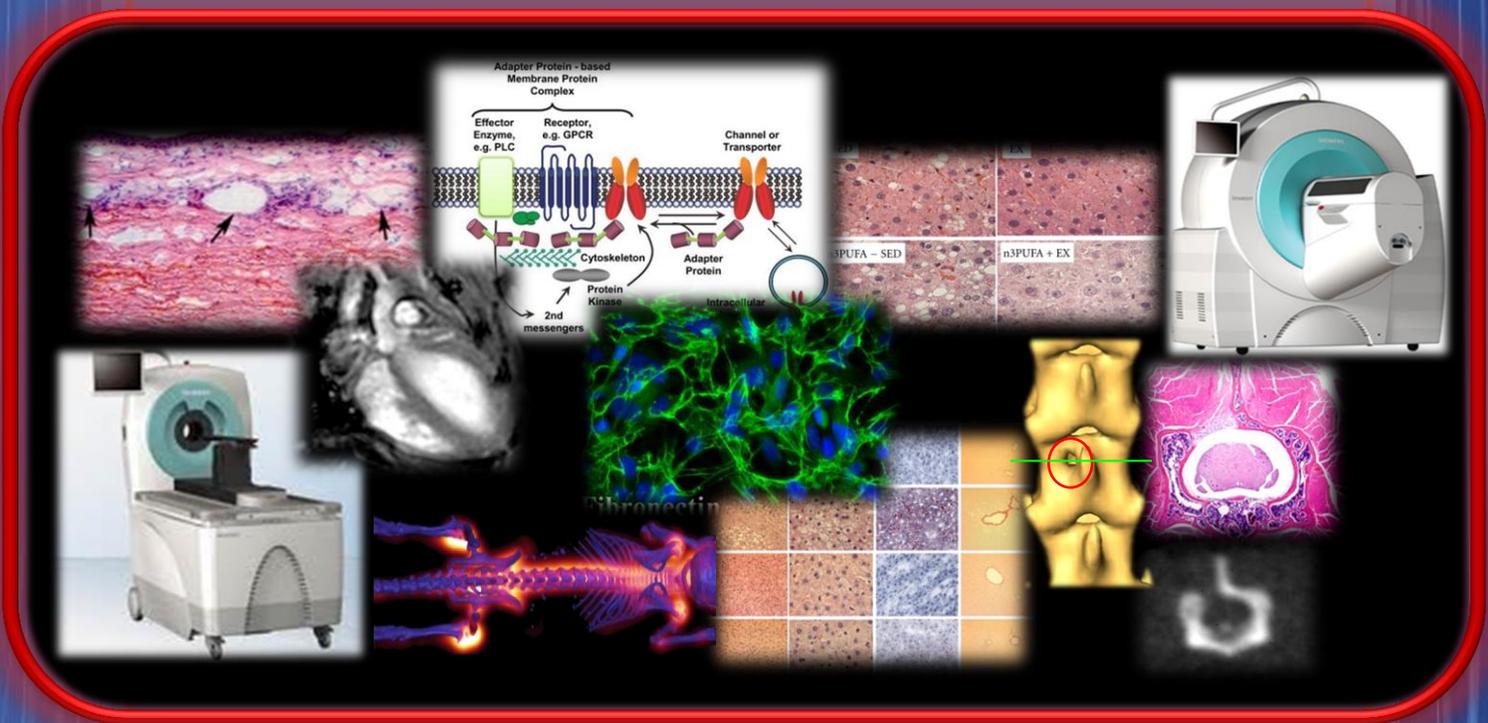


# Research and Development 2013 Highlights



Harry S Truman Memorial Veterans' Hospital  
Columbia, Missouri

**Truman VA**



Veterans Health Administration  
**Research & Development**  
Improving Veterans' Lives [www.research.va.gov](http://www.research.va.gov)



# Research and Development 2013 Highlights



Harry S Truman Memorial Veterans' Hospital  
Columbia, Missouri



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# Preface

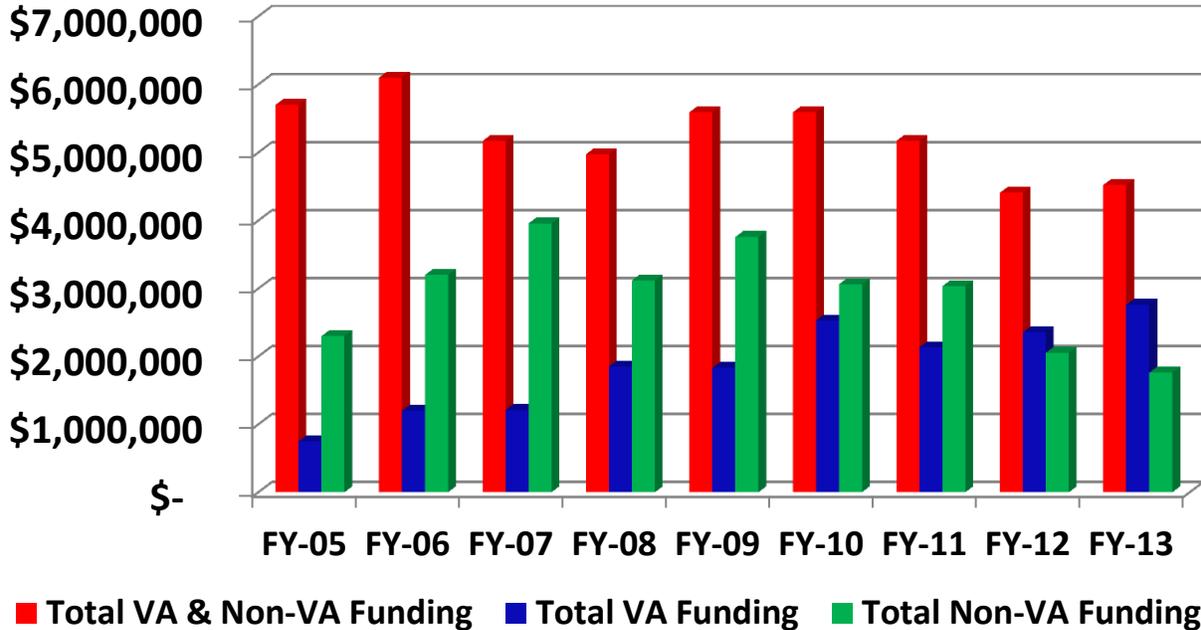
We at the Harry S. Truman Memorial Veterans' Hospital are proud of our investigators' accomplishments as described in the Research and Development Milestones 2013. In the Department of Veterans Affairs, the clinical and research missions are closely intertwined. This relationship is one reason that the VA provides such high quality medical care. Problems encountered in clinical care become the topic of research projects. Those research projects seek ways to translate their findings back to the bedside or clinic to improve the care of our veteran population. As the ensuing pages describe, our basic scientists and clinician investigators are studying a wide range of medical issues that are important not only to our veterans, but to the health our nation as well.

Adam Whaley-Connell, DO, MSPH  
Associate Chief of Staff, Research and Development



# HSTVA R&D Funding Profile

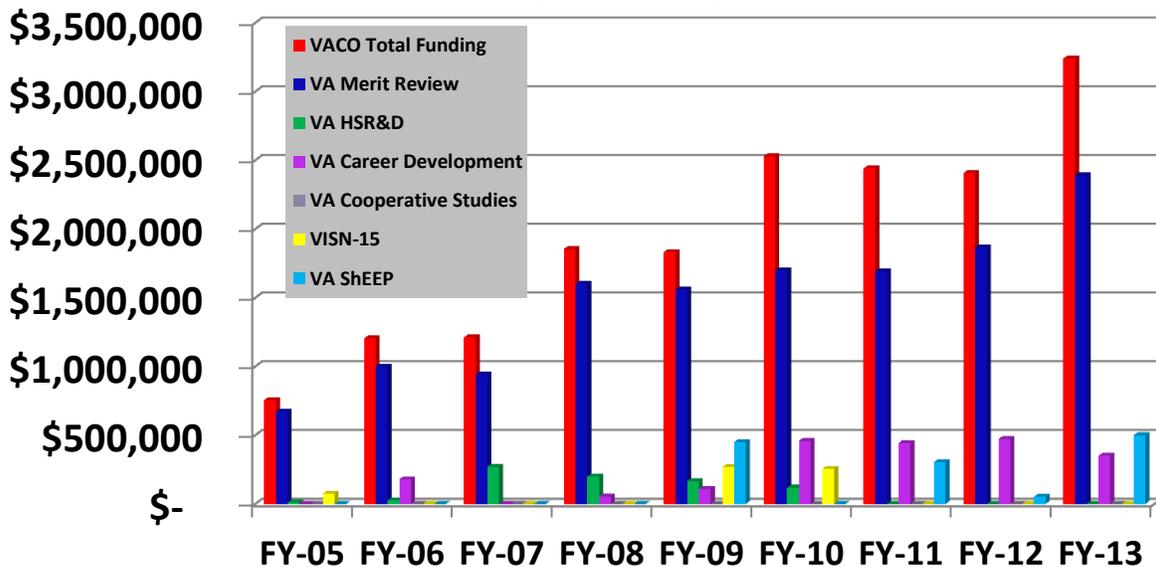
FY-05 to FY-13



The R&D Funding Profile above reflects total research funding (VA and Non-VA dollars) expended for the Truman VA medical research program during the period October 1, 2004 through September 30, 2013. The graph below represents the breakdown of total VA funding awarded to the Truman VA by funding category.

# HSTVA R&D VA Funding Profile

FY-05 to FY-13



# Truman VA Research & Development Program

## Summary Statistics\*

<b><u>R&amp;D Projects</u></b>	<b><u>2013</u></b>	<b><u>2012</u></b>	<b><u>2011</u></b>	<b><u>2010</u></b>	<b><u>2009</u></b>
Total Ongoing R&D Projects.....	90	75	82	97	96
New Projects initiated.....	25	11	13	22	19
Multi-year R&D Projects.....	70	63	68	75	77

### **Investigators**

Active Investigators.....	38	40	40	41	40
MD's.....	11	13	15	17	16
MD, PhD's.....	1	1	1	1	2
PhD's.....	23	22	21	20	21
Pharm D's.....	3	0	2	1	1
RN, BSN, or MSN's.....	0	1	1	1	1

### **Project Involvement**

Human Subject Use.....	34	24	27	39	37
Animal Subject Use.....	51	43	44	50	51
Investigational Drug Use.....	18	9	9	7	8
Investigational Device Use.....	2	2	2	3	4
Radioisotope Use.....	40	33	35	38	9
Biohazard Use.....	53	47	48	53	55

### **Funding Source**

VA.....	17	12	12	12	11
NIH.....	13	14	17	25	23
Other federal Agency.....	11	11	12	11	11
Other Govt./Academic Institution.....	34	20	23	26	25
Private Company.....	6	7	7	7	7
Voluntary Agency or Foundation.....	10	11	10	4	4
Self-Funded.....	16	18	20	29	29

\*Based on annual ePromise Project Report





Discovery & Innovation for Veterans' Health

## **Truman VA Medical Center & Missouri Foundation for Medical Research**

**Partners to Advance Discovery & Innovation for Veterans' Health**

*Our Mission:*

*To acquire and administer funds to support and sustain the advancement of healthcare knowledge and discovery for the benefit of America's Veterans.*

### **The Missouri Foundation for Medical Research supports VA Investigators**

**In 2013, the Missouri Foundation for Medical Research contributed more than \$440,500 in support of Research & Education at the Harry S Truman Memorial Veterans' Hospital.**

➤ Equipment and Material for VA labs:	\$ 54,715
➤ Salary support for lab techs, nursing, MU post Doc students	\$222,778
➤ Awards, Grants to individual investigators	\$ 1,525
➤ Lab supplies and services	\$149,067
➤ VA Staff development, travel, conferences, publications	<u>\$ 12,448</u>
	\$440,533

In 1988, Congress passed legislation allowing VA medical centers to establish state chartered not-for-profit corporations. This unique partnership dramatically broadened the VA's ability to accept private and non-VA public funds to support VA research and education. ***The Missouri Foundation for Medical Research*** was chartered in 1991 as a 501-c-3 tax exempt organization.

**[www.mofmr.org](http://www.mofmr.org)**

***Gifts to the Missouri Foundation for Medical Research are tax deductible.***

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\*Indicates PI research biographies data from 2012.

During the 2013, there were 42 VA investigators conducting research at the Truman VA. 31 of the 42 VA investigators are listed on the following pages.



## Kul Aggarwal, MD

Chief, Cardiology Section, Truman VA  
Professor of Clinical Medicine, University of  
Missouri – Columbia, School of Medicine

### Acute Coronary Syndromes, Antiplatelet Agents, Coronary Interventions

#### CLINICAL TRIALS:

1. **IMPROVE-IT Study.** Improved Reduction of Outcomes: VYTORIN Efficacy International Trial. Simvastatin Vs Vytorin in Acute Coronary Syndromes
2. **SOLID-TIMI-52 study.** Stabilization of Plaques Using Darapladib trial a phase III, randomized, double-blind, parallel-group, placebo-controlled, multinational event-driven trial
3. **PEGASUS-TIMI-54 study.** PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome
4. **REVEAL-TIMI 55 TRIAL.** (Randomized EValuation of the Effects of Anacetrapib through Lipid-modification). Sponsor Oxford University, UK
5. Drug Eluting Versus Bare Metal Stents in Saphenous Vein Graft Interventions (DIVA Study): A VA Co-operative Study. CSP 571.

Rajpurohit, N., Garg, N., Garg, R., Choudhary, A., Fresen, J., Boren, S., Dellsperger, K.C., Webel, R., **Aggarwal, K.**, and Alpert, M.A. "Early Versus Delayed Percutaneous Coronary Intervention for Patients with Non-ST Segment Elevation Acute Coronary Syndrome:

Chan, A., Mehra, A., and **Aggarwal, K.** "Quality Improvement Strategy in Reducing Radiation Exposure." *The Annual Scientific Session f the American College of Cardiology*, Chicago, IL, March 2012.

## Ulus Atasoy, MD, MA

Staff Physician, Truman VA  
Assistant Professor & Vice Chairman of  
Research, Departments of Surgery &  
Molecular Microbiology & Immunology,  
University of Missouri – Columbia

### Study of Posttranscriptional Gene Regulation in Breast Cancer and Allergen Driven Asthma

#### Breast Cancer Models

We are interested in exploring the role that RNA binding proteins (RBP) play in the development of breast cancer. The RBP, HuR, which we have cloned, has been hypothesized to be a tumor maintenance gene which allows for malignant tumor growth and metastasis. We have developed methods to identify new cancer targets which HuR may be regulating.

#### Allergen Driven Asthma

Asthma and allergies have been greatly increasing in the US and other developed countries the last 30 years for unknown reasons. We are investigating the hypothesis that the RBP, HuR, plays a role in regulating genes involved in the development of asthma. We have made animal models which over- or under-express HuR and are using them to better understand posttranscriptional gene regulation.

#### Wound Healing

The third major project in our laboratory involves wound healing. Certain patients re-develop ventral hernias after primary operations. This necessitates further surgeries. We have developed genome profiling methods which allow us to predict which patients may develop ventral hernias. This data can assist the clinician in approaches to these patients.



## Shawn B. Bender, PhD

Research Health Scientist, HSTMVH  
Research Assistant Professor in the  
Department of Medicine-Endocrinology,  
Diabetes, and Metabolism, University of  
Missouri School of Medicine

### Mineralocorticoid Receptors and Coronary Microvascular Dysfunction in Insulin Resistance and Diabetes

The overall goal of our research program is to understand the underlying mechanisms regulating coronary microvascular dysfunction associated with insulin resistance and diabetes. Coronary microvascular dysfunction is an independent risk factor for the development of future cardiovascular events. This dysfunction accounts for up to 63% of cardiac perfusion defects in patients with type 2 diabetes, a rapidly growing patient population in Western cultures. Unfortunately, a substantially higher prevalence of diabetes and coronary dysfunction is found in the Veteran population. Because coronary microvascular dysfunction contributes to the significant number of patients with diabetes-related cardiac ischemia, infarct, and sudden death, this condition is an important issue for VA healthcare.

