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Advance Research Digest

University of Tennessee Graduate School of  
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Winter 1-1-2014

## **Advance (Winter 2014) - From Lab to Life: Importance of Clinical Research**

University of Tennessee Medical Center

University of Tennessee Graduate School of Medicine

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# ADVANCE

ADVANCING RESEARCH FROM LAB TO LIFE

*A Biannual Research Digest of the University of Tennessee Medical Center and UT Graduate School of Medicine*

## FROM LAB TO LIFE: Importance of Clinical Research

### ON THE HORIZON:

Finding new ways to treat the underlying cause of cystic fibrosis

### RESEARCH SPOTLIGHT:

Urologist studies impact of testosterone replacement therapy on fertility

### STUDIES IN BRIEF:

- Understanding emphysema interventions

WINTER 2014

# SPIRIT OF DISCOVERY...

## OBSERVATIONS

This issue of *Advance* features several areas of clinical research occurring at UT Medical Center. Clinical trials offer many benefits to all supporters. They offer the patient hope through treatment opportunities that are not readily available by providing the patients access to the novel therapies and offer the physician scientists with more treatment options and the ability to expand their experience in the academic research arena. Clinical trials also offer the institution with yet another opportunity to expand its influence and build upon its image in geographic s an academic institution. Finally, clinical trials offer the potential of a revenue stream to defray the cost of some health care services and other in- house initiated research. Other clinical research efforts, such as the work being done on NIH or SBIR grants will significantly impact patient care in the future. This issue of *Advance* introduces our newly appointed Radiology Chair, Dr. Laura Findeiss, MD., FSIR. She brings diverse medical experience to further integrate with the Interventional Radiology and clinical research efforts both in the Graduate School of Medicine and UTMCK. The Department of Medicine has several physicians working on three industry sponsored clinical trials that are all featured in this issue, as well as, a clinically-relevant imaging compound that was recently presented at the annual meeting of the Society of Nuclear Medicine (SNM), where it received significant media attention. Jonathan Wall, Ph.D. and Michael Karlstad, Ph.D. have both received large federal grants to support their current research efforts. All of these clinical research efforts at UTMCK truly highlight our goal to advance research from lab to life.



*Paul J. Ottaviano, M.S., M.B.A.*  
Director of Clinical Trials Research Operations

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### ADVANCE

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*Advance* is produced by the University of Tennessee Graduate School of Medicine. The mission of the digest is to spotlight research programs at the institution and explain how the work of our researchers impacts health care in East Tennessee and beyond.

#### Institutional Review Board

All research using human volunteers follows stringent federal regulations that require a review by an Institutional Review Board (IRB) before it is approved. The IRB committee is comprised of physicians, pharmacists, scientists, researchers and non-scientific community representatives. The members review research protocol to ensure protections are in place.

Faculty from the UT Graduate School of Medicine influence medical care across the world by publishing and presenting. For a comprehensive list of publications and presentations, visit <http://gsm.utmck.edu/scholars>

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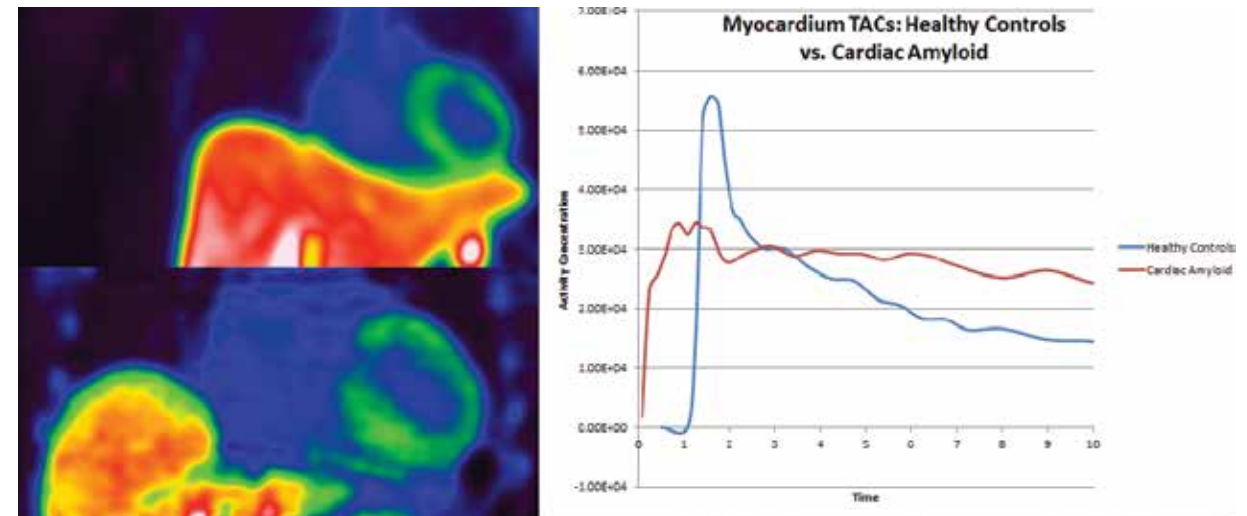




