by small proteins, e.g. p21, which cause growth arrest. Our laboratory has shown that butyrate mediates this inhibition of colon cancer cell growth *in vitro* via transcriptional induction of the cell cycle inhibitor, p21. We have further defined the molecular mechanisms which are involved in the 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. Cyclin B1 is a cell cycle promoter which is increased in colon cancer cells and we are now actively involved in studies which address the regulation and importance of this cell cycle 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 the 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. Qinhui Song, M.D., Ph.D. — Instructor in Surgery

III. List of Current Funding

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

2. "Regulation of cyclin B1 gene expression by butyrate in colon cancer cells"
   Harvard Medical School, Minority Medical Faculty Development Bridge Award
   Project Period: 07/01/04-06/30/05
   Principal Investigator: Dr. Sonia Archer

IV. Applications 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

V. Divisional Accomplishments in the Past Year

1. Over the past year, I have made significant advancements in determining the molecular mechanisms underlying the regulation of cyclin B1 gene expression by butyrate in colon cancer cells. This interesting work has continued to attract students and residents to come to the laboratory to participate.

2. At the national level, I continued active service as a Councilor on the Executive Committee of the Association for Academic Surgery. I also served as a member of the Nominating Committee of the Association for Academic Surgery.

VI. 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 2nd year Harvard Medical School Students.

2. 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. This past year, I mentored three students (undergraduate, graduate, and medical school) in the laboratory. I assisted the undergraduate student in designing a research project which was used in his application for the Westinghouse/ Siemens Competition. He has since been accepted at Cornell University.

Graduate School and Graduate Medical School Courses

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

Invited Presentations (Local, National, and International)

1. Invited Speaker: "Pathophysiology and Management of Postoperative Ileus". Winchester Hospital, Winchester, MA.

2. Invited Speaker: Medical Lecturer at Church Activities – Informal talks at various churches in greater Boston area, 3-4 times per year.

VII. Plans for the Coming Year

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 has been submitted for publication. With the acquisition of additional grant funding (NIH R-O1), 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.

Educational Programs

1. I will continue to teach the HMS G.I. Pathophysiology and Surgical Core Clerkship courses, and other courses as needed.

VIII. Bibliography (1/1/04-12/31/04)

Original Articles (in press)

1. **Archer SY**, Johnson J, Kim HJ, Ma Q, Mou H, Daesety V, Meng S, Hodin RA. The histone deacetylase inhibitor, butyrate, downregulates cyclin B1 gene expression via a p21/ WAF-1 dependent mechanism in human colon cancer cells. *Am J Physiol Gastrointest Liver Physiol* 2004; in press.

Reviews, Chapters, and Editorials

1. Shields HM, Atlas S, Chung D, Kumar W, Schaefer M, Sheridan T, Stockwell D. Risk management foundation colorectal cancer screening algorithm. In: **Archer SY** et. al, editors. Risk Management Foundation, 2004.

George L. Blackburn, M.D.,Ph.D.
Jin-Rong Zhou, Ph.D.
Section of Surgical Nutrition
Center for the Study of Nutrition Medicine (CSNM)
Nutrition Metabolism Laboratory (NML)

I. Narrative Report

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 (*Aspergliius awamori*) on the prevention of obesity and inflammation. 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 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 selenium on prostate cancer (Dr. Arthur Sytkowski, 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.

Members of the Zhou Laboratory
Back L-R: Drs. Pan, Zhou, Mai, Wu, and Wu.
Front L-R: Drs. Li, Lin, Singh, Zhao.

Clinical Research

Obesity

This year, the Center for the Study of Nutrition Medicine (CSNM) responded to the need to investigate many new and exciting surgical options for the treatment of obesity and its complications. We have a 30-year extensive experience conducting longitudinal studies particularly in multicenter settings. We are particularly well equipped with the infrastructure to develop clinical investigation and outcomes assessment. CSNM provides sophisticated, scientific nutrition interventions that are utilized to support research, training and patient care in many disease states. The CSNM mission is in line with the medical center's “bench-to-bedside” mission.

In February 2004, Public Health Commissioner Christine Ferguson requested that the newly established Betsy Lehman Center for Patient Safety and Medical Error Reduction convene an Expert Panel to study weight loss surgical programs and procedures as they directly relate to patient safety. After consulting with stakeholders, the Massachusetts Coalition for the Prevention of Medical Errors (its advisory committee), and sites performing weight loss surgeries in the state, the Lehman Center convened a 24-member Expert Panel. This panel included leading authorities in the fields of obesity treatment, patient safety, nutrition, medical practice, managed care, pediatrics, nursing and ethics, as well as a consumer representative. Dr. Alan Harvey of Brigham and Women’s Hospital served as Chair of the panel, and I was asked to serve as Vice-Chair.

Each task group addressed five issues: (1) patient safety recommendations; (2) strategies for medical error reduction; (3) strategies for implementation of system improvements; (4) credentialing needs for systems and practitioners; and (5) research needed for the future. They met on a regular basis, presenting preliminary and then final recommendations to the expert panel, which met monthly from February through July. The full expert panel voted on the final recommendations at the last meeting in July. This process produced evidence-based recommendations aimed at ensuring that the procedures performed in Massachusetts are carried out under circumstances that make them as safe as possible for patients. CSNM undertook the task of coordinating the preparation of the executive report and ten taskforce reports and an editorial for publication in Obesity Research (Feb 2005). Already major insurance providers and sites performing weight loss surgeries in Massachusetts have adopted the recommendations. The U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality has abstracted the report. CSNM in cooperation with the Center for Minimally Invasive Surgery will provide a Harvard Medical School, Division of Continuing Medical Education course entitled.” Patient Safety in Obesity Surgery: Defining Best Practices.”

The CSNM in cooperation with Christina C. Wee, MD, MPH of the Division of General Medicine and Primary Care Medicine will submit on February 1, 2005 an NIH RO1 grant entitled “Understanding How Patients Value Bariatric Surgery.”

This grant recognizes that while bariatric surgery is one of the few effective long-term treatments for obesity, it is neither risk-free nor universally effective, with recent evidence suggesting that long-term surgery-related weight loss and benefits may be less than previously thought. Publicity surrounding surgery-related deaths and complications reinforce the ambivalence some clinicians have about bariatric surgery and raise concerns about how patients make decisions about undergoing surgery. To appreciate whether the benefits outweigh the adverse effects of surgery for individual patients, we must first understand patients' expectations for surgery and how patients value different outcomes associated with surgery. Because of obesity's profound physical and psychosocial consequences, patients may value quality of life (QOL) benefits more than clinical benefits. Unrealistic expectations, however, may color the value patients place on surgery, causing patients to accept higher than reasonable surgical risks and to be less satisfied with even the best surgical outcomes.

Health utility measurement is a valid and universal means of quantifying how patients value different health outcomes, which allows patients to consider all factors important to them. We propose to interview and clinically follow a diverse group of 500 patients undergoing bariatric surgery at two medical centers, and measure their health utility and QOL over time. By assessing patients' health utility before and after surgery and estimating gains in utility, we can determine the actual value patients place on bariatric surgery. In addition, we shall examine patients' motivations for surgery, their value for modest weight loss, and their understanding of surgical risks in order to examine whether these and other baseline factors predict the value patients will derive from surgery. Finally, we shall examine the association between different health outcomes and changes in health utility as an innovative means of determining the relative importance of different QOL and clinical outcomes on the value patients derive from surgery.

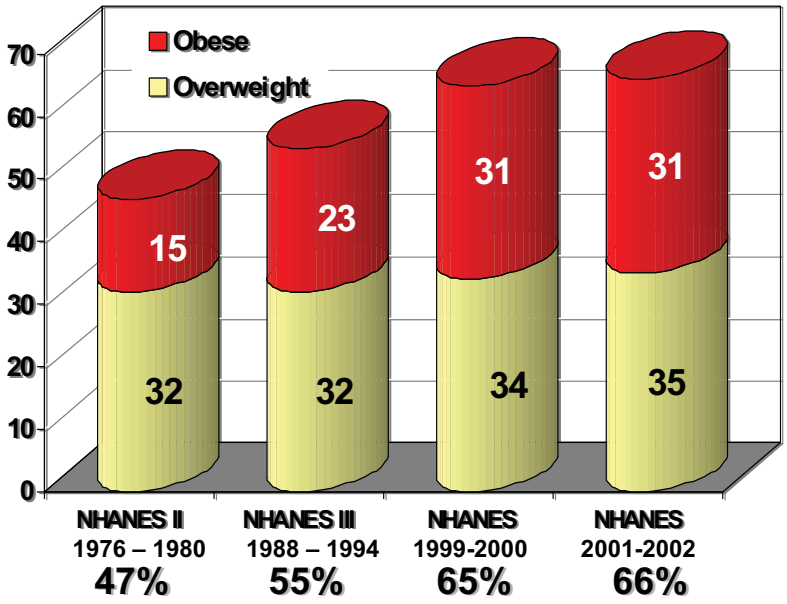
In accomplishing these goals, findings from this study will help patients and clinicians make more informed decisions about bariatric surgery. In addition, our findings may identify subgroups of patients who are most likely to derive value from surgery. Finally, results from this study will facilitate more accurate valuation of surgery in cost-effective analyses that incorporate patients' perspectives, and shed light on whether the benefits experienced by many undergoing surgery outweigh the adverse effects experienced by others.

Malnutrition

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.

The perception that people rarely succeed at weight reduction is, in fact, a misperception. Between 1999-2000 and 2001-2002, there were no significant changes among adults in the prevalence of overweight, obesity, or extreme obesity, or among children aged 6 through 19 years in the prevalence of at risk for overweight. The National Heart, Lung, and Blood Institute (NHLBI) defines

successful long-term weight loss as an intentional reduction of 10% from baseline maintained for one year. Modest weight loss is not only beneficial but also achievable for overweight and obese patients. Of the Americans who have tried to lose weight, almost fifty percent of them have maintained their weight loss successfully for at least one year. The remaining half, those who seem unable to prevent or reverse their obesity, challenge us to mobilize our resources, confront issues at the heart of the obesity epidemic, and develop new solutions. Our work to date has paid off for millions of people. We've stopped the epidemic of obesity. Now it's time to do more by joining health care practitioners with all other stakeholders in this effort to prevent and reverse it.



Prevalence of Overweight and Obesity U.S. Adults, Age 20-74* Years
U.S. Obesity Rates Begin to Level Off
*Age-adjusted by the direct method to the year 2000 U.S. Bureau of the Census.

Hormone Replacement Therapy

In collaboration with OB/GYN, we continue to 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. The pilot and feasibility study as been accepted for publication and the recruitment for the full trial will complete recruitment by next year.

Breast Cancer and Dietary Fat

Despite preclinical and observational studies suggesting benefit, dietary fat influence on breast cancer outcomes has been controversial. We conducted a

randomized trial to test whether an intensive dietary intervention to reduce dietary fat intake was more effective than a control condition in postmenopausal women with primary resected breast cancer receiving conventional cancer management. The primary endpoint was relapse-free survival.

A total of 2,437 women were randomized 40:60 to either a dietary intervention or control group. Dietary fat intake reduction was greater in the dietary intervention group compared to the control group (fat grams/day at 12 months, 33.3 ± 16.7, mean ± standard deviation (SD) versus 51.3 ± 24.2, respectively, $p<0.001$). Women in the dietary group also had a weight loss of about seven pounds. After a median of 60.0 months, 277 events (local, regional, distant, or ipsilateral recurrence or new contralateral breast cancer) were reported: 96 of 975 in the dietary group and 181 of 1462 in the control group. A relapse-free survival difference favored dietary intervention over control (Hazard Ratio (HR) 0.76, 95 percent confidence interval (95% CI) 0.60 - 0.98, P=0.034) for adjusted Cox model analysis reflecting a 3.2 percent absolute difference in relapse-free survival after 8 years.

A lifestyle intervention resulting in dietary fat intake reduction improves the relapse-free survival of postmenopausal breast cancer patients receiving conventional cancer management.

TABLE 1. Number of Servings from the Food Guide Pyramid at Baseline and 12 months by the WINS[a] Study Group.

	Baseline (mean±SD[b])		12 Months (mean±SD)	
Food group	SA[c] (n=50)	NSA[d] (n=113)	SA (n=50)	NSA (n=113)
Bread	5.7±2.2[y]	5.7±2.3	4.8±2.1[xy]	5.5±1.9[x]
Vegetables	3.4±1.3	3.5±1.9	3.4±1.5	3.2±1.6
Fruits	2.3±1.4	2.5±1.6	2.7±1.4	2.1±1.6
Dairy	1.8±1.1	1.6±1.0	2.0±1.6	1.7±1.5
Meat	2.0±0.9	2.1±1.3	1.7±1.0	1.9±0.8
Fats, Oils, Sweets	4.8±3.6[y]	5.4±3.1[z]	3.0±2.4[xy]	4.2±3.0[x]

[a]WINS=Women's Intervention Nutrition Study
[b]SD=standard deviation
[c]SA=strictly adherent group (n=50)
[d]NSA=not strictly adherent group (n=113)
[x]Means are significantly different between groups within a time period.
[y]Means are significantly different for SA group across time
[z]Means are significantly different for NSA group across time.
(Reprinted from J. Am. Diet Assoc., Vol. 104, Winters et al., Dietary patterns in women treated for breast cancer who successfully reduce fat intake: the Women's Intervention Nutrition Study (WINS), 551-559, 2004,

II. List of Current Employees

1. Edward C. Mun, M.D.	Assistant Professor of Surgery
2. Lalita Khaodhiar, M.D.	Instructor in Medicine
3. Weijun Pan, MD, Ph.D.	Visiting Scientist
4. Zhiming Mai, Ph.D.	Senior Research Fellow
5. Anne McNamara RN	Research Associate
6. Michelle Sherwood, RD	Research Associate
7. Min Lin, BA	Research Assistant
8. Xin Li, MD	Research Associate
9. Aijita Singh, Ph.D.	Postdoctoral Fellow
10. Lei Wu, MD	Visiting Scientist
11. Zhanggui Wu, Ph.D.	Research Associate
12. Fengfei Wang, Ph.D.	Postdoctoral Fellow
13. Barbara Ainsley, DTR	Administrative Assistant
14. Susan Sidell	Administrative Coordinator
15. Belinda Waltman	Research Assistant
16. Rita Buckley, MBA	Medical Writer

III. 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
   Principal Investigator: David Nathan
   Co-Investigator: George Blackburn, M.D., Ph.D.

2. "Low-Fat Diet in Stage II Breast Cancer: Outcome Trial"
   AHF/NCI 5R0l-CA45504-11
   Project period: 01/01/97 – 12/30/04
   Principal Investigator: Daniel Nixon
   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
   Principal Investigator: Hope Ricciotti, M.D.
   Co-Investigator: George Blackburn, M.D., Ph.D.

4. "The Boston Obesity Nutrition Research Center (BONRC) "
   NIDDK/NIH P30DK46200
   Project Period: 9/30/98-3/31/03 4/01/03-4/01/08
   Principal Investigator: Barbara Corkey
   Associate Director: George Blackburn, M.D., Ph.D.

5. "Exercise, Diet, and Sex Hormones in Postmenopausal Women"
   RO1 CA105204-01
   Project Period: 09/01/04-8/31/05
   PI: Anne McTiernan, MD, Ph.D.
   Co-Investigator: George L. Blackburn, M.D.,Ph.D.

Jin-Rong Zhou, Ph.D.

1. "Chemoprevention of Bladder Cancer by Soybean Bioactive Comp."
   National Institutes of Health, 5R01CA092546-02
   Project period: 06/01/2003-05/31/2005
   Principal Investigator: Jin-Rong Zhou, Ph.D.
   Co-Investigator: George Blackburn, M.D., Ph.D.

2. "Interaction between Dietary Soy Components and Tamoxifen"
   NIH/NCCAM, 5RO1-AT00863-03
   Project period: 09/12/2001-05/31/2005
   Principal Investigator: 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, 5RO3 CA101041-02
   Project period: 05/01/2003-04/30/2005
   Principal Investigator: Jin-Rong Zhou, Ph.D.

4. "Genistein and prevention of HER2-overexpressing Breast"
   National Institutes of Health, 1RO3 CA112644-01
   Project period: 09/21/2004-08/311/2006
   Principal Investigator: Jin-Rong Zhou, Ph.D.

5. "Prevention of bladder cancer progression by sulforaphane"
   National Institutes of Health, 1RO3 CA112640-01
   Project period: 09/30/2004-08/31/2006
   Principal Investigator: Jin-Rong Zhou, Ph.D.

6. "Effects of soy products on estrogen insufficiency-induced tamoxifen-nonresponsive Breast Cancer"
   Susan Komen's Breast Cancer Research Foundation
   Project period: 05/01/2004-04/30/2006
   Principal Investigator: Jin-Rong Zhou, Ph.D.

7. "Effects of AglyMax on the Prevention and Treatment of Obesity and Prostate Cancer"
   Nichimo Co., Japan
   Project period: 03/01/2001-05/31/2006
   Principal Investigator: Jin-Rong Zhou, Ph.D.

8. "Effects of Soy Isoflavones on Menopausal Hot Flashes"
   Nichimo Co., Japan
   Project period: 06/03/02 – 6/03/05
   Principal Investigator: H. Ricciotti, M.D.
   Co-Investigator: Jin-Rong Zhou, Ph.D.

9. "Trace elements and the development of prostate cancer"
   Department of Defense, Idea Award
   Project period: 01/01/2002-12/31/2004
   Principal Investigator: Arthur Sytkowski, M.D.
   Co-Investigator: Jin-Rong Zhou, Ph.D.

10. "Functional Erythropoietin Receptors expressed by Human Prostate Cancer Cells"
    Department of Defense, Idea Award
    Project period: 04/01/2003-04/30/2006
    Principal Investigator: Arthur Sytkowski, M.D.
    Co-Investigator: Jin-Rong Zhou, Ph.D.

IV. Applications Pending Review and Funding

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

1. A Web based Approach to Treat Obesity in Primary CareGroup
   RO3 DK067883-01
   Project Period: Pending
   PI: Christina Wee, M.D.
   Co-Investigator: George L. Blackburn, M.D., Ph.D.

2. Calcium and Weight Management
   The Beverage Institute for Health & Wellness LLC
   Project Period: Pending IRB approval
   PI: George L. Blackburn, M.D., Ph.D.

Jin-Rong Zhou, Ph.D.

1. "Black Tea Bioactives for prostate cancer prevention"
   National Institutes of Health, RO1 AT001623
   Project period: 07/01/2005-06/30/2010
   PI: Jin-Rong Zhou, Ph.D.

2. "Mechanisms of androgen independent prostate cancer"
   National Institutes of Health, RO1
   Project period: 07/01/2005-06/30/2010
   PI: Steve Balk, M.D., Ph.D.
   Co-Investigator: Jin-Rong Zhou, Ph.D.

3. "Bioactive components in cruciferous vegetables and prevention of breast cancer progression"
   American Institute for Cancer Research
   Project period: 07/01/2005-06/30/2007
   PI: Jin-Rong Zhou, Ph.D.

V. Divisional Accomplishments in the Past Year

Research Accomplishments (new grants):
George L. Blackburn, M.D., Ph.D.

1. Exercise, Diet, and Sex Hormones in Postmenopausal Women
   R01 CA105204-01
   Project Period: 09/01/04-8/31/05
   PI: Anne McTiernan, MD, Ph.D.
   Co-Investigator: George L. Blackburn, M.D.,Ph.D.

Jin-Rong Zhou, Ph.D.

1. "Genistein and prevention of HER2-overexpressing breast cancer"
   National Institutes of Health, RO3 CA112644
   Project period: 09/21/2004-08/30/2006
   PI: Jin-Rong Zhou, Ph.D.

2. "Prevention of bladder cancer progression by sulforaphane"
   National Institutes of Health, RO3 CA112640
   Project period: 09/30/2004-08/31/2006
   PI: Jin-Rong Zhou, Ph.D.

3. "Effects of soy products on estrogen insufficiency-induced tamoxifen-nonresponsive breast cancer"
   Susan Komen's Breast Cancer Research Foundation
   Project period: 05/01/2004-04/30/2006
   PI: Jin-Rong Zhou, Ph.D.

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

1. Fellow in the American Society for Nutrition Sciences.
2. Vice-Chair of Commonwealth of Massachusetts Betsy Lehman Center for Patient Safety and Medical Error Reduction Expert Panel on Weight Loss Surgery.
3. NIH Grant Reviews - NIDDK Special Emphasis Panel Loan Repayment Study
   Section 2004.
4. NIH grant review SSS-U(03) Diabetic retinopathy and traditional Japanese medicine Nutrition Curriculum Subcommittee, Division of Nutrition, Harvard Medical School.

5. Invited attendee of US Dept. of Health and Human Services Agency for Healthcare Research and Quality. Safety Issues in Bariatric Surgery: Expert Panel Meeting. October 14, 2004, Rockville, MD.
6. Member of Louisiana Obese Subjects Study (LOSS) Data Safety Monitoring Board.
7. Chair person, Harvard Medical School, Division of Nutrition, 6th Postgraduate Nutrition Symposium: Science-Based Solutions to Obesity: What is the Role of Academia, Government, and Industry?
8. Chairperson, HMS, Division of Nutrition & The American Dietetic Association Foundation Program: Science-Based Solutions to Obesity: What is the Role of Academia, Government, and Industry and Healthcare Professionals?
9. Invited panelist: The Politics of Food, Agriculture, and Nutrition ----Issues, Insights, and Imperatives for 2005, December 15, 2004, Washington, D.C.

Jin-Rong Zhou, Ph.D.

1. Member, NCI, Special Emphasis Panel "Cancer Prevention Research and Epidemiology".
2. Foreign Reviewer member, Italian Association for Cancer Research (AIRC).
3. Member, Chemo/Dietary Prevention (CDP) Study Section, NCI/NIH.
4. Ad-hoc member, Prostate Cancer PO1 Review Cluster (NCI-D RPRB (S3)).
5. Ad-hoc member, Cancer Therapeutics PO1 Review Cluster (NCI-C RPRB (X1)).
6. Nutrition Curriculum Committee, Division of Nutrition, Harvard Medical School.

VI. 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

II. 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. There is a workshop on the diagnosis and treatment of the Metabolic Syndrome and a new project is the creation of a journal.

2. HMS, Department of Continuing Medical Education, Enhancing the Safety of Parenteral and Enteral Nutrition. Cambridge, MA. November 7-9, 2004 Course Director.

3. HMS, Department of Continuing Medical Education, " Practical Approaches to the Treatment of Obesity: Obesity Medicine: Emergence of a New Discipline" Cambridge, MA. June 24-26, 2004 Course director.

4. Chair person, Harvard Medical School, Division of Nutrition, 6th Postgraduate Nutrition Symposium: Science-Based Solutions to Obesity: What is the Role of Academia, Government, and Industry?

Invited Presentations (Local, National, International)

1. Agribusiness Seminar Harvard Business School, Cambridge, MA "Obesity in America and What to do about it. January 4, 2004.

2. Cambridge Hospital, Surgical Grand Rounds Cambridge, MA "Hyperglycemia and the ICU" January 29, 2004.

3. Gillette Center for Women's Cancer, Massachusetts General Hospital Boston, MA " Diet and Breast Cancer" April 20, 2004.

4. Beth Israel Deaconess Medical Center Radiation Therapy Annual Meeting, Newton, MA "Cancer Cachexia and Nutrition Treatment" April 28, 2004.

5. American Dietetic Association, Chicago, IL "Forecasting Nutrition Science News and Research" May 15, 2004.

6. Massachusetts Association of Health Plans Ethics Forum, Waltham, MA "Bariatric Surgery: Exploring the Ethical Issues" June 9, 2004.

7. American Dietetic Association Commission on Dietetic Registration in Weight Management, Waltham, MA "Current Research and Future Possibilities" June 17, 2004.

8. Massachusetts Coalition for the Prevention of Medical Errors, Burlington, MA "Weight Reduction Surgery Expert Panel Presentation" August 16, 2004.

9. International Federation for the Surgery of Obesity Tokyo, Japan " Is Obesity Surgery Safe or High Risk? September 10, 2004.

10. Balance Lifestyle Global Advisory Meeting Paris, France " Health Literacy" September 17, 2004.

11. Contemporary Forum Obesity Treatment and Prevention Seattle, WA "Future directions of obesity treatment and prevention: New pharmacology, techniques, and strategies" September 21, 2004.

12. Food Safety, Sustainability, and Consumer Health, AHOLD International Boston, MA " Obesity " September 22, 2004.

13. Dietetic Interns Research Day, Beth Israel Deaconess Medical Center, Boston, MA "Introduction to Career in Research" September 27, 2004.

14. Medscape Web Cast "Long-term dietary interventions: Effects on weight loss and health" September 29, 2004.

15. American Dietetic Association Anaheim, CA "Science-Based Solutions to Obesity: What is the Role of Academia, Government, and Industry and Healthcare Professionals? October 2, 2004.

16. Massachusetts Medical Society and Boston Obesity Nutrition Research Center Annual Meeting Waltham, MA "Popular Diets Introduction-Moderator" October 8, 2004.

17. Contemporary Forum Obesity Treatment and Prevention Washington, DC "Surgery as a treatment approach for obesity" "Evaluating the Surgical Candidate: Criteria, Work-up, and long-term management" October 25-26, 2004.

18. Beth Israel Deaconess Medical Center Surgical Research Meeting Boston, MA "Outcome of Women's Intervention Nutrition Study (WINS) November 1, 2004.

19. 2nd Annual World Congress on the Insulin Resistance Syndrome Meeting Los Angeles, CA " Obesity, the Metabolic Syndrome and Cancer" November 20, 2004.

20. Pri-Med Updates, Philadelphia PA "Practical Approaches to the Treatment of Obesity" December 2, 2004.

21. Massachusetts Department of Public Health WIC annual Meeting, Worcester, MA" Tipping the Scales" December 9, 2004.

22. Dietetic Interns Obesity Day Boston, MA "Current Trends in Obesity" December 13, 2004.

Jin-Rong Zhou, Ph.D.

Undergraduate and medical school courses

Spring 2004 Tutor, Preventive Medicine and Nutrition, Harvard Medical School.

Abstracts presented at Local, National, and International Meetings

1. Pan W, **Blackburn GL, Zhou JR**. A novel extract of fermented soy germs inhibits LPS-induced TNF-alpha production in vitro and in vivo. Experimental Biology'04, Washington, DC, 2004.

2. Singh AV, **Blackburn GL, Zhou JR**. Soy bioactive components inhibit bladder cancer growth in vitro and in vivo. American Association for Cancer Research, Orlando, FL, 2004.

3. Zerbini LF, Wang Y, Czibere A, Cho JY, Wei W, Joseph M, **Zhou JR,** Libermann TA. New insights into apoptosis induction in prostate cancer cells. American Association for Cancer Research, Orlando, FL, 2004.

Invited Presentations (Local, National, and International)

1. Invited speaker: "Soy and isoflavone intake inhibits experimental induced prostate cancer" VII World Soybean Conference/IV International Soybean Processing and Utilization Conference, Foz do Iguacu, Brazil., Feb, 2004.

2. Invited speaker: "Soy and Lifestyle Related Disease Prevention", 11th International Symposium on the SHR and Cardiovascular Prevention. Spokane, WA, USA. May 2004.

VII. Plans for the Coming Academic Year

Staff Changes/Recruitments

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

1. Welcome Daniel Rooks, Ph.D. to the CSNM to collaborate with the Gastric Bypass Team submitting an RO1.
2. Hire Full time Registered Dietitian to replace staff.
3. Hire research assistant to work on new clinical trial

Jin-Rong Zhou, Ph.D.

1. To recruit 1-2 postdoctoral fellows/Research Associates

Plans for Research (NewGrants/Programs)

George L. Blackburn, MD, Ph.D.

1. Collaborate with Anne McTiernan on WINS II Proposal
2. Collaborate with Christina Wee-Kuo (Dept of Medicine) on two RO1's
   A Web based Approach to Treat Obesity in Primary CareGroup
   Understanding How Patients Value Bariatric Surgery

Jin-Rong Zhou, Ph.D.

1. To submit 2 new RO1's (including 1 competing renewal), 1-2 R21, and 1-2 RO3.
2. To expand research on natural products and cancer prevention.
3. To expand collaborations within BIDMC, Dr. Steve Balk and Dr. Towia Libermann on prostate cancer and breast cancer research.
4. To expand collaborations with Dr. David Lee in McLean Hospital/HMS on natural products and prostate cancer research.

VIII. Bibliography (01/01/04 – 12/31/04)

Original Articles

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*. 2004; 104:551-9.

2. Zerbini L, Wang Y, Czibere A, Correa R, Cho JY, Ijiri K, Wei W, Joseph M, Gu X, Grall F, Goldring M, **Zhou JR**, Libermann T. NF-kappaB mediated repression of GADD45 alpha and gamma is essential for cancer cell survival. *Proc Natl Acad Sci* USA 2004; 101:13618-23.

3. **Zhou JR**, 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* 2004;108: 8-14.

4. **Zhou JR**, Yu L, Zerbini L, Libermann TA, **Blackburn GL**. Progression to androgen-independent LNCaP human prostate tumors: Cellular and molecular alterations. *Int J Cancer* 2004; 110:800-6.

Reviews, Chapters, and Editorials

1. **Blackburn GL**, Mun EC**.** Hepatic impact of surgery for weight loss. *Semin Liver Dis* 2004; 24:369-78.

2. Walker WA, **Blackburn GL**. Nutrition and gene regulation. *J Nutr* 2004; 134 Suppl 1: 2434-36.

3. **Zhou JR**, Erdman JW Jr. Soy consumption and cancer prevention: A critical review. In: Bendich A, Deckelbaum R, editors. Preventive nutrition. New Jersey: Humana Press Inc., 2004. pp. 23-55.

4. **Zhou JR**. Soy and the prevention of lifestyle-related disease. *Clin Exp Pharmacol Physiol* 2004; 31 Suppl 2: 14-9.

Reviews, Chapters, and Editorials (in press)

1. **Zhou JR**. Soy-food and soy-drug interactions in prevention and treatment of cancer. In: Thompson LU, Ward WE, editors. Food drug synergy and safety. CRC Press. 2004; in press.

2. **Zhou JR**. Flavonoids as inhibitors of metastasis. In: Awad AB, Bradford PG, editors. Nutrition and cancer prevention. Marcel Dekker, Inc. 2004; in press.

Clinical Communications

1. **Blackburn GL**. Low-Carb Diet Lowdown. *HealthNews*, 2003; July 9(7):1-2

2. **Blackburn GL**. Experienced Surgeons Are a Cut Above. *HealthNews,* 2004 Jan 10 (1):12-13.

3. **Blackburn GL**.A New Risk for Fractures? *HealthNews*, 2004 July 10 (7):12.

Nonprint Materials

1. **Blackburn GL.** Making scientific sense of different dietary approaches, Part I: Meeting dietary needs, achieving weight loss. Medscape Diabetes & Endocrinology 6 (1), 2004. February 26, 2004. Available at http://www.medscape.com/viewarticle/469768.

2. **Blackburn GL.** Making scientific sense of different dietary approaches, Part II: Evaluating the diets. Medscape Diabetes & Endocrinology 6 (1), 2004. March 9, 2004. Available at http://www.medscape.com/viewarticle/470747.

Abstracts

1. **Zhou JR**, Mai Z, Lin M, **Blackburn GL**. Soy isoflavone genistein potentiates the efficacy of tamoxifen treatment to estrogen-dependent human breast tumor in a mouse model. *FASEB J* 2004; 18:A1110.

2. Mai Z, **Blackburn GL, Zhou JR**. Synergistic inhibitory effect of genistein in combination with tamoxifen on HER-2-overexpressing BT-474 human breast cancer cell growth. *FASEB J* 2004; 18:A1111.

3. **Zhou JR**, Mai Z, **Blackburn GL**. Soy isoflavone genistein synergistically enhances the preventive effect of tamoxifen on the growth of estrogen-dependent MCF-7 human breast cancer cells in vitro and in vivo. *Cancer Epidemiol Biomarkers Prev* 2004; 13(11, pt 2): A119.

