Frontiers (Fall 2008) - Focus on Research: How it Improves Patient Care

University of Tennessee Medical Center
University of Tennessee Graduate School of Medicine

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At UT Graduate School of Medicine in Knoxville, we’re conducting medical research, some of which cannot be accomplished anywhere else. Through collaborations, our world-class researchers and faculty physicians have access to equipment and treatments that often mean UT is the first to move breakthroughs from labs to patient care. Not just state-of-the-art. One-of-a-kind.

We’re building a healthier world beginning right here in Tennessee. And that’s work we can all appreciate.

CONTRIBUTION

Finding tomorrow’s treatments, today.
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Dear Alumni and Friends,

As the region’s only academic medical center, we are proud to provide the widest array of comprehensive services for our patients and their families. Our focus on patient care is complemented by focused research to help us learn more about diseases and to improve the delivery of care.

In this issue of Frontiers, we highlight examples of research being conducted at the University of Tennessee Medical Center. Our researchers are making great strides and are learning more and more about cancer, Alzheimer’s disease, the effects of anesthesiology, and other topics in keeping with our strategic focus. You will see research does not always take place in a laboratory and is just as likely to be found at the bedside. Our patients benefit from the skill and expertise of health professionals who are constantly asking the question “why”?

True academic medical centers bring together outstanding patient care, challenging clinical training, and stimulating research and we are proud to provide these advantages for the patients we serve from throughout East Tennessee. I hope you enjoy this issue and the opportunity to learn more about the importance of research and how its many shapes and forms impact our lives and the care we provide for our patients.

Sincerely,

Joseph R. Landsman, Jr.
President and Chief Executive Officer
University Health System, Inc.

The Graduate School of Medicine combines with the University of Tennessee Medical Center to create a very active academic medical center. As such, our faculty have direct responsibility for the education of future physicians/dentists and for biomedical and health service research. This, of course, is in addition to providing the best professional medical care through their clinical practices. All of these responsibilities are linked in our academic medical center to serve our community, as well as in the state of Tennessee and the nation. This issue of Frontiers showcases several of our research efforts, many of which have gained international recognition.

Our faculty physicians and researchers are at the forefront of medical discovery in areas such as cancer, neurological and vascular diseases, pain management, imaging, and health literacy. We want to thank our many collaborators and business partners who help us meet our mission of providing the most comprehensive diagnostic and treatment options.

On a personal note, I want to congratulate our faculty for their multidisciplinary collaboration bringing us to the forefront of medical care and research. It is our unique academic medical center that ensures our community that it will receive the most advanced level of care possible.

Sincerely,

James J. Neutens, PhD, FASHA
Dean
UT Graduate School of Medicine
The Importance of Medical Research

One of the great benefits the University of Tennessee Medical Center provides to our community is serving as a source of new discovery that leads to improved medical treatment, even before it’s readily available to the rest of the world. We take this responsibility very seriously.

The beginning of the modern era of medicine was sparked by the idea that medical treatment of disease should be based on well-designed research. With all the diseases known to humankind, it’s clear that this is a huge undertaking none-the-less. Everyone deserves medical treatment based on good science, not guesswork.

Research processes used today fall into three major divisions: basic research (often called bench research), translational research, and clinical research. Here is a general overview of each:

**Basic Research** is used to make discoveries in a controlled environment, frequently in a laboratory setting or on a computer. It’s where basic understanding of the medical issue at hand unfolds.

**Translation Research** takes the discoveries from the basic research setting and “translates” them into methods for treatment or diagnosis of specific diseases and determines if the research should progress to the larger clinical setting.

**Clinical Research** takes the discoveries to clinical application. It starts with very basic interventions, which lead to larger and more complex research designs that ultimately define the standard of treatment.

Throughout the entire process, strict rules and continuous oversight control the way research is carried out. All clinical research must be approved by the Institutional Review Board, a committee of experts, whose primary role is to protect the welfare and safety of research participants. As the region’s only academic medical center, the University of Tennessee Medical Center and UT Graduate School of Medicine are proud to make our contribution to the progress of medical care through research. In this issue of *Frontiers*, we share with you some of what we’re doing in all three areas—basic, translational, and clinical research. Our physicians and researchers are committed to working together to bring new and more effective treatments to the patients we serve. It is who we are.

*Steven R. Ross, DPh, MS*

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“I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I
I took the one less traveled by,
And that has made all the difference.”

Robert Frost
Women develop both cardiovascular disease and peripheral arterial occlusive disease at older ages than men. The difference in this onset, it was thought, is due to the protective effect of female estrogen hormones until menopause. That is why many researchers and physicians expected hormone replacement therapy (HRT) to benefit women in helping to prevent cardiovascular events. But recent clinical trials indicate that the protective effect of HRT works only for women who start taking the therapy before they have a cardiovascular procedure, such as an endovascular stent. Recent studies by the Vascular Research Laboratory at the University of Tennessee Medical Center confirm that postmenopausal women who receive HRT after vascular reconstruction procedures face a greater risk that these reconstructions will fail.

Oscar Grandas, MD, an assistant professor of surgery at UT Graduate School of Medicine and the scientific director of the Vascular Research Laboratory, has taken these clinical findings to the basic science lab to answer the fundamental question of how HRT affects vascular functions and causes an altered response of the vascular wall. The findings suggest that women who are taking HRT have a greater chance of developing intimal hyperplasia, a form of vascular wall thickening, than women not on the drug therapy. This is believed to be because the HRT modifies the balance of the enzymes that regulate the deposition of proteins and the movement of cells within the vascular wall layers, which causes thickening on the inside structure of the vessel. When the inside of the vessel is thickened, it can close off and lead to stent or bypass graft failure.
“This bench study deals with not only what happens to the vessels as a result of drug therapy, but also how the timing of when a woman begins HRT affects her outcome,” says Grandas. “Understanding how the cells inside the vascular system react to hormone exposure will lead to knowledge of how to better care for our patients.”