# DETERMINATION OF CARDIAC AMYLOID INVOLVEMENT

Cardiac amyloidosis is a rare, debilitating and inevitably fatal disease with an average survival of only 4-9 months, from diagnosis. This disease can often manifest with symptoms similar to other more common cardiac conditions. Early and accurate diagnosis of this condition is key to providing the best possible care for these patients. Karen Wells, M.D., Alan Solomon, M.D. and Jonathan Wall, PhD., in the Department of Medicine, began using Florbetapir, a commercially available and FDA-approved

imaging compound for amyloid detection in the brains of patients with Alzheimer's disease, in patients with cardiac amyloidosis. This study was designed to examine whether or not this compound could effectively image amyloid outside of the brain, specifically within the heart. Initial results from this study showed promise; however, standard clinical PET/CT imaging techniques were unable to show a significant difference between patients with cardiac amyloidosis and healthy subjects. Dr. Osborne,



along with Alan Stuckey and Shelley Acuff, Director of Clinical Research for the MITRP, began working with the group on this project in 2012 and data acquisition was moved to the new state of the art Biograph mCT PET/CT scanner installed at the University of Tennessee Cancer Institute. Dr. Osborne re-examined the image data acquired during the scans and was able to show, with a new type of analysis, there were substantial differences between amyloid patients and healthy subjects. These results indicated that using dynamic PET imaging may make it possible to identify patients with cardiac amyloidosis.

The problem with dynamic method of PET imaging used to study these patients is that it is not performed routinely in the clinic and the scan can last more than an hour. This makes it extremely difficult to schedule into a busy clinical practice. Therefore, Drs. Osborne and Wells once again reviewed the data and found that the scan time could be reduced to only 20 minutes. Further analysis showed that a comparison of

the heart image between 0-5 minutes with that at 15-20 minutes could be used to differentiate amyloid patients from the healthy test subjects. Specifically, the ratio of the Standard Uptake Values (SUVs) in the heart provided the information to accurately demonstrate cardiac amyloidosis using Florbetapir.

This study provided preliminary support for assessing cardiac amyloidosis using a new clinically-relevant method using an FDA-approved amyloid imaging compound that was easily accessible to clinicians worldwide. The method may yield a sensitive imaging test for the detection and diagnosis of cardiac amyloidosis. This work was presented at the annual meeting of the Society of Nuclear Medicine (SNM) in Vancouver where it received significant media attention garnering an Aunt Minnie press release as well as headlining the daily SmartBrief sent to all members of the SNM. 📌

## WHY THIS MATTERS:

USE OF NOVEL COMPOUNDS FOR RAPID DEFINITIVE CLINICAL DIAGNOSIS MAY ALTER PATIENT MANAGEMENT AND PROVIDE PATIENTS WITH IMPROVED SURVIVAL.

# VERTEX PHARMACEUTICALS SPONSORS CYSTIC FIBROSIS TRIAL

Ongoing research to find a treatment for cystic fibrosis may finally pay off. Bruce Ludwig, M.D., Medical Director, Adult Cystic Fibrosis Program and the clinical trial team are partnering with Vertex Pharmaceuticals, Inc. to study the underlying mechanism of the gene that causes cystic fibrosis and its protein product.

