

February 27, 2008

Dear Colleagues and friends,

On behalf of The University of Arizona, we are honored to welcome you to the first Cardiovascular Research/Industry Partnerships Symposium. This event was initiated by the College of Medicine Dean's Research Council and it is our hope that this will be a valuable resource to the UA Biomedical Research community. It is our feeling that events such as this truly exemplify the breadth of collaborative and interdisciplinary research ongoing at The University of Arizona.

The main objective of today's Symposium is to provide a platform for discussing current cardiovascular research and the process of interacting with industry and setting up collaborations. This event provides a venue for our faculty and representatives from industry to network and provides a taste and feel of current biomedical research ongoing at the UA. The morning panel discussion will open the dialogue for initiating successful collaborations and the breakout sessions will allow in-depth discussions to occur. Posters for our faculty will also be on display throughout the day to highlight exciting research taking place here. We encourage you to participate in the tours of the BIO5 Institute and the new College of Medicine Medical Research Building. Both buildings are examples of the University's commitment to modern, collaborative research.

Please enjoy the science and networking at today's event.

Sincerely,



Leslie Tolbert, PhD
Vice President for Research
University of Arizona



Keith A. Joiner, MD, MPH
Vice Provost for Medical Affairs
Dean, College of Medicine

The University of Arizona Faculty Profiles

APPLIED CARDIOVASCULAR RESEARCH LABORATORIES (ACRL)

ACRL Focus: The role of inflammation / oxidative stress in the severity of ischemic injury associated with type 2 diabetes, artificial heart patients, air pollution and stroke.

Ongoing Research Studies

- 1.) The Pathobiology of Neutrophil-Mediated Ischemia-Reperfusion Injury in the Type 2 Diabetic Heart.
- 2.) The Role of the Inflammatory Response in the Severity of Myocardial Ischemic Injury Associated with Inhalation of the Particulate Matter Fraction of Air Pollution.
- 3.) Development of Bio-compatible Bio-materials for Cardiovascular Applications.

Partnering Opportunities

- 1.) Develop and evaluate methods and treatments to ameliorate the inflammatory/oxidative component to ischemic injury in the heart and brain.
- 2.) In collaboration with Drs. Maria Altbach and Zhonglin Liu, non-invasive cardiac imaging studies to evaluate therapies aimed to improve longer-term myocardial recovery following an ischemic event.
- 3.) Evaluate the inflammatory response of blood components to novel bio-material surfaces.

Relevant Publications

- 1.) McDonagh PF, Hokama, J.Y., Gale SC, Logan JJ, Davis-Gorman G, Goldman S and J.G. Copeland. Chronic Expression of Platelet Adhesion Proteins is Associated with Severe Ischemic Heart Disease in Type 2 Diabetic Patients. *Journal of Diabetes and Its Complications*. 17: 269-278. 2003.
- 2.) Dokken B and McDonagh P. Role of Innate Immune Dysregulation in Diabetic Heart Failure. In: *Immune Dysfunction and Immunotherapy in Heart Disease*. Watson and Larson ed. Blackwell-Futura. 2007.
- 3.) Stephen C. Gale, Grace Davis-Gorman, Jack G. Copeland and Paul F. McDonagh. Perflubron Emulsion Prevents PMN Activation and Improves Myocardial Functional Recovery After Cold Ischemia and Reperfusion. *Journal of Surgical Research*. 138: 135-140. 2007.
- 4.) La Bonte, Laura; Davis-Gorman, Grace; Stahl, Gregory and Paul McDonagh. Complement Inhibition Reduces Injury in the Type 2 Diabetic Heart Following Ischemia and Reperfusion. *American Journal of Physiology Heart Circ Physiol*. In Press. 2008.

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ADVANCED MAGNETIC RESONANCE IMAGING LABORATORY

RESEARCH OVERVIEW

Our research group is focused on the development of novel magnetic resonance imaging (MRI) techniques for improving the diagnosis of disease. We develop novel acquisition and reconstruction strategies and we work closely with clinicians and scientists to develop better and more efficient techniques aimed at improving the diagnosis of heart disease and cancer. One of the major goals is to be able to derive parameters for the quantification of disease from data acquired within the time constraints of a clinical MRI examination. The idea is to complement the current qualitative-approach of diagnosis with a quantitative or "parametric" approach.

Our research team also provides support for both clinical investigators and basic scientists that are interested in incorporating imaging into their clinical or pre-clinical research protocols. This enables the use of non-invasive MRI methods to obtain anatomical and functional information of organs such as the heart and blood vessels as a means to follow up pathological disorders, their progression and response to treatment.

CURRENT PROJECTS

- Detection of Lipid Infiltration in the Heart (Collaborators: Vincent Sorrell MD, Frank Marcus MD from the Sarver Heart Center, Ali Bilgin, PhD from the Dept. of Electrical and Computer Engineering).
- Non-invasive monitoring of heart transplant rejection (Collaborators: Vincent Sorrell, MD Jack Copeland, MD from the Sarver Heart Center).
- Characterization of cardiac masses (Collaborators: Vincent Sorrell, MD from the Sarver Heart Center, Ali Bilgin, PhD from the Dept. of Electrical and Computer Engineering).
- Imaging of prolonged ventricular fibrillation (Collaborators: Robert Berg, MD and Vincent Sorrell, MD from the Sarver Heart Center).
- Non-invasive imaging of ischemia-reperfusion injury (Collaborators: Paul McDonagh, PhD and Betsy Dokken, PhD from the Dept. of Surgery, and Jean-Philippe Galons, PhD from the Dept. of Radiology).

Funding for these projects provided by the NIH and the American Heart Association.

BENEFITS TO INDUSTRY

- State-of-the-art MRI instrumentation for both clinical and pre-clinical imaging. Scanners are available for research during regular week hours. Our clinical and pre-clinical MRI facilities are operated by experienced research technologists.
- Interaction with interdisciplinary teams providing access to clinical, scientific, and technical expertise.
- Interaction with students and post-doctoral fellows.
- Access to patients and animal models.

LINKS TO RESEARCH FACILITIES AND PUBLICATIONS

<http://www.radiology.arizona.edu/research/mri/mri.htm>

<http://www.radiology.arizona.edu/research/altbachlab/altbachlab.htm>

<http://www.radiology.arizona.edu/research/mri/wholebody.htm>

<http://bmr.arl.arizona.edu>



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Please also see the "Clinical Cardiovascular Imaging Research Program" and "Applied Cardiovascular Research Laboratories" pages in this CVD-industry book.

Cardiovascular Molecular Imaging in Center for Gamma-Ray Imaging

Laboratory Research Interests: The Center for Gamma-ray Imaging (CGRI) is a research resource funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The overall objectives of cardiovascular molecular imaging projects supported by the center are to expand the biomedical applications of small-animal Single Photon Emission Computed Tomography (SPECT) imaging systems being developed and to pave the way for new collaborative researches in cardiovascular disease. We are developing various small animal models for basic studies in cardiology, investigating cardiovascular radiopharmaceutical kinetics to noninvasively assess myocardial injury and pathophysiological development. Using multiple molecular imaging platforms and small-animal models, we are seeking to explore the molecular aspects of novel cardioprotective strategies against myocardial ischemia-reperfusion injury. Current molecular imaging platforms include myocardial perfusion imaging, myocytic apoptosis/necrosis imaging, cardiovascular inflammation imaging, metabolism imaging and stem-cell tracking.

Potential Industry Collaborations: Recent development of molecular techniques has resulted in PET and SPECT becoming pivotal enabling technologies for translational research. SPECT imaging is maturing into an important technology for drug discovery and drug development. The molecular SPECT imaging platforms in CGRI can effectively bridge the translational research projects to provide *in vivo* information on cardiovascular drug effects in experimental animals and humans. We are interested in working with industry to investigate cardioprotective effects of new drugs and interventions on myocardial ischemia-reperfusion injury. We would also like to work with industry for new cardiovascular radiopharmaceutical development.

