



DEPARTMENT OF SURGERY

Research Opportunities for Residents
2009-2010

James S. Goydos, M.D.

Division of Surgical Oncology

Dr. Goydos' research interests continue to be centered on a newly discovered set of oncogenes that appear to be important in the pathogenesis of melanoma and other cancer types including breast cancer and colon cancer. These genes, known as Metabotropic Glutamate Receptors (GRMs), are being studied in Dr. Goydos' laboratory and he has developed a consortium of researchers at CINJ and Rutgers that is working on different aspects of GRM interactions in cancer. These other researches include Dr. Joseph Bertino, Dr. Eileen White, Dr. Suzie Chen, Dr. David Gorski, Dr. Eric Rubin, and Dr. Michael Reiss. Residents rotating through this lab may work on any of multiple projects that are currently ongoing including laboratory correlative studies of an ongoing project entitled "*A Phase 0 Trial of Riluzole in Patients with Resectable Stage III and IV Melanoma*" that involves examination of human melanoma samples obtained from patients receiving a glutamate-blocking agent on this trial. Other projects include work on different aspects of an R01-funded study entitled "*Validating Grm1 as a Therapeutic Target in Melanoma*" that involves bench top studies and animal work. Finally, we are involved in multiple National and International collaborations using melanoma tissues and cell lines and the Residents often help with these studies as well. Dr. Goydos' laboratory is mainly involved in Translational Research, moving laboratory discoveries to the clinic and studying clinical specimens in the lab. His lab is located in the CINJ main building and is staffed by experienced technicians who can help with all aspects of the projects.

Contact information

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Stephen F. Lowry, M.D. & Steve Calvano, Ph.D.
Division of Surgical Sciences

The main focus of our laboratory is to understand the mechanisms that underlie the systemic inflammatory response that occurs in severely injured patients or those with infections. Approximately twenty years ago, this laboratory was involved in seminal work that demonstrated that cytokines elaborated from mononuclear phagocytes play a major role in initiating and amplifying the systemic inflammatory response. We continue to investigate the regulation of pro- and anti-inflammatory cytokines and their receptors. Additionally, we have embarked on studies investigating the importance of leukocyte turnover in modulation of the systemic inflammatory response. At the molecular/genetic level we are working to determine the effects of genetic mutations and polymorphisms on the susceptibility and clinical course of patients with systemic inflammation or sepsis. Finally, gene expression array and real-time PCR analyses are being used to determine changes in the pattern of gene expression in normal volunteers given a small dose of bacterial endotoxin, normal volunteers subjected to different routes of nutritional support, and patients in the SICU setting.

Our laboratory employs a four-pronged approach using *in vitro* models, animal models, normal human volunteer studies conducted in the Clinical Research Center and studies of severely-injured ICU patients. This approach facilitates the rapid translation of laboratory and basic science findings to the clinic.

Recent Publications:

Qian WJ, Jacobs JM, Camp DG, Monroe ME, Moore RJ, Gritsenko MA, **Calvano SE, Lowry SF**, Xiao W, Moldawer LL, Davis RW, Tompkins RG, Smith RD. Comparative proteome analyses of human plasma following *in vivo* lipopolysaccharide administration using multidimensional separations coupled with tandem mass spectrometry. *Proteomics* 5:572-584, 2005

Cobb JP, Mindrinos MN, Miller-Graziano C, **Calvano SE**, Baker HV, Xiao W, Laudanski K, Brownstein BH, Elson CM, Hayden DL, Herndon DN, **Lowry SF**, Maier RV, Schoenfeld DA, Moldawer LL, Davis RW, Tompkins RG. Application of genome-wide expression analysis to human health and disease. *Proc Natl Acad Sci (USA)* 102:4801-4806, 2005

Qian WJ, Monroe ME, Liu T, Jacobs JM, Anderson GA, Shen Y, Moore RJ, Anderson DJ, Zhang R, **Calvano SE, Lowry SF**, Xiao W, Moldawer LL, Davis RW, Tompkins RG, Camp DG, Smith RD. Quantitative proteome analysis of human plasma following *in vivo* lipopolysaccharide administration using 16O/18O labeling and the accurate mass and time tag approach. *Mol Cell Proteomics* 4:700-709, 2005

Wittebole X, Coyle SM, Kumar A, Goshima M, **Lowry SF, Calvano SE**. Expression of tumour necrosis factor receptor and Toll-like receptor 2 and 4 on peripheral blood leucocytes of human volunteers after endotoxin challenge: a comparison of flow cytometric light scatter and immunofluorescence gating. *Clin Exp Immunol* 141:99-106, 2005

Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, Chen RO, Brownstein BH, Cobb JP, Tschoeke SK, Miller-Graziano C, Moldawer LL, Mindrinos MN, Davis RW,

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Tompkins RG, **Lowry SF**. A network-based analysis of systemic inflammation in humans. *Nature* 437:1032-1037, 13 Oct 2005.

Nathens AB, Johnson JL, Minei JP, Moore EE, Shapiro M, Bankey P, Freeman B, Harbrecht BG, **Lowry SF**, McKinley B, Moore F, West M, Maier RV. Inflammation and the host response to injury, a large-scale collaborative project: Patient-oriented research core-standard operating procedures for clinical care: I. Guidelines for mechanical ventilation of the trauma patient. *J Trauma* 59:764-769, 2005.

Bowers DJ, **Calvano JE**, Alvarez SM, Coyle SM, Macor MA, Kumar A, Calvano SE, **Lowry SF**. Polymorphisms of heat shock protein-70 (HSPA1B and HSPA1L LOCI) do not influence infection or outcome risk in critically ill surgical patients. *Shock* 25:117-122, 2006.