Cystic Fibrosis is the most common fatal genetic disorder of Caucasians, affecting about 30,000 people in the US. It is a genetic

defect in a protein that impacts the transport of chloride, sodium and water in all ducts of the body. This can cause bronchiectasis with chronic and recurrent lung infections, often with resistant bacteria. Patients also suffer from malnutrition, diabetes, liver disease, respiratory issues and sometimes death. Most current medications are directed to treat symptoms of the disease, but now there is a drug approved to treat the root cause of the disease.



This trial studies the Vertex drug, Kalydeco, combined with Lumacaftor in patients with cystic fibrosis. The pairing should improve transportation to the membrane and improve lung function. If proven to work, the outcome would benefit at least 50% of patients with cystic fibrosis who carry two copies of the DeltaF508 mutation. The Food and Drug Administration called the collaboration of the two drugs, “breakthrough therapy designation,” for its effort to speed the development of potential treatments for life-threatening diseases or conditions.

“These patients would not be able to receive this type of medication if it were not for this clinical trial,” said Ludwig.

Ludwig and his team expect to see significantly improved lung function in patients and improved weight control in the short term. He hopes the long term effects will translate to improved survival rates, reduced infections and hospitalizations and eventually turn cystic fibrosis into a much more controllable disease.

“Being able to continue to participate in trials like these give them hope for their future,” added Ludwig. “Hope that one day there will be a cure for the disease that challenges their daily lives.”