Relevant Citations: Liu Z, Kastis GA, Stevenson GD, Barrett HH, Furenlid LR, Kupinski MA, Patton DR, Wilson DW. Quantitative analysis of acute myocardial infarction in rat hearts with ischemia-reperfusion using a high-resolution stationary SPECT system. *J Nucl Med.* 2002;43:933-9.

Liu Z, Stevenson GD, Kastis GA, Barrett HH, Bettan M, Furenlid LR, Wilson DW, Pak KY. High-resolution imaging with ^{99m}Tc-glucarate for assessing myocardial injury in rat models exposed to different durations of ischemia followed by reperfusion. *J Nucl Med.* 2004;45:1251-9.

Liu Z, Zhao M, Zhu X, Furenlid L R, Chen Y-C, Barrett H H, In vivo dynamic imaging of myocardial cell death using ^{99m}Tc-labeled C2A domain of Synaptotagmin I in a rat model of ischemia and reperfusion, *Nucl Medi Biol.* 2007;34:907-15.

Liu Z, Barrett HH, Stevenson GD, Furenlid LR, Wilson DW, Woolfenden JM, and Pak KY, Evaluating the protective role of ischemic preconditioning in rat hearts using a stationary small-animal SPECT imager and ^{99m}Tc-glucarate, *Nucl Medi Commun.* 2007;29:120-8.



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Disease Mechanisms of Chronic Inflammation/Oxidative Stress

Laboratory Research Interests: In 1956, Harman proposed the free radical theory of aging (J Gerontol 11:298). The basis of this theory is that by-products of normal metabolism include oxygen-derived, reactive species that cause oxidative damage to cells. Over time, the accumulated damage speeds up the aging process and leads to disease. Since 1956, many studies have correlated oxidative stress with human diseases, including cancer, cardiovascular disease, diabetes and neurodegenerative disorders. In these diseases, a low level of chronic inflammation appears to be one source of the oxidative stress. A likely connection between optimal health and limited oxidative damage to cells has not been lost on the public. The sale of antioxidant supplements is a multibillion dollar industry. It seems only a matter of time before measurements of oxidative stress technologies are incorporated into the practice of medicine.

My laboratory is working to understand how chronic inflammation or oxidative stress promotes disease. Our current focus is on cancer. Results from studies with model systems for lymphoma, breast and skin cancer have shown us that the cancer cells' ability to handle oxidative stress influences their susceptibility to apoptosis. We have found that oxidative stress-resistant cancer cells have concurrently acquired resistance to apoptosis. This finding has implications for effective cancer therapy. We are working to identify the key molecules that sense oxidative stress, are involved in the mechanism of apoptosis and may be dysfunctional in cancer cells. These may be novel targets for cancer treatment, or for predicting treatment outcome.

Potential Industry Collaborations: Bringing measurements of oxidative stress into clinical practice will likely require the development of novel technologies for measuring oxidative stress in biological samples, and clinical trials to validate the application of these. I am interested in collaborating with industry to develop and test such technologies. Although my current focus is on cancer, I believe these methods will also be applicable to cardiovascular disease.

Relevant Citations:

Tome, M.E., Lutz, N.W. and Briehl, M.M. Overexpression of catalase or Bcl-2 alters glucose and energy metabolism concomitant with dexamethasone resistance. *Biochim. Biophys. Acta* 1693:57-72, 2004.

Tome, M.E., Briehl, M.M. and Lutz, N.W. Increasing the antioxidant defense in WEHI7.2 cells results in a more tumor-like metabolic profile. *Int. J. Mol. Med.* 15:497-501, 2005.

Tome, M.E., Johnson, D.B.F., Rimsza, L.M., Roberts, R.A., Grogan, T.M., Miller, T.P., Oberley, L.W., Briehl, M.M. A redox signature score identifies diffuse large B-cell lymphoma patients with a poor prognosis. *Blood* 106:3594-3601, 2005.

Tome, M.E., Johnson, D.B.F., Samulitis, B., Dorr, R.T., Briehl, M.M. Glucose 6-phosphate dehydrogenase overexpression models glucose deprivation and sensitizes lymphoma cells to apoptosis. *Antioxid Redox Signal* 8:1315-1327, 2006.



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Medical Screening for Cardiovascular Disease and Acute CV Effects in Firefighters

Laboratory Research Interests: The Environmental and Occupational Health Section of The University of Arizona Mel and Enid Zuckerman College of Public Health has developed a continuing collaboration with clinics for the fire departments in Tucson and Phoenix providing medical surveillance for over 2,000 active duty firefighters. Although our previous research has focused on pulmonary end-points, we are interested in expanding our research to identify new methods of imaging atherosclerotic disease in firefighters as well as evaluating new markers of disruptions in physiologic pathways leading to myocardial infarctions.

Potential Industry Collaborations: Sudden cardiac deaths account for 44% of the line-of-duty deaths in firefighters, and generally occur in firefighters with underlying cardiovascular disease, many of whom have been previously asymptomatic. Firefighters are evaluated annually as part of a medical screening program. Current screening tests are not adequate to identify firefighters at high risk of an on-duty cardiovascular event. We are interested in working with industry to evaluate existing and new imaging techniques to improve medical screening for atherosclerotic heart disease in the fire service.

Fire suppression, the first phase of firefighting at an incident, carries the highest risk for cardiovascular deaths, and yet we do not understand the effects of this activity, including the contribution of smoke and heat exposure, on pathways involved in the development of a myocardial infarction. We are interested in collaboration with industry to evaluate acute changes in cardiac function or biomarkers in pathways associated with myocardial infarctions associated with fire suppression activities.

Relevant Citations: Burgess JL, Nanson CJ, Gerkin R, Witten ML, Hysong TA, Lantz RC. Rapid decline in sputum IL-10 concentration following occupational smoke exposure. *Inhalation Toxicology* 2002;14:133-140.

Burgess JL, Witten ML, Nanson CJ, Hysong TA, Sherrill DL, Quan SF, Gerkin R, Bernard AM. Serum pneumoproteins: a cross-sectional comparison of firefighters and police. *American Journal of Industrial Medicine* 2003;44:246-253.

Burgess JL, Fierro MA, Lantz RC, Hysong TA, Fleming JE, Gerkin R, Hnizdo E, Conley SM, Klimecki W. Longitudinal decline in lung function: evaluation of interleukin-10 genetic polymorphisms in firefighters. *Journal of Occupational and Environmental Medicine* 2004;46:1013-1022.

Josyula AB, Kurzius-Spencer M, Littau SR, Yucesoy B, Fleming J, Burgess JL. Cytokine genotype and phenotype effects on lung function decline in firefighters. *Journal of Occupational and Environmental Medicine* 2007;49:282-288.



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Research Description

Research in my laboratory is focused on the contribution of gap junctions, the direct intercellular communication pathway, and their comprising proteins, the connexins, to vascular function in health, disease and injury. The significance of gap junction mediated communication to human health is increasingly evident from the human diseases caused by expression of defective connexins, including: peripheral neuropathies, cardiac developmental malformations, deafness, cataracts and skin diseases. The diverse phenotypes in mice arising from Cx gene ablation and substitution lend further support to the importance of gap junctions to development and function of the cardiovascular system, in particular, and to the animal in general. We study gap junctions relative to their two primary functions: 1) intercellular exchange of the signaling molecules that support homeostasis and coordinated tissue function in health and disease, and 2) suppression of cell proliferation. Cells of the cardiovascular system express one or more of four connexin proteins (Cx37, Cx40, Cx43 and Cx45). Our long-term goal is to identify the unique contributions of these connexins to coordinated vascular function in healthy and diseased blood vessels, to vascular remodeling and angiogenesis, and to tumor and endothelial cell growth suppression. We use a variety of approaches to address these issues, including: electrophysiology and fluorescence microscopy on cells (tumor and vascular) and blood vessels to quantify the function of differentially composed and regulated gap junctions; site directed mutagenesis and transgene expression strategies to assess site-specific regulation of gap junction function; cell cycle analysis and growth curves to assess (mechanisms of) growth suppression; and surgical models (coarctation and hindlimb ischemia) to evaluate *in vivo* consequences of connexin expression on vascular remodeling and coordinated vascular function.