Kotani J, Avallone NJ, Lin E, Goshima M, **Lowry SF**, **Calvano SE**. Tumor necrosis factor receptor regulation of bone marrow cell apoptosis during endotoxin-induced systemic inflammation. *Shock* 25:464-471, 2006.

Calvano JE, Bowers DJ, Coyle SM, Macor M, Reddell MT, Kumar A, **Calvano SE**, **Lowry SF**. Response to systemic endotoxemia among humans bearing polymorphisms of the toll-like receptor 4 (hTLR4). *Clin Immunol* 121:186-190, 2006.

Coyle SM, **Calvano SE**, **Lowry SF**. Gender influences *in vivo* human responses to endotoxin. *Shock* 26:538-543, 2006.

Payen D, Sablotzki A, Barie PS, Ramsay G, **Lowry S**, Williams M, Sarwat S, Northrup J, Toland P, Booth FV. International integrated database for the evaluation of severe sepsis and drotrecogin alfa (activated) therapy: analysis of efficacy and safety data in a large surgical cohort. *Surgery* 141:548-561, 2007.

Wittebole X, Hahm S, Coyle SM, Kumar A, **Calvano SE**, **Lowry SF**. Nicotine exposure alters *in vivo* human responses to endotoxin. *Clin Exp Immunol* 147:28-34, 2007.

Gupta A, Berg DT, Gerlitz B, Richardson MA, Galbreath E, Syed S, Sharma AC, **Lowry SF**, Grinnell BW. Activated protein C suppresses adrenomedullin and ameliorates lipopolysaccharide-induced hypotension. *Shock* 28:468-476, 2007.

Alvarez SM, Katsamanis-Karavidas M, Coyle SM, Lu S-E, Macor M, Oikawa LO, Lehrer P, **Calvano SE**, **Lowry SF**. Low-dose steroid alters *in vivo* endotoxin-induced systemic inflammation but does not influence autonomic dysfunction. *J Endo Res* 13:358-368, 2007.

Lowry SF, **Calvano SE**. Challenges for modeling and interpreting the complex biology of severe injury and inflammation. *J Leuk Biol* 83:553-557, 2008.

Russom A, Sethu P, Irimia D, Mindrinos MN, **Calvano SE**, Garcia I, Finnerty C, Tannahill C, Abouhamze A, Wilhelmy J, Lopez MC, Baker HV, Herndon DN, **Lowry SF**, Maier RV, Davis RW, Moldawer LL, Tompkins RG, Toner M, and the Inflammation and Host Response to Injury Large Scale Collaborative Research Program. Microfluidic leukocyte isolation for gene expression analysis in critically ill hospitalized patients. *Clin Chem* 54:891-900, 2008.

Dhainaut, JF, Laterre PF, Janes J, Artigas A, Beilman G, Fein IA, de Figueiredo L, Heiselman D, Levine RL, Schein R, Seneff M, Sollet JP, Bailey J, Booth F, Meyer MC, Nelson DR, Sashegyi A, **Lowry SF**. International integrated database for the evaluation of severe sepsis (INDEPTH): Clinical evaluation committee report on the safety of drotrecogin alfa (activated) therapy. *Curr Med Res Opin* 24:1187-1197, 2008.

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Towfigh S, Cheadle WG, **Lowry SF**, Malangoni MA, Wilson SE. Significant reduction in incidence of wound contamination by skin flora through use of microbial sealant. Arch Surg 143:885-891, 2008.

Artigas A, Beilman G, Dhainaut JF, Fein A, de Figueiredo L, Heiselman D, Laterre PF, Levine R, **Lowry S**, Schein R, Seneff M, Sollet JP, Janes J, Bailey J, Toland P, Booth F, Sashegyi A, Meyer MC. International integrated database for the evaluation of severe sepsis (INDEPTH): Clinical evaluation committee report on the safety of drotrecogin alfa (activated) therapy (DrotAA). Surgery (in press), 2008.

Kleiman DA, Calvano JE, Coyle SM, Macor MA, **Calvano SE**, **Lowry SF**. A single nucleotide polymorphism in the *MDM2* promoter and risk of sepsis. Am J Surg (in press), 2008.

Foteinou PT, **Calvano SE**, **Lowry SF**, Androulakis IP. Translational potential of systems-based models of inflammation. Clin Transl Sci (in press), 2008.

Foteinou PT, **Calvano SE**, **Lowry SF**, Androulakis IP. Modeling Endotoxin-Induced Systemic Inflammation Using an Indirect Response Approach. Math Biosci (in press), 2008.

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Gary B. Nackman, M.D.
Division of Vascular Surgery

Dr. Nackman supervises the research laboratory of the Division of Vascular Surgery. The central objective of the basic science program is to develop an improved understanding of the important cell-cell and cell-biomaterial interactions within the vasculature. The focus of this program has been translational research. The areas of interest include:

Identifying mechanisms responsible for vascular wall remodeling
Measuring hemodynamic forces in blood vessels
Studying the interactions of the constituent cells of a blood vessel with biomaterials
Identifying mechanisms responsible for shear stress induced endothelial detachment from biomaterials

We have developed and validated a unique endothelial cell-smooth muscle cell flow model co-culture system. This novel model provides a better understanding of the role of ECs in the modulation of SMC behavior, and the ability to study methods to improve endothelial cell adaptation to the mechanical force of shear stress. We have identified that human vascular smooth muscle cells improve endothelial cell adaptation to shear stress and have used this observation to initiate a program to study methods of improving endothelial adaptation. This project is funded by both the NIH and the NJ Center for Biomaterials. An exciting research direction has been a focus on understanding why man is unable to heal a prosthetic vascular graft with an endothelium, a distinct difference from other mammals.

The laboratory is fully equipped to perform cell culture, protein chemistry, immunohistochemistry, animal protocols, molecular biology and fluid-flow experiments. Personnel include a full time laboratory technician with over 10 yr. of experience and a graduate student. Dr. Nackman spends 75% of his time focused on Research and directly supervises residents and students. In the past, a vascular surgery fellow has spent time in the laboratory as well. However, with increased clinical demands and the need to become proficient in endovascular surgery, the fellows have had a decreased emphasis on basic science research in recent years. There is a good balance of opportunity for joining existing projects along with the development of independent projects for residents. Individuals that have previously spent time in the laboratory have presented their work at many national and regional forums including the Society of University Surgeons, Association for Academic Surgery, Society of Vascular Surgery, NJ Vascular Society, and the NJ chapter of the American College of Surgeons.

Gary B. Nackman, M.D.
Division of Vascular Surgery

Recent Publications:

Imegwu O, Graham AM, Nackman GB, Heterotypic Smooth Muscle Cell/Endothelial cell interactions differ between species. J Surg Res 2001; 98(2):85-88.

Nackman GB, Adrienne B, Graham A, Predictors of health following surgery for aortoiliac occlusive and aneurysmal disease, presented at the 62nd annual meeting of the SUS, Chicago, 2001, Surgery 2001; 130(2):370-377.

Nackman GB, Sutyak J, Lowry SF, Rettie C. Predictors of educational outcome: factors impacting performance on a standardized clinical evaluation, presented at the 35th annual meeting for the AAS, Nov. 2001. J surg Res 2002; 106(2):314-318.

Brevetti LA, Nackman GB, Shindelman LE, Ciocca RG, Crowley JG, Graham AM. Influence of endovascular training on fellowship and general surgical training. J Surg Res, 107:319-320, Sept. 2002.

Nackman GB, Bermann M, Hammond J. Effective use of human simulators in surgical education. J Surg Res, 2003.

Brevetti LS, Nackman GB, Shindelman LE, Ciocca RG, Crowley JG, Graham AM, Influence of an endovascular program on surgical training. J Surg Res 115(1):100-105, 2003.

Vogel TR, Shindelman LE, Nackman GB, Graham AM, Efficacious use of nitinol stents in the femoral and popliteal arteries. J of Vasc Surg, 2003.

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Edmund C. Lattime, Ph.D.
Division of Surgical Oncology

The primary focus of our laboratory is the study of the tumor host interaction with the ultimate goal being the design of effective immunotherapy regimens for cancer. The interaction between the host immune system and tumor is a multifaceted one with the generation of productive immunity requiring the cooperation of immune cells from multiple lineages. Tumor recognition involves the expression of a number of cell surface molecules and once activated, lymphocytes produce a cascade of regulatory factors leading to the expression of localized and systemic immune responses. Further complicating the system, tumor cells themselves can produce immune suppressive factors.

In studies of human melanoma and bladder cancer with relevant murine models of each, our laboratory has characterized the tumor host interaction and is the first to have shown that the cytokine IL10 which down regulates the development of cellular immunity is produced in both types of cancer in-vivo. In addition, we have discovered that epithelial bladder tumor cells are capable of presenting soluble antigens to the immune system, thus suggesting a new approach to tumor immunotherapy.

Following the above characterization, a significant focus of current studies in our laboratory lies in the development of genetic approaches towards immunotherapy. Recombinant vaccinia virus vectors are being explored as a means of transfecting tumor cells in-vivo in-situ with the ultimate goal of enhancing immunity. In this approach, viruses are engineered to contain the genes for immunologic helper factors such that when injected into tumors, they infect the tumor cells and cause the infected tumor to produce the enhancing cytokines. In a related approach, viruses are also being engineered to inhibit the production of tumor produced factors such as IL10 above which suppress the immune response.

Most recently, studies in our laboratory have included a new initiative towards the design of genetic vaccine strategies for breast cancer. Given an enhanced understanding of how immune responses are not only initiated but focused towards cell mediated or humoral (antibody producing) arms, we are in the process of “designing” genetic vaccines which will enhance the specific arms of an immune response. This latter focus will be greatly enhanced by the outstanding clinical and basic science resources focused on breast cancer at The Cancer Institute of New Jersey.

In addition to the above preclinical studies, we have translated these studies into active clinical trials. We are currently accruing to Phase I trial in bladder cancer where, as described above, we are instilling a recombinant poxvirus that encodes the gene for GM-CSF into the bladder of patients before cystectomy. We have already demonstrated success in gene transfer into the bladder epithelium and enhanced immune cell infiltration. We hope to open a second study of intra-pancreatic gene transfer in patients with inoperable pancreas cancer. Both studies have significant opportunity for carrying out correlative studies of gene transfer and bioavailability as well as the examination of local and systemic immune responses.

Edmund C. Lattime, Ph.D.
Division of Surgical Oncology

Relevant Publications:

Mastrangelo, M.J., Maguire, H.C. Jr., Eisenlohr, L.C., Laughlin, C.E., Monken, C.E., McCue, P.A., Kovatich, A.J., and Lattime, E.C. Intratumoral recombinant GM-CSF encoding virus as gene therapy in patients with cutaneous melanoma *Cancer Gene Therapy* 1999, 6:409-422.