We have ongoing studies in rodent models of obesity and insulin resistance to determine involvement of the aldosterone-binding mineralocorticoid receptor (MR) to the development of coronary microvascular dysfunction. These models include vascular cell type-specific MR knockout models fed either a standard or 'Western' diet to induce insulin resistance and vascular dysfunction. These studies will help to identify potential therapeutic targets downstream of the MR that may reduce the incidence of coronary dysfunction and cardiac perfusion defects in Veterans with diabetes.

**Bender, S.B.**, McGraw, A.P., Jaffe, I.Z., and Sowers, J.R. "Mineralocorticoid Receptor-Mediated Vascular Insulin Resistance: An Early Contributor to Diabetes-related Vascular Disease?" *Diabetes*, 62 (2013): 313 - 319.

## Kunal Chaudhary, MD

Staff Physician, Truman VA  
Physician, Specialty Care, Truman VA  
Clinical Associate Professor, University of  
Missouri – Columbia

### To Find if Antifibrotic Agent Decorin Administered with Nanoparticles or Adeno-associated Virus Inhibit Peritoneal Fibrosis in Animal Models and Lead to Better Preservation of Peritoneal Membrane

Peritoneal dialysis (PD) has been used to treat renal failure in human patients for the last three decades. Membrane preservation by use of antifibrotic agents in animal models of PD has shown promise. Exposing the peritoneal membrane to antifibrotic agents that delay or prevent the onset of fibrosis could enable patients to continue treatment for longer duration. Decorin is a proteoglycan and component of extracellular matrix. It binds and inactivates all three isoforms of TGF $\beta$  and has been shown to decrease fibrosis in many tissues. Adenovirus (AAV) mediated decorin (Ad-Decorin) gene transfer has been shown to be effective in the treatment of bleomycin induced lung fibrosis in murine models. Also, decorin gene transfer has shown significant reduction in collagen deposition in the submesothelium and decreased mesenteric hydroxyproline deposition in the peritoneal tissue in a rat model of peritoneal dialysis. More recently Gold Nano particles (GNP) have been used as a drug delivery vehicle in tumor thermal therapy, as well as delivery of transmucosal insulin. We are studying a rat model of Peritonitis to compare the effect of treatment with Decorin using AAV and GNP as vehicles. It is our belief that Decorin delivered via GNP would be less biohazardous and more effective as compared to Ad-Decorin therapy in decreasing peritoneal membrane fibrosis and preserve the peritoneal membrane allowing the PD patients to continue with PD therapy.



## Kathleen M Darchuk, PhD

*Clinical Psychologist, Truman VA  
Adjunct Assistant Professor of Psychiatry,  
University of Missouri – Columbia*

### **Pain Characteristics of Veterans Participating in a Primary Care Depression Management Program**

The purpose of this research project is to examine pain characteristics, psychiatric status, and treatment utilization of Veteran's participating in a primary care depression management program.

Major depression is one of the most prevalent and debilitating illnesses in the VA health care system, with most patients being treated within the primary care setting. Translating Initiatives for Depression into Effective Solutions (TIDES) is a telephone-based primary care intervention that has been shown to decrease symptom severity and improve functional status in veterans with depression. However, depression and chronic pain are highly comorbid and research has yet to examine the impact of pain on primary care interventions for depression. This research project aims to examine the effect of pain on various medical and psychological treatment factors and outcomes.

We have an ongoing study to determine 1) the pre-treatment pain characteristics of Veteran's in depression care management and 2) any differential outcomes for pain vs. non-pain patients on measures of depression, functioning, and quality of life. This information will help to improve pain and depression management in primary care.

## Susan Deutscher, PhD

*Research Scientist, Truman VA  
Professor Biochemistry –University of Missouri  
- Columbia*

### **Phage Display Technologies for Peptide-based Cancer Imaging and Therapy**

Our laboratory is interested in discerning the role of carbohydrate and protein-protein interactions in cancer. Work focuses on applying novel combinatorial phage display approaches and structural biochemistry to characterize these interactions. Combinatorial chemistry and phage display allows for the rapid selection from many millions of sequences to find peptide molecules that bind almost any given target such as cancer antigens. Once radiolabeled, the peptides act as selective cancer imaging and therapeutic agents. New work has focused on using phage display and protein engineering to improve the pharmacokinetics of the peptides for translation into clinical use. This work will help early diagnosis and treatment of many cancers that effect Veterans, including prostate, breast, ovarian, and colon cancer.

Newton-Northup, J.R., Dickerson, M.T., Ma, L., Besch-Williford, C.L., and **Deutscher, S.L.** "Inhibition of Metastatic Tumor Formation In Vivo by a Bacteriophage Display-derived Galectin-3 Targeting Peptide." *Clinical and Experimental Metastasis* 30 (2013): 119 - 132.

Larimer, B.M., Thomas, W.D., Smith, G.P. and **Deutscher, S.L.** "Affinity Maturation of an ERBB2-Targeted SPECT Imaging Peptide by In Vivo Phage Display." *Molecular Imaging and Biology*. DOI:10.1007/s11307-014-0724-5.



## Thomas Dresser, PhD, MD

Chief of the Nuclear Medicine Clinic,  
Truman VA  
Chief of Clinical Support Service Line,  
Truman VA  
Clinical Professor in Radiology & Internal  
Medicine, School of Medicine  
Director, Nuclear Cardiology Training Program,  
Department of Internal Medicine, School of  
Medicine, University of Missouri –  
Columbia

### Correlation of Myocardial Perfusion Imaging (MPI) and Cardiac Catheterization

This is an ongoing chart review study. Patients who have had MPI and cardiac catheterization have the data reviewed with respect of determining how the studies correlate and how they affect clinical care. There are over 2,500 cases in data file. Analysis of this data has resulted in 6 posters or presentations at the national level and 3 published articles.

Sidhu, M., Chan, A.K., Chockalingam, A., and **Dresser T.** "Myocardial Perfusion Imaging Analysis in Patients with Regurgitant Valvular Heart Disease." *J Nucl Cardiol.* 18.2 (2011): 309 -13. doi: 10.1007/s12350-011-9344-5.

## William Fay, MD

Staff Physician, Truman VA  
*JW and Lois Winifred Stafford Distinguished  
Chair in Diabetes & Cardiovascular  
Research*  
Professor of Internal Medicine, Medical  
Pharmacology & Physiology  
Director, Division of Cardiovascular Medicine,  
University of Missouri – Columbia

### Molecular Genetics of Coagulation Disorders

Dr. Fay's lab activated a new VA Merit Review award in January 2013. The grant is entitled "Role of Fibrinolytic System in Vein Graft Remodeling." The 4-year award will fund experiments designed to explore the mechanisms that regulate the structural and functional changes that occur in veins after they are grafted into the arterial circulation. Each year many thousands of veterans undergo coronary artery and peripheral artery bypass graft surgery to treat blocked coronary and peripheral arteries. Veins harvested from the legs are commonly used as bypass grafts. However, within 10 years after bypass surgery 40% of all cardiac venous bypass grafts occlude and the majority of peripheral arterial venous bypass grafts occlude, often with life-threatening consequences. The molecular and cellular processes that cause vein bypass grafts to remodel, narrow, and occlude are not well understood. The proposed experiments will examine the roles of plasminogen activator inhibitor-1 (PAI-1) and vitronectin (VN), proteins that control blood clotting and cell migration, in the remodeling of bypass grafts. We anticipate that the information gained from our studies will lead to new approaches to prevent and treat vein bypass graft disease.

**Fay, W.P.** *Pathophysiology of Arterial Thrombosis.* Ed. Baliga, R. Specialty Board Review: Cardiology. New York, NY: McGraw-Hill, 2012, pp 999-1004.



## Olga Glinskii, MD

Research Investigator, Truman VA  
Research Assistant Professor, University of  
Missouri - Columbia

### Estrogen-dependent Remodeling of Brain Vascular Networks

Sex-hormone deficiencies in women are frequently associated with increased risk of several pathological conditions in the brain system including stroke and cerebral or dura mater aneurysms leading to increased incidence of intracranial hemorrhage, dural venous sinus thrombosis, and spontaneous cerebrospinal fluid leaks. All these conditions may result in a significant neurologic morbidity and decline in cognitive abilities. Data from our laboratory indicate that following the cessation of the ovarian hormone production vasculature of dura mater (membrane covering brain) undergo dramatic remodeling, resulting in a loss of capillaries, weakening of blood vessel walls, and increase in vessel permeability. As the result, defective and leaky blood vessels become the possible risk factors predisposing one to brain vascular injury. This process is accompanied by changes in growth factors signaling pathways that normally maintain vascular integrity, negatively affecting brain venous blood outflow. Our research is aimed at understanding molecular mechanisms by which estrogen provide vasoprotection and dissecting undesirable effects of estrogen from its beneficial mechanisms of action.

