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Advance Research Digest

University of Tennessee Graduate School of
Medicine

Summer 2011

Advance (Summer 2011) - Finding a Link: Genetics and Concussion

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

FINDING A LINK

Genetics and Concussion

Could your child be genetically predisposed to a more severe concussion?

ON THE HORIZON:

HRT, Gene Therapy and Vascular Disease

RESEARCH SPOTLIGHT:

Taking it to the Streets: Research That's More Than Skin Deep

STUDIES IN BRIEF:

- HPV-Related Oral Cancer
- Protein Detected in Breast Cancer

CLINICAL TRIALS

SUMMER 2011

UT THE UNIVERSITY OF TENNESSEE
MEDICAL CENTER

Wisdom for Your Life.

THE UNIVERSITY of TENNESSEE **UT**
GRADUATE SCHOOL of MEDICINE



Spirit of Exploration...

OBSERVATIONS



Welcome to the inaugural issue of *Advance*, a biannual research digest for alumni, friends and colleagues.

Advance is produced by the University of Tennessee Graduate School of Medicine to highlight the wide-ranging research and people who are part of the research enterprise of the region's only academic medical center: the University of Tennessee Medical Center and UT Graduate School of Medicine.

We are grateful to the leaders of University of Tennessee Medical Center for their support of this communication and for their unflagging support of the spirit of inquiry that pervades our institutions. In addition to excellence in patient care and education, our academic medical center sponsors extensive research in both the clinical and laboratory settings. In that endeavor, we collaborate with the University of Tennessee, Knoxville (UTK), UT College of Veterinary Medicine, Oak Ridge National Laboratory (ORNL) and other research institutions to seek answers to complex medical problems. We train students, physicians and scientists to become the researchers of the future and approach health care with the curiosity that will lead to improvement in the lives of our patients.

Research and researchers, alike, take many forms. Some of our researchers have taken clinical problems to the laboratory and are delving into very fundamental questions on the molecular level. Some are clinicians performing prospective trials of new techniques or treatments. Others are trying to find ways to improve the delivery of healthcare by looking retrospectively in order to parse out clues to enhance future outcomes.

In partnership with our colleagues at UTK, we are looking at medical care delivery and how decisions are made, hoping to enhance patient safety and access as well as reduce the cost of medical care. With ORNL, we are looking at how images are interpreted with an eye to eventual computerization. The UTK College of Engineering is helping develop new devices and educational simulators for our physicians and scientists, so they may effectively practice in our new Medical Simulation Center, improving their skills in a virtual setting.

Our researchers are scientists dedicated to pure science, and they are physicians who in addition to providing clinical care seek answers through research that will also help their patients. It is the nature of an academic medical center like ours to pursue new solutions and solve diverse questions in the quest for excellence.

All of this intellectual vigor requires hefty funding and support from the institutions. The immediate return is not always visible. The UT Graduate School of Medicine supports the ongoing research efforts because we understand that the atmosphere of inquiry is vital to our mission of superior patient care and education.

Our academic medical center sustains this effort through its budget, grants from funding agencies and foundations and through generous gifts from benefactors who understand the crucial role medical research plays for our community and for mankind. In addition, some departments and physicians allocate portions of their practice income to research in areas of their expertise.

The results, as you will see in this publication, create a robust catalogue of outstanding work portending an exciting future for the University of Tennessee Medical Center and the patients we serve.

Mitchell Goldman, M.D.
Assistant Dean for Research

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ADVANCE

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Publishers

James Neutens, Ph.D., Dean
Mitch Goldman, M.D., Assistant Dean
Eddie Moore, M.D., Associate Dean

Managing Editor

Amanda F. Johnson, APR

Contributors

Amanda F. Johnson, APR
Mitch Goldman, M.D.
William Smith, M.D.

Design

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 healthcare 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.

Contact Us

Advance
UT Graduate School of Medicine
1924 Alcoa Highway, D-116
Knoxville, TN 37920
Telephone: 865-305-9190
E-mail: AdvanceDigest@utmck.edu
Web: <http://gsm.utmck.edu>

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FEATURED RESEARCHER »»»»»»»» *THE DRIVE AND VISION OF*



Alan Solomon, M.D.

Stone by stone, this laborer crafts walls and pathways across his tranquil property. The stonework, an avocation, is precise and lovely and reflects the man’s drive and vision, traits that define Alan Solomon, M.D., and his work at the UT Graduate School of Medicine, where he serves as professor of Medicine and directs the Human Immunology and Cancer Program. He has given most of his adult years as a physician and medical researcher to improve the quality of life of his patients.