4. **Zhou JR**, Mai Z, **Blackburn GL**. Genistein and tamoxifen combination synergistically inhibits the growth of HER2-overexpressing BT-474 human breast cancer cells via apoptosis induction and down-regulation of surviving expression. *Cancer Epidemiol Biomarkers Prev* 2004; 13(11, pt 2): A122.

Mark P. Callery, M.D.

I. Narrative Report

Pancreatic cancer is an extraordinarily lethal disease. It is profoundly resistant to any therapy currently available. Our research focuses on the identification of the molecular mechanisms that underlie this phenomenon. We have undertaken three different approaches to reveal these mechanisms.

1. We have examined the expression and potency of three major death receptors TNF-R, TRAIL-R and Fas in mediating cytotoxicity in pancreatic cancer cell lines. We have analyzed the expression of major anti-apoptotic factors, cell cycle regulators and death receptor decoys (DcRs) in comparison with normal pancreas tissues and five other human malignant tumor cell lines. By using RNA interference (RNAi) we demonstrate that predominant Bcl-x_L over-expression plays a critical role in pancreatic cancer chemoresistance. The knockdown of predominant Bcl-x_L overexpression significantly reduces the viability of pancreatic cancer cells to TNF-α and TRAIL mediated apoptosis by sublethal-dose single and combined antitumor drugs. Tumor xenograft athymic mouse model is used to assess the role of Bcl-x_L overexpression in tumorigenicity, *in vivo*.

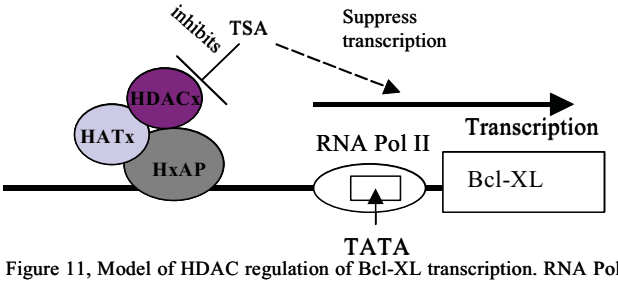


Figure 11, Model of HDAC regulation of Bcl-XL transcription. RNA Pol II transcription machinery is recruited to Bcl-XL promoter. A putative HDAC (HDACx) interacts with a histone acetylase (HATx) and a HDACx-associated protein (HxAP). This complex is recruited to Bcl-XL promoter region. HATx may acetylate HxAP and suppresses Bcl-XL transcription. However, HDACx inhibits HATx-mediated acetylation of HxAP and releases the suppression. TSA, however, inhibits the deacetylase activities of HDACx and may cause HDACx degradation. This may release the suppression of HATx and increases the acetylation of HxAP and decreases Bcl-XL transcription.

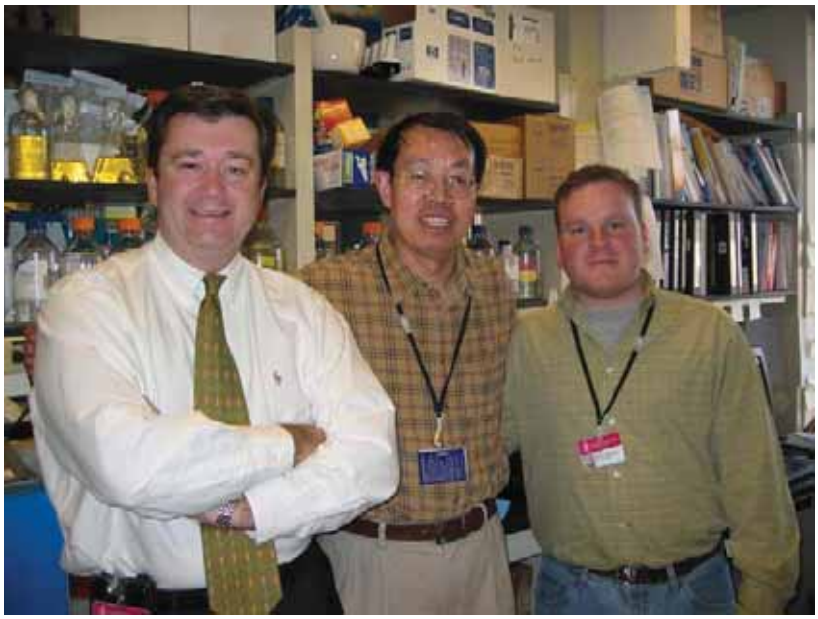
2. We are investigating the role of histone deacetylase-1 (HDAC-1) overexpression in tumor survival. Histone acety-ltansferases (HATs) and HDACs affect gene expression by altering the acetylation status of histones and some transcription factors on target gene promoters. We have found that pancreatic cancer cell lines co-overexpress HDAC-1/3 and ERK1/2. In particular, trichostatin A-induced depletion of HDAC-1 is associated with significant apoptosis in the cultures of pancreatic cancer cell lines. Trichostatin A-triggered HDAC-1 degradation coincides with ERK1/2 depletion. These studies support the notion that HDAC-1 overexpression is associated with chemoresistance, and the stability of ERK1/2 may be regulated by acetylation. We are constructing HDAC-1 RNAi knockdown vectors to investigate these issues.

3. We are interested in the identification of HDAC-1 target genes that may regulate chemoresistance. HDAC-1 is a transcription regulator. Exogenous HDAC-1 overexpression increases HIF-1α and VEGF productions, suggesting that HDAC-1 overexpression may be very critical to tumor angiogenesis and survival. However, it is unknown which other genes are specifically regulated by

HDAC-1. We will employ microarray hybridization to identify HDAC-1 specific target genes. The understanding of HDAC-1 target genes and their specific roles in chemoresistance is very important for gene-orientated chemotherapy.

II. List of Current Employees

1. Jirong Bai, D.V.M., Ph.D. — Instructor in Surgery
2. Aram Demirjian, M.D. — Research Fellow
   Surgical Resident



Members of the Callery Lab
Drs. Callery, Bai, and Demirjian

III. List of Current Funding

1. Research Support
   Beth Israel Hospital Foundation
   Project Period: 7/1/02-6/30/03
   Principal Investigator: Mark P. Callery, M.D.

2. Aram Demirjian, Department of Surgery, HMS
   National Institutes of Health, 5-T32-DK07754-06
   Project Period: 2004-6/30/09
   Principal Investigator: David Soybel, M.D.
   This award provides support for Dr. Demirjian's Research Fellowship

IV. Applications Pending Review/Funding

1. "Overcoming Chemoresistance in Pancreatic Cancer"
   National Institutes of Health R01
   Project Period: 07/1/05-06/030/09
   Principal Investigator: Mark P. Callery, M.D.
   Co-Investigator: Jirong Bai, D.V.M., Ph.D.

2. "Targeting Histone Deacetylase-1 to Defeat Pancreatic Cancer Chemoresistance"
   National Institutes of Health R01
   Project Period: 12/01/05-11/30/09
   Principal Investigtor: Jirong Bai, D.V.M., Ph.D.
   Co-Investigator: Mark P. Callery, M.D.

V. Divisional Accomplishments in the Past Year

During the past year, we have made the following important discoveries.

1. We have demonstrated that different pancreatic cancer cell lines coexpress high-level TRAIL-R, Fas, and TNF-R1, but are strongly resistant to apoptosis triggered by the death receptors. Death receptor decoys DcR2 and DcR3 overexpression may partly contribute to the resistance of pancreatic cancer cells to TRAIL-R and Fas-mediated cytotoxicity. However, predominant Bcl-x_L overexpression plays a vital role in the chemoresistance of pancreatic cancer.

2. We have developed Bcl-x_L RNAi knockdown retroviral vectors that cause a 100% depletion of endogenous Bcl-x_L overexpression in transduced pancreatic cancer cells. The knockdown of the predominant Bcl-x_L overexpression significantly reduces the viability of pancreatic cancer cells to TNF-α, TRAIL mediated apoptosis by sublethal-dose single and combined antitumor drugs, including geldanamycin, PS-341, trichostatin A (TSA) and doxorubicine. TSA suppresses tumor cell growth by inactivating histone deacetylase activities and ERK pathways.

3. We have found that geldanamycin and PS-341 or trichostatin A synergistically block NF-kB signaling and induce apoptosis in most pancreatic cancer cell lines. PS-3241/geldanamycin and PS-341/TSA regimens reduce the viability of pancreatic cancer cells by an average of 61% and 79%, respectively. PS-341/TSA combination effectively disrupts Akt/PKB and ERK pathways, inactivates histone deacetylase activities, and causes apoptosis by activating caspase cascades in pancreatic cancer cells. Therefore, PS-341 and TSA combination may be a novel therapeutic strategy for pancreatic cancer.

V. Report of Teaching

Undergraduate and Medical School Courses

1. Dr. Callery is active in several courses and teaching activities at the Harvard Medical School.

Graduate School and Graduate Medical Courses

1. Aram Demirjian, a surgery resident fellow, who joined my laboratory in June 2004 and works on a project entitled: NF-κB, RelA, and cRel differentially regulate chemoresistance in pancreatic cancer.

Abstracts Presented at Local, National, and International Meetings

1. 7th Annual Meeting of the American Society of Gene Therapy, Minneapolis, MN. "RNAi-mediated depletion of Bcl-x_L sensitizes pancreatic cancer cells to TNF-α induced apoptosis". June 2-6, 2004.

2. American HepatoPancreatoBiliary Association Annual Meeting. "Developing novel biological therapies that drive apoptosis and overcome chemoresistance in pancreatic cancer cells" .

III. American HepatoPancreatoBiliary Association Annual Meeting. "Bcl-x_L depletion sensitizes pancreatic cancer cells to ligand-mediated apoptosis".

VI. Plans for the Coming Academic Year

1. Pursue specific aims of two submitted grant proposals, with special emphasis on establishing mouse xenograft models of Bcl-x_L knockdown pancreatic tumors.

VII. Bibliography (1/1/04-12/31/04)

Original Articles

1. Chandler NM, Canete JJ, **Callery MP**. Caspase-3 drives apoptosis in pancreatic cancer cells after treatment with gemcitabine. *J Gastrointest Surg* 2004;8(8):1072-8.

2. Chandler NM, Canete, JJ, **Callery MP**. Increased expression of NF-kappa B subunits in human pancreatic cancer cells. *J Surg Res* 2004;118(1):9-14.

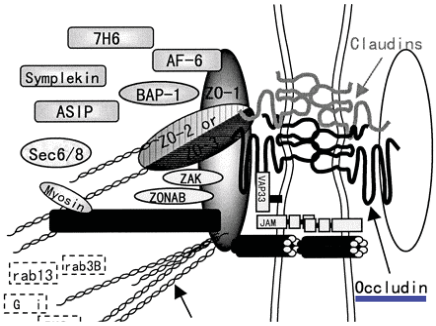
Original Articles (in press)

1. Jirong B, Jianhua S, Aram D, Vollmer Jr CM, Marasco W**, Callery MP**. Predominant Bcl-x_L knockdown disables anti-apoptotic mechanisms: Tumor necrosis factor-related apoptosis inducing ligand-based triple chemotherapy overcomes chemoresistance in pancreatic cancer cells in vitro. *Cancer Res* 2004; in press.

Susan J. Hagen, Ph.D.
GI Physiology Research Laboratory

I. Narrative Report

Our current NIH sponsored research is concerned with gastric barrier function during health and disease, and our projects include mechanisms that regulate tight junction organization and permeability in the stomach, gastric mucosal restitution after injury, and cell death and survival in gastric epithelial cells. Although we are particularly interested in the regulation of barrier function/malfunction during *Helicobacter pylori* (HP) infection and how defects in the gastric mucosal 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.



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

Tight junction Permeability

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, it was shown that when occludin, one of two proteins that seal the para-cellular space (inset), is knocked-out, mucosal damage occurs in the stomach that is identical to infection with HP. Lack of occludin affected only 2 tissues, the stomach and testis, suggesting that occludin regulates a novel pathway in these tissues. Because little is known about how occludin regulates development and/or maintenance of tight junctions at the surface of the gastric mucosa or in gastric glands, new culture models were recently developed by us to study the cell and molecular regulation of occludin in gastric surface and chief cells. How infection with HP alters occludin localization and mucosal permeability are studies currently underway in the laboratory.

Gastric Mucosal Restitution after Injury

This laboratory is most well known for studies concerning 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. We recently proposed a novel idea that H^+/lactate export, via the monocarboxylate transporter, 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. Current studies are concerned with understanding the role of monocarboxylate transport in restitution.

Cell Death

A new area of investigation in the laboratory is concerned with understanding pathways that regulate cell death and survival of gastric epithelial cells. These new studies were initiated because Th1 cytokines, liberated during HP infection, kill gastric epithelial cells rather than affecting tight junction integrity as occurs in other GI cells. In all inflammatory diseases of the stomach, including HP, death of gastric chief and parietal cells within the gastric gland results in atrophy, which is the major initiating factor in the progression to gastric cancer. In work nearly ready for publication, a novel idea will be proposed that gastric chief and parietal cells have a single, non-overlapping, cell death pathway that is regulated by unique factors and physiology. Chief cells express Bcl-x, which is regulated by transcriptional mechanisms, whereas parietal cells express BAD, which is regulated by phosphorylation on three serine residues. The lab is currently working to understand the regulation of these pathways using isolated cell models.

II. List of Current Employees

Research Laboratory

1. Kimihito Tashima, Ph.D.	Research Fellow
2. Asli Muvaffak, Ph.D.	Research Fellow
3. Saeko Yanaka	Student, Tokyo University
4. Jacob Sanders	Student, Harvard University

Core Facilities

Imaging

1. Dan Brown, M.S.	Sr. Research Associate
2. Justine Curley, M.S.	Research Assistant

Histology

1. Suzanne White, B.S.	Histotechnologist

Surgical Research

1. T. Andrew French. B.A.	Administrative Coordinator

Members of the Hagen Laboratory and core group
Back L-R: Susan Hagen, Justine Curley.
Front L-R: Suzanne White, Asli Muvaffak,Dan Brown, Kimihito Tashima.

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 - 05/31/2008
   Principal Investigator: Susan J. Hagen, Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "Biology of Alimentary Epithelia in Health and Disease"
   National Institutes of Health, P30 DK34854
   Project period: 9/1/2005-8/31/2010
   Principal Investigator: Dr. Wayne Lencer, Children's Hospital
   Subcontract: "Imaging Core Facility"
   Subcontract Principal Investigator: Susan J. Hagen, Ph.D.

V. Divisional Accomplishments over the Past Year

Individual/Research Accomplishments

1. I was asked to sit on 2 NIH study sections in 2004. The first invitation was to review applications for an ad hoc section set-up to review conflict applications. The second invitation was to review application for the Gastrointestinal Mucosal Pathobiology (GMPB) Study section. Subsequently, I was asked to become a charter member of the GMPB study section, which will be for a 5 year period starting in October of 2005.

2. I was invited as one of two keynote speakers at the 2004 Parietal Cell Club, which met at EB04 in Washington, DC.

3. The abstract I submitted to EB04, #2 below, was judged as high priority and was selected for oral presentation in the GI Pathobiology Forum of the American Physiological Association-GI section.

4. I was invited to Japan to present the Luncheon Seminar (Keynote Address) at the Annual Meeting of the Japanese Ulcer Society in Shiga, Japan. I was the first non-Japanese and first woman to deliver an address at that meeting in its history.

5. I was invited as a session chair (Session IV; *Helicobacter pylori*, Inflammation, and Tissue Injury") and Invited Speaker (same session) at the IUPHAR-GI section meeting, "Advances in GI Pharmacology; From Acid Secretion to Mucosal Protection" in Shiga, Japan. November, 2004.

6. I was invited to serve as an abstract reviewer in the Esophageal, Gastric, and Duodenal Disorders section of the American Gastroenterological Association (AGA).

7. I was invited to co-chair an AGA Research Forum "Upper GI Mucosal Injury and Repair Mechanisms" at DDW in May of 2004.

8. Jacob Sanders, a Research Scholars Institute (RSI) student from MIT who worked with Kimihito Tashima and me during the summer of 2004, won two awards for the work he did in the laboratory. First, Jacob's final paper and oral presentation were ranked one of the 5 best in the RSI program that summer (chosen from 90 entries). Second, Jacob's paper was selected as an Intel semifinalist in a tough competition worldwide. The paper is pending consideration as a Finalist in the Intel competition. Jacob was recently accepted "Early Decision" to Harvard University as an undergraduate student.

Abstracts Presented at Local, National, and International Meetings

1. Kimihito Tashima's abstract entitled "Establishment of High Resistance and Low Permeability Cultured Chief Cells from the Rat Stomach" was selected for oral presentation at the IUPHAR-GI section meeting in Shiga, Japan. November, 2004.

2. **Hagen SJ**, Yang DX, Fox JG. Expression of cell death and survival proteins in the gastric mucosa predict specific cell death pathways for gastric epithelial cells. This was presented as an oral presentation at Experimental Biology; April, 2004.

3. Tashima K, Muvaffak A, **Hagen SJ.** Gastric chief and surface cells from the rat stomach have unique tight junction structure and permeability characteristics. This was presented as a poster at Experimental Biology; April, 2004.

4. Kimihito Tashima presented a poster at the BIDMC Research Day entitled, "Establishment of High Resistance and Low Permeability Cultured Chief Cells from the Rat Stomach". October, 2004.

5. Asli Muvaffak presented a poster at the BIDMC Research Day entitled, "EGF, TGF-β_2, and Matrix Proteins Induce Tight Junction Reorganization in Rat Gastric Mucosal-1 (RGM-1) Cells". October, 2004.

Administrative Accomplishments

1. I continued as Associate Director for Research in the Department of Surgery. Accomplishments this year were successful completion of the Annual Research Report and "Funding Sources for Residents". We also assembled a Guidelines Manual, which is to help streamline administrative tasks in Surgical Research.

2. I continued to direct the Morphology, Histology, and Confocal Microscopy Core Facilities and to provide oversight and consultation for imaging experiments in the hospital and for members of the Harvard Digestive Diseases Center.

VI. Report of Teaching

Undergraduate and Medical School Courses

1. I participated in the Body Block at Harvard Medical School from 9/01/2004 10/31/2004 as co-director of the histology laboratory.

Summer and Medical Students

1. I and Kimihito Tashima were mentors for Mr. Jacob Sanders from the Research Scholars Institute (RSI) at MIT. Jacob was in the laboratory for 5 weeks from June-August of 2004. Jacob plans to return to the lab in 2005 as an undergraduate student at Harvard University.

2. Susan Hagen and Kimihito Tashima were mentors for Ms. Saeko Yanaka, who did a research rotation in the laboratory for 3 weeks in September of 2004. Saeko is a 1st year undergraduate student at Tokyo University in Japan. She worked successfully to improve the pepsinogen secretion assay for chief cell cultures. Saeko will return to the laboratory in September of 2005 for another research rotation.

3. Kimihito Tashima and Asli Muvaffak participated in the 2004 Explorations Program, a program at HMS to foster an interest in the Biomedical Sciences for Boston Public Middle School Students. Brigita Rachko and Kiara Thomas, from the Mission Hill School, visited the lab this year.

Invited Presentations (Local, National, and International)

1. Invited Speaker: Parietal Cell Club, Washington, DC. "BAD Apples Die Young: A New Mechanism that Links Survival and Physiology in Gastric Parietal Cells". April 18, 2004.

2. Invited Speaker: Principal Investigators Forum for the Clowes Visiting Professor, Department of Surgery, BIDMC. "Mechanisms that Regulate Atrophy of Parietal and Chief Cells During *H. pylori* Infection". November 4, 2004.

3. Invited Speaker: Annual Meeting of the Japanese Ulcer Society, Shiga, Japan. "Glutamine Protection Against Atrophy and Metaplasia During *H. pylori* Infection". November 19, 2004.

4. Invited Speaker: IUPHAR-GI Symposium, Advances in GI Pharmacology: From Acid Secretion to Mucosal Protection, Shiga, Japan. "Pathways Predicted to Regulate Parietal and Chief Cell Deletion, and Gland Atrophy during *H. pylori* Infection". November 21, 2004.

VII. Plans for the Coming Academic Year

Plans for Research

1. I plan to write another R01 application for the October 1 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. I plan to finish many other manuscripts which need to be published.

3. A new postdoctoral fellow, Songhua Zhang, MD, will begin work on June 1. She receives her PhD from Tskuba University Medical School in Japan in June of 2005.

4. A graduate student from Korea, Ms. Boram Cha, will spend 3 months in the laboratory working with Dr. Muvaffak on cAMP regulation of tight juctions in gastric surface cells.

5. I plan to resubmit the shared instrument grant application entitled "Confocal Microscope for the BIDMC Imaging Core Facility". The application will be submitted to the National Institutes of Health, Shared Instrument Grant Program on March 22, 2005. I am the application PI.

Educational Plans

1. I plan to continue to teach histology for the Body Block at HMS and plan to host another RSI student this summer.

Kimihito Tashima, Ph.D.

Asli Muvaffak, Ph.D.

VIII. Bibliography (1/01/04-12/31/04)

Original Articles

1. **Hagen SJ**, Morrison SW, Law CS, Yang DX. Restitution of the bullfrog gastric mucosa is dependent on a DIDS-inhibable pathway not related to HCO_3^- ion transport. *Am J Physiol Gastrointest Liver Physiol* 2004; 286:G596-605.

Reviews, Chapters, and Editorials

1. **Hagen SJ**, Hasselgren P-O, Odom-Andrews P. Annual Report, Department of Surgery, BIDMC, Lexington, MA: Minuteman Press, January 2004.

Educational Materials

1. **Hagen SJ**. Funding Sources for Residents; 2004.

2. **Hagen SJ**, Figueroa J. Guidelines for Surgical Research; 2004.

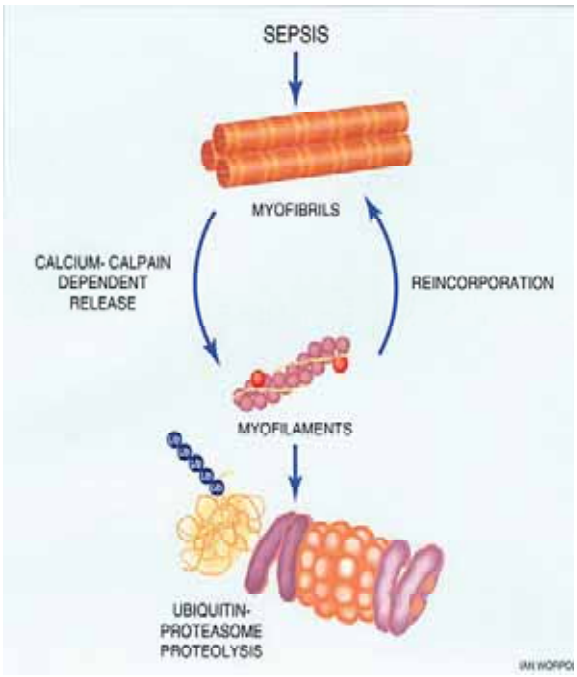
Abstracts

1. **Hagen SJ**, **Yang DX**, Fox JG. Expression of cell death and survival proteins in the gastric mucosa predict specific cell death pathways for gastric epithelial cells. *FASEB J* 2004; 18(5): A1268.

2. Tashima K, Muvaffak A, **Hagen SJ.** Gastric chief and surface cells from the rat stomach have unique tight junction structure and permeability characteristics. *FASEB J* 2004; 18(4):A710.

Per-Olof Hasselgren, M.D, Ph.D.

I. Narrative Report



The research efforts in our group 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/EBPβ and δ and the nuclear coactivator p300 in the regulation of the newly described ubiquitin ligases MuRF1 and atrogin-1. In addition, the role of calcium and calcium-calmodulin kinase II (CaMK II) in the regulation of muscle proteolysis is being investigated.

In other studies, the regulation of IL-6 production in gut mucosa and enterocytes is examined. IL-6 is a pleiotropic 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 human enterocytes stimulated with IL-1β. In other experiments we have defined transcription factors (NF-kB, AP-1, and C/EBP) involved in the activation of the IL-6 gene in stimulated enterocytes. We are currently 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 ongoing experiments, we are defining signaling pathways that are involved in heat shock-induced potentiation of enterocyte IL-6 production and have found evidence that the PI3K/Akt pathway may be important for this response. Because IL-6 may exert protective effects in enterocytes/gut mucosa, treatments that augment IL-6 production and

understanding the mechanisms of stimulated 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.	Research Fellow
5. Wei Wei, Ph.D.	Research Fellow
6. Amy Evenson, M.D.	Research Fellow Surgical Resident
7. Natasha Reilly, B.S.	Research Assistant
8. Sally Gwin, B.S.	Administrative Coordinator

Members of the Hasselgren Laboratory
Back, L-R: Wei Wei, Michael Menconi, Per-Olof Hasselgren, Moin Fareed
Front, L-R: Natasha Reilly, Amy Evenson, Hongmei Yang

III. List of Current Funding

1. "C/EBP and IL-6 Production in Mucosa and Enterocytes"
   National Institutes of Health, 1R01 DK60546-02
   Project Period: 05/01/2003 – 02/28/2007
   Principal Investigator: Per-Olof Hasselgren, M.D.

2. "C/EBP, Atrogin-1, and Muscle Wasting"
   National Institutes of Health, 1R01 NR008545-01
   Project Period: 09/30/2004 – 08/31/2009
   Principal Investigator: Per-Olof Hasselgren, M.D.

3. "C/EBP, p300, and Atrogin-1 in Muscle Wasting"
   National Institutes of Health, F32 DK066964-01
   Individual National Research Service Award
   Period: 12/01/2003 – 11/30/2005
   Principal Investigator: Amy Evenson, M.D.
   Sponsor: Per-Olof Hasselgren, M.D.

IV. Applications Submitted and Pending Review/Funding

1. "Muscle Protein Turnover and Amino Acid Uptake in Sepsis"
   National Institutes of Health, R01 DK37908-16
   Project Period: pending (competing renewal)
   Principal Investigator: Per-Olof Hasselgren, M.D.

Michael Menconi, PhD.
Hongmei Yang, Ph.D.

Amy Evenson, M.D.

Hongmei Yang, Ph.D.
Wei Wei, Ph.D.

V. Divisional Accomplishments in the Past Year

Research Accomplishments

1. A new R01 grant funded, R01 NR008545
2. Sponsored NRSA grant for Amy Evenson, F32 DK066964
3. Organized Annual Residents' Research Competition
4. Clowes Visiting Professorship in Surgical Research (Yuman Fong, M.D.)

Individual Accomplishments

1. NIH Study Section, January 2004
2. Selliger Visiting Professor, Department of Surgery, Johns Hopkins University, Baltimore, MD, March 2004

3. Invited speaker: "Calpain and Calpastatin in Muscle Wasting during Sepsis". Cachxia in Aging and Cancer Conference, Chicago, IL, December 2004
4. Named George H.A. Clowes Professor of Surgery, December 2004

VI. Report of Teaching

1. Surgical Clerkship, Medical Students: Endocrine Surgery – Thyroid/Parathyroid

VII. Plans for the Coming Academic Year

Continued collaboration and joint lab meetings with several other Harvard-based research groups in the field of muscle wasting with the ultimate goal of creating a Muscle Wasting Center. Preliminary contact has been established with the NIH to explore the feasibility to apply for a Program Project in Muscle Wasting-related research.

Catherine Cahill, Ph.D.

Wei Wei, Ph.D.

VIII. Bibliography (01/01/2004 – 12/31/2004)

Original Articles

1. Cai D, Frantz JD, Tawa NE, Melendez PA, Lidow HGW, **Hasselgren PO**, Frontera WR, Lee J, Glass DJ, Shoelson SE. Ikkbeta/NF-kB activation causes severe muscle wasting in mice. *Cell* 2004;119:285-98.

2. **Hasselgren PO**. Surgery in Sweden at the time of Halsted. *Arch Surg* 2004;139:100-112.

3. Hershko DD, Robb BW, Wray CJ, Luo GJ, **Hasselgren PO**. Superinduction of IL-6 by cycloheximide is associated with mRNA stabilization and sustained activation of p38 MAP kinase and NF-kB in cultured Caco-2. *J Cell Biochem* 2004;91:951-61.

4. Li BG, **Hasselgren PO**, Fang CH, Warden DG. Insulin-like growth factor-I blocks dexamethasone-induced protein degradation in cultured myotubes by inhibiting multiple proteolytic pathways. *J Burn Care Rehab* 2004;25:112-18.

5. Menconi M, Wei W, Yang H, Wray C, **Hasselgren PO**. Treatment of cultured myotubes with the calcium ionophore A23187 increases proteasome activity via a CaMK-II-caspase-calpain-dependent mechanism. *Surgery* 2004;136:135-42.

Sally Gwin
Administrative Coordinator

Moin Fareed, Ph.D.

Original Articles (in press)

1. Wei W, Fareed M, Evenson A, Menconi M, Yang H, Petkova V, **Hasselgren PO**. Sepsis stimulates calpain activity in skeletal muscle by decreasing calpastatin activity but does not activate caspase-3. *Am J Physiol* 2004; in press.

2. Yang H, Menconi M, Wei W, Petkova V, **Hasselgren PO**. Dexamethasone upregulates the expression and activity of the nuclear cofactor p300 and its interaction with C/EBP beta in cultured myotubes. *J Cell Biochem* 2004; in press.

3. Yang H, Mammen J, Wei W, Menconi M, Evenson AR, Fareed M, Petkova V, **Hasselgren PO**. The expression and activity of C/EBP beta and delta are upregulated by dexamethasone in skeletal muscle. *J Cell Physiol* 2004; in press.

Reviews, Chapters, and Editorials (in press)

1. **Hasselgren PO**, Menconi M, Fareed M, Yang H, Wei W, Evenson A. Novel aspects on the regulation of muscle wasting in sepsis. *Int J Biochem Cell Biol* 2004; in press.

2. **Hasselgren PO**, Hubbard WH, Chaudry IH. Metabolic and inflammatory responses to trauma and infection. In: Baker RJ, Fischer JE, editors. Mastery of surgery. Philadelphia: Lippincott, Williams, and Wilkins. 2004; in press.

Abstracts

1. Evenson A, Fareed M, **Hasselgren PO**. Sepsis-induced muscle proteolysis is blocked by glycogen synthase kinase (GSK)-3 beta inhibitors. *J Am Coll Surg* 2004;199:S37-8.

2. Evenson AR, Menconi M, Mitchell JC, **Hasselgren PO**. Dexamethasone increases protein degradation in cultured myotubes through a calcium-calmodulin kinase II (CaMK II)-dependent mechanism. *J Surg Res* 2004;121:277-8.

3. Evenson AR, Mitchell JC, Menconi MJ, **Hasselgren PO**. Glycogen synthase kinase 3-beta (GSK3-beta) inhibitors decrease protein degradation in L6 myotubes. *J Surg Res* 2004;121:314-5.

Daniel B. Jones, M.D., F.A.C.S.
Section for Minimally Invasive Surgery
Center for Minimally Invasive Surgery (CMIS)
Teleconferencing, Simulation and Technical Skills Lab
Bariatric Program

I. Narrative Report

Our group integrates clinical activity and teaching into innovation and education research. We have focused on minimally invasive surgery, bariatric surgery, and technical skill acquisition. Bench-top work last year has led to technical innovations in instrumentation for laparoscopic adjustable banding, robotic colonoscopy, and fibrin glue repair of inguinal hernia repair. CMIS has trained medical students, residents, research fellows, clinical fellows and surgeons worldwide in advanced laparoscopic techniques.

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 educational programs as part of the Teleconferencing, Simulation and Technical Skills Lab. First year students observe live surgery telebroadcasts to student groups learning anatomy. During clerkships, students also interact with surgeons from the teleconference center in small groups. These unique learning approaches are being studied and compared to traditional pathways. The web link is www.bidmc.harvard.edu/mis.

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 only make the hernia operation less invasive but also potentially eliminate the need for incisions. The project is currently funded through the Center for the Integration of Medicine and Innovative Technology (CIMIT), a research consortium of Harvard hospitals and the MIT.