## Vladislav V. Glinskii, MD

Research Health Scientist, Truman VA  
Assistant Professor, Pathology & Anatomical  
Sciences, University of Missouri –  
Columbia

### Molecular Mechanisms of Cancer Metastasis and Anti-Metastatic Drug Development

Dr. Glinskii research program is focusing on investigating the molecular and cellular mechanisms of breast and prostate cancer metastasis and developing new approaches to cancer therapy. Metastasis is the major cause of prostate cancer-related morbidity and mortality causing intractable pain, pathological fractures, spinal cord compression, and ultimately death. Studies from Dr. Glinskii group demonstrated that interactions mediated by cancer-associated Thomsen-Friedenreich glycoantigen and carbohydrate binding protein galectin-3 regulate several critical steps in metastasis such as metastasis-associated endothelium activation, tumor cell arrest in target organ vasculature, homotypic tumor cell aggregation, and metastatic cell clonogenic survival and growth thus identifying these interactions as potential targets for therapeutic interventions. Consequently, Dr. Glinskii group has developed series of small molecular weight non-toxic carbohydrate-based compounds specifically inhibiting galectin-3 and Thomsen-Friedenreich antigen. Investigation of anti-metastatic properties of these compounds is a major focus of the ongoing research in Dr. Glinskii laboratory.

Glinskii, O.V., Sud, S., Mossine, V.V., Mawhinney, T.P., Anthony, D.C., Glinsky, G.V., Pienta, K.J., and **Glinskii, V.V.** "Inhibition of Prostate Cancer Bone Metastasis by Synthetic TF Antigen Mimic/Galectin-3 Inhibitor Lactulose-L-Leucine." *Neoplasia*, 14 (2012): 65 - 73.



## Vamsi P. Guntur, MD, MSc

*Staff Physician, Truman VA  
Assistant Professor, Department of Internal  
Medicine - Pulmonary, Critical Care, &  
Occupational Medicine, University of  
Missouri – Columbia*

### **Early Detection and Novel Therapeutics of Inflammatory and Malignant Airway Diseases**

My primary research goal is to identify a non-invasive method for detection of early airway diseases, primarily lung cancer. Early diagnosis will facilitate in targeted early treatment and improve overall outcomes of lung cancer. As a corollary, we are also involved in studies investigating the presence of byproducts of lung cancer in the blood, as a risk stratification tool. Our ultimate goal is to develop a less invasive diagnostic tool for identification of lung cancer; thereby, benefiting the VA healthcare system, since a significant proportion of veterans are smokers and have a high risk for lung cancer.

We completed several bench and animal studies investigating the role of microscopic nanoparticles that may preferentially identify with lung cancer cells. Further studies of microscopic particles that target lung cancer may help us find these cancers earlier, and thereby treat them earlier, which will portend a better prognosis. We also have ongoing studies to determine if we can detect byproducts of lung cancer (e.g. cancer DNA) in blood. This will help us to risk stratify patients with lung nodules as high or low risk for lung cancer, and hopefully recommend specific treatment earlier.

Ongoing and/or upcoming investigations include:

1. Detection of plasma DNA and DNA methylation biomarkers for early detection of lung cancer – with an MU oncology researcher.
2. Detection of lung tumors in mice using targeted nanoparticles – with an MU veterinary oncology researcher.
3. Application of radiolabeled peptides targeting bombesin receptors as diagnostic and therapeutic agents.

## Shadi Haddadin, MD

*Staff Physician, Hematology/Oncology,  
Truman VA  
Clinical Assistant Professor in the Departments  
of Internal Medicine, Hematology & Medical  
Oncology, University of Missouri –  
Columbia*

The overall goal of our research program is to evaluate the role of targeted radiotherapy in combination with chemotherapy in the treatment of cancer, specifically prostate and small cell lung cancer. I have been working with Dr. Timothy Hoffman in this area since 2010. After joining as a full-time staff member of the Harry S. Truman Memorial Veterans' Hospital, I assumed a lead role in establishing our facility as one of the newest members of the Alliance for Clinical trials in Oncology. As I continue in collaboration with Dr. Hoffman, my current research involves castration resistant metastatic prostate cancer, where we are exploring different combinations of radioisotopes in the treatment. In addition, we are exploring the role of Bombesin receptor targeted therapies in small cell lung cancer.



## Carla Hansel, PharmD

Pharmacist, Truman VA

### Pharmacist-based Clinic Using a Novel Approach to Treat Hypertension

Dr. Hansel's VA research program seeks to improve the methods of blood pressure management by utilizing plasma rennin activity (PRA) level as a tool in directing antihypertensive therapy for optimal control of hypertension (HTN) in study subjects. By using monotherapy or minimizing the number of antihypertensive medications used, Dr. Hansel's research team is hypothesizing that the PRA model will be more effective than the current practice in lowering blood pressure to the target recommended by the Joint National Committee (JNC-7) in the veteran population.

## Timothy J. Hoffman, PhD

Research Career Scientist, Truman VA  
Director, VA Biomolecular Imaging Center  
Professor of Internal Medicine, Chemistry, and  
The Nuclear Science & Engineering  
Institute, University of Missouri – Columbia

### Nuclear Oncology using Therapeutic Radiopharmaceuticals and Molecular Imaging

Dr. Hoffman's research program is currently focused on developing tumor targeting diagnostic and therapeutic radiopharmaceuticals. Dr. Hoffman and his research team have developed peptide targeting technology specific for receptors expressed in prostate, breast, and lung cancers. The laboratory is investigating multiple peptide based diagnostic and therapeutic radiopharmaceuticals incorporating  $^{99m}\text{Tc}$ ,  $^{111}\text{In}$ , and  $^{67}\text{Ga}$  for use with clinical SPECT imaging,  $^{64}\text{Cu}$ ,  $^{68}\text{Ga}$ , and  $^{18}\text{F}$  for use with clinical PET imaging, and  $^{177}\text{Lu}$  and  $^{90}\text{Y}$  for use in targeted radiotherapy. Utilizing preclinical models of human metastatic prostate cancer, Dr. Hoffman's laboratory is developing novel ways to optimize radiotherapeutic agent delivery by employing receptor targeted in vivo radiotherapy combined with cell cycle inhibiting chemotherapeutics.

Dr. Hoffman also directs the VA Biomolecular Imaging Center which provides preclinical molecular imaging technology to VA and affiliated medical researchers. The VA BIC is comprised of a combined Micro-SPECT/CT system, a Micro-PET system, and a 7 Tesla small bore MRI system.

Winkelmann, C.T., Figueroa, S.D., Sieckman, G.L., Rold, T.L., and Hoffman, T.J. "Non-invasive microCT Imaging Characterization and In Vivo Targeting of BB2 Receptor Expression of a PC-3 Bone Metastasis Model." *Molecular Imaging & Biology* 14.6 (2012): 667 - 675. PMID: 22314281



## Jamal A. Ibdah, MD, PhD, AGAF

Staff Physician, Truman VA  
Senior Associate Dean for Research, School of  
Medicine  
Director, MU Institute for Clinical &  
Translational Science & Division of  
Gastroenterology & Hepatology  
Raymond E. and Vaona H. Peck Chair in  
Cancer Research  
Professor of Medicine & Medical Pharmacology  
& Physiology, University of Missouri –  
Columbia

### The Metabolic Syndrome and Nonalcoholic Fatty Liver Disease

The metabolic syndrome is a combination of risk factors (including insulin resistance, hypertension, and dyslipidemia), that when occurring together are known to increase the risk of heart disease, diabetes, and nonalcoholic fatty liver disease. Currently, it is estimated that 25-30% of Americans have the metabolic syndrome and fatty liver disease. These percentages are even higher among Veterans. We are conducting experiments in several animal models known to development the metabolic syndrome and fatty liver disease in order to determine the underlying mechanisms regulating fatty liver disease development and progression. This includes examining mitochondrial function and insulin resistance in isolated cell culture and in multiple tissues, including liver, muscle, and fat. In addition, we are examining how lifestyle modifications, such as diet and exercise, can be used as preventative and treatment strategies for the metabolic syndrome and nonalcoholic fatty liver disease.