Gomella, L.G., Mastrangelo, M.J., McCue, P.A., Maguire, H.C. Jr., Mulholland, S.G., and Lattime, E.C. Phase I study of intravesical vaccinia virus as a vector for gene therapy of bladder cancer 2001, *J. Urology* 166(4):1291-5.

Yang, A.S. and Lattime, 2003 E.C. Tumor-induced IL-10 Suppresses the Ability of Splenic Dendritic Cells to Stimulate CD4 and CD8 T Cell Responses. *Cancer Res.* 63:2150-2157.

Yang, A.S. and Monken, C.E., and Lattime, E.C. 2003 Intratumoral vaccination with vaccinia expressed tumor antigen and GM-CSF overcomes immunological ignorance to tumor antigen. *Cancer Research* 63:6956-6961.

Strair, R.K., Schaar, D., Medina, D., Todd, M.B., Aisner, J., DiPaola, R.S., Manago, J., Knox, B., Jenkinson, A., Senzon, R., Baker, C., Dudek, L., Ciardella, M., Kuriyan, M., Rubin, A. and Lattime, E.C. 2003, Anti-neoplastic effects of partially HLA-matched irradiated blood mononuclear cells in patients with renal cell carcinoma, *J. Clin., Oncol.* 21:3785-3791..

Yang, A.S., and Lattime, E.C. Interleukin-10-induced immune suppression in cancer. In: *Cancer Immunotherapy at the Crossroads: How Tumors Evade Immunity and What Can Be Done*, edited by J. H. Finke and R. M. Bukowski, Humana Press, New Jersey 2003, p. 157-172.

DiPaola, R., Plante, M., Kaufman, H., Petrylak, D., Israeli, R., Lattime, E., Manson, K., Schuetz, T. 2006, A Phase I trial of pox PSA vaccines (PROSTVAC(R)-VF) with B7-1, ICAM-1, and LFA-3 co-stimulatory molecules (TRICOMtrade mark) in patients with prostate cancer, *J. Transl. Med.* 4:1-5.

Lattime, E.C. and Gerson, S.L. Introduction: gene therapy of cancer. *Seminars in Oncology* 2006; 32: 535-536.

Zhang, Z., Monken, C.E., Zhang, Y., Lenard, J., Mizushima, N., Lattime, E.C., Jin, S., 2006. Cellular autophagy machinery is not required for vaccinia virus replication and maturation, *Autophagy* 2:91-95.

Ge, R., Rajeev, V. Ray, P., Lattime, E.C., Rittling, S., Medicherla, S., Protter, A., Murphy, A., Chakravarty, J., Dugar, S., Schreiner, G., Barnard, N., and Reiss, M. 2006. Inhibition of growth and metastasis of mouse mammary carcinoma by selective inhibitor of transforming growth factor- β type I receptor kinase in-vivo. *Clin. Cancer Research* 12:4315-4330,

Beatrice Haimovich, Ph.D.
Division of General Surgery

Residents are invited to participate in a research project in the emerging field of autophagy. Autophagy is a process used by cells to compartmentalize and self-digest long-lived and/or damaged proteins and organelles. The process is also triggered under stress-conditions such as periods of nutrient deprivation when the cell “eats” itself in order to survive. In the course of autophagy, cargos, including damaged mitochondria or proteins, are sequestered into double-membrane enclosed vesicles/vacuoles called autophagosomes. The cargos are then delivered to the interior of lysosomes where they are ultimately consumed by resident hydrolases. The early stages of autophagy are regulated by a number of autophagy related genes (Atg). Pharmacological inhibitors of autophagy and Atg targets for suppression of autophagy by small interfering RNAs (siRNAs) have been described and can be used to manipulate autophagy *in vitro*.

Circulating monocytes and tissue macrophages are important cellular components of host immune surveillance. Lipopolysaccharide (LPS; endotoxin) derived from the outer wall of Gram-negative bacteria is a major inducer of host inflammatory responses. LPS binds to receptors expressed on the surface of monocytes and macrophages. Although excessive inflammatory responses triggered by LPS can lead to sepsis, there is also evidence that exposure to LPS enhances host resistance against invading pathogens. The goal of our research effort is to test the hypothesis that LPS enhances the host resistance to pathogens by triggering autophagy. The study is expected to reveal crucial information related to host-pathogen interaction and mechanisms for immune cell survival in the face of a pathogenic challenge. If the proposed link between the protective effect of LPS and autophagy is confirmed, it will impact new avenues for investigation and targets for development of pharmacological interventions that could prevent sepsis and/or improve survival.

Select Publications Co-authored by Residents

1. DiFazio, L.T., C. Stratoulis, R.S. Greco, and B. Haimovich. 1994. Multiple platelet surface receptors mediate platelet adhesion to surfaces coated with plasma proteins. *Journal of Surgical Research*. 57:133-137.
2. Katz, D.A., Haimovich, B., and R.S. Greco. 1994. Neutrophil activation by expanded polytetrafluoroethylene is dependent on the induction of protein phosphorylation. *Surgery*. 116:446-455.
3. Katz, D.A., Haimovich, B., and R.S. Greco. 1995. The FcγRII, FcγRIII, and CD18 receptors mediate in part neutrophil activation on a plasma coated ePTFE surface. *Surgery*. 118:154-161.
4. Haimovich, B. DiFazio L., Katz, D., Greco, R.S., Dror, Y., and A. Freeman. 1997 A new method for membrane construction on ePTFE vascular grafts: effect on surface morphology and platelet adhesion. *Journal of Applied Polymer Science*. 63:1391-1400.
5. De La Cruz, C. Haimovich, B. and R.S. Greco. 1998. Immobilized IgG and Fibrinogen differentially effect the cytoskeletal organization and bactericidal function of adherent neutrophils. *Journal of Surgical Research* 80:28-34.
6. De La Cruz, C. B. Haimovich, and R.S. Greco. 1998 Adhesion to ePTFE and Dacron induces neutrophil death. *Surgical Forum* XLIX:326-328.
7. Haimovich, B., Ji, P. Ginalis, E. Kramer, R. and Greco, R.S. 1999. Phospholipase A2 enzymes regulate αIIbβ3-mediated, but not FcγRII receptor-mediated, pp125FAK phosphorylation in platelets. *Thrombosis and Haemostasis* 81:618-624.