In collaboration with MGH Weight Loss Program, we have developed a rodent model to study the laparoscopic adjustable band compared to the gastric bypass. Studies evaluate central gut neuroendocrine changes after surgery, specifically ghrelin, POMC pathway, PYY 3-3. Bariatric efforts have also resulted in publication of evidence based best practices in Massachusetts, hospital clinical care pathways, and SAGES national consensus statement on the surgical treatment of morbid obesity. The web link is www.bidmc.harvard.edu/bariatric.

II. List of Current Employees

1. Leo Villegas, M.D.	Skills Lab Coordinator
2. Angi Walsh, RN	Nurse Educator
3. Deb Zoll	Administrator

Collaborators

1. Ben Schneider, M.D.	Section MIS, BIDMC
2. Vivian Sanchez, M.D.	Section MIS, BIDMC
3. Jonathan Critchlow, M.D.	Section MIS, BIDMC
4. Lee Kaplan, M.D.	Weight Loss Center, MGH
5. David Rattner, M.D.	Surgery, MGH
6. David Brooks, M.D.	Surgery, BWH
7. George Blackburn, M.D., Ph.D.	Surgery, BIDMC

III. 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
   Principal Investigator: Ashish Patel, M.D.
   Mentor: Daniel B. Jones, M.D.

2. "Educational Training Grant, CMIS"
   United States Surgical/ Tyco
   Principal Investigator: Daniel B. Jones, M.D.

3. "Task Performance Using head Mounted Display"
   Stryker Endoscopy
   Project Period: 07/2003-07/2005
   Principal Investigator: Shishir Maitel, M.D.
   Mentor: Daniel B. Jones, M.D.

IV. Applications Pending Review and Funding

1. Development of a rat model of adjustable gastric banding to accelerate the design of effective, minimally invasive therapies for human obesity
   Principal Investigator: Shishir Maitel, M.D.

2. Thirty-thirty: An Approach to Increasing Exercise in Patients Prior to Bariatric Surgery. Principal Investigator: Dan Jones

3. Developing a Virtual Lapband Trainer
   Principal Investigator: Dan Jones

4. Developing a Digital Stomach Model for Lapband Training
   Principal Investigator: Dan Jones

5. Physically Realistic Virtual Surgery
   Principal Investigator: Daniel Jones

V. Divisional Accomplishments in the Past Year

1. We have established the Teleconferencing, Simulation and Technical Skills Lab

as a major educational resource for the Harvard community. We plan to become the first accredited Regional Learning Center for the American College of Surgeons next year with expansion of a mock ICU and mock operating room for team training and validation of new simulators.

2. We have developed a laparoscopic adjustable band in rodents. This allows for comparison to gastric bypass procedure. Work by Dr. Shishir Maitel may lead to better understanding of weight loss and control of diabetes.

3. Development of a self correcting colonoscope may make the procedure safer and therefore more available as a screening tool. Dr Patel's work was recognized at MIT semifinal in 50K competition as best technological innovation in 2004.

Patents Pending

1. Safe nasogastric tube: Ashish Patel. M.D.
2. Laparoscopic adjustable band instrumentation : Daniel Jones, M.D.
3. Laparoscopic adjustable band for rodents: Shishir Maitel, M.D.

Individual Accomplishments

1. SAGES Board of Governors
2. James IV Travel Fellowship
3. SAT Foundation Trustee
4. Chair, SAGES TOP 14 Videos
5. SAGES Appropriateness Statement on Treatment of Morbid Obesity
6. Chair, SAGES Learning Center

VI. Report of Teaching

Undergraduate and Medical School Courses

1. Louis Rivera, a medical student at HMS, participated in summer research project assessing skills assessment among students with mentors Ben Schneider and Daniel Jones.

Graduate School and Graduate Medical Courses

Course Director

1. Center MIS Course Series with Lab

Oct. 30, 2004	MIS Nursing
Nov. 05, 2004	Inguinal Hernia Repair: Laparoscopic Advances
Dec. 10, 2004	Ventral Hernia Repair laparoscopic Advances

2. Center MIS Video Sessions, with the aim to promote exchange between BIDMC, MGH, BWH

7/05/04	Laparoscopic Hernia
8/02/04	Laparoscopic Splenectomy

Resident Trainees

Ashish Patel, M.D.	Resident Researcher
Shishir Maitel, M.D.	Resident Researcher

Clinical MIS Fellows

Vivian Sanchez, M.D.	MIS Fellow
Christopher Boyd, M.D.	MIS Fellow
Thomas McIntyre, M.D.	MIS Fellow

Invited Presentations (Local, National, and International)

1. Boston Surgical Society, Boston, MA "Surgical education and training: new paradigms for learning". Jan 5, 2004.

2. Brigham & Womens' Hospital, (Surgery Grand Rounds), Boston, MA. "Laparoscopic bariatric surgery: effective treatment for morbid obesity." January 7, 2004.

3. MIS Bariatrics for Nurses Center for Minimally Invasive Surgery, Boston, MA. "MIS Bariatrics for Nurses". January 10, 2004.

4. MIS Bariatrics for Nurses. Center for Minimally Invasive Surgery, Boston, MA. (Team Building) January 10, 2004.

5. Metrowest Medical Center, Framingham, MA. Secialty Grand Rounds. January 21, 2004.

6. BIDMC, Boston, MA "Obesity Surgery, New patient Information Program February 5, 2004.

7. University of Pittsburgh Fourth Annual Minimally Invasive Surgery Symposium, British Columbia, Canada, "Essential bariatric equipment" February 20, 2004.

8. Carl J. Shapiro Institute for Education and Research Seminar Series in Faculty Development, Boston, MA. February 27, 2004.

9. AORN 51st Congress, San Diego, CA "Minimally invasive bariatric surgery: pre-congress session." March 20, 2004.

10. Guglielmi C, Cedorchuk M, Harvey R, Jones DB, Reihle L, Tassone D, Villegas L, Association of Perioperative Registered Nurses, San Diego, CA. "Facilitating team development in advanced minimally invasive surgery" March 20, 2004.

Association of Perioperative Registered Nurses, San Diego, CA, March 20, 2004.

11. Patel A, Jones DB, Critchlow J. Choice of fundoplication technique during laparoscopic Heller myotomy. SAGES, Denver, CO, March 31, 2004.

12. Sanchez V, Schneider B, Kelly J, Jones DB. The LapBand: Massachusetts experience: SAGES, Denver, CO, March 31, 2004.

13. BIDMC, Boston, MA. “Laparoscopic adjustable band. New patient information at BIDMC”. April 7, 2004.

14. American College of Surgeons, Boston, MA, 32nd Annual Spring Meeting. “Laparoscopic gastric bypass for morbid obesity.” April 24, 2004.

15. IDMC, Center for MIS, Boston, MA “Laparoscopic versus open incisional hernia repair” May 1, 2004.

16. LapBand. Second Annual Lone Star Update on Minimally Invasive Surgery, San Antonio, TX May 8, 2004.

17. Second Annual Lone Star Update on Minimally Invasive Surgery, San Antonio, TX, “Surgical simulation: a new paradigm for learning” May 6, 2004.

18. The Society for Surgery of the Alimentary Tract “Laparoscopic band for obesity”. Meet the Professor Luncheon, 45th Annual Meeting, New Orleans, LA, May 18, 2004.

19. BIDMC, Boston, MA “Laparoscopic inguinal hernia repair: live telebroadcasts. International MIS Course” May 27, 2004.

20. Center for Medical Simulation, Cambridge, MA “Birds of a feather”. Simulation workshop. August 19, 2004.Harvard Club, Boston, MA. “Nuevas herramientas quirurgicas. International MIS Course”May 27, 2004.

21. International MIS Course, Boston, MA. “Inguinal hernia live telebroadcast.” May 27, 2004.

22. CIMIT, Boston, MA “New Surgical Tools and Methods of Training.” June 8, 2004.

23. BIDMC, Boston, MA “Obesity surgery: work up, procedure, and initial post op period.” PACU educational series. June 9, 2004.

24. American Society for Bariatric Surgery, San Diego, CA Moderator. “Devil is in the details” June 15, 2004.

25. American Society for Bariatric Surgery, San Diego, CA “Laparoscopic RYGB cadaver course” June 18, 2004.

26. BIDMC, Boston, MA “ Laparoscopic inguinal hernia repair: resident school”. August 23, 2004.

27. Cape Cod Hospital, Hyannis, MA. “Laparoscopic obesity surgery.” Sept 2, 2004.

28. SAGES.”Laparoscopic gastric bypass: technique” Advanced laparoscopic foregut and bariatric surgery workshop. September 10, 2004.

29. Museum of Science, Boston, MA “Simulation and virtual reality.” September 18, 2004.

30. Hospital Central Militar Aula Magna, Mexico City, Mexico. “Gastroplastia laparoscopica con banda gastrica adjustable . Curso Avanzado De Cirugia Endoscopica” September 20, 2004.

31. Hospital Central Militar Aula Magna, Mexico City, Mexico “Laparoscopic gastric bypass live telebroadcast. Avanzado De Cirugia Endoscopica” September 20, 2004.

32. Hospital Central Militar Aula Magna, Mexico City, Mexico “Bypas gastrico laparoscopico . Curso Avanzado De Cirugia Endoscopica.” September 20, 2004.

33. Hospital Central Militar Aula Magna, Mexico City, Mexico, “Adiestramiento para cirugia laparoscopica avanzada. Curso Avanzado De Cirugia Endoscopica.” September 20, 2004.

34. Museum of Science, Boston, MA. “Obesity surgery in America: a minimally invasive approach to a national epidemic.” September 26, 2004.

35. American College of Surgeons, (SAGES-ASBS Joint Symposium), New Orleans, LA, “Defining Weight Loss” October 12, 2004.

36. American College of Surgeons, (SAGES-ASBS Joint Symposium), New Orleans, LA, “Defining Weight Loss” October 12, 2004.

37. Advanced Laparoscopic Bariatric Surgery. Dallas, TX “The Role of the Lap Band”, October 22, 2004.

38. Advanced Laparoscopic Bariatric Surgery. Dallas, TX, “Entero-enterostomy, antecolic vs retrocolic limb passage” October 22, 2004.

39. Advanced Laparoscopic Bariatric Surgery. Dallas, TX “Bariatric surgery in the elderly and adolescent” October 23, 2004.

40. Pri-Med: Current Issues in Primary Care, Boston, MA "Surgical obesity: recent advances." October 31, 2004.

Abstracts Presented at Local, National, and International Meetings

1. Chang CG, Simms T, Adams-Huet B, Sakhaee K, **Jones DB**, Provost D, A comparison of the absorption of calcium citrate and calcium carbonate following Roux-en-Y gastric bypass. American Society for Bariatric Surgery, San Diego, CA, June 15, 2004.

2. Guglielmi CL, Canacari E, Austin A, Cedorchuk M, Harvey R, Hunter S, **Jones DB**, Reihle L, Tassone DH, Villegas L. Facilitating team development in advanced minimally invasive surgery. Annual Meeting AORN, San Diego, CA, March 21, 2004.

3. Kordorffer JR, Dunne JB, Tesfay ST, Brunner WC, **Jones DB**, Rege RV, Sierra R, Touchard CL, Scott DJ. Multicenter construct validity for Southwestern laparoscopic videotrainer stations. Association Surgical Education, Houston, Texas, April 2, 2004.

4. Maithel S, Stylopoulos N, Davis PJ, **Jones DB**, Rattner DW, Kaplan LM. Deficient leptin signaling does not prevent weight loss after Roux-en-Y gastric bypass. North American Association for the Study of Obesity 2004 Annual Meeting.

5. Sanchez VM*, Schneider BE, Shikora SA, Kelly J, Shaw P, **Jones DB**. " Laparoscopic adjustable gastric band: the Massachusetts experience. 50th Annual Meeting of the Massachusetts Chapter of the American College of Surgeons, Waltham, MA. * Dr. Sanchez won the Resident Award for this work.

6. Stylopoulos N, Maithel SK, **Jones DB**, Rattner D, Kaplan LM. "Increased energy expenditure accounts for a substantial portion of the weight loss after Roux-en-Y gastric bypass in rats". Presented at the annual meeting of the American Gastroenterological Association; New Orleans, LA. May 18, 2004.

7. Stylopoulos N, **Maithel S, Jones DB**, Rattner DW, Kaplan LM. Roux-en-Y gastric bypass is equally effective in genetic and diet induced obesity in rats. North American Association for the Study of obesity 2004 Annual Meeting.

8. Stylopoulos N, Maithel S, **Jones DB**, Rattner DW, Kaplan LM. Roux-en-Y gastric bypass in rats blunts responsiveness to the food environment. North American Association for the Study of obesity 2004 Annual Meeting.

VII. Plans for the Coming Academic Year

Educational Programs

1. I plan to remain Course Director for the Center MIS Course Series with Lab.

Jan	7-8, 2005	Gastric Bypass Laparoscopic Advances
Jan	20-21, 2005	Colorectal Surgery: Laparoscopic Advances
Feb	12, 2005	Bariatric Nursing
Mar	4-5, 2005	Obesity Surgery: Laparoscopic Advances

2. On July 7-9, 2005, we plan to hold the Patient Safety in Obesity Surgery course.

3. We plan to continue the Center MIS Video Sessions, as below:

9/13/05	Laparoscopic Cholecystectomy
10/04/05	Laparoscopic Ultrasound
11/01/05	Laparoscopic Appendectomy
12/06/5	Laparoscopic Nissen/ Hiatal Hernia
1/03/05	Laparoscopic CBDE
2/07/05	Laparoscopic Adjustable Band
3/07/05	Laparoscopic Gastric Bypass
4/04/05	Laparoscopic Colectomy
5/02/05	Laparoscopic Adrenalectomy
6/06/05	Laparoscopic Heller Myotomy

VIII. Bibliography (01/01/04-12/30/04)

Original Articles

1. **Jones DB**, DeMaria E, Provost DA, DeMaria E, Smith CD, Morgenstern L, Schirmer B. Optimal management of the morbidly obese patient: SAGES appropriateness conference statement. *Surg Endosc* 2004;18(7):1029-37.

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*;2004;14:60-66

3. Wilkiemeyer MB, Bieligk 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* 2004;18(5):852-7.

Original Articles (in press)

1. Hamza MA, Schneider BE, Recart A, White P, Ogunnaika B, Provost D, Villegas L, **Jones DB**. Role of heated and humidified intraperitoneal gases during Roux-en-Y laparoscopic surgery – effect on temperature, postoperative pain, and recovery times. *J Laparendosc Adv Surg Tech* 2004; in press.

2. Hoover SJ, Berry MP, Jackes L, Baykal A, **Jones DB**, Anthony T, Naftalis EZ, Peters G, Huth JF, Rege RV, Leitch AM. Ultrasound-guided breast biopsy curriculum for surgical residents. *Am J Surg* 2004; in press.

3. Kelly J, Tarnoff M, Shikora S, Thayer B, **Jones DB**, Forse RA, Fanelli R, Lautz D, Buckley F, Munshi I, Coe N. Best care recommendations for surgical care in WLS, *J Obes* 2004; in press.

4. Korndorffer JR, Clayton JL, Tesfay S, Brunner WC, Sierra R, Dunne JB, **Jones DB**, Rege RV, Touchard BS, Scott DJ. Multicenter construct validity for Southwestern laparoscopic video trainer station. *Am J Surg* 2004; in press.

5. Maithel SK, Villegas L, Stylopoulos N, Dawson S, **Jones DB**. Simulated laparoscopic performance using head-mounted display. *Am J Surg* 2004; in press

6. Maithel SK, Sierra R, Korndorfer J, Callery M, Neuman PF, Dawson S, **Jones DB**, Scott DJ. Construct and face validity comparison of three laparoscopic surgery simulation trainers: MIST-VR, Endotower, and CELTS. Results from the 2004 SAGES Learning Center, *Surg Endosc* 2004; in press.

7. Min Yoo, **L Villegas**, **Jones DB**. Basic ultrasound curriculum for medical students: validation of content and phantom. *J Laparoendosc Adv Surg Tech* 2004; in press.

8. Villegas L**, Jones DB**, Lindberg G, Chang C, Fleming J. Laparoscopic hepatojejunostomy via PTFE-covered stent successfully achieves internal drainage of common bile duct obstruction. *Ha ic* 2004; in press.

Reviews, Chapters, and Editorials

1. Carter SL, Critchlow J, **Jones DB**. Complications of laparoscopic surgery. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd Edition. New York: Marcel Dekker Inc.; 2004: p.87-94.

2. Desai KM, Soper NJ, **Jones DB**. Nissen fundoplication. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004: p.259-72.

3. Diaz S, Soper NJ, **Jones DB**. Suturing and knot tying. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd Edition. New York: Marcel Dekker, Inc.; 2004: p.51-68.

4. Hamilton EC, **Jones DB**. Cholecystectomy. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004. p.181-96.

5. Hamilton EC, **Jones DB.** Common bile duct stones. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004. p.197-206.

6. Maithel SK, **Jones DB**. Access and port placement. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004. p.35-46.

7. Schneider BE, **Jones DB**, Provost DA: Obesity surgery: laparoscopic Roux-en-Y and gastric band procedures. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004. p.553-68.

8. Schneider B, Sanchez V, **Jones DB**. How to implant the laparoscopic adjustable band for morbid obesity. *Contemporary Surgery* 2004; 60(6): 256-64.

9. Scott DJ, **Jones DB**. Skills training. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004, p.101-11.

10. Scott DJ, **Jones DB**. Inguinal hernias. In: Jones DB, Wu JS, Soper NJ, editors. Laparoscopic surgery: principles and procedures, 2nd edition. New York: Marcel Dekker, Inc.; 2004. p.303-16.

Reviews, Chapters, and Editorials (in press)

1. Jones SB, **Jones DB**. Preoperative evaluation of the healthy laparoscopic patient. In: Whelan RL, Fleshman J, editors. The SAGES manual of peri-operative management in minimally invasive surgery. New York: Springer-Verlag; 2004; in press.

2. Lee M, Provost D, **Jones DB**. Use of fibrin sealant in laparoscopic gastric bypass for morbid obesity. *J Obesity Surgery* 2004; in press.

3. Mun E, V Sanchez V, **Jones DB**. Postoperative assessment, documentation and follow-up. In: Schauer PR, editor. Laparoscopic obesity surgery. New York; Springer-Verlag, 2004; in press

4. Sanchez V, Provost D, DeMaria E, Blackburn G, **Jones DB**. Reoperative bariatric surgery, In: Callery MP (editor) Handbook of reoperative general surgery, 2004; in press.

5. Schneider BE, **Jones DB**. Transabdominal transgastric gastrojejunoscopy. In: Schauer PR, editor. Laparoscopic obesity surgery. New York; Springer-Verlag, 2004; in press.

6. Scott DJ, **Jones DB**. Virtual reality training and teaching tools. In: Eubanks S, Soper NJ (editors). Mastery of endoscopic andlLaparoscopic surgery. Baltimore: Lippincott, Williams, and Wilkins. 2004; in press.

7. Watson M, Watson M, **Jones DB**. Laparoscopic common bile duct exploration. In:Van Heerden J, Farley DR, editors. Operative techniques in general surgery. Philadelphia: W.B. Saunders. 2004; in press.

Books, Monographs, and Textbooks

1. **Jones DB**, Wu JS, Soper NJ. Laparoscopic Surgery: Principles and Procedures, 2nd Edition, Revised and Expanded. New York: Marcel Dekker, Inc; 2004.

Clinical Communications

1. Provost DA, **Jones DB**. Clinical predictors of leak: the author replies. *Surg Endosc* 2004; 18:560.

Educational materials

1. Kelly JJ, Buckley F, Coe N, Fanelli R, Forse RA, Hutter M, **Jones DB**, Lautz D, Munshi I, Shikora S, Tarnoff M, Thayer. Consensus guidelines for patient safety in weight loss surgery: a report from the Surgical Care Task Force to the Massachusetts Department of Public Health, July 2, 2004.

Nonprint materials

3. **Jones DB** (ed): SAGES Top 14 Videos, 2nd Edition, Cine-Med, 2004.

Abstracts

1. Maithel SK, Stylopoulos N, Rattner D, **Jones DB**, Kaplan L. Roux-en-Y gastric bypass in rats alters hypothalamic weight regulation through a decrease in circulating ghrelin levels. *Gastroenterology* 2004;126(4):A256.

2. Maithel S, Villegas L, **Jones DB**. Laparoscopic surgical performance using a head-mounted display. *Surg Endosc* 2004;18:A238

.

3. Stylopoulos N, Maithel SH, **Jones DB**, Rattner DW, Kaplan L. Increased energy expenditure accounts for a substantial portion of the weight loss after Roux-en-Y gastric bypass in rats. *Gastroenterology*. 2004;126(4):A90.

Edward C. Mun, M.D.

I. Narrative Report

Basic Research

The basic research effort in my laboratory is concerned with 1) the effects of metabolic stress in the form of hypoxia and ischemia on epithelial Cl^- secretory in native human intestinal mucosa, 2) involvement of purinergic signaling pathways in the secretory response, and 3) the modulatory role of basolateral K^+ channel activity on the regulation of ischemia-induced secretion. Additional projects involve regulation of the gene expression of adiponectin (insulin sensitizing) receptor (AdipoR1 and R2) in muscle and liver in obesity and diabetes.

Clinical Research

For clinical research, my group investigates the changes of glucose tolerance and insulin sensitivity following physical reduction of visceral fat mass by laparoscopic omentectomy. Diabetic obese patients with body mass index of 30-40 undergo omentectomy and their insulin resistance is evaluated by various parameters including serum insulin, glucose tolerance, peripheral vascular reactivity, profiles of various metabolic hormones and cytokines including adiponectin, leptin, PYY, GLP-1 and GIP.

II. List of Current Employees

1.	Jae Won Choe, M.D., Ph.D.	Research Fellow
2.	Kyrah Davis, B.A.	Research Assistant

III. List of Current Funding

1. "Intestinal Transport during Metabolic Stress"
   NIH/NIDDK K08 DK 02604
   Project period: 12/01/1998 – 9/1/2004
   Principal Investigator: Dr. Edward C. Mun

2. BIDMC Special Research Discretionary Fund

IV. Divisional Accomplishments

Research Accomplishments

1. Adiponectin receptor expression has been studied in mouse muscle tissue culture and shows a regulatory event by its own ligand, adiponectin hormone, and dexamethasone. No other metabolic hormones and cytokines appear to be affecting AdipoR1 or R2 gene expression significantly including IL-6, TNF-α. Adiponectin receptor (R1 and R2) expression in seems to correlate with the

degree of obesity and insulin resistance in human liver and muscle tissue samples.

2. Omentectomy surgery part of the IRB-approved Laparoscopic omentectomy project is completed. A total of 6 diabetic patients successfully underwent preoperative glucose tolerance and insulin sensitivity studies as well as omentectomy without complications. Longitudinal efficacy of this therapy on diabetes is being evaluated by follow-up glucose tolerance study. All serum pertinent metabolic markers including adiponectin, PYY, GLP-1, GIP along with insulin and glucose are being assayed for detailed hormonal data. Data analysis will be followed by a summary manuscript detailing the beneficial effects of the omentectomy procedure in diabetic patients.

Individual Accomplishments

1. Several invited lectures regarding obesity surgery and complications both at the BIDMC and at national meetings.

V. Report of Teaching

Undergraduate and Medical School Courses

1. Mentored a total of 3 students this year through the Core Clerkship in Surgery for third year HMS students. During a 2 week rotation on general surgery service, each student received didactic teaching sessions in the clinical office, during ward rounds, and in the operating room. Additionally, I participated in the Saturday lecture series and gave clinical lectures on “Gastrointestinal Bleeding”.

Graduate School and Graduate Medical Courses

1. As an attending surgeon on the general surgical service, Purple Surgery Team, 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 have moderated several teaching rounds and Chief’s rounds covering broad general surgical subjects including reflux disease surgery, bariatric surgery, small bowel obstruction, etc.

Invited Presentations (Local, National, and International)

1. “Procedural considerations in gastric bypass”
   Harvard CME course
   Beth Israel Deaconess Medical Center, Feb 2004

2. “Ante- vs. Retrocolic Roux Limb Passage in Gastric Bypass”
   Harvard CME course
   Beth Israel Deaconess Medical Center, Dec 2004

3. "Practical Approaches to the Treatment of Obesity"
   Harvard MED-CME
   Royal Sonesta Hotel, Cambridge, June, 2004

4. "Current Status of Bariatric Surgery in the US"
   The annual meeting of Korean Gastroenterology Association
   Seoul, Korea, Nov, 2004

5. "Overview of Laparascopic Banding Procedure"
   The annual meeting of International Federation of Surgery of Obesity
   Tokyo, Japan, Sep, 2004

VI. Plans for the Coming Academic Year

Staff Changes/Recruitments

No immediate plans for staff changes or recruitments.

Plans for Research

1. Continue collaborations with Dr. Christos Mantzoros and Mary Elizabeth Patti (Joslin), who function as advisors and co-investigators on gut hormone research. Bi-weekly meetings are on- going with these investigators. Publish original articles from the current data. Continue with presentations at the national scientific meetings. Broaden joint research endeavors with Joslin Diabetes Center in basic and clinical research.

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 (1/01/2004-12/31/2004)

Original Articles

1. Aldhahi W, **Mun E**, Goldfine AB. Portal and peripheral cortisol levels in obese humans. *Diabetologia* 2004; 47(5):833-6.

Reviews and Book Chapters

1. Blackburn GL, **Mun EC**. Hepatic impact of surgery for weight loss. *Semin Liver Dis* 2004; 24:371-9.

Sareh Parangi, M.D.

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 and thyroid cancer model. Projects involve use of a transgenic insulinoma model as well as orthotopic models to test novel antiangiogenic therapies. Animals are monitored by doppler ultrasound and magnetic resonance imaging during antiangiogenic therapy to look specifically at tumor vasculature. Gene therapy with antiangiogenic agents is also used to affect tumor progression

1. Angiogenesis and pancreatic tumor progression.
2. Use of antiangiogenic drugs in combination to treat tumors.
3. Antiangiogenic gene therapy.
4. Molecular effects of Thrombospondin on endothelial cells in vivo and in vitro
5. Development of an orthotopic model of thyroid cancer, and treatment with antiangiogenic agents.

II. List of Current Employees

1. Xue Feng Zhang, Ph.D.	Research Fellow
2. Shao-Jun Zhu, M.D.	Research Fellow
3. Eric Galardi	Research Assistant
4. Shabber Ladha	Pre-Med Student (Summer 2004)
5. Shireen Olumi	Undergrad Student (Summer 2004)

III. List of Current Funding

1. "Role of IGF-1 in Pancreatic Cancer"
   American Cancer Society
   Project Period: 2001-2004
   Co-Investigator: Sareh Parangi, M.D.

2. "Inhibition of Angiogenesis by Angiogenesis by Thrombospondin-1"
   NIH/NCI
   Project Period: 2002-2007
   Co-Investigator: Sareh Parangi, M.D.

3. "Antiangiogenic Therapy of Pancreatic Cancer"
   NIH/NCI 5K08CA088965-03
   Project Period: 8/7/02-07/31/07
   Principal Investigator: Sareh Parangi, M.D.

4. "Multivoxel MRs of Human Breast Cancers at 3T"
   National Institutes of Health
   Project Period: 2004-2007
   Co-investigator: Sareh Parangi, M.D.

5. "Antiangiogenic Therapy of Thyroid Cancer"
   American Thyroid Association, Thy Ca Award
   Principal Investigator: Sareh Parangi, M.D.

IV. Divisional Accomplishments in the Past Year

Research Accomplishments

1. Collaborated with cytolopathology on IRB approved study on fine needle aspiration of follicular thyroid lesions for molecular differentiation of follicular thyroid cancer from follicular adenoma.
2. Developed an orthotopic model of thyroid cancer in mice and got funding through the American Thyroid Association to study antiangiogenic therapy in this animal model.
3. Helped establish the use of a database for analysis of endocrine surgery patients at BIDMC.
4. Looked at the Role of PET/CT scanning in patients with thyroid nodules in the preoperative setting.

Individual Accomplishments

1. Submitted several abstracts and articles.
2. Received a grant from the American Thyroid Association for study of antiangiogenic agents in thyroid cancer.
3. Became an official certified instructor in ultrasound, certified by the American College of Surgeons National Ultrasound Faculty for teaching head and neck ultrasound to residents and faculty.
4. Became a member of the American Thyroid Association and a member of the Boston Surgical Society.

V. Report of Teaching

Abstracts Presented at Local, National, and International Meetings

1. Zhang XF,Galardi E, Duquette M, Lawler J , **Parangi S. "**Comparison of antiangiogenic therapy with thrombospondin type I repeats and gemcitabine in an orthotopic model of pancreatic cancer in SCID mice". Forum American College of Surgeons; New Orleans. October, 2004.

2. Bin R, Zhang XF, Galardi E, Perrozzi C, Duquette M, Lawler J, Khosravifar R, **Parangi S**. "Proapoptotic and survival signaling pathways plays a role in Thrombospondin type I repeat mediated apoptosis in human microvascular

endothelial cells". Forum American College of Surgeons; New Orleans. October, 2004.

VI. Plans for the Coming Academic Year

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

2. Submit Research papers.

3. Look at the role of fine needle aspiration under ultrasound guidance in patients with incidentally detected thyroid nodules under 8 mm, Write IRB Protocol for this

4. Initiate a multicenter collaboration with UCSF on molecular analysis of fine needle aspiration material obtained from thyroid nodules. Write IRB Protocol for this.

5. Improve the Endocrine Surgery Database.

6. Add additional personnel to my laboratory, possibly including a surgical resident.

VII. Bibliography (01/01/2004-12/31/2004)

Original Articles

1. Gremmels JM, Kruskal JB, **Parangi S,** Kane RA. Hemorrhagic cholecystitis simulating gallbladder carcinoma. *J Ultrasound Med* 2004; 23(7):993-5.

2. Mitchell J, **Parangi S.** Thyroid incidentalomas: A new epidemic. *Curr Surg* 2004; 61(6):545-51.

3. Stephan S, Datta K, Wang E, Li J, Brekken R.A., Parangi S, Philip E, Thorpe PE, Mukhopadhyay D. Effect of rapamycin alone and in combination with anti-angiogenesis therapy in an orthotopic model of human pancreatic cancer. *Clin Cancer Res* 2004;10 (20): 6993-7000.

Original Articles (in press)

1. Mitchell J, **Parangi S**. Angiogenesis in benign and malignant thyroid disease. *Thyroid* 2004; in press.

2. Mitchell J, **Parangi S**. The thyroid incidentaloma: an increasingly frequent consequence of radiologic imaging. *Sem Ultrasound CT MR* 2004; in press.

3. Ren B, Wang Y, Ndebele K, Chen F, Wang, Y, **Parangi S**. Multiple signaling is involved in endostatin-mediated apoptosis in ECV 304 endothelial cells. *Front Biosci* 2004; in press.

4. Zhang XF, Galardi E , Duquette M, Delic M, Lawler J , **Parangi S**. Anti-angiogneic treatment with thrombospondin-1 three type I repeats recombinant proteins in an orthotopic human pancreatic cancer model *Clin Caner Res* 2005; in press.

Nonprint materials

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

Nicholas E. Tawa Jr, M.D., Ph.D.

I. Narrative Report

Basic Research

In continuation of our past work, which focuses on the mechanisms by which dietary protein deficiency reduces muscle proteolysis, we have performed experiments demonstrating that pre-conditioning with a low protein diet prevents the rise in protein breakdown and loss of muscle size induced by catabolic stimuli, including denervation, fasting, or free radical exposure. In studies performed in conjunction with D. Cai and S. Sholeson of the Joslin Clinic, we demonstrated that in the muscles of transgenic mice, in which the NF-kB inflammatory cascade is constitutively activated, rates of protein turnover are almost twice as great as in normal muscle. This observation explains the atrophy which occurs in the transgenic muscles and it suggests an important role for the NF-kB signaling pathway in the regulation of muscle size. In unrelated experiments, we have shown that the amino acid leucine inhibits protein degradation in cultured muscle cells by activating the protein kinase mTor, thus suppressing the ATP-ubiquitin-proteasome dependent pathway for proteolysis. Leucine also blocks the induction of proteolysis by glucocorticoids in these cells, and we are presently defining the molecular mechanisms for this interaction.