NORTH AND SOUTH

A native New Yorker, Solomon graduated from Duke University School of Medicine in 1957 and then completed an internship at Mount Sinai Hospital in New York. He then did something most medical school graduates did not do: He chose to undergo another three years of clinical training at Montefiore and Mount Sinai hospitals, plus four years of research training

at the National Institutes of Health’s National Cancer Institute and The Rockefeller Institute for Medical Research.

Finally, he finished his self-imposed rigors of training and began working. Then the phone rang.

TENNESSEE CALLING

“I got a call from Dr. Amoz Chernoff, who was director of the UT Memorial Research Center,” Solomon says. “He asked if I would be interested in coming to Tennessee.”

The year was 1966. Medical research had few regulations, and without the internet, researchers waited months for new information to reach library shelves. MRI, CT and PET scans did not exist, and anti-cancer drugs were only a dream.

In this setting, Solomon came to UT where his research and clinic duties were devoted to cancer. In 1992, he was one of eight medical scientists in the U.S. to be named an American Cancer Society Clinical Research

ALAN SOLOMON, M.D.

Professor. Subsequently, his efforts have focused on a disease known as amyloidosis.

Amyloid is the term for a misfolded, “gum-up-the-works” form of a variety of proteins that can form hair-like fibers, or fibrils, that are deposited into vital organs, like the heart, kidneys, pancreas or brain. This process leads to organ failure and eventually, death. Amyloid-associated illnesses include Alzheimer’s disease, adult (Type-2) diabetes, rheumatoid arthritis and a condition related to multiple myeloma called primary or AL amyloidosis.

“The goal of our amyloid research is to develop new means of diagnosis and more effective treatment,” Solomon says. “We are convinced that we can make a significant impact on these diseases by improving the prognoses and reducing the suffering of our patients.”

Today, the fruits of this research are being applied directly to the patient.

“To see the discoveries in the laboratory being translated to the clinic indeed is a major achievement, but even though these illnesses cannot be cured at present, we will at least make them more chronic and improve the quality of life.”

PROMISE, FAITH, FAMILY

“Everyone, regardless of who they are, can do something to contribute to the healing of the world,” Solomon says, reflecting belief in a central Jewish tenant and a strong paternal influence.

Solomon’s father came from a very poor immigrant family and dropped out of school at age 12 to support his family. He found a way to go to school at night and eventually completed law school to become a senior partner in a large law firm

in New York. He was the recipient of several honorary doctoral degrees and four endowed professorships in law and medicine.

Today, rooted in faith and family, backed by a lifetime of wisdom and spurred by a passionate quest, Solomon made a promise almost 15 years ago.

“A patient of mine had amyloid disease and later died. At her funeral, I promised her husband that we’d do something to affect this disease that took his wife, and when I make a promise, I try to keep it,” he says.

“I owe a debt of gratitude to my patients and my talented colleagues who truly have been partners in this work. I’m also thankful to the private and public agencies that have provided the financial support to fund our research.”

Just as one stone leads to the next, Solomon remains optimistic that through his and his colleagues’ research, advances in medicine will lead to others to benefit all humanity. ▲



SUNSCREENERS

Taking It to the Streets: Research That's More than Skin Deep

You might have seen him in his “sun suit.” Sans jacket and tie, it’s a giant, friendly sunshine. But the sun suit doesn’t just attract attention. For Jim Lewis, M.D., assistant professor of Surgery and surgical oncologist, it’s a silly way to reach people about a serious subject.

Skin cancers are, indeed, serious, even deadly, but they are often preventable. More than 120,000 people are diagnosed each year with melanoma, which is cancer of the pigment cells and the deadliest form of skin cancer. Of those, about 45% are invasive, resulting in someone dying from melanoma every hour in the U.S. Melanoma, if caught early, can be cured through surgery.

Other skin cancers also should not be ignored: squamous cell carcinoma, cancer of the outer layer of skin cells; and basal cell carcinoma, cancer of the deepest layer of skin cells and the most common skin cancer.

To help people understand the importance of caring for their skin and identifying abnormal skin lesions, Lewis, along with Valerie Sams, M.D., third-year resident in Surgery, and Georgette Samaras, UT Cancer Institute’s outreach coordinator, have embarked on a community outreach program,



Jim Lewis, M.D., in his “sun suit.”

