Winter 2012

Advance (Winter 2012) - Healthy Babies... Healthy Moms: Making a Difference in the Health of Pregnant Women in East Tennessee

University of Tennessee Medical Center

University of Tennessee Graduate School of Medicine

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Healthy Babies... Healthy Moms

Making a Difference in the Health of Pregnant Women in East Tennessee

On the Horizon:
Focusing on Huntington’s Disease

Research Spotlight:
Breaking Through Barriers: A New Peptide Sees Plaque in the Brain

Studies in Brief:
• Using Forensic Science to Solve Dentistry Mysteries
• Discovering How Animals and Humans Share Disease and Clues to Treatments

Clinical Trials

Winter 2012
Spirit of Exploration...
This edition of Advance highlights the fact that the University of Tennessee Medical Center and UT Graduate School of Medicine are involved in collaborative research with other institutions. Our research enterprise has grown so vast that partnering with different organizations often is the most robust way to focus diverse expertise on a single problem.

Our institutions collaborate with the University of Tennessee, Knoxville, College of Engineering, School of Public Health, Department of Nutrition and College of Veterinary Medicine, as well as Oak Ridge National Laboratory (ORNL) and the UT Health Science Center in Memphis to name a few. The valuable partnerships formed by these joint efforts lead to better research. These partnerships also yield an advantage in obtaining funding from national organizations.

Many human medical problems can be solved through engineering solutions or have analogies in the veterinary world, where solutions benefit both human and non-human patients. The juxtaposition of clinicians and basic scientists in diverse fields often creates a relationship that advances research in problems found in clinical care. Having the computational and nuclear expertise of ORNL close by enables sophisticated approaches to complex medical issues.

The Graduate School of Medicine is uniquely poised to take advantage of these resources, and as part of an academic medical center, we are using collaborative opportunities to advance our knowledge, understanding and treatment of the ailments of our patients.

Mitchell Goldman, M.D.
Assistant Dean for Research
Amy LeBlanc and husband, Casey, enjoy reading with their daughters, Erica and Isabelle. LeBlanc’s research that combines animal and human health is unique in the world.

We need to know what normal looks like before we can understand abnormal.

~Amy LeBlanc

Some people have it. Some simply do not. It’s a deep sense of curiosity. It’s asking, “Why” and “What if” and not being satisfied until an answer is found.

Thankfully, Amy LeBlanc, D.V.M., associate professor and director of Translational Research, Molecular Imaging and Translational Research Program, possesses that deep curiosity and the education and skills to act upon it to the benefit of patients. But the unique part of LeBlanc’s story is that for her, patients are both the two-legged and four-legged varieties.

In a unique joint position with the UT Graduate School of Medicine and the UT College of Veterinary Medicine, LeBlanc studies non-invasive ways to detect and monitor response to treatment for diseases in dogs, and in front of her is an ever-widening field of opportunities to translate her findings to the detection and care of diseases in humans.

**Academic to Begin With**

LeBlanc’s father is a chemical engineer, and her mother is a teacher.

“I think my parents would say I was academic to begin with, and I loved animals and science from a young age,” says LeBlanc with a quick laugh that fills the room.

For most of her life, LeBlanc thought she would become a veterinarian in a private practice. Eventually, her sense of curiosity told her otherwise.

During her veterinary school years, LeBlanc became fascinated with oncology and decided she wanted to delve into that specialty by pursuing additional post-graduate training. After completing a medical oncology residency, LeBlanc began practicing veterinary oncology in Tampa, Florida. While she enjoyed the work, she had “a nagging feeling that this can’t be all there is,” she says. “I realized I wanted to be on the edge of what’s known and what’s not known.”

**A Curious Turn of Events**

In May 2004, she and husband, Casey, a veterinary clinical pathologist, moved to Knoxville to accept faculty positions at the UT College of Veterinary Medicine.

“Almost never are two positions like those
open at the same time,” LeBlanc says in amazement. “It just never happens. But we are lucky to be here in Knoxville.”