Clinical Research

I am involved as a Principal Investigator and as a Co-Investigator in many clinical trials.

II. List of Current Employees

1. Jamie Mitchell, M.D.	Research Fellow Surgical Resident

III. List of Current Funding

1. The Beth Israel Deaconess Surgical Group Foundation, Boston, MA
2. Transkaryotic Therapies Inc., Cambridge, MA
3. Baxter Pharmaceutical Products Inc, New Providence, NJ

IV. Divisional Accomplishments in the Past Year

1. I was asked to give Medical Grand Rounds, Melrose-Wakefield Hospital, Melrose, MA.
2. I was asked to give Surgical Grand Rounds, Boston Children's Hospital, Boston, MA.
3. I attended the Dermatology Nurses Association Annual Meeting; Orlando, FL.

V. Report of Teaching

Undergraduate and Medical School Courses

1. Lectured on topics of trauma management, nutrition, and surgical oncology to HMS surgical clerkship students and to Residents in training.

2. Led weekly didactic nutrition conference for hospital dieticians, nurses, and related personnel.

Graduate School and Graduate Medical Courses

1. Teaching of Surgical Residents and Fellows by didactic rounds and clinics, preceptorships, and formal lectures.

CMR Courses

1. Instructor, Advanced Trauma Life Support Course, American College of Surgeons, Beth Israel Deaconess

Abstracts Presented at Local, National, and International Meetings

1. Mitchell, JC, Evenson, A, Hasselgren, PO, **Tawa, NE**. Leucine inhibits proteolysis by the mTor kinase signaling pathway in skeletal muscle. 38th Annual Meeting, Association for Academic Surgery, 2004.

2. Panka DJ, McDermott DF, **Tawa NE**, Atkins MB, Koon H, Ko YJ, Famoyin C, Mier JW. Sequential decitabine and dacarbazine in the treatment of melanoma. 12th SPORE Investigators Workshop, National Cancer Institute, Baltimore, 2004; p126

VI. Plans for the Coming Academic Year

Basic Research

1. Determining the basis for the suppression of muscle proteolysis which occurs in conditions of dietary protein deficiency and prolonged fasting. The role.of endocrine mechanisms, specifically the interaction between insulin signaling and thyroid and adrenal status, will be a specific focus for the coming period. Exploring the potential contribution of novel gut or adipocyte- derived hormones to the reduced muscle proteolysis is another goal.

2. Studying the mechanisms by which antecedent dietary protein deficiency prevents muscle atrophy caused by fasting, denervation, and oxygen free radicals.

3. Recent discoveries suggest that the signaling mechanisms for the activation of intracellular protein breakdown in skeletal muscle by oxygen free radicals might

involve pathways suggested to have a role in cellular responses to caloric restriction and aging. These signaling mechanisms (Sirt, HIF, FOXO) have attracted great interest. We will explore whether the suppression of protein breakdown by antecedent protein deficiency in these conditions involves intersection with such pathways.

Clinical Research

1. Role of sentinel lymph node mapping for predicting the natural history of invasive squamous cell carcinomas of the trunk and extremities.

2. Prognostic indicators for thin invasive melanomas.

3. Utility of magnetic particles for sentinel lymph node mapping.

VII. Bibliography (1/1/04-12/31/04)

Original Articles

1. Cai D, Frantz JD, **Tawa NE**, Melendez PA, Oh BC, Lidov HGW, Hasselgren PO, FronteraWR, Lee J, Glass DJ, Shoelson SE. IKKβ/NF-κB activation causes severe muscle wasting in mice. *Cell* 2004;119:285-98

Reviews, Chapters, and Editorials

1. Jagoe T, **Tawa NE,Jr**, Goldberg AL. Protein and amino acid metabolism in muscle. In: Engel AG, Franzini-Armstrong C, editors. Myology. Third edition. New York: McGraw-Hill, 2004; 535-64.

2. **Tawa NE Jr,** Maykel JA, Fischer JE. Metabolism in Surgical Patients. In: Townsend CM, editor. Sabiston Textbook of Surgery. 17th Edition. New York: WB Saunders, 2004. pp. 137-81

Reviews, Chapters, and Editorials (in press)

1. **Tawa NE, Jr**. Re-operative Surgery for Melanoma. In: Callery M, editor. Handbood of Reoperative General Surgery. Blackwell Scientific Publishing; 2004; in press.

NEUROSURGERY

Julian K. Wu, M.D., Chief

Division Members

Edwin G. Fischer, M.D.
Ihab John Ibrahim, M.D.
Adel M. Malek, M.D., Ph.D.
Efstathios (Steve) Papavassiliou, M.D.
Simcha J. Weller, M.D.

Adel M. Malek, M.D., Ph.D.
Molecular and Cellular Hemodynamics

I. Narrative Report

Our group is interested in the application of quantitative and molecular tools to elucidate the role of hemodynamic forces in cerebrovascular pathophysiological states, such as cerebral aneurysms and carotid and intracranial atherosclerosis. The laboratory's efforts are focused in integrating both basic and clinical research.

Basic Research

Computational Fluid Dynamic (CFD) Modeling of Aneurysms and Atherosclerosis

Using (CFD) techniques, we are estimating the hemodynamic conditions in and around cerebral aneurysms in an effort to predict their propensity to expand and rupture or stabilize. An additional application of this technique is the study of the effect of endovascular embolic devices such as endovascular coils on the alteration of intra-aneurysmal flow to predict long-term recanalization. The technique is also being used to evaluate the change in hemodynamics following cervical carotid stenting to help predict the risk of carotid restenosis.

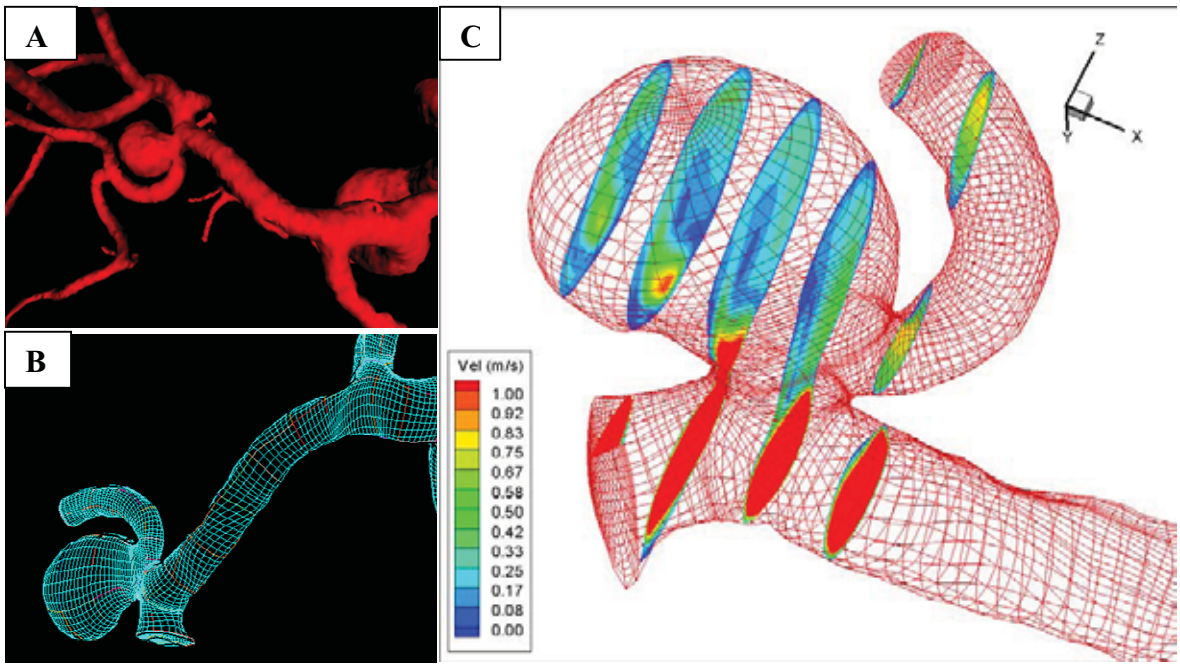


Figure 1. Analysis of hemodynamics at the inflow of an intracranial left middle cerebral artery (MCA) aneurysm using the technique developed in our laboratory. The 3D angiography dataset is segmented into a 3D spatial model (A). The space model is then processed to obtain a high-quality hexahedral mesh (B). The mesh is then used to perform the CFD simulation using boundary conditions to obtain the hemodynamic parameters such as the instantaneous blood flow velocity profile (C); note the high velocity gradient at the inflow zone of the aneurysm.

Mechanotransduction of Hemodynamic and Osmotic Forces in Endothelial Cells

We are studying the changes in structure and function of endothelial cells in response to fluid shear stress and osmotic forces. These are important in the understanding of the vessel wall response to hemodynamics in and around aneurysms and atherosclerotic lesions. We are also evaluating the structural and functional changes in response to osmotic mannitol therapy.

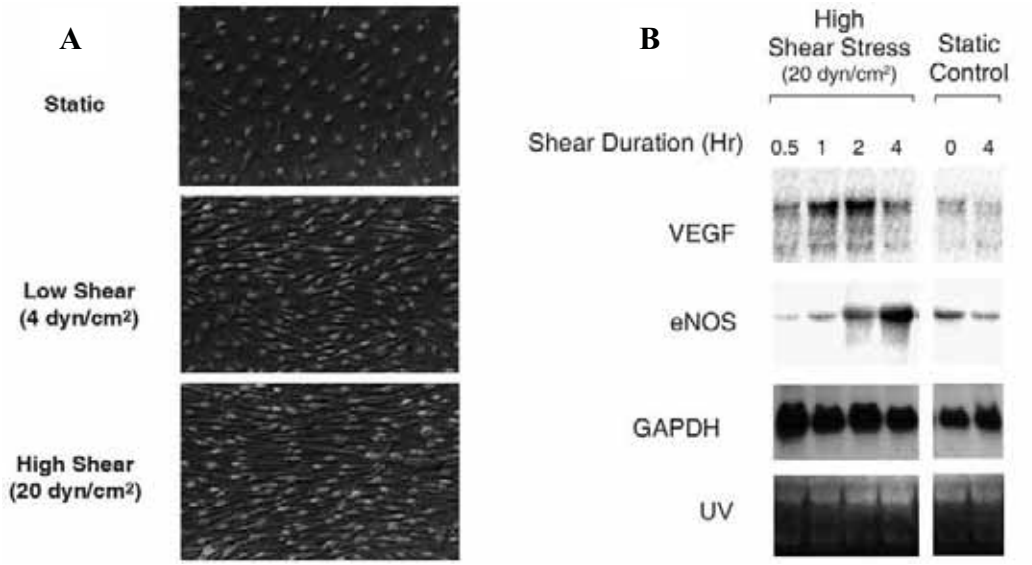


Figure 2. Morphological and functional response of endothelium to fluid flow. Bovine brain microvascular endothelial cells (BMEC) were exposed to no flow (A, top) or to hemodynamic fluid shear stress of venous (4 dyn/cm^2; A, middle) or arterial magnitude (20 dyn/cm^2; A, bottom) for 18 hours. Note the shear magnitude-dependent alignment and orientation with the direction of flow. Northern blot analysis demonstrates a time-dependent induction of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase mRNA.

Spatiotemporal Data Fusion/Information Extraction in Cerebral Angiography

In collaboration with engineers at Draper Laboratory, we are developing new techniques for data extraction from 2D digital subtraction angiograms and 3D datasets obtained during intracranial interventional procedures in order to help develop an enhanced-reality system for assisting the operator in detecting real-time changes in the cerebral vasculature during the treatment of cerebrovascular lesions.

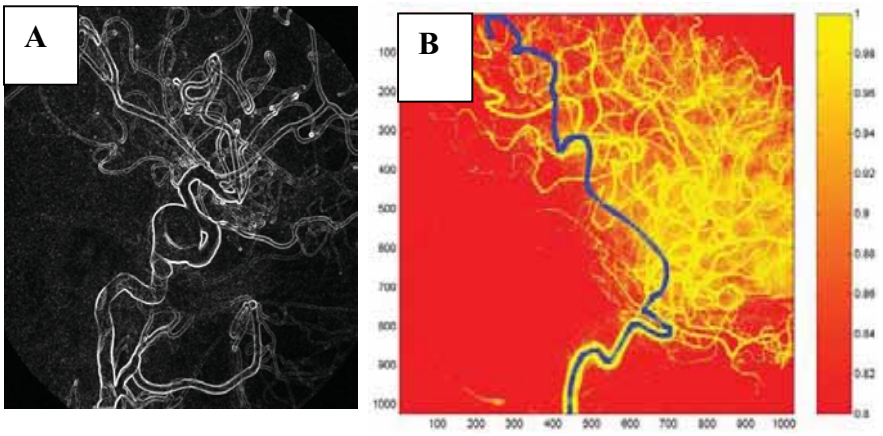


Figure 3: Quantitative analysis of the digital subtraction images obtained during cerebral angiography. Edge detection algorithm provides clear delineation of the blood vessels on a lateral projection angiogram of the intracranial internal carotid artery (A). Proprietary analysis tools enable the delineation of each branch of the internal carotid artery (blue tracing, B).

Clinical Research

Parent Vessel Response to Intracranial Aneurysm Stent-Coil Therapy

We are using high-resolution imaging techniques to evaluate the response of the parent vessel to the intracranial placement of flexible stents and adjunct endovascular coils in patients. We have demonstrated that stent-coil therapy is associated with a small degree of intimal hyperplasia even in the absence of any balloon angioplasty that may be injurious to the vascular wall.

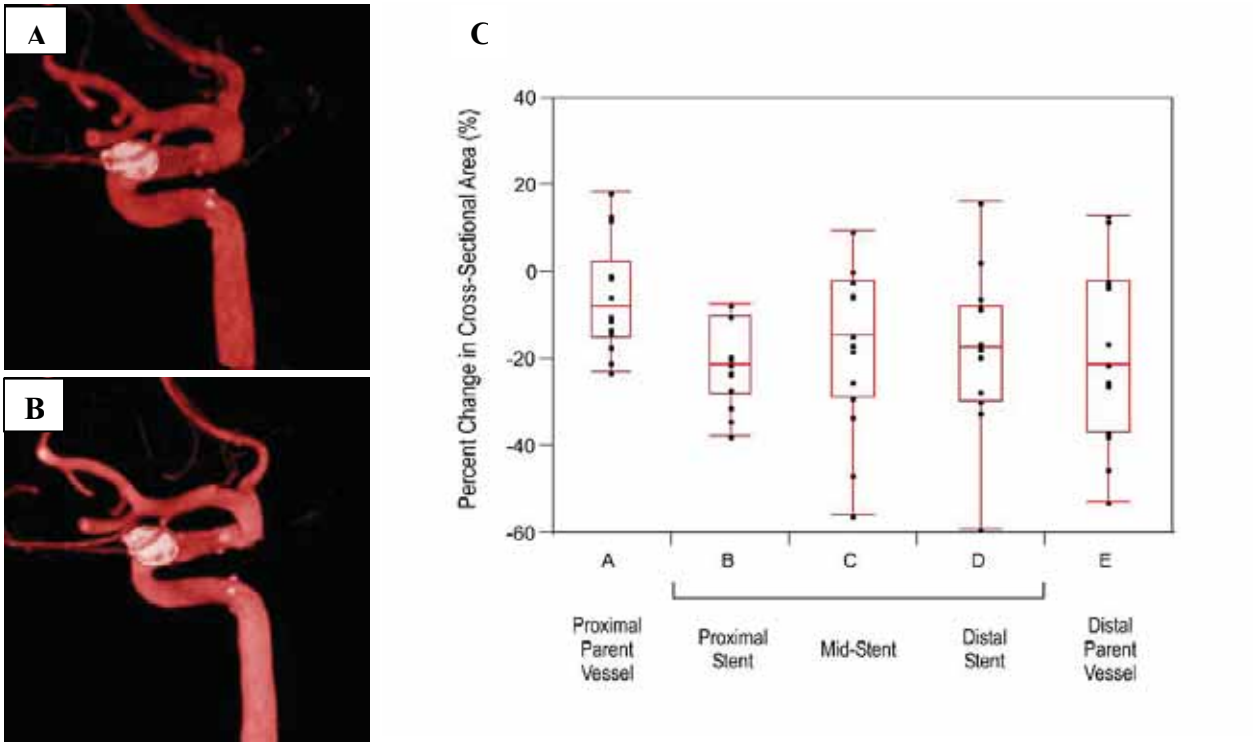


Figure 4. Stent-coil treatment of a intracranial ophthalmic carotid artery aneurysm shows the post-treatment (A) and follow-up (B) spatial model (coils appear in white; stent ends as small dots proximal and distal to lesion). Quantitative morphometric analysis of the size caliber before and after treatment at five separate points encompassing the parent vessel proximal and distal to stent (C). Points B-E show a statistically significant decrease in the cross-sectional area illustrating the remodeling process and intimal hyperplasia.

II. List of Current Employees

1. Edward Kim, M.S. — Research Assistant
2. Daniel Hoit, M.D. — Research Fellow/Resident in Neurosurgery

3. List of Current Funding

1. "Molecular Biology of Cerebral Aneurysm Development"
   BIDMC
   Project Period: 07/01/2003-06/30/2008
   Principal Investigator: Adel M. Malek, Ph.D.

2. "Endothelial Flow Response Characterization using Micromachined Channel MEMS Technology"
   Draper Laboratory
   Project Period: 01/01/2004-02/28/05
   Principal Investigator: Adel M. Malek, Ph.D.

IV. Divisional Accomplishments in the Past Year

Research Accomplishments

1. We have developed the workflow necessary for the study of hemodynamics in and around cervical and intracranial vascular lesions. This system extracts a high-quality hexahedral mesh from a rotational angiography volume dataset, and then uses CFD techniques to enable analysis of real patient data. Early findings point to the presence of a high shear stress gradients near the inflow zone of cerebral aneurysms.

2. In conjunction with the Alper lab in Molecular Medicine, we have uncovered a role for Rho in the endothelial cytoskeletal response to osmotic stress.

3. We have developed a partnership with Gridpro Inc. through the Technology Ventures Office (TVO) to develop an automatic mesh generation algorithm for high-throughput analysis of 3D aniography datasets.

4. In collaboration with scientists at Draper Lab, we have developed a new technique for detecting changes in the operative field using spatiotempotal analysis techniques.

5. Using high-resolution 3D-RA techniques, we uncovered a slight but significant degree of intimal hyperplasia in intracranial stent-coil therapy.

V. Report of Teaching

Abstracts presented at Local, National, and International Meetings

1. Hoit D, **Malek AM**. Morphometric high-resolution 3-D analysis of intracranial parent vessel remodeling induced by the Neuroform stent. Joint Section of the AANS/CNS/ASITN meeting; New Orleans, LA. February, 2005.

VI. Bibliography (1/1/04-12/31/04)

Original Articles (in press)

1. Hoit D, **Malek AM**. Parent vessel intimal hyperplasia in wide-necked aneurysms treated with a self-expanding intracranial stent. *Neurosurgery* 2004; in press.

Reviews, Chapters, and Editorials (in press)

1. Edlow J, **Malek AM**, Ogilvy CS. Aneurysmal subarachnoid hemorrhage. *Lancet* 2004; in press.

2. Hoit D, **Malek AM**. Fusion of 3-dimensional calcium rendering with rotational angiography to guide the treatment of a giant intracranial aneurysm. *Neurosurgery* 2004; in press.

Books, Monographs, and Textbooks (in press)

1. **Malek AM,** Schirmer CM. Stent angioplasty for the treatment of intracranial cerebrovascular disease. In: Proctor MR, Black PM, editors. Minimally invasive neurosurgery. New Jersey: Humana Press; 2004, in press.

Julian K. Wu, M.D.
Neurosurgery Brain Tumor Laboratory

I. Narrative Report

The Neurosurgery Brain Tumor Laboratory is designed to provide an integrated environment for clinicians, medical students, residents, 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 research that range from basic research to translational investigations associated with clinical trials. We have archived over 500 brain tumor specimens over the past 10 years and continue to maintain a brain tumor tissue bank. This year Dr. Wu has teamed up with Dr. Eric Wong of Neurology, co-director of the Brain Tumor Center, to study:

a. Mechanisms of systemic tumor metastasis to the brain.
b. Markers in the cerebrospinal fluid for diagnosis and prognostication.
c. Angiogenesis and tumor invasion of malignant gliomas.

II. List of Current Employees

1. Diana Lee	Research Assistant
2. Angela Tam	Research Assistant (Neurology)

III. List of Current Funding

Basic Research

1. Beth Israel Deaconess Medical Center, Department of Surgery.

Clinical Funding

1. Phase III edotecarin trial for recurrent glioblastoma multiforme (Pfizer/Pharmacia).
2. Type I interferon and acrboplatin for inhibition of Erb-B activity (Amgen).
3. Prinomastat with temozolomide for recurrent glioblastoma multiforme (Auguron Pharmaceuticals).
4. DepoCyt in patients with neoplastic meningitis (Skyepharma).
5. A pilot study of irinotecan, thalidomide, and doxycycline for recurrent malignant gliomas (Celgene).
6. DepoCyt and temozolomide for neoplastic meningitis from breast cancer (Enzon).

IV. Report of Teaching

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.

Abstracts Presented at Local, National and International Meetings

1. Appignani B, Hackney D, Wong E, Duhamel G, **Wu J**, Marquis R, Alsop D. Artertial Spin Labeling Perfusion Imaging for the Evaluation of Brain Tumors at 3 Tesla. International Society for Magnetic Resonance Imaging in Medicine, 2004.

2. Pinker S, Halgren E, Ulbert I, Dale A, Schomer D, **Wu JK**. Grammatical Processing in Broca's Area: Evidence from MRI and Intracranial Electrophysiology. Human Brain Mapping Conference, 2004.

3. Wong ET, Barron L, Bloom J, **Wu J**. Durable Responses from Immunochemotherapy with Rituximab and Temozolomide in Patients with Central Nervous System Lymphomas. Cancer Biotherapy & Radiopharmaceuticals. The Tenth Annual Conference on Cancer Therapy with Antibodies and Immunoconjugates, Princeton, NJ, 2004.

V. Plans for the Coming Academic Year

During the next academic year we plan to continue our research activities, teaching and training responsibilities and administrative duties as outlined in the first section.

VI. Bibliography (1/1/04-12/31/04)

Original Articles

1. Wong ET, Tishler R, Barron L, **Wu JK**. Immunotherapy with rituximab and temozolomide for central nervous system lymphomas. *Cancer* 2004; 101:139-45.

Reviews, Chapters, and Editorials

1. Perides G, **Wu JK**. Molecular markers of metastatic disease. In: Black P, Loeffler J, editors. Cancer of the nervous system. Baltimore: Lippincott, Williams & Wilkins; 2004. p. 849-54.

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.

Sumner A. Slavin, M.D.
Plastic Surgery Research Center

I. Narrative Report

Basic Research

One of our research projects is to restore lymphatic flow by promoting lymphangiogenesis through the use of specific growth factors incorporated into an alginate biodegradable hydrogel. The delivery rate in alginate gels can be predetermined and its local, rather than systemic administration, can be of great advantage. We have completed *in vitro* proliferation and migration studies using specific lymphatic endothelial cell growth factors, VEGF-C and angiopoietin-2. These two growth factors were previously incorporated into alginate gels. We are now conducting *in vivo* experiments using these biodegradable gels in a mouse tail lymphedema model.

Another research project in our group involves the use of laser capture microdissection to isolate lymphatic endothelial cells from human lymphedematous and normal adipose tissue samples, and to isolate mRNA and evaluate differential gene expression through Affymetrix gene-chip arrays. Genes over or under expressed will be analyzed and studied for their potential role in lymphoangiogenesis.

Clinical Research

Over the past year, Drs. Sumner Slavin and Loren Borud continue to develop a *Lymphedema Treatment Center.* The Lymphedema Program is starting to gain national recognition. Over 100 patients have already been seen and treated, and the program is attracting patients from throughout the United States and abroad. A second clinic day each month as been added to the schedule for consultations and follow-up, and a *Patient Handbook* has been developed for patients.

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.

A patient database has been established at the clinic. This clinical data is leading to research projects/papers by attending physicians and residents. Drs. Slavin and Borud are currently managing the preparation of manuscripts involving treatment of scrotal lymphedema, lipedema, lymphocele following thigh lift procedures, and treatment of lower extremity lymphedema using suction-assisted lipectomy. Several of these have already been submitted for publication and in abstract form to a number of regional, national, and international meetings.

II. List of Current Employees

1. Loren J. Borud, M.D.	Instructor in Surgery
2. Mauricio A. Contreras, M.D.	Instructor in Surgery
3. Bernard Lee, M.D.	Instructor in Surgery
4. Adam Tobias, M.D.	Instructor in Surgery
5. Joseph Upton, M.D.	Assoc Clin Professor of Surgery
6. Jennifer Forgione	Administrative Coordinator
7. 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: 07/01/2001-06/30/2005
   Principal Investigator: Mauricio A. Contreras, M.D.

2. "Program for Aesthetic and Reconstructive Breast Surgery"
   Peter Sharp Foundation
   Project Period: 2005-2007, with possibility of renewal
   Principal Investigator: Sumner A. Slavin, M.D.

IV. Applications Submitted and Pending Review/Funding

1. "Gene Expression in Secondary Lymphedema Due to Breast Cancer Treatment"
   American Cancer Society, ID No. 7789
   Submitted 3/31/2005
   Project Period: 07/01/05-06/30/2008
   Principal Investigator: Sumner A. Slavin, M.D.

V. Divisional Accomplishments over the Past Year

1. Through the efforts of Drs. Slavin, Tobias, and Broud, funding was secured to establish the *Peter Jay Sharp Foundation Program for Aesthetic and Reconstructive Breast Surgery*. The grant will aid in BIDMC's efforts to become a regional center for breast surgery and lymphedema treatment. Although centered at the BIDMC, the Harvard-wide fellowship, will allow fellows to participate in and conduct research on breast cases across the Harvard System: BIDMC, Brigham and Women's Hospital, Children's Hospital, Massachusetts General Hospital, and the Shriners Burns Hospital. July-August, 2005 is the target date for starting the program.

2. Dr. Slavin, with help from Geoffrey Brahmer, established the *Robert M. Goldwyn, M.D., Distinguished Visiting Lectureship* with Harvard Medical School. To fund the lectureship, more than 8000 letters of solicitation were

sent to Plastic Surgeons across the world in late November. To date, the fund has accrued $65,000 in donations.

3. The Lymphedema Treatment Program is gaining national recognition. Over 100 patients have already been seen and treated. A second clinical day has been added to the schedule each month. A *Lymphedema Handbook* has been developed for patients.

4. Our scientific collaboration on lymphedema 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.

5. 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. In this current year, Senate Bill 848 passed the Massachusetts State Senate.

Individual Accomplishments
Dr. Slavin

1. Dr. Slavin received the Jubilee Medal of the Swedish Medical Society. November, 2004.

Dr. Lee

1. Dr. Lee and Geoffrey Brahmer worked to gain approval for donation of a liposuction machine to the Museum of Science, Boston. The machine was used for a scientific display on obesity in October, 2004.

VI. Report of Teaching

Undergraduate and Medical School Courses

1. 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. Dr. Contreras continued to train surgical residents in the T-32 program to do micro-vascular techniques in animal models (mouse, rat, rabbit). This experience will be utilized for their research project.

2. Dr. Borud was an instructor in the BIDMC “Microsurgical Training Course,” July and August, 2004.

3. Surgical interns and plastic surgery residents were introduced to the special challenges and approaches in clinically treating patients with lymphedema. Residents are now involved in writing papers/abstracts for papers and presentations.

4. The BIDMC Division of Plastic Surgery had a "Splint and Cast Workshop". September, 2004.

Invited Presentations (Local, National, and International)
Dr. Slavin

1. Keynote Speaker: 1) "Rise and Fall of Immediate Breast Reconstruction in North America", 2) "Options for Bilateral Breast Reconstruction", 3) "Skin Sparing Mastectomy and Immediate Reconstruction with a Latissimus Dorsi Myocutaneous Flap", and 4) "Correcting Deformity Caused by Breast Conservation". All presentations were given at the Royal College of Surgeons in England for the Oncoplastic Breast Surgery Master Class Symposium; Isle of Jersey. June 2004.

2. Keynote Speaker: 1) "Challenges for the General Surgeon and the Plastic Surgeon in the Management of Breast Cancer", and 2) "Complications in Breast Aesthetic Surgery". Both presentations were given at the Joint Annual Meeting of the Swedish Medical Society and the Swedish Association of Plastic Surgeons; Gothenburg, Sweden. November. 2004.

3. Invited Speaker: "The Difficult Breast Augmentation". Institute of Reconstructive and Plastic Surgery, NYU School of Medicine, Cutting Edge Symposium V. November, 2004.

4. Invited Speaker: "Reconstruction with Free TRAM Flap". European Society of Reconstructive Breast Surgery, 5th Dusseldorfer Symposium; "Breast Cancer Treatment: A Multidisciplinary Challenge". June, 2004.

5. Invited Speaker: "Trends, Concepts, and Problems in Breast Reconstruction". Annual Meeting of the American Society of Plastic Surgeons; Philadelphia, PA. October, 2004.

6. Invited Speaker: "Management of the BRCA Positive Patient: Reconstructive Options". Annual Meeting of the American College of Surgeons, Philadelphia, PA. October, 2004.

7. Invited Speaker: "Preoperative and Postoperative Care of the Breast Cancer Patient.". National Meeting of Radiation Oncologists; Boston. October, 2004.

Dr. Borud

1. "Lymphedema Update". Harvard Plastic Surgery Grand Rounds. February, 2004.

2. "Difficult Wounds". BIDMC Department of Surgery, Grand Rounds. March, 2004.

3. "What's New in Lymphedema". Mt. Auburn Hospital, Surgery Grand Rounds. May, 2004.

4. "Lymphedema". Tufts New England Medical Center, Surgery Grand Rounds. October, 2004.

5. Invited Speaker: "Molecular Mechanisms in Lymphatic Disease". Inaugural Gordon Conference devoted to lymphatic disease: "Molecular Mechanisms in Lymphatic Function and Disease"; Ventura, California. March, 2004.

6. Invited Speaker: "Difficult Wounds: Parts I & II". BIDMC Division of Plastic Surgery. November-December, 2004.

Dr. Contreras

1. Invited Speaker: NE Lymphedema Support Group at the Lahey Clinic; Woburn, MA. May, 2004.

Dr. Lee

1. "Mandible Fractures". BIDMC Plastic Surgery Division Grand Rounds; March, 2004.

2. "Plastic Surgery and Obesity". Museum of Science; Boston. July, 2004.

Dr. Tobias

1. Invited Speaker: "DIEP Flaps". BIDMC PACU Nursing Rounds. March, 2004.

2. Invited Speaker: "Perforator Flaps". BIDMC Clinical Center Nursing Rounds. April, 2004.

3. Invited Speaker: "State of the Art Breast Reconstruction". St. Luke's Hospital Grand Rounds. May, 2004.

4. Invited Speaker: "Advances in Breast Reconstruction". BIDMC Plastic Surgery Division Rounds. May, 2004.

5. Invited Speaker: "Advances in Breast Reconstruction". Hospital of the University of Pennsylvania, Plastic Surgery Division Rounds. June, 2004.

Mr. Brahmer

1. Invited Speaker: "Images of the Body". Harvard Plastic Surgery Grand Rounds, Shriners Burns Hospital. March, 2004.

2. Testified before the Insurance Committee for Senate Bill 848, an act to mandate insurance coverage for lymphedema.

3. With Mary Beth Heffernan, Director of Government Relations, coordinated a campaign for passage of Bill 848 through the Massachusetts Senate. Although the bill did not pass the House of Representatives, this effort led to high-level educational meetings with HMO lobbists and with the Medical Directors of all HMO's in Massachusetts, which is planned for 1/25/2005.

