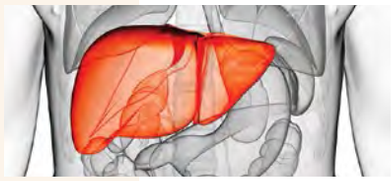
rocket science

The University of Toledo
College of Medicine and Life Sciences

Volume V, 2014

Exploring the effects of obesity with a wider angle See inside


Center for Diabetes and
Endocrine Research (CeDER)



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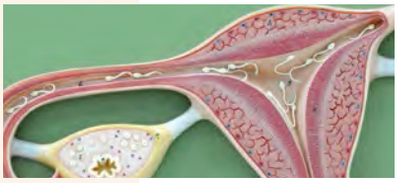

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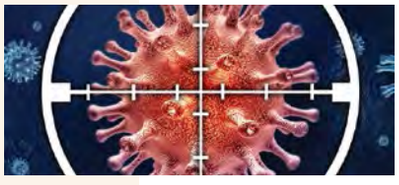

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This year marks the 50th anniversary of the founding of the Medical College of Ohio which is now the University of Toledo College of Medicine and Life Sciences. As a College of Medicine alumnus and the Interim Dean of the College of Medicine and Life Sciences, I am extremely proud of the great progress that we have made in the past 50 years. There will be many celebrations during this year including a gala event the day following graduation of the College of Medicine and Life Sciences medical school class of 2014. As we celebrate our past, we continue to focus on our future growth. The most recent addition to our growing campus is the new Interprofessional Immersive Simulation Center (IISC) at The University of Toledo. Advanced technology in the Center aims to transform the way future health care professionals learn to care for patients and provide unique opportunities for students in disciplines spanning the arts, humanities, natural sciences and engineering. Construction is nearly complete for the three-story, 65,000-square-foot center on the UT Health Science Campus where the latest technologies will stimulate new education, training and collaborative opportunities. In addition to supporting faculty and students at the University, the Interprofessional Immersive Simulation Center works with global industry collaborators, the U.S. military and other health-care organizations to provide unique professional training opportunities.

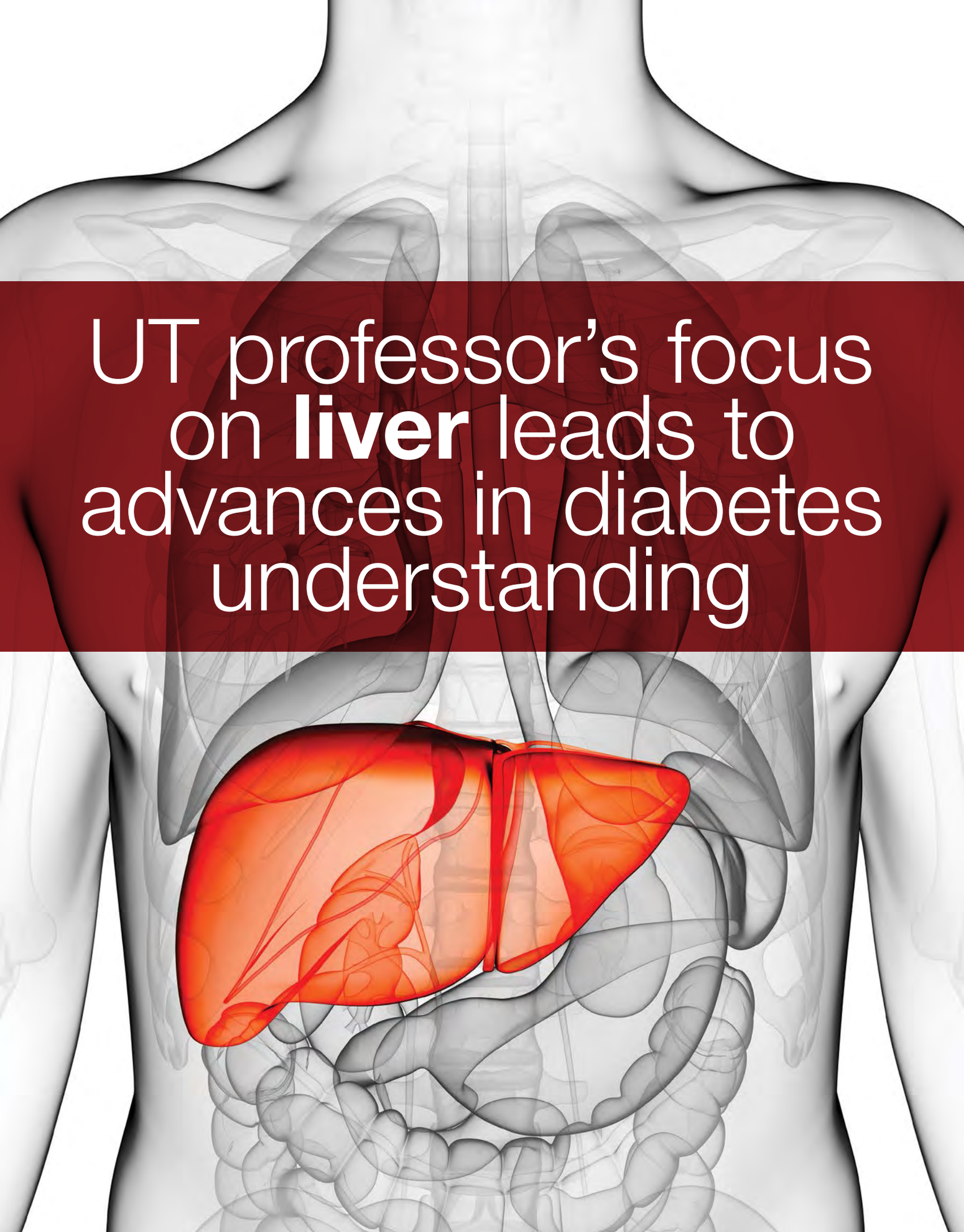
In this issue of Rocket Science we highlight some of our current researchers and their very important work at the university. Dr. Sonia M. Najjar is the Founding Director of the Center for Diabetes and Endocrine Research (CeDER) which was established in 2006 to serve as a center for research focusing on curbing the spread of obesity and diabetes in the State of Ohio through work on the metabolic syndrome. CeDER has been established within the Department of Physiology and Pharmacology, but also includes many members from other departments and colleges at the University of Toledo and its Medical Center. Doctor Najjar is also the Fredrick W. Hiss Endowed Professor in Diabetes Research and has recently received the 2014 YWCA Milestone Award in the field of Science.

I hope that you enjoy this edition of Rocket Science and are able to share our excitement as we begin the second 50 years of our mission to "improve the human condition by providing a world-class education for the next generation of physicians and scientists, by creating new knowledge that is translated into cutting edge clinical practice, and by providing the highest level of professionalism and compassion as we deliver university quality health care."

Sincerely,

Ronald A. McGinnis M.D.
Interim Dean of the College of Medicine and Life Sciences

UT professor's focus on **liver** leads to advances in diabetes understanding



When Dr. Sonia Najjar first started studying diabetes, medical research on the illness was focused mainly on the pancreas. It is a logical connection, she says, because the pancreas secretes insulin. But her desire as a scientist to investigate how things work led her instead to the liver.

As the first organ that receives insulin, the liver has the responsibility of clearing insulin from the blood. If 50 percent of insulin is to be cleared by the liver in the first pass, what happens if it doesn't do that job well?

It's that scientific curiosity that lead Dr. Najjar to focus her studies on CEACAM1, a protein on the surface of liver cells that she proved plays a key role in regulating insulin level and action.

In healthy individuals, glucose is sent into the blood stream after food containing sugar and starch is digested and absorbed. This signals the pancreas to secrete insulin. Insulin is essential because it signals cells in muscle to take up glucose and fat cells to take up both fat and glucose. But when there is too much insulin in the blood, cells become unresponsive to insulin and hence, insulin resistance develops. To compensate for insulin resistance, the pancreas secretes more insulin. With time this causes a defect in the function of insulin secreting cells in the pancreas, exacerbating the problem and leading to Type 2 diabetes.

"Diabetes is a growing problem throughout the world, and in particular in the United States and right here in Ohio," Dr. Najjar said. "The rate of death from diabetes and complications in Ohio is twice the national average. This is something that cannot be ignored."

The rate of death from diabetes and complications in Ohio is twice the national average.

If too much insulin is bad, there must be something that regulates it. Dr. Najjar began to look at CEACAM1, which is the protein in the liver that is activated when insulin binds to the insulin receptor. So what would happen if this protein were defective and insulin clearance in the liver could not be performed? Dr. Najjar set to find out by developing mouse models genetically designed with the protein being inactivated in the liver, or lacking this protein entirely, which was about a three-year process in itself.

The impact matched her hypothesis. Mice with defective CEACAM1 or devoid of CEACAM1 had too much insulin in the blood and became obese with a large amount of belly fat and extra circulating fatty acids, indicating that fat tissue could no longer store fat, and that overall insulin resistance had developed.

"Mice with inactivated CEACAM1 developed insulin resistance and that was an important discovery to show that insulin clearance plays a role in insulin action and fat metabolism," Dr. Najjar said.

Clinical studies have shown that the CEACAM1 level is markedly reduced in the liver of obese humans with fatty liver disease. The lower CEACAM1 is in the liver, the more advanced the fatty liver disease becomes. This emphasizes the importance of this protein in human disease.

Dr. Najjar's laboratory was the first to discover a molecular link between insulin clearance and insulin resistance. It was a key finding in research on a disease that affects millions of people. According to the American Diabetes Association, there are 25.8 million children and adults with diabetes and 79 million more people with prediabetes.

Dr. Najjar is now advancing that research by investigating if the same protein is a key factor in nonalcoholic steatohepatits, or NASH, which is liver inflammation caused by fat buildup.

The liver is not good at storing fat and a healthy liver sends it to the adipose tissue where it belongs, Dr. Najjar explains. But chronically elevated insulin takes its toll as it causes production of fat in the liver and eventually, even

fat tissue cannot store any more, so fat ends up building up in the liver and other parts of the body causing fatty liver disease and atherosclerosis, along with other metabolic and cardiovascular diseases.

