“The structure of science gradually grows, but only as it is built upon a firm foundation of the past.”

Owen Chamberlain
American Physicist, 1920-2006
The university’s sponsored research has increased 28 percent over the past five years and 267 percent over the past 10.

More than 60 percent of MCG’s $73.9 million in sponsored research funding comes from the National Institutes of Health.

National Institutes of Health funding in the MCG School of Medicine has grown approximately 119 percent since 1998.

The MCG School of Medicine ranks second among like-sized schools in direct sponsored research.

The Schools of Allied Health Sciences and Nursing have formed the MCG Interdisciplinary Practice and Research Center to optimize clinical and research initiatives in both schools.

The School of Dentistry has shown steady increases in research funding, with initiatives in areas including tissue regeneration and the effects of green tea polyphenols on conditions as diverse as cancer and autoimmune disease.

At a Glance

MCG concentrates its research efforts in the thematic areas of cancer, cardiovascular disease, diabetes/obesity, infection/inflammation and neurological disease.

One privilege of my position is to annually compile examples of MCG’s most groundbreaking research and present it to you in this magazine, *MCG Tomorrow*.

The name says it all: The biomedical research we are conducting today will change the shape of health care tomorrow. “Tomorrow” is almost as literal as it is metaphorical. The university’s emphasis on translational research is moving discoveries from bench to bedside at breakneck speed. It is thrