Winter 1-1-2014

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

University of Tennessee Medical Center

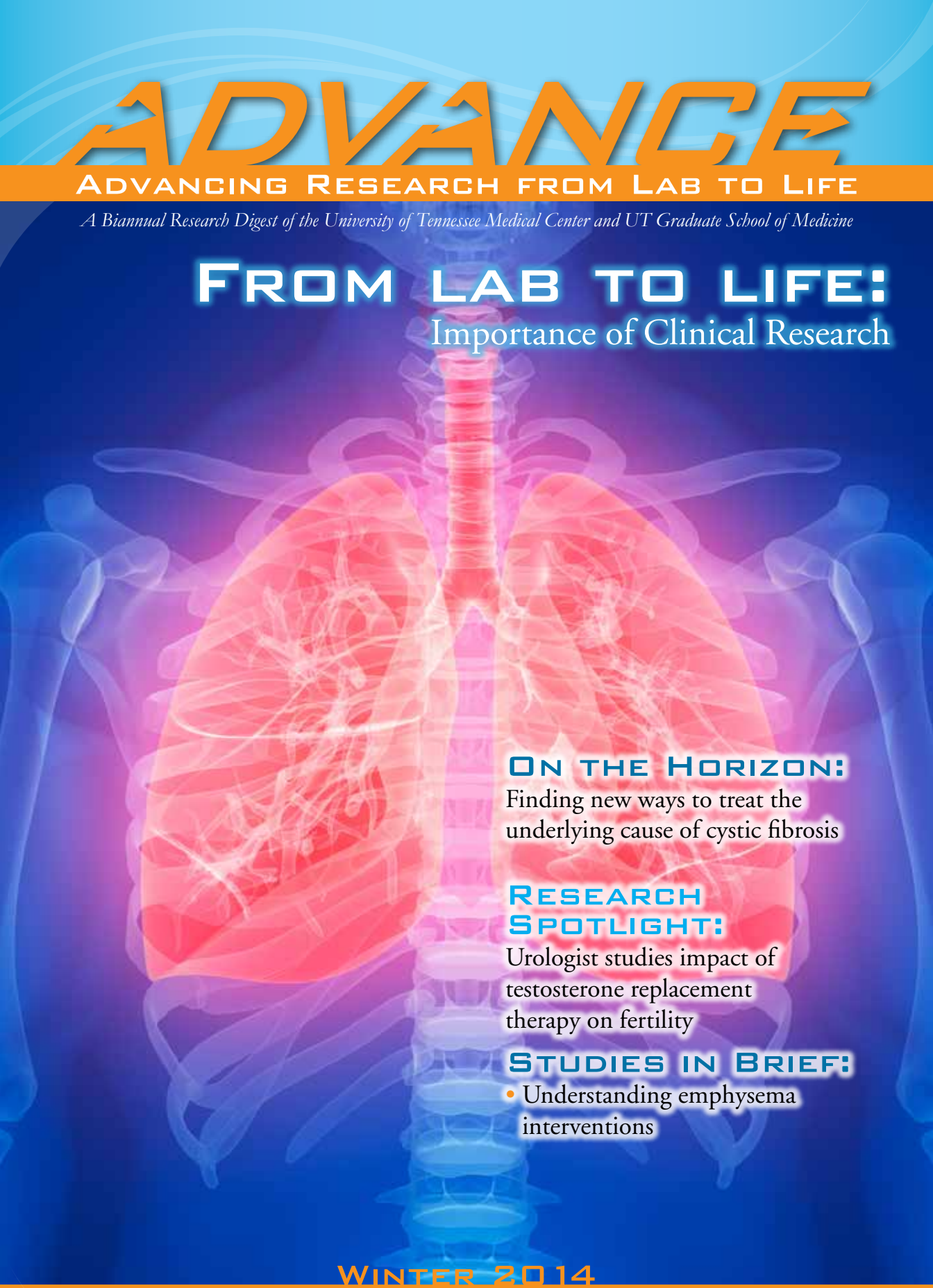
University of Tennessee Graduate School of Medicine

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

The University of Tennessee Medical Center
Wisdom for Your Life.

The University of Tennessee Graduate School of Medicine

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 UTMC. 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

Table of Contents

Advance
Issue 6: Winter 2014

Publishers
James Neutens, Ph.D.
Mitch Goldman, M.D.
Eddie Moore, M.D.