WHY THIS MATTERS:

EARLY DETECTION OF MELANOMA AND OTHER SKIN CANCERS CAN SAVE A LIFE.

called SunScreeners. The program provides on-site skin screenings and allows community members to enroll in a research program that provides evaluation and diagnosis of skin lesions and support for further examination by a specialist.

“We believe we must educate people about skin cancers,” Lewis said. “Early detection leads to cures, so we take the opportunity for screenings to the communities.”

Donning his sun suit, Lewis and his team set up SunScreeners at outdoor sports events and community festivals and visit senior centers and wellness programs at area businesses.

Some community members just want to have a skin blemish examined on the spot, but others sign up for the research program, which includes on-site dermal photography of the skin lesion.

“Using the dermal photography, we classify lesions from benign [not harmful] to very problematic,” Lewis said. “We will then contact participants with results of their screenings and for some, help them find a dermatologist or other specialist. Six months later, we will follow up with the participants to evaluate the effectiveness of the program.

“We’ve screened more than one thousand people, and the majority had only benign lesions. For the small percent of people who were referred to a specialist, we believe we potentially saved their lives,” he concluded.

For more information about SunScreeners or how you can participate in the research program, contact Georgette Samaras at 865-305-8577. ▲

ADVICE FROM THE SUNSCREENERS

Prevent Sunburn

Limit or avoid sun exposure between 10 a.m. and 4 p.m.

Avoid Tanning Beds

Tanning bed users have 2.5 times the risk of squamous cell carcinoma and 1.5 times the risk for basal cell carcinoma. Exposure to tanning beds before age 35 increases melanoma risk by 75%.

Use Sunscreen

“SPF” refers to “sun protection factor,” the amount of time you will be protected from a burn. Use a sunscreen with an SPF of 15 or higher. Sunscreens should be liberally applied about 20 minutes before sun exposure.

MELANOMA: WHAT TO LOOK FOR

Melanoma, the deadliest form of skin cancer, can be identified in several ways:

- *A spot that is new, irregularly shaped and dark brownish with darker or black areas*
- *A mole that grows darker, bigger or firmer, itches or tingles and/or flakes and bleeds*
- *A lesion with an irregular border*
- *A bump that is shiny, firm and dome shaped*
- *A dark lesion under a fingernail or toenail or on the palm or sole.*

If you are concerned about your skin, call your doctor today.

FINDING A LINK: GENETICS AND CONCUSSION



Tom Terrell, M.D., and colleagues are investigating a connection between genetics and concussion.

Could your child be genetically predisposed to a more severe concussion? Could his genetics indicate a slower recovery from a concussion? Tom Terrell, M.D., associate professor in Family Medicine and associate director of the Sports Medicine Fellowship, and Ken Bielak, M.D., associate professor and Sports Medicine Fellowship director, are leading a study to answer those questions.

Terrell and Bielak are attempting to find a biological link to the association between genetic makeup and concussion risk in athletes. The study is funded by the National Operating Committee on Standards for Athletic Equipment and is the largest prospective cohort study of its kind in the U.S. It has the participation of 15 colleges and universities in the Southeast and about 2,500 athletes in collision sports.

Concussion is an injury to the brain due to rapid rotation of the head caused by trauma to the head or other part of the body. It causes transient alteration in the brain's neurological status and can have long-term effects. Loss of consciousness does not necessarily accompany concussion.

In the study, athletes who sustain a concussion voluntarily submit DNA samples, which are analyzed at Duke University. The team is investigating whether genetic polymorphisms (variations in individual DNA sequence between individuals) increase the risk of sustaining concussion; influence the severity of acute sports concussions; and impact the duration of symptoms.

So far, 120 concussions have been collected, and results of the genetic analysis are forthcoming.

WHY THIS MATTERS:

ATHLETES SUFFER MORE THAN ONE MILLION CONCUSSIONS EACH YEAR. AS MORE LIGHT IS SHED ON THE SERIOUS NATURE OF BRAIN INJURY, INCLUDING CONCUSSION, WE LEARN MORE ABOUT HOW TO CARE FOR OUR ATHLETES AND ACCIDENT VICTIMS.



CONCUSSION CENTER

The Department of Family Medicine is establishing a Concussion Center in its new Sports Medicine Clinic to serve concussed athletes in the community. The Sports Medicine Clinic offers services from sports medicine physicians for a variety of sports- and non-sports-related accidents and injuries. For information call 865-305-9352.