Ashraf, I., Paracha, S., Paracha, S.R., Arif, M., Choudhary, A., Godfrey, J., Clark, R., Abdullah, O., Matteson, M.L., Puli, S.R., **Ibdah, J.A.**, Dabbagh, O., and Bechtold, M.L. "Warfarin use during Fecal Occult Blood Testing: A Meta-analysis." *Gastroenterol Res* 5 (2012): 45-51.

Borengasser, S.J., Rector, R.S., Uptergrove, G.M., Morris, E.M., Perfield, J.W., Booth, F.W., Fritsche, K.L., **Ibdah, J.A.**, and Thyfault, J.P. "Exercise and Omega-3

## Sharad Khare, PhD

Research Health Scientist, Truman VA  
Associate Professor, Department of Internal  
Medicine – Gastroenterology & Hepatology,  
University of Missouri – Columbia

### Role of Ursodeoxycholic Acid in Colon Cancer Chemoprevention

Environmental factors, including dietary fats, are implicated in colonic carcinogenesis. Dietary fats modulate secondary bile acids including deoxycholic acid (DCA) concentrations in the colon, which are thought to contribute to the nutritional-related component of colon cancer risk. Research in my laboratory focuses on regulation of Cyclooxygenase-2 (Cox-2) gene expression by bile acids. We have previously shown that DCA promotes colonic carcinogenesis in the azoxymethane (AOM) model of colon cancer. In contrast, another bile acid, ursodeoxycholic acid (UDCA) inhibits AOM tumor incidence. Supporting the relevance of these findings in humans, two recent studies indicate that UDCA inhibited dysplasia and tumor development in patients with ulcerative colitis complicated by primary sclerosing cholangitis. Another study in patients with primary biliary cirrhosis suggested that UDCA might inhibit sporadic colonic adenoma recurrence. We have found that tumor inhibiting UDCA also reverses the AOM-induced increase in Cox-2 expression. Cox-2 inhibitors inhibit colonic tumor development *in vivo* in humans and experimental animal models. However, long-term use of Cox-2 inhibitors in colorectal adenoma secondary prevention trials was associated with an enhanced risk of serious vascular events. Alternate ways of inhibiting Cox-2 signaling may include suppression of Cox-2 protein expression by chemopreventive agents. We have demonstrated that UDCA significantly suppressed Cox-2 protein expression in AOM tumors and expression of Cox-2 is tightly controlled at the transcriptional level. More recently, we have employed a cell culture model to dissect the molecular mechanisms involved in Cox-2 regulation. In this system, Cox-2 is strongly induced by tumor-promoting DCA and this induction is inhibited by tumor-preventing UDCA. This cell culture model will, therefore, allow us to elucidate the *cis*- and *trans*-acting elements that mediate Cox-2 suppression by UDCA.



## John R Lever, PhD

Research Scientist, Truman VA  
Associate Professor of Radiology & Medical  
Pharmacology & Physiology, University of  
Missouri – Columbia

### Development and Use of Radioactive Tracers for Cancer or Substance Abuse Studies

Dr. Lever's research is focused on the development of novel radioactive tracers, and their use *in vitro* and *in vivo* to gain a better understanding of cancer or substance abuse. Areas of current interest include: 1) the development of opioid receptor binding compounds labeled with radiometals that facilitate non-invasive imaging and therapy of lung cancers; 2) the development of radioactive photoaffinity probes for studies of the dopamine transporter / cocaine receptor; and 3) *in vitro* and *in vivo* studies of the interactions of cocaine with sigma receptors that may aid in development of novel anti-cocaine medications.

Lever, J.R., Miller, D.K., Green, C.L., Ferguson-Cantrell, E.A., Watkinson, L.D., Carmack, T.L., Fan, K-H, and Lever, S.Z. "A Selective Sigma-2 Receptor Ligand Antagonizes Cocaine-induced Hyperlocomotion in Mice." *Synapse*, 68 (2014): 73 - 84.

Sage, A.S., Oelrichs, C.E., Davis, D.C., Fan, K-H, Nahas, R.I., Lever, S.Z., Lever, J.R., and Miller, D.K. "Effects of *N*-phenylpropyl-*N'*-substituted Piperazine Sigma Receptor Ligands on Cocaine-induced Hyperactivity in Mice." *Pharmacol Biochem Behav*, 110 (2013): 201 - 207.

## Michael R. Lewis, PhD

Research Health Scientist, Truman VA  
Associate Professor, Veterinary Medicine and  
Surgery, University of Missouri – Columbia

### Radiopharmaceuticals for Imaging and Therapy of Cancer

Dr. Lewis's research program focuses on the synthesis, development, evaluation, and application of radiopharmaceuticals for imaging and radiotherapy of cancer. The immediate relevance of his research program to clinical imaging and therapy is the use of biomolecules that bind to cell surface or oncogene molecules overexpressed by tumor cells. His group currently has three major research projects: 1) synthesis and evaluation of radiometal-labeled antisense compounds for targeted molecular imaging and radiotherapy, 2) development of radiolanthanide-labeled agents for pretargeted radioimmunotherapy, and 3) synthesis and evaluation of technetium-99m- and rhenium-186/188-cyclized somatostatin analogues for tumor imaging and therapy.

Mohsin, H., Jia, F., Bryan, J.N., Sivaguru, G., Cutler, C.S., Ketring, A.R., Miller, W.H., Simón, J., Frank, R.K., Theodore, L.J., Axworthy, D.B., Jurisson, S.S., and Lewis, M.R. "Comparison of Pretargeted and Conventional CC49 Radioimmunotherapy Using <sup>149</sup>Pm, <sup>166</sup>Ho, and <sup>177</sup>Lu." *Bioconjugate Chemistry* 22 (2011): 2444-52.

Statham-Ringen, K.A., Selting, K.A., Lattimer, J.C., Henry, C.J., Green, J.A., Bryan, J.N., Jia, F., and Lewis, M.R. "Evaluation of a B-cell leukemia-lymphoma 2-specific Radiolabeled Peptide-nucleic Acid Conjugate for Scintigraphic Detection of Neoplastic Lymphocytes in Dogs with B-cell Lymphoma." *American Journal of Veterinary Research* 73 (2012): 681-688.



## Lixin Ma, PhD

Research Scientist, VA Biomolecular Imaging  
Center, Truman VA  
Associate Professor of Radiology, University of  
Missouri - Columbia

### Development of Multimodal Imaging Contrast Agents and Magnetic Resonance Imaging Techniques

Dr. Ma's research includes the development of new and improved magnetic resonance imaging (MRI) techniques and novel multimodal imaging contrast agents, for early detection of abnormal structures, functions and molecular events on *in vivo* systems. The diagnostic specificity has been a huge problem in the management and treatment of cancer patients. One of Dr. Ma's research focuses is to design tissue-specific nanoparticle conjugates to enhance the detection specificity of prostate cancer on MRI and fluorescence mediated tomography (FMT). These nanoparticles are composed of site-specific targeting vectors (peptides or antibodies), fluorescence or MR imaging sensors and a nanoparticle core, and have multimodal functions for targeting and molecular imaging using MRI and FMT. Furthermore, her laboratory is developing ultrafast 3D/4D MRI methods to quantitatively measure the cardiac diastolic dysfunction, an early functional abnormality in the heart under diabetes mellitus. Dr. Ma's group also conducts research using NMR spectroscopy and molecular dynamics methods for the determination of structure, dynamics and function of biologically active proteins and peptide-protein complex.

Cai, Q.Y., Yu, P., Besch-Williford, C., Smith, C.J., Sieckman, G.L., Hoffman, T.J., and **Ma, L.** "Near-Infrared Fluorescence Imaging of Gastrin Releasing Peptide Receptor Targeting in Prostate Cancer Lymph Node Metastases." *The Prostate* 73 (2013): 842 - 854.

Zhang, M., **Ma, L.**, and Yu, P. "Dual-Band Fourier Domain Optical Coherence Tomography with Depth-Related

## Janelle Maland, PharmD, BCOP

Clinical Oncology Pharmacist, Truman VA

### Trends in Adjuvant Chemotherapy among Veterans with Stage IIb or III Colon Cancer

The overall aim of the study is to describe trends in adjuvant chemotherapy use between 2003 and 2008 among Veterans diagnosed with stage IIb or stage III colon cancer.

This is a retrospective cohort study of patients with a diagnosis of stage IIb or stage III colon cancer at 27 VA medical centers located throughout the U.S. Based on current guidelines, adjuvant chemotherapy is recommended for patients with stage III disease and should be considered for patients with high-risk stage II colon cancer.

The goal is for patients to complete their intended cycles of chemotherapy without dose reductions or delays. However, this can be difficult given the toxicities of the medications and concomitant health problems of the patient.

Although studies have evaluated temporal trends in the use of adjuvant chemotherapy, none have comprehensively described the care (e.g., prevalence of adjuvant chemotherapy, time to treatment, intended versus received chemotherapy) and associated outcomes in all adults with stage IIb and stage III colon cancer. Veterans have been included in studies of colon cancer, but to our knowledge these studies did not assess temporal trends in care and outcomes.



## Matthew P. Martens, PhD

Research Scientist, Truman VA  
University/Affiliate Appointment, University of  
Missouri – Columbia

### Personalized Drinking Feedback Interventions for OEF/OIF Veterans

The primary objective of this project is to assess the efficacy of a computer delivered personalized drinking feedback (PDF) intervention among veterans of the wars in Afghanistan and Iraq (OEF/OIF). Interventions that utilize personalized drinking feedback, such as comparing one's alcohol use to relevant norms, summaries of alcohol-related problems experienced, and family history of alcoholism, have been shown to be efficacious even without one-on-one clinical contact. These "PDF-only" interventions are innovative, low cost, and relatively easy to disseminate, but their effectiveness at preventing hazardous alcohol use among non-college populations is largely unknown. Therefore, the primary purpose of the study will be to test the effectiveness of a computer delivered PDF-only intervention at preventing hazardous alcohol use and alcohol-related problems among OEF/OIF military veterans. A secondary aim will be to examine potential mediators and moderators of intervention effectiveness. Subjects will be randomized to either a PDF or educational information condition, and will complete measures of alcohol use, alcohol-related problems, and other alcohol-related variables at baseline, one-month, and six-month follow-up.

Klanecky, A.K., Cadigan, J.M., Weaver, C.C., Rogers, R.E., Osborn, Z.H., and **Martens, M.P.** "Mental Health Symptoms and Alcohol use Frequency: The Moderating Effect of Spouse/partner Presence in OEF/OIF Veterans." *The annual meeting of the Association for Behavioral and Cognitive Therapies*, National Harbor, MD, November, 2012.

## Rajiv R. Mohan, PhD

Health Research Scientist, Truman VA  
Professor, Ophthalmology & Resident  
Research Coordinator, University of  
Missouri – Columbia  
<http://medicine.missouri.edu/ophthalmology/faculty/mohan-r/>

Trauma, injury, or infection to the eye lead to corneal scarring and/or neovascularization and affect approximately 1.5 million Americans/yr. This highlights the importance of improving current therapies, and developing newer therapies for treating corneal diseases. Dr. Mohan's laboratory is attempting to define novel tissue-selective controlled viral and nonviral gene therapy approaches for corneal diseases and dystrophies using AAV- and nanotechnology-based vectors. His laboratory has identified several vectors (adeno-associated virus, lentivirus, plasmid and hybrid nanoparticles), optimized minimally invasive topical and microinjection vector delivery techniques and various combinations of vector and vector-delivery techniques to introduce therapeutic genes selectively into the stroma of normal and diseased corneas in vivo using animal models. In addition, his laboratory is investigating the safety and efficacy of various therapeutic genes for treating corneal diseases such as corneal scarring and angiogenesis utilizing newly defined controlled gene therapy modalities and rabbit as well as rodent models.

Photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK) laser surgeries are frequently used worldwide to treat refractive errors, corneal scars, and corneal dystrophies. Although laser eye surgeries are safe and precise they are associated with complications, such as haze, halos, and regression of the PRK, while LASIK can lead to dry eye, epithelial ingrowth and flap wrinkles. Multiple cytokines and growth factors as well as inflammatory cells have been shown to play an important role in corneal wound healing following laser injury. Disturbances in normal healing often lead to myofibroblast formation and haze development in the cornea. Dr. Mohan's laboratory investigates molecular mechanisms and signaling pathways associated with corneal wound healing and are working to identify preventative and/or interventional strategies to further improve laser eye surgery outcomes.



## J. Steven Morris, PhD

Research Scientist, Truman VA  
Senior Research Scientist, University of  
Missouri Research Reactor Center

### Nutritional Epidemiology: Trace Elements and Chronic Disease

Our trace-element nutrition and epidemiology research program investigates the influence of trace-element nutrients and toxic trace elements on the incidence, progression, morbidity and mortality of chronic diseases such as cancer, cardiovascular disease, diabetes, HIV-AIDS, and osteoarthritis. Our laboratory uses neutron activation analysis and mass spectrometry to measure trace-element status in prospectively-collected biologic monitors from subjects participating in longitudinal case-control epidemiological studies.

For example, selenium is required by the human in very small amounts to produce and maintain the selenoproteome through which its biochemical functions are accomplished. At intakes only modestly greater than the nutritional requirement, selenium may become a risk factor for at least some chronic disease. This protective-factor/risk-factor duality may occur over the selenium-intake range that exists in the U.S., particularly among that growing fraction of the population routinely using dietary supplements. One goal of our laboratory is to identify the optimal range of selenium intake and how it may differ depending on other existing risk factors.

## Lakshmi Pulakat, PhD

Research Scientist, Truman VA  
Professor of Medicine, University of Missouri –  
Columbia

### Genomics and Proteomics of Signaling in Hypertension, Diabetes, and Metabolic Syndrome

Co-existence of insulin resistance, hypertension, and obesity significantly enhances mortality due to cardiovascular diseases and poses a major burden on our health care system. The most difficult challenge in diagnosing and treating insulin resistance and related cardiomyopathies resides in their asymptomatic nature that prevents early detection of these abnormalities. The vast diversity in the genetic backgrounds of the burgeoning population suffering from this metabolic/functional disorder, and the dissimilarity in patient responses to different types of pharmacologic therapy are indicative of significant pathophysiological differences. Goal of our research is to identify common molecular regulators that orchestrate these metabolic and functional changes, since that would provide better markers for early diagnosis and novel drug targets for effective treatment of insulin-resistance related cardiomyopathies. We employ genomic and proteomic approaches to unravel novel molecular regulators that induce transition of heart tissue to insulin resistance status.

**Pulakat, L.**, Aroor, A.R., Gul, R. and Sowers, J.R. "Cardiac Insulin Resistance and MicroRNA Modulators." *Experimental Diabetes Research* (2012): 654904. doi:10.1155/2012/654904

Gul, R., Ramdas, M., Mandavia, C., Sowers, J.R., and **Pulakat, L.** "RAS-mediated Adaptive Mechanisms in Cardiovascular Tissues: Confounding Factors of RAS Blockade Therapy and Alternative



## Thomas Quinn, PhD

Research Scientist, Truman VA  
Professor Biochemistry, University of Missouri  
– Columbia

### Melanoma Therapy with Rhenium-Cyclized Alpha-Melanocyte Stimulating Hormone Peptide Analogs

Dr. Quinn's research program is focused on the development of radiolabeled peptides and proteins as tumor specific diagnostic and therapeutic agents. Combinatorial peptide and antibody fragment libraries are being employed by Dr. Quinn's laboratory to identify molecules that preferentially bind tumor antigens. The tumor-avid peptides and antibody fragments are subsequently engineered to bind the medically important radionuclides into their structures.