In line with a typical tenure-track faculty position at the Veterinary Medical Center, LeBlanc was able to begin research while fulfilling clinical service and teaching roles. She soon learned about incredible technology available just across the Tennessee River at the UT Graduate School of Medicine, and by 2009, with the encouragement of James Neutens, Ph.D., dean of the Graduate School of Medicine, and James Thompson, D.V.M., Ph.D., dean of the College of Veterinary Medicine, LeBlanc had a joint appointment between the two institutions, doing what she loves: Answering “what if.”

“It was a natural progression to where I wanted to focus my research efforts,” LeBlanc says. “We have a unique set of resources, technology and people that you cannot find anywhere else in the world.”

Understanding Abnormal

LeBlanc is putting this unique environment to good use. Her goal is to help researchers in various fields realize the potential of PET/CT (Positron Emission Tomography/Computed Tomography) imaging. She sees a big picture not many medical or veterinary professionals see or know exists: Knowledge gained from using PET/CT imaging for human health can help animals; conversely, using PET/CT and new PET tracers to diagnose and monitor treatment in animals can further human health.

“Animals with spontaneous diseases, like heart failure, diabetes and cancer, can help us understand similar diseases in humans. We have incredible technology and expertise here, so we should be asking, ‘How else can we use this technology to benefit both?’”

LeBlanc has high demands for her research: In addition to complying with all regulations governing research, it must be both ethically sound and mutually beneficial for veterinary medicine and human medicine. Protocols are followed and regularly scrutinized.

At present, LeBlanc is using the non-invasive PET/CT imaging facility to determine how normal dog brains use glucose for fuel, so she and others around the world can compare with brain activity of dogs suspected of having inflammatory brain disease.

“We need to know what normal looks like before we can understand abnormal,” she says.

This study is one of several headed by LeBlanc that is unique in the world. Nowhere else and no one else in the world has ever done such studies. She recounts a time recently when she attended an international conference and watched as her research findings were used to support the presenter’s findings.

“It was an exciting moment, knowing the work we are doing here is impacting the way physicians think about diagnosing and treating their patients,” says LeBlanc. “In the end, I’d like to see drugs and imaging tools come into the marketplace for humans and animals, understanding the knowledge we gain is transferrable to both. Someone’s mother or brother will get that drug, which would not be available if we hadn’t been here, if we hadn’t wondered about the possibilities.”

One of Amy LeBlanc's current research programs is inflammatory brain disease in dogs and how to draw correlation to human health.
Why this matters:

In Tennessee, gestational diabetes affects up to 14% of pregnancies, and more than one of every three women in East Tennessee is obese. Research that brings healthier babies into the world, who go home with healthier mothers, affects generations.

You might call the folks in the Department of Obstetrics/Gynecology determined dreamers.

They are Bobby Howard, M.D., chair of the department; Jo Kendrick, W.H.N.P.-B.C., certified diabetes educator; and Dawn Coe, Ph.D., University of Tennessee, Knoxville, Department of Kinesiology, Recreation and Sport Studies. Through two research programs, this group is tackling gestational diabetes and obesity, two health issues that threaten the lives and health of pregnant women and their babies.

If only everyone dreamed as these professionals do.

In 2009, Kendrick and Coe teamed to determine the effect of moderate activity on controlling gestational diabetes. Maintaining blood glucose in pregnant women means healthier moms and babies.

“My dream is to determine how many steps it takes each day to maintain normal blood glucose levels in women with gestational diabetes to avoid the use of insulin during pregnancy,” Kendrick says.

First, Kendrick and Coe validated a pedometer that could be used to accurately count the daily steps of pregnant women. Then, eight pregnant women who had gestational diabetes enrolled in the research study, and throughout the first
part of 2011, each woman had her blood glucose continuously monitored during moderate-intensity walking and sedentary trials.