Beatrice Haimovich, Ph.D.

Division of General Surgery

Select Publications Co-authored by Residents

8. Nazdam J, De La Cruz, C. Greco, R.S. and B. Haimovich. 2000. Neutrophil adhesion to vascular prosthetic surfaces triggers a non-apoptotic cell death *Annals of Surgery*, 231:587-599.
9. Nazdam J., Haimovich, B. and Greco, R.S. 1999. N-acetyl-L-cysteine, cyclosporin, and cytochalasin D inhibit neutrophil death on vascular prosthetic surfaces. *Surgical Forum IX*:529-531.
10. Popowich Y., Greco, R.S., and Haimovich, B. 2001. PMN exposure to a quantified bacterial load leads to a rapid, nonapoptotic cell death. *Surgical Forum LII*:344-346.
11. Chang, S. Popowich, Y, Greco R.S. and Haimovich, B. 2003. Neutrophil survival on biomaterials is determined by surface topography. *Journal of Vascular Surgery*, 37:1082-90.

Recent Publications

- 1: [Haimovich B, Venkatesan MM.](#)
Shigella and Salmonella: death as a means of survival.
Microbes Infect. 2006, 8(2):568-77. Review. PMID: 16297650
- 2: [Zhang Z, Lin SY, Neel BG, Haimovich B.](#)
Phosphorylated alpha-actinin and protein-tyrosine phosphatase 1B coregulate the disassembly of the focal adhesion kinase c-Src complex and promote cell migration.
J Biol Chem. 2006, 281(3):1746-54. PMID: 16291744
- 3: [Koterski JF, Nahvi M, Venkatesan MM, Haimovich B.](#)
Virulent *Shigella flexneri* causes damage to mitochondria and triggers necrosis in infected human monocyte-derived macrophages.
Infect Immun. 2005, 73(1):504-13. PMID: 15618190

Peter M. Scholz, M.D.
Division of Cardiothoracic Surgery

Cardiac Physiology Laboratory

The main emphasis of our basic science laboratory is to understand how the second messenger cyclic nucleotides cGMP and cAMP regulate cardiac function and metabolism in health and disease. The incidence of congestive heart failure is steadily increasing . With the limited number of patients able to receive a cardiac transplant - the only definitive treatment- finding ways of prevention is of paramount importance. Cardiac hypertrophy represents a positive, adaptive response to chronically elevated workload but is also a primary risk factor for the development of congestive heart failure. One of our previous residents in the laboratory was the first to show that the cGMP pool is markedly elevated in an experimental model of hypertrophy as a result of increased production.

The nitric oxide-cyclic GMP (cGMP) and the natriuretic peptide-cGMP signal transduction systems act as "endogenous brakes" in isolated cardiac myocytes and in intact hearts. It has a protective role against excessive sympathetic activity in pressure overload hypertrophy. In heart failure, the myocardial cyclic GMP level is further elevated but its negative functional and metabolic effects are reduced due to a defect in its signaling pathway. The primary objective of this laboratory is to determine the mechanism(s) responsible for the maladaptation of the nitric oxide-cGMP system and more recently the natriuretic peptide signaling system in heart failure and to correct it. The longterm goals are to determine the mechanism that initiates the transition from compensated cardiac hypertrophy to congestive heart failure and develop novel strategies for its prevention.

Our research interests also include the role cGMP plays in ischemia / reperfusion, stunning and aging.

Over the years we have developed a number of experimental models of cardiac hypertrophy and failure in dogs and rabbits. More recently we have established a pressure overload model in mice using transverse aortic constriction. Subjecting specific knockout and transgenic mouse models to the stress of pressure overload will give us new tools to study the mechanisms of interest. With the established clinical heart transplant program at Robert Wood Johnson Medical School we are also able to extent our studies to human heart failure.

The laboratory has been supported by the NIH since 1988. It is well equipped and has a large team to help carry out the necessary functional, metabolic and biochemical studies in intact animal preparations as well as in isolated cardiomyocytes. The research experience for the residents has always been very productive. They are able to participate in numerous ongoing projects as well as pursue new ideas of their own. All residents from our laboratory have presented their work at national meetings.

Peter M. Scholz, M.D.
Division of Cardiothoracic Surgery

RECENT PUBLICATIONS:

Leone RJ, Straznicka M, Scholz PM and Weiss HR: Cyclic GMP attenuates cyclic AMP stimulated inotropy and oxygen consumption in control and hypertrophic hearts. *Bas Res Cardiol* 95:28-38, 2000.

Straznicka M, Scholz PM, Gong G, Weiss HR: Nitroprusside reverses lengthened time of contraction in stunned canine cardiac myocytes. *J Cardio Pharm* 35:219-226, 2000.