Collaborative interactions that extend our studies to relevant human models, or expand our approaches to include the proteomic and genomic consequences of connexin expression would be of particular interest.

Recent Publications:

Ek-Vitorin, J.F., T.J. King, N.S. Heyman, P.D. Lampe, **J.M. Burt**. Selectivity of Cx43 channels is regulated through PKC-dependent phosphorylation *Circ. Res.* 98(12):1498-505, 2006.

Lampe PD, Cooper CD, King TJ, **Burt J.M.**. Analysis of Connexin43 phosphorylated at S325, S328 and S330 in normoxic and ischemic heart. *J Cell Sci.* 119:3435-42, 2006.

Heyman, NS and JM Burt Cx43 junctional dye selectivity is constant and described by a simple aqueous pore. *Biophysical J.*, 94(3):840-54, 2008.

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Proteomic Identification of Biomarkers of Heart Failure

Heart failure is an end point of several types of heart diseases. Diagnosis of heart failure depends on a combination of tests. The level of BNP serves as an important measurement for the degree of heart failure and is essential for monitoring the effectiveness of therapeutic treatment. However, the blood test for BNP alone has about 80% accuracy for heart failure diagnosis. The BNP protein has a relative short half life and the test for BNP requires a clinical laboratory. Novel biomarkers of heart failure will help to increase the accuracy of blood test based diagnosis. Although serum protein profiling provides a route for novel biomarker discovery, the tremendously dynamic range of serum proteins, the relatively low abundant biomarker proteins and other complicating factors have prohibited quick identification of novel biomarkers of heart failure. We have found that cardiomyocytes in culture provide a productive system for biomarker discoveries using a proteomic method. In our preliminary studies, we have found a unique protein (Protein XC) from cardiomyocytes exposed to oxidants by shotgun LC-MS/MS analyses of proteins secreted by cardiomyocytes. Once identified from the cell culture model, in vivo animal models can be used to validate the candidacy of the biomarkers. Elevated Protein XC was found in the plasma of mice with doxorubicin induced dilated cardiomyopathy or with myocardial ischemia induced by coronary artery ligation in our laboratory. Recent clinical studies have found an increased level of Protein XC in the blood of heart failure patients, suggesting that our approach is productive and valid. We plan to take advantage of the molecular changes associated with cardiomyocyte injury and will generate a pool of candidate biomarkers for future validation in clinical studies. We expect that certain types of novel protein biomarkers will allow the development of convenient at home or in office tests for quick diagnosis of heart failure.

Ongoing cardiac projects in the lab:

- Oxidative injury associated with myocardial infarction
- Transcription factors regulating cardiac protection
- Corticosteroid induced cytoprotection
- Progesterone induced cardiac protection



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Chronic Heart Failure Using Animal Models Of Ischemic Heart Failure

Dr. Goldman runs a large laboratory and clinical research operation at the Tucson VA. The major financial support for the work in the basic laboratory comes from the Veterans Administration (VA) Merit Review Program, the VA Cooperative Studies Program, the NHLBI, the Hansjörg Wyss Foundation, the WARMER Foundation, the Biotechnology, and the Pharmaceutical industry. The work with the Biotechnology and Pharmaceutical industry includes contract work. Dr. Goldman works closely with Dr. Hoang Thai; together they support a number of young investigators in the laboratory. The main focus of the basic laboratory is studying chronic heart failure using animal models of ischemic heart failure. Over the years, the laboratory has investigated the pathophysiology and treatment of chronic heart failure. The laboratory is currently working on the number of different projects ranging from cell-based therapy to neurohormonal/immune blockade in the treatment of heart failure. The basic work has a translational emphasis; we have a strong track record of bringing products and agents from the laboratory to the bedside.

While Drs. Goldman and Thai run the clinical research laboratory, it is a collaborative effort; all the Cardiology Staff physicians at the Tucson VA do clinical research. We have four research nurses, a physician and two research technicians employed by the Clinical Research Laboratory; they do an excellent job of enrolling patients and supporting investigators in clinical trials. The emphasis of the clinical cardiovascular research operation at the Tucson VA is on investigator initiated clinical research and large scale clinical trials. We do studies supported by the VA, the NIH, and the Pharmaceutical Industry. Over the years, Dr. Goldman has been PI or Co-PI on a number of large multicenter trials sponsored by the VA Cooperative Studies Program. These trials have focused on graft patency after coronary artery bypass surgery. Dr Goldman is currently Co-PI with Dr. Gulshan Sethi from the Sarver Heart Center and Dr. William Holman from the University of Alabama and the Birmingham VA on a VA multicenter center to examine radial artery versus saphenous vein graft patency. Dr. Thai is Co-PI on a large single center trial to examine chronic resynchronization therapy in chronic heart failure. An example of investigator initiated research that successfully brought a drug from the bench to the bedside is Dr. Goldman's work on a thyroid hormone analog to treat heart failure. Dr. Goldman and Dr. Eugene Morkin from the Sarver Heart Center were PIs on the only VA sponsored Phase II clinical trial that examined a thyroid hormone analog as treatment for heart failure. This analog was developed by Drs. Goldman, Morkin, and Bahl at the VA and University of Arizona, the patent was assigned to the University and in turn licensed to a small biotechnology company.

Recent relevant citations:

Goldman et al., *Journal of American College of Cardiology* 44;11:2149-2156, 2004.

Thai et al., *Circulation* 114:1933-1939, 2006.

Maitra et al., *J Cardiovascular Pharmacology* 50,5:526-534, 2007.



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Cytoskeletal protein interactions during cardiac development and cardiac disease

Laboratory Research Interests: The primary focus of my laboratory is to identify the molecular components and signaling mechanisms that regulate cytoskeletal (contractile) protein interactions during cardiac development and in cardiac disease. In my lab, we vigorously pursue new techniques from many disciplines and work with different experimental systems to ensure that we use the best approaches for the problems we choose to investigate. While the proteins we study are present in most, if not all cell types, striated muscle has proven to be an ideal model system to study the regulation of the cytoskeleton due to the precise organization and polarity of contractile proteins within repeating sarcomeric units. Elucidation of the molecular mechanisms underlying myofibril assembly and maintenance in normal muscle are pivotal for understanding the properties that are required for efficient contraction. Moreover, it is has become increasingly apparent that this research is critical for understanding the molecular bases for certain forms of heart and skeletal muscle diseases.

Potential Collaborations with Industry

I. Investigating the impact of actin and other sarcomeric protein mutations on cardiac dysfunctions.

Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), the most common hereditary cardiac conditions, are frequent causes of sudden cardiac death and are often associated with an adverse disease course. It is now well established that both HCM and DCM are frequently caused by mutations in sarcomeric components. Thus, deciphering the molecular mechanisms by which genetic mutations in structural proteins affect cardiac function is one of the primary goals of my laboratory. In particular, cardiac α -actin, a protein we have been investigating for ~15 years, is the predominant isoform of actin expressed in adult heart and carries multiple functions in the sarcomere. We predict that expressing mutant actins in primary cultures of cardiac myocytes, and in cardiomyocytes derived from murine embryonic stem cells (see below), will result in dramatic cellular changes. Thus, we seek to establish partnerships with the aim of identifying new human mutations and investigating the functional and mechanistic consequences of the expressed mutations at the levels of force generation, contractile activity and muscle architecture.