The Vascular Research Laboratory at the University of Tennessee Medical Center is known as a leader in developing treatments to enhance patients’ lives. The research done here takes common clinical problems to the laboratory and returns large contributions to the medical community and its knowledge base. Scott Stevens, MD, director of endovascular surgery and a professor of surgery at UT Graduate School of Medicine, says, “One of the most important things about vascular research is being able to take what we learn and apply it clinically to help our patients at the Heart Lung Vascular Institute.”

Scott Stevens, MD

“The picture on the left shows a normal carotid artery, and the one on the right shows a carotid artery exhibiting intimal hyperplasia, a form of vascular wall thickening.”

Heather Grieve

Hormone Replacement Therapy (HRT) modifies the enzyme balance that regulates protein deposition and cell movement within the vascular wall layers. This protein is called matrix metalloproteinases (MMPs). MMPs allow cells in the outer layers to move into the inner layer of the blood vessel, which causes thickening and eventually narrowing of the blood vessel. The graph below shows the effect of hormone exposure on vascular smooth muscle cells, with the resulting increase in the activity of the MMP’s protein, which UT researchers believe play a central role in the unexpected unfavorable effect of HRT in women and vascular disease.

Levels of MMP-2 Activity

The picture on the left shows a normal carotid artery, and the one on the right shows a carotid artery exhibiting intimal hyperplasia, a form of vascular wall thickening.”
Curiosity. Answering the “what ifs.”

A drive for improvement. These are the qualities shared by most of the physicians in the Department of Anesthesiology who conduct research. Certainly they do their jobs very well. They provide the best possible care for patients from the moment the patients are admitted for surgery until they leave the Medical Center; they provide services for more than 18,000 procedures during surgeries; and they provide medical management for many other patients throughout the University of Tennessee Medical Center.

But our anesthesiology team doesn’t stop there. They simply cannot. Their medical curiosity and high ideals won’t let them. So they also conduct continual research in how to improve patient care and how to advance the science of anesthesiology beyond current standards. In our academic medical center setting, this groundbreaking research thrives—and many times, because it is conducted locally, our patients benefit first.

“I do research simply because I have clinical and basic science questions for which I would like answers,” says Robert Craft, MD, UT Graduate School of Medicine associate professor and vice chair of anesthesiology.

“I believe academic physicians should be the ones attempting to answer these questions, since we have the resources at this academic medical center and graduate school of medicine. We also have the responsibility to educate resident physicians on the methods of investigation.”

The anesthesiology research lab supports the anesthesiology faculty physicians and resident physicians who are conducting research on pain and nausea management, blood clotting, cardiovascular disease, the effects of anesthesia, and more.

“**We help the physicians find answers.**

Roger Carroll, PhD
Director of Anesthesiology Research

“Our lab provides the bench laboratory skills and equipment to facilitate clinical research projects,” says Roger Carroll, PhD, a professor and the director of Anesthesiology Research. “We also advise on the design and execution of proposed research projects and assist with the final statistical analysis. We help the physicians find answers.”

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**Examples of Anesthesiology Research**

**Blood-clotting**

Hemorrhage associated with blood-clotting disorders, or coagulopathy, is a major cause of death and complications in trauma patients. Russ Langdon, MD, Roger Carroll, PhD, and their team are studying whether the rigidity of blood during blood clotting affects the fatality rate and how platelets in the blood during trauma can affect the need for or the risks of blood transfusion. Their study could help physicians in the Emergency Department assess coagulopathy and other disorders at an early stage during treatment of a trauma, and could indicate more effective interventions.

**Cardiovascular Disease**

Using data from previous studies on aspirin resistance, Robert Craft, MD, Jack Chavez, MD, and other investigators are testing the correlation of aspirin resistance in patients with a history of cardiovascular disease and the formation in their blood of an agent that constricts blood vessels. This study could help physicians more effectively treat patients who have cardiovascular disease but also experience aspirin resistance.
Anesthesia

An upcoming study, headed by Robert Craft, MD, will use positron emission tomography (PET) technology to look at the molecular and anatomical targets of anesthesia. A better understanding of the actions of anesthesia can help anesthesiologists control and increase the success of its use. This study will also provide information about the origin of human consciousness, which in turn could help explain disturbances of consciousness such as coma, autism, and schizophrenia.

Another progressive study on anesthesia is helping physicians safely use anesthetic agents during upper-gastrointestinal endoscopies and colonoscopies. Physicians Stephen Patteson, MD, Jerry Epps, MD, and others used brain-wave function to determine the depth of sedation achieved by using certain anesthetic agents for endoscopies. They found that the level of sedation is consistent with general anesthesia and that for maximum patient safety, medical professionals with formal anesthesiology training should administer the anesthetic during endoscopies.

(From front) Stephen Patteson, MD; Robert Craft, MD; Jack Chavez, MD; and Roger Carroll, PhD, gather in the Anesthesia Research Facility where they and others conduct clinical research.
Research Collaborations: Focused on the Goal

Economic woes are affecting many areas of life. From gas and food prices to the costs of mortgage and college loan repayments, consumers and businesses are finding ways to ease the pinch. Partnerships with industry are one solution that allows our academic medical center to stay focused on the goal—ground-breaking research results that help improve lives.

As nonprofit institutions and government agencies such as the National Institutes of Health (NIH) reduce research funding to respond to economic conditions, companies and universities are turning to joint collaborations to continue important medical and industrial research.
For-profit companies that make medicines and medical equipment are finding it increasingly important to gain access to the top-notch scientists at academic medical centers. Likewise, institutions housing research expertise are finding that corporate partnerships can provide financing that allows globally significant medical research to continue revealing answers important to us all.

“Partnering with industry allows the scientific brainpower of our academic medical center to blend with the business firepower of industry, a major advantage to patients seeking the latest treatments and newest medical equipment,” explains vascular surgeon Scott Stevens, MD, a researcher and professor. “You see, once the Federal Drug Administration (FDA) approves a new medical device, the manufacturer will seek out those institutions known to have a strong track record in that specialty and can also adhere to the very stringent guidelines set by the FDA for the use of the new device. This is one reason why the University of Tennessee Medical Center can provide treatments for people with vascular disease that are not available anywhere else in the region.”