“We believe the study will reveal if there is genetic predisposition to more severe concussions,” Terrell said. “These findings may potentially determine how quickly athletes should return to play or whether they should play collision sports at all. For those who have suffered concussions, our findings might provide promising information about the risk for additional concussions and the duration of recovery time. With larger long-term studies, we may be able to predict who is vulnerable to more severe concussions.”

This milestone in the research marks not an ending but a springboard for further study. Terrell and Bielak now are working with researchers in the Molecular Imaging and Translational Research Program as well as physicians in the Emergency Department. The goal of this collaboration is to ultimately help accident victims who suffer brain injury and investigate new ways to image concussion using positron emission tomography/computed tomography (PET/CT).

For more information about the concussion study or to register to participate in the study, visit www.concussionresearch.com or contact Terrell at 865-305-9352. ▲



THE ABCS OF CLINICAL TRIALS AND HOW YOU CAN BENEFIT

William B. Smith, M.D., President, Volunteer Research Group



Deborah Tuggle is participating in a clinical trial under the direction of William Smith, M.D., and believes it's her way to help future generations.

Clinical trials are a type of medical research conducted to collect data on the safety and effectiveness of new treatments, most commonly devices, vaccines or drugs.

Product development exists in four phases:

Phase I - Short trials evaluating basic safety and metabolism

Phase II - Early evaluation of effectiveness, safety and appropriate dose

Phase III - Large trials to determine efficacy and side effects for submission to the FDA for approval

Phase IV - Post-marketing studies to answer additional questions about marketed drugs or determine new indications.

“This is my way of contributing to future generations,” says Deborah Tuggle, a clinical trials participant. “Medicines that have helped me in the past were developed through studies just like these, and eventually these will help someone. I like being a part of that process.”

Individuals who participate in clinical trials may benefit in a variety of ways:

- Playing a more active role in their own health care
- Being involved in the discovery of new treatments for those suffering from various illnesses
- Gaining access to new research treatments before they are widely available
- Undergoing medical examinations and lab work at no cost and
- Possibly being compensated for their travel, time and inconvenience.

“Clinical trials research offers an opportunity for patients to be a part of the future of medicine,” says Timothy Panella, M.D., chair of Department of Medicine. “If people do not participate in these studies, the advancement of medical care comes to a standstill. We stand on the shoulders of others, and the patients at the top edge are those participating in clinical trials; it’s altruism at its finest.”

Volunteer Research Group (VRG) is an entity for pharmaceutical-sponsored clinical trials located at the University of Tennessee Medical Center. VRG currently is seeking volunteers with high cholesterol, low kidney function, liver disease, congestive heart failure or prior myocardial infarction and for adults who are generally healthy. For a complete list of enrolling studies and to find out how you can become a participant, visit www.VRGUT.com or call 865-305-DRUG (3784). ▲

WHY THIS MATTERS:

CLINICAL TRIALS ADVANCE HEALTHCARE AND BRING TREATMENTS MORE QUICKLY TO PATIENTS.

A NEW DISEASE ON THE RISE: HPV-RELATED ORAL CANCER

It's a subject many people are too embarrassed to discuss. Not so with Eric R. Carlson, D.M.D., M.D., chair of Oral and Maxillofacial Surgery. His research is showing findings so startling that he believes he must talk about it: The possible association between oral cancer and intimate oral contact.

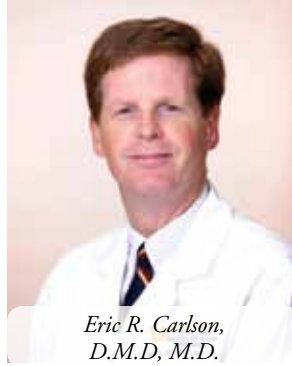
For the first decade of Carlson's practice beginning in 1990, oral cancer in the patients he treated was primarily caused by well accepted carcinogens, namely tobacco and alcohol. The patients were typically older men.

Starting in 2000, Carlson began seeing young, non-tobacco-using, otherwise healthy men presenting with oral cancer, most commonly tongue cancer. He believed the cancer might be caused by human papillomavirus (HPV), a DNA virus known to cause cervical cancer in women.

Carlson was right.

After studying the patients' tumors, he found HPV in more than half of the specimens, and more research has led to the belief that HPV is likely transmitted through intimate oral contact.