NASH and atherosclerosis are twin diseases, both being characterized by fat build up, inflammation, oxidative stress and other features. Chronically elevated insulin appears to underlie several of the common features of these diseases. While atherosclerosis is more commonly diagnosed because of notable symptoms like chest pain, fatty liver disease can go undetected.

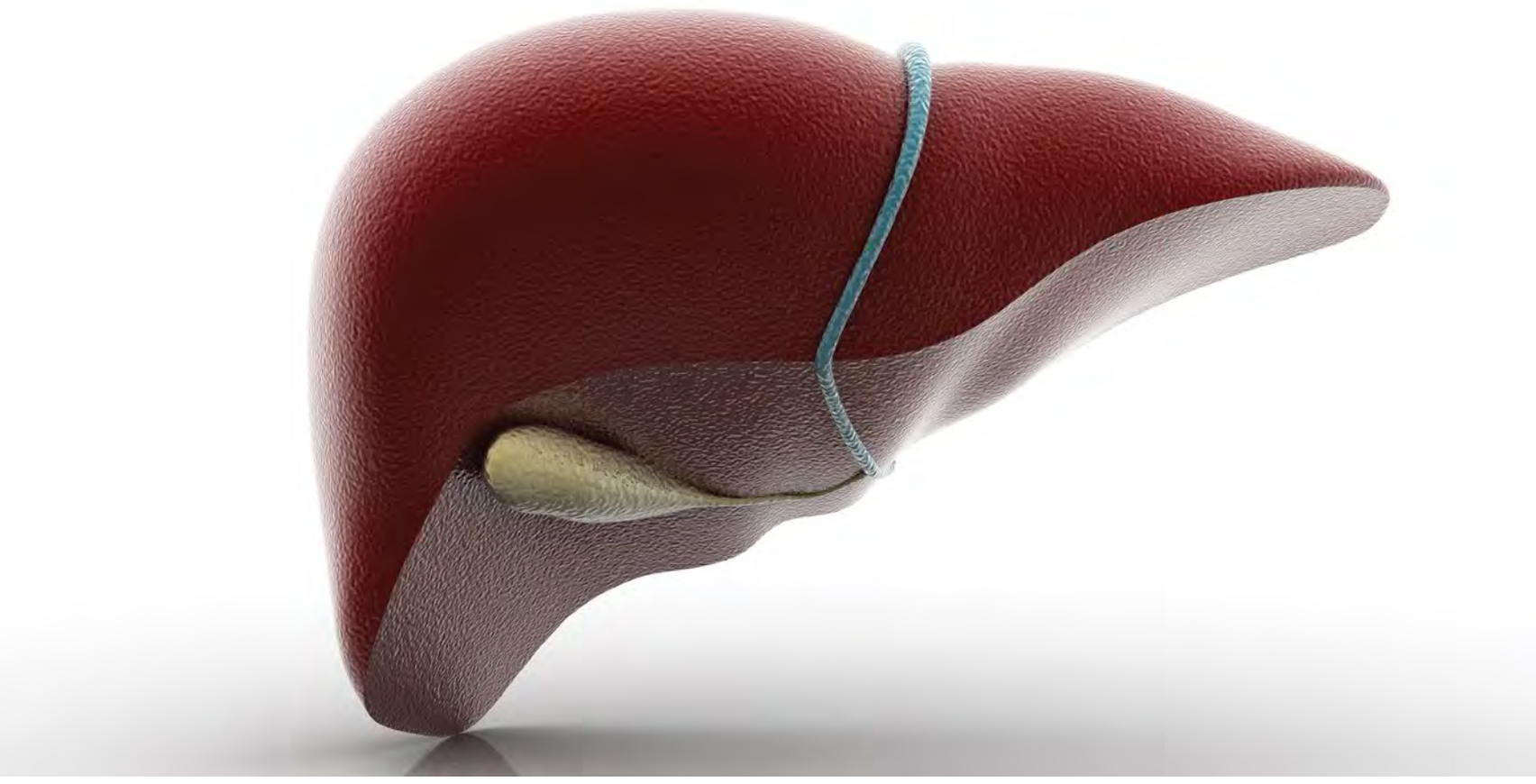
It's also not necessary for a person to be obese to have excess fat in their liver. They can instead be "fatty on the inside," Dr. Najjar said.

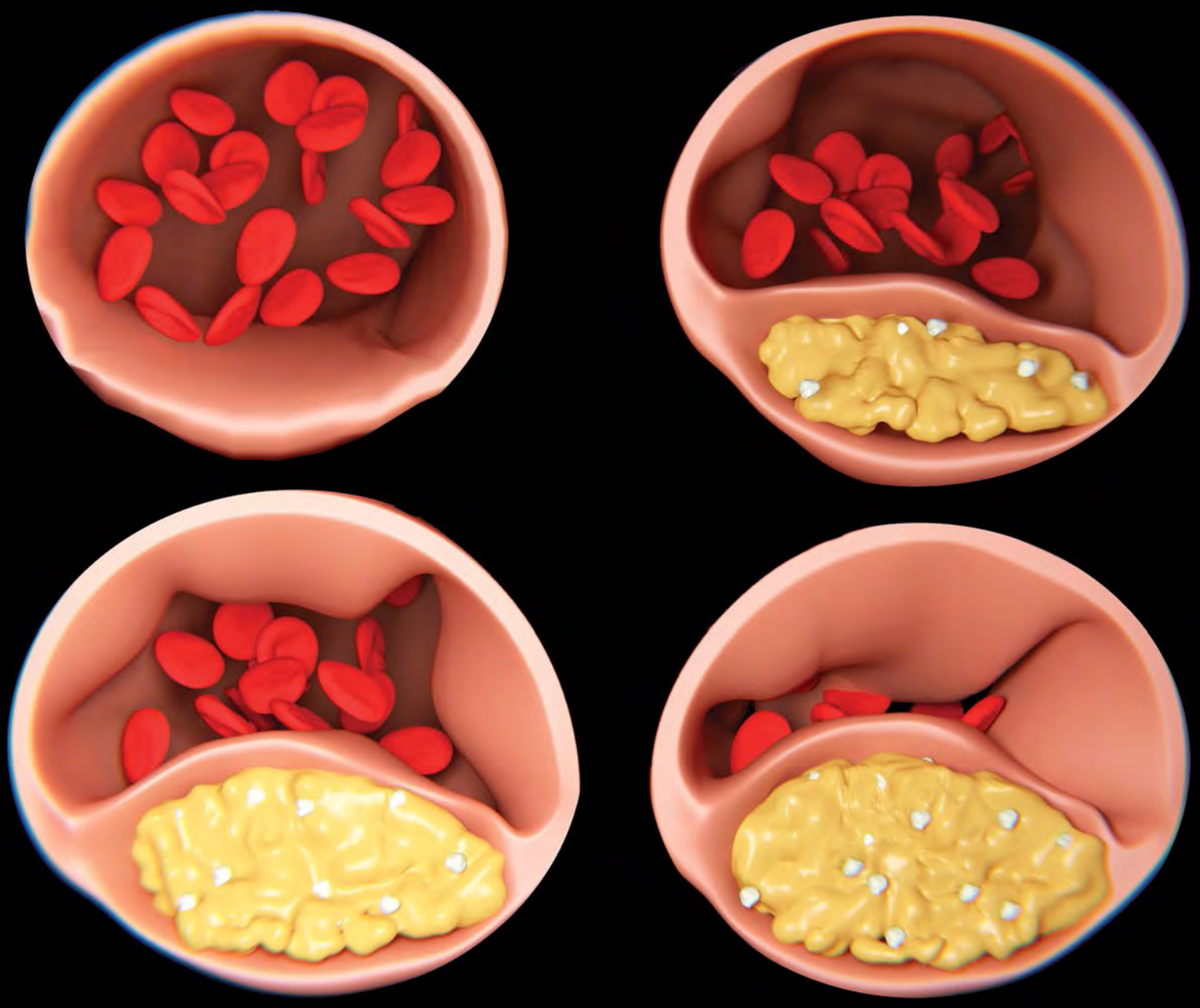
"Cholesterol lowering medications may limit cholesterol in the blood, but they do not always limit progression of atherosclerosis," Dr. Najjar said. "This could be due to the fact that physicians do not often link atherosclerosis to fatty liver disease, and hence, they treat the symptoms but not the cause."

Dr. Najjar's continued research into CEACAM1 will answer questions about how genetics, diet and exercise impact the levels of the protein and what that means for insulin clearance. More work also is being done on this protein, which also plays a role in atherosclerosis and NASH. Additional work at the Najjar laboratory focuses on how obesity is linked to common types of cancer.

Understanding insulin clearance is the key to creating effective therapeutic targets

"If we can target CEACAM1 and develop a way to maintain a higher level of the protein for effective insulin clearance, we can reduce diabetes, fatty liver disease, atherosclerosis and hypertension" Dr. Najjar said. "Understanding insulin clearance is the key to creating effective therapeutic targets for those diseases caused by insulin resistance, and we are committed to advancing this important line of research." ■





TARGETING SPECIFIC PROTEINS

TO SLOW THE PROGRESSION OF ATHEROSCLEROTIC LESIONS

Pharmaceutical commercials show cholesterol swimming through the coronary arteries — the arteries that supply the heart muscle with blood — and gradually building up along the arterial walls, but this does not portray an accurate picture of the most dangerous form of cardiovascular disease, atherosclerosis.