II. Development of Novel Models of *De Novo* Cardiac Myofibril Assembly.

The formation of perfectly aligned myofibrils in cardiac muscle represents a dramatic example of supramolecular assembly in eukaryotic cells; the mechanisms by which this occurs are still incompletely understood. This is largely due to a lack of suitable cell models that faithfully recapitulate cardiac myofibril assembly that occurs during embryonic development. Because there were no *in vitro* systems to study *de novo* mammalian cardiac muscle assembly, we established a murine embryonic stem (ES) cell culture system for cardiac myofibril assembly in collaboration with Dr. Parker Antin (Dept. of Cell Biology and Anatomy) to be used to knock out (and subsequently "knock in") selected genes required for efficient contractile activity (e.g., tropomodulin). This model will be used to evaluate the intracellular function(s) of particular proteins of interest and their distinct domains. Although ES cells have been used to investigate various molecular aspects of cardiogenesis, few if any studies have taken advantage of their unique properties to investigate mechanisms of myofibril assembly. We seek partnerships to fully utilize this model system to study cardiac muscle structure, function and dysfunction

Relevant References.

Ono, Y., Schwach, C., Antin, P.B. and C.C. Gregorio. 2005. Disruption in the Tmod1 gene compromises cardiomyocyte development in murine embryonic stem cells by arresting myofibril maturation. *Dev. Biol.* 282:336-48.

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Pancreas and Intestinal Transplantation

Laboratory Research Interests:

- Pancreas islet and kidney transplantation for the treatment of diabetes and secondary complications
- Surgical and transplant options for patients with end-stage liver, pancreas, kidney and intestinal failure from benign and malignant diseases
- Application and advancement of minimally invasive surgery including robotics
- Risk analysis and quality control of benign and malignant disorders of the pancreas, liver, and intestine
- Tolerance induction using donor-specific cell augmentation via the portal vein
- Impact of refined surgical techniques on length and cost of hospitalization

Relevant Citations:

- PARASKEVAS, S., KANDASWAMY, R., HUMAR, A., GILLINGHAM, K.J., GRUESSNER, R.W., PAYNE, W.D., NAJARIAN, J. S., SUTHERLAND, D.E., MATAS, J.: Risk factors for rising creatinine in renal allografts with 1 and 3 yr survival. Clin Transplant 20 (6): 667-772 (2006).
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- MEIER-KRIESCHE, H., LI, S., GRUESSNER, R.W.G., FUNG, J.J., BUSTAMI, R.T., BARR, M.L., LEICHTMAN, A.B.: Immunosuppression: Evolution in Practice and Trends, 1994-2004. Am. J. Transplant. 6:1111-1131 (2006).
- DUNN, T.B., LINDEN, M.A., VERCELLI, G.M., GRUESSNER, R.W.: Factor V Leiden and hepatic artery thrombosis after liver transplantation. Clin. Transplant. 20:132-135 (2006)
- PARASKEVAS, S., COAD, J.E., GRUESSNER, A., KANDASWAMY, R. HUMAR, A., SUTHERLAND, D.E., Posttransplant lymphoproliferative disorder in pancreas transplantation: a single-center experience. Transplant. 80:613-622 (2005).
- CASINGAL, VP, ASOLATI, M., HUNTER, D., GRUESSNER, R.W.: Emergent autotransplantation of a renal allograft. Clin. Transplant. 19:563-565 (2005).
- NATH, D.S., GRUESSNER, A., KANDASWAMY, R., GRUESSNER, R.W., SUTHERLAND, D.E., HUMAR, A.: Late anatomic leaks in pancreas transplant recipients – clinical characteristics and predisposing factors. Clin. Transplant. 19:220-224 (2005).



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Vascular Occlusive Disease

Laboratory Research Interests: A research focus of the laboratory is on the Pathogenesis of Vascular Occlusive Disease. Blood vessels are dynamic structures, being able to make rapid and lasting changes in vessel structure and function and our research is using molecular cellular and genetic approaches to investigate SMC cadherins in critical roles of cell-cell adhesion and cell signaling during neointima formation by SMCs. Identification of the role of cadherins and characterization of the mechanisms for their contribution to stenosis is one important area of vascular research because these studies are generating information for the improvement of diagnosis and therapy of vascular occlusion. Thus, exploring mechanisms for *N-cadherin* mediated gene expression program is to understand the molecular mechanisms signaling in stenosis.

Angiogenesis has an essential role in supporting growth in wound healing and in pathogenesis of occlusive vascular disease. Angiogenesis is a complex sequential process involving temporal and spatial coordination of growth factor and integrin signaling pathways. However, the cellular and molecular mechanisms underlying vascular patterning in particular the signals for tubular morphogenesis are not well understood.

Potential Industry Collaborations:

Enhancement and inhibition of Angiogenesis. Our studies involve a role for members of the Hedgehog family of morphogenetic factors in both intrinsic and extrinsic induction of blood vessel network formation.

Vascular smooth muscle cell remodeling contributes to the pathogenesis of atherosclerosis and restenosis. Increased rates of VSMC apoptosis are thought to lead to thinning of the fibrous atherosclerotic plaque and thereby instability, while migration of VSMCs to the intima, and inappropriate VSMC proliferation, contribute to intimal thickening that occurs in atherosclerosis and restenosis. Our studies are on the cadherin mediated cell-cell adhesion (N-cadherin and cadherin-11) and modulation of apoptosis, migration and proliferation.

Relevant Citations:

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DIASTOLIC HEART FAILURE RESEARCH

BACKGROUND

Patients with heart failure (HF) who have symptoms with mild activity or rest (NYHA Class III and IV) have very poor long-term outcomes, with up to 50% of patients dying within four years of symptom onset despite optimal medical therapy. There are 5 million patients with HF in the US today and 550,000 new cases per year. There are two clinical subsets of HF in clinical practice, diastolic HF (DHF) and systolic HF (SHF). Epidemiological studies indicate that 50% of HF cases are associated with normal ejection fraction - that is DHF - and the risk for death for DHF is equal to or greater than SHF. In addition, virtually all cardiac patients have diastolic dysfunction with or without HF. An abnormal neurohormonal activity has been validated as a major mechanism for the progression of cardiac remodeling in SHF owing to the response to neurohormonal based therapeutics. However, the stimuli for ventricular remodeling in DHF remain uncertain and as a result there are no FDA approved therapeutics for DHF. Because the prevalence of DHF is an inexorable disease associated with unacceptably high morbidity and mortality, new advances in DHF treatment are needed.

INVESTIGATIVE APPROACH

Our group has reported that there is a direct relationship between the passive stiffness and extracellular matrix (ECM) fibrillar collagen maturation processes. The focus of our proposed research is to regulate two enzymes responsible for this ECM collagen maturation through modulation of selective cytokine pathways.

MARKETING STATEMENT

- There is an exceedingly large and increasing market size.
- There are no approved FDA therapeutics for this indication.
- We are targeting two specific enzymes.
- We are modulating these enzymes through defined cytokine receptors.

OUR EXPERTISE

Rodent modeling and clinical associations

Rodent pressure-volume loop analysis and transthoracic ECHO

Real-time PCR with corresponding protein analysis

In vitro modeling; cardiac and immunologic

Flow cytometry, Mass spectrometry, and HPLC

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Treatment of Abdominal Aneurysms and Aortic Disease

Laboratory Research Interests:

Active clinical and basic research efforts are ongoing in the areas of open and endoluminal treatment of abdominal aneurysms and complex aortic disease; noninvasive evaluation of peripheral vascular disease; hemodialysis access treatment of carotid and vertebral artery disease to prevent stroke; diabetic foot problems, limb salvage surgery, leg bypass surgery, and treatment and prevention of graft stenosis.

Potential Industry Collaborations:

Imaging of peripheral graft stenosis using different modalities
Biomaterials and their application to peripheral grafts
Pathogenesis of vein graft stenosis and analysis of gene expression signatures

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Cardiovascular Epidemiology, Interventional Cardiology, and Echocardiography

Mohammad-Reza Movahed, MD, PhD is an Associate Professor of Medicine at The University of Arizona College of Medicine and the Director of the Coronary Care Unit and Medical director of Heart Transplant program at the University of Arizona Medical Center. He is an interventional cardiologist with board certifications in cardiovascular disease, interventional cardiology, nuclear cardiology and echocardiography.

Dr. Movahed received his MD/PhD degree from Hannover Medical School in Hannover, Germany. He completed his interventional fellowship training at Yale University hospital and was an Assistant Clinical Professor of Medicine at the University of California, Irvine before his appointment at UMC.

Dr. Movahed is an accomplished physician, clinician, researcher and teacher with more than 80 peer reviewed publications. He recently published an important new classification of coronary artery bifurcation lesions and techniques. His main research interests are in cardiovascular epidemiology, interventional cardiology, and echocardiography. He has received numerous awards and grants. He has many patents in the area of coronary intervention. He has two recent patent applications for simple defibrillator and coronary artery stent system designed for coronary bifurcation intervention.

Dr. Movahed is a fellow of *The American College of Physicians*, *The American College of Cardiology*, *The Society of Coronary Angiography and Intervention* and *The American College of Chest Physicians*.

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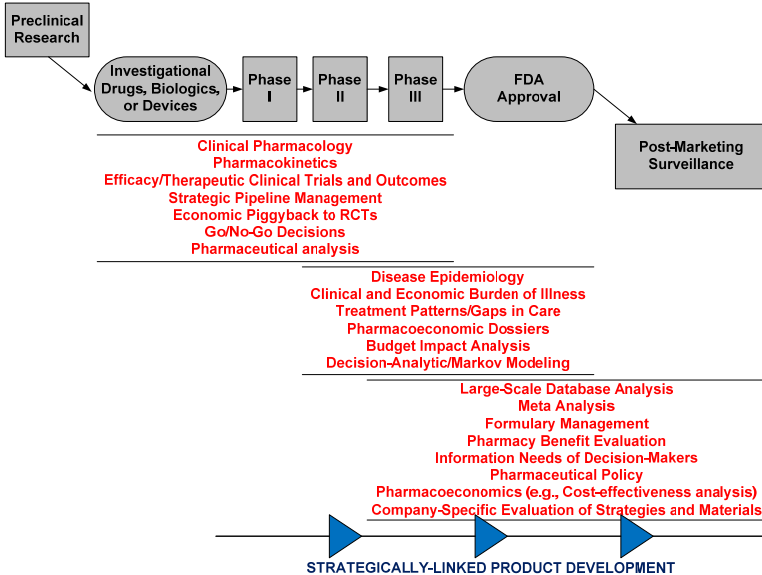
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Cardiovascular Focus

- Heart failure; Dyslipidemia; Coronary artery disease/Acute coronary syndrome; Hypertension; Peripheral arterial occlusions; Anticoagulation/Antiplatelet therapy (includes clinical assessment of therapeutic monitoring devices); Mechanical circulatory assist devices; Heart transplantation; Diabetes; Pharmacogenomics

Research Capabilities and Expertise

- Clinical trials (Phase II/III efficacy and outcomes studies); Clinical pharmacology; Pharmacokinetics; Therapeutic outcomes of cardiovascular drugs (e.g., clinical drug-drug interaction studies, meta-analysis of cardiovascular therapies)
- Pharmacoepidemiology and drug safety (medication errors, risk management); Compliance and adherence; Disease management
- Pharmacoeconomics/Cost-effectiveness analysis; Decision-analytic modeling; Advanced methodology and mathematical statistics; Piggyback RCTs; Outcomes analysis
- Pharmaceutical economics and policy; Industrial economics and corporate finance; Asset valuation; Capital markets; Risk and return of pharmaceutical research and development; Competitive strategy; Venture capital; Biotechnology
- Pharmaceutical/Xenobiotic analytical and formulation capabilities
 - Proteomics (in conjunction with George Tsapralis, Ph.D., Arizona Proteomics Consortium)
 - Pharmaceutics: Formulation/reformulation, stability/compatibility testing, and delivery of parenteral cardiovascular drugs (in conjunction with Samuel Yalkowsky, Ph.D.)



Clinical Cardiovascular Imaging Research Program

This program was established after the successful recruitment of Dr. Vincent L. Sorrell to the University of Arizona. His major interests in multimodality cardiac imaging are to establish relative values of diagnostic imaging tools and to develop fiscally responsible diagnostic imaging protocols. This approach is referred to 'responsible imaging' and lends itself to clinical investigations with a focus on outcome trials. Collaboration with basic and clinical radiologists, adult and pediatric cardiologists, psychologists, oncologists, pathologists, nuclear medicine and emergency medicine physicians provides fertile ground for these trials.

Expertise

Comprehensive cardiac MRI and cardiac CT examinations are performed using established and institutional-developed imaging sequences. State-of-the-art 1.5T and 3.0T magnets and 64 detector CT scanners provide outstanding cardiac images. Dr. Sorrell has been formally trained in both imaging modalities and also holds subspecialty board certification in nuclear cardiology and echocardiography (3D; TDI; SRI; speckle; etc). This allows optimal multi-modality comparisons at a single institution.

Current Research Activities

In 2007, 17 peer-reviewed 'cardiac imaging' publications, book chapters, and/or abstracts were published. An example of our current collaborative, multi-modality clinical research includes:

1. Collaborative Investigation of Sudden Cardiac Death using clinical parameters, cardiac MRI, echocardiography, genetic markers, and functional MR spectroscopy.
2. Multimodality, non-invasive investigation of Cardiac Transplant Rejection.
3. Multimodality, non-invasive investigation of Myocardial Ischemia using Myocardial Perfusion Imaging with radio-isotope SPECT imaging, myocardial contrast echocardiography, and 1st pass perfusion CMR.

Industry Collaboration

We are able to provide state-of-the-art images required for pharmaceutical and industry investigations. Opportunities for clinical and pre-clinical investigations using commonly employed state-of-the-art clinical imaging modalities (echocardiography, nuclear SPECT, CMR, CCT) is available. Current NIH or industry-supported investigations include: (1) ICD device implantation; (2) ARVD diagnosis; (3) assessment of myocardial ischemia; (4) central aortic waveform assessment as predictor of syncope; (5) central aortic waveform assessment as predictor of left ventricular dysfunction; and (6) safety of echo contrast agents.

This investigator interprets echocardiograms for industry-sponsored phase II and III trials. Development of a regional, southwest echo or CMR core lab is possible.

Selected Relevant References:

1. **SORRELL VL, Baweja G. Cardiovascular MRI in the Year 2020 (and Beyond): Changing How We Risk-Stratify Healthy Patients.** Journal of Cardiovascular Reviews and Reports. 2004;238.
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4. **SORRELL VL. The complementary role of cardiac MRI to 2D and Doppler Echocardiography in the Diagnosis and Management of Patients with Cardiovascular Disease.** Echocardiography. 2007, 24 (2):182.



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Please also see Advanced Magnetic Resonance Imaging Laboratory in this CVD/Industry booklet.

Impaired Insulin Action and Mitochondrial Function in Cardiometabolic Disease

Laboratory Research Interests: Insulin resistance and mitochondrial dysfunction are nearly universal in tissues from type II diabetic, metabolic syndrome and obese-sedentary patients. Moreover, physical inactivity and over-nutrition contribute to metabolic dysregulation, in part, by up-regulating the renin-angiotensin-aldosterone system (RAAS), inflammatory cytokines, and reactive oxygen species (ROS) generation. Our objective is to define the role of these factors in decreasing the metabolic actions of insulin and mitochondrial function in skeletal and cardiac muscle. To this end, we utilize well defined animal models and cell culture preparations, while studying metabolically healthy and dysmetabolic human volunteers under controlled hormone and nutrient conditions (e.g. euglycemic-hyperinsulinemic clamp). We also employ proteomic (mass spectrometry and 2D-gel) techniques to identify mitochondrial proteome changes, post-translational protein modifications, and to measure protein turnover rates using stable isotope tracers. Similar techniques are utilized to identify potential protein bio-markers for metabolic disease in blood and urine specimens.