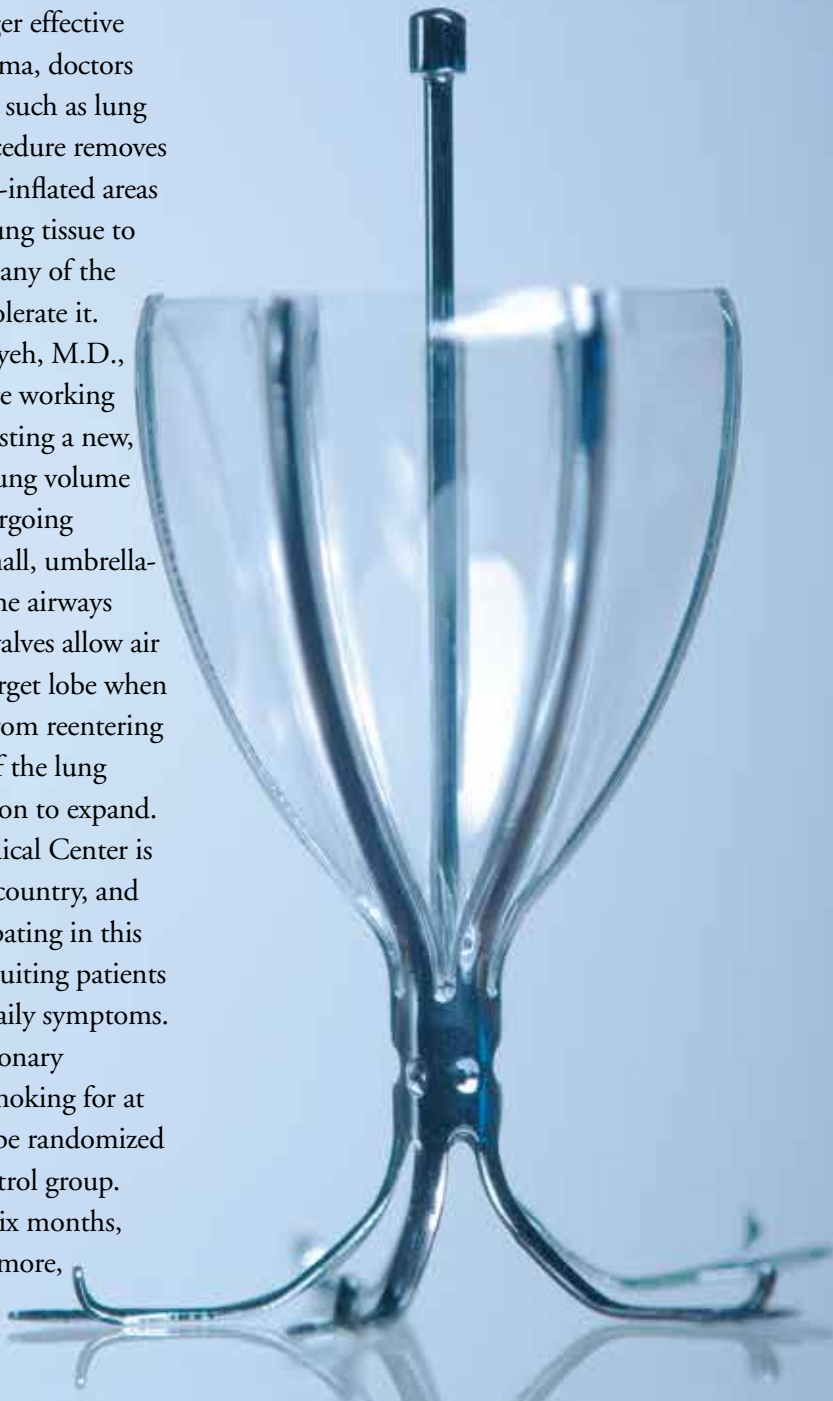


# EMPROVE CLINICAL TRIAL: EVALUATING A NON-SURGICAL TREATMENT APPROACH TO SEVERE EMPHYSEMA

When medical therapy is no longer effective for patients with advanced emphysema, doctors often have to consider interventions such as lung volume reduction surgery. This procedure removes the most severely damaged and over-inflated areas of the lung, allowing the healthier lung tissue to expand. It is a major surgery and many of the people who need it are too frail to tolerate it.

Paul Branca, M.D., James Shamiyeh, M.D., and Michael McCormack, M.D., are working on the EMPROVE trial, which is testing a new, minimally invasive way to provide lung volume reduction for patients without undergoing surgery. Using a bronchoscope, a small, umbrella-shaped, one-way valve is placed in the airways leading to the damaged lung. The valves allow air and secretions to come out of the target lobe when the patient exhales but prevent air from reentering on inhalation. The damaged part of the lung deflates, allowing the healthier portion to expand.

The University of Tennessee Medical Center is one of fewer than 20 centers in the country, and the only center in Tennessee participating in this trial. The trial is now open and recruiting patients with severe emphysema who have daily symptoms. Patients must have completed pulmonary rehabilitation and must have quit smoking for at least four months. Participants will be randomized to either valve treatment or to a control group. They will be closely monitored for six months, then at yearly intervals. To find out more, please contact the trial coordinator, Lauren Davis, at 865-305-7975. ▲



## WHY THIS MATTERS:

THIS MINIMALLY INVASIVE TECHNIQUE MAY BE ABLE TO PROVIDE IMPROVED QUALITY OF LIFE TO PEOPLE WHO SUFFER FROM SEVERE EMPHYSEMA.

## IN BRIEF »»»»»»»»»»

# DEVELOPMENT OF AN ATMOSPHERIC PLASMA APPLICATOR TO TREAT CHRONIC WOUNDS



Research team: Alex Nelson, Eric Karlstad, Michael Karlstad, Ph.D., Emily Paulus

Five to seven million Americans are treated annually for chronic wounds that arise from diabetes, lower extremity arterial disease, lower extremity venous disease and edema, pressure ulcers, and traumatic injuries, including burns. Michael Karlstad, Ph.D., Department of Surgery is a principal investigator on a two-year Small Business Innovation Research (SBIR) grant awarded to Advanced Plasma Products, Inc., from the National Institute of General Medical Sciences, which aims to develop a prototype for treating these wounds. Karlstad's two other principal investigators include Kimberly Kelly-Wintenberg, the general manager and director of business development from Advanced Plasma Products, Inc. (Knoxville, TN) and Garth James, Ph.D., a professor in the University of Montana

Center for Biofilm Engineering will help in this endeavor.