“The results were significant,” Coe says. “We learned that moderate activity only one time each day sustained lower blood glucose levels for up to three hours.”

Now, the next phase—a larger cohort who will undergo different levels of prescribed activity and monitoring—will continue through 2013.

Obesity is another health threat to women and babies’ health during pregnancy, one that Bobby Howard, M.D., dreams of eradicating.

“We know that during pregnancy, obesity results in complications including a higher rate of Cesarean delivery, surgical complications, anesthesia complications and impaired wound healing,” Howard says. “The baby’s health also is compromised with an increased risk of birth defects, macrosomia and stillbirth.”

Howard has embarked on a research program that will help educate pregnant women about the risks of obesity to their and their babies’ health as well as help them monitor their diet and activity levels. Using today’s technology helps.

Each woman in the study has been provided pedometers and an internet-capable device for documenting their daily activity and food intake on a specially designed web site. Howard and others will access the information to help their patients understand how to adjust their lifestyles to combat obesity—and have healthier babies.

Dawn Coe, Ph.D., Bobby Howard, M.D., and Jo Kendrick, W.H.N.P.-B.C., are tackling gestational diabetes and obesity to help ensure healthy moms and babies.
Using p5 peptide developed by Jonathan Wall, Ph.D., amyloid in a mouse model glows brightly in a PET scan. The peptide can breach the blood-brain barrier and is helping researchers determine the cause of Alzheimer’s and other diseases.

Jonathan Wall, Ph.D., a professor and director of Preclinical and Diagnostic Molecular Imaging Laboratory and his collaborators, Steven Kennel, Ph.D., and Amy LeBlanc, D.V.M., have developed and are testing new imaging agents that might be good for patients who suffer from amyloid-related diseases like Alzheimer’s disease and Type 2 diabetes, as well as certain cancers, such as melanoma.

People with Alzheimer’s and Type 2 diabetes develop amyloid, a substance comprised of sticky protein fibers and sugar molecules. Doctors are uncertain what role amyloid plays in these diseases, but they believe it causes destruction of brain cells and the insulin-making cells in the pancreas. Because of this uncertainty, there is an urgent need to see the sticky substance to accurately diagnose and stage disease and monitor therapies patients are using. Until now, seeing amyloid in these patients occurred only in autopsies.

Wall has developed a new peptide imaging agent, a tiny protein he’s named “p5.” This peptide seeks out and binds special sugar

**Peptide p5 is the only imaging agent in the world to bind the sugar molecules in amyloid or tumors. It is unique.**

**Why this matters:**

While p5 does not yet destroy amyloid, it does bind to every type of amyloid. It brings us one giant leap closer to understanding Alzheimer’s disease and diabetes and in developing rapid methods for accurate diagnosis and treatment strategies, leading ultimately to a cure for amyloid-associated diseases and cancer.
molecules that are found in amyloid deposits and surprisingly on certain tumor cells, including melanoma tumors. Under the right conditions, the p5 peptide can breach the blood-brain barrier and through PET (positron emission tomography) scans and other techniques has been shown in preclinical tests to stick to amyloid in the brains of animals with Alzheimer’s-like disease.

Wall expects that with appropriate modifications, p5 may eventually image amyloid in patients with Alzheimer’s disease and diabetes better than other imaging agents because it can specifically seek the amyloid. Peptide p5 is the only imaging agent in the world to bind the sugar molecules in amyloid or tumors. It is unique.

In addition, Wall and Kennel have been able to detect melanoma tumors on animals that are brought by their owners for care. LeBlanc uses this technique to assist in the diagnosis and monitoring of dogs suffering with melanoma.

“In the U.S., our ability to detect amyloid deposits is limited,” said Wall. “We’ve made amazing progress, but we need to move faster. P5 is the next generation of amyloid imaging agents, and it holds much promise for helping people with Alzheimer’s and diabetes as well as those suffering from certain forms of cancer.”