Dr. Quinn's laboratory is working on two main projects: 1. Radiolabeled  $\alpha$ -MSH Peptide Analogs: The goal of this project is to design radiolabeled alpha-melanocyte stimulating hormone ( $\alpha$ -MSH) analogs for melanoma imaging and therapy.  $\alpha$ -MSH is a small tridecapeptide hormone that is involved in control of skin coloration.  $\alpha$ -MSH receptors have been identified on human and mouse melanoma cells making them attractive targets for the development of new peptide imaging and/or therapeutic radiopharmaceuticals. 2. Tumor Binding Peptides Selected from Bacteriophage Display Libraries: A combinatorial approach is being used to search for small polypeptides that bind the cancer associated Thomsen-Friedenreich (T) glycoantigen and ErbB-2 receptor with high affinities and specificities. Random peptide bacteriophage display libraries were screened for molecules that bound T-antigen and ErbB-2. Two T-antigen binding peptide sequences, P30 and P10, have been shown to bind free T-antigen in solution, T-antigen displaying proteins, and breast carcinoma cells displaying T antigen on their surfaces. The P30 peptide has been shown to inhibit T-antigen mediated tumor cell adhesion between malignant melanoma cells and adhesion between tumor cells and endothelial cells.

## R. Scott Rector, PhD

Research Health Scientist, Truman VA  
Assistant Professor, Departments of Internal  
Medicine, Gastroenterology & Hepatology  
& Nutrition & Exercise Physiology,  
University of Missouri – Columbia

### Hepatic Mitochondria and Insulin Resistance in Fatty Liver and Type 2 Diabetes

The overall goal of our research program is to understand the underlying molecular mechanisms regulating nonalcoholic fatty liver disease (NAFLD) and hepatic insulin resistance and their contribution to type 2 diabetes development and progression.

NAFLD is a chronic, progressive liver disease that affects 30% of all US adults. NAFLD is strongly linked to type 2 diabetes, with an estimated 80% of type 2 diabetics having NAFLD. Unfortunately, the Veteran population has a significantly higher prevalence of diabetes and NAFLD than the general population. Because NAFLD leads to a significant number of patients with cirrhosis and need for liver transplantation, this condition is an important issue for the VA healthcare system.

We have ongoing studies in rodent models of obesity, NAFLD, and type 2 diabetes to determine if hepatic insulin resistance associated with NAFLD develops secondary to hepatic mitochondrial dysfunction and is a significant contributing factor in the development of type 2 diabetes. In addition, we are examining the effectiveness of lifestyle modifications and pharmacological interventions in the treatment of NAFLD and type 2 diabetes. These studies will help to identify therapeutic targets and better treatment options with future application in reducing the incidence of type 2 diabetes and NAFLD in Veterans.

**Rector, R.S.**, Morris, E.M., Ridenhour, S., Meers, G.M., Hsu, F.F., Turk, J., and Ibdah, J.A. "Selective Hepatic Insulin Resistance in Mice Heterozygous for a Mitochondrial Trifunctional Protein Defect." *Hepatology* 57.6 (2013): 2213-2213. PMID: 23359250.



## Cheryl L. Shigaki, PhD, ABPP

Research Scientist, Truman VA  
Assistant Professor, Department of Health  
Psychology, School of Health Professions,  
University of Missouri – Columbia

### RAhelp.org: Online Self-management Program for Adults with Rheumatoid Arthritis

Previous studies have shown that people with rheumatoid arthritis who attend self-management programs experience improved quality of life and deal with fewer disability problems. Typically, such programs are conducted in clinics and are not always available to everyone, given limitations on transportation and mobility. The online program and features used in this study were designed to help remove the transportation and disability barriers for persons with rheumatoid arthritis. This study could also help reduce the cost and manpower needed to offer education in places such as support groups, VA hospitals and senior centers.

Researchers are examining results from approximately 100 adults recruited nation-wide, with rheumatoid arthritis and whether they benefited from online workshops. In the workshops, participants learned methods for reducing pain, fatigue and stress, and promoting self-esteem, self-sufficiency, and relationships. The study examines the following outcomes:

- psychological well-being
- levels of pain
- quality of life
- global health status
- social support

## Charles Jeffrey Smith, PhD

Research Health Scientist, Truman VA  
Associate Professor, Department of Radiology,  
University of Missouri – Columbia

### Peptide-Based Targeting Vectors for Diagnosis and Treatment of Human Cancers

Dr. Smith's research focuses on molecular imaging (MI) and therapy of human cancer. For the previous 10 years, our research group has focused our efforts on development of novel cell-targeting radioligands, nanoparticles, and/or fluorescent/magnetic resonance imaging (MRI) agents based upon a GRPR (Gastrin Releasing Peptide Receptor)-targeting, monovalent peptide. Recently, our research efforts have begun to focus on development of novel, multivalent agents that are capable of targeting multiple biomarkers using only a single radioligand or fluorescent probe. This includes but is not limited to PSMA (prostate-specific membrane antigen),  $\alpha_v\beta_3$  integrin, and the GRPR. Because cancer cells seem to differentially express specific receptors depending upon factors that may include chronicity and metastatic nature, it logically follows that a compound capable of targeting more than one biomarker would have the potential of binding to both early and chronic/metastatic stages of cancer, enabling not only a more prompt and accurate diagnostic profile for both, but also a much more precise and efficient mode of normal tissue-sparing therapy with far fewer side effects.

Cai, Q.Y., Yu, P., Besch-Williford, C., **Smith, C.J.**, Sieckman, G.L., Hoffman, T.J., and Ma, L. "Near-infrared Fluorescence Imaging of Gastrin Releasing Peptide Receptor Targeting in Prostate Cancer Lymph Node Metastases." *Prostate* 73.8 (2013): 842 - 54. PMID:23280511

Jackson, A., Retzliff, L., Nanda, P., and **Smith, C.J.** (2011) Molecular Imaging of Breast Cancer Tissue via Site-directed Radiopharmaceuticals. *Breast Cancer Cells*



## James R Sowers, MD

Staff Physician, Truman VA  
Professor of Medicine, Medical Pharmacology  
& Physiology, University of Missouri –  
Columbia, School of Medicine

### Regulation of Insulin Metabolic Signaling in Cardiovascular Tissue under Physiological and Pathophysiological Conditions

Research in our laboratory focuses on the regulation of insulin metabolic signaling in cardiovascular tissue under physiological and pathophysiological conditions. Loss of insulin metabolic signaling (insulin resistance) is a cardinal event in the pathogenesis of hypertension associated with the metabolic syndrome and diabetes mellitus. Insulin metabolic signaling through the IRS-1/PI3K/Akt pathway normally promotes endothelial derived vaso-relaxation and cardiac diastolic relaxation.

There are a number of environmental and intrinsic signaling abnormalities that can collectively lead to insulin resistance and consequent hypertension and metabolic/diabetic cardiomyopathy. Consequently, our studies have focused on the role of the renin-angiotensin-aldosterone system (RAAS) and obesity in the development of insulin resistance in cardiovascular tissue. We employ cell biology, proteomics rodent imaging techniques to explore the impact of over-nutrition and the tissue RAAS individually and collectively in the promotion of cardiovascular insulin resistance. We work with our world class microcirculation team to evaluate impaired cardiac and skeletal muscle insulin mediated regulation of microvascular blood flow. Over the past several years my research team has focused on the role of serine-kinase mediated site-specific serine phosphorylation of the critical insulin signaling docking protein IRS-1 as a critical juncture for over-nutrition and tissue RAAS in promoting cardiovascular insulin resistance. Recently our research has been directed to the role of over-nutrition and Ang II and mTOR/S6K1 signaling in regulation of insulin sensitivity and cardiovascular function.

**Sowers, J.R.** "Diabetes Mellitus and Vascular Disease." *Hypertension* 61.5 (2013): 943-7. PMID: 23595139.

## Mahesh M. Thakkar, PhD

Research Health Scientist, Truman VA  
Associate Professor and Director of Research,  
Department of Neurology, University of  
Missouri – Columbia

### Cellular and Molecular Basis of Sleep-wakefulness

The overall goal of our research program is to understand the neuronal mechanisms responsible for controlling sleep and mediating the effects of sleep loss on behavioral and mental functions. This will help us develop efficacious and targeted treatments for sleep disorders.

Our research uses animal models to study sleep. A combination of multidisciplinary techniques including electrographic recording of sleep coupled with electrophysiological, biochemical, molecular and immunohistochemical techniques are used in our laboratory. Novel and cutting edge technologies including antisense and siRNA technologies are used to produce transient knockdown of a target gene *in vivo*, and their effects on sleep is monitored.

Currently, we are investigating the brain mechanisms responsible for causing insomnia and associated sleep disturbances in post-traumatic stress disorder (PTSD). PTSD is highly prevalent in veterans returning from active combat. Sleep disturbances especially insomnia and recurrent nightmares are the hallmark of PTSD.