This phase II multi-principal investigator NIH proposal will allow the investigative team to pursue development of an atmospheric plasma applicator to treat chronic wounds in diabetes. Karlstad's research team will be responsible for experiments designed to demonstrate the therapeutic potential of atmospheric plasma to improve wound healing by the removal of microorganisms from the biofilm of chronic diabetic wounds. Karlstad's collaborators on the small business grant include Patricia Coan, D.V.M., Ph.D, Jason Collier, Ph.D., and Deidra Mountain, Ph.D. Brian Daley, M.D. and Jeffery Hecht, M.D., from the Department of Surgery, will serve as clinical consultants. ▲

## WHY THIS MATTERS:

A SIGNIFICANT NUMBER OF CHRONIC DIABETIC WOUNDS DO NOT HEAL AFTER A YEAR OF TREATMENT WITH CURRENT TECHNOLOGIES. THIS APPLICATION AIMS TO DEVELOP AN ATMOSPHERIC PLASMA APPLICATOR FOR TREATMENT OF CHRONIC WOUNDS. THE RESEARCH TEAM IS WORKING TO DESIGN A COMMERCIAL PROTOTYPE THAT IS CAPABLE OF INACTIVATING MICROORGANISMS, INCLUDING, BIOFILM TO IMPROVE WOUND HEALING WITHOUT CAUSING DAMAGE TO SURROUNDING TISSUES.

## THE DEPARTMENT OF MEDICINE PARTICIPATES IN CLINICAL TRIAL



ventilated patients. The doctors conducting this industry sponsored trial believe the levels achieved by inhaling the antibiotics should be able to effectively and safely treat infections with multi-drug resistant bacteria.

“We are fortunate not to currently have this problem in our hospital,” said Rajiv Dhand, M.D. “However, in many other hospitals, physicians are finding it increasingly difficult to effectively treat infections caused by

Pneumonia is one of the most common infections among critically ill patients in intensive care units nationwide. A bigger concern to physicians is that the infection is sometimes resistant to multiple antibiotics, making it difficult to treat.

Rajiv Dhand, M.D., Paul Branca, M.D., Carol Ellis, M.D., Tina Dudney, M.D., Michael McCormack, M.D., and Department of Medicine fellows at the University of Tennessee Medical Center are studying ways to combat pneumonia by using inhaled antibiotics in

such resistant organisms and alternative methods of treatment are urgently needed.”

These physicians believe inhaling the antibiotics, in addition to usual standard of care, could provide an additional means of combating such serious, and even fatal, infections.

Inhaled therapies allow several advantages for patients. Lower doses, with higher concentrations of the drug, will enhance antibacterial activity against resistant pathogens. Furthermore, patients will experience better tolerability due to lower prescribed doses.

Another possible benefit is that if aerosolized medication is able to be delivered to the lungs with more efficiency than is currently possible, then it may prove useful as adjunctive therapy for patients in the future.

This multi-center study will prospectively determine the role of inhaled antibiotics in addition to usual standard of care antibiotics for treatment of pneumonia in ventilated patients.