Clinical trials are medical research that helps bring new devices, vaccines or drugs more quickly to patients. As part of an academic medical center environment, physicians and researchers at the Graduate School of Medicine conduct clinical trials to pursue answers for their patients and advance the field of medicine overall.

Scott Stevens, M.D., is a professor in the department of Surgery and a passionate researcher in vascular pathology. He heads the University of Tennessee Medical Center Aorta Center, the only site in East Tennessee to be selected to participate in an FDA-approved clinical trial studying stent repair of Acute Complicated Type B Aortic Dissections (Medtronic Dissection Trial—U.S. Study). This is an investigational device, limited by Federal (or United States) law to investigational use.

This study represents a joint effort of the cardiothoracic, vascular and endovascular services at the Aorta Center to provide available options to treat patients with this highly challenging and lethal disease. The trial currently is enrolling.

Stevens also leads several registry programs, which are post-approval studies of devices in use. One registry is assessing outcomes of the use of stents with distal protection in the treatment of obstructive carotid artery disease. Another is assessing the use of thrombectomy with varying catheter lengths for patients with peripheral vascular disease; embolism and thrombosis; or venous thrombosis.

For more information about these studies, contact Susan Rawn, coordinator, Clinical Research, at 865-305-9227.

Clinical trials at the University of Tennessee Medical Center also are ongoing. One trial currently under way investigates the recurrence of tumors in patients with non-small cell lung cancer. The trial, called MAGRIT, is sponsored by GlaxoSmithKline, a pharmaceutical company, and is being conducted at several centers around the world. Currently open for enrollment, MAGRIT evaluates an investigational lung cancer treatment called MAGE-A3 ASCI (antigen-specific cancer immunotherapeutic). ASCI works with the patient’s own immune system to fight the cancer. In this study, the treatment specifically targets the MAGE-A3 antigen, which is a substance sometimes found on lung cancer cells.

The purpose of MAGRIT is to measure how well the MAGE-A3 ASCI works in preventing cancer from coming back when given to patients with non-small cell lung cancer whose tumors express MAGE-A3 and who have had tumors removed by surgery.

For more information about the MAGRIT clinical trial, contact Barbara Munsey, director, Research Compliance and Oncology Clinical Trials, at 865-305-7136.

A comprehensive list of clinical trials being conducted across the country can be found at www.clinicaltrials.gov.
In a major breakthrough, Valerie Berthelier, Ph.D., assistant professor and director of the Graduate School of Medicine's Conformational Diseases and Therapeutics Laboratory, in collaboration with Christopher Stanley, Ph.D., Neutron Scattering Science Division at Oak Ridge National Laboratory (ORNL), are the first in the world to image the earliest formation of the mutant huntingtin protein. This protein is believed to be responsible for causing Huntington's disease, a hereditary neurological disorder that is always fatal and affects one in 10,000 Americans, and this earliest formation of the protein is believed to be the most toxic.

Using a neutron-scattering instrument at ORNL, the team was able to learn how the protein begins aggregating. Researchers believe that once the mutant protein forms aggregates, or clumps, the brain cannot naturally remove them, leading to Huntington's disease.

Now that the toxic proteins have been revealed, the next step is to develop drugs to combat the formation of clumps or remove the toxicity of the initial protein. This knowledge also will aid in the study of other protein-aggregation diseases, including Alzheimer's and Parkinson's.

Berthelier also is investigating the aggregation of amyloid (dangerous fibrils) in the pancreas, ultimately to draw a link to Type 2 diabetes.

The pancreas is a gland shaped much like a bunch of grapes that is located behind the stomach. It aids in protein digestion and produces insulin directly into the bloodstream to help the body metabolize carbohydrates.

When the pancreas cannot produce insulin or the body does not properly use the insulin produced, Type 2 diabetes results. But what is the cause of the pancreas malfunctioning? Berthelier and her team know patients with Type 2 diabetes have deposits of amyloid in their pancreases. While the association of pancreatic amyloid and development of Type 2 diabetes is known, a direct causative role for the amyloid has not been established.