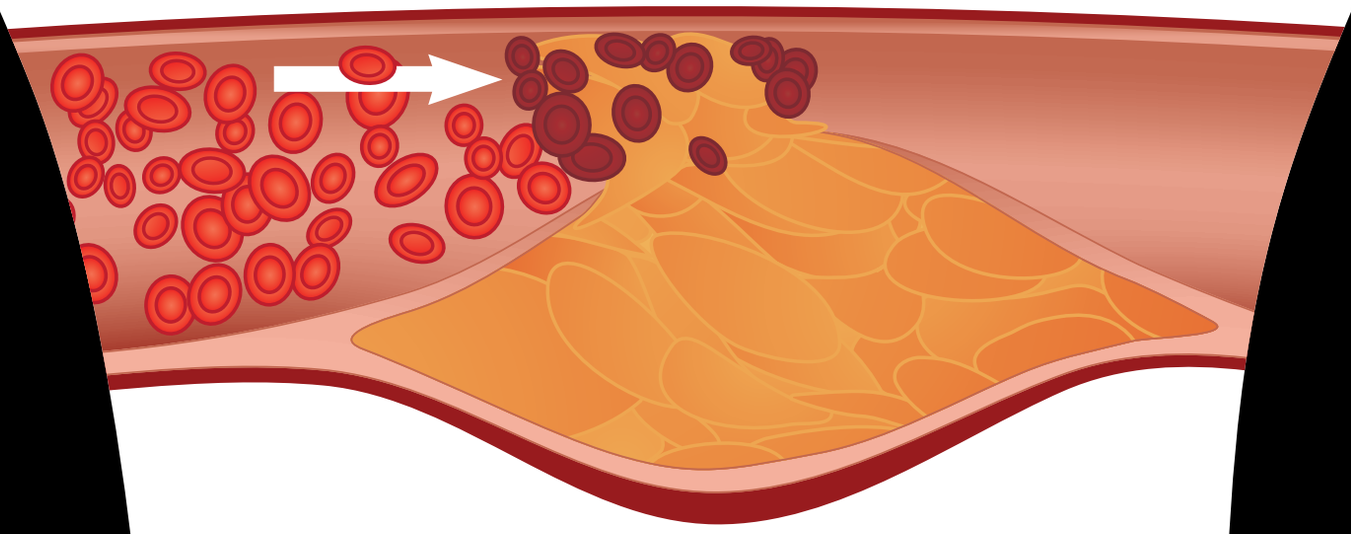
Atherosclerosis, a disease that causes hardening and narrowing of arteries, involves a chronic inflammatory reaction that takes place underneath the endothelium, the lining of the blood vessel lumen. Atherosclerosis is originally triggered by accumulation of excess LDL, a circulating form of cholesterol. This inflammatory focus, or lesion, continues to grow with accumulation of lipids, inflammatory cells and cell debris until the lesion ruptures and triggers blood clotting, or thrombosis. Those blood clots, in turn, can abruptly block blood flow, promptly causing heart attacks or stroke. Every year, atherosclerosis, the major cause of coronary heart disease, is responsible for one in five deaths due to cardiovascular disease.

"Patients can have fairly large lesions and not be aware because a reduction of the arterial lumen of approximately 75 percent or more is usually necessary to cause significant reduction in blood flow and thus, ischemia. That is when the individual could feel symptoms such as chest pain," said Dr. Guillermo Vazquez, associate professor in the Department of Physiology and Pharmacology. "There are two major therapeutic approaches aimed at avoiding that worst-case scenario of a ruptured lesion or "plaque": preventing or slowing the growth of the lesion or, once the plaque is already there, trying to make it stable to minimize the risk of rupture."

There has been much work already on the risk factors of atherosclerosis such as high blood pressure, high cholesterol, diabetes and cigarette smoking. A healthy diet and regular exercise, as well as therapeutic management of other risk factor conditions, are still among the best recommendations for prevention of coronary artery disease. Vazquez's research is aimed at better understanding the molecular and cellular mechanisms that lead to the formation and progression of atherosclerotic lesions and to identify potential new targets that can be exploited to develop new strategies in the treatment of this disease.

THOSE BLOOD CLOTS, IN TURN, CAN ABRUPTLY BLOCK BLOOD FLOW, PROMPTLY CAUSING HEART ATTACKS OR STROKE.

Dr. Vazquez's research focuses in particular on a certain membrane channel protein — TRPC3 — that is found in the endothelial cells of blood vessels, including the coronary arteries that supply the heart with blood. Dr. Vasquez and his group discovered that endothelial TRPC3 channels are required for signaling cascades in these endothelial cells that, in turn, regulate the expression of cell adhesion molecules on the surface of these cells. Such cell adhesion molecules are critical in the process of recruiting monocytes (a type of white blood cell) from the blood to the lesion, where they promote the process of atherosclerosis. Within the lesion, macrophages — another type of white cell that is derived from monocytes ––– also contribute to atherosclerosis, and these macrophages also express abundant TRPC3 protein. A second line of research in Vazquez's lab studies the role of TRPC3 in the regulation of macrophage apoptosis (programmed cell death), a critical event in determining plaque growth and stability. These sequences of events, and the TRPC3 channel protein that is required for these events to



ATHEROSCLEROSIS IS A MULTIFACTORIAL DISEASE AND THUS IT WOULDN'T BE SURPRISING IF A MULTI-TARGETING APPROACH IS NEEDED TO OBTAIN MORE EFFECTIVE CLINICAL OUTCOMES

happen, are thus a logical place to look for ways to interrupt or prevent the development of atherosclerotic lesions in coronary arteries and elsewhere.

To accomplish these goals, his lab makes use of genetic mouse models that lack the TRPC3 protein in the endothelium or in macrophages, to study the impact of this protein expression and function on atherosclerotic lesion size and composition. These mice are fed a high fat "Western" diet, and the development of atherosclerotic lesions is examined at specific points in time during the following weeks and months. The size and complexity of the lesions are investigated to find out if they are smaller in size, if the onset of the lesion is delayed and/or if their composition has changed. Recent preliminary findings by Vazquez's group show that mice lacking TRPC3 in macrophages have lesions with smaller necrotic cores – plaques that are more stable and are at less risk of rupture.

While cautioning that much more research is needed, Vazquez says that, if these results are confirmed by future studies, the TRPC3 protein in endothelium or in the macrophage could be an attractive candidate as a molecular target for therapies to treat or prevent atherosclerosis. These follow-up studies are currently ongoing in his lab at UT.

"Atherosclerosis is a multifactorial disease and thus it wouldn't be surprising if a multi-targeting approach is needed to obtain more effective clinical outcomes" he said. "Our interest is to identify specific targets that could be part of that approach to help people who suffer from this disease."

Vazquez began his work with TRPC3 channels at the National Institutes of Health before joining The University of Toledo in 2007. He was interested in continuing that work with a focus on atherosclerosis because cardiovascular disease impacts a huge population, including some in his own family.

Cardiovascular disease is the number one killer in America. Every year about 715,000 Americans have a heart attack and 600,000 people die from heart disease in the United States, according to the Centers for Disease Control and Prevention.

"Unfortunately many do not notice symptoms until it's too late," Vazquez said. "With increased monitoring and better treatments, hopefully we can help more people and reduce the negative statistics." ■

CAMPUS CAPSULES

Nobel Prize laureate speaks at UT

Seven years after Dr. Mario Capecchi received a Nobel Prize for his work in genetics, the Distinguished Professor of Human Genetics and Biology at the University of Utah School of Medicine, gave two lectures at UT on March 18 and 19.

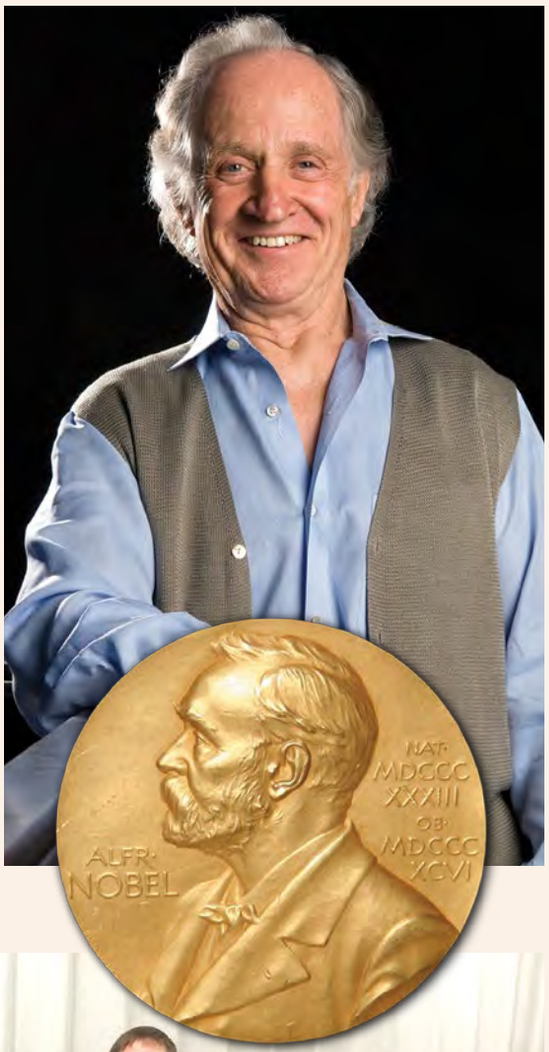
"Dr. Capecchi is not only a skilled scientist but also a brilliant educator and speaker," said Dr. Akira Takashima, professor and chairman of the UT Department of Medical Microbiology and Immunology.

In Capecchi's lecture, "The Making of a Scientist An Unlikely Journey" he discussed the triumphs and tribulations he experienced on his path to becoming who he is today and discussed the importance of science in our society.

"This lecture is meant to stimulate people into wanting to go into science and why I think science is fun," Capecchi said. "What makes science seem hard is jargon. If you strip out the jargon, what we do really isn't that complicated."

Capecchi won the Noble Prize along with Sir Martin Evans and Dr. Oliver Smithies for their work with gene targeting in mouse embryo-derived stem cells. This research could lead not only to better management, but to cures for virtually every known human disease.

Capecchi also gave a University Distinguished Lecture entitled "Gene Targeting into the 21st Century: Mouse Models of Human Diseases from Cancer to Neuropsychiatric Disorders" to scientists and academics at UT about his work with genetics.



CAMPUS CAPSULES

College of Medicine receives continued accreditation

The College of Medicine and Life Sciences has received continued accreditation from the Liaison Committee on Medical Education (LCME).

The LCME voted to continue the college's accreditation for a full eight-year term. An accreditation team visited campus in late April for a thorough four-day review to examine compliance with its 134 accreditation standards.

"This award of continued accreditation for the next eight years and the positive remarks from the survey team affirm our belief that UT medical students are receiving a world-class education at our institution," said Dr. Jeffrey P. Gold, former dean of the College of Medicine and Life Sciences.