The University of Tennessee Graduate School of Medicine is home to many such research collaborations, which inevitably bring cutting-edge treatments and technologies to the Medical Center. Researcher Jonathan Wall, PhD, explains the process in this way: “Companies are much more likely to establish clinical trials at institutions that have helped with the science from the beginning. First, a company making a compound or device asks us to use our science to investigate why and how the product works. Once that is determined and the FDA approves the use of the product, companies are likely to return to the institution to perform the subsequent clinical trials. That’s what makes having an academic medical center in our area so very important. It gives our community access to cutting-edge equipment, treatments, and diagnostic techniques.”

Thanks to research collaborations with Siemens, the PET/CT scanners at the University of Tennessee Medical Center are state of the art. “We absolutely have one of the best clinical imaging platforms in the world,” says Wall.

Very high FDA standards and protocols must be met before any new devices, equipment, or treatments can be used, and patients must request and then agree to their use in treatment.

Brian J. Daley, MD, a professor, researcher, and surgeon, explains why companies seek partnerships with the University of Tennessee Medical Center. “All our research is rigorously controlled, government-monitored research. Companies know we provide a medically sound setting for a safe, productive, responsible project.” Fostering relationships between the Medical Center and industry can mean the East Tennessee community is first in line to access the latest FDA-approved therapeutics. “The Medical Center is a national leader in the endovascular field and is known for the very fine treatments done here,” says Stevens. “Companies know we have expertise and processes already in place that they cannot cost-effectively pull together quickly, and they contact us to begin approved treatments here.”

(From left) Researchers John H. Dougherty, MD; David Townsend, PhD; Jonathan Wall, PhD; Scott Stevens, MD; and Valerie Berthelier, PhD
Examples of Collaborative Research

Alzheimer's Vaccine – Patients from across the country may soon be traveling to the University of Tennessee Medical Center to receive the first monoclonal antibody vaccine that might reduce the debilitating effects of Alzheimer's disease. John Dougherty, MD leads one of the elite group of centers worldwide that is evaluating the latest antibody therapy for the treatment of Alzheimer's.

Amyloidosis Diagnosis and Treatment Response – UT Graduate School of Medicine researchers are working with a company to develop noninvasive methods to determine whether a patient has amyloidosis, a condition that occurs in a significant number of patients with rheumatoid arthritis. Using some of the world's most sophisticated imaging equipment, the researchers are helping the world of medicine understand and diagnose the disease and monitor patients' response to therapy.

Aortic Aneurysm: Repair and Pressure Monitoring – Partnering with Oak Ridge National Laboratory (ORNL) and CarioMems, a Georgia Tech start-up company, the University of Tennessee Medical Center's endovascular research team used the world's most powerful computing programs to study images of aneurysms and determine the rupture risk caused by pressure in weakened, ballooned areas in blood vessels. Armed with this information, Medical Center physician researchers used pressure-sensor technology designed for military jet engines to help craft a miniature radio chip that can be embedded into a vessel during a stent procedure. In subsequent office visits, a wandlike device outside the body can be used to read the vessel pressure inside the body.

Biodistribution Studies – A pharmaceutical company, Advion, has worked over the last 12 months with UT Graduate School of Medicine and David Townsend, PhD and Jonathan Wall, PhD assisting them by tagging novel compounds with radioactive molecules and monitoring these with PET/CT imaging to determine where the molecules distribute in the body.

Clotting-Agent Safety – David Cassada, MD and a team of researchers from the University of Tennessee Medical Center's Department of Surgery are helping substantiate the safety of a company's topical preparation to quickly clot blood during spinal and vascular surgery. This same team helped research a sealant that "glues" vessels together following bypass grafting surgeries. The product is now on the market and used in medical facilities worldwide.

Huntington's Studies – In the UT Graduate School of Medicine Conformational Diseases and Therapeutics Research lab, Valerie Berthelier, PhD is homing in on Huntington's disease, a lethal condition that results from the degeneration of brain cells. Working with ORNL's Neutron Scattering Science division, she is focusing on identifying molecules created as the disease progresses, a study that may result in new therapies.

“Companies know we provide a medically sound setting for a safe, productive, responsible project.”
Brian J. Daley, MD
Institutional Review Board

Ensuring Safe and Ethical Research

All research studies using human volunteers must follow stringent federal regulations that require a review by an Institutional Review Board (IRB) before the study is approved. The IRB Committee, comprised of physicians, pharmacists, scientists, researchers, and non-scientific community representatives, reviews research protocol to ensure protections are in place for people volunteering in the study.

We thank the current and past members of the IRB at the UT Graduate School of Medicine who have given countless hours to ensure patient safety and promote life-changing research. Current members include:
If asked to explain the word “neuroscience,” most of us would likely use the words “brain science” somewhere in our simple description. However, as you might guess, this branch of the life sciences is much more complex, concerning itself with the anatomy, physiology, biochemistry, or molecular biology of the entire nervous system, including the brain, spinal cord, and network of sensory cells throughout the body.

Scientists are fascinated by neuroscience research, in particular studies focused on several well-known diseases—Alzheimer’s, Huntington’s, Parkinson’s. Each of these diseases can significantly impact quality of life, and researchers at the University of Tennessee Medical Center’s Cole Neuroscience Center and UT Graduate School of Medicine are making discoveries that can detect, and sometimes delay, their onset.

John H. Dougherty, MD conducts research on Alzheimer’s disease that may affect 15 million people by 2050.
Research in fighting these crippling diseases starts at the smallest level: the molecule. A research team led by George Kabalka, PhD, professor, Robert H. Cole Chair in Neuroscience, and director, Basic Research, Department of Radiology, UT Graduate School of Medicine, builds molecules that have never existed before to target the causes of these diseases.

“We work with physicians and biologists to discover molecules that naturally target organs or diseases,” says Kabalka, “and with that knowledge, we can envision how to put a short-lived radioisotope into the molecule, which travels straight to the tumor or diseased area within the body.”

That’s when imaging, namely positron emission tomography (PET), becomes invaluable.

“Using modern medical imaging, physicians can evaluate the activity level of the disease, which enables them to both diagnose and monitor the disease prior to, during and after treatment,” says Kabalka. “We’ve already successfully used this technology in patients, and with additional medical funding, our research can continue to expand.”

The molecules created in Kabalka’s labs are used for research in oncology and amyloid diseases and in the fight against Parkinson’s and Alzheimer’s.

Patients with Parkinson’s disease have a decrease in the activity of neuroreceptors in the brain, leaving victims incapable of initiating or controlling movement. Kabalka’s team has created isotopically labeled neuroreceptor molecules that travel to the neuroreceptors, and using PET imaging, can show physicians the activity—or lack of activity—in the brain.

Similar research with promising results is being conducted for Alzheimer’s.

Alzheimer’s disease is a condition that cripples the ability of millions of older Americans to think and manage their lives. However, says John Dougherty, MD, director of the Cole Neuroscience Center, because of the soaring numbers of people with the disease, the search for a cure for Alzheimer’s promises breakthroughs in patient care across the board.

“It’s a disease that has great impact, because people live for a long time with it and they slowly get worse,” says Dougherty. “Because the population of people 85 and older is going to grow tremendously, by the year 2050 there will be 14 or 15 million people with Alzheimer’s disease.”

This is why researchers at the Cole Neuroscience Center, in the UT Graduate School of Medicine Human Immunology and Cancer Program run by Alan Solomon, MD, in the UT Graduate School of Medicine Molecular Imaging and Translational Research Program headed by David Townsend, PhD, and in Kabalka’s group, are leading several research initiatives focused on Alzheimer’s and other neurological disorders.

One of the largest research efforts in neuroscience is just getting under way. A $300 million study of the use of monoclonal antibodies, disease-fighting agents reproduced from a single cell,
to battle Alzheimer's disease is enrolling patients at some 100 sites across the United States, including the University of Tennessee Medical Center. Initially approved for the treatment of about 16 patients in the study, the Medical Center could eventually contribute data on up to 50 patients, Dougherty says.

Researchers believe Alzheimer's disease affects patients' brains through clusters of protein fragments, known as amyloid. It is believed these clusters accumulate and attract other proteins to form abnormal plaques in brain tissue, which cause degeneration. Monoclonal antibodies engineered to neutralize amyloid have been proved to work in laboratory studies.

“In laboratory models,” says Dougherty, “the monoclonal antibody produces a spectacular response. It sucks the amyloid out of the brain and improves memory.” Early clinical tests were so promising that the FDA approved moving forward with the multi-center trial of the monoclonal antibody.

Solomon's group at the Graduate School of Medicine has been researching amyloid-related diseases—including Alzheimer's, Parkinson's, Lou Gehrig's, Huntington's, type 2 diabetes, amyloidosis, and others—for decades. One recent study reported a link between foie gras prepared from goose or duck liver and the type of amyloid found in arthritis or tuberculosis; another identified a structurally unique protein in a rare dental tumor that may assist in targeting therapy for other cancers such as breast, lung, and gastrointestinal.

Work by Brian O'Nuallain, PhD, a member of Solomon's team, may also be useful in delaying Alzheimer's disease. He discovered an intravenous antibody product that is used as antibody-replacement therapy for patients with autoimmune disease contains naturally occurring human antibodies that bind to A-beta, the protein fragment believed to be the chief culprit in Alzheimer's disease. Antibodies are proteins that attach to foreign proteins and remove or neutralize them.

Dougherty says success in the treatment of other neurological disorders, such as Parkinson's disease, could be models for the fight against Alzheimer's. “The new mantra in Alzheimer's disease is prevention and delay,” he says. “If you can put off the symptoms of Alzheimer's disease three to five years, you can decrease the number of people with the disease by half.”

And prevention and delay of these diseases ultimately improves your quality of life—for life.

Exercise Your Brain

It is always good to exercise your brain. Performing daily brain tests will help keep your brain active and healthy. Try this brain test now:

1. Say the days of the week backwards, then in alphabetical order.

2. Say the months of the year in alphabetical order. Easy? Well, why don't you try doing so backwards, in reverse alphabetical order.

3. Find the sum of your date of birth, mm/dd/yyyy. Want more exercise? Do the same with friends' and relatives' date of birth.

4. Name two objects for every letter in your complete name. Work up to five objects, trying to use different items each time.

5. Wherever you are, look around and within two minutes, try to find 5 red things that will fit in your pocket, and 5 blue objects that are too big to fit.

Harriet Vines, PhD

Illustration of the areas of the cerebral cortex commonly affected by Alzheimer's disease.
As an organization that relies heavily on private donations to stay on the cutting edge of technology and to fund innovative treatments and programs, the University of Tennessee Medical Center has been fortunate to have a long-time friend and financial supporter in the Robert H. and Monica M. Cole Foundation.

Following a diagnosis of Parkinson’s disease in 1967, Bob Cole was moved to find a way to support research and treatment methods for others with the same illness. The result was an initial $1 million endowment, made in 1968, which established the Cole Foundation. Support of the University of Tennessee Medical Center has continued over the years.

In 1994 a grant was provided to enable the Graduate School of Medicine to create the Cole Foundation Endowed Chair of Neuroscience. Its first professor, George W. Kabalka, PhD, is widely recognized as a leader in neuroscience research and whose discoveries resonate far beyond the halls of the Medical Center.

The Medical Center’s Brain and Spine Institute, too, has benefited tremendously from the Cole Foundation’s support, receiving a generous grant that led to the creation of the Cole Neuroscience Center. The center is dedicated to helping those who suffer from neurological conditions such as Alzheimer’s, epilepsy, Parkinson’s, and multiple sclerosis.

The Cole Foundation has also actively supported the University of Tennessee Medical Center Pastoral Care Program, which focuses on the physical, spiritual, and emotional aspects of healing for both patients and their loved ones. Adding to the list, the Medical Explorations program, a mentoring program for young people interested in healthcare careers, has received financial support from the foundation.

For 40 years the Cole Foundation has remained committed to its original mission of helping others. The Cole family continues to be active in the foundation’s management, and several of its members sit on the board of directors, providing generous guidance to the many programs the foundation supports. Through the continued support of the Cole family and the Cole Foundation, researchers and physicians at the University of Tennessee Medical Center and UT Graduate School of Medicine have access to resources that inspire discoveries and offer so many new hope and improved quality of life.