Abstracts Presented at Local, National, and International Meetings

1. **Borud LJ**, Grunwaldt L, Janz BA, Mun E. Components separation combined with abdominal wall plication for repair of large abdominal wall hernias following bariatric surgery. BIDMC Research Day, October 8, 2004.

2. Janz BA, **Borud LJ**, **Slavin SA**. The evaluation of lower extremity edema and differentiating lipedema from lymphedema. BIDMC Research Day, October 8, 2004.

3. Halperin T, **Slavin SA**, Olumi AF, **Borud LJ**. Surgical management of scrotal lymphedema. BIDMC Research Day, October 8, 2004.

VII. Plans for the Coming Academic Year

Clinical Lymphedema Program

1. Drs. Slavin and Borud are currently managing the preparation of manuscripts involving treatment of scrotal lymphedema, lipedema, lymphocele following thigh lift procedures, and treatment of lower extremity lymphedema using suction-assisted lipectomy. Several of these have already been submitted in abstract form to a number of regional, national, and international meetings.

2. Dr. Borud is currently completing manuscripts and has submitted abstracts on a variety of clinical topics including hernia repair with components separation, panniculectomy following massive weight loss. He is currently writing book chapters on lip reconstruction and on the staging of body contouring procedures.

3. 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

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

1. Drs. Slavin and Contreras will re-submit to the American Cancer Association a Grant Application (March 1, 2005) entitled: “Gene Expression in Lymph-edematous Adipose Tissue”.

2. Dr. Contreras will submit an RFA NIH Grant application (February 1, 2005) entitled: “Peripheral Progenitor Endothelial Cells and Lymphoangiogenesis as a New Therapy for Secondary Lymphedema”.

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

4. Dr. Contreras continues to work on both basic science research projects. In vivo evaluation of Alginate gels with VEGF-C and Ang-2 in a mouse tail lymphedema model, as well as Laser Capture Microdissection for lymphatic endothelial cell in lymphedematous and normal adipose tissue.

Staff Changes/Recruitments

1. A PhD is needed for work in Gene Expression in Lymphedematous Adipose tissue research, as well as in other molecular and clinical aspects of the lymphatic system and lymphedema.

VIII. Bibliography (1/1/04-12/31/04)

Original Articles (in press)

1. Greene AK, **Borud L**, **Slavin SA**. Blood pressure monitoring and venepuncture in the lymphedematous extremity. *Plast Reconstr Surg* 2004; in press.

Books, Monographs, and Text Books

1. **Borud LJ**, **Upton J**. Applied embryology of the extremities. In: Argenta L et al, editors. Basic science for surgical specialists. Philadelphia: WB Saunders; 2004. pp. 223-30.

Books, Monographs, and Text Books (in press)

1. Patel J, **Borud LJ**, **Upton J**. Neuromas of the upper extremity. In: Warfield CA, Fausett HJ, editors. Manual of pain management, 2nd Edition. Philadelphia: Lippincott, Williams & Wilkins. 2004; in press.

Educational Material

1. **Forgione J**. Lymphedema patient information packet and handbook. BIDMC, 2004.

Nonprint Materials

1. **Contreras MA**. Videotape: Microvascular dissection of the mouse tail as a model for lymphedema. This videotape will be used for teaching surgical residents and NIH-T32 trainees.

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.
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 macro-circulation. During the last few years, I developed the Microcirculation Lab, which tests the micro-vasculature 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 mainly funded by grants from the NIH, American Diabetes Association, and the Juvenile Diabetes Research Foundation. In addition, we conduct investigator-initiated studies that are funded by the pharmaceutical industry.

I am interested in the relationship between functional changes in the vascular reactivity and structural changes of the skin. In collaboration with investigators from other labs, such as Jon A. Buras, M.D, Ph.D and Christiane Ferran, M.D., Ph.D., we are currently involved in the study of mechanisms, such as eNOS and RAGE and PARP activation, which are involved in endothelial dysfunction that is present in diabetic patients.

My laboratory is also collaborating with small biotech companies. This collaboration has resulted in funding from the NIH, either in the form of SBIR or SBTT grants. The main aim of these collaborations is to develop new techniques that can improve our diagnostic abilities or develop new therapeutic interventions that will treat long-term diabetic complications.

Dr. Veves in his office.

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.

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.

Finally, research in my lab, in collaboration with Roy Freeman, M.D., examines the natural history of the progression of peripheral neuropathy in diabetic patients.

II. List of Current Employees

1. Lalita Khaodhiar, M.D.	Instructor in Medicine
2. Thanh T Dinh, D.P.M.	Instructor in Surgery
3. Thomas Lyons, D.P.M.	Instructor in Surgery
4. Christina Lima	Research Coordinator
5. Lydia Longoria	Research Coordinator
6. Christina Marc	Research Coordinator

III. List of Current Funding

1. "Vascular and Metabolic Changes in the Diabetic Foot"
   National Institutes of Health, 5R01- HL075678-02
   Project period: 10/01/03-08/31/06
   Principal Investigator: Aristidis Veves, M.D.

2. "Natural History of Peripheral Diabetic Neuropathy"
   National Institutes of Health, 1R01-NS046710-01A2
   Project period: 1/1/05-1/31/09
   Principle Investigator: Aristidis Veves, M.D.

3. "Micro- and Macro-vascular Abnormalities and Diabetic Foot Ulceration"
   American Diabetes Association
   Project period: 2/01/03-1/31/06
   Principal Investigator: Aristidis Veves, M.D.

4. "Effect of Valsartan in Ventricular Function and Aortic Elasticity"
   Novartis Pharma, Inc.
   Project period: 09/01/02-08/31/05
   Principal Investigator: Aristidis Veves, M.D.

Subcontracts

1. "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: Csaba Szabo, M.D.
Principal Investigator on the BIDMC subcontract: Aristidis Veves, M.D.

2. "Imaging early markers of diabetic microvascular complications in peripheral tissue"
National Institutes of Health, RFA-DK-02-001
Project period: 10/01/02-09/30/05
Principal Investigator: George L. King, M.D.
Principal Investigator on the BIDMC subcontract: Aristidis Veves, M.D.

3. "Restoring diabetic tactile sense using mechanical noise".
National Institutes of Health
Period: 1/1/05 – 12/31/06.
Principle Investigator: Jason Harry, Ph.D.
Principal Investigator on the BIDMC subcontract: Aristidis Veves, M.D.

4. "Hyperspectral Imaging to assess, predict foot ulceration"
National Institutes of Health
Period: 1/1/05 – 1/1/06
Principle Investigator: Jenny Freeman, MD.
Principal Investigator on the BIDMC subcontract: Aristidis Veves, M.D.

IV. Narrative of Divisional Accomplishments over the Past Year

Research Accomplishments (new grants)

1. 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 continued the study that is funded by the three-year clinical research grant from the American Diabetes Association and the three-year NIH grant. The main aim is to study the relationship between vascular abnormalities and diabetic foot ulceration. Finally, I was awarded a 5-year NIH grant that will investigate the natural history of peripheral neuropathy. In addition, I am the PI for BIDMC in a SBIR (R44) NIH grant awarded to Jason Harry from Afferent Inc. and a SBTT (R41) NIH grant awarded to Jenny Freeman from HyperMed Inc.

Individual Accomplishments

1. As a member of the Medical Science Review Committee of the Juvenile Diabetes Research Foundation International, I participated in 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. Ad hoc member, NHLBI Mentored Patient Oriented Research Career Development Award Panel for K23, K24 and K25 applications and R13 Conference Grants

4. I continue (since 2000) to serve as an Associate Editor for the journal: Wounds: A Compendium of Clinical Research and Practice.

5. I was asked to act as a peer reviewer for the journals: Diabetes, Diabetologia, Diabetes Care Diabetic Medicine, Journal of Diabetes and its Complications, Circulation, and New England Journal of Medicine.

V. Report of Teaching

Educational Activities

1. I was involved in the training of podiatry residents. More specifically, I was responsible for teaching them about the principles of clinical research and supervised them when they wrote a research proposal. Finally, I helped the podiatry residents learn to review important papers that were published and that were relevant to diabetic foot problems.

2. Gautam Shrikhande, M.D. and Salvatore Scali, M.D., surgical residents who are doing research this academic year participated in two of our studies.

3. In collaboration with the Medical School of University of Rochester, we have established the Robert L. Caldwell Vascular Research Internship. Each year a first year medical student is assigned a summer internship in my lab. This year, Katherine Dudley spent two months in our unit.

Invited Presentations (Local, National, and International)

1. "Endothelial Dysfunction in Diabetes". 5th Boston Vascular Fellows Basic Science Seminar; Boston, MA. January 2004.

2. "Endothelial Function in the Microcirculation in Diabetes". Elli Lilly and Company; Indianapolis, IN. March 2004

3. "Clinical Research in Peripheral Arterial Disease". National Institutes of Health Grantees' Meeting; Bethesda, MD. March 2004.

4. "Roger Pecoraro Lecture", American Diabetes Association 64th Annual Scientific Sessions; Orlando, FL. June 2004.

5. "Microvascular Dysfunction in the Diabetic Foot: Is It Clinically Significant"? Louisiana Podiatric Medical Association; New Orleans, LA. October 2004.

6. "The Role of Microcirculation in Diabetic Foot Pathology". Harvard Medical School; Boston, MA. November 2004.

7. "Vascular Abnormalities in the Diabetic Foot". The University of Texas Health Science Center, Orthopedics Dept; San Antonio, TX. December 2004.

8. "Wound Healing: Science and Industry". St. Thomas, VI "Skin Microcirculation Abnormalities in Diabetes". December 2004.

Professional and Educational Leadership

2003- Series Editor, Contemporary Diabetes, Humana Press, Totowa, NJ

Awards and Honors

I was asked to deliver the Roger Pecoraro Lecture at the American Diabetes Association 64th Annual Scientific Sessions for my contribution to research in the field of diabetic foot problems.

VI. Plans for the Coming Academic Year

My main object this coming year is to continue studies that are funded by the ADA and NIH. In addition, I plan to start the three other studies that are funded by the NIH and I am the PI or the PI for the BIDMC. Finally, we plan to complete the other studies that were initiated the previous years and publish the results in prestigious journals.

VII. BIBLIOGRAPHY (01/01/04-12/31/04)

Original Articles

1. 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* 2004;53(2):222-7.

2. Economides PA, Caselli A, Tiani E, Khaodhiar L, Horton ES, **Veves A.** The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes. *Diabetes J Clin Endocrinol Metab* 2004;89(2):740-7.

3. Shetty GK, Economides PA, Horton ES, Mantzoros CS, **Veves A.** Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers and vascular reactivity in diabetic patients and subjects at risk for diabetes. *Diabetes Care* 2004;27(10):2450-7.

Original Articles (in press)

1. Economides PA, Khaodhiar L, Caselli A, Caballero AE, Keenan H, Bursell S, King GL, Johnstone MT, Horton ES, Veves A. The effect of vitamin E on the endothelial function of the micro- and macro-circulation and the left ventricular function of type 1 and 2 diabetic patients. *Diabetes* 2004; in press.

Reviews, Chapters, and Editorials

1. Dinh D, **Veves A**. Microcirculation in the diabetic foot: An update. *Int J Lower Extrem Wounds* 2004;3:60-1.

2. Dinh T, **Veves A**. The Diabetic Foot. In: DeFronzo RA, Ferrannini E, Keen H, Zimmet P, editors. International Textbook of Diabetes Mellitus, 3rd edition. Chichester, England: John Wiley & Sons; 2004. p. 1315-32.

Reviews, Chapters, and Editorials (in press)

1. Dinh T, **Veves A**. Microcirculation of the diabetic foot. *Curr Pharm Des* 2004; in press.

2. Hile C, **Veves A**. Microcirculation of the diabetic foot. In: Johnstone MT, Veves A, editors. Diabetes and Cardiovascular Disease, 2nd edition. Totowa: Humana Press. 2004; in press.

3. Khaodhiar L, **Veves A.** Therapeutic interventions to improve endothelial function in diabetes. In: Johnstone MT, Veves A, editors. Diabetes and Cardiovascular Disease, 2nd edition. Totowa: Humana Press. 2004; in press.

4. Skljarevski V, **Veves A**. Impact of diabetes on vasculature – focus on nervous system. *Curr Diabetes Rev* 2004; in press.

Dr. Veves and his research team
Drs. Lima, Longoria, Veves, Khaodhiar, and Dinh.

TRANSPLANTATION

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

Division Members

Fritz H. Bach, M.D.
Scott R. Johnson, M.D.
Seth J. Karp, M.D.
Khalid Khwaja, M.D.
Takashi Maki, M.D., Ph.D.
Anthony P. Monaco, M.D.
Leo E. Otterbein, Ph.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 recently received an honorary doctorate degree from the University of Vienna.

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 is participating in an NIH sponsored 5-year trial examining the role of transplantation in HIV+ patients and is one of the most active centers. A number of other clinical studies are ongoing.

The laboratory of Seth J. Karp, M.D. is examining the genes responsible for liver development and regeneration. So far his studies have identified approximately 20 genes, of which half are novel with no known function. A second project seeks to determine lineage commitments in the developing and regenerating liver that may suggest a strategy for recapitulating liver organogenesis in vitro. Finally, his laboratory is also examining similarities in the transcriptional profiles of the developing liver and liver tumors that may allow the development of genetic markers for tumor aggressiveness and molecular targets for therapy. Dr. Karp is the recipient of an NIH K08 award and an American College of Surgeons Faculty Development Award for his research studies.

The laboratory of Leo E. Otterbein, Ph.D. focuses on the gas molecule carbon monoxide and the potent therapeutic effects when used at low concentrations in models of shock, transplantation and vascular injury. This work stems from the study of the heme oxygenase-1, also a focus of the laboratory as this inducible enzyme, which has been labeled a protective gene generates CO as a product during the catalysis of heme. His research support is for the study of the mechanisms of action of CO including identifying novel targets of its action. He is particularly interested in cell signal transduction and has focused on the mitogen activated protein kinases (MAPK), PPARγ and hypoxia inducible factor (HIF1α) in particular this year. These genes, while not containing heme moieties, the otherwise presumed cellular target of CO, are critically involved in allowing CO to exert protective effects.

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 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., Ph.D.

I. Narrative Report

My group focuses on the effects of heme oxygenase-1 (HO-1) and two of the products of HO-1 degradation of heme in models of shock, transplantation and vascular injury. We are particularly interested in cell signal transduction and have focused on the mitogen activated protein kinases (MAPK) and other signaling molecules in particular this year.

We studied the effects of biliverdin/bilirubin in ischemia-reperfusion injury (IRI) in models of the small intestinal and liver transplantation as well as in intimal hyperplasia following balloon injury. Most have begun a study of the signaling events consequent to biliverdin administration in LPS stimulated macrophages. Biliverdin acted to ameliorate the undesirable consequences of decreased function and tissue injury in IRI likely based on its potent anti-inflammatory properties. Interestingly, biliverdin did not achieve these results in the same manner as carbon monoxide (CO), another agent we tested in the small bowel transplantation model even though both agents prevented bowel dysfunction and cell damage. Biliverdin suppressed the expression of the adhesion molecules and markedly reduced the infiltration of host leukocytes into the bowel, something that CO did not do. This is in concert with our findings that bilirubin suppressed adhesion molecules on cultured endothelial cells stimulated with TNF-α while CO did not.

The studies on the suppression of smooth muscle cell (SMC) proliferation following balloon injury provided further evidence that the beneficial effects of biliverdin/bilirubin are mediated by pathways different from the effects of CO. Both biliverdin/bilirubin and CO suppressed SMC proliferation *in vitro* and intimal hyperplasia *in vivo,* however, the signaling molecules that effected these changes were different for CO and biliverdin. Even though both molecules involved modulation of p38 MAPK, biliverdin suppressed p38 while CO stimulated p38. We hypothesize that this is due to the differential modulation of p38α and p38β by CO and biliverdin. As a part of the study with biliverdin and intimal hyperplasia, we studied the downstream signaling molecules involved in those effects. Interestingly, biliverdin modulated the phosphorylation of Rb leading to hyperphosphorylation of that molecule and consequent suppression of action of transcription factors such as YY1 that are needed for SMC proliferation. This again was different from the effects of CO.

We extensively studied the effects of expressing HO-1 in a model of tolerance induced by DST. The conclusions from that study showed that not only did induction of HO-1 increase the efficacy of DST stimulated tolerance, but blocking of HO-1 eliminated the tolerance-inducing effects of DST. This finding suggests that HO-1 may be a critical molecule that is needed for T regulatory mediated tolerance, something we are testing further. Also in that study, we confirmed the earlier findings of the previous years that HO-1 expression leads to antigen induced cell death (AICD). However, in this case we showed additionally that HO-1

expression did not lead to the death of T regulatory cells, although exact quantitation of those effects must still be accomplished.

II. List of Current Employees

1. Hideyasu Sakihama, M.D., Ph.D.	Instructor in Surgery
2. Hongjun Wang, Ph.D.	Instructor in Surgery
3. Soo Lee	Research Assistant
4. Barbara Wegiel	ExchangeStudent/Research Fellow
5. Eva Czismadia	Research Assistant
6. Julienne Carty	Administrative Assistant

III. List of Current Funding

1. "Xenotransplantation of Protected Porcine Islets"
   Riva Foundation/Harvard Medical School
   Project Period: 09/01/03 – 08/31/06
   Principal Investigator: Fritz H. Bach, M.D.

2. "CO Timing Studies in Rats"
   AGA Linde Healthcare
   Project Period: 09/01/03 – 12/31/05
   Principal Investigator: Fritz H. Bach, M.D.

3. "Vascular Access Graft (VAG) Proof of Concept Studies"
   AGA Linde Healthcare (Bach, Fritz H.)
   Project Period: 09/01/03 – 12/31/05
   Principal Investigator: Fritz H. Bach, M.D.

4. "Regulation of Endothelial Cell Apoptosis by HO-1 and CO"
   NIH 5R01HL 067040-04
   Project Period: 07/01/01-04/30/05
   Principal Investigator: Fritz H. Bach, M.D.

IV. Applications Pending Review and Funding

1. Heme oxygenase-1 and Chronic Rejection
   National Institutes of Health
   Project Period: 07/01/05 – 06/30/10
   Principal Investigator: Fritz H. Bach, M.D.

2. Heme oxygenase-1 in Diabetes and Rheumatoid Arthritis
   RIVA Foundation
   Project Period: 05/01/05 – 12/01/06
   Principal Investigator: Fritz H. Bach, M.D.

V. Divisional Accomplishments over the Past Year

Patents

1. I have continuing involvement in the litigation of several patent applications for the use of carbon monoxide as a therapeutic.

2. I have taken over the funding and execution of a patent on the use of biliverdin/bilirubin and other molecules of the HO-1 system (except CO).

V. Plans for the Coming Academic Year

Staff Changes/Recruitments

1. I will have another post-doctoral fellow joining me from Poland and a student from Vienna.

VI. Bibliography (1/1/04-12/31/04)

Original Articles

1. Akamatsu Y, Haga M, Tyagi S, Yamashita K, Graca-Souza AV, Ollinger R, Czismadia E, May GA, Ifedigbo E, Otterbein LE, **Bach FH**, Soares MP. Heme oxygenase-1-derived carbon monoxide protects hearts from transplant associated ischemia reperfusion injury. *FASEB J* 2004;18:771-2.

2. Fondevila C, Shen XD, Tsuchiyashi S, Yamashita K, Csizmadia E, Lassman C, Busuttil RW, Kupiec-Weglinski JW, **Bach FH**. Biliverdin therapy protects rat livers from ischemia and reperfusion injury. *Hepatology* 2004; 40(6):1333-41.

3. Lavitrano M, Smolenski RT, Musumeci A, Maccherini M, Slominska E, Di Florio E, Bracco A., Mancini A, Stassi G, Patti M, Giovannoni R, Froio A, Simeone F, Forni M, Bacci ML, D'Alise G, Cozzi E, Otterbein LE, Yacoub MH, **Bach FH**, Calise F. Carbon monoxide improves cardiac energetics and safeguards the heart during reperfusion after cardiopulmonary bypass in pigs. *FASEB J* 2004;18:1093-5.

4. Nakao A, Otterbein LE, Overhaus M, Sarady JK, Tsung A, Kimizuka K, Nalesnik MA, Kaizu T, Uchiyama T, Liu F, Murase N, Bauer AJ, **Bach FH**. Biliverdin protects the functional integrity of a transplanted syngeneic small bowel. *Gastroenterology* 2004;127:595-606.

5. Schillinger M, Exner M, Minar E, Mlekusch W, Mullner M, Mannhalter C, **Bach FH**, Wagner O. Heme oxygenase-1 genotype and restenosis after balloon angioplasty: a novel vascular protective factor. *J Am Coll Cardiol* 2004; 43(6):950-7.

6. Soares MP, Seldon MP, Gregoire IP, Vassilevskaia T, Berberat PO, Yu J, Tsui TY, **Bach FH**. Heme oxygenase-1 modulates the expression of adhesion molecules associated with endothelial cell activation. *J Immunol* 2004; 172(6):3553-63.

7. Yamashita K, McDaid J, Ollinger R, Tsui TY, Berberat PO, Usheva A, Csizmadia E, Smith RN, Soares MP, **Bach FH.** Biliverdin, a natural product of heme catabolism, induces tolerance to cardiac allografts. *FASEB J* 2004;6:765-7.

Original Articles (in press)

1. McDaid J, Yamashita K, Chora A, Ollinger R, Strom TB, Li XC, **Bach FH**, Soares MP. Heme oxygenase-1 modulates the allo-immune response by promoting activation-induced cell death of T cells. *FASEB J* 2004; in press.

2. Nakao A, Neto JS, Kanno S, Stolz DB, Kimizuka K, Liu F, **Bach FH,** Billiar TR, Choi AM, Otterbein LE, Murase N. Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin, and both. *Am J Transplant* 2004; in press.

3. Ollinger R, Bilban M, Eratl A, Froio A, McDaid J, Tyagi, S, Csizmadial E, Graca-Souza, AV, Liloia A, Soares, MP, Otterbein LE, Usheva A, Yamashita K, **Bach FH**. Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation. *Circulation* 2004; in press.

Reviews, Chapters, and Editorials

1. **Bach FH**. Looking back 25 years. *Trends Immunol* 2004;12:619-20.

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

I. Narrative Report

Basic Research

My current laboratory research is focused on understanding the mechanisms of antibody-mediated rejection in ABO incompatible allografts and the development of accommodation post-transplant. We are examining the ability of endothelial cells, the target of antibody-mediated rejection, to upregulate protective genes (genes that are anti-inflammatory, anti-apoptotic and anti-proliferative in some cases), including those encoding heme oxygenase-1 (HO-1), A20, Bcl-2, and Bcl-x_L. Expression of protective genes in the endothelial cells and smooth muscle cells protects these cells from undergoing activation that leads to inflammation and graft rejection. We hypothesize that treatment of the donor and recipient by inducing HO-1 or administering a product such as CO or biliverdin will protect the endothelial cells from antibodies and complement. We are testing our approach in a rodent model and will follow this with large animal models (pig and cynomolgus monkeys) in which ABO incompatible animals are tested. This work is being done in collaboration with Fritz Bach, M.D., and Leo Otterbein, Ph.D. in our division.

A second area of focus is the development of a non-human primate model of liver transplantation and the testing of novel tolerogenic immunosuppressive regimens. We are developing method for the successful transplantation of the liver in cynomolgus monkeys. We are planning to examine the ability of interleukin-2 and interleukin-15 fusion proteins and rapamycin (with or without donor specific transfusions) to induce a permanent state of tolerance as has been shown in a monkey islet cell transplant model. The mechanism is limitation of the early expansion of activated T cells, accentuation of their subsequent apoptotic clearance, amplifying their depletion by antibody dependent mechanisms, while preserving CD4+CD25+ T cell dependent immunoregulatory networks. The balance between cytopathic and regulatory T cells is thereby tipped toward regulatory cells. We believe this may be a potent and effective means of inducing tolerance in the non-human primate model of liver transplantation and will have clinical applicability. This work is being done in collaboration with Terry Strom, M.D., Maria Koulmanda, Ph.D., and Scott Johnson, M.D.

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 cortico-

steroid 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 co-investigators in an NIH/NIAID Clinical Trials in Organ Transplantation study of novel immunosuppressive protocols. 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; use of donors after cardiac death for kidney, liver, and pancreas transplantation; 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 post-transplant; induction post-liver transplant with anti-CD52 monoclonal antibody; use of FTY720, a novel new immunosuppressive drug, in kidney transplantation.

II. List of Current Funding

1. "Pilot study to determine the safety and efficacy of infusion of donor specific cytokine-mobilized peripheral blood bone marrow stem cells (PBSCs) into renal allograft recipients to induce donor specific hyporesponsiveness/ unresponsiveness evidenced by reduction in prednisone and other immunosuppressive maintenance drug requirements"
   SangStat Medical Corporation
   Project Period: 2000-2006
   Co-Investigator: Douglas W. Hanto, M.D.

1. "A one-year, multicenter partially blinded, double-dummy, randomized study to evaluate the efficacy and safety of FTY720 combined with reduced-dose or full-dose Neoral and corticosteroids versus mycophenolate mofetil (MMF, CellCept) combined with full-dose Neoral and corticosteroids in *de novo* adult renal transplant recipients"
   Novartis Pharmaceuticals Corporation
   Project Period: 2004-2005
   Co-Investigator: Douglas W. Hanto, M.D

2. "Delayed induction with Zenapax for successful steroid elimination"
   Roche Laboratories
   Project Period: 2004-2006
   Co-Investigator: Douglas W. Hanto, M.D.

3. "Open label, prospective, randomized controlled, multi-center study assessing fixed dose *vs* concentration controlled CellCept regimens for patients following a single organ renal transplantation in combination full dose and reduced dose calcineurin inhibitors"

Roche Laboratories
Project Period: 2004-2006
Co-Investigator: Douglas W. Hanto, M.D.

4. "OPTIMA: Optimizing Prograf therapy in maintenance allografts"
Fujisawa Healthcare
Project Period: 2004-2008
Co-Investigator: Douglas W. Hanto, M.D.

5. "Clinical Trials in Organ Transplantation"2004-2009
NIH/NIAID
Project Period: 2004-2009
Co-Investigator: Douglas W. Hanto, M.D.

6. "Solid organ transplantation in HIV: Multi-site study"
NIH/NIAID
Project Period: 2004-2009
Co-Investigator: Douglas W. Hanto, M.D.

III. Applications Submitted and Pending Review/Funding

1. "Randomized prospective trial of calcineurin based vs TOR (target of rapamycin) based immunosuppression in the absence of steroids after liver transplantation"
Novartis Pharmaceuticals Corporation
Project Period: 2005-2007
Co-Principal Investigator: Douglas W. Hanto, M.D.

2. "T32 Training Grant in Transplant Immunology"
NIH/NIAID
Project Period: 2005-2010
Co-Principal Investigator: Douglas W. Hanto, M.D.

IV. Report of Teaching

Invited Presentations (local, national and international)

1. Invited Speaker: "Malignancies and Transplantation, Before and After: What We Know and Don't Know." University of Minnesota Transplant Conference, Department of Surgery, Minneapolis, MN; February 18, 2004.

2. Invited Speaker: "Association of Immunosuppressive Regimens with Post-transplant Lymphoproliferative Disorder, Graft Survival and Patient Survival after Renal Transplantation". Roche Satellite Symposium, XX Annual Congress of the Transplantation Society; Vienna, Austria; September 6, 2004.

3. Invited Speaker: "Pursuit of a Peaceful Death in the Face of Technology: Euthanasia and Physician Assisted Suicide". Halsted Society 78th Annual Meeting, Palo Alto, CA; September 11, 2004.

Abstracts Presented at Local, National, and International Meetings

1. Kauffman HM, Cherikh WS, Cheng Y, **Hanto DW**, Kasiske BL, Kahan BD. TOR inhibitor maintenance immunosuppression is associated with a reduced incidence of post-transplant malignancies. XX International Congress of the Transplantation Society. Vienna, Austria, September 5-10, 2004, abstract #079.

V. Bibliography (01/01/04-12/31/04)

Original Articles

1. Brown RS, Rush SH, Rosen HR, Langnas AN, Klintmalm GB, **Hanto DW**, Punch JD. SRTR report on the state of transplantation. Liver and intestine transplantation. *Am J Transplant* 2004;4:81-92.
2. 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* 2004;187:274-9.
3. Paranjape C, Johnson SR, Khwaja K, Goldman H, Kruskal J, **Hanto DW**. Clinical characteristics, treatment, and outcome of pancreatic Schwannomas. *J Gastrointest Surg* 2004; 8(6):706-12.

Original Articles (in press)

1. **Hanto DW**, Fishbein TM, Pinson CW, Olthoff KM, Shiffman ML, Punch JD, Goodrich NP. Liver and intestine transplantation: summary analysis, 1994-2003. *Am J Transplant* 2004; in press.
2. Johnson SR, Khwaja K, Pavlakis M, Monaco AP, **Hanto DW**. Older living donors provide excellent quality kidneys: A single center experience. *Clin Transplant* 2004; in press.
3. Wray CJ, Lowy AM, Matthews JB, Park S, Choe KA, **Hanto DW**, James LE, Soldano DA, Ahmad SA. The significance and clinical factors associated with a sub-centimeter resection of colorectal metastases. *Annals Surg Oncol* 2004; in press.

Reviews, Chapters, and Editorials

1. Cherikh WS, Kauffman HM, Swinnen LJ, **Hanto DW**. Response: Type of induction immunosuppression and posttransplant lymphoproliferative disorder. *Transplantation* 2004;78:634.
2. **Hanto DW**. Reply to letter to the editor written by Daily OP and Kauffman HM. *Transplantation* 2004;77:1309-10.
3. **Hanto DW**. Association of type of induction with posttransplant

lymphoproliferative disorders. *Am J Transplant* 2004;4: 1552.

4. **Hanto DW**. Retransplantation after post-transplant lymphoproliferative diseases (PTLD): When is it safe? *Am J Transplant* 2004;17:1733-34.

Reviews, Chapters, and Editorials (in press)

1. Kauffman HM, Cherikh WS, McBride MA, Cheng YA, Delmonico FL, **Hanto DW**. Transplant recipients with a history of a malignancy: risk of recurrent and *de novo* cancers. *Transplant Rev* 2004; in press.

Books, Monographs and Textbooks (in press)

1. **Hanto DW**, Johnson SR. Liver transplantation. In: Baker RJ, Fischer JE, editors. Mastery of Surgery. Philadelphia: Lippincott, Williams and Wilkins. 2004; in press.
2. **Hanto DW**, Johnson SR, Khwaja K, Karp SJ. Transplantation of the liver and intestine. In: Norton JA, Bollinger RR, Chang AE, Lowry SF, Mulvihill SJ, Pass HI, Thompson RW, editors. Essential Practice of Surgery. Second Edition. New York: Springer-Verlag Inc. 2004; in press.

Clinical Communications

1. Byrnes V, Cardenas A, Afdhal N, **Hanto D**. Symptomatic focal nodular hyperplasia during pregnancy: a case report. *Ann Hepatol* 2004;3:35-37.

Clinical Communications (in press)

1. Lima MA, **Hanto DW**, Curry MP, Wong MT, Dang X, Koralnik IJ. Atypical radiological presentation of progressive multifocal leukoencephalopathy following liver transplantation. *J NeuroVirology* 2004; in press.

Abstracts

1. Alexopoulos S, **Hanto D**, Strom T, Zheng X. Tolerance induction using IL-21 antagonizing fusion protein. *Am J Transplant* 2004;4 Suppl 8:186.
2. Alexopoulos S, Sanchez-Fueyo A, **Hanto D**, Zheng X, Strom TB. Regulatory T-cell proliferation and gene expression in response to alloantigen stimulation. *Am J Transplant* 2004;4 Suppl 8:263.
3. Kaufmann HM, Cheng Y, Cherikh WS, McBride MA, **Hanto DW**, Delmonico FL. Recipient history of cancer is independently associated with increased post-transplant *de novo* malignancies and decreased survival. *Am J Transplant* 2004;4 Suppl 8:205.
4. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance of immunosuppression with TOR inhibitors is associated with a reduced incidence of *de novo* malignancies. *Am J Transplant* 2004;4 Suppl 8:297.