Potential Industry Collaborations:

To accomplish our aims more sensitive and precise methods to measure oxidative stress at systemic and cellular levels are required. Likewise, accurately characterizing sub-cellular proteome changes and post-translational protein modifications will depend on improved cell fractionization and isolation of low abundance proteins. Moreover, accurately measuring physical activity in free living humans and experimental animals remains problematic, while novel and specific anti-oxidants and RAAS inhibitors would prove beneficial to our line of work.

Relevant Citations:

Wei, Y., J.R. Sowers, S.E. Clark, W. Li, C.M. Ferrario, and **C.S. Stump**. Angiotensin II-induced skeletal muscle insulin resistance is mediated by NF-kappaB activation via NADPH oxidase. *Am. J. Physiol. Endocrinol. Metab.*, [Epub ahead of print] Dec. 11, 2007.

Asmann, Y.W., **C.S. Stump**, K.R. Short, J.M. Coenen-Schimke, Z. Guo, M.L. Bigelow, and K.S. Nair. Skeletal muscle mitochondrial functions, mitochondrial DNA copy numbers, and gene transcript profiles in type 2 diabetic and non-diabetic subjects at equal levels of low or high insulin and euglycemia. *Diabetes*, 55 (12): 3309-3319, 2006.

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Congestive Heart Failure Research

HOANG THAI, M.D., FACC, FSCAI

Dr. Thai is an Assistant Professor of Medicine in the Section of Cardiology, Sarver Heart Center at the University of Arizona and Director of the Cardiac Catheterization Laboratory and Interventional Cardiology at the Southern Arizona VA Health Care System Medical Center.

Dr. Thai's research interests are focused on the neuro-hormonal activation of the endothelium in heart failure and tissue engineering as a therapeutic modality post myocardial infarction. In 1999, Dr. Thai was awarded a three-year National Research Career Development grant from the National Veteran's Affairs Research Office to study the effects of angiotensin receptor blockade (ARB) on impaired endothelial function in heart failure. In addition he is collaborating with researchers from the University of Maryland and Yale University in a Phase I study examining the feasibility of using a fibroblast construct to repair/regenerate myocardial tissue in ischemic heart failure.

In the clinical research arena; Dr. Thai currently serves on the executive committee that oversees a national VA Cooperative Clinical trial looking at the role of DITPA, a thyroid analogue, in chronic heart failure (he is also a principal investigator in this study nationally). Dr. Thai is also the director for the core angiography laboratory for VA CSP study #474 (looking at the radial artery as a conduit for CABG) and director for the core echo laboratory for VA CSP study # 526 (DITPA in chronic heart failure). In addition, Dr. Thai also serves on the endpoints committee for VA CSP study # 465 (Glycemic control and complications in type 2 diabetes mellitus). Dr. Thai also serves as a local PI for a number of interventional cardiology studies, the most interesting of which is the NIH sponsored FREEDOM study in which diabetic patients with multi-vessel coronary disease are randomized to percutaneous versus CABG as a revascularization strategy. Recently, Dr. Thai was awarded a \$250,000 grant from Boston Scientific to evaluate the role of Cardiac Resynchronization Therapy in Reversing Severe Mitral Regurgitation. This study is under IRB review and will begin sometime in 2008.

Relevant Citations:

1. **H Thai**, L Castellano, E Juneman, H Phan, Rose Do, M Gaballa, S Goldman. Pretreatment with angiotensin receptor blockade prevents left ventricular dysfunction and blunts LV remodeling associated with acute myocardial infarction. Circulation 114: 1933-1939, 2006.
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3. M Gaballa, J Sunkomat, G Ewy, **H Thai**, E Morkin, S Goldman. Grafting an acellular 3-D collagen scaffold onto a non-transmural cryo-injured myocardium induces neo-angiogenesis and retards cardiac remodeling. Journal of Heart and Lung Transplantation 15 (8): 946-954, 2006.
4. Huang R, Sacks J, Barbieri C, **Thai H**, Goldman S, Morrison D. Impact of Stents and Abciximab on Survival From Cardiogenic Shock Treated With Percutaneous Coronary Intervention. Catherization and Cardiovascular Interventions, Volume 65, Number 1, p 26-33.

Novel ultrasonic techniques to image electrical and mechanical events in the heart

Laboratory Research Interests: The Experimental Ultrasound and Neural Imaging Laboratory (EUNIL) develops novel techniques using ultrasound, light and/or radio frequency to image excitable tissue, such as the brain, heart and skeletal muscle.

Potential Industry Collaborations: Electrical cardiac mapping during an interventional EP procedure is a laborious technique that usually takes several hours to complete. Accurate and precise identification of abnormal cardiac currents is paramount to a successful cardiac ablation. The state-of-the art mapping technique uses multi-electrode catheter arrays to image the cardiac wave. This approach is laborious with relatively poor spatial resolution. We propose using ultrasound combined with existing technology to provide real-time 3D images of current flow with sub-mm resolution based on the acoustoelectric interaction between pressure and electrical current. We have devised Ultrasound Current Source Density Imaging to ultimately improve the EP procedure and hold a patent (pending) through the University of Michigan (with potential licensing with the University of Arizona) to develop this technology for cardiac and other applications involving electrophysiology. Industrial support is critical component of further developing this new technology.

Relevant Citations:

Olafsson R, RS Witte, S-W Huang and M O'Donnell. "Ultrasound Current Source Density Imaging." *IEEE Transactions on Biomedical Engineering*, accepted (2007).

Witte RS, R Olafsson and M. O'Donnell. "Imaging current flow in lobster nerve cord using the acoustoelectric effect." *Applied Physics Letters*, Apr 9 (90): 163902 (2007). Special selection by American Physical Society for *Virtual Journal of Biol Phys Res*.

Olafsson, R, R.S. Witte, S-W Huang and M. O'Donnell. "Detection of electrical current in a live rabbit heart using the acoustoelectric effect." *Proc. 2007 IEEE Ultrasonics Symposium*, in press (2007).

Witte RS, R Olafsson, M O'Donnell. "Current Mapping of Biopotentials using the Acousto-Electric Effect." UM FILE 3236, patent pending (Jan 2008), Univ. of Michigan.



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UNIVERSITY OF ARIZONA OFFICE OF RESEARCH AND CONTRACT ANALYSIS

The Mission of the Office of Research and Contract Analysis is to facilitate research and development activities sponsored by internal and/or external agencies and organizations.

The Office of Research and Contract Analysis is responsible for:

- Clinical Trial Agreements
- Confidentiality Agreements
- Incoming Material Transfer Agreements and Biomedical Material Transfer Agreements
- Research Agreements
- Subcontracts
- Teaming Agreements
- Memoranda of Understanding

In support of this mission, ORCA:

- Maintains a competent staff, fully trained to meet its responsibilities, and highly motivated to achieve superior performance.
- Develops an awareness of the need for mutual understanding and effort in the solution of problems
- Responds quickly to the needs of the faculty, administrators, business managers and sponsors, fully meeting their expectations for quality service.
- Negotiates with sponsors, and subcontractors concerning grants, contracts, non-disclosure agreements, material transfers and other agreements related to extramural funding, so that they conform to the laws of the State of Arizona, policies of the University and the Arizona Board of Regents.
- Interprets policies of the University and sponsors regarding sponsored projects.
- Prepares, executes, and maintains standard agreements, subcontracts, and other agreements related to extramural funding.
- Certifies compliance with University and government regulations concerning protection of human subjects, recombinant DNA, conflict of interest, lobbying, drug free workplace, debt and debarment, and other Federal assurances and certifications.
- Signs as authority, on behalf of the Arizona Board of Regents, for accepting all types of awards, including grants, contracts, and other agreements, and for all campus units.