Mrs. Monica M. Cole with a portrait of her husband, Robert H. Cole.
There's an innovative concept in medicine known as translational research," says Eric Carlson, DMD, MD, chairman of the Department of Oral and Maxillofacial Surgery at the University of Tennessee Medical Center. “Translational research involves taking a basic science concept and converting it to the clinical level, so something that's discovered in the lab can translate into a benefit for patient care.”

In the field of cancer research, clinicians at the University of Tennessee Medical Center, such as Carlson, are teaming up with colleagues in the basic sciences. And the results have been impressive.
Carlson says he works with “a world-class team in molecular imaging and translational research. When I came here six years ago, one of my expressed intentions was to collaborate with as many basic science researchers in the Medical Center as possible. I’ll develop a clinical idea, and they put it into scientific language. This represents a perfect collaboration between a clinician and a researcher. That’s one of the elements of my career that I thoroughly enjoy.”

These translational collaborations have generated several fruitful lines of research. With physicist David Townsend, PhD, director of the UT Molecular Imaging and Translational Research Program, Carlson is studying the use of PET/CT imaging in staging oral and head-and-neck cancers.

In cancers of the oral cavity, metastasis usually occurs first in the lymph nodes on the side of the neck closest to the primary cancer. The dilemma for physicians, says Carlson, is that in many of these cases, the cancer metastasizes to the nodes in the neck that can’t be detected by clinical exams or imaging studies.

PET/CT, a pairing of positron emission tomography (PET) and computed tomography (CT), has rapidly become the imaging tool of choice in such cases. It was devised 10 years ago by Townsend and Ron Nutt, PhD, then CEO of CPS Innovations, a PET company based in Knoxville that is now part of Siemens Molecular Imaging.

The combination of CT, which images the anatomy and location of suspicious growths or enlarged lymph nodes, and PET, which identifies abnormal or suspicious metabolic activity that can be characteristic of cancer, helps clinicians identify and localize cancerous tissues. Carlson and other clinicians rely on PET/CT imaging because of the images’ quality and their usefulness to clinicians in determining the best way to fight cancer.

This continued research increases the likelihood that the PET/CT device and molecular markers will continue to be improved. Because surgeons routinely remove lymph nodes in the neck, the ongoing study allows comparison of the lymph nodes removed during surgery with the preoperative images as a check on those images’ accuracy. While PET/CT is important for effective...
diagnosis and treatment (“I’m at the point where I don’t feel comfortable treating a patient with head and neck cancer without PET/CT,” Carlson says), recent research led by Carlson, Townsend, and co-workers found that PET/CT alone detected only about 30% of metastases in those patients. These data reveal an opportunity to improve the PET/CT procedure—one that Carlson and Townsend are actively pursuing in their research.

Carlson is also collaborating in other translational research endeavors, including work with David Gerard, PhD, in studying the connections between the genetic makeup of specific cancer cells and the way they behave biologically. “The underlying fact,” says Carlson, “is that cancer is a genetic disease and the genome creates a certain behavior.” Using a procedure called complimentary DNA (or cDNA) microarray analysis, he says, “we’re going to take the last 100 or 200 cancers I’ve removed and examine the genetics of those cancers. Dr. Gerard will try to predict the biologic behavior, which I will know (the biologic behavior) based on the follow-up of these patients. Results of this study may lead to examining the genome of a cancer at the time of the initial biopsy, resulting in the ability to predict the behavior of that cancer. Therapy may be adjusted accordingly in a proactive fashion.”

Translation Please…

Eric Carlson, DMD, MD, (third from left) with the surgical team.
Townsend has partnered with other clinicians too, including recent work with Wahid Hanna, MD, chief of the Medical Center’s oncology division, on the use of PET/CT to assess response to chemotherapy as early as possible in patients with non-small-cell lung cancer.

“Traditionally,” says Hanna, “we give three cycles of chemotherapy—the cycles would each be about three weeks long. Then we would wait two weeks and evaluate the response. Unfortunately, if we do that and we discover the patient has not responded, we’ve wasted valuable time.” If the patient doesn’t respond to one chemotherapy regimen, another may be tried, but as the cancer progresses the patient’s condition may weaken. “Sometimes it’s a race between us and the cancer,” Hanna says.

In a study of 18 patients, Hanna reports that PET/CT imaging was able to accurately predict responses to chemotherapy as early as just three weeks into treatment. He’s now testing a larger group of 50 patients to confirm those results. If the results hold, PET/CT might be used to fine-tune chemotherapy early in the treatment.

“There are now approximately 15 million people living in this country who have survived cancer. They’re survivors because of the research that occurred over the past 50 years.”

John L. Bell, MD

Because this kind of research improves patient outcomes, it has long been part of what the Medical Center is all about. “We do the most research of any medical facility in town,” says Barbara Munsey, the center’s clinical trials manager. “In an academic medical center like ours, it’s a major part of our mission. It’s understood that we’re doing research for the greater good.”

“Basic science, clinical and translational research allows us to identify ways to diagnose cancers earlier and to treat people with less toxicity and fewer side effects,” says John L. Bell, MD, director of the University of Tennessee Medical Center’s Cancer Institute. “There are now approximately 15 million people living in this country who have survived cancer. They’re survivors because of the research that occurred over the past 50 years.”

New Discovery

The discovery of a structurally unique protein in jaw tumors by scientists at the University of Tennessee Graduate School of Medicine’s Human Immunology and Cancer Program could have important implications for the diagnosis and treatment of certain diseases.

An article published in the May/June 2008 issue of Molecular Medicine by a team headed by Alan Solomon, MD, reported the discovery of odontogenic ameloblast-associated protein (ODAM). The team found that amyloid associated with a rare jaw tumor was composed of ODAM fragments, the first evidence of expression of the unusual protein.

Subsequently the team made antibodies to ODAM, as well as recombinant ODAM, and serendipitously found the molecule was expressed not only in jaw tumors but also by other epithelial cancers, including breast, gastrointestinal, and lung. Patients with these malignancies were also found to have significant titers of anti-ODAM antibodies in their blood.