Seth J. Karp, M.D.

1. Narrative Report

Basic Research

Basic research in the laboratory is concerned with the molecular basis for liver development and regeneration. Ultimately we would like to apply this knowledge to produce liver tissue substitutes, enhance liver regeneration, and understand liver cancer.

Multiple projects are ongoing in the laboratory. The first involves a screen for genes that are important for liver development and regeneration. Identification of genes upregulated during liver regeneration is possible using a variety of technologies. Similarly, identification of genes expressed during liver development is fairly straightforward. The large number of genes involved in both processes makes it difficult to discover which genes are important and potentially clinically useful. We are employing a strategy based on the hypothesis that genes common to both processes will be particularly important for control of liver growth. By looking at these processes together we have identified approximately 20 genes we consider to be high yield. Approximately half of the genes are novel, with no known function. These are currently being analyzed using real time PCR, in situ hybridization, gene-trap knockouts, RNA inhibition, and transgenic overexpression.

The second project seeks to determine lineage commitments in the developing and regenerating liver. We believe understanding which cells give rise to which cells *in vivo* will suggest a strategy for recapitulating liver organogenesis *in vitro*. Using transgenic mice that express an inducible recombinase in the liver and a target construct that fluoresces when the recombinase is activated, we are able to heritably mark liver cells in a temporally-restricted manner. Following the cells and their progeny is then possible after various experimental manipulations.

The final project searches for similarities in the transcriptional profiles of the developing liver and liver tumors. We hypothesize that the genetic programs involved in determining tumor aggressiveness are similar to different developmental stages of the liver. Using microarray technology we hope to develop genetic markers for tumor aggressiveness and molecular targets for therapy

Clinical Research

Clinical research examines which donor factors portend poor survival for the renal allograft. We determined that donor kidneys that suffer acute tubular necrosis around the time of harvest can be safely transplanted if there are no other significant co-morbidities. We also characterized the outcomes when these kidneys have moderate pathological changes on biopsy.

II. List of Current Employees

1. Nicole Nesbitt — Research Assistant

III. List of Current Funding

1. "Activin Signaling in Liver Size and Regeneration"
   National Institutes of Health, 7K08DK064 648-02
   Project period: 07/01/2003-08/30/2008
   Principal Investigator: Seth J. Karp, M.D.

2. "Molecular Analysis of Liver Development and Regeneration"
   American College of Surgeons Faculty Development Award
   Project Period 07/01/03-07/01/04
   Principal Investigator: Seth J. Karp, M.D.

II. Applications Submitted and Pending Review/Funding

1. "Lineage Analysis in the Developing and Regenerating Liver"
   American Society of Transplant Surgeons (ASTS)

III. Narrative of Divisional Accomplishments over the Past Year

Research accomplishments

Establishing the laboratory demanded the majority of my time over the last few months. We are beginning to generate data and identified approximately 20 genes that may play a role in liver development and regeneration. Functional studies of these genes are underway.

Individual accomplishments

I was assignment to the Vanguard Committee of the ASTS Organizer for the ASTS basic science research course for 2006.

VI. Report of Teaching

Graduate School and graduate medical courses:
Operative and ward teaching of fellow and residents

VII. Plans for the Coming Academic Year

Staff changes/Recruitments
Karen Ho, a surgical resident from the Brigham and Women's Hospital will be joining the lab.

VIII. Bibliography (01/01/04-12/31/04)

Original articles

1. **Karp SJ**, Hawxby A, Burdick J. Axillo-renal bypass graft: a novel approach for dialysis access. *J Vasc Surg* 2004; 40:379-80.

Anthony P. Monaco, M.D.
Takashi Maki, M.D., Ph.D.
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 FTY720 in preventing and curing autoimmune diabetes in NOD mice, a mouse model of type 1 diabetes. We 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.	Keisuke Minamimura, M.D.	Research Fellow
2.	Tetsuo Kodaka, M.D.	Research Fellow
3.	Rita Gottschalk	Research Assistant

III. List of Current Funding

1. "Induction of Tolerance to Allografts"
NIH 5R01AI01 4551-26
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, 5R01DK060721-04
Project period: 12/01/01 - 11/30/05
Principal Investigator: Takashi Maki, M.D., Ph.D.

3. "Induction of Allograft Tolerance in non-human Primates" (RFA, Non-human Primate Immune Tolerance Cooperative Study Group) 5401AI051694-03
Project period: 09/15/02 - 06/30/07
Principal Investigator: Anthony P. Monaco, M.D.
Co-Principal Investigator: Takashi Maki, M.D., Ph.D.

4. "Prevention and Reversal of Autoimmune Diabetes by FTY720"
   Novartis Pharma
   Project period: 01/01/03 - 12/31/05
   Principal Investigator: Takashi Maki, M.D., Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "Induction of Unresponsiveness to Allografts"
   NIH 2 RO1 AI14551
   Project period: 07/01/05 - 06/30/09
   Principal Investigator: Anthony P. Monaco, M.D.

V. Divisional Accomplishments over the Past Year

Research Accomplishments

1. Oral Presentation at the American Transplant Congress, Boston, MA, May 17, 2004. **T. Maki**, N. Ogawa, J.F. List, J.F. Habener. "Transient short course of polyclonal anti-T cell antibody for cure of full blown diabetes".

2. Oral Presentation at the XX International Congress of the Transplantation Society, Vienna, September 5-10, 2004. **T. Maki**, K. Minamimura. "$CD4^{+}CD25^{+}$ T cells that survive after T cell depletion by polyclonal anti-T cell antibody (ALS) are potent inhibitor of alloresponses".

3. Oral Presentation at the XX Internationl Congress of The Transplantation Society, Vienna, September 5-10, 2004**. T. Maki**, R. Gottschalk, N. Ogawa, **A.P. Monaco**."Continuous administration of FTY720 starting at any stages of insulitis prevents subsequent development of autoimmune diabetes in NOD mice".

4. Poster Presentation at the XX Internationl Congress of The Transplantation Society, Vienna, September 5-10, 2004. K. Minamimura, H. Yagita, Xian C. Li, T. **Maki**. "Emergence of CD4+CD44hiOX40+ and CD8+CD44hiCD122+ memory type T cells after T cell abrogation by polyclonal anti-T cell antibody (ALS)".

5. Poster Presentation at the XX International Congress of the Transplantation Society, Vienna, September 5-10, 2004. A. Kanamoto, **A.P. Monaco, T**. **Maki**. "Chimerism plays an active role in transplantation tolerance induced by ALS, rapamycin and donor bone marrow infusion".

6. Poster presentation at BIDMC Research Day, October 8, 2004. **T. Maki**, R. Gottschalk, N. Ogawa, **A.P. Monaco**."Prevention and Cure of Autoimmune Diabetes in NOD mice by continuous administration of FTY720".

7. Poster presentation at BIDMC Research Day, October 8, 2004. K. Minamimura, **T. Maki**. "$CD4^{+}CD25^{+}$ T cells that survive after T cell Abrogation by Polyclonal anti-T Cell Antibody (ALS) are potent inhibitor of Alloresponses".

VI. Report of Teaching

1. Pathology Department Laboratory Medicine Lecture Series, February 16, 2004Takashi Maki, M.D., Ph.D. "HLA".

2. Invited presentations local, national and international. Takashi Maki, M.D., Ph.D. "Induction of Transplantation Tolerance: Role of Chimerism" Mitsui Surgical Lecture, Mitsui Memorial Hospital, Tokyo, Japan, April 19, 2004.

3. Takashi Maki, M.D., Ph.D. "Transplantation tolerance: Role of Chimerism and Immunosuppression by Antilymphocyte Serum" Tohoku University School of Medicine, Department of Surgery Special Lecture, Sendai, Japan, April 26, 2004.

4. Takashi Maki, M.D., Ph.D. "Treatment of Autoimmune Type 1 Diabetes with Polyclonal anti-T Cell Antibody: Experimental Study" Fukui Medical School, Department of Surgery, Fukui, April 27, 2004.

5. Plenary Presentation at Beth Israel Deaconess Medical Center Research Day, October 8, 2004 Takashi Maki, M.D., Ph.D. "Induction of Tolerance by mixed Chimerism".

6. Transplant Immunology Seminar December 21, 2004: Takashi Maki, M.D., Ph.D., "Tolerance Induction with T cell Depletion and Donor Bone Marrow Infusion"

VII. Plans for the Coming Academic Year

Plans for Research (new grants/programs)

1. Program Project Grant (PI, Terry B. Strom) (Resubmission)
   Project 1. Barriers to Allograft Tolerance with lymphodepletion (PI: T. Maki)

2. Research Grant
   "Treatment of overtly diabetic NOD mice" (PI: T. Maki)
   NIH competitive renewal.

VIII. Bibliography (1/1/2004-12/31/2004)

Original Articles

1. Kanamoto A, **Monaco AP**, **Maki T**. Active role of chimerism in transplantation tolerance induced by ALS, rapamycin, and bone marrow cell infusion. *Transplantation* 2004; 78: 825-30.

2. Kanamoto A, **Maki** T. Chimeric donor cells play an active role in both induction and maintenance phases of transplantation tolerance induced by mixed chimerism. *J Immunol* 2004, 172: 1444-48.

3. Ogawa N, Jim List, Joel Habener, **Maki T**. Cure of overt type 1 diabetes in NOD mice by transient treatment with antilymphocyte serum and exendin-4. *Diabetes* 2004, 53: 1700-05.

Original Articles (in press)

1. **Maki T**, Gottschalk R, Ogawa N, **Monaco AP**. Prevention and cure of autoimmune diabetes in NOD mice by continuous administration of FTY720. *Transplantation* 2004; in press.

Reviews, Chapters and Editorials

1. Morris PJ, **Monaco AP**. Organ donation: altruism or self interest? *Transplantation* 2004;77(1):149-50.

2. Morris PJ, **Monaco AP**. Editorial Comment: regulatory T cells finally get the attention they deserve. *Transplantation* 2004;77 Suppl 1: S2-3.

3. Morris PJ, **Monaco AP**. A meta-analysis from the Cochrane Library reviewing interleukin 2 receptor antagonists in renal transplantation. *Transplantation* 2004;77(2):165.

4. Morris, PJ, **Monaco AP**. Ethical issues and xenotransplantation. *Transplantation* 2004;78:1.

Leo E. Otterbein, Ph.D.

II. Narrative Report

My group focuses on the gas molecule carbon monoxide (CO) and the potent therapeutic effects of CO when it is used at low concentrations in models of shock, transplantation and vascular injury. This work stems from the study of heme oxygenase-1, als.o a focus of the laboratory as this inducible enzyme, which has been labeled a protective gene generates CO as a product during the catalysis of heme. My research focus is to study of the mechanisms of action of CO including identifying novel targets of its action. We are particularly interested in cell signal transduction and have focused this year on mitogen activated protein kinases (MAPK), PPARγ, and hypoxia inducible factor (HIF1α). These genes, while not containing heme moieties, the otherwise presumed cellular target of CO, are critically involved in allowing CO to exert protective effects.

In studies this year, we employed genomics and microarray analyses to identify novel targets of CO in macrophages. As observed in **Figure 1**, we performed kinetic experiments (**Fig. 1*A***) to evaluate the early events of gene expression in response to CO in the presence and absence of endotoxin. The genes are categorized as shown (**Fig. 1*B,C***). Detailed bioinformatics revealed the transcription factor early growth response gene-1 (egr-1) as being inhibited by CO in response to LPS. In other studies, we showed inhibition of egr-1 by CO in the lung (**Figure 2**). Further dissection of this gene revealed that PPARγ is induced during the pretreatment period and if this inhibited by either genetic (siRNA) or via selective chemical inhibition, the protective effects of CO in the lung are lost. Exposure of mice to LPS (**Fig. 2*B***) results in an increase in inflammation and tissue damage as evidenced by the increased myeloperoxidase (MPO) activity (a marker of neutrophil presence) as well as malondialdehyde (MDA) (a marker of lipid peroxidation). The increases are ameliorated by CO and moreover the CO effect is lost in the presence of the selective inhibitor of PPARg (GW9662). Data not shown goes on to demonstrate that it the induction of PPARγ in macrophages involves the mitochondria. As PPARγ itself has no heme molecule, the cytochrome oxidases

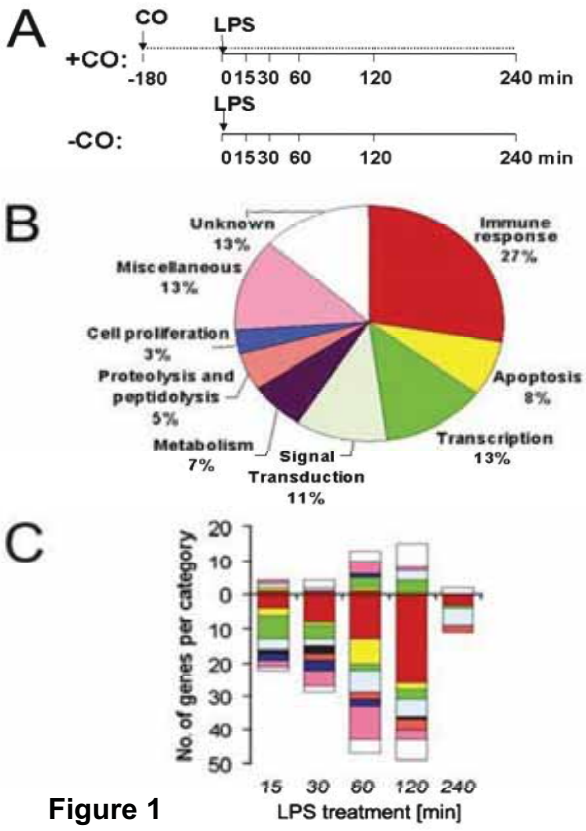


Figure 1

are particularly sensitive to CO binding. The working hypothesis now is that CO, via binding to the heme molecules in the oxidases, results in a mild and transient generation of reactive oxygen species (ROS). This elicitation in an ROS burst occurs by 5 minutes and disappears by 1 hr. Our preliminary data rapid stabilization of HIF1α expression. Our focus this upcoming year will be to confirm these observations and delve more into the mechanisms by which this occurs. We are currently investi-gating these events and gene expression patterns and applying them to other cell types of interest, particularly those related to vascular injury and organ rejection following transplantat-ion, where CO has shown potent salutary effects.

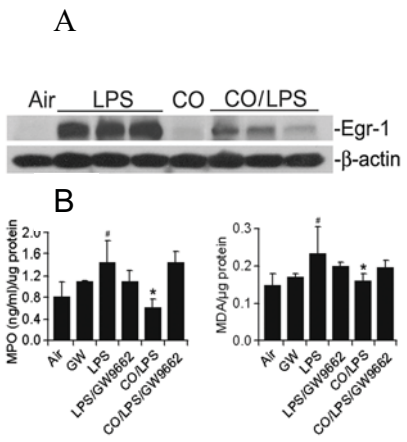


Figure 2

III. List of Current Employees

1.	Beek Yoke Chin, Ph.D.	Instructor in Surgery
2.	Jeffery Scott, Ph.D.	Research Fellow
3.	David Gallo, M.S.	Research Associate Associate HMS
4.	Aaron May	Research Assistant
5.	Eva Czismadia	Research Assistant

IV. List of Current Funding

1. "Carbon Monoxide to Prevent Circulatory Collapse"
   NIH 7 R01 HL076167-02; NHLBI
   Project period: 4/1/04-3/31/08
   Principal Investigator: Leo E. Otterbein, Ph.D.

2. "Anti-Inflammatory Effects of Carbon Monoxide in the Lung
   NIH 7 R01 HL071797-03; NHLBI
   Project Period: 8/1/03-5/31/07
   Principal Investigator: Leo E. Otterbein, Ph.D.

3. "Investigations of Mechanisms of Action of Carbon Monoxide as an Anti-Inflammatory and Anti-Proliferative Agent in Vascular Disorders"
   Linde Gas Therapeutics, Stockholm Sweden
   Project Period: 2004-2006
   Principal Investigator: Leo E. Otterbein, Ph.D.

4. "Mechanisms of Cutoprotection in Acute Lung Injury"
   NIH: PO 071797-03

Project Period: 2003-2008
Principal Investigator: Augustine Choi
Subcontract PI: Leo E. Otterbein, Ph.D.

5. "Carbon Monoxide, Cigarette Smoking and IBD"
Chrohn's and Colitis Foundation of American
Project Period: 2004 to 2006
Principal Investigator: Scott Plevy, M.D.
Subcontract PI: Leo E. Otterbein, Ph.D.

V. Applications Submitted and Pending Review/Funding

1. "Carbon monoxide to prevent lung and liver injury; the role of iNOS and PPARγ"
Phillip Morris External Research Program
Project Period: 2005-2008
Principal Investigator: Leo E. Otterbein, PhD

2. "Heme oxygenase-1 and Organ Transplantation"
National Institutes of Health
Project Period: 2005-2010
Principal Investigator: Fritz H. Bach, M.D.
Co-Investigator: Leo E. Otterbein, Ph.D.

3. " Heme oxygenase-1 in Diabetes and Rheumatoid Arthritis"
RIVA Foundation
Project Period: 2005-2006
Principal Investigator: Fritz Bach, M.D.
Co-Investigator: Leo E. Otterbein, Ph.D.

VI. Divisional Accomplishments over the Past Year

Research Accomplishments

In August, I joined the faculty of Surgery at Harvard Medical School in the Division of Transplantation at BIDMC as a visiting assistant professor and have been involved in getting the laboratory up and functional. I am a part of the training grant that was submitted and am actively collaborating with new colleagues towards integrating my research interests with theirs and have begun sketching out potential program grants.

Patent Disclosures

I have continuing involvement in the litigation of nine patent applications for the use of carbon monoxide as a therapeutic.

Individual Accomplishments

I have been elected to the American Heart Association study sections for mid-Atlantic affiliate and recently to the New England affiliate. This is a four year commitment. I was a part of an NIH special emphasis panel for an RFA evaluating

grants directed towards Type II diabetes and vascular injury. I served as a primary reviewer for grants from the Austrian research foundation.

VI. Report of Teaching

I was chosen to give the Senior Vice-Dean's lecture at the University of Pittsburgh. I was elected based on my work and achievements as a junior investigator. I lectured at the surgical lecture series for the department. My lab was an integral part of abstracts presented at the American College of Surgeons, the Society of Vascular Surgeons and the American Thoracic Society. These abstracts have been submitted as manuscripts

VII. Plans for the Coming Academic Year

Staff Changes/Recruitments

I will have two new people joining the lab as postdoctoral fellows. One is an anesthesiologist from Osaka University in Japan and the other from the University of Vienna, Austria.

VIII. Bibliography (1/1/04-12/31/04)

Original Articles

1. Akamatsu Y, Haga M, Tyagi S, Yamashita K, Graca-Souza AV, Ollinger R, Czismadia E, May, GA, Ifedigbo E, **Otterbein LE**, Bach FH, Soares MP Heme oxygenase-1-derived carbon monoxide protects hearts from transplant associated ischemia reperfusion injury *FASEB J* 2004; 18:771-2.

2. Lavitrano M, Smolenski RT, Musumeci A, Maccherini M, Slominska E, Di Florio E, Bracco A, Mancini A, Stassi G, Patti M, Giovannoni R., Froio A, Simeone, F, Forni M., Bacci ML, D'Alise G, Cozzi E, **Otterbein LE**, Yacoub MH, Bach FH, Calise F. Carbon monoxide improves cardiac energetics and safeguards the heart during reperfusion after cardiopulmonary bypass in pigs. *FASEB J* 2004; 18:1093-5.

3. Nakao A, **Otterbein LE**, Overhaus M, Sarady JK, Tsung A, Kimizuka K, Nalesnik MA, Kaizu T, Uchiyama T, Liu F, Murase N, Bauer AJ, Bach FH. Biliverdin protects the functional integrity of a transplanted syngeneic small bowel. *Gastroenterology* 2004; 127:595-606.

4. Neto JS, Nakao A, Kimizuka K, Romanosky AJ, Stolz DB, Uchiyama T, Nalesnik MA, **Otterbein LE,** Murase N. Protection of transplant-induced renal ischemia-reperfusion injury with carbon monoxide. *Am J Physiol Renal Physiol* 2004; 287:F979-89.

5. Sarady JK, Zuckerbraun BS, Bilban M, Wagner O, Usheva A, Liu F, Ifedigbo E, Zamora R, Choi, AM, **Otterbein LE.** Carbon monoxide protection against endotoxic shock involves reciprocal effects on iNOS in the lung and liver.

FASEB J 2004; 18:854-6.

6. Song R, Zhou Z, Kim PK, Shapiro RA, Liu F, Ferran C, Choi, AM, **Otterbein LE**. Carbon monoxide promotes Fas/CD95-induced apoptosis in Jurkat cells. *J Biol Chem* 2004; 279:44327-34.

7. Song R, Mahidhara RS, Zhou Z, Hoffman RA, Seol DW, Flavell RA, Billiar TR, **Otterbein LE**, Choi AM. Carbon monoxide inhibits T lymphocyte proliferation via caspase-dependent pathway. *J Immunol* 2004; 172:1220-6.

Original Articles (in press)

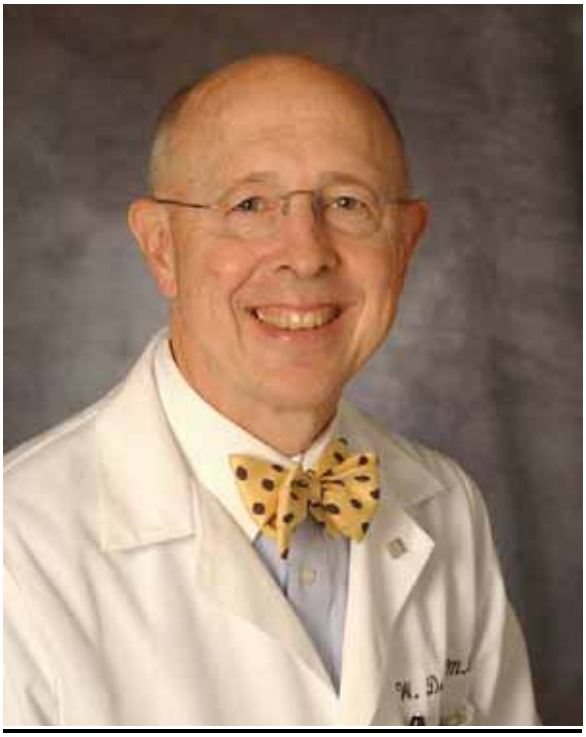
1. Nakao A, Neto JS, Kanno S, Stolz DB, Kimizuka K, Liu F, Bach FH, Billiar TR, Choi AM, Otterbein LE, Nurase N. Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin, and both. *Am J Transplant*. 2004; in press.

Reviews, Chapters, and Editorials

1. Kim PK, Zuckerbraun BS, **Otterbein LE**, Vodovotz Y, Billiar TR. 'Til cell death do us part: nitric oxide and mechanisms of hepatotoxicity. *Biol Chem* 2004; 385:11-5.

2. Ryter SW, **Otterbein LE**. Carbon monoxide in biology and medicine. *Bioessays* 2004; 26:270-80.

UROLOGY



William DeWolf, M.D., Chief

Division Members

Soloman Berg, M.D.
Paul A. Church, M.D.
Anurag (Andy) Das, M.D.
Robert C. Eyre, M.D.
Sandra M. Gaston, Ph.D.
Gary Kearney, M.D.
Michael Kearney, M.D.
Ann A. Kiessling, Ph.D.
Michael Malone, M.D.
Abraham Morgentaler, M.D.
Aria F. Olumi, M.D.
Brian Saltzman, M.D.
Martin 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-epithial interaction, virology (AIDS), neurology and clinical outcomes analysis. The urology laboratory community involves at least four Ph.D'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 neurology 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. Our Division is heavily involved in NIH outcomes research directed towards various quality of life issues and hopefully will expand to both malignant and non malignant diseases. 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.

I. Narrative Report

Basic Research

The basic research component of my own research deals with biochemical characterization of a stem cell antigen that we originally described in 1992. 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). Human embryonal carcinoma tumor antigen Gp200/GCTM2, is podocalyxin. This molecule is a 528 amino acid membrane 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 kidney, 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 what podocalyxin is interacting with 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. Immunoprecipitation 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.

Mike Schopperle in the research laboratory.

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 manu-scripts have been generated.

II. List of Current Employees

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

III. List of Current Funding

1. Intramural

IV. Divisional Accomplishments over the Past Year

Research Accomplishments

We 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 and provide some insight into why a glucose transporter is interacting with a sialomucin in cancer cells. This work is also being developed to understand the effect of differentiation on the expression on embryonal stem cell marker TRA-1-60 as it is expressed on podocalyxin. Basically upon differentiation of EC stem cells the TRA-1-60 marker is lost. Results now show that antibodies to TRA-1-60 and podocalyxin recognize the 200 kilodalton TRA-1-60 stem cell antigen in protein preps of undifferentiated EC cells. However protein blots of undifferentiated EC cells exposed to retinoic acid reveal that the TRA-1-60 epitope is no longer detectable with TRA-1-60 antibodies. This model is being developed as a previously used EC based differentiation model adapted to stem cell research.

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.

V. Report of Teaching

Undergraduate and Medical School Courses

Undergraduate Research Opportunities Program.
This is an MIT-based teaching program in which 3-5 undergraduates rotate through our laboratory on 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.

Faculty Sponsored – AUA Scholar Award
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

Staff Changes/Recruitments
There will be no change in the research staff for my research work.

Plans for Research
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 (01/01/04 -12/31/04)

Original Articles

1. George DJ, Regan MM, Oh WK, Tay MH, Manola J, DeCalo N, Duggan S, **DeWolf W,** Kantoff PW, Bubley GJ. Radical prostatectomy lowers plasma vascular endothelial growth factor (VEGF) levels in patients with prostate cancer. *Urology* 2004;63:327-32.

2. Kerfoot BP, Baker H, Volkan K, Church PA, Federman DD, Masser BA, **DeWolf WC**. Development and initial evaluation of a novel urology curriculum for medical students. *J Urol* 2004;172:278-81.

3. Kerfoot BP, Baker H, Volkan K, Church PA, Federman DD, Masser BA, **DeWolf WC**. Development of a validated instrument to measure medical student learning in clinical urology: A step toward evidenced based education. *J Urol* 2004; 172:282-85.

4. San Francisco IF, Regan MM, Olumi AF, **DeWolf WC**. Percent of positive cores for cancer is a better preoperative predicator of cancer recurrance after radical prostatectomy than prostate specific antigen*. J Urol* 2004;171:1492-9.

5. San Francisco IF, **DeWolf WC**, Peehl DM, Olumi AF. Expression of transforming growth factor beta-1 and growth in soft agar differentiate prostate carcinoma associated fibroblasts from normal fibroblasts. *Int J of Cancer* 2004;112:213-18.

6. San Francisco IF, Regan MM, **DeWolf WC**, Olumi AF. Outcome of patients after radical retropubic prostatectomy: A comparison of prostate cancer diagnosed using extended needle biopsy technique versus non extended needle biopsy technique. *Uro Oncology* 2004;4:85-90.

7. Sosna J, Pedrosa I, DeWolf WC, Mahallati H, Lenkinski RE, Rofsky MN. MR imaging of the prostate at 3 Tesla: comparison of an external phased arrest coil to imaging with an endorectal coil at 1.5 Tesla*. Acad Radiol* 2004; 11(8): 857-62.

8. Zhang X, Jin TG, Yang H, **DeWolf WC**, Khosravi-Far R, Olumi AF. Persistant c- FLIP (L): Expression is necessary and sufficient to maintain resistance to TRAIL mediated apoptosis in prostate cancer. *Cancer Res* 2004;64:7086-91.

Reviews, Chapters, and Editorials

1. **DeWolf WC**, Gaston SM. The cell cycle and it's revelance to the urologist. *J Urol* 2004;171(4):1674-81.

Abstracts

1. Gaston S, Rogg J, Vu D, Lee J, Goldner D, Genenga E, Lenkinski R, **DeWolf WC**. Gene expression profiles that underlie the biologic events visualized by magnetic resonance spectra (MRS) of human prostate cancer: Chlorine kinase. *J Urol* 2004;171:A221.

2. Gaston S, Vu D, Brice M, Goldner D, Rogg J, Lee J, Genega E, **DeWolf WC**. Tissue print profiling of prostate needle biopsy: Obtaining comprehensive tissue sampling for molecular marker analysis without compromising microscopic evaluation of the biopsy cores. *J Urol* 2004;171:A309.

3. Gaston S, Rogg J, Lee J, Vu D, Goldner D, Brice M, Genega E, Lenkinski R, **DeWolf WC.** Gene expression profiles that underlie biological events

visualized by magnetic resonance spectra (MRS) of human prostate cancer: Choline kinase. *Proc Am Assoc Cancer Res* 2004;45:A932.

4. San Francisco I**,** Regan M, **DeWolf WC**, Olumi AF. Hydronephrosis is associated with lower prostate specific antigen, later diagnosis and poorly differentiated prostate cancer: Implications for a lower screening threshold. *J Urol* 2004;171:A167.

5. San Francisco I, **DeWolf WC**, Peehl M, Olumi AF. Expression of transforming growth factor – B1 and growth in soft agar differentiate prostate carcinoma-associated fibroblasts from normal prostate fibroblasts. *Proc Am Assoc Cancer Res* 2004;45:A382.

6**. Schopperle W, DeWolf WC**. The human stem cell marker TRA-1-60 functions as a cell adhesion/protein anchoring membrane glycoprotein on embryonal carcinoma cells. *J Urol* 2004;171:A309.

7. Zhang Z, Tai-Guang J, Yang H, **DeWolf WC**, Khosravi-Far R**,** Olumi AF. TRAIL mediated apoptosis is regulated by e-FLIP(L) in prostate cancer. *Proc Am Assoc Cancer Res* 2004;45:A4959.

Sandra M. Gaston, Ph.D.

I. Narrative Report

Basic Research

My laboratory is interested in the individual biological differences that can influence the behavior of human cancers, with a major emphasis on prostate cancer. We are fortunate to have access to well-documented human clinical samples, and we have developed a number of innovative technologies that allow us to perform detailed molecular analyses of these valuable specimens without compromising patient care. These include a set of tissue print and print-phoresis technologies that allow us to generate spatial-molecular maps of tumor markers in biopsies and surgical specimens while preserving the tissue for diagnostic histopathology. Currently, we are utilizing our newly-developed tissue print technologies to investigate the molecular events that differentiate locally invasive prostate cancer from indolent tumors. This effort has produced a number of new biomarkers that may be useful in the management of patients with an early diagnosis of prostate cancer.

Dr. Sandra Gaston

We have also developed a set of micro-bioassays that allow us to evaluate bioavailable androgens in complex biological fluids. In an animal model, our bioassays can measure changes in bioavailable serum androgen in response to soy based dietary supplements (in this model, bioavailable serum androgen, as measured by bioassay, is distinct from total and free serum testosterone). In collaboration with the Zhou laboratory in Surgery, we found that our bioassay detected decreases in bioavailable serum androgen that were associated with inhibition of androgen-sensitive prostate cancer by soy dietary supplements; serum total and free testosterone showed no such association. Currently we are investigating the relationship between bioavailable serum androgen (as measured by bioassay) and androgen-dependent gene expression in cell culture models of prostate cancer. We anticipate that that this strategy may be useful for designing pharmacological and dietary interventions for prostate cancer patients who want to incorporate complementary therapies into their cancer care program.

Clinical research

For the last four years, in addition to my research laboratory, I have been the director of the BIDMC Andrology Laboratory. Andrology is the study of male fertility, and the primary clinical service of the BIDMC Andrology laboratory is semen analysis with a total volume of about 30 patients/month. Although the

clinical service will no longer be available at BIDMC, the clinical research component of the Andrology laboratory remains active under my direction. Our major current research focus is on genetic polymorphisms that result in either increased or decreased susceptibility to mitochondrial toxins, as measured by the effects of these toxins on sperm mitochondrial respiration and motility.