Does the amyloid polypeptide in the pancreas cause Type 2 diabetes?

The researchers are investigating the aggregation properties of the amyloid and identifying small compounds that can alter the aggregation phenomena.

Why this matters:
Research into the root cause of Huntington’s disease and Type 2 diabetes can be the first step in eliminating these diseases that affect millions of Americans and for people with Huntington’s disease is always fatal. This research also can lead to discoveries in other amyloid-associated diseases, such as Alzheimer’s and Parkinson’s.
Christopher P. Stephens, Ph.D., is leading a new research program that is growing... quite literally.

Regenerative medicine is a field of science that began in earnest in the 1990s. It combines medicine and engineering to help the body heal itself using the body’s own cells to regenerate organs or tissue. It can be used for skin injuries, neuromuscular disorders, joint replacements, cartilage regrowth and organ repair.

In his work, Stephens, a research assistant professor in the Department of Surgery and the Center for Materials Processing at the UT College of Engineering, along with collaborator Madhu Dhar, Ph.D., at the UT College of Veterinary Medicine, are developing methods to induce regeneration using equine stem cells. Stem cells are not fully differentiated, so they have the ability to grow into different tissue types, including bone, muscles and connective tissue. Stephens’s work requires the use of adult donated stem cells, not embryonic stem cells, and horses are used because their physiology is similar to human conditions and can provide therapeutic benefit to the companion animal.

In the novel research, stem cells are painlessly removed from a horse and placed in culture with a scaffold created by Stephens. With the ultimate goal of creating scaffolds that encourage cell growth for various uses, currently Stephens is conducting initial compatibility testing.

“Our initial scaffold allowed for cell growth primarily on the surface,” Stephens said. “That was promising, but the cell growth needs to infiltrate the scaffold in order to produce a tissue. We are now developing a scaffold that is a naturally degradable polymer with a pore structure to enable in-growth of cells. Once we’ve achieved adequate cell adhesion and growth, that material will be placed in a horse to promote healing of the animal’s bone fracture or wound.”

Success means the horse’s body begins healing itself by regenerating cells using those implanted—not healing with scar tissue but with new, healthy tissue.

For Stephens, this is just the beginning. Relying on funding and FDA approval, he eventually will use regenerative medicine to create vascular bypass vessels and tissue-engineered venous valves. To that end, he is developing a bioreactor with collaborators at the University of Houston, which will provide chemical and biomechanical signals to the cells, mimicking a natural environment. Testing of cell regeneration in this bioreactor should begin in May 2012.

Why this matters:
Last year in America, more than 112,000 people waited for organ transplants. Work in regenerative medicine will allow for treatment of diseases that are currently untreated due to organ/tissue shortages. It also will promote new treatments for diseases, such as diabetes and heart disease. By learning how tissue grows, disease processes can be better understood, leading to more targeted treatments for patients.
Comparing x-ray images and forensic anthropological skeletal specimens helps link dental pathology to systemic diseases. Shown here are x-ray and skeletal evidence of a failed root canal resulting in infection in the body.

Dentists have long been able to see how diseases of the teeth and gums affect the body, but now, our research is revealing that systemic disease can first be spotted in the mouth.

The department of General Dentistry’s Gary McCown, D.D.S., assistant professor, O. Lee Wilson, D.M.D., associate professor, and Murray Marks, Ph.D., associate professor, are applying dental science to forensic anthropological skeletal specimens from the Regional Forensic Center and University of Tennessee’s Body Farm. The team is comparing long-term dental and alveolar (tooth socket) bone diseases with radiographic appearance and medical records. This study may lead to further evidence linking dental pathology to other systemic diseases like diabetes, heart disease, stroke and cancer.