Follow-up efforts, says Daniel Kestler, PhD, a lead researcher in the study, “are directed toward delineating why ODAM is expressed in these cancers, as well as the function of this protein, its role in tumorigenesis, and especially whether it can serve as a novel tumor biomarker.”

John Yates
The University of Tennessee Medical Center has long been known for its commitment to advancing the science of medicine. It’s not just part of our vision, it’s part of our culture. From nurses to pharmacists, medical professionals who directly care for patients are actively involved in research aimed at providing better treatments for our patients. But this research doesn’t take place in a laboratory with test tubes and microscopes. It takes place at the bedside, and new discoveries are made each day.

An excellent example of this bedside approach to research involves the Department of Pharmacy, where staff members often look for ways to improve patient care through investigational, scientific methods. In many medical settings, patient falls are the most common causes of injuries. Patients sometimes try to leave their bed unassisted when they are unable and become injured as the result of a fall.

Oftentimes, the patients are elderly, but some pharmacists noticed a number of falls involving patients younger than 65. A great deal of national research linked medication to falls in elderly populations; however, none existed for those 65 years of age and younger. Therefore, a team of pharmacists at the Medical Center...
decided to study the link between medications and falls for this younger population. They found that patients who fell were taking more medications than those who didn’t fall and identified two types of medications: benzodiazepines and anticonvulsants. The medications caused an increase in the risk for falls. Because of this study, caregivers now have another means of identifying those patients who are at a greater risk for falling. This, in turn, provides better care.

The pharmacy department has also been working on evaluating standards related to the medication distribution system. Many hospitals use automated systems to provide safe, accurate and efficient medication distribution on each unit. The systems, however, need some improvements to ensure safe transfer of medications and information when patients are moved from one area of the hospital to another. At the University of Tennessee Medical Center, a patient-specific management software, never before used in the country, was tested and shown to enhance patient safety and medication efficiencies.

“The great thing about an academic medical center like the University of Tennessee Medical Center is that employees feel they can take part in improving the standard of care applied throughout the country,” says Director of Pharmacy, Kim Mason.

In the Neonatal Intensive Care Unit, a study is underway to evaluate different types of phototherapy devices. Phototherapy is commonly used in infants to help the body process bilirubin, which causes jaundice. The Medical Center uses three types of phototherapy devices, but the medical community as a whole has not conducted any research to evaluate the effectiveness of one type of light over another.

As part of the research, patients consenting to the study are monitored to find out which phototherapy devices are the most effective and have the fewest side-effects. It is expected that this much-needed study will lead to more effective ways of treating babies with high bilirubin levels. Results of this study will soon be published so healthcare providers around the world can benefit from the work being done here at the University of Tennessee Medical Center.

In each of these examples, it is clear that research isn’t necessarily carried out in a laboratory. It can be performed in a variety of ways, but regardless of where it takes place, the driving force behind the research performed at the Medical Center is still the same. It is… and always will be… the desire to improve our patients’ standard of care and quality of life.
Patient care at the University of Tennessee Medical Center takes place in Knoxville, but the healthcare expertise of our physicians and scientists spans the globe. Through peer-reviewed scientific publications, UT Graduate School of Medicine experts help treat patients and shape ongoing research across the world.

Publications in 2007-08 that focused on our primary clinical areas include:

**Brain/Spine/Neuroscience**

**Amyloid: The Journal of Protein Folding Disorders 2008**
- Charles Murphy, Daniel Kestler, James Foster, Shuching Wang, Sallie Macy, Stephen Kennel, Eric Carlson, John Hudson, Deborah Weiss, Alan Solomon
  “Odontogenic Ameloblast-Associated Protein Nature of the Amyloid Found in Calcifying Odontogenic Tumors and Unerupted Tooth Follcles”

**Biochemistry January 9, 2007**
- Ronald Wetzel, Shankaramma Shivaraprasad, Angela Williams
  “Plasticity of Amylloid Fabrics”

**Biochemistry February 6, 2007**
- Brian O’Neill, Anton Allen, Stephen Kennel, Deborah Weiss, Alan Solomon, Jonathan Wall
  “Localization of a Conformational Epitope Common to Non-Native and Filibrin Immunoglobulin Light Chains”

**Brain Pathology April 2007**
- Mahlon Johnson, Charles Stevenson, Reid Thompson, James Atkinson, Phillip Boyer
  “December 2006: 31-Year-Old Woman With Hemiparesis”

**Proceedings of the National Academy of Sciences of the United States of America June 1, 2007**
- Alan Solomon, Tina Richey, Charles Murphy, Deborah Weiss, Jonathan Wall, Gunilla Westermark, Per Westermark
  “Amyloidogenic Potential of Folate Gras”

**Cancer**

**Acta Cytologica 2007**
- Lisa Duncan, Sanjivini Jacob, Steven Atkinson
  “Fine Needle Aspiration Cytologic Findings of Micropapillary Carcinoma in the Lung: A Case Report”

**Cancer Cytopathology February 25, 2008**
- Lisa Duncan, Sanjivini Jacob, Elizabeth Hubbard
  “Evaluation of p16(INK4a) as a Diagnostic Tool in the Triage of Pap Smears Demonstrating Atypical Squamous Cells of Undetermined Significance”

**Journal of Biological Chemistry August 1, 2007**
- Romaine Fernando, James Foster, Amber Bible, Anders Strom, Richard Pestell, Mahadev Rao, Arnold Santon, Seung Joon Baek, Kiyoshi Yamaguchi, Robert Donnell, Maria Cekanova, Jay Wimalasena
  “Breast Cancer Cell Proliferation Is Inhibited by BAD: Regulation of Cyclin D1”

**Journal of Oral and Maxillofacial Surgeons 2007**
- J. Michael McCoy and Eric Carlson
  “Surgical Management of Odontogenic Tumors”

**Journal of Oral and Maxillofacial Surgery September 2007**
- N. Fazil Erdem, Eric Carlson, David Gerard, Albert Ichiki
  “Characterization of 3 Oral Squamous Cell Carcinoma Cell Lines With Different Invasion and/or Metastatic Potentials”