ORCA Contact Information:

- Please direct your questions or need for assistance to Lewis Barbieri, Director at (520) 626-3050.
- Please visit ORCA's website at: <http://www.orca.arizona.edu/>

Office of Technology Transfer

Getting to Business

The scope, depth, and renown of our research enterprise make the University of Arizona an ideal partner for companies seeking a premier source of project-specific expertise, intellectual property licensing opportunities, or broad, long-term research relationships.

Whether focused on finding solutions to specific problems with near-term practical impact or pushing back the frontiers of basic knowledge with support from state and federal sponsors, University of Arizona faculty and students in the physical, biological, and information sciences produce a stream of new inventions and works of authorship that can drive societal change and help companies gain a competitive advantage.

And whether our industry partners choose to engage as sponsor, licensee, or collaborator, the Office of Technology Transfer helps to contractually coordinate the intellectual property components of the relationship in order to prepare University of Arizona innovations for further development, application, and delivery to society

The Business of Innovation...

New knowledge of ourselves and our surroundings, new methods for understanding and solving problems of importance to society, and new technologies to measure and build on what we find in nature all remain hallmarks of a great research university. In parallel, companies prosper when they develop knowledge, methods, and technologies into practical products and services reliably available to end users. The Office of Technology Transfer seeks to expand and coordinate the links between those two forms of enterprise.

... for UA Researchers

To a UA principle investigator, the business of innovation includes securing access to the financial, personnel, and infrastructure resources necessary for a large research program, and the steps necessary to make the results known to the sponsors and the scholarly community. Working with these faculty and student researchers even before innovative advances are made, OTT explains the significance and use of intellectual property management tools such as confidential disclosure agreements and material transfer agreements, and of methods to reconcile academic publication with preservation of intellectual property rights. Once a new invention or work of authorship is created, OTT identifies ownership, weighs the various routes for dissemination and, when a commercial route or "planned commons" is appropriate, identifies and consolidates the associated intellectual property rights in the innovation.

... and for Agile Companies

For a company, the business of innovation includes creating or acquiring rights to a promising invention or work of authorship, along with continued access to the innovator, and then securing and investing the staff, funds, and facilities to refine, test, produce, market, and deliver a new product or service based on the innovation.

To assist these companies, OTT works with our researchers to identify innovations and encapsulate the associated intellectual property rights into transactional assets, such as patents and copyrights with clear title.

Licensing those IP rights to local and national companies for further development is OTT's main responsibility. Specific terms are case-specific, but often include a license issue fee, recovery of patent costs, and reasonable royalties. The intent is a financial return to Arizona citizens and the UA research enterprise, while ensuring that the licensee has ample incentive to develop the innovation for timely delivery to end users.

... with Help from OTT and Colleagues

Success in technology transfer requires teamwork, with each position contributing domain-specific expertise to the overall process. OTT regularly coordinates with an outstanding team of professionals at the University of Arizona and nearby institutions. Together, we manage the process from negotiating terms in research funding agreements, through strategizing IP rights during early stages of research, to perfecting and consolidating rights, working with teams of entrepreneurship students to help pinpoint and expand concrete business opportunities, calling upon local experts for SBIR and other small business advice, and channeling fledgling companies to our affiliated high-tech incubator facilities.

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Company Profiles

Boehringer-Ingelheim, Laboratories of Tom Peterson

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The four laboratories I manage are responsible for identifying and prosecuting novel targets in the area of heart failure.

The steps and timeline for getting a research agreement approved, a study initiated, and time to final report would help project teams at my institution plan ahead.

For time limited projects, this knowledge would permit us to determine early whether the Univ. of Arizona would meet the timelines recommended by management.

Gould, WR, SM Baxi, R Schroeder, YW Peng, RJ Leadley, **JT Peterson** and LA Perrin. Gas6 receptors Axl, Sky and Mer enhance platelet activation and regulate thrombotic responses. *Journal of Thrombosis & Haemostasis*, 3(4):733-741, 2005.

Peterson, JT. The importance of estimating the Therapeutic Index – MMP inhibitors a case study. *Cardiovascular Research*, 69:677-87, 2006.

Kohrt, JT, KJ Filipski, WL Cody, CF Bigge, F La, K Welch, T Dahring, JW Bryant, D Leonard, G Bolton, L Narasimhan, E Zhang, **JT Peterson**, S Haarer, V Sahasrabudhe, N Janiczek, S Desiraju, M Hena, C Fiakpui, N Saraswat, R Sharma, S Sun, SN Maiti, R Leadley, JJ Edmunds. The discovery of glycine and related amino acid-based factor Xa inhibitors. *Bioorganic & medicinal chemistry* 2006;14 (13):4379-92.





Daiichi-Sankyo

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Daiichi Sankyo Co., Ltd., Japan's second largest pharmaceutical company and a global leader in pharmaceutical innovation since 1899. The company is dedicated to the discovery, development and commercialization of innovative medicines that improve the lives of patients throughout the world.

The primary focus of Daiichi Sankyo's research and development is cardiovascular disease, including therapies for dyslipidemia, hypertension, diabetes, and acute coronary syndrome. The company is also pursuing the discovery of new medicines in the areas of glucose metabolic disorders, infectious diseases, cancer, bone and joint diseases, and immune disorders.

From as early as 1899, when Daiichi Sankyo pioneers discovered epinephrine, through the isolation of B-vitamins, the development of the first statin (a class of medications used to treat high cholesterol) and the first glitazones for diabetes, Daiichi Sankyo's legacy of innovation has stood the test of time. These discoveries have established a lasting impact on the field of medicine and highlight the company's commitment to discovering medicines that improve the lives of patients with chronic disease.

With a century of groundbreaking discovery by its Japanese parents as a guide, Daiichi Sankyo unites rigorous research and invention with operational excellence to deliver medicines that put lives into balance and add to the balance of life.

For more information, please visit www.dsus.com.

Robert S. Kellar, Ph.D.

Dr. Kellar has more than 11 years of experience in research and product development. Dr. Kellar recently joined Histogen from his positions as co-owner and President of Development Engineering Sciences, a firm based in Flagstaff, Arizona. Kellar's experience in the biomedical industry includes prior positions with W.L. Gore & Associates and Advanced Tissue Sciences, where he was involved with commercial worldwide management of research, product development, business, marketing, and sales. Kellar has authored over 7 papers and is the inventor on 5 patents and patent applications. Kellar also serves on the Scientific Advisory Board for TheraGen, a cell therapy company investigating the cardiovascular applications of the cell-based human tissue patch, Anginera™. Dr. Kellar also holds an Adjunct Professor Faculty position in Mechanical Engineering at Northern Arizona University.

Laboratory Research Interests:

Dr. Kellar's research interests are in the fields of tissue engineering and regenerative medicine. This includes ongoing cell-based research using newborn human fibroblasts as a cardiac patch for use in patients with ischemic cardiac tissues. Currently, this technology is being evaluated in clinical trials in the US under the sponsorship of TheraGen, Inc. Additionally, Dr. Kellar's research at Histogen, Inc. includes manipulating the culture conditions of cells in bioreactors to generate unique embryonic-like cellular by-products. These cellular by-products include embryonic-like human extracellular matrix and conditioned media that have the potential to be used for a variety of research-based products and clinical applications.

Relevant Citations:

Kellar, RS, Shepherd, BR, Larson, DF, Naughton, GK, and Williams, SK. Cardiac Patch Constructed from Human Fibroblasts Attenuates Reduction in Cardiac Function after Acute Infarct. Tissue Engineering, 11(11/12):1678-1687 (2005).

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Kronos Science Laboratory

www.kronoslaboratory.com

Laboratory Research Interests: Kronos Science Laboratory (KSL) is an independent company affiliated with the Kronos Optimal Health Company and non-profit affiliate Kronos Longevity Research Institute. KSL is dedicated to the discovery and implementation of innovative new technologies for the improvement of human health and longevity.