II. List of Current Employees

1. Dana Goldner	Research Assistant
2. Dang Vu	Research Student
3. Jonathan Rogg	Research Student
4. Courtney Klaips	Research Student
5. Tendai Chizana	Research Student
6. Albert Su	Research Student
7. Ting Ting Fu	Research Student
8. Efren Gutierrez	Harvard Medical Student

III. List of Current Funding

1. "Tissue Print Micropeels for Molecular Profiling Cancer"
   National Institutes of Health, 1R21 CA112220-01
   Project Period: 01/01/2005-1/31/07
   Principal Investigator: Sandra M. Gaston, Ph.D

2. "3T Magnetic Resonance and
   Spectroscopy of Prostate Cancer"
   General Electric Industry Sponsored Research
   Project period: 01/01/2002 - present
   Principal Investigator: Robert Lenkinski, Ph.D. (BIDMC Radiology)
   Co-Investigator: Sandra M. Gaston, Ph.D.

3. "Harvard/Michigan Prostate Cancer Biomarker Clinical Center"
   National Institutes of Health, U01 CA113913
   Early Detection Research Network: Clinical Epidemiological and Validation Centers
   Project period: 2005-2010
   Principal Investigator: Martin Sanda, M.D.
   Collaborator: Sandra M. Gasto, Ph.D.

4. "Androgen Receptor Biochips: Prostate Cancer Management"
   National Institutes of Health, NCI R21/R33 CA86365
   Project period: 2000-2005
   Principal Investigator: Ian Hunter, Ph.D. (MIT)
   Subcontract PI: Sandra M. Gaston, Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "Prostate MRI and MRS: Correlations with Gene Expression"

National Institutes of Health, PA-04-088
Project Period: 7/1/2005 – 06/30/2007
Principal Investigator: Sandra M. Gaston, Ph.D.

2. "Biomarkers for Early Detection of Invasive Breast and Prostate Cancers"
National Institute of Health RFA-CA-05-023
Early Detection Research Network: Biomarker Development Laboratories
Project Period: 7/1/05 – 6/31/10
Principal Investigator: Bruce Zetter, Ph.D.
Subcontract PI: Sandra M. Gaston, Ph.D.

V. Divisional Accomplishments in the Past Year

Research accomplishments

With NIH and intramural research support, my laboratory has continued to advance the development of a set of novel "tissue printing" technologies that allow us to transfer a microscopic layer of cells and extracellular matrix from the surface of fresh tissue specimens onto nitrocellulose membranes. We have combined tissue print techniques with specific protein and RNA/DNA detection methods to generate two-dimensional maps of molecular markers in radical prostatectomy specimens. Using these maps, we have identified clusters of molecular markers that co-localize with sites of microscopic invasion of cancer into the prostate capsule. This year, we published some of our major findings on markers of tumor invasion of the prostate capsule and an overview of our tissue printing techniques in Nature Medicine.

Because tissue print techniques do not damage tissue specimens, we have been able to utilize this platform technology to obtain molecular marker profiles from human prostate needle biopsies obtained from radical prostatectomy specimens. Specifically, we have demonstrated that we can generate both mRNA and protein molecular marker profiles from needle biopsy cores while preserving the tissue for standard H&E pathology and for immunohistochemical studies. This finding is an important part of our pre-clinical preparation for a proof-of-principle clinical trial in which molecular profiling will be evaluated in the assessment of prostate needle biopsies obtained for patient diagnosis.

In clinical practice, it is widely recognized that immunoassay levels of total testosterone and free testosterone are relatively poor predictors of physiological androgen status in adult males, especially in the "borderline range." With NIH and CaPCURE support, we are continuing to advance the development of micro-scale bioassays that can be used to monitor bioavailable androgen receptor (AR) ligand in complex biological fluids. In our most recent NIH progress report, we show that the response of our yeast AR bioassay to serum androgen reflects the endogenous androgen response of prostate cancer cells (LAPC4) across the range of physiological serum testosterone concentrations. Our results support the hypothesis that our yeast based AR bioassay can provide a useful biomarker of the net level of bioactive androgen in the serum of prostate cancer patients before and after hormonally based interventions.

With support from General Electric Industry Sponsored Research, we have used tissue prints to produce “molecular whole mounts” of radical prostatectomy specimens that can be mapped point-to-point with structures visualized *in vivo* by magnetic resonance imaging (MRI) and magnetic resonance spectra (MRS). Currently, we are collaborating with Dr. Robert Lenkinski and other investigators in the BIDMC 3T MRI/MRS Program to profile the patterns of mRNA expression that underlie the MRI/MRS choline peak that is characteristic of prostate cancer.

Mitochondrial toxicity can present a significant limitation to the clinical application of new therapeutic agents, and current pre-clinical models are inadequate to efficiently screen for this adverse activity. Because the motility of mammalian spermatozoa is exquisitely sensitive to the status of the mitochondria in the sperm midpiece, we have developed a novel *in vitro* bioassay that utilizes motile spermatozoa to detect individual differences in susceptibility to drugs and toxins that inhibit mitochondrial respiration. Utilizing both clinical samples and samples from an animal model (domestic boars), we have identified individuals whose pattern of sensitivity or resistance to specific classes of mitochondrial toxins could have important clinical consequences. Currently, we are characterizing genetic polymorphisms that we have found to be associated with increased sensitivity to the drug oligomycin. We anticipate that this study will provide proof-of-principle for a new pharmacogenomic screening strategy that can be used to identify the human chromosomal and/or mitochondrial alleles that give rise to individual differences in sensitivity/resistance to specific inhibitors of mitochondrial respiration.

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. In addition, we have identified patterns of collagen fragments in the nipple aspirate fluid (NAF) of breast cancer patients that are currently being evaluated as potential biomarkers for non-invasive screening/early diagnosis.

One of my students, Jonathan Rogg, received a Howard Hughes summer research fellowship for his work in my laboratory.

Individual Accomplishments

For a second year, I was named to the NIH National Cancer Institute Special Emphasis Panel to review grant applications submitted to the “Innovative Technologies for the Molecular Analysis of Cancer” (IMAT) program.

I was awarded an NIH grant to advance the development of a set of tissue print technologies that can be utilized to profile mRNA tumor markers from human prostate and breast tissue specimens. This grant application was given a priority score in the top 1 percentile of NIH grants, and represents the first phase of an R21/R33 project under the NCI “Innovative Technologies for the Molecular Analysis of Cancer” (IMAT) program.

VI. Report of Teaching

1. I was a tutor for the HMS course “Principles of Pharmacology” in the spring of 2004.

2. I was a tutor for HMS course “The Human Body” in the fall of 2004.

3. I was a research mentor for the following undergraduate/medical students:

Dana Goldner	MIT Student
Jonathan Rogg	MIT Student
Courtney Klaips	MIT Student
Piali Mukhopadhyay	MIT Student
Hubert L. Roberts	MIT Student
Erika Lin	MIT Student
Efren Gutierrez	Harvard Medical Student

Invited Presentations (Local, National, and International)

1. Invited Speaker: “Tissue-Print and Print-Phoresis Platform Technologies for the Molecular”. University of Michigan Comprehensive Cancer Center S.P.O.R.E. in Prostate Cancer, Ann Arbor MI, September 2004.
2. Invited Speaker: “Molecular Profiles of Tumor Invasion of the Prostate Capsule”. Countway Urology Rounds. Brigham and Women’s Hospital, Boston MA, April 2004.
3. Invited Speaker: “Real Patients, Real Tumors: Molecular Profiles of Prostate Cancers in Radical Prostatectomy Specimens”. BIDMC Surgery Research-Junior Faculty Research Seminar Series, November 2004.
4. Invited Speaker: “Molecular Profiles of Prostate Cancers in Radical Prostatectomy Specimens”. Harvard Genitourinary Data Club, December 2004.

Abstracts Presented at Local, National, and International Meetings

1. **Gaston SM**, Vu D, Brice MJ, Goldner DL, Rogg JG, Lee JM, Jung M. Lee, Genega EM, Rubin MA, Lenkinski RE and DeWolf WC. “Tissue Print Profiling of Prostate Needle Biopsies: Obtaining Comprehensive Tissue Sampling for Molecular Marker Analysis without Compromising Microscopic Evaluation of the Biopsy Cores”. Dana Farber/Harvard Cancer Center Renal and Prostate Cancer SPORE Retreat, October 2004.

2. **Gaston SM**, Soares MA, Siddiqui MM, Vu D, Lee JM, Goldner DL, Shih JC, Perides G, Lavin PT, Bloch BN, Upton MP, Genega EM, Rubin MA, Lenkinski RE. “Tissue Print Maps of Molecular Markers of Prostate Cancer Invasion: What Can We Learn by Adding a Spatial Dimension to Molecular Profiles in Surgical Specimens?” Basic, Translational, and Clinical Advances in Prostate Cancer (AACR Research Conference), November 2004.

VII. Plans for the Coming Academic Year

New Research Initiatives

1. This year we are beginning our new NIH grant "Tissue Print Micropeels for Molecular Profiling of Cancer". This will allow us to accelerate the development of tissue print protocols to profile molecular markers in human tissue specimens without compromising histological pathology diagnosis. Our focus this next year is the identification of the most appropriate set of markers for a proof-of-principle clinical trial in which molecular profiling will be evaluated in the assessment of prostate needle biopsies.

2. We have shown that tissue print technology can be used to generate molecular profiles of mastectomy surgical specimens. Our priority effort for this project continues to be the characterization of molecular markers that can be used to identify invasive cancer at the surgical margins of partial mastectomy specimens. In addition, this next year we will be working with Ambion Inc to develop a simplified protocol for extracting mRNA from breast tissue-prints (currently this is a more laborious process than preparing prostate tissue-print mRNA). Our objective is to design a breast tissue-print mRNA extraction protocol that can be readily translated into a kit or automated platform.

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

   Gary Latham, PhD, Senior Scientist, Ambion, Inc. has agreed to collaborate with us in the evaluation of one of Ambion's newly developed technologies for RNA preparation. Our goal is to determine if (as we expect) we can use their new reagents to significantly improve the efficiency of our tissue-print RNA profiling protocols.

   Douglas C. Wallace, Ph.D., Professor of Molecular Medicine and Director of the Center for Molecular and Mitochondrial Medicine and Genetics, has graciously offered to collaborate with us in a comparison of the mitochondrial polymorphisms we identify in our toxin sensitivity screen (the sperm motility bioassay) with the mitochondrial polymorphisms that he and his colleagues have identified in different human populations. The resulting information on the prevalence of these genetic variants will be used to design follow-on studies of the most common human alleles associated with mitochondrial toxin sensitivity.

   New Recruitment Activities

   As both a member of the Harvard Medical School (HMS) faculty and a Visiting Scientist in the MIT Center for Biomedical Engineering, I have been able to develop a network of research students through the MIT undergraduate research program (UROP). This next year, I will continue to recruit from this highly talented pool of students. In addition, with the encouragement of Mr. Paul Levy, I will be working with the BIDMC development office to begin to build

a private donor base to provide stipend support for students who make significant contributions to biomedical research at BIDMC.

Educational Activities

For the last four years, I have been a member of the Teaching Faculty of Harvard Medical School. This year I will continue to teach first year Harvard Medical Students in the Principles of Pharmacology and in the Human Body courses. In addition, my laboratory will again host middle school students from the Harvard Medical School "Explorations" program

VIII. Bibliography (1/1/04-12/31/04)

Original articles (in press)

1. **Gaston SM,** Soares MA, Siddiqui MM, Vu D, Lee JM, Brice MJ, Shih JC**,** Upton MP, Perides G, Baptista J, Lavin PT, Bloch BN, Genega EM, Rubin MA, Lenkinski RE. Tissue-Print and print-phoresis as platform technologies for the molecular analysis of human surgical specimens: Mapping tumor invasion of the prostate capsule. *Nat Med* 2004; in press.

2. Hutchinson LM, Chang EL, Becker CM, Ushiyama N, Shih M-S, DeWolf WC**, Gaston SM**, Zetter BR. Use of thymosin β15 as a urinary biomarker in human prostate cancer. *Prostate* 2004; in press.

Reviews, Chapters, and Editorials

1. DeWolf WC**, Gaston SM**. The cell cycle and its relevance to the urologist. *J Urol* 2004; 171(4):1674-81.

Abstracts

1. **Gaston SM,** Vu D, Brice MJ, Goldner DL, Rogg JG, Lee JM, Genega EM, DeWolf WC. Tissue print profiling of prostate needle biopsies: Obtaining comprehensive tissue sampling for molecular marker analysis without compromising microscopic evaluation of the biopsy cores. 2004; *J Urol* 171(4): A483.

2. **Gaston SM,** Rogg JG, Vu D, Lee JM, Genega EM, Lenkinski RL, DeWolf WC. Gene expression profiles that underlie the biological events visualized by magnetic resonance spectra (MRS) of human prostate cancer: choline kinase. *J Urol* 2004; 171(4): A221.

3. **Gaston SM,** Rogg JG, Lee JM, Vu D, Goldner DL, Brice MJ, Genega EM, Lenkinski RL, DeWolf WC. Gene Expression profiles that underlie biological events visualized by magnetic resonance spectra (MRS) of human prostate cancer: choline kinase. *Proc Amer Assoc for Cancer Res* 2004; 45: A213.

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

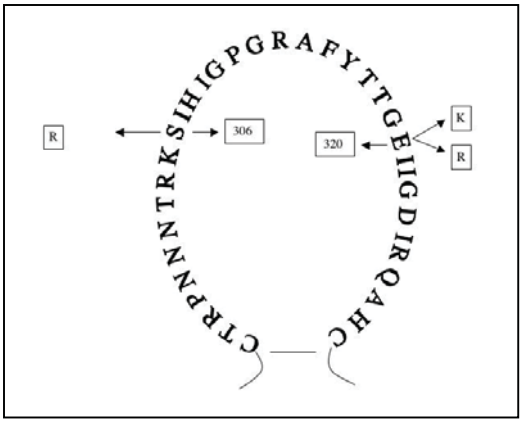
I. Narrative Report

The long-term goals of our research are to understand tissue specificity and controls on retrovirus gene expression in genitourinary tract tissues and embryos. Studies of HIV infection of male GU tract tissues began over 20 years ago 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.

Genetic and phylogenetic analyses of HIV genes

Genetic and phylogenetic analyses of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a longitudinal study design. Prior studies utilizing Maximum-Likelihood algorithms have illustrated unique clustering patterns of HIV quasi-species isolated from paired blood and semen specimens from long term study subjects. Importantly, several study subjects have demonstrated the appearance of therapy resistance-conferring mutations in semen before they appear in blood.

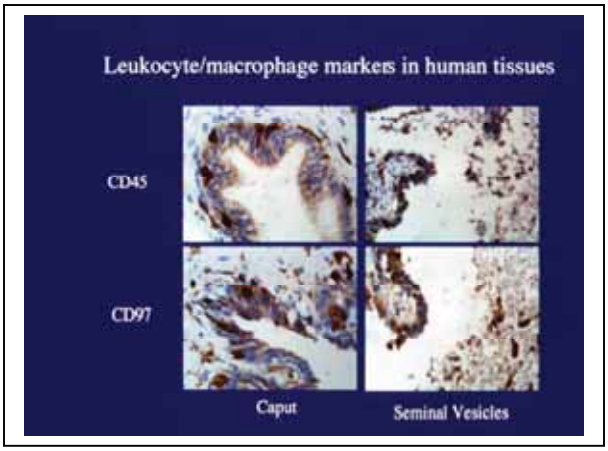
More recent analyses of HIV envelope genes have revealed compartmentalization of syncytium-inducing virus species (utilize chemokine receptor CXCR4) and non-syncytium-inducing virus species (utilize chemokine receptor CCR5). This confirms and extends some reports that HIV variants which utilize CCR5 receptors to gain access to host cells are the sexually transmitted virus species. During the subsequent course of infection, blood HIV variants mutate to express envelopes that preferentially bind to CXCR4 rather than CCR5. This switch in virus tropism is due to point mutations at one or two amino acid residues (S306R or E320K,R) in the V3 loop of HIV*env*, and is accompanied by more rapid disease progression due to loss of CD4+ lymphocytes incorporated into lymph node syncytia.



The switch in virus tropism has traditionally been attributed to the high error rate inherent in the virus reverse transcriptase, but more recent studies have revealed another possibility. A family of deaminases, CEM15 (APOBEC3G) function as an innate cellular defense mechanism against retroviral infection. This is in keeping with the remarkably high (45%) percentage of the human genome comprised by retroviral elements, thought to arise through ancient retroviral infection.

CEM15 deaminates cytosine in the nascent DNA strand synthesized by viral reverse transcriptase during the process of infection. The resulting uracil residue triggers destruction of the nascent DNA strand by intracellular DNAses. If, however, the nascent DNA is not destroyed, the positive strand has an adenosine substitution for the guanosine residue that formerly paired with the cytosine. To determine if such mutations influence disease progression, we are in the process of analyzing two subsets of our HIV sequence data: 53 unique sequences of the V3 loop of Gp120 from a long-term non-progressor and 82 unique sequences of protease from a man who developed therapy resistance at 32 months of treatment. The logistics of archiving and analyzing a growing data set of gene sequences have necessitated the development of a custom database, which has been recently completed in MySQL. We have begun to use the database as the starting point for sequence analyses.

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. Previous studies used mouse model systems to characterize the tissue distribution of leukocyte subsets in testis, epididymis and seminal vesicles. More recent studies have attempted parallel experiments in human tissues. The figure to the right illustrates immunostaining (red-brown color) of human epididymis and seminal vesicles for the pan-leukocyte marker, CD45, and the tissue-specific macrophage marker, CD97. These are possible host cells for HIV infection.



Several lines of evidence, including work from this laboratory, indicate the prostate is immunosuppressed. This characteristic could play an important role in prostate diseases, such as prostatitis and prostate cancer. We have previously reported that prostatitis may drive HIV disease by promoting the development of therapy resistance mutations. For these reasons, we hope to explore the bacterial species present in prostatic tissues. We will use PCR amplification of bacterial ribosomal gene sequences, followed by sequencing the PCR products and identification through GenBank searches. This work is just beginning.

II. List of Current Employees

1. Bryan Desmarais	Research Assistant
2. David Chiavatago	MS Biotechnology Student
3. Joe Laverde	MS Biotechnology Student
4. Anil Purohit	Harvard Medical Student
5. Jonathon Lyon	Research Assistant

6. Nathan Neville — Research Assistant
7. Stephen Eyre — Research Assistant

III. List of Current Funding

1. "Role of the Male Genital Tract in HIV Disease"
   NIH/NIDDK 5R-1 DK052761-08
   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. Applications Submitted and Pending Review/Funding

1. "Retrovirus Expression in Male Genitourinary Tract Tissues"
   New R21, submitted 1/05/05
   This is an application that tests the hypothesis that the Moloney murine leukemia virus-related endogenous retrovirus expressed at very high levels in mouse epididymis.

V. Divisional Accomplishments over the Past Year

Research Accomplishments

1. The longitudinal genetic and phylogenetic analyses of HIV genes is now proceeding rapidly. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men, including those on therapy. To establish tissue specific reservoirs of disease, we are initiating a collaboration with Southwest Biomedical Research Foundation to analyze tissue biopsies from HIV-infected chimpanzees.

2. The novel class of macrophages in male mouse and human tissues 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 on-going.

3. We have completed a pilot survey of male mouse genital tract RNAs and DNAs for presence and expression of the endogenous retrovirus, MERV-L. This work formed the basis for the R21 application submitted in Jan., 2005.

4. We have instituted pilot studies to detect bacteria in semen and prostate tissues using PCR-amplification of bacterial ribosomal RNA gene sequences.

Individual Accomplishments

Dr. Kiessling
1. Member, ZRG1 AARR-C 02 study section "AIDS Immunology and Pathogenesis". National Institutes of Health, 2004.
2. Invited Faculty, Swiss Biotechnology Council, Panel Discussion, "Emerging Biomedical Technologies", November, 2004.
3. Invited Faculty, Serono Symposium, "ART and the Law", November, 2004.

Dr. Eyre
1. Member, American Urologic Association Investment Board.
2. Treasurer, New England Section of the American Urologic Association.
3. Dr. Eyre was honored with the Practicing Urologist Award, New England Section of the American Urological Association, 2004.

VI. Report of Teaching

Undergraduate and medical school courses
1. Dr. Kiessling presented a lecture on sexually transmitted diseases and human sexuality, Department of Biology, Brandeis University.
2. Drs. Church and Eyre gave multiple lectures to medical students rotating through the Surgical Core Clerkship, HMS 2nd and 3rd year medical students.
3. Dr. Church was Director of the BIDMC rotation of the Surgical Core Clerkship, Third Year, Lecture Series, Harvard Medical School.
4. Dr. Eyre was Director of the Senior Surgical Residency Rotation, Faulkner Hospital.

Invited presentations (lLocal, National, and International)

Dr. Kiessling
1. Invited Speaker: "Human Embryonic Stem Cells: the Present and the Future". Grand Rounds in the Department of Obstetrics and Gynecology, Cedars-Sinai Hospital, Los Angeles, CA, July, 2004.
2. Invited Speaker: "Human Embryonic Stem Cells: the Present and the Future". Grand Rounds in the Department of Internal Medicine, Methodist Hospital, Los Angeles, CA, July, 2004.
3. Invited Speaker: "Human sexuality and sexually transmitted diseases" Department of Biology.

Dr. Eyre
1. Invited Speaker: "The Specialty of Urology", National Youth Leadership Forum in Medicine, Boston, MA, July, 2004.
2. Invited Speaker: "Bacteria in Semen", Annual Meeting of the New England Section, American Urological Association, Amelia Island, FL, Sept, 2004.

Abstracts Presented at Local, National and International National Meetings

1. Eyre RC, Mullen TM, Kiessling RL, Kiessling AA "Presence in mice and men of a novel class of leukocytes essential for normal development of male mouse reproductive tract". American Urological Association, San Francisco, CA, May, 2004.

2. Eyre RC, Desmarais B, Steinberg J, Kiessling AA Detection and identification of bacterial DNA and HIVgag in the semen of HIV infected men, Americal Urological Association, San Francisco, CA, May, 2004.

VII. Plans for the Coming Academic Year

1. We recruited three new staff members: Joseph Loverde, David Chiavageto, Jonathon Lyon.
2. We will initiate our collaboration with the Southwest Biomedical Research Foundation to study HIV species in tissue biopsies.
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 physician. There has been confusion about how to structure the CCI consent for this two-center study.
4. We will continue to seek funding for our proposed endogenous retrovirus studies of male urogenital tissues.

VIII. Bibliography (01/0/04 – 12/31/04)

Nonprint Materials

1. **Eyre SJ**. Faculty, Adult Complicated Urinary Tract Infections, a Telesymposia series sponsored by Bayer Pharmaceutical for primary care practioners.

Aria F. Olumi, M.D.

I. Narrative Report

Basic Research

PROJECT 1: STROMAL-EPITHELIAL INTERACTIONS REGULATE DEVELOPMENT OF BENIGN PROSTATIC HYPERPLASIA.

Development, growth and tumorigenesis in the prostate is closely regulated by the stromal-epithelial crosstalk, therefore, identifying the signal transduction pathways between prostate epithelial cells and the surrounding stromal cells will enable us to better understand the normal and abnormal biology in prostatic diseases. We hypothesize that expression of particular stromal genes is one of the components that regulates the proliferation, cell death and differentiation of prostatic epithelial cells leading to BPH in adulthood.

The Jun-family proteins that are early transcription factor molecules have been shown to regulate stromal-epithelial interactions via paracrine modulation. Moreover, the Jun family member proteins have been shown to play an important role in proper development of the genitourinary organs. The balance between the different Jun-family expression in the stroma may be one of the determinants of the ultimate survival or death signals that the stroma may exert on prostatic epithelial cells.

This project focuses on paracrine signals form stromal cells with genetically modified Jun-family proteins that may regulate epithelial proliferation, cell death and differentiation. These studies can 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.

TNF-related Apoptosis Inducing Ligand (TRAIL) has been shown to induce apoptosis in a variety of tumorigenic and transformed cell lines but not in normal cells, hence making TRAIL an ideal cancer therapeutic agent with minimal cytotoxicity. FLICE Inhibitory Protein (c-FLIP) is an important regulator of TRAIL-induced apoptosis. We have demonstrated that persistent expression of c-FLIP(L) is inversely correlated with the ability of TRAIL to induce apoptosis in prostate cancer cells. In a series of correlative and functional studies we have shown that persistent expression of c-FLIP(L) is necessary and sufficient to regulate sensitivity to TRAIL mediated apoptosis in prostate cancer cells. Deciphering the molecular mechanisms of resistance to TRAIL can improve the efficacy of pro-apoptotic agents in treatment of malignancies.

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 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-Testosterone, 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.

1. List of Current Employees

1. Xiaoping Zhang, M.D., Ph.D.	Research Fellow
2. Liang Zhang, M.D., Ph.D.	Research Fellow
3. Xu Huang, Ph.D.	Research Fellow
4. Wenhua Li, Ph.D.	Research Fellow

2. List of Current Funding

1. “Regulation of Primary and Metastatic Adenocarcinoma of Prostate by the Associated Stoma”
   CaPCURE
   Project Period: 10/1997-9/1998
   Principal Investigator: A. Olumi M.D.

2. “Pilot Project: The Role of Anti-Apoptotic Factors in Evasion of Prostate Tumors from TRAIL-Induced Apoptosis
   National Institutes of Health/Harvard Prostate SPORE
   Project Period: 11/2002 – 10/2004

Principal Investigator: P. Kantoff
Principal Investigator of Pilot Project: A. Olum, M.D.

3. "Stromal-Epithelial Interactions in Development of BPH"
   National Institutes of Health, 5K08DK 064 062-02
   Project Period: 7/2003 – 06/2008
   Principal Investigator: A. Olumi M.D.

4. "Role of c-FLIP(L) in modulating apoptosis in prostate cancer
   Howard Hughes Medial Institute/SPORE
   Project Period: 05/2004 – 04/2005
   Principal Investigator: A. Olumi M.D.

5. "Role of a c-FLIP(L) in Apoptosis"
   Department of Defense Prostate Cancer Program
   Project Period: 11/2004 – 09/2006
   Principal Investigator: A. Olumi M.D.

3. Applications Pending Review and Funding

1. "Mechanisms of resistance to TRIAL induced apoptosis in prostate cancer"

   Howard Hughes Medical Institute
   Project Period: 05/2004 – 04/2005
   Principal Investigator: A. Olumi, M.D.

2. "Regulation of c-FLIP (L) by c-FOS/AP-1 in TRAIL-Induced apoptosis in prostate cancer"
   Prostate Cancer Foundation
   Project Period: 01/01/05 – 12/31/05
   Principal Investigator: A. Olumi, M.D.

3. AP-1 Family member protein, c-FOS, a pro-apoptotic molecule and transcriptional regulator of c-FLIP (L)
   U.S. Department of Defense
   Project Period: 01/01/06 – 12/31/08
   Principal Investigator: A. Olumi, M.D.

4. Divisional Accomplishments over the Past Year

Research Accomplishments

1. NIH/NIDDK—K08 grant was renewed.
2. I was able to obtain funding from Howard Hughes Medical Institute and expect to receive funds from Department of Defense in November of 2004.
3. I hired three new post-docs for my research laboratory.

Individual Accomplishments

1. Invited grant reviewer: Department of Defense Prostate Cancer Program (3rd year).
2. Journal of Urology – Investigative Urology Editorial Board Member.
3. Scientific Session Moderator: New England American Urological Annual Meeting.

4. 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).
3. Resident teaching – Harvard Program in Urology
4. Monthly one-on-one evaluation with interns and residents.
5. Weekly faculty representative for the Harvard Urology Program conferences.
6. Monthly one-on-one evaluation with interns and residents.

Abstracts Presented at National Meetings

1. San Francisco IF, DeWolf WC, Peehl DM, **Olumi AF**. Expression of transforming growth factor-beta 1 and growth in soft agar differentiates between prostate carcinoma-associated fibroblasts from normal prostate fibroblasts in-vitro. American Association of Cancer Research Meeting. Orlando, FL; 2004.
2. Zhang X, San Francisco IF, DeWolf WC, Jin T, Khosravi-Far R, **Olumi AF**. Persistent c-FLIP(L) expression is necessary and sufficient to regulate sensitivity to TRAIL-mediated apoptosis in prostate cancer. American Association of Cancer Research Meeting, Orlando, FL; 2004.
3. San Francisco IF, Regan, MM, DeWolf WC, **Olumi AF**. Hypogonadism is associated with lower prostate specific antigen, later diagnosis and poorly differentiated prostate cancer: implications for a lower screening threshold. American Urological Association Annual Meeting. San Francisco, CA; 2004

V. Plans for the Coming Academic Year:

1. To apply for new Department of Defense – Idea Development Award in order to supplement my newly funded Department of Defense – New Investigator Award.

VI. Bibliography (01/01/04 - 12/31/04)

Original Articles

1. San Francisco IF, Regan MM, **Olumi AF,** DeWolf WC. Percent of positive cores for cancer is a better preoperative predictor of cancer recurrence after radical prostatectomy than prostate specific antigen. *J Urol* 2004;171:1492-9.
2. San Francisco IF, DeWolf WC, Peehl DM, **Olumi AF**. Expression of transforming growth factor-beta 1 and growth in soft agar differentiates between prostate carcinoma-associated fibroblasts from normal prostate fibroblasts in-vitro. *Int J Cancer* 2004;112:213-8.
3. San Francisco IF, Regan MM, DeWolf WC, **Olumi AF**. Outcome of patients after radical retropubic prostatectomy: a comparison of prostate cancer diagnosed using extended needle biopsy technique versus non-extended needle biopsy technique. *UroOncology* 2004;4(2):85-90.
4. Zhang X, Jin TG, Yang H, DeWolf WC, Khosravi-Far R, **Olumi AF**. Persistent c-FLIP(L) expression is necessary and sufficient to regulate sensitivity to TRAIL-mediated apoptosis in prostate cancer. *Cancer Res* 2004;64:(19):7086-91.

Reviews, Chapters and Editorials

1. **Olumi AF**, Richie JP. Urologic Surgery, In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston textbook of surgery: The biological basis of modern surgical practice. Elsevier-Saunders Publishing; 2004.2283-318.

Clinical Communications

1. Kuten A, **Olumi AF**, Goldsmith J, Monahan-Earley RA, Dvorak AM, Genega EM. Pathologic quiz case. A symptomatic renal tumor. Juxtaglomerular cell tumor. *Arch Pathol Lab Med* 2004;128(9):e112-4.

2. **Olumi AF**. Self-retraction clamp for dissection of the posterior prostatic fossa during radical retropubic prostatectomy. *Scientific WorldJournal* 2004;4 Suppl 1:260-2.

Martin G. Sanda, M.D.

I. Narrative Report

Basic Translational Research

The principal areas of research in the Sanda laboratory include studies elucidating mechanisms of T cell tolerance and immune evasion in prostate cancer, and evaluation of prostate cancer antigens as targets for immunotherapy and biomarkers for cancer screening and severity assessment. This laboratory provides a unique environment for learning how translational research, utilizing transgenic mice, can concurrently address issues important for developing new therapy while also characterizing fundamental issues of basic tumor immunology.

Clinical Research

The Sanda group also conducts prostate cancer clinical outcomes research. These studies include the PROST-QA consortium, a national consortium of prostate cancer referral centers (Beth Israel Deaconess Medical Center, Cleveland Clinic, MD Anderson Cancer Center, UCLA, University of Michigan, and Washington University) wherein combined evaluation of cancer control, satisfaction with care, and quality of life provides comprehensive characterization of prostate cancer care quality. Patients and their spouse/partners are interviewed by a third-party phone survey facility to evaluate their satisfaction with the cancer care they received as well as their outcomes in a broad range of quality of life domains, including sexual, urinary, bowel, and hormonal functioning. These patients' cancer control status is followed by clinical coordinators at the treatment sites and annotated in a web-based, password-protected database. This study, led by Dr. Sanda, has enrolled over 1000 participants, treated by over 40 physicians nationwide, and is the largest ongoing, NCI-funded prospective study of prostate cancer quality of life.