In cervical cancer, the incorporation of HPV in a woman's DNA can, under certain circumstances, produce cancer proteins (oncoproteins) that inhibit two important tumor suppressor genes. Carlson believes this is the same process that can cause cancer in the mouths and throats of people, particularly those with more frequent exposure.



*Eric R. Carlson,
D.M.D., M.D.*

It is becoming well accepted that more frequent exposure to the virus increases the risk of developing an HPV-related oral cancer.

Even more shocking, the American Medical Association recently

stated that 50% of men are HPV positive and 80% of women are HPV positive by the age of 50.

“Over the past decade, societal practices have changed,” Carlson said. “HPV-related oral cancer is becoming more commonly observed, but we are narrowing the gap in our knowledge of these cancers. Next, we want to determine why some men have HPV but do not develop oral cancer and study the cancer of monogamous partners to see if the HPV viruses match in men with HPV-related oral cancers and their female partners with HPV-related disease in the cervix. This scientific observation will get us closer to concluding a cause-and-effect relationship associated with this social disease.”

In the meantime, counseling young people about the risks of exposure to HPV is imperative. Also, HPV vaccines for both young women and men between the ages of nine and 26 are available. ▲

WHY THIS MATTERS:

WE NOW KNOW THERE ARE DIFFERENT TYPES OF ORAL CANCER: THOSE ASSOCIATED WITH HPV AND ORAL CANCERS NOT ASSOCIATED WITH HPV. AN IMPORTANT PART OF OUR OBSERVATION IS THAT PATIENTS WITH HPV-RELATED ORAL CANCERS HAVE A BETTER PROGNOSIS THAN THOSE PATIENTS WITH ORAL CANCERS ASSOCIATED WITH THE EXCESSIVE USE OF TOBACCO AND ALCOHOL. ALSO, REVEALING THIS SOCIAL DISEASE KEEPS OUR YOUNGER POPULATION HEALTHIER.

IDENTIFYING HOW HRT AND GENE THERAPY AFFECT VASCULAR DISEASE



Deidra Mountain, Ph.D., and her team are researching causes of vascular disease.

Estrogen and progesterone could be contributing to vascular disease, and the researchers in the Vascular Research Laboratory are asking, “Why?” The team is using information discovered years ago by physicians in the Division of Vascular/Transplant Surgery that showed women receiving hormone replacement therapy (HRT) who also had vascular disease requiring interventions often had more adverse outcomes after their procedures than women who were not undergoing HRT. The team is identifying the vascular cell mechanisms that seem to be influenced by the estrogen and progesterone in HRT with the goal of developing ways to help women.

Now, the team, led by Deidra Mountain, Ph.D., assistant professor of Vascular/Transplant

Surgery, are continuing their fight against vascular disease by examining gene therapy. Gene therapy is the delivery of genetic material into a living cell that incorporates the new genetic instructions to alter a disease process. This type of therapy shows promise in the treatment of many diseases, including vascular, but delivering the genes in a safe and non-toxic way has been a formidable problem.

Mountain’s team is testing a delivery agent made from biodegradable polymer that does not have the harmful side effects of traditional agents. They have successfully silenced (altered) dysfunctional genes in laboratory tests and will proceed with testing in biological samples. Success here could lead to gene therapy for vascular disease and research into many other diseases. ▲

WHY THIS MATTERS:

INSTEAD OF TREATING SYMPTOMS OF VASCULAR DISEASE, GENE THERAPY ALTERS THE FUNCTION OF GENES THAT ARE CONTRIBUTING TO THE DISEASE, THEREFORE, HELPING THE BODY HEAL ITSELF OR PREVENT THE DEVELOPMENT OF THE DISEASE. GENE THERAPY COULD BE AN INNOVATIVE TREATMENT FOR MANY DISEASES.