In addition to collaborating on and supporting the research being conducted by colleagues and clients, KSL conducts its own basic and translational research in the fields of optimal health and human aging. One of the laboratory's areas of expertise is in the field of cardiovascular disease. A major, ongoing project focuses exclusively on human aging and directed by Kronos Science Laboratory is the *Kronos Longitudinal Aging Study or KLAS*. Other areas of interest include Alzheimer's disease, Inflammation, Oxidative Stress, Endocrinology and Nutrition. Services provided include custom assay development, esoteric and traditional testing services, custom data retrieval and reporting, multi-center trial support, investigator support, advanced specimen storage, tracking and retrieval, custom sample collection and shipment kit development.

Services Provided: KSL not only conducts research in the area of cardiovascular disease, but also offers clinical testing as well. As a CLIA certified laboratory, we can provide testing on a clinical or research basis. The Kronos Science Cardiovascular Risk Assessment test panel is designed to provide physicians with a complete evaluation and understanding of their patients' cardiovascular risk and protection.

KSL, has a state-of-the-art laboratory with significant analytical testing capability. With a dedicated research and development group, KSL can work with other researchers to develop assays of interest and provide analytical capabilities to perform testing.

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Medtronic, Inc.

Medtronic is the world leader in medical technology providing lifelong solutions for people with chronic disease. We offer products, therapies and services that enhance or extend the lives of millions of people. Each year, 6 million patients benefit from Medtronic's technology, used to treat conditions such as diabetes, heart disease, neurological disorders, and vascular illnesses.

Our Cardiac Rhythm Disease Management division is focused on managing the entire spectrum of cardiac rhythm disorders to improve long-term patient care. With this intent in mind, multiple Medtronic businesses work together using a comprehensive strategy that results in innovative solutions. These solutions allow physicians to monitor and treat their patients' changing cardiac conditions over a lifetime.

Pacing systems

Pacing systems designs and manufactures pacemakers that treat patients with bradycardia. While working with pacing systems for over fifty years, we are dedicated to providing a continuous stream of innovation and technological advancements to successfully restore patients that suffer from bradycardia to full and healthy lives.

Defibrillation systems

Defibrillation systems develops and manufactures implantable defibrillators for treatment of patients with tachyarrhythmias. Implantable defibrillators are proven to reduce mortality in specific patients at risk for sudden cardiac death. However, it is clear that technological advances can continue to improve acceptance of this life saving therapy.

Cardiac Resynchronization Therapy systems

Cardiac resynchronization therapy (CRT) is a proven treatment for selected patients with heart failure-induced conduction disturbances and ventricular dyssynchrony. When used in combination with optimal medical therapy CRT is designed to reduce symptoms and improve cardiac function by restoring the mechanical sequence of ventricular activation and contraction.

Diagnostic and Monitoring systems

Patients who experience transient symptoms that may suggest a cardiac arrhythmia and patients with clinical syndromes at increased risk for arrhythmias may benefit from an implantable monitoring system. The Insertable Loop Recorder is an implantable patient and automatically activated cardiac monitoring system. This system can record an ECG at the time of a syncopal episode that may help rule in or rule out life-threatening arrhythmias.

OVERVIEW: Phrixus Pharmaceuticals, Inc. is a new company created to develop an already clinically tested compound, Carmeseal™ or poloxomer-188, for heart failure (HF). HF is a deadly syndrome that affects more than 5 million people in the United States for which the only known "cure" is heart transplantation. The mortality rate of HF patients within 5 years of diagnosis is greater than 50%. While several therapies are available to treat abnormal contraction, there are currently no therapies that target impaired relaxation (diastolic dysfunction) of heart muscle seen in over 2 million patients. Carmeseal is a first-in-class biological membrane sealant, whose use in diastolic dysfunction the Company has optioned exclusively. This compound has already generated an acceptable safety profile in phase 3 clinical trials for un-related indications. Phrixus will seek FDA approval to initiate phase 2 clinical trials for the treatment of acute decompensation episodes in chronic HF ("acute" HF) in 2008 and anticipates product approval for 2012. Long term, Phrixus will seek a corporate partner to develop Carmeseal for chronic HF. Phrixus will also develop Carmeseal as a chronic therapy for the treatment of Duchenne Muscular Dystrophy. As its pipeline grows, PPI expects to go public based on strong clinical results, unless it is purchased in a trade sale.

Phrixus Pharmaceuticals, Inc.

Number of Employees: 4

Funding to date: \$1.5 million (privately held)

Investors: Biosciences Research and Commercialization Center (Kalamazoo, MI), Michigan Corporate Formation and Growth Fund and Michigan Pre-Seed Fund (Lansing, MI), Ann Arbor SPARK (Ann Arbor, MI), and private investors

Other funding: SBIR grants (NIH)

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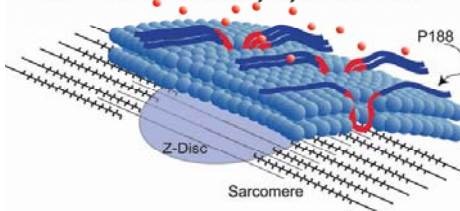
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HISTORY: Phrixus was founded in 2006 by a team of entrepreneurs and drug developers based on the work by Dr. Metzger, a world-renowned muscle biologist at the University of Michigan. Dr. Metzger and colleagues demonstrated that Poloxamer-188 can act as a "molecular band-aid" that seals microscopic tears in the cell membrane of cardiac muscle cells from dystrophic mice, and as a result, decreases intracellular calcium concentrations and develops tension upon passive stretch (Yasuda et al., 2005. Nature 436: 1025-1029). This results in greatly improved cardiac hemodynamics and survival in response to a stress challenge. Phrixus has expanded this original intellectual property to cover heart failure of all etiologies and has demonstrated improved cardiac hemodynamics in the rat myocardial infarction model of heart failure. Phrixus's founders have a keen interest in targeting the large unmet

need in heart failure, particularly in the area of diastolic dysfunction which has been underserved by large pharmaceutical companies. The management team has extensive experience in drug development, commercialization and company building. In addition, Phrixus has recruited premier researchers and physicians in the heart failure-muscular dystrophy arena to its Scientific and Medical Advisory Board.

Passive Stretch in mdx Myocytes with P188



Schematic of a muscle sarcolemma with tears plugged by P-188. The red dots are calcium ions

Theregen

Theregen, Inc.

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Company Overview

Theregen, Inc. is repurposing an existing FDA-approved device for cardiac applications. Anginera, an epicardial patch, induces repair and restoration of regional heart function. Theregen has a capital efficient business model that includes a small head count, low burn rate, limited R&D costs, no manufacturing risks, a reliable, secure supply of products, and two Phase I trials in progress. We have demonstrated for the first time in humans, that Anginera induces the growth of mature blood vessels in damaged cardiac tissue, stimulates tissue repair, and improves ventricular wall motion.

Anginera's technology uses an FDA-approved cell line of human fibroblast cells. The fibroblast cells are cultured on a three-dimensional bioabsorbable scaffold material to create a viable tissue [Naughton, 2002]. When applied as an epicardial patch to an ischemic area of the heart, the living tissue provides cytokines and growth factors needed to induce angiogenesis and tissue repair.

Phase I – CABG Trial

The company's first clinical trial for Anginera is as an adjunct therapy in patients undergoing CABG surgery. Theregen's Phase I safety trial began when Anginera was successfully placed for the first time on a patient's diseased heart by a surgical team of Yale physicians at the Veteran's Administration Hospital in West Haven, CT. The patient was undergoing CABG surgery at the time. Anginera patches were applied to the surface (epicardium) of the heart on a portion that shows reversible ischemia that is not addressable by bypass.

While the primary focus in the Phase I CABG trial is to test safety of the product, Theregen has demonstrated that Anginera's biologic activity promotes the formation of structurally and functionally significant blood vessels in diseased cardiac tissue. This therapy could represent a significant advantage in the treatment of diffuse small vessel disease. The 15-patient study is being conducted at Yale University, the University of Maryland and the University of Pennsylvania. Enrollment is complete and imaging studies are being analyzed.

References

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