The last accreditation visit eight years ago wasn't as positive with a number of areas that needed to be addressed, but the most recent report described a rejuvenated medical college, he said.

Out of five broad categories LCME evaluates on each visit, the site visitors found no negative findings in the topics of institutional setting, faculty or educational resources. The accreditation team specifically praised the Interprofessional Immersive Simulation Center, saying, "the investment in a greatly expanded new center with a focus on interprofessional education is laudable."

The LCME also praised the Center for Creative Instruction, noting the department has been "instrumental in developing new technologies to enhance the educational mission of the college" and called "educationally innovative" the development of the virtual interactive cadaver dissection experience "Anatomy Revealed."

"This continued accreditation speaks to the strength of our medical college and the positive path we are on into the future," UT President Lloyd Jacobs said.

Tie One On raises awareness and funds for cancer research

More than 500 people donned a bow tie on Feb. 5 for The University of Toledo's annual Tie One On fundraiser event that raised an estimated $30,000 for cancer care, awareness and outreach.

"We couldn't be happier with the turnout, especially the large number of students who came out this year for a fun night of fashion and basketball that raises awareness about cancer care and research," said Lawrence J. Burns, vice president for external affairs and Tie One On founder.

Participants received their bow ties at a pregame event in the Fetterman Athletic Training Facility and then watched the UT men's basketball game take on rival Bowling Green. The Rockets beat the Falcons, 83-76, in front of 6,031 fans.

Tie One On raises money through a silent jersey auction along with the $100 donation from participants and $20 from students for which they received a bow tie or bow tie necklace, tickets to the game and access to the pregame reception. The estimated $30,000 in donations for 2014 is in addition to the more than

$40,000 Tie One On previously has raised for cancer care, awareness and outreach.

Tie One On has become a yearlong effort with cancer survivors honored during each men's basketball home game with tickets to special designated Tie One On seats in Savage Arena. Cancer awareness lectures also are held throughout the year at the Eleanor N. Dana Cancer Center at UTMC.

Dean's Club Symposium honors endowed chairs and professorships

The Dean's Club Symposium of The University of Toledo (UT) College of Medicine and Life Sciences was held in April to recognize the endowed chairs and endowed professorships made possible by philanthropy.

"These honorees are among UT's most distinguished educators, researchers and healthcare providers," said Dr. Ron McGinnis, interim dean of the College of Medicine and Life Sciences.

"This is also an opportunity to once again express our thanks to the individuals and organizations who, through their generous gifts, are contributing to the advancement of science and the health of the community."

The following endowed chairs and professors were honored:

- Dr. Christopher Cooper: Mercy Health System Chair of Excellence in Education
- Dr. Deepak K. Malhotra: University of Toledo College of Medicine and Life Sciences Endowed Professorship in Nephrology
- Dr. William Maltese: Helen and Harold McMaster Endowed Chair in Biochemistry and Molecular Biology
- Dr. Kelly J. Manahan: Rita T. Sheely Endowed Chair in Obstetrics and Gynecology
- Dr. Sonia Najjar: Frederick W. Hiss Endowed Professor in Diabetes
- Dr. Thomas Schwann: S. Amjad Hussain Professor of Thoracic and Cardiovascular Surgery
- Dr. Steven Selman: Frank D. Stranahan Endowed Chari for Oncological Research
- Dr. Akira Takashima: Robert A. Stranahan Chair in Microbiology and Immunology
- Dr. Gretchen Tietjen: Clair Martig Endowed Chair in Neurology
- Dr. James Willey: George Isaac Endowed Chair in Cancer Research

The Dean's Club was established to help the UT College of Medicine and Life Sciences and the UT Medical Center meet a three-part mission of excellence in medical education, research and clinical care. Members' gifts provide essential funds for scholarships, faculty research support and other innovative programs.

UT FACULTY MEMBER FOCUSES ON BROWN FAT TO MITIGATE BONE-WEAKENING SIDE EFFECTS OF ANTI-DIABETES DRUGS

Diabetes, obesity, osteoporosis — these are a trinity of public health issues that plague an aging and increasingly sedentary national population. Research headed by Dr. Beata Lecka-Czernik, UT professor of orthopaedics, physiology and pharmacology, both demonstrates troubling links between these diseases and offers insights into potential new treatments.

The link begins with a family of TZD (thiazolidinedione) drugs introduced in the late 1990s to treat diabetes mellitus type 2. Rather than boost insulin levels or reduce glucose levels, as older anti-diabetes drugs do, TZDs sensitize muscle, liver and fat cells to the beneficial effects of insulin so that these cells can utilize glucose as an energy source. Clinical studies show strong evidence that TZD drugs such as Actos can also improve the insulin secretion capacity of pancreatic islet beta cells and, further, that they protect these cells from the stress of higher insulin production as well.

Unfortunately, there are side effects of TZD drugs. These include edema with an associated risk of congestive heart failure and liver damage. Because of this, the use of TZD drugs has been restricted in the United States and Europe.

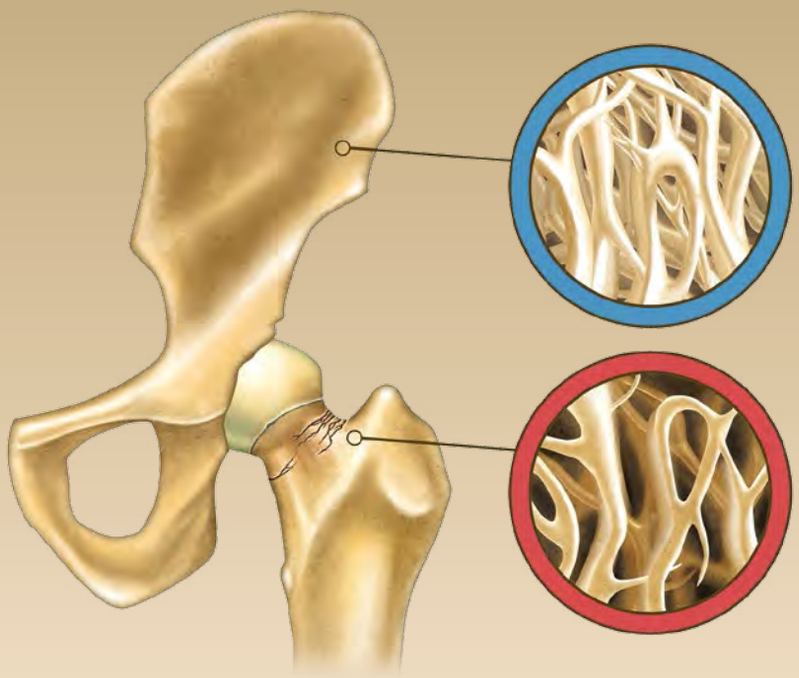
Moreover, Lecka-Czernik says, researchers have only recently come to understand that there is a troubling link between TZD therapies and another condition already associated with both types of diabetes: osteoporosis, or bone loss, with its associated risk of bone fractures.

"One of the earliest findings our research team made was that anti-diabetic drugs had a negative effect on bone," says Lecka-Czernik, who holds an appointment in the UTMC Department of Orthopaedic Surgery and membership in UT's Center for Diabetes and Endocrine Research. "These drugs are very beneficial in treating diabetes, but along with the beta cells, they target the protein also responsible for the differentiation of stem cells in the bone." Indeed, among the team's findings is the fact that more than one protein and more than one mechanism are involved in regulating these differentiating stem cells. The TZD-targeted protein controls differentiation of bone stem cells toward either osteoblasts (bone-forming cells) or adipocytes (fat cells). The potential effect on bone is clear, she says: "By targeting this protein we actually change the differentiation of stem cells toward adipocytes, at the cost of bone formation.

ONE OF THE EARLIEST FINDINGS OUR RESEARCH TEAM MADE WAS THAT ANTI-DIABETIC DRUGS HAD A NEGATIVE EFFECT ON BONE

"So the patients who are taking these anti-diabetes drugs are losing bone." Her team first demonstrated this effect in animals, in a pioneering study published in 2004 that was splashed across news media, including the New York Times. Three years later, she notes, came additional seminal papers showing that humans receiving TZD drug therapies have higher bone fracture rates, thus confirming what Lecka-Czernik's team had observed in mice.

Patients suffering from type 1 diabetes, Lecka-Czernik says, were already known to have a high fracture rate, seven times higher than the general population. "In type 2," she adds, "it was thought that patients were actually protected from fractures because they have higher bone mass, probably from high insulin levels. Recently, though, it was shown that while they have higher bone mass, bone quality is compromised, leading to increased fractures, which then heal slowly. High levels of circulating glucose have an adverse effect on bone because they decrease bone quality, making bone more stiff and breakable.



"It's as if you compare a fresh branch from a tree and one that's dry. They may have the same mass, but one is much easier to break.

"In addition, patients are being treated with these anti-diabetes drugs, so now they have four-fold more fractures. That's especially a concern in post-menopausal women and the elderly."

However, that link was only the beginning of her team's interest in the link between disorders of bone metabolism and those of energy metabolism, the latter involving the body's metabolizing of glucose and fat. They're focusing now on a certain type of body fat — brown fat, abundant in infants and hibernating animals — whose beneficial effects have only recently been studied.

Lecka-Czernik explains, "It's a metabolically active fat that takes the fatty acids and triglycerides from the body's circulation very quickly, thus providing energy.

"Regular brown fat is something we're born with; newborns have it between their scapulae [shoulder blades]. This fat, when burned, provides a lot of energy in the form of heat, protecting newborns from losing heat."

As humans age, they tend to lose brown fat; for years it was thought that adults lacked it entirely. Recent research, though, revealed its presence around the neck and spine, in deposits that are tiny yet very active metabolically. Experiments have shown that the deposits come to the fore to raise the body's core temperature when this becomes dangerously low. Other studies have shown connections between levels of brown fat and diabetes (low levels) and between levels of brown fat and obesity (low as well).

One type of brown fat possesses particular benefits to the body. This is brown-like, or "beige" fat, which can be induced pharmacologically in ordinary subcutaneous fat.

WE FOUND THAT BEIGE FAT IS RELEASING FACTORS THAT RESULT IN BONE FORMATION.

