



Research and Development 2012 Highlights



Harry S. Truman Memorial Veterans' Hospital
Columbia, Missouri



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Preface

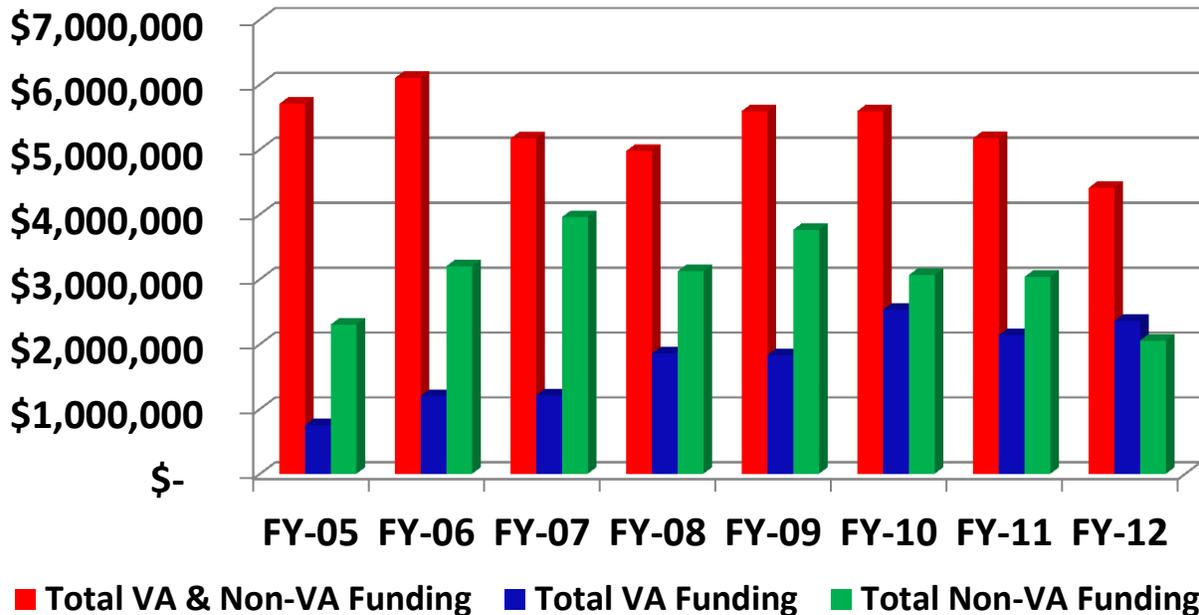
We at the Harry S. Truman Memorial Veterans' Hospital are proud of our investigators' accomplishments as described in the Research and Development Milestones 2012. In the Department of Veterans Affairs, the clinical and research missions are closely intertwined. This relationship is one reason that the 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