Patel KN, Weiss HR, Scholz PM: Reduction in the level of cardiac cyclic GMP worsens contractile delay in myocardial stunning. *J Surg Research* 92, 114-119, 2000.

Patel KN, Yan L, Gandhi A, Scholz PM, Weiss HR: Interaction between the opposing functional effects of cyclic AMP and cyclic GMP in hypertrophic cardiac myocytes. *Basic Research in Cardiology* 96(1):34-41, 2001.

Lazar MJ, Patel K, Scholz PM and Weiss HR: Ethanol-induced reduction in myocardial O₂ consumption can be attenuated by inhibiting guanylyl cyclase. *J Cardiovasc Pharmacol* 38:512-519, 2001.

Zhang Q, Molino B, Yan L, Haim T, Vaks Y, Scholz PM and Weiss HR: Nitric oxide and cGMP protein kinase activity in aged ventricular myocytes. *Am J Physiol Heart Circ* 281:H2304-H2309, 2001.

Huang, M.W., P.M. Scholz and H.R. Weiss. Increases in myocardial cyclic GMP attenuate contractile delay in myocardial stunning. *Can. J. Physiol. Pharmacol* 80(8):804-810, 2002

Weiss, H.R., M.J. Lazar, J. Tse and P.M. Scholz. Aging blunts nitric oxide s effects on myocardial O₂ consumption. *Clin. Exp. Pharmacol. Physiol.* 29(10):924-930, 2002

Rodriguez R, Molino B, Weiss HR, Scholz PM: Negative metabolic and coronary flow effects of decreases in cAMP and increases in cGMP in control and renal hypertensive rabbit hearts. *J Appl Physiol* 97: 439-445, 2004

Zhang Q, Scholz PM, He Y, Tse J, Weiss HR: Cyclic GMP signaling and regulation of SERCA activity during cardiac myocyte contraction. *Cell Calcium*: 37:259-266, 2005

Su J, Scholz PM and Weiss HR: Differential effects of cyclic GMP produced by soluble and particulate guanylyl cyclase on mouse ventricular myocytes. *Exp Biol Med* 230:242-250, 2005

Zhang Q, Lazar M, Molino B, Rodriguez, Davidov T, Su J, Tse J, Weiss HR, Scholz PM: Reduction in interaction between cGMP and cAMP in dog ventricular myocytes with hypertrophic failure. *Am J Physiol* 289:H1251-H1257, 2005

Peter M. Scholz, M.D.
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RECENT PUBLICATIONS:

Su, J, Tse J, Scholz PM, Weiss HR: Alterations in ventricular myocyte contraction caused by C-type natriuretic peptide and nitric oxide in eNOS-/-mice. *J Mol Cell Card* 39(6):920-8, 2005

Davidov T, Weiss HR, Tse J, Scholz PM: Chronic nitric oxide synthase blockade desensitizes the heart to the negative metabolic effects of nitric oxide. *Life Sci.* 2006 Sep 20;79(17):1674-80

Katz E, Zhang Q, Weiss HR, Scholz PM: T4-induced cardiac hypertrophy disrupts cyclic GMP mediated responses to brain natriuretic peptide in rabbit myocardium. *Peptides.* 2006 Sep;27(9):2276-83.

Zhang Q, Goel N, Rodriguez R, Scholz PM, Weiss HR: Importance of ryanodine receptors in effects of cyclic GMP is reduced in thyroxine-induced cardiac hypertrophy. *Eur J Pharmacol.* 2006 May 10;537(1-3):45-51.

Moalem J, Davidov T, Zhang Q, Grover GJ, Weiss HR, Scholz PM: Negative inotropic effects of C-type natriuretic peptide are attenuated in hypertrophied ventricular myocytes associated with reduced cyclic GMP production. *J Surg Res.* 2006 Sep;135(1):38-44.

Moalem J, Weiss HR, Davidov T, Rodriguez R, Molino B, Lazar MJ, Scholz PM: Heart failure reduces both the effects and interaction between cyclic GMP and cyclic AMP. *J Surg Res.* 2006 Aug;134(2):300-6.

Zhang S, Rodriguez R, Scholz PM, Weiss HR: Functional interaction of a beta-adrenergic agonist and cyclic GMP phosphodiesterase inhibitor in control and hypertrophic cardiomyocytes. *Pharmacology.* 2006; 76(2): 53-60.

Moalem J, Davidov T, Katz E, Scholz PM, Weiss HR: Atrial natriuretic peptide reverses the negative functional effects of stunning in rabbit myocardium. *Regul Pept.* 2005 Dec 15;132(1-3):47-52.

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Division of Neurosurgery
Member, Cancer Institute of New Jersey

Stem Cell Therapeutics

Our research focus is on genetic engineered stem cells for therapeutic regenerative medicine, and we are one of the first laboratories in the nation to receive public funding for stem cell biology through the New Jersey Commission on Stem Cell Research. One current project focuses on the isolation and characterization of 'adult' stem cells from human placenta, in collaboration with Celgene Cellular Therapeutics. A second project focuses on the use of chemotactic receptors to manipulate embryonic stem cells in vitro, such that we can direct their migration and fate determination upon cell transplant in vivo. We use several experimental models and techniques including cell/molecular biology and classical and reverse genetics. Cells are engineered in vitro using gene transfer technology for both gain and loss of function analysis. Cells are then examined after transplantation in preclinical models in vivo, including their ability to rescue a genetic deficiency and their ability to promote tissue repair after trauma.

Recent Publications:

Yoshikawa, S. et al. (2003). Wnt-mediated axon guidance through the Drosophila Derailed receptor. *Nature* 422:583-588.