UTMC is one of more than 150 sites worldwide participating in the trial. ▲



### WHY THIS MATTERS:

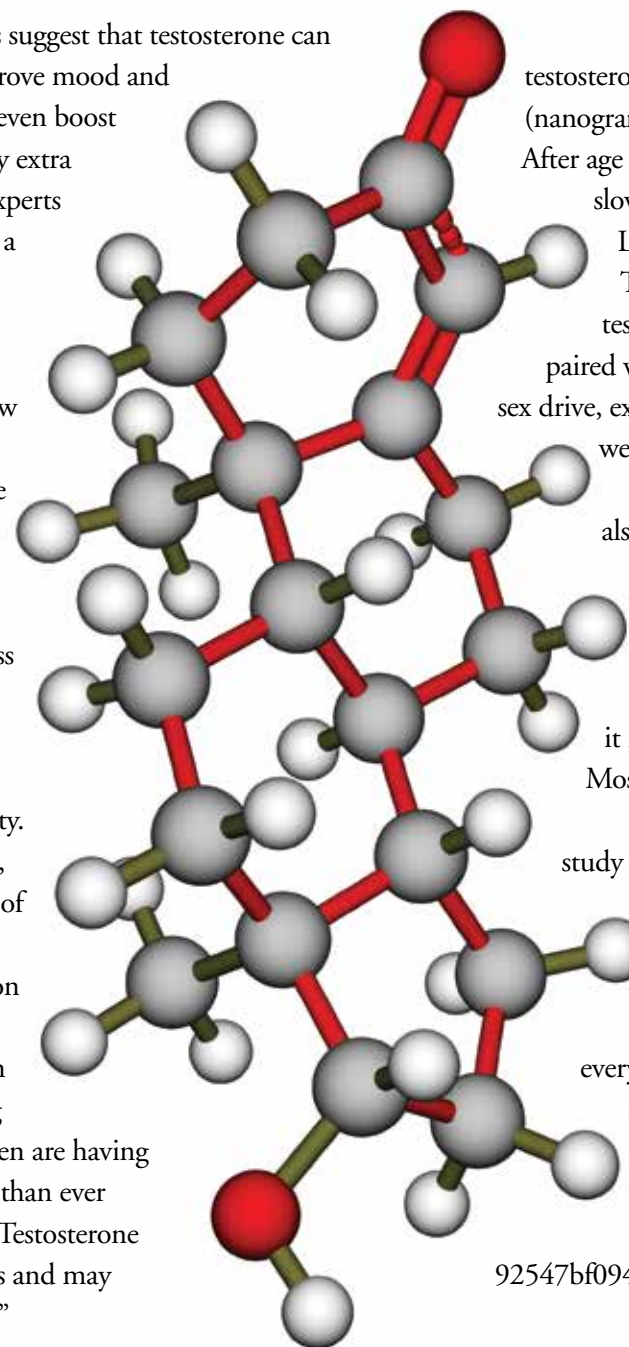
THESE PATIENTS ARE CONSIDERED TO HAVE A VERY SERIOUS CONDITION WITH A FAIRLY HIGH MORTALITY RATE. THEREFORE, WE ARE LOOKING FOR WAYS TO REDUCE THE MORBIDITY AND MORTALITY RATE OF THESE PATIENTS.

## DOCTORS INVESTIGATE IMPACT OF TESTOSTERONE REPLACEMENT THERAPY

Radio and TV ads suggest that testosterone can cure depression, improve mood and sexual performance, even boost energy and melt away extra pounds. Hormone experts say those looking for a quick fix are turning to Rejuvenation Clinics (RC) to treat hypogonadism, or low testosterone.

While testosterone replacement therapy is proven to improve sex drive, erectile function, muscle mass and bone density, there is little known about these drugs’ effect on men’s fertility.

Jared Moss, M.D., chief resident, Dept. of Urology, studied the impact of rejuvenation hormones on sperm count. “Rejuvenation Clinics are becoming more popular and men are having children at later ages than ever before,” said Moss. “Testosterone reduces sperm counts and may compromise fertility.”



The normal range of testosterone is 300 to 1,000 ng/dL (nanograms per deciliter) of blood. After age 30, men typically have a slow decline of testosterone.

Low testosterone, or Low T, is generally indicated at a testosterone level under 300, paired with symptoms such as low sex drive, excessive fatigue, depression and weight gain.

The data from his study also suggests that there is a link between prostate cancer and testosterone. “Testosterone does not cause prostate cancer, but it may exacerbate it if it is already there,” said Moss.

Findings from Dr. Moss’ study were featured in The Washington Post. For the full article please see [http://www.washingtonpost.com/national/health-science/everything-you-need-to-know-about-low-testosterone-but-were-afraid-to-ask/2013/06/24/3bdeb2d6-d764-11e2-a016-92547bf094cc\\_story.html](http://www.washingtonpost.com/national/health-science/everything-you-need-to-know-about-low-testosterone-but-were-afraid-to-ask/2013/06/24/3bdeb2d6-d764-11e2-a016-92547bf094cc_story.html) ▲

### WHY THIS MATTERS:

MANY OF THE MEN, AS WELL AS PHYSICIANS WHO PRESCRIBE TESTOSTERONE, ARE NOT AWARE THAT TESTOSTERONE REPLACEMENT THERAPY IMPACTS FERTILITY NEGATIVELY.





# ADVANCE

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