Managing Editors
Kristen Bass, M.S.
Brittany Nauta, M.S.

Contributors
Mitch Goldman, M.D.

Photography
Kandi Hodges

Design
Jerry Tracy/J Squared Graphics

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.

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Contact Us
Advance
UT Graduate School of Medicine
1924 Alcoa Highway, U-11
Knoxville, TN 37920
Telephone: 865-305-9749
E-mail: kbass@utmck.edu
Web: http://gsm.utmck.edu

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Dr. Laura Findeiss Returns to GSM as Radiology Chair

Laura Findeiss, M.D., FSIR, a radiologist with a diverse professional background that includes training in surgery at the UT Graduate School of Medicine as well as practicing emergency medicine in rural Tennessee, has been appointed Chair of Radiology for the UT Graduate School of Medicine as of August 1, 2013. Dr. Findeiss is a noted vascular and interventional radiologist, coming from the University of California Irvine Medical Center where she was Division Chief of Vascular and Interventional Radiology and Co-Director of UC Irvine's Ablative Oncology Center.

Dr. Findeiss received her medical degree from the University of Pittsburgh School of Medicine in 1997 followed by two years of General Surgery Residency at the UT Graduate School of Medicine. She completed her Diagnostic Radiology Residency at Virginia Mason Medical Center in Seattle, Washington, in 2004, followed by a fellowship in Vascular and Interventional Radiology at the University of Washington Medical Center.

As chair, Dr. Findeiss said she plans to use her diverse medical experience to further integrate Radiology with multidisciplinary teams at The University of Tennessee Medical Center. She said, "My goal is to determine how we can best support the institution and the exciting work the clinics are doing here. Radiology is an important part of the healing component of our mission, and we work with a lot of referring physicians. I hope to use Radiology as a hub so that diverse medical professionals work together to support patient care."

Dr. Findeiss lectures nationally on a range of Vascular and Endovascular topics, image-guided treatment of vascular anomalies, and minimally invasive cancer interventions, including tumor ablation. She holds national leadership roles as a member of the Executive Council of the Society of Interventional Radiology, the SIR Foundation Board of Directors, and the Leadership Committee of the American Heart Association's Cardiovascular Radiology and Intervention Council.

Besides certifications in Diagnostic Radiology and Vascular and Interventional Radiology, Dr. Findeiss is certified by the American Board of Vascular Medicine in Endovascular Medicine and is a Registered Physician in Vascular Interpretation. She has been honored as a Fellow in the Society of Interventional Radiology (FSIR), as well as obtaining Fellow status in the American Heart Association.

Dr. Findeiss's personal research interests are peripheral arterial disease/vascular disease and in this area limb perfusion/revascularization for critical limb ischemia. She has an interest in tissue perfusion imaging, and in ways to non-invasively predict response of the critically ischemic or ulcerated limb to revascularization therapies.

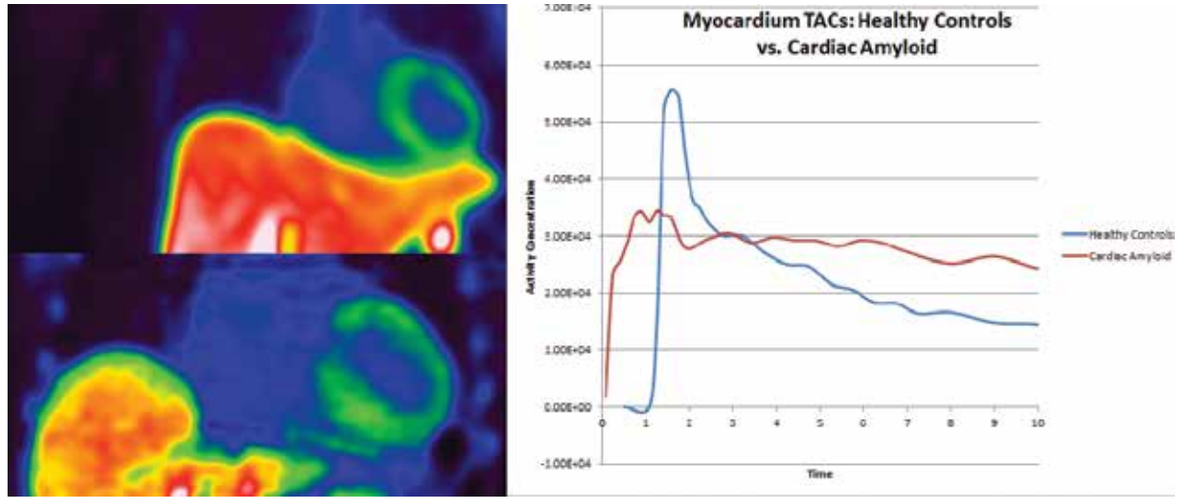
> My goal is to determine how we can best support the institution and the exciting work the clinicians are doing here.
> -Laura Findeiss, M.D.

She has experience and interest in clinical trials related to peripheral interventions and response of tumors to directed therapy, specifically, response to hepatocellular carcinoma to the spectrum of liver directed therapies available. Dr. Findeiss is particularly interested in the role of post-therapy tumor hypoxia in angioneogenesis and subsequent tumor growth. In particular, looking at hypoxia imaging agents in this regard.

As the department chair, Dr. Findeiss's major research goal for the Department of Radiology is moving the Molecular Imagining and Translational Research Program (MITRP) forward within the department as a comprehensive research enterprise incorporating basic science, translational imaging research, and investigation of clinical applications of novel radiotracers in collaboration with our UT Centers of Excellence. MITRP can offer an integrated platform for bench to bedside investigations for researchers within and external to the institution, providing support for a broad spectrum of research endeavors. With the internationally recognized basic science program, advanced animal imaging facility, and best in class clinical PET facility with near-term development of the on-site radiopharmacy, the opportunities for clinically relevant scientific advances are abundant.

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 Minne 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.

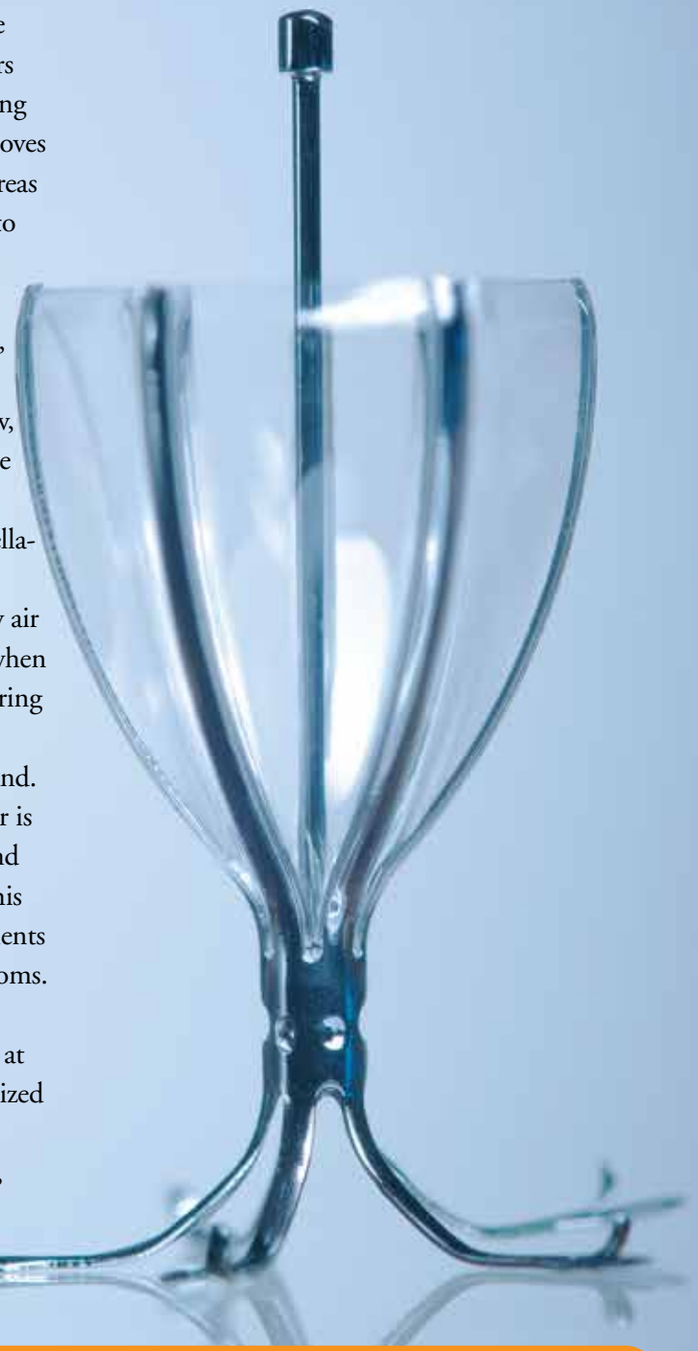
"Being able to continue to participate in trials like these give them hope for their future," added Ludwig. "Hope that one day there will be a cure for the disease that challenges their daily lives."