Using their mouse model, Lecka-Czernik's team found that mice with induced beige fat possessed a great deal more bone than the control mice. She explains, "We found that beige fat is releasing factors that result in bone formation. Later, we identified pharmacological compounds that can boost beige fat activity and production of these factors. Moreover, these compounds have the same beneficial effects as TZDs to treat diabetes."

It's a discovery that could allow us to mimic the beneficial effects of TZD drugs on diabetes and, at the same time, prevent the unwanted side effect of TZD drugs on bone.

"We believe this could become a new anti-diabetes therapy," she says. "Instead of targeting bone cells, it will target fat cells to create beneficial factors for bone as well as for optimum glucose metabolism. So you'd get two results in one drug: anti-osteoprotic and anti-diabetic therapy."

The U.S. Federal Drug Administration is very much aware of the connections between anti-diabetes drugs and bone loss, she notes, so all such drugs being developed are screened for possible bone-loss effects.

"In fact, I just spoke to a pharmaceutical company developing anti-diabetes drugs, and they're preparing a new clinical trial on post-menopausal women because there's a high bone loss during that period that later often leads to a high fracture rate in the hip."

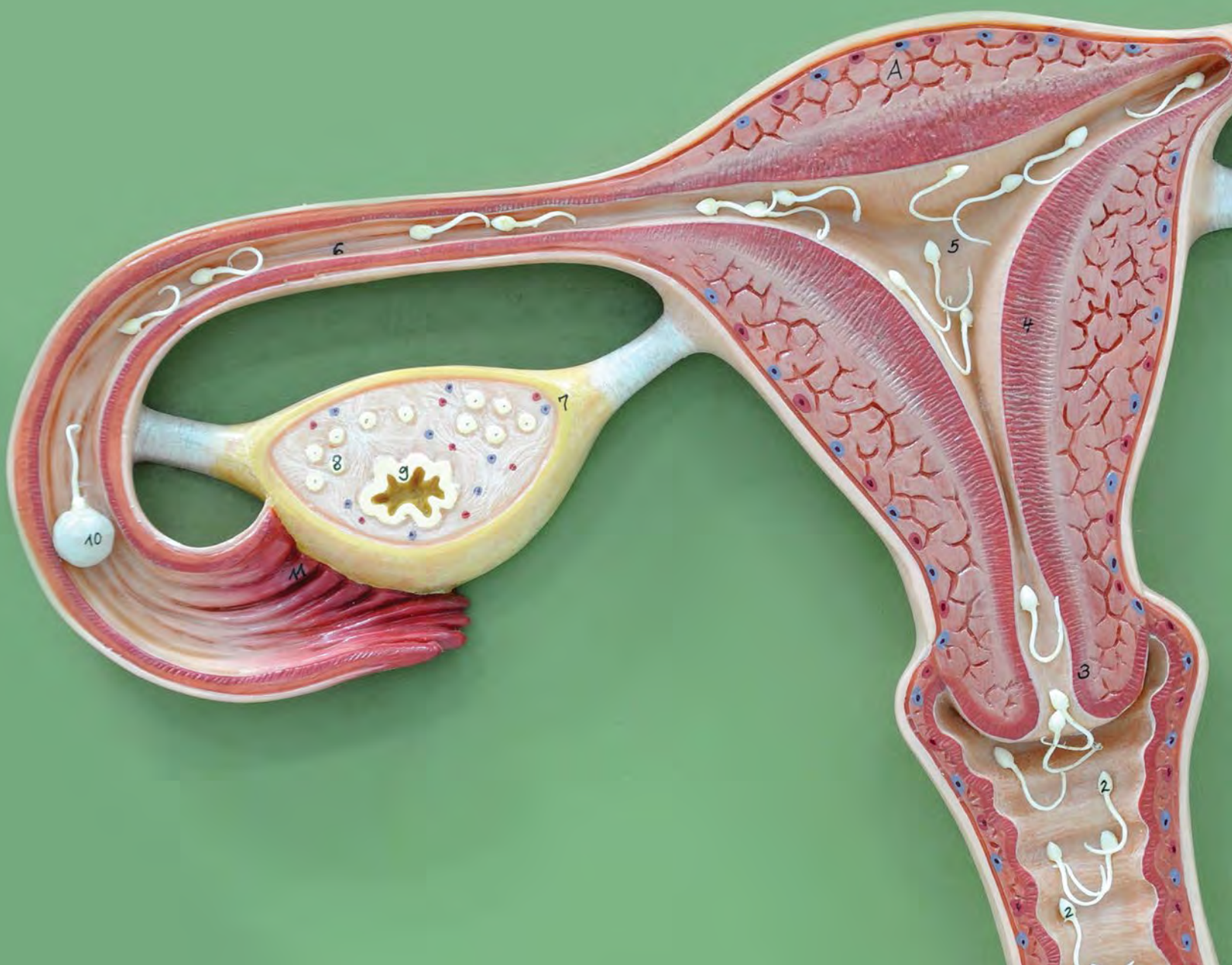
The links between diabetes, osteoporosis and obesity represent a translational body of work, she says, that continues to generate a great deal of interest from the clinical side.

"Anti-diabetes drugs do not cure the disease, only manage it," she notes. "It's the same with drugs to fight osteoporosis; you cannot stop taking them, and over time there are undesirable side effects that develop with their longstanding use. Therefore there is an urgency in developing drugs with an ideal safety profile.

"That urgency — mitigating these side effects — is the challenge we've undertaken." ■

Brain/body/baby

Research explores the causes of infertility within a complex medical condition



Some health statistics are glaring for women: Cardiovascular disease kills a woman each minute. Ten percent of women older than age 20 have diabetes.

According to the National Institutes of Health, a lesser-known statistic that affects millions of women and is the catalyst for more than $4 billion in health care costs annually in the United States: One in 10 women of reproductive age have polycystic ovary syndrome (PCOS), a condition that alters endocrine function and impairs fertility.

Poorly named and not well understood, PCOS can affect women's health in a number of ways. Dr. Jennifer Hill, professor of physiology and pharmacology at UT, said PCOS is linked to hypertension, diabetes, certain cancers, cardiovascular disease, sleep apnea and other health conditions, in addition to its significant effects on fertility.

"PCOS is called a syndrome, rather than a disease, because we don't yet know what causes it, even though it was identified more than 70 years ago," Hill said. "It's probably more complex than a single genetic factor."

"The fact that it affects so many women and puts them at risk for metabolic disease," she said, "makes innovative research even more important." Hill is pursuing research to identify the origins of this condition.

"The cornerstone of our laboratory efforts is timed, targeted genetic manipulation using the power of tissue-specific gene deletion," Hill explained. "Combined with anatomical, electrophysiological and physiological techniques, this approach offers a powerful tool for investigating the hypothalamic control of metabolism and fertility."

The hypothalamus, a portion of the brain roughly the size of an almond, is located near the center of the brain. As part of the reproductive axis, the hypothalamus is responsible for certain metabolic processes, including synthesizing and secreting hormones that control the pituitary gland.

Cells in the hypothalamus produce gonadotrophin-releasing hormone (GnRH), which is responsible for stimulating the anterior pituitary gland to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones, in turn, are essential to both the growth of follicles that nurture the eggs within a woman's ovaries, and to the release of an egg ready for fertilization, resulting in pregnancy.

Hill said the communication between the hypothalamus and the reproductive organs can be impaired. Part of her research focuses on how this system is influenced by leptin, a hormone made by fat cells, and by proopiomelanocortin, or POMC, a precursor protein made by neurons in the hypothalamus. Both leptin and POMC are produced when plenty of food is eaten and stored as fat.

"It makes sense that, if you have an abundance of energy stores, your body can tell that it's a good time to reproduce," Hill said. "You'll have enough stores to support a pregnancy and produce milk for the offspring. Neurons in the hypothalamus can sense that and alter the activity of the GnRH neurons."

Hill theorizes that the sensitivity of hypothalamic neurons to factors like leptin is essential to fertility, and that alterations in such sensitivity can lead to reproductive problems. "One possibility is that neurons that sense leptin in a person with PCOS become resistant to it," she said. "The receptors for leptin stop working. The consequence is that there is no longer a message to the GnRH neuron that there are plenty of energy reserves."

Hill conducted previous research on mice with genetically-engineered POMC neurons that could not sense leptin or insulin. "We made a mouse model that has a genetic alteration in POMC neurons so these neurons no longer sense leptin or insulin, another indicator of plentiful calories," she said. "We found these mice had metabolic and reproductive problems that were reminiscent of PCOS."

Her current research focuses on two specific issues. The first is whether inflammatory factors produced by fat tissue fuel PCOS symptoms.

Obesity worsens PCOS symptoms. "In obese people, fat tissue becomes inflamed," Hill said. "When too much fat is stored in individual fat cells, the cells become stressed and produce inflammatory factors, like cytokines. It's a low-grade version of what you'd see with a cut; there's a release of cytokines that travel through the bloodstream and may have negative effects on the ovary or the brain."

The second aspect of Hill's research focuses on a neuropeptide produced by POMC neurons called beta-endorphin, whose production is controlled by leptin and insulin. "The hypothesis we have been testing is whether the amount of beta-endorphin being produced is insufficient to control GnRH neuron activity. We have suppressed beta-endorphin genetically in one group of mice to see what happens to their phenotype."

Hill's research results are scheduled for publication by spring 2014.

One of the goals of this research is to give women with PCOS and reproductive problems some hope

Hill, who joined UT in 2009 after academic and research positions at the University of Texas Southwestern, Harvard University/Beth Israel Deaconess Medical Center and Northwestern University, hopes her results can be applied to future diagnostic and treatment methods for women who have PCOS.

In addition to Hill's work on fertility problems associated with obesity, she plans to also explore brain-body connections in underweight women with reproductive difficulties.

"One of the goals of this research is to give women with PCOS and reproductive problems some hope," Hill said. "If we can correct the communication between their ovaries and brain, ovulation and childbearing may become possible for them. Also, if we can prevent inflammation and insulin resistance in these women, a whole host of future problems like diabetes and heart disease may be prevented. That is what we are working toward." ■

WHAT IS PCOS?