Bennett, M.R. et al. (2003). Aberrant growth and differentiation of CNS glial progenitors in neurofibromatosis type 1 mutants. *J. Neuroscience* 23:7207-7217.

Wong, Y.F., et al. (2003). Expression genomics of cervical cancer: molecular classification and prediction of radiotherapy response by DNA microarray. *Clinical Cancer Research* 9: 5485-5492.

R.D. McKinnon, S. Waldron and M.E. Kiel (2005). PDGF alpha-Receptor Signal Strength Controls an RTK Rheostat That Integrates Phosphoinositol 3'-Kinase and Phospholipase C-gamma Pathways during Oligodendrocyte Maturation. *J. Neuroscience* 25(14): 3499-3508.

Labrador, J.P., D. O'Keefe, S. Yoshikawa, R.D. McKinnon, J.B. Thomas and G. Bashaw (2005). The homeobox transcription factor even-skipped regulates Netrin-receptor expression to control dorsal motor-axon projections in *Drosophila*. *Current Biol.* 15(15):1413-1419.

Reilly, J.E., A. Chang, A. Gordon, D. Zhao, K. Chen, M. Kiel, D.O'Keefe, S. Yoshikawa, J.B. Thomas and R.D. McKinnon. Asymmetric distribution of attractive (DCC/Unc40) and repulsive (Unc5) netrin receptors on migrating glia (in preparation).

Paul B. Haser, M.D.
Division of Vascular Surgery

My research efforts have been focused on two areas of vascular surgery which the Division has developed as areas of tertiary expertise: aortic aneurysmal disease and carotid disease. Access to a large patient population has allowed clinical data gathering as part of patient care to be valuable as a guide towards present care, as well as newer technologies that have afforded less invasive intervention. Past SF-36 data as well as the on-going collection of the patients psychosocial interaction, and a planned economic impact and perception regarding the care will further round out the community impact aneurysmal disease has had/will potential have for New Jersey. Our Division's ability to compare our large series with state and national database registries as part Todd Vogel, M.D., M.P.H - another member of the Division of Vascular Surgery - will further assist in developing a greater understanding of the importance aneurysmal disease has as well as potential influence health care policies.

In regards to carotid surgery, because of the large potential study population and the past record of superior results within the Division, interest in the impact of present open surgical correction (carotid endarterectomy) as well as newer primarily investigational aspects of stenting intervention allows us the opportunity to look directly at both clinical and bench model research. Utilizing both database analysis as well as bench model ex-vivo specimens, direct correlation to the intervention can be studied. Because of our good fortune to have Shauhua Li, Ph.D. working with tissue culture and stem cell vascular studies, we have the chance to look at a direct bed-side to bench-work model for carotid intervention.

Present medical school student and Rutgers pre-medical student collaboration has begun to show promising results towards productive and interesting research. For further information, please feel free to contact me directly.

Sincerely,

Paul B. Haser, MD, FACS
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Henry Hsia, MD

Division of Plastic Surgery

Good surgical outcomes depend on wound healing that is successful, but not overly robust. In other words, fibrosis can be just as pernicious a problem for surgical patients as the poorly healing wound. However, our understanding of how our bodies achieve this balance remains incomplete, and so our ability to manage clinical situations when such balance is not achieved has remained likewise suboptimal, providing an impetus for my interest in wound healing research.

My research focuses on understanding the biological mechanisms behind tissue repair and scarring, and more specifically, on the role that the extracellular matrix plays in regulating wound cell behavior. While the importance of growth factors in wound healing is well known, less recognized is the equally important contribution of the extracellular matrix in regulating cell behavior. Matrix proteins such as fibrin and fibronectin not only provide structural support but also have growth factor-like regulatory effects that initiate intracellular signaling cascades altering gene expression and cellular behavior.

Recent work in my lab has centered on the extracellular matrix protein known as tenascin-C, a 200-kD protein that modulates adhesion within the wound matrix. This included the development of a novel adenoviral vector allowing high-level specific expression of this protein within wound cells. Expression of large proteins in mammalian cells has been difficult to achieve. This work demonstrated the feasibility of using such vectors to induce expression of large matrix proteins that can influence cell behavior. While constructed primarily with the goal of permitting further research, this vector also represents a significant proof in principle that adenoviral vectors encoding large proteins with clinical applications can be achieved. This vector is being used to study the paracrine effects of tenascin-C on neighboring cells. Other projects include ones centered on fibroblast differentiation with the goal of developing in vitro models for wound healing that can allow investigations leading to translational applications in the clinic.

For further information:

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Dr. Langenfeld, M.D.

Division of Thoracic Surgery

Dr. Langenfeld not only has devoted his career operating on lung cancer patients his research is also focused on lung cancer. The research has been intended to find novel ways to treat and diagnose lung cancer.

Dr. Langenfeld's laboratory identified a novel protein found in lung cancer called bone morphogenetic protein 2 (BMP2). They found BMP2 is highly expressed in nearly all lung carcinomas. They have shown that BMP2 significantly enhances tumor growth at least in part by promoting the development of a blood supply that is needed to sustain the growth of a tumor. BMP2 was also shown to promote cancer cell migration and enhance the ability of cancer cells to spread to other parts of the body.

Dr. Langenfeld's laboratory developed a new method to isolate specialized cancer cells from lung cancers. These specialized cancer cells have the characteristics of stem cells and are thought to be the population of cancer cells that propagate the growth of a tumor. If this hypothesis is correct then cancer therapy in the future should be directed specifically at this population of cancer cells. Dr. Langenfeld's future studies will examine the mechanisms controlling these specialized cancer cells and whether they can be turned into another cell type which is not capable of sustaining tumor growth.