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.

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

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 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 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:

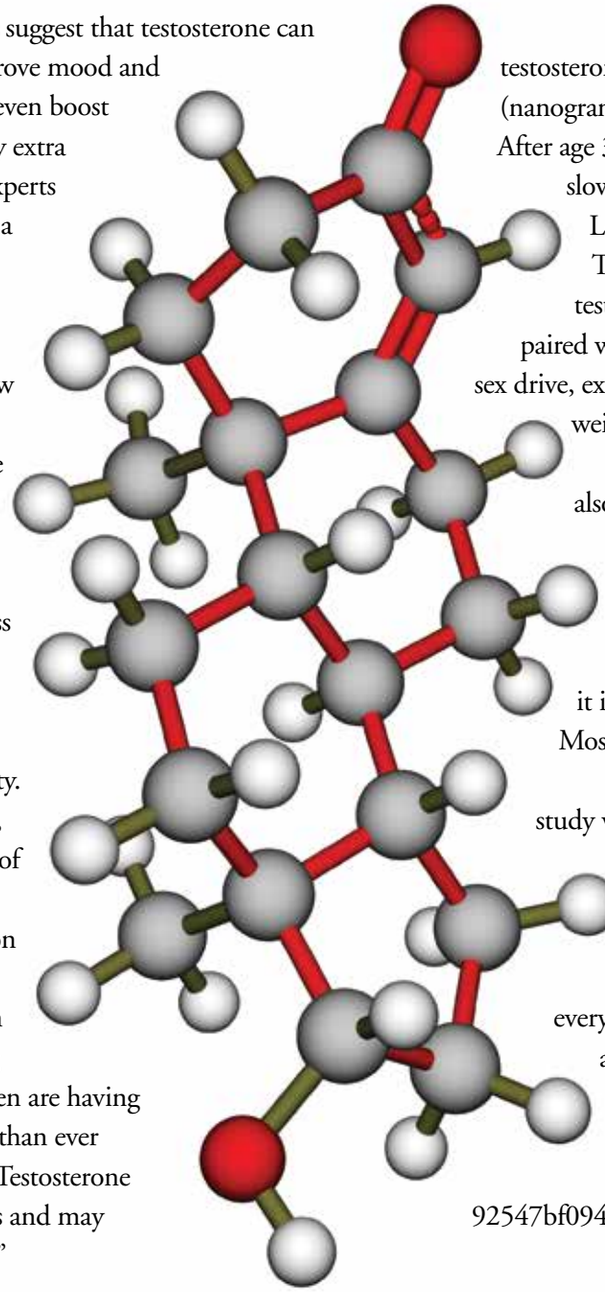
These patients are considered to have a very serious condition with a fairly high mortality rate. Therefore, we are looking for ways to reduce the morbidity and mortality rate of these patients.

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

Why this matters:

Many of the men, as well as physicians who prescribe testosterone, are not aware that testosterone replacement therapy impacts fertility negatively.

Preclinical Diagnostic Imaging of Amyloid

Jonathan Wall, Ph.D., professor in the Department of Medicine and director of the Preclinical and Diagnostic Molecular Imaging Laboratory, **received a four-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases,** a subsidiary of the **National Institutes of Health** to study "Preclinical Diagnostic Imaging of Amyloid."

It is well known that patients with Alzheimer's and other disorders, such as type 2 diabetes, develop amyloid, a substance composed of sticky protein fibers and sugar molecules that builds up in the brain or other organs in the body. Doctors do not know whether this material causes the diseases, or whether the diseases lead to amyloid formation. However, in less common diseases, such as light chain amyloidosis, a rare but devastating illness caused by the aggregation of antibody-related light chain proteins in organs such as the heart, liver, kidneys and spleen, there is no doubt that amyloid presence in the organs is the cause of the disease.