In addition, we are also investigating the role of sleep and sleep disturbances in alcohol use disorders. PTSD and alcohol problems often occur together and pose a serious health risk. We are in the process of investigating whether sleep disturbances in PTSD are the cause for increased risk toward the development of alcoholism.

Sharma, R., Lodhi, S., DeRoode, D., Sahota, P., and **Thakkar, M.M.** "Ethanol Withdrawal is Associated with the Downregulation of Orexin Gene Expression but Not with the Activation of Orexin Neurons." (2013). Under Revision.



## John P. Thyfault, PhD

Research Health Scientist, Truman VA  
Associate Professor, Departments of  
Nutrition and Exercise Physiology  
and Medicine, University of Missouri -  
Columbia

### Physical Inactivity, Low Fitness and the Development of Fatty Liver and Type 2 Diabetes

Insulin resistance, the first step in the progression of type 2 diabetes, occurs when the insulin produced by the body no longer causes appropriate metabolic responses in skeletal muscle, liver, and vascular tissues. Fatty liver (excessive storage of fat in the liver) is a primary cause of insulin resistance in the liver. Unfortunately, insulin resistance, fatty liver and type 2 diabetes are rampant diseases in Veterans. Our lab examines how physical inactivity and low fitness mechanistically lead to fatty liver and insulin resistance. We also mechanistically examine how exercise and increased fitness treat these conditions.

Rector, R.S. and **Thyfault, J.P.** "Does Physical Inactivity Cause Non-alcoholic Fatty Liver Disease?" *J Appl Physiol* 111 (2011): 1828 -1835.

**Thyfault, J.P.**, Rector, R.S., Uptergrove, G.M., Borengasser, S.J., Morris, E.M., Wei, Y., Laye, M.J., Clark, S.E., Qi, N., Burant, C., Koch, L.G., Britton, S.L., and Ibdah, J.A. "Rats Selectively Bred for Low Aerobic Capacity have Reduced Hepatic Mitochondrial Oxidative Capacity and Susceptibility to Hepatic Steatosis and Injury." *J Physiol* 587.8 (2009): 1805 - 1816.

## Adam Whaley-Connell, DO, MSPH, MED

Associate Chief of Staff for Research and  
Development, Truman VA  
Associate Professor of Medicine, University of  
Missouri – Columbia, School of Medicine

### Angiotensin II and Aldosterone Mediated Renal Insulin Resistance

Diabetes mellitus and the development of kidney disease are extremely common and contribute to the increasing healthcare costs associated with complications due to diabetes. My work explores a hormone system that contributes to kidney injury as seen in diabetes. The kidney injury we hypothesize is largely due to "oxidative stress" that damages a certain cell line in the kidney that controls loss of protein in the urine. By defining the pathways this hormone system injures the kidney, identification of pharmacological interventions may follow. The work in this project utilizes small rodent models wherein we infuse the two hormones (e.g. Angiotensin II and Aldosterone) with various interruption strategies to determine the individual impact on kidney injury. To explore more mechanistic pathways, our lab utilizes two cell lines to determine the impact of these hormones on signaling pathways that result in kidney injury. Work on this project highlights novel imaging techniques such as PET imaging of the kidney to assess glucose utilization as a mediator of injury as well as a novel cell line, podocytes, which are critical in regulation of filtered protein in the urine.

Habibi, J., Hayden, M.R., Ferrario, C.M., Sowers, J.R., and **Whaley-Connell, A.** "Salt Loading Promotes Kidney Injury via Fibrosis in Young Female Ren2 Rats." *Cardiorenal Med* 4 (2014): 43 - 52.

**Whaley-Connell, A.T.**, Habibi, J., Aroor, A., Ma, L., Hayden, M.R., Ferrario, C.M., DeMarco, and V.G., Sowers, J.R. Salt Loading Exacerbates Diastolic Dysfunction and Cardiac Remodeling in Young Female Ren2 Rats." *Metabolism* 62.12 (2013): 1761 - 71.



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Ahmed, K.T., Almashhrawi, A.A., Rahman, R.N., Hammoud, G.M., and Ibdah, J.A. "Liver Disease in Pregnancy: Diseases Unique to Pregnancy." *World J. Gastroenterol* 19 (2013): 7639-46. PMID: 24282353, PMCID: PMC3837262.

Almashhrawi, A.A., Ahmed, K.T., Rahman, R.N., Hammoud, G.M., and Ibdah J.A. "Liver Disease in Pregnancy: Diseases not Unique to Pregnancy." *World J. Gastroenterol* 19 (2013): 7630-8. PMID: 24282352, PMCID: PMC3837261.

Amin, A.P., Whaley-Connell, A.T., Li, S., Chen, S.C., McCullough, P.A., and Kosiborod, M.N.; KEEP Investigators. "The Synergistic Relationship between Estimated GFR and Microalbuminuria in Predicting Long-term Progression to ESRD or Death in Patients with Diabetes: Results from the Kidney Early Evaluation Program (KEEP)." *Am J Kidney Dis* 61(4 Suppl 2) (2013): S12-23. PMID: 23507266.

Aroor, A.R., Demarco, V.G., Jia, G., Sun, Z., Nistala, R., Meininger, G.A., and Sowers, J.R. "The Role of Tissue Renin-Angiotensin-Aldosterone System in the Development of Endothelial Dysfunction and Arterial Stiffness." *Front Endocrinol (Lausanne)* 4 (2013): 161. PMID: 24194732.

Aroor, A.R., McKarns, S., Demarco, V.G., Jia, G., and Sowers, J.R. "Maladaptive Immune and Inflammatory Pathways Lead to Cardiovascular Insulin Resistance." *Metabolism* 62.11 (2013): 1543-52. PMID: 23932846.

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Bender, S.B., Davis, J.W., Rector, R.S., Laughlin, M.H., and Sowers, J.R. "Characterization of the Coronary Vascular Transcriptome in a Rat Model of Metabolic Syndrome." *Poster Presented at the FASEB J 27 (lb645)*, Boston, Massachusetts, 2013.

Cadigan, J.M., Weaver, C.C., Rogers, R.E., Osborn, Z.H., and Martens, M.P. "Veteran Specific Drinking Norms and the Moderating Effect of Group Identity as Predictors of Alcohol Outcomes among OEF/OIF Veterans." *Poster presented at the annual meeting of the Research Society on Alcoholism*, Orlando, Florida, June 2013.

Cai, Q-Y, Gallazzi, F., Guthrie, J., Robertson, D., Hoffman, T.J., and Ma, L., "A High Affinity and Selectivity MRI Contrast Agent for Targeting GRP Receptors on Prostate Cancer." *World Molecular Imaging Congress*, Savannah, Georgia, September 18 - 21, 2013. (Presentation #SS39)

Cai, Q-Y, Yu, P., Hoffman, T.J., and Ma, L. "Near-Infrared Fluorescence Imaging of Lymph Node Metastases by Targeting the Gastrin Releasing Peptide Receptor." *Association for Clinical Research Training (ACRT)/ Society for Clinical and Translational Science (SCTS) Joint Annual Meeting*, Washington, DC, April 17 - 19, 2013.

Donnelly, L.L., Rold, T.L., Richmond, K.L., Szczodroski, A.F., Sieckman, G.L., Haddadin, S., and Hoffman, T.J. "Preclinical evaluation of combination Lu-177-BB2R antagonist targeted radiotherapy and chemotherapy for the treatment of castration resistant prostate cancer." *Veterinary Cancer Society Meeting*, Minneapolis, Minnesota, October 19, 2013. (Awarded the Robert S. Brodey Memorial Award for outstanding clinical research by a veterinary resident)

Eck, C.D., Sharma, A., Rodier, J.T., Sinha, N.R., Stallard, A.N., Sinha, P.R., Siddiqui, S., and Mohan, R.R. "Development of PCR-based Gene Array for Angiogenesis Diagnosis and Treatment." *Poster Presented at Health Science Research Day*, School of Medicine, University of Missouri, Columbia, USA, November 14, 2013.

Glinskii, O. "Intracranial Microvascular Remodeling. Role of Estrogen." *Department of Medical Pharmacology and Physiology*, University of Missouri School of Medicine Seminar, October 2013.

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