Truman VA R&D Funding Profile

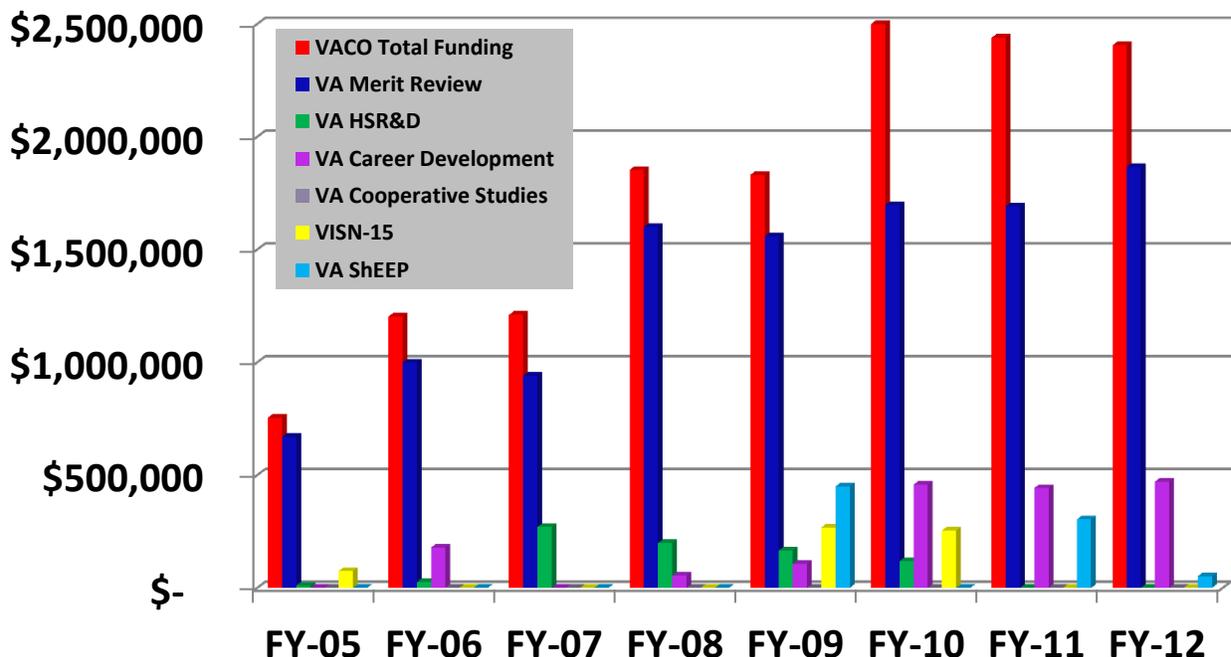
FY-05 to FY-12



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, 2012. The graph below represents the breakdown of total VA funding awarded to the Truman VA by funding category.

Truman VA R&D VA Funding Profile

FY-05 to FY-12



Truman VA Research & Development Program

Summary Statistics*

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

Investigators

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

Project Involvement

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

Funding Source

VA.....	12	12	12	11
NIH.....	14	17	25	23
Other federal Agency..	11	12	11	11
Other Govt./Academic Institution..	20	23	26	25
Private Company.....	7	7	7	7
Voluntary Agency or Foundation.....	11	10	4	4
Self-Funded .	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 and 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 2012, the Missouri Foundation for Medical Research contributed \$442,939 in support of Research and Education at the Harry S Truman Memorial Veterans' Hospital.

➤ Equipment and Material for VA labs:	\$ 49,224
➤ Salary support for Lab Techs & Post Doctoral Students	\$ 37,238
➤ Awards and Grants to Individual Investigators	\$ 41,937
➤ Lab Supplies and Services	\$172,191
➤ VA Staff development, travel, conferences	<u>\$113,564</u>

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

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

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Discovery & Innovation for Veterans' Health

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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.



Kunal Chaudhary, MD

*Staff 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 β 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 Health 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 affect Veterans, including prostate, breast, colon, and lung 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* (2012): DOI 10.1007/s10585-012-9516-y.

Kumar, S. R., Gallazzi F., Quinn, T.P., and **Deutscher, S.L.** "Cu-64-labeled Peptide for PET Imaging of Breast Carcinomas Expressing the Thomsen-Friedenreich Carbohydrate Antigen." *Journal of Nuclear Medicine* 52 (2012): 1 - 8.

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 2,400 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 Scientist, Truman VA
Research Assistant Professor, University of
Missouri – Columbia

Estrogen-dependent Remodeling of Brain Vascular Networks

Sex-hormone deficiencies in older population are frequently associated with a number of pathological conditions in the central nervous system, including depression, anxiety, decline in memory and cognitive ability, increased incidence of stroke and intracranial aneurysm, as well as higher incidence of Alzheimer's disease, resulting in impaired quality of life in older men and women. Data from our laboratory indicate that following the cessation of the ovarian hormone production vasculature of meninges (membranes covering brain) undergo dramatic remodeling, resulting in a loss of capillaries and increase in vessel permeability. This process is accompanied by a reduction in the expression of angiopoietin-1 (a protective factor that normally maintains vascular integrity). As the result, blood vessels become defective and leaky, creating possible risk factors predisposing one to brain vascular injury. Our research is aimed at understanding molecular mechanisms that govern blood vessels remodeling in brain and meninges, as well as how different regimens of sex hormone therapy can interfere with this process, leading to distinct outcome.



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 VA research program is focusing on investigating the molecular and cellular mechanisms of 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.

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.



Haddadin, Shadi, 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}Tc , ^{111}In , and ^{67}Ga for use with clinical SPECT imaging, ^{64}Cu , ^{68}Ga , and ^{18}F for use with clinical PET imaging, and ^{177}Lu and ^{90}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

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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. "Opioid Receptors and Ligands: Targets for Cancer Imaging and Therapy." *Medchem*, 2 (2012): 142-147.

Lever, S.Z., Xu, R., Fan, K-H, Ferguson-Cantrell, E.A., Carmack, T.L., Watkinson, L.D., and **Lever, J.R.** "Synthesis, Radioiodination and *in vitro* and *in vivo* Sigma Receptor Studies of N-1-allyl-N'-4-phenethylpiperazine Analogs." *Nucl Med Biol* 39 (2012): 401 - 414.