II. List of Current Employees

1. Mariam Eljanne, Ph.D.	Research Associate
2. Daohong Chen, M.D., Ph.D.	Research Fellow
3. Kyrsten Haram, B.A.	Research Assistant
4. Corey Probst, B.A.	Clinical Research Assistant
5. Renee Gatewood	Administrative Assistant

III. List of Current Funding

1. "Survivor HRQOL/Spouse Satisfaction after Prostate Therapy"
   National Institutes of Health, 7R01CA 095662-03
   Project Period: 7/1/02-6/30/07
   Principal Investigator: Martin Sanda, M.D.

2. "Modulating Tolerance for Prostate Cancer Antigen Vaccine"
   National Institutes of Health, 7R01 CA82419-05
   Project Period: 04/01/00-03/31/05
   Principal Investigator: Martin Sanda, M.D.

3. "Role of Fas in Prostate Cancer Tolerance"
   National Institutes of Health, P50 DK065313-01
   Project Period: 09/01/03 – 08/30/08
   Principal Investigator: M. Day
   Project Director: Martin Sanda, M.D.

4. "UM Prostate Cancer SPORE"
   National Institutes of Health, P50 CA69568-02A1
   Project Period: 09/01/03 – 08/30/08
   Principal Investigator: K. Pienta
   Co-Investigator: Martin Sanda, M.D.

Other Ongoing Research

1. "NCI – Radiation Therapy Oncology Group (RTOG) Trial 0232
   National Protocol Chair: B. Prestidge
   Urology Co-Chair: M. Sanda, M.D.

IV. Applications Submitted and Pending Review/Funding

1. "Harvard/Michigan Prostate Cancer Biomarker Clinical Center (an NCI Early detection Network Clinical Evaluation Center"
   National Institutes of Health, U01 CA113913
   Project Period: 03/01/05 – 04/30/10
   Principal Investigator: Martin Sanda, M.D.

V. Divisional Accomplishments in the Past Year

Research Accomplishments:

1. Secured (new) O'Brien Center Project grant; transferred two R01 grants to BIDMC

VI. Report of Teaching

Undergraduate and Medical School Courses:

1. MIT-Harvard Undergraduate HST Program Faculty Supervisor (C Wang, A Yonekura, undergraduate students)

Graduate School and graduate medical courses:

1. Urology clerkship, HMS

VII. Plans for the Coming Academic Year

Staff Changes/Recruitments:

1. Hire additional postdoctoral (lab) researcher; clinical data manager; research nurse

Plans for Research:

1. Begin research of the Harvard-Michigan Prostate Biomarker Clinical Center (award anticipated to be funded 3/1/05, see above)

VIII. Bibliography (01/01/04-12/31/04)

Original Articles

1. Dash A, Dunn RL, Resh J, Wei JT, Montie JE, **Sanda MG**. Patient, surgeon, and treatment characteristics associated with homologous blood transfusion requirement during radical retropubic prostatectomy: multivariate nomogram to assist patient counseling. *Urol* 2004; 64(1):117-22.

2. Hofer MD, Kuefer R, Varambally S, Li H, Ma J, Shapiro GI, Gschwend JE, Hautmann RE, Sanda MG, Giehl K, Menke A, Chinnaiyan AM, Rubin MA. The role of metastasis-associated protein 1 in prostate cancer progression. *Cancer Res* 2004;64(3):825-9.

3. Hollenbeck BK, Wei JT, **Sanda MG**, Dunn RL, Sandler HM. Neoadjuvant hormonal therapy impairs sexual outcome among younger men who undergo external beam radiotherapy for localized prostate cancer. *Urol* 2004;63(5):946-50.

4. Kumar-Sinha C, Shah RB, Laxman B, Tomlins SA, Harwood J, Schmitz W, Conzelmann E, **Sanda MG**, Wei JT, Rubin MA, Chinnaiyan AM. Elevated alpha-methylacyl-CoA racemase enzymatic activity in prostate cancer. *Am J Pathol* 2004;164(3):787-93.

5. Sreekumar A, Laxman B, Rhodes DR, Bhagavathula S, Harwood J, Giacherio D, Ghosh D, **Sanda MG**, Rubin MA, Chinnaiyan AM. Humoral immune response to alpha-methylacyl-CoA racemase and prostate cancer. *J Natl Cancer Inst* 2004;96(11):834-43.

6. Underwood W 3rd, Wei J, Rubin MA, Montie JE, Resh J, **Sanda MG**. Postprostatectomy cancer-free survival of African Americans is similar to non-African Americans after adjustment for baseline cancer severity. *Urol Oncol.* 2004;22(1):20-4.

7. Underwood W, De Monner S, Ubel P, Fagerlin A, **Sanda MG**, Wei JT. Racial/ethnic disparities in the treatment of localized/regional prostate cancer. *J Urol* 2004;171(4):1504-7.

Reviews, Chapters, and Editorials

1. Hollenbeck BK, Dunn RL, Wei JT, Sandler HM, **Sanda MG**. Sexual health recovery after prostatectomy, external radiation, or brachytherapy for early stage prostate cancer.
Curr Urol Rep 2004;5(3):212-9.

VASCULAR AND ENDOVASCULAR SURGERY

Frank W. LoGerfo, M.D., Chief

Division Members

David R. Campbell, M.D.
Christiane Ferran, M.D., Ph.D.
Allen D. Hamdan, M.D.
Frank B. Pomposelli, Jr., M.D.
Marc Schermerhorn, M.D.
Sherry D. Scovell, M.D.

Frank W. LoGerfo, M.D.
Vascular Surgery Research Laboratory

Christiane Ferran, M.D., Ph.D.
Vascular Immunobiology Laboratory

Allan D. Hamdan, M.D.
Clinical Research in Vascular Surgery

I. Narrative Report

Basic Research

The Vascular Surgery Research Laboratory, directed by Dr. Logerfo, 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 as 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. Laser-Capture Microdissection (LCM), a relatively new technology developed by the National Institutes of Health, which is available at Beth Israel Deaconess Medical Center, permits selection of cells within a chosen area of tissue. This technology is currently being employed by our laboratory to further localize alterations in gene expression. 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 using various *in vitro* cell culture assays. This information is now being used to identify targets for RNA silencing. We have established our ability to silence RNA in cell culture and in the vein graft wall.

For biomaterials research, the Vascular Surgery Research Laboratory designed and patented several novel biomaterial surfaces. An infection-resistant ionic polyurethane was developed in Phase I and II STTR grants in which quinolone antibiotics were incorporated into the polymer using textile dyeing techniques, with this surface demonstrating antimicrobial activity both *in vitro* and *in vitro*. This biomaterial can be used to comprise a wide range of implantable devices such as catheters, wound dressings and vascular grafts, avenues which are currently being explored. A similar ionic polyurethane was then employed to seal FDA–approved knitted Dacron vascular grafts using a patented perfusion technology. As part of a Phase II STTR grant, these sealed vascular grafts were evaluated at various acute and chronic time periods using a canine carotid arterial grafting model. A porcine cardiac surgical model to evaluate a novel infection-resistant Dacron prosthetic valve sewing cuff with optimum antimicrobial properties is currently in the development stages in order to complete the objectives of a Phase II SBIR grant. We have also developed *in vitro*, as described in our Phase I STTR proposal, a

novel small-diameter nanofibrous polyurethane vascular graft via electrospinning technology. Lastly for metallic implants comprised of titanium such as bone joints and dental posts, we have completed early development of a novel titanium surface with mitogenic properties via covalent linkage of bone morphogenic protein-2 (an osteoblast mitogen).

The Vascular Immunobiology Laboratory, directed by Dr. Ferran, has a major research interest in the field of vascular biology, mainly intimal hyperplasia, as well as the micro- and macro-vascular complications of diabetes, transplantation, including xenotransplantation and islet transplantation, as well as autoimmune diabetes, acute liver failure, and liver regeneration. More specifically, work in the Vascular Immunobiology Laboratory is focused on the understanding of the function (s) of the anti-apoptotic genes A20, Bcl-2, Bcl-x_L and A1 in different cell types, their relationship to the pathophysiology of diseases and their potential therapeutic use in organ transplantation, diabetes, atherosclerosis, diabetic vasculopathy and liver regeneration. This interest is based on the original finding that these genes, mainly A20, serve a broad cytoprotective function in endothelial cells (EC), islets, and hepatocytes, and an atheroprotective function in smooth muscle cells (SMC). Expression of A20 in endothelial cells, islets and hepatocytes not only protects the cells from apoptosis by interrupting the activation of the caspase cascade but also serve a broad anti-inflammatory purpose by blocking activation of the transcription factor NF-κB. Uniquely, A20 also promotes hepatocyte proliferation hence liver regeneration by down-regulating the cell cycle brake $p21^{waf1}$ (**Figure 1**). This novel finding implicates that A20 based therapies may be highly beneficial for patients presenting with severe liver damage but who still have a fraction of viable hepatocytes. Protecting this reduced functional liver mass in the face of ongoing inflammation would meet metabolic demands and allow enough time for regeneration. Expression of A20 is particularly promising for reducing the donor graft size necessary for living donor liver transplantation as well as extensive liver resection for the cure of neoplasia. Expression of A20 in SMC, on the other hand inhibit their proliferation and sensitizes neointimal (i.e. the major component of atherosclerotic lesions), but not medial SMC, to apoptosis through a novel NO dependent mechanism. A20 fulfills most of the criteria required for an ideal atheroprotective therapy that confers an athero-resistant phenotype to both EC and SMC. A20 is anti-inflammatory and anti-proliferative in SMC, is pro-apoptotic in neointimal SMC and is anti-inflammatory and anti-apoptotic functions. We propose that A20 based therapies hold strong promise for the prevention and cure of vascular neointimal disease including atherosclerosis, transplant arteriosclerosis, and in-stent

Figure 1

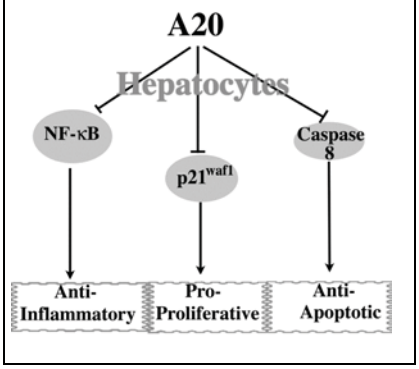
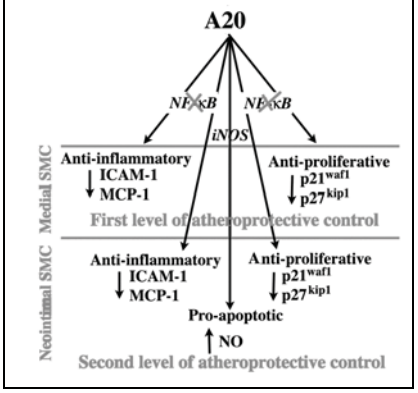


Figure 2



restenosis by protecting from apoptosis hence significantly protects from atherosclerosis, diabetic vasculopathy and transplant associated vasculopathy (**Figure 2**). This hypothesis is strengthened by our recent demonstration of impaired expression of A20 in diabetic patients that could account for their increased susceptibility to atherosclerosis. Preliminary evidence suggest that decreased A20 expression in is in part due to the untoward effects of hyperglycemia but also depends on still undefined factors that are likely genetically determined.

Clinical Research

Clinical Research in Vascular Surgery, directed by Dr. Hamdan, continues to be very active in both retrospective database review as well as participation in major clinical trials. In addition to adding to the vascular literature, we are very interested in insuring the quality of our outcomes in all surgical procedures. Recently we finished enrollment and follow-up in an important Phase III multicenter randomized trial looking at the use of a transcription factor decoy (E2F) in an attempt to decrease intimal hyperplasia and restenosis in vein grafts. We were the number one center as far as enrollment. The preliminary review of the data, unfortunately, showed no benefit in the use of E2F. This is, in itself, an important finding. In addition, due to our prominence in the study, we will have access to the database which will essentially be an evaluation of the current state of the art in peripheral bypass surgery in the United States. We hope to be able to undertake several projects related to the database in the near future.

The second trial is the CREST trial, which is evaluating carotid stent vs. endarterectomy. We have a unique situation where our surgeons are both involved in the surgical arm as well as the endovascular/stenting arm. Four of the five surgeons in the Division are registered in the surgical arm and one of the surgeons is registered in both the surgical and endovascular arm. Two additional surgeons also have privileges to perform the stents with the supervision of Dr. Marc Schermerhorn, in our group. We look forward to being an active participant in this, the most important trial of carotid artery disease since the NASCET trial.

The third trial is a collaborative trial with the Brigham and Women's Hospital through the NIH. Its goal is to prospectively follow approximately 300 patients who are undergoing lower extremity bypass grafts using vein. The main interest of the study is evaluation of inflammatory markers such as C reactive protein, VCAM and ICAM, and to see how their baseline expression in patients differs and how that may or may not determine the results of the bypass. Another exciting feature of the study is that all patients will agree to allow us to keep blood and if new genetic markers related specifically to vascular disease and atherosclerosis are identified we will be able to evaluate those samples. We have enrolled approximately 15 patients at this point. This will become a very fruitful area for further research.

II. List of Current Employees

Vascular Surgery Research Laboratory

1. Mauricio A. Contreras, M.D.	Instructor in Surgery
2. Matthew D. Phaneuf, B.S.	Assistant Laboratory Director
3. Barry A. Gross, B.S.	IS Development
4. Thomas S. Monahan, M.D.	Research Fellow
5. Alexandra Popescu-Vladimir	Research Associate
6. Nicholas D. Anderson B.S.	Graduate Student
7. Puja Aggarwal	Undergraduate Student
8. Monica Jain	Undergraduate Student
9. Haig Panossian	Undergraduate Student
10. Kerry A. Sousa	Undergraduate Student
11. Vaishali B. Patel, B.S.	Administrative Assistant

Immunobiology Research Laboratory

1. Soizic Daniel, Ph.D.	Instructor in Surgery
2. Salvatore T. Scali, M.D.	Research Fellow (T-32 Trainee)
3. Gautam Shrikhande, M.D.	Research Fellow (T-32 Trainee)
4. Peter Min Kim, M.D.	Research Fellow
5. Sowmya Senani, M.S.	Student
6. Himani Patel	Undergraduate Student
7. Roy Arjoon	Undergraduate Student

III. List of Current Funding

1. “Mechanisms of Prosthetic Arterial Graft Failure”
   National Institutes of Health, 2R01 HL021796-21
   Project Period: 1978 - May, 2008
   Principal Investigator: Frank W. LoGerfo, M.D.
   Co-Principal Investigator: Christiane Ferran, M.D., Ph.D.

2. “Harvard-Longwood Research Training Program in Vascular Surgery (T32)”
   National Institutes of Health - Heart, Lung and Blood Institute T32 HL007734-11
   Project Period: 1993 - June, 2009
   Principal Investigator: Frank W. LoGerfo, M.D.

3. “William J. von Liebig Research Training in Vascular Surgery”
   William J. von Liebig Foundation
   Project Period: 2001 - 2005
   Principal Investigator: Frank W. LoGerfo, M.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. "Infection-Resistant Prosthetic Heart Valve Sewing Cuffs"
   NIH - Small Business Innovative Research Grant (Phase II)
   Project Period: 2003 - 2005
   Principal Investigator: Allen D. Hamdan, M.D.

6. "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: 2002 - End of Recruitment
   Principal Investigator: Allen Hamdan, M.D.

7. "Protective Effect of A20 Against Transplant-Associated Vasculopathy"
   Roche Organ Transplantation Research Foundation
   Project Period: 11/1/2001-12/31/2004
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

8. "Improved Liver Function and Regeneration with A20"
   NIH RO1 Grant # DK063275-03
   Project Period: 01/01/2003-12/31/2007
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

IV. Applications Submitted and Pending Review/Funding

1. "A Nanofibrous Biocomposite Small-Diameter Graft"
   NIH - Small Business Innovative Research Grant (Phase II)
   Project Period: 2005 - 2007
   Principal Investigator: Mauricio A. Contreras, M.D.
   Co-Investigators: Frank W. LoGerfo, M.D. and Thomas S. Monahan, M.D.

2. "Impaired Atheroprotective Functions in Type I Diabetes"
   NIH RO1 DK072141-01
   Project Period requested: 07/01/2005-06/30/2010
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

3. "Vascular Remodeling in Transplant Arteriosclerosis"
   NIH RO1 HL080130-01
   Project Period requested: 07/01/2005-06/30/2010
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

4. "Impaired Atheroprotective Responses in Diabetes".
   Application submitted by Salvatore Scali, MD, surgical resident at the BIDMC to the Loan Repayment Program (LRP), NIH.
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

5. "Atheroprotective Function of A20 in Medial and Neointimal Smooth Muscle Cells"
   Application submitted by Mark Fisher, MD, surgical resident at the BIDMC to the Loan Repayment Program (LRP), NIH.
   Principal Investigator: Christiane Ferran, M.D., Ph.D.

V. Narrative of Divisional Accomplishments in the Past Year

Research Accomplishments-Basic

Vascular Surgery Research Laboratory

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. 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, is being 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 various genes such as MARCKs 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 obtaining a strategic partner for this technology with our collaborators at the University of Rhode Island.

3. <u>"Development of a Biologically-Active Prosthetic Graft"</u>

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 was 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. Patency of Hemashield control grafts and PEU-D grafts was comparable at all time intervals, with all grafts except one remaining patent at each time period. The only failed graft, a PEU-D graft, was occluded when explanted at 30 days. This failure, which occurred early, was due to a technical error at the time of implantation as indicated by independent histopathological analysis. At 3 and 7 days, there was a similar foreign body immune response to the prosthetic grafts. At 14 and 30 days there were comparable amounts of thrombus on the luminal surface of both grafts. Proliferation and migration of endothelial and smooth muscle cells (neointima) was limited to 1 or 2 cm at the CCA and prosthetic graft anastomosis, with no difference in either the Hemashield control or PEU-D graft. However, there was an increase in new blood vessels formed on the PEU-D grafts, which could be the result of VEGF immobilization. For the 30 day explants, the collagen coating on the Hemashield graft was showing signs of being resorbed as indicated by the presence of "bare" fibers within the capsule. In contrast, the PEU sealant was still intact, with no visible degradation/resorption. There is a sign of non-uniform sealing on the capsular surface as indicated by the circular defects evident on the

surface. This type of pore formation would explain the higher water permeation values of the PEU-D segments as compared to the Hemashield grafts. As far as physical properties, there was no difference in tensile strength between unimplanted and grafts that were implanted for either 3 or 30 days. Additionally, the 30 day Hemashield control grafts had comparable tensile strength, indicating that the strength of the graft comes from the Dacron and not the collagen sealant that is being resorbed. Thus, development of a polyurethane sealant with protein binding properties may have a significant role for medical devices such as vascular grafts, catheters and artificial organs.

4. "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.

5. "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 Phase I proposal was 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. A novel small-diameter (4mm internal diameter) vascular graft comprised of ionic polyurethane (PEU) was synthesized. The physical and chemical properties of the novel graft were then characterized. The potent antithrombin agent recombinant hirudin (rHir) was then covalently bound to functional groups within the polymer, resulting in an antithrombotic surface. *In vitro* surface antithrombin properties were characterized, completing the Phase I objectives. Phase II of this project, which will be submitted in April 2005, will evaluate these PEU grafts in a canine carotid arterial grafting model. Development of a bioactive small-diameter vascular graft would have a significant impact on small vessel repair and replacement.

6. "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 August 2004 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.

Vascular Immunobiology Research Laboratory

1. Over the past year, we have mainly extended our program to studying the impact of A20 upon diabetic vasculopathy. Our preliminary results resulted in the discovery that diabetes mellitus impairs the expression of atheroprotective genes such as A20. A20 is blunted in diabetic patients due to metabolic disturbances aggravated by genetically determined factors specific to patients with type I DM. This work has set the basis for an NIH grant proposal whose review is currently pending. This work was also the subject of a proposal to the NIH loan repayment program (LRP) that was successfully awarded to Gautam Shrikhande, M.D.

2. We have also been successful in expanding our work demonstrating the beneficial effect of A20 already established disease. Our data demonstrate that expression of A20 in neointimal smooth muscle cells induces the regression of established lesions via its unique capacity to sensitize neontimal SMC to apoptosis via a NO dependent mechanism. These provocative and exciting results have been expression in medial smooth muscle in preventing intimal hyperplasia to studying its impact on finalized in two manuscripts submitted for publication to the Journal of Experimental Medicine. This work was also the subject of a proposal to the NIH LRP that was successfully awarded to Virendra Patel, M.D.

3. We have also expanded our work on the effect of A20 upon liver regeneration and demonstrated that this gene has the unique capacity to promote liver regeneration via decreasing the expression of the cell cycle brake $p21^{waf1}$. Data was presented at the annual BIDMC competition for surgical residents by Christopher Longo, M.D. and received an award. Results were also finalized on a manuscript submitted for publication in *Hepatology.*

Research Accomplishments-Clinical

1. We have recently presented two papers at the national vascular meeting, The Society for Vascular Surgery. Both of those papers, one written by our fellow and one by a surgical resident are published in the *Journal of Vascular Surgery*. In addition, we have had two papers presented at the American College of Surgeons by surgical residents and another paper presented at the New England Society for Vascular Surgery. All three of these papers are pending review at major journals. In addition, there are a number of ongoing research projects in development.

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 (Full Patent Submitted).
7. 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

Dr. Ferran

1. Reviewer for the NIH. SRG: Pilot and Feasibility Program in Islet Cell Biology, December 1^{st} –December 2^{nd} 2004, Bethesda, MD.

2. Reviewer for several peer-reviewed, high-ranked journals including: *Blood, Atherosclerosis, Thrombosis and Vascular Biology, Transplantation, American Journal of Transplantation, American Journal of Kidney Diseases, Nephrology Dialysis and Transplantation.*

VI. Report of Teaching

Undergraduate and Medical School Courses

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 Harvard Medical School hospitals (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital).

2004 Summer Students

Nicholas Andersen	Harvard Medical School
Anthony Giordano	SUNY Upstate Medical University
Atul Kamath	Harvard Medical School
Marc Mecoli	Univ. of Cincinnati School of Medicine
Mary Catherine Olson	Ohio State Univ. College of Medicine
Jeremiah Smith	Southern Illinois Univ. School of Med.

Dr. LoGerfo

As program director of the William J. von Liebig Research Training in Vascular Surgery summer program, six students were enrolled during the summer of 2004. Nicholas Anderson, from Harvard Medical School, spent the summer in my laboratory under the tutelage of Dr. Thomas Monahan (PGY-3). Nick has a keen interest in both surgery and research and has continued to work in the lab during his second year at the medial school. A second student, Anthony Giordano, from SUNY Upstate Medical School, work in our clinical office doing clinical research.

Dr. Christiane Ferran

The Vascular Immunobiology Laboratory had 3 summer students who spent between 8 and 11 weeks of work in the laboratory (June- August 2004). All benefited from bench top teaching as well as didactic teaching sessions

2004 Summer Students

Jeremiah Smith – Scholar of the Von Liebig Foundation for Vascular Biology, Medical student at South Western Medical School Illinois.
Himani Patel – Summer college student, currently sophomore at Boston University.
Roy Arjoon – Summer student, currently sophomore at Boston University.

Graduate School and Graduate Medical Courses

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 remain 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.

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.

Trainee	General Surgery Training Program
Thomas S. Monahan, M.D.	Brigham and Women's Hospital
Richard Bradford, M.D.	Beth Israel Deaconess Medical Center
Salvatore Scali, M.D.	Beth Israel Deaconess Medical Center
Gautam Shrikhande, M.D.	Beth Israel Deaconess Medical Center
Grace J. Wang, M.D.	Massachusetts General Hospital

Dr. LoGerfo

1. There are two post-graduates in my laboratory: Thomas Monahan, M.D. and Alexandra Popescu-Vladimir, M.D. Tom is a surgical resident in the BIDMC general surgery training program who is in his second year of the T-32 program. Alexandra is pursuing a position in a medical residency.

Dr. Ferran

1. Weekly teaching sessions for the 2 surgical residents and a Master of Science who are working in the laboratory, as well as informal bench based teaching.

    a. Salvatore T. Scali, MD. Surgical Resident, BIDMC.
    b. Gautam Shrikhande, MD. Surgical Resident, BIDMC.
    c. Sowmya Senani MS, Graduate Student.

Invited Presentations, (Local, National, and International)

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

1. Invited Speaker: "A20 and the Molecular Basis of Prometheus Myth". Beth Israel Deaconess Medical Center, Clowes Visiting Professorship Series. July 2004.

2. Invited Lecturer: "The Vascular Response to Injury". Beth Israel Deaconess Medical Center, Vascular Biology Course for Undergraduate Summer Students, August 2004.

3. Invited Speaker: "Xenotransplantation: State of the Art". Middle Eastern Society for Organ Transplanation; Ankara, Turkey. December 2004.

Christopher Longo, M.D. (Resident-Research Fellow)

1. Invited Speaker: "A20 Confers a Proliferative Advantage to Hepatocytes and Promotes Liver Regeneration". Dr. Longo was asked to give an oral presentation as one of three finalists for the surgical resident competition in the Department of Surgery, BIDMC. June 2004.

Virendra I. Patel, M.D. (Resident-Research Fellow)

1. Invited Speaker: "A20 Blocks Smooth Muscle Cell Activation and Proliferation and Inhibits Neointimal Hyperplasia". Dr. Patel was asked to present as a semi-finalist in the annual surgical research competition in the Department of Surgery, BIDMC. June 2004.

2. Invited Speaker: "A20 Induces Regression of Neointimal Lesions via Sensitization of Smooth Muscle Cells to Apoptosis". Dr. Patel was asked to

present as a semi-finalist in the annual surgical research competition in the Department of Surgery, BIDMC. June 2004.

Gautam Shrikhande M.D. (Resident-Research Fellow)

1. Invited Speaker: "Inadequate A20 Expression in the Vessel Wall of Diabetic Patients: Implication in Increased Atherosclerosis?" Dr. Shrikhande was asked to present as a semi-finalist in the annual surgical research competition in the Department of Surgery, BIDMC, June 2004.

Abstracts Presented at National Meetings

1. Contreras MA, **Monahan TS, Kalish JA,** Phaneuf MD, Dempsey DJ, Mitchell RN, Quist WC, **LoGerfo FW.** In *vivo* evaluation of a new dacron-polyurethane surface with vascular endothelial cell growth factor and recombinant hiuridin. Presented as a "Late Breaking Abstract at Experimental Biology, Abstract #69;LB337, April 2004.

2. **Monahan TS**, **Shrikhande GV**, Pomposelli FB, Skillman JJ, Campbell DR, Scovell SD, **LoGerfo FW**, Hamdan AD. Preoperative cardiac evaluation does not improve or predict perioperative or late survival in asymptomatic diabetic patients undergoing elective lower extremity arterial reconstruction. *Society for Vascular Surgery*, June 2004

3. **Shrikhande GV**, **Monahan TS,** Pomposelli FB, Skillman JJ, Campbell DR, Scovell SD, **LoGerfo FW,** and Hamdan AD. Left ventricular ejection fraction does not predict perioperative cardiac morbidity but does predict late survival in lower extremity arterial reconstruction. *New England Society for Vascular Surgery*, September, 2004.

4. Monahan TS, Contreras MA, Phaneuf MD, Anderson ND, Pompescu-Vladimir A, Bid MJ. Dempsey DJ, Mitchell RN, **LoGerfo FW**, Hamdan AD. In vivo testing of an infection resistant prosthetic material. *American College of Surgeons*, October 2004.

VII. Plans for the Coming Academic Year

Vascular Surgery Research Laboratory

Staff Changes/Recruitments

1. Dr. Monahan will return to the general surgery training program in June 2004.
2. Mr. Nicholas Andersen will join the lab on a full-time basis in May 2004.

Plans for Research

1. Continue to evaluate RNA interference technology. 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 infection-resistant Dacron sewing cuffs.

3. Prepare for implantation studies for biocomposite electrospun fibrous textile materials.

4. Initiate studies of matrix bonded biomaterials.

Vascular Immunobiology Laboratory- Staff changes/recruitments

1. Mark Fisher, M.D. is a surgical resident at the BIDMC who will begin a 2 year research fellowship supported by the T32. Dr. Fischer will start on July 1, 2005.

2. Duran Ustek, Ph.D. will come to the laboratory as a Research Fellow in 2005.

Plans for Research / Grant applications to be submitted

1. "Altered expression of angiogenic modulators in diabetic retinopathy" .RO1 to be submitted July 1st 2005 to the NIH –NIDDK. Principal Investigator: Christiane Ferran M.D., Ph.D.

VIII. Bibliography (1/1/04-12/31/04)

Original Articles

1. Aulivola B, Hamdan AD, Hile CN, Sheahan MG, Skillman JJ, Campbell DR, Scovell SD, **LoGerfo FW,** Pomposelli FB. Major lower extremity amputation: Outcome of a modern series. *Arch Surg* 2004;139(4):395-9.

2. Aulivola B, Hamdan AD, Hile CN, Sheahan MG, Skillman JJ, Campbell DR, Scovell SD, **LoGerfo FW**, Pomposelli FB. Popliteal artery aneurysms: a comparison of outcomes in elective versus emergent repair. *J Vasc Surg* 2004;39(6):1171-7.

3. Choi H, Bide MJ, Phaneuf MD, Quist WC, **LoGerfo FW**. Antibiotic treatment of silk to produce novel infection-resistant biomaterial". *Textile Res J* 2004;74(4):333.

4. Daniel S, Arvelo MB, Patel VI, Longo CR, Shrikhande G, Shukri T, Mahiou J, Sun DW, Mothley C, Grey ST, **Ferran C**. A20 protects from TNF, Fas and NK mediated cell death by inhibiting caspase 8 activation. *Blood* 2004;104(8):2376-84.

5. Makhlouf L, Grey ST, Dong V, Csizmadia E, Arvelo MB, Auchincloss H Jr., **Ferran C***, Sayegh MH* (*co-last authors). Depleting anti-CD4 monoclonal antibody cures new onset, prevents recurrent autoimmune diabetes and delays allograft rejection in non-obese diabetic mice. *Transplantation* 2004; 777: 990-7.

6. Song R, Zhou Z, Kim PKM, Shapiro RA, Liu F, **Ferran C**, Choi AMK, Otterbein LE. Carbon monoxide promotes Fas/CD95-induced apoptosis in Jurkat cell. *J Biol Chem* 2004; 279(43):44327-34.

Original Articles (in press)

1. Monahan TS, Shrikhande GV, Pomposelli FB, Skillman JJ, Campbell DR, Scovell SD, **LoGerfo FW, Hamdan AD**. Preoperative cardiac evaluation does not improve or predict perioperative or late survival in asymptomatic diabetic patients undergoing elective lower extremity arterial reconstruction. *J Vasc Surg* 2004; in press.

2. Scovell SD, **LoGerfo FW**, **Hamadan AD**. Preoperative cardiac evaluation does not improve or predict perioperative or late survival in asymptomatic diabetic patients undergoing elective lower extremity arterial reconstruction". *J Vasc Surg* 2004; in press.

3. Storz P, Doppler H, **Ferran C**, Grey ST, Toker A. Functional dichotomy of A20 in apoptotic and necrotic cell death. *Biochem J* 2004; in press.

Books, Monographs, and Text Books (in press)

1. **LoGerfo FW**, Hamdan AD. Management of foot lesions in the diabetic patient. In: Vascular Surgery, 6th Ed. Rutherford, RB., 2004; in press.

2. Nadig SN, **Hamdan AD**. Atherosclerosis and peripheral vascular disease: sequelae obesity and diabetes. In: Obesity and Diabetes. Humana Press 2004; in press.

Dr. Allan Hamdan