According to the National Institutes of Health, polycystic ovary syndrome is characterized by the following symptoms:

- Fertility impairment
- Irregular menstruation (oligoovulation) or absence of menstrual periods in women of reproductive age (ovulatory dysfunction)
- Acne
- Weight gain
- Excess hair growth on the face and/or body (hirsutism)
- Thinning scalp hair
- Ovarian cysts (polycystic ovarian morphology)
- Mental health problems, such as depression

Women with PCOS often are resistant to the biological effects of insulin and have high insulin levels, putting them at risk for type 2 diabetes, high cholesterol and high blood pressure. Obesity appears to worsen the condition.

UT researcher studies obesity by examining adipocytes, determining their *fates*

At the cellular level, fate plays a central role, and such fates have important implications for obesity and its consequences. When bioscientists speak of a cell's fate, they refer to what that cell will become: the role it will play in the body's overall structures. Although to some extent limited in what they can ultimately become, cells can "choose" to fulfill different fates. Once that "choice" is made, the cell is said to be committed. This means that under the proper conditions committed cells become differentiated to a final cell fate wherein they can then perform specialized functions to serve the needs of the body.

The fates of cells — and especially the fates of cells destined to become fat cells — are the heart of research performed by Dr. Cynthia Smas, associate professor of biochemistry and cancer biology. She studies cells fated to become adipocytes, or fat cells. Her work, which has been funded by the National Institutes of Health, addresses the mechanisms underlying the formation of preadipocytes (fat cell precursors), their differentiation to mature adipocytes, and the molecular functions of mature adipocytes.

Adipocytes are cells that primarily compose adipose tissue and are the only cells in the body specialized for safely storing excess nutritional energy as fat. Her research has strong implications for the scientific understanding of obesity. The theme of her work can be considered, she adds, as two sides of a coin representing obesity: "Obesity is affected by many things: whether [there are] too many adipocytes, or [there are] adipocytes that are overly large and full of lipids. When the fat storage capacity of adipose tissue is exceeded, lipids are taken up by other tissues, where they become toxic and can cause death of critical cell types such as cardiac cells and beta [insulin-producing] cells of the pancreas."

Scientists have known for a long time, she notes, that adipose tissue is the storage site for excess energy in the form of triglycerides, and that this tissue is very hormonally responsive to meet the body's energy needs.

She adds, "But recently we've come closer to answering some major questions regarding the factors surrounding the formation of adipocytes and their lineage — their derivation from tissue that's not yet differentiated. Every cell in the body has its own lineage.

"How will cells respond to certain signals to move it toward its final fate, its final differentiation?"

In regard to the formation of adipocytes and adipose tissue, Smas focuses on the fate of preadipocytes. These precursor cells are present in adipose tissues and can differentiate into mature adipocytes in response to intrinsic nutritional and hormonal signals. Preadipocytes become adipocytes via the process of cell differentiation known as adipogenesis.

Certain transcription factors — proteins that can switch on and off many genes to, for instance, program a lineage — have been identified as important for adipogenesis and adipocyte function. Most have been initially studied in cell culture, where the cells can be treated with certain chemicals that cause them to move from preadipocyte to adipocyte.

Identifying the necessary signals was important for researchers, she adds, but another critical question was the origin of preadipocytes in the body. As Smas notes, mesenchymal stem cells in embryonic connective tissue can differentiate into different fates: adipocytes, connective tissue, muscle or bone. "How are those stem cells programmed to become one thing and not another?" she asks.

"How will cells respond to certain signals to move it toward its final fate, its final differentiation?"

"Until a few years ago, the tools to answer that question didn't exist. It now appears that under certain experimental settings, preadipocytes can arise from different places, like bone marrow, in addition to adipose tissue. Partially committed mesenchymal stem cells can migrate into adipose tissue and there they can differentiate into preadipocytes, which under the correct conditions can become the adipocytes present in fat tissue. Within adipose tissue, precursors to adipocytes are found closely associated with capillary blood vessels.

"Today we have more markers for stages of adipogenesis — from precursor preadipocytes to mature fat cells — enabling my own work in closely studying preadipocytes and adipogenesis."

Her research team utilizes cell culture models to compare genes that are expressed in the preadipocyte stage with those in the adipocyte stage. "We had a hundreds-long list of these genes, a large number of which had not been studied in the adipocyte lineage until now," she says. "With bioinformatic analysis, we found that a group of approximately 40 genes — that had been primarily studied in regard to axon guidance in the nervous system — were enriched for expression in preadipocytes. These genes encode secreted and cell membrane-bound proteins that include ligands and receptors that function in communicating cell signals."

Smas adds, "We don't know how these axon-guidance molecules function adipogenetically, but several have been implicated in bone cell formation pathways, which is a clue, given the apparently inverse molecular connection that is emerging between the adipogenic and osteogenic (i.e. bone cell formation) differentiation programs.

"The other category that we're looking at are any potential transcription factors on that long list. You can generally recognize transcription factors by their motifs of amino acids that fall into different classes. Again, we're looking for ones that are not well studied and are more specific to preadipocytes, to that differentiation of lineage."

Seeking likely candidates in a large classification of transcription factors called the "zinc finger" family — after a characteristic protein structure — Smas and her team identified around fifty such genes that have not been widely studied. By manipulating the genes in culture, over-expressing them or diminishing their expression, they hope to identify which, if any, can control the preadipocyte phenotype or the ability of preadipocytes to become adipocytes.

"It's easier to find the cellular candidates than to perform all the requisite functional studies!" she laughs. "Different molecular tools must be developed for each gene we pursue.

"Adipocytes are the only body cells designed to safely store lipids. One inroad into attacking obesity is to control the functionality of adipocytes. If somehow we could make them even better at storing lipids, we wouldn't get the toxic overflow, the cause of so many negative effects of obesity: fatty liver or pancreatic beta cell death resulting in the body's inability to make insulin."

In regard to these possibilities, Smas is also keenly interested in what molecular pathways define the healthy adipocyte and how these are altered in the obese state. Adipose cells secrete many endocrine factors called adipokines, which function either locally or systemically in the bloodstream as true hormones to communicate the metabolic status of adipose tissue to other organs.

In an obese individual, Smas says, "the expression or function of these adipokines is deranged, with the result that they're setting up pro-inflammatory or other aberrant signals that are detrimental to the rest of the body.

"So we're interested in what's unique about the adipocyte, both metabolically and at the level of gene expression. The ultimate goal is to make an adipocyte that's as healthy as possible." To this end, her laboratory has discovered a new gene, which they have termed RIFL (*refeeding* induced fat and liver). Her studies have determined that RIFL indeed encodes a new adipokine. "We were interested in RIFL because of its enriched expression in adipocytes and we determined that it encodes a secreted protein. As such, our work has shown that RIFL is a new endocrine factor in lipid metabolism."

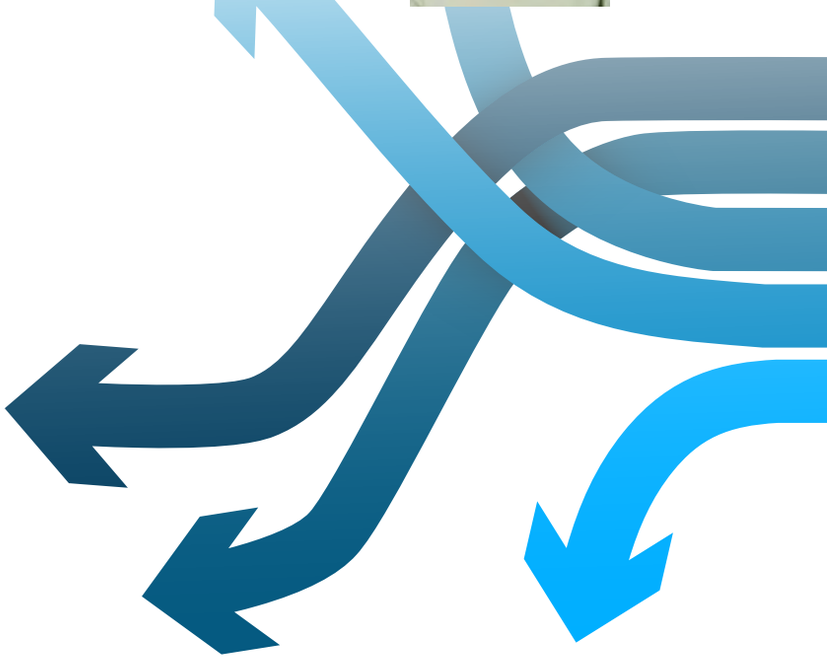
Recent studies on RIFL by the Smas laboratory, as well as the phenotype of RIFL knock-out mice, have shown that the gene has a very important role in controlling triglyceride levels in the bloodstream.