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 ^{149}Pm , ^{166}Ho , and ^{177}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
Assistant Professor of Radiology, University of
Missouri – Columbia

Magnetic Resonance Imaging to Study Cancer, Heart, and Brain

Dr. Ma's research includes the development of new and improved magnetic resonance imaging (MRI) techniques, the design of novel MRI contrast agents and multimodal molecular probes, and their applications to early detection of alterations in anatomical structures, functions and molecular events on *in vivo* systems. One of her focuses is to design tissue-specific nanoparticle imaging enhancing agents for early detection of cancer or brain disease in patients. These nanoparticles are composed of peptides, imaging probes and nano-sized core, and have multimodal functions for diagnostic and molecular imaging using MRI and fluorescence mediated tomography. Furthermore, her laboratory is developing high-temporal resolution cine-MRI techniques and quantitative methods to detect early changes in the heart. The group successfully showed that the techniques enabled determination of the delayed diastolic relaxation in insulin-resistant heart and detection of the effects of drug treatments over time in these hearts. She also conducts research using NMR spectroscopy techniques and molecular dynamics methods for the determination of structure, dynamics and function of biologically active peptides and peptide-protein complex.

Hirst, B., Zheng, Y.R., Yang, M., and **Ma, L.** "3D Spatio-Temporal Analysis for Compressive Sensing in Magnetic Resonance Imaging of the Murine Cardiac Cycle." *SPIE Medical Imaging V.1* (2013): 8669 - 79. In press.

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*



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

Research Health 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 α -MSH Peptide Analogs: The goal of this project is to design radiolabeled alpha-melanocyte stimulating hormone (α -MSH) analogs for melanoma imaging and therapy. α -MSH is a small tridecapeptide hormone that is involved in control of skin coloration. α -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.

Morris, E.M., Fletcher, J.A., Thyfault, J.P., and **Rector, R.S.** “The Role of Angiotensin II in Nonalcoholic Steatohepatitis.” *Molecular and Cellular Endocrinology* (2012). PMID: 22579612

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. Peptide receptor targeted radionuclide therapy (PRT) is a method of site-directed radiotherapy that specifically targets human cancers expressing a cognate receptor-subtype in very high numbers. Ideally, the procedure targets only the primary or metastatic disease, with little radiation damage to normal, collateral tissues. For treatment strategies of this type to be effective, it is critical to first evaluate the biological profile of the drug. MI is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems. MI is a non-invasive procedure that involves clinical in vivo administration of a biologically-active, receptor-specific, targeting molecule conjugated to a radioligand, nanoparticle, and/or fluorescent/magnetic resonance imaging probe followed by acquisition and quantification of signal by PET, SPECT, MRI, fluorescence imaging, or ultrasound. Site-directed MI procedures are capable of addressing many of the critical issues associated with PRT and are therefore necessary to describe the effective balance between the clinical benefits and risks of this treatment strategy.

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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.

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Mahesh M. Thakkar, PhD

Research 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.

John P. Thyfault, PhD

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

Physical Inactivity, Low Fitness and the Development of Insulin Resistance 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 which result in high blood sugar levels. Both insulin resistance and type 2 diabetes have independently been shown to dramatically increase the risk of heart disease, and unfortunately, over 20% of Veterans have type 2 diabetes. Our lab examines how physical inactivity and low fitness leads to maladaptations in liver, muscle, and vasculature that cause insulin resistance and type 2 diabetes, and how increased physical activity improves the function of these tissues after the onset of disease.

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

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Adam Whaley-Connell, DO, MSPH

Research Scientist, 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.

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Nistala, R., Sowers, J.R., and **Whaley-Connell, A.** “Over-nutrition Contributes to Tubulointerstitial Fibrosis by Targeting Nutrient-sensing Kinases: Role for the

John Whited, MD, MHS

Associate Chief of Staff, Research &
Development, Truman VA

Health Services Implications of Telemedicine Interventions

Telemedicine is the use of electronic communication technology to deliver health care. Typically telemedicine is used to provide this care between two or more sites separated by a distance. Dr. Whited’s research program assesses the effectiveness and outcomes of telemedical care, particularly as it relates to dermatologic (skin) and ophthalmologic (eye) conditions. Previous research conducted by Dr. Whited has shown that telemedicine used for dermatology (teledermatology) results in comparable diagnostic outcomes, that is, teledermatology functions as well as an in-person visit when making a diagnosis of a skin condition. Further, Dr. Whited has shown that teledermatology results in a quicker time to intervention (the time between the generation of the consult and the beginning of the management of the skin condition) and that teledermatology can be a cost-effective means of providing care. Current research is evaluating the effect of teledermatology on quality of life, clinical course, and economic outcomes. Additionally, Dr. Whited has used economic modeling techniques to predict the cost of implementing a teleophthalmology system used for screening for diabetic eye disease.

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