**Journal of Oral and Maxillofacial Surgery May 2008**
- N. Fazil Erdem, Eric Carlson, David Gerard
  “Characterization of Gene Expression Profiles of 3 Different Human Oral Squamous Cell Carcinoma Cell Lines With Different Invasion and Metastatic Capacities”

**Journal of Psychosocial Oncology 2008**
- Derek Hopko, John Bell, Maria Armento, Sarah Robertson, Melissa Hurn, Nicole Wolf, Christine Mullan
  “The Phenomenology and Screening of Clinical Depression in Cancer Patients”

**Molecular Medicine April 20, 2008**
- Daniel Kestler, James Foster, Sallie Macy, Charles Murphy, Deborah Weiss, Alan Solomon
  “Expression of Odontogenic Ameloblast-Associated Protein (ODAM) in Dental and Other Epithelial Neoplasms”

**Health Literacy: Patient and Physician Communications**

**American Journal of Health-System Pharmacy January 1, 2008**
- Steven Roskos, Lorraine Wallace, Barry Weiss
  “Readability of Consumer Medication Information for Intranasal Corticosteroid Inhalers”

**Diabetes Technology and Therapeutics February 2008**
- Lorraine Wallace, Amy Keenum, Steven Roskos, Richelle Koopman, Kristie Young
  “Blood Glucose Monitor Quick Reference Guides: Are They Suitable for Patients?”

**Health Place October 24, 2007**
- Lorraine Wallace, Jennifer Devoe, Ian Bennett, Steven Roskos, George Fryer Jr.
  “Perceptions of Healthcare Providers’ Communication Skills: Do They Differ Between Urban and Non-Urban Residents?”

**Journal of General Internal Medicine November 2007**
- Lorraine Wallace, Jennifer Devoe, Edwin Rogers, Maticarman Malagom-Rogers, George Fryer Jr.
  “The Medical Dialogue: Distinguishing Differences Between Hispanic and Non-Hispanic Whites”

**Journal of Lower Genital Tract Disease October 2007**
- Kimberly Forte, Nikka Zie, Lorraine Wallace
  “In My Own Words: Misunderstanding of Pap Smears and Colposcopy Among Appalachian Women”

**Journal of Opioid Management November-December 2007**
- Lorraine Wallace, Amy Keenum, Steven Roskos
  “Comprehensibility and Readability of Patient Self-Administered Opioid Assessment Screening Tools”

**Journal of Pain March 21, 2007**
- Steven Roskos, Amy Keenum, Lindsay Newman, Lorraine Wallace
  “Literacy Demands and Formatting Characteristics of Opioid Contracts in Chronic Nonmalignant Pain Management”

**Journal of Pain June 12, 2007**
- Lorraine Wallace, Amy Keenum, Steven Roskos, Kelly McDaniel
  “Development and Validation of a Low-Literacy Opioid Contract”

**Journal of Surgical Research June 15, 2007**
- Lorraine Wallace, David Cassada, Edwin Rogers, Michael Freeman, Oscar Grandas, Scott Stevens, Mitchell Goldman
  “Can Screening Items Identify Surgery Patients at Risk of Limited Health Literacy?”

**Patient and Education Counseling January 4, 2008**
- Lorraine Wallace, Amy Keenum, Steven Roskos, Gregory Blake, Strant Colwell, Barry Weiss
  “Suitability and Readability of Consumer Medical Information Accompanying Prescription Medication Samples”

**Heart/Lung/Vascular**

**British Medical Journal Publishing Group 2007**
- Jose Aycinena and Brian Daley
  “Acute Pancreatitis”

**Circulation 2007**
- Bret Rogers
  “Dysynchrony Transmural Echocardiogram as a Predictor of Response to Cardiac Resynchronization”
Journal of Cardiothoracic Surgery
January 24, 2008
Jeffrey Everett, Harold Burkhardt
“Coronary Artery Aneurysm: Case Report”

Journal of Controlled Release April 2, 2007
Vladimir Shvareva, Melpo Christodoulou-Solomidou, Arnaud Scherpereel, Eric Samonek, Evgenia Argunov, Samira Tlibaa, Jenny Picka, Stephen Kennel, Steven Albellab, Vladimir Muzyanov
“Factors Modulating the Delivery and Effect of Enzymatic Cargo Conjugated With Antibodies Targeted to the Pulmonary Endothelium” Michael Diener, John Allord, Stephen Kennel, Saed Mirzadeh

Journal of Surgical Education
May-June 2007
Michael Lebow, David Cassada, Michael Freeman, Oscar Granadas, Scott Stevens, Mitchell Goldman, Michael Freeman
“Acute Pancreatitis as a Complication of Percutaneous Mechanical Thrombectomy”

Radiation Protection Dosimetry
June 18, 2007
Tina Dudney, Trent Nichols, Laurence Miller, George Kahallka
“Microdosimetric Study for Interpretation of Outcomes From Bovon Neutron Capture Therapy: Clinical Trials”

Vascular and Endovascular Surgery
August-September 2007
Jacob Babbee, Scott Stevens, Thomas Gaines, Judson Gash
“Endovascular Repair of Cervical Aortic Arch Aneurysm”

Daniel Surpin, Scott Stevens, Daniel Kizreeder, Judson Gash
“Acute Thrombosis of a Mesenteric Artery Drug-Eluting Stent Following Clotpigugelization”

Imaging
Journal of the American Chemical Society April 25, 2007
Michael Diener, John Allord, Stephen Kennel, Saed Mirzadeh
“(212)F@C(60) and Its Water-Soluble Derivatives: Synthesis, Stability, and Suitability for Radioimmunotherapy”

Journal of Endourology November 2007
Wesley White, Nikhiti Zite, Judson Gash, W. Bedford Waters, Wayne Thompson, Frederick Klein
“Low-Dose Computed Tomography for the Evaluation of Flank Pain in the Pregnant Population”

Journal of Nuclear Medicine May 2007
Claude Nahamas, Wahid Hanna, Lindi Wahl, Mistrty Long, Karl Hubner, David Townsend
“Time Course of Early Response to Chemotherapy in Non-Small Cell Lung Cancer Patients With 18F-FDG PET/CT”

Journal of Oral and Maxillofacial Surgery
December 2007
Claude Nahamas, Eric Carlson, Lisa Duncan, Todd Blodgett, Jason Kennedy, Misty Long, Chris Carr, Karl Hubner, David Townsend
“Positron Emission Tomography/Computed Tomography (PET/CT) Scanning for Preoperative Staging of Patients With Oral/Head and Neck Cancer”

Journal of Urology November 2007
Wesley White, Frederick Klein, Judson Gash, W. Bedford Waters
“Prospective Radiographic Followup After En Bloc Ligation of the Renal Hilum”

Molecular Imaging and Biology
March-April 2007
Joseph Thie, Karl Hubner, Francis Isadony, Gary Smith

Pediatric Radiology August 2007
Daniel Kizreeder and J. Herman Kan
“Mesenteric Lymphatic Malformation”

Physics in Medicine and Biology
February 21, 2008
David Townsend
“Multimodality Imaging of Structure and Function”

Radiology February 2007
Todd Blodgett, Carolyn Metler, David Townsend
“PET/CT: Form and Function”

Seminars in Nuclear Medicine May 2008
David Townsend
“Positron Emission Tomography/Computed Tomography”

Journal of Vascular and Interventional Radiology
2007
Justin Caughron
“Catheter-Directed Thrombolysis and Mechanical Thrombectomy of a Thrombosed Persistent Sciatic Vein in a Patient With Klippel-Trenaunay Syndrome”

Women’s Health and Pediatrics
American Journal of Reproductive Immunology January 2008
Antonin Bukovsky and Michael Caudle
“Immune Physiology of the Mammalian Ovary—A Review”

Journal of Pediatric Surgery January 2008
“Efficacy of Laparoscopic Cholecystectomy in the Pediatric Population”

Journal of Perinatology February 2008
Mark Gaylord, Maureen Greer, John Botti
“Improving Perinatal Health: A Novel Approach to Improve Community and Adult Health”

Journal of Perinatology September 2007
Mark Anderson, Terry Longhofer, Ward Phillips, David McKay
“Passive Cooling to Initiate Hypothermia for Transplanted Encaphalopathic Newborns”

Progress in Molecular Subcellular Biology 2007
Antonin Bukovsky
“Cell Commitment by Asymmetric Division and Immune System Involvement”

Springer 2008
Niklas Zite
“Gynecology for the Primary Care Physician”

Urology August 17, 2007
M. Eric Brewer, Wesley White, Frederick Klein, Leslie Klein, W. Bradford Waters
“Validity of Pelvic Pain, Urgency, and Frequency Questionnaire in Patients With Interstitial Cystitis/Painful Bladder Syndrome”

Additional research was highlighted in the following publications:

Dalton Transactions February 14, 2008
Min-Liang Yao, Scott Borella, Travis Quivv, George Kabalka
“Boron Tribalide Mediated Halodilation of Aryl Aldehydes: Reaction and Mechanistic Insight”

Disease-a-Month 2007
Bruce Lustig and Angelina Lazaris
“Musculoskeletal Tuberculosis”

Ionic Liquids in Organic Synthesis 2007
George Kabalka, Gang Deng, Boliu Venkatiah
“Organic Synthesis in Ionic Liquids Utilizing Organometallic Reagents”

Journal of Biological Chemistry
September 14, 2007
Zhiho An, Hong Wang, Ping Song, Miao Zhang, Xuegeng Gong, Miao Zou
“Nicotine-Induced Activation of AMP-Activated Protein Kinase Inhibits Fatty Acid Synthase in 3T11J Adipocytes: A Role for Oxidant Stress”

F. Matthew Mihelic, M. David Stockton, Stephen Cole, Gregory Blake
“The Changing Role of Physicians in Disaster Management and Hospital Incident Command”

George Kabalka, Min-Liang Yao, Scott Borella, Zhonghua Wu, Yu-Hong Ju, Travis Quivv
“Boron Tribalide Mediated Allyne-Aldehyde Coupling Reactions: A Mechanistic Investigation”

Journal of Surgical Research January 2007
Robert Gillis, Brian Daley, Blaine Enderson, Daniel Kestler, Michael Karlstad
“Regulation of Apoptosis in Eicosapentaenoic Acid-Treated HL-60 Cells”

The Journal of Urology January 2008
Wesley White, Cindy Dobmeyer-Dittrich, Frederick Klein, Lorraine Wallace
“Sacral Nerve Stimulation for Treatment of Refractory Urinary Retention: Long-Term Efficacy and Durability”

Urology June 2007
Michael Brewer, Robert Wilmoth, Blaine Enderson, Brian Daley
“Prospective Comparison of Microscopic and Gross Hematuria as Predictors of Bladder Injury in Blunt Trauma”

Kandi Hodges
23
Fall 2008
Heart, Lung, Vascular: Update for Primary Care Providers
UT Conference Center, Knoxville

Regardless of age or race, cardiovascular and pulmonary diseases affect a large number of Tennesseans. This year’s conference will explore symptomatic aortic stenosis, abdominal aortic aneurysm, hypertension, peripheral vascular disease, and lipid-lowering strategies in at-risk patients based on specifics for race and gender groups.

New strategies and treatment options are coming to light every day. “Heart, Lung, Vascular: Update for Primary Care Providers” is a course that can help physicians, nurses, and allied health professionals tackle this looming health issue by providing the latest information and tools from regional experts.

November 8
Dr. R. Ben Alley Endowed Lecture Series
Morrison’s Conference Center,
University of Tennessee Medical Center

The featured speaker is Leon Assael, DMD, professor and chair of the Department of Oral and Maxillofacial Surgery at the Oregon Health and Science University School of Dentistry. A graduate of Columbia, Harvard, and Vanderbilt universities, Assael will share his knowledge of facial injuries, facial pain, and maxillofacial nerve injuries—his primary clinical interest—with lecture participants in November. The biennial Dr. R. Ben Alley Endowed Lecture Series recognizes the late R. Ben Alley, DDS, who was a leading oral and maxillofacial surgeon at the University of Tennessee Graduate School of Medicine.
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