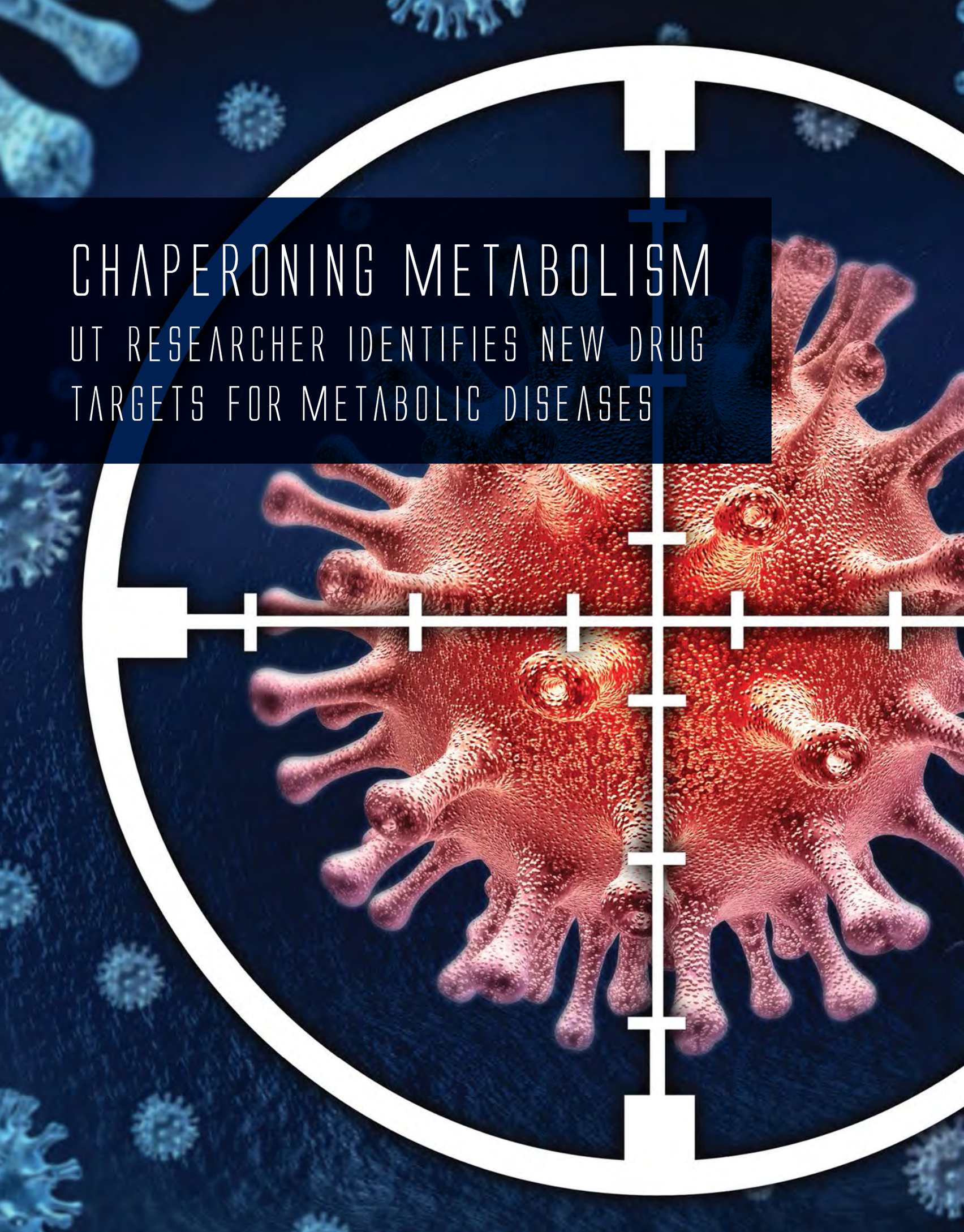
As she explains, "When the RIFL gene is knocked out in mice, the mice have a very low level of serum triglycerides. In humans, highly elevated levels of serum triglycerides are implicated, for example, in heart and kidney disease.

"You might say elevated serum triglycerides (hypertriglyceridemia) exist at a toxic nexus that impacts the systemic metabolism of many organs. To have a new pathway to control levels of serum triglyceride is a critical goal in obesity research."

The work conducted by the Smas laboratory on the identification and characterization of RIFL in lipid metabolism was published in May 2012 in *The American Journal of Physiology –Endocrinology and Metabolism*, with postdoctoral associate Gang Ren as lead author. Since that time, the Smas laboratory has made important strides forward in dissecting the mechanisms of RIFL action in control of serum triglyceride levels, with a manuscript describing these insights in preparation for journal submission. Because RIFL has a profound effect on regulation of serum triglycerides, combined with the fact that it is a secreted factor present in the circulation, Smas believes that RIFL is an excellent candidate for biomarker development studies and also as a potential novel target for drug development in the control of hypertriglyceridemia.

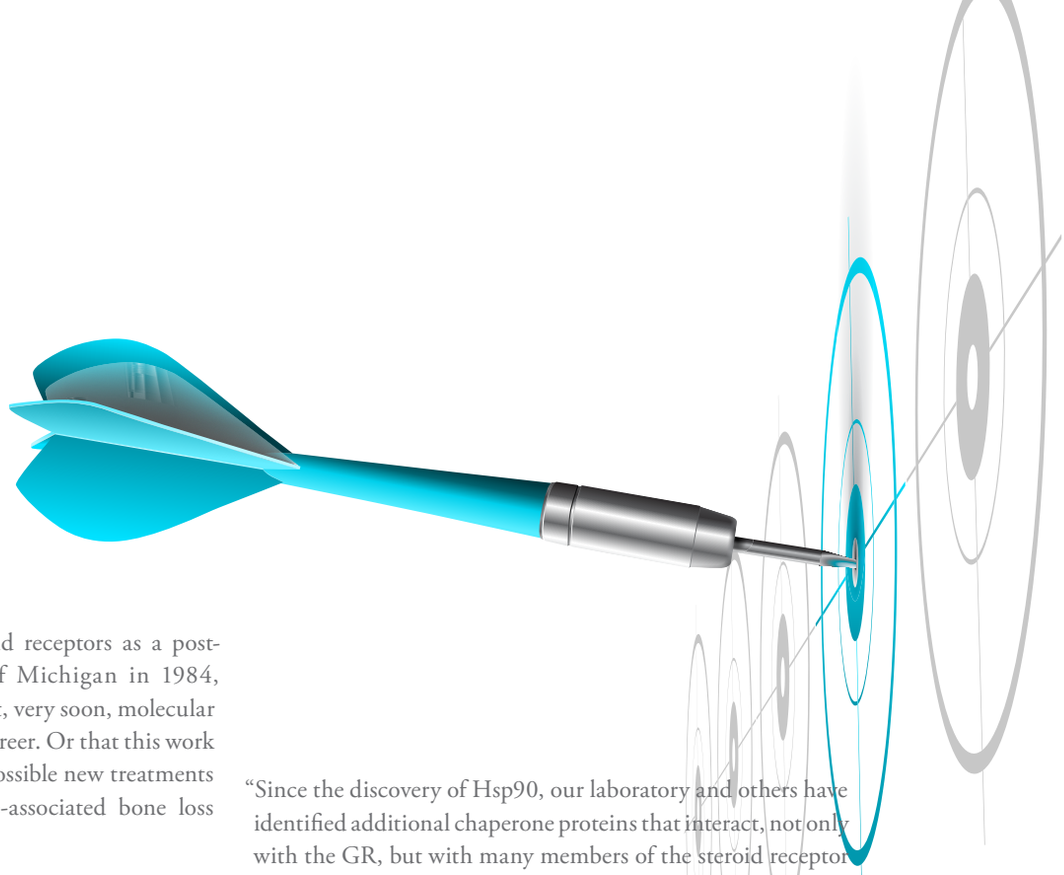
In both her studies of preadipocytes and her ongoing efforts at identifying new genes critical for adipocyte function in lipid metabolism, Smas is optimistic that her efforts will strike gold: "By better understanding preadipocytes we can potentially target obesity before its formation, at the preadipocyte stage. On the other hand, by better understanding adipocytes we can tackle the toxic consequences of too much fat." ■





CHAPERONING METABOLISM

UT RESEARCHER IDENTIFIES NEW DRUG TARGETS FOR METABOLIC DISEASES



When he began studying steroid receptors as a post-doctoral fellow at the University of Michigan in 1984, Dr. Edwin R. Sanchez had no idea that, very soon, molecular chaperones would be the focus of his career. Or that this work would lead to new insights into, and possible new treatments for, obesity, type-2 diabetes and age-associated bone loss (osteoporosis).

Dr. Sanchez, assistant director of UT's Center for Diabetes and Endocrine Research (CeDER) and professor in the Department of Physiology and Pharmacology, was told then that his research would involve phosphorylation of a particular steroid receptor, the glucocorticoid receptor (GR).

"'You're going to label it with phosphate, purify it and prove it's a phospho-protein,'" Dr. Sanchez said, recalling what his mentor, Dr. William B. Pratt, had instructed. "But we didn't get one protein; we got two. That wasn't supposed to happen."

Repeating the test yielded the same result: two bands equaled two proteins, leading the researcher and his mentor on a chase to identify exactly what they'd seen on the electrophoretic gels.

"We went to the trouble of finding out what the second band was and found that it was a protein called heat shock protein 90 (Hsp90), a molecular chaperone. We were the first laboratory to discover a steroid receptor chaperone. My project had changed overnight, literally with the very first experiment I had done."

As did his career-long focus. Nearly 30 years later, in a laboratory about 45 miles south of his old stomping grounds, Dr. Sanchez and his colleagues continue to study the amazing – and intricate – properties of steroid receptor chaperones.

BUT WE DIDN'T GET ONE PROTEIN; WE GOT TWO. THAT WASN'T SUPPOSED TO HAPPEN.

"Since the discovery of Hsp90, our laboratory and others have identified additional chaperone proteins that interact, not only with the GR, but with many members of the steroid receptor family," Dr. Sanchez said. "We now know of two FK506-binding proteins (FKBP51 and FKBP52), one cyclophilin (Cyp40) and one phosphatase (PP5) that are recruited to steroid receptor complexes via Hsp90. Our goal is to find out how each of these chaperones controls the molecular activities of steroid receptors and their physiological responses."

Steroid hormones, he explained, are molecules secreted by various endocrine glands in the human body, including the adrenals, ovaries and testes. Released into the bloodstream, the hormones have the ability to enact biochemical responses from specific cells and tissues. Of these, cortisol is probably the most important. It is secreted from adrenal glands and is the main hormone to activate the GR. In so doing, cortisol has been found to control almost all physiological processes in the body, ranging from suppression of inflammation to regulation of glucose and lipid metabolism.

But, Dr. Sanchez noted, some members of the steroid receptor family can be bound by compounds that are derivatives of metabolism, such as fatty acids. A vital receptor activated by fatty acids is the peroxisome proliferator-activated receptor-Γ (PPARγ).

"Steroid hormones and fatty acids can pass through cell membranes of target cells," Dr. Sanchez said. "Once inside, they bind their specific receptor in the cytoplasm, causing the receptor to travel to the nucleus, where it binds to regulatory regions of genes to alter levels of proteins and enzymes in the cell. In this way, both cortisol and fatty acids can control lipid or glucose metabolism by increasing or decreasing the amount and kinds of enzymes involved in production of these metabolites."

Though it sounds straightforward, a complex wave of regulation is needed for these receptors to fold properly into the three-dimensional shapes needed for precise functioning as transcription factors.

"This is where the chaperone proteins come into play," said Dr. Sanchez. "A chaperone protein helps regulate the activity of a client protein, a receptor or another protein or enzyme. The chaperone's main role is to control the folding of the client protein, which can then lead to altered phosphorylation of the protein. Altering the folding even in small ways can modulate the function.