PUBLICATIONS:

Langenfeld, J., Abou-Nukta, F., Langenfeld, E., Bone Morphogenetic protein-2 is highly expressed in lung cancer and enhances the migration and invasion of lung cancer cell lines. Society of University Surgeons, Chicago, IL. February 2001.

Langenfeld, J., Abou-Nukta, F., Langenfeld, E., Bone Morphogenetic protein-2 (BMP-2) stimulates angiogenesis *in vivo* and regulates vascular endothelial growth factor (VEGF) expression in the A549 human lung cancer cell line. Surgical Forum, Clinical Congress of the American College of Surgeons, New Orleans, LA. October 2001.

Langenfeld, J., Langenfeld, E., Bone Morphogenetic Protein-2 Stimulates Angiogenesis in Developing Tumors. 2003 Proceedings of the American Association for Cancer Research., Annual Meeting, Toronto-Ontario, Canada. April 2003

Langenfeld, John, Langenfeld, Elaine, BMP-2 Stimulates and Inhibits Proliferation of A549 Cells Through Distinct Signaling Pathways. 2004 Proceedings of the American Association for Cancer Research., Annual Meeting,, Orlando, Florida March 2004

Langenfeld, John E. Elaine Langenfeld, Yingxin Kong. Bone Morphogenetic Protein 2 (BMP-2) promotes foci formation through the activation of mammalian target of rapamycin, 2005 Proceedings of the American Association for Cancer Research., Annual Meeting, Anaheim, California April 2005

Dr. Langenfeld, M.D.

Division of Thoracic Surgery

Langenfeld, J. Bone Morphogenetic Protein-2, A Multipurpose Cytokine in the Progression of Lung Cancer. Sixth International Conference on Bone Morphogenetic Proteins, Cavtat/Dubrovnik, Croatia October 2006

Todd R. Vogel, MD, MPH, FACS

Viktor Y. Dombrovskiy, M.D., Ph.D., M.P.H.

The Division of Vascular Surgery and the Department of Surgery

Our research interests are focused on Health Services Research and Outcomes Research in all areas of surgery. Outcomes studies cover a variety of research studies: population-based studies of disease incidence and mortality; patient-oriented research, such as quality of life studies; evaluation of the quality of healthcare, including use (overuse and underuse) of various services, impact of hospital/surgeon volume and regionalization of the more complex surgical procedures on results of surgical care, patient safety and medical errors reduction; small-area variations and trend-analysis in the use of surgical procedures; evaluation of access to healthcare and estimation of its cost; etc. Analyzing large populations significantly reduce various biases existing in small institutional projects. Results are intended to improve decision making by clinicians, health care administrators and patients, in revision of existing policies, and finally in improving health care delivery.

Currently, we conduct research projects in some of the above areas with large cohorts of patients using data from large computerized administrative databases. These retrospective databases provide a large population-based sample of all surgical procedures and information on patient diagnoses and comorbidities, medical care received during admission, resource utilization (length of stay, total and detailed charges/cost), medical facility characteristics (location, ownership, teaching status), payers, etc. Nationwide Inpatient Sample (NIS) is the largest all-payer inpatient database in the US containing information on approximately 8 million hospital admissions each year at 1000 hospitals that is a 20% national sample. The State Inpatient Database (SID) and State Ambulatory Surgery Database (SASD) are the whole datasets that allow analyzing and comparison of surgical practices and outcomes in an inpatient and outpatient settings in the state. We are currently working on the design of projects based on the analysis of the Medicare data. These national data contain information about health services for population at age 65 years and above which is an important segment of surgical population. The results of our analytical studies using administrative databases are valuable for hypothesis-generating information for evaluating surgical performance and improving surgical quality.

RECENT PUBLICATIONS:

Vogel TR, Su LT, Gaston-Symons R, Flum DR. Lower extremity angioplasty for claudication: a population-level analysis of 30-day outcomes. *J Vasc Surg.* 2007 Apr;45(4):762-7.

Vogel TR, Symons RG, Flum DR. A population-level analysis: the influence of hospital type on trends in use and outcomes of lower extremity angioplasty. *Vasc Endovascular Surg.* 2008 Feb-Mar;42(1):12-8.

Vogel TR, Symons RG, Flum DR. The incidence and factors associated with graft infection after aortic aneurysm repair. *J Vasc Surg.* 2008 Feb;47(2):264-9.

Vogel TR, Symons RG, Flum DR. Longitudinal Outcomes After Endovascular Repair of Abdominal Aortic Aneurysms. *Vasc Endovascular Surg.* 2008 June 25.

Vogel TR, Cantor JC, Dombrovskiy VY, Haser PB, Graham AM. AAA Repair: Socio-Demographic Disparities in Management and Outcomes. *Vasc Endovascular Surg.* 2008 Aug 11.

Vogel TR, Dombrovskiy VY, Lowry SF. Trends in Post-Operative Sepsis: Are We Changing Outcomes? *Surg Infect.* (In press).

Vogel TR, Dombrovskiy VY, Haser PB, Graham AM. Carotid Stenting and Endarterectomy in the United States: Age and Outcomes. *J Vasc Surg.* (In press).

Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid rise in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244-1250.

Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Occurrence and outcomes of sepsis: Influence of race. *Crit Care Med* 2007;35:763-768.

Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Facing the challenge: Decreasing case fatality rates in severe sepsis despite increasing hospitalizations. *Crit Care Med* 2005;33: 2555-2562.

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