DENTAL PROTEIN COULD IMPROVE BREAST CANCER DIAGNOSIS

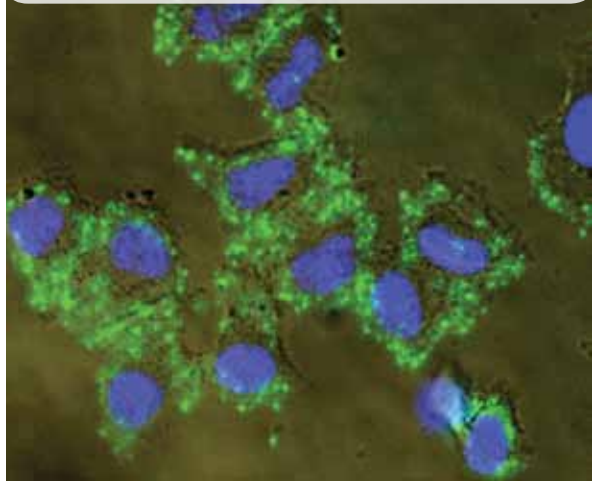
Daniel Kestler, Ph.D., Charles Bruker, M.D., and their colleagues in the Human Immunology and Cancer Program have investigated a protein, called ODAM (odontogenic ameloblast associated), in certain odontogenic (dental) tumors. Interestingly, it has been detected in breast, lung and gastrointestinal cancers, melanoma and other malignancies. The findings and discoveries on this molecule could improve the diagnosis and treatment of some cancers, of particular interest to the team's clinical members, surgical oncologists John Bell, M.D., and James Lewis, M.D.

Proteins are the primary components of cells, affecting their growth, function and regulation. The researchers found that localization of the ODAM protein in cells correlated with the stage of breast cancer and melanoma, a cancer of skin's pigment cells. Further, the expression of the ODAM protein was introduced into cultures of highly invasive human breast tumor cells in the laboratory, and the researchers saw significant increase of tumor growth and invasiveness.

A number of patients who have participated in the study also were found to have measurable levels of antibodies to the protein in their blood.

“This suggests an immune recognition of this protein as a possible tumor expressed antigen and that the molecule or its interactions may prove

ODAM protein (fluorescent green) is photographed among breast cancer cells (blue). The ODAM protein could help in the diagnosis of breast and other cancers.



important for cancer evaluation and therapy,” said Kestler.

If the protein can serve as a tumor biomarker (a substance that can be traced in the body), cancers can be diagnosed earlier or perhaps linked to specific treatment, which might improve chances for survival.

The protein, created by a natural gene previously not known to produce a protein, was first discovered in the Molecular Biology Laboratory by Alan Solomon, M.D., director, Human Immunology and Cancer Program. ▲

WHY THIS MATTERS:

WHILE A RELATIVELY LOW NUMBER OF PEOPLE WHO SUFFER FROM CERTAIN DENTAL TUMORS COULD BENEFIT FROM THE IDENTIFICATION OF THIS NOVEL PROTEIN, THOUSANDS WHO SUFFER FROM BREAST, LUNG AND OTHER CANCERS WILL BENEFIT FROM THE NEW RESEARCH AND POSSIBLE DIAGNOSTIC TREATMENT POTENTIALS THAT THE STUDIES ON ODAM WILL HAVE OPENED.

NEWS»

RESIDENTS, FELLOWS PRESENT RESEARCH



Residents and fellows at the UT Graduate School of Medicine review research presentations.

More than 40 residents and fellows presented abstracts during Research Days that summarized research in both case studies and original projects. Topics included blood transfusion in trauma; dental infection and correlation to systemic illness; improving resident-patient communication; MRSA infections in the head and neck; gene therapy and others.

“Research Days are a direct extension of the Graduate School of Medicine’s mission to improve patient care through research and scholarly activity,” said William Metheny, assistant dean, Graduate Medical and Dental Education. “The events are celebrations of the culmination of faculty mentoring that teaches the next generation the discipline of scientific inquiry and discovery.”

NIH GRANT AWARDED FOR WOUND HEALING RESEARCH

A research study jointly led by the UT Graduate School of Medicine Shock, Trauma and Nutrition laboratory and Advanced Plasma Products Inc. received funding from the National Institutes of Health. The Small Business Innovation Research grant, totaling \$341,000, will fund research in the development of an atmospheric plasma application to improve wound healing.

RESEARCHER RECOGNIZED AT CONFERENCE

Christopher Stephens, Ph.D., assistant professor, Regenerative Medicine laboratory, received an Award of Excellence at the Comparative and Experimental Medicine and Public Health Symposium held at the University of Tennessee College of Veterinary Medicine. The award recognized his research described in a presentation, “Generation of Three-Dimensional Tissue Using Stem Cell Seeding of Polymeric Scaffolds.”

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 of the research programs described in this issue of *Advance*, please contact the UT Graduate School of Medicine at 865-305-9290 or visit us online: <http://gsm.utmck.edu/research/main.cfm>.

Thank you.

ADVANCE

UT Graduate School of Medicine
1924 Alcoa Highway, D-116
Knoxville, TN 37920



ADVANCING RESEARCH
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