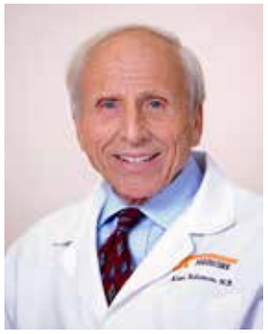
There is an urgent need to image amyloid in order to accurately diagnose and determine the stage of the disease and monitor the therapies used to treat patients. However, in the United States there are no clinically available methods to image amyloid in patients, except in those with Alzheimer's disease. Many patients travel to Europe for a scan, where the technology is available. With the help of his team, including Steven Kennel, PhD; Alan Stuckey, BA, CNMT; Tina Richey, MS; Sallie Macy, BA; Craig Wooliver, MLT; Emily Martin, BS; and Angela Williams, MS, Dr. Wall has developed a series of new imaging agents aimed at advancing the diagnosis and treatment of patients with amyloid-related diseases. Dr. Wall's new imaging agent is a peptide, a protein he has named p5. In preclinical testing, radioactive p5 has been shown to bind to amyloid in the brain and other organs, making the amyloid visible through positron emission tomography (PET) imaging and other techniques. It is expected that with appropriate modifications, p5 may eventually be used in the clinical setting to image amyloid throughout the body.

Why this matters:

In the U.S., our ability to detect amyloid deposits is limited," Dr. Wall said. "We've made amazing progress, but we need to move faster. The peptide p5 is the next generation of amyloid-imaging agents, and it holds much promise for helping people with amyloid-related diseases".

News»

Alan Solomon, M.D., retires



Alan Solomon, M.D. retired from the University of Tennessee after 47 years. During his tenure at UT, Dr. Solomon served as a Professor in the Department of Medicine and as the Director of the Human Immunology and Cancer Research Program. He held National Institutes of Health grants for four decades and maintained a very successful clinical practice. He has given most of his adult years as a physician and medical researcher to improve the quality of life of his patients.

Reni Leslie, IRB Associate Director, retires

After 32 years of service to the University of Tennessee, Reni Leslie retired at the end of 2013. For 18 of those 32 years, Reni served the Graduate School of Medicine as Assistant Director of the Internal Review Board.

Gawrysiak's dissertation published

Former Cole Neuroscience Center PhD student, Michael Gawrysiak, had his dissertation, titled "Pragmatic Psychodynamic Psychotherapy for a Patient with Depression and Breast Cancer: Functional MRI Evaluation of Treatment Effects", published in the American Journal of Psychotherapy.

UTMC appoints Clinical Trial Director

University of Tennessee Medical Center appointed Paul Ottaviano as the Clinical Trial Director. Mr. Ottaviano has over 35 years of executive leadership, entrepreneurial, research, and teaching experience in the healthcare industry. In addition he has taught undergraduate and graduate college level courses from time to time as an adjunct professor, served on the boards of colleges, presidential advisory committees, and lead efforts to commercialize intellectual property at Emory School of Medicine. He will be joined by Janet Parkey, CPA and several current site coordinators and regulatory document staff in various clinical departments at the University of Tennessee Medical Center (UTMC). Together they will develop the operation and attract sponsors of drugs, biologics, and devices to work with the newly created division and its physician and medical staff supporters at UTMC.

Roger Carroll, Ph.D., retires

Roger Carroll, Ph.D. has retired after 29 years of service to the University of Tennessee. Dr. Carroll's research efforts predominately focused on the area of peri-operative coagulation testing and management, with particular focus on assessment of platelet function in a clinically relevant manner. He was a valued faculty member of the Department of Anesthesia who will be greatly missed.

Your Chance to Advance

The people at the UT Graduate School of Medicine would be happy to discuss our research programs and how your support can help advance healthcare. For information about philanthropic giving to the UT Graduate School of Medicine Office of Research, please contact the development office at 865-305-6611 or development@utmck.edu.

If you would like more information about any research programs described in this issue of Advance, please contact the UT Graduate School of Medicine's Research Coordinator, Kristen Bass, at 865-305-9749 or visit online: http://gsm.utmck.edu/research/main.cfm.

Thank you.

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1924 Alcoa Highway, D-116
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Publication #R08-6350-001-001-14 (13PB32RS)