**Why this matters:**
**Dentists at the UT Graduate School of Medicine are learning that the first signs of systemic disease may be witnessed in the gums, teeth and underlying bone tissue. With this knowledge, dental patients can be referred to medical specialists who may diagnose systemic disease sooner or prevent it altogether.**
Empowering medical students with a passion for research and an understanding of how research affects patient care was the hope of I. Reid Collmann, M.D., former dean of the UT Graduate School of Medicine. To help bring that hope to reality, the Collmann Medical Student Education Endowment gives young future doctors time in research labs, working alongside experienced researchers.

First- and second-year medical students and pre-medicine students in undergraduate school can apply for the eight-week summer program at the Graduate School of Medicine. Last summer, four students participated, studying in a variety of specialities.

Students chosen for the 2011 program and their respective research topics include:

**Caroline Conley:** Human Nutrition  
**Vincent Irish:** Medicine and Vascular Disease  
**Jerrin Olivia Nabers:** Nutrition and Anesthesiology  
**Wissam Tobea:** Conformational Diseases

Graduate School of Medicine faculty who mentored the students include:

Valerie Berthelier, Ph.D.  
Roger Carroll, Ph.D.  
Robert Craft, M.D.  
Michael Karlstad, Ph.D.  
Deidra Mountain, Ph.D.

For information on the Collmann Endowment, contact Missy Maples, Student Affairs coordinator, at 865-305-9618.
EXECUTIVE DEAN COMMENTS
ON FUTURE OF RESEARCH

Professionals at the UT Graduate School of Medicine received clear direction from David M. Stern, M.D., executive dean and interim vice chancellor for research at the UT Health Science Center during a recent visit to Knoxville: Partnerships.

“The only way to succeed in this economic and healthcare atmosphere is to partner with the [University of Tennessee Medical Center] and the community,” Stern said. “Research endeavors need to add value to [patient care] now more than ever.”

Stern called for a redefined research mission, one that supports comparative effectiveness research for patient-centered outcomes.

The UT Graduate School Medicine will continue to refine the direction of its programs. By dovetailing many of the institution's research programs with the Centers of Excellence at the University of Tennessee Medical Center, research will continue to grow, and the clinical programs at the centers will be able to provide more cutting-edge patient care.

RESEARCH IN NICU TECHNOLOGY, CORNEAL DEFECT RECEIVE FUNDING

Research being conducted by Christopher P. Stephens, Ph.D., research assistant professor, and others has received recognition and funding from the Morris Animal Foundation. The research investigates new methods using adult donated stem cells and scaffolding to repair corneal ulceration in horses, the most common eye problem in humans, horses, dogs and cats.

Stephens, Vichien Lorch, M.D., and Mark Gaylord, M.D., also received funding from the University of Tennessee for technology development to aid premature infants in neonatal intensive care. The work is in collaboration with the Department of Mechanical Engineering at the University of Houston.

This research includes the development of four new technologies:

- Soft Hydrated Coating for Cannula: The coating is developed from cellulose in Stephens’s laboratory and should improve the seal in infants’ nostrils.

- Computer-diagnostic Stethoscope: The novel computer-interfaced stethoscope will detect heart and lung sounds of premature infants. Using digital recorders on the stethoscopes, the team will be able to use the heart and lung sounds to create diagnostic software.

- Apnea Stimulation Device: A new device will interface with infants’ apnea monitors to gently stimulate infants when Apnea of Prematurity is detected.

- Breathing-assist Chest Plate: Using a soft polymer to form a seal against the infant’s skin and create a slight vacuum, the chest plate will facilitate respiration. The chest-plate technology could eliminate the use of endotracheal tubes.

BURN RESEARCH FUNDED

Christy Lawson, M.D., instructor in the Department of Surgery, received the Norman Yoshimura Grant from the American Society of Parenteral and Enteral Nutrition Rhoads Research Foundation for her work on the connection between angiotensin and insulin in burn trauma.

Often in burn trauma, insulin resistance is increased. The study investigates the crosstalk between angiotensin—a hormone that raises blood pressure—and insulin to regulate glucose levels and aid in treatment of victims of burns.

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.