"The chaperones I study turn out to modulate the folding and phosphorylation of GR and PPARγ and can dramatically affect their activities in interesting ways."

A particular chaperone, the protein phosphatase PP5, currently receiving attention, could factor heavily into new treatment options for diabetes and obesity, if the theories of Sanchez' team crystallize in the lab.

"Our initial experiments with PP5 showed that when it dephosphorylated the GR, the activity of GR as a transcription factor was reduced," Dr. Sanchez said. "But when PP5 dephosphorylated PPARγ, the opposite occurred — its activity was increased.

The discovery, he noted, was made by Dr. Terry D. Hinds, Jr., now an assistant professor in the Department of Physiology and Pharmacology, when he was a graduate student.

"Terry and I went on to theorize that PP5 must be serving as a fulcrum or decision point in cells in order to increase either GR activity or PPARγ activity," Dr. Sanchez said. "To test this, we employed a cell culture model of adipogenesis, which is the process by which cells change from precursors into fat or adipocyte cells capable of storing lipid. In adipocytes, cortisol acting via GR serves to promote the breakdown and secretion of lipids, while fatty acids via PPARγ promote lipid synthesis and storage.

"Sure enough, we found that PP5 in cultured adipocytes was inhibiting the lipolytic activity of GR, while promoting the lipid storage activity of PPARγ. The question we need to answer now is whether PP5 is doing the same thing in living, breathing mammals."

In mammals, PPARγ is vital to metabolic function, helping to regulate fatty acid storage and glucose metabolism. Genes activated by PPARγ are catalysts for the production of new fat cells and for the process of lipid uptake by these cells.

"In humans, PPARγ is the target of the multi-billion dollar drugs Avandia® and Actos® that are used to treat diabetes," Dr. Sanchez said. "PPARγ stores lipid in adipose tissue. If lipid stays in adipose and doesn't interfere with liver and muscle function, it can help alleviate the symptoms of type-2 diabetes."

Characterized by the liver's and skeletal muscles' non-responsiveness to insulin, type-2 diabetes mellitus causes an inappropriate accumulation of glucose in the blood, leading to many of the deleterious and life-threatening effects of diabetes.

Although Avandia has been shown to be useful in managing type-2 diabetes, it is not without controversy. The medication was reviewed in 2010 by investigators at the Food and Drug Administration for risks to patients' cardiovascular health, and use was significantly restricted later that year. According to Dr. Sanchez, the drug also negatively affects bone density.

"PPARγ promotes the differentiation of bone marrow stem cells into adipose, thus opposing the process of new bone formation. As a potent activator of PPARΓ, Avandia has been found to decrease bone density in humans, a condition otherwise known as osteoporosis."

With these issues in mind, Dr. Sanchez and colleagues have created a strain of mice that is completely devoid of PP5. Based on their cell studies, the PP5-deficient mice were expected to have elevated GR but reduced PPARγ activities in key metabolic organs, such as muscle, liver and adipose tissues. Because PPARγ especially promotes the formation of new adipose cells, they also expected to see reduced fat tissue mass in the mutant mice.

"Luckily for us," Dr. Sanchez said, "this turned out to be the case. These mice are very lipid lean. Their abdominal adipose, or belly fat, is almost entirely gone and the other adipose tissues are nearly gone, as well. Their livers and muscles appear to be normal."

Just like humans, as mice age they accumulate fat in the abdomen, hips and thighs, telltale areas where middle-aged humans show weight gain; this is a contributing factor to the development of type-2 diabetes. According to Dr. Sanchez, the PP5-deficient mice are resistant to this age-dependent process.

"When we saw this, we predicted that the mutant mice should be more sensitive to the actions of insulin," Dr. Sanchez said. "We collaborated with the director of CeDER, Dr. Sonia Najjar, to perform metabolic tests. Sure enough, these mice are much more sensitive to insulin, with reduced blood glucose levels."

OUR GOAL IS TO FIND OUT HOW EACH OF THESE CHAPERONES CONTROLS THE MOLECULAR ACTIVITIES OF STEROID RECEPTORS AND THEIR PHYSIOLOGICAL RESPONSES.

To investigate bone physiology, Dr. Sanchez is collaborating with Dr. Beata Lecka-Czernik, CeDER member and associate professor in the Department of Orthopedic Surgery and the Department of Physiology and Pharmacology.

"Once again, we found what we expected: the mutant mice showed almost a complete absence of fat-bearing cells in the bone marrow of the femur. More importantly, the femurs of these mice also had higher bone density."

The next step, he said, is to treat the mutant mice with Avandia to test their responsiveness to the diabetes drug. "If PPARγ activity is really lost in these mice, Avandia should have no effect. Then, we'll treat the mice with cortisol to see if there is elevated GR activity, especially in adipose. But of course, the ultimate goal is to develop drugs that target PP5."

UT, he said, has been granted a provisional patent based on the PP5 research and could partner with pharmaceutical companies to further investigate its clinical potential.

Dr. Sanchez' team also is studying other chaperones. "My last graduate student, Dr. Lance A. Stechschulte, discovered that FKBP51 [another chaperone protein] not only controls steroid receptors, but also regulates phosphorylation pathways in cells important to both cell growth and metabolism. We are very excited about the potential of these new studies." ■

COLLEGE OF MEDICINE CLASS NOTES

Dr. J. William Wulf (MED '85) was elected to the position of Chief Executive Officer of Central Ohio Primary Care Physicians, Inc.

Dr. Ryan Szepiela (MED '06, Res '10) was a recipient of a 2013 "20 under 40 Leadership Recognition Award" presented in September 2013. He was selected from a field of 109 candidates. The 20 under 40 program focuses on individuals under the age of 40 who have distinguished themselves in their careers and/or the community.

Dr. Mathew Weimer (MED '05) is among a select group of physicians honored by the American Academy of Family Physicians Foundation for his commitment to education in the field of family medicine.

Lance A. Talmage, M.D. (Eng '60, MED '64), was inducted into the Ottawa Hills Hall of Fame on April 13, 2013. A former Ottawa Hills Boosters Club president, Dr. Talmage served as team physician for the Ottawa Hills football team from 1981-2004 and for all girls sports teams from 1978-1986. For his outstanding service, he received the Ohio Outstanding Team Physician Award from the Ohio State Medical Association and Ohio High School Athletic Association in 2002.

Dr. Talmage was an Ohio delegate to the American Medical Association for 20 years. He served as president of the Ohio State Medical Association from 1998-1999, as president of the Toledo-Lucas County Academy of Medicine in 1994-1995 and as president of the medical staff at Toledo Hospital from 1989-1991. He was appointed by Ohio's governor to the State Medical Board of Ohio in 1999 and reappointed in 2004 and 2009. He served as board secretary for nine years. He was elected to a three-year term on the board of directors of the Federation of State Medical Boards (FSMB). This year, he was elected chair of the FSMB, a national organization representing 70 medical and osteopathic state boards within the United States and its territories.

He has been a member of the Lucas County Domestic Violence Task Force and United Way Cabinet. He has served as president of the University of Toledo Alumni Association during the 2000-2001 school year, and on the University of Toledo Foundation Board of Trustees. Currently, he is a member of Pi Kappa Phi Fraternity National Foundation Board of Directors. Dr. Talmage has been honored in the community with the University of Toledo "Blue T Award in 2002 and the "Gold T Award" in 2010, and the Waite High School Hall of Fame in 1996.

Dr. Talmage was also named chair-elect of the Federation of State Medical Boards (FSMB), a national organization representing 70 medical and osteopathic state boards nationwide. A practicing gynecologist and a clinical professor at UTMC, he previously served on the FSMB Board of Directors.

Cheryl Bihn, M.D. (MED '93) joined the physical medicine and rehabilitation department at Mayo Clinic Health System in La Crosse, Wisconsin.

Arthur C. Kendig, M.D. (MED '03), a specialist in heart rhythm disorders, joined the staff of South Carolina Heart Center, which has offices in Columbia, Camden, Bamberg and Hartsville.

Zachary M. Gatton, M.D. (MED '07), completed his four-year residency in anesthesiology at The University of Louisville Hospital, where he was named the Outstanding Resident in acute pain and regional anesthesiology. He accepted a position at Knox Community Hospital in Mount Vernon, Ohio.

Cynthia Kenmuir, M.D., Ph. D (PhD '10, MED '11) is a resident in neurology at The University of Pittsburgh Medical Center, with plans to complete her fellowship training in interventional neurology.

Death notices

Dr. Michelle Irons (MED '92), Toledo at 49.

Dr. James Chengelis (MEd '82, MED '87), Brookline, Mass., at 58.

Dr. Donald A. Baker (Ed '66, MED '76, Res '81), Toledo at 69. He was an assistant professor of orthopedic surgery. He joined the MCO faculty in 2001. He received a football scholarship to UT, where he played for the Rockets from 1961 to 1963. Baker graduated with a bachelor's degree in education in 1966 and was an assistant football coach for the Rockets from 1969 until 1970, the first two seasons of Toledo's 35-0 streak. He returned to the classroom to pursue medicine and graduated from MCO in 1976 and completed his residency there in 1981. In 2003, Baker was inducted into the Varsity 'T' Club for his gridiron play. He was a member of the UT Foundation Board of Trustees. The family suggests contributions to the Dr. Donald A. Baker Scholarship Fund through the UT Foundation.

Dr. Scott Longevin (MED '86), Cincinnati, Ohio at 54.

Richard Prutow ('76 MED), San Diego, Calif. at 71.

Dr. Charles B. Travis III (MED '80), Largo, Fla. at 74. Dr. Travis III completed his residency in the MCO Department of Family Medicine and three years later was appointed as a volunteer faculty member with the title of clinical assistant professor in family medicine. In 1990, he joined the MCO faculty as an assistant professor of family medicine and was promoted to associate professor in 2000. For three years, he also served as medical director of the Physician Assistant Program in the School of Allied Health. He received an award from the Lucas County Alcohol and Drug Addiction Services Board in 2001 for establishing a curriculum on drug and alcohol issues at MCO. He retired from the University in 2005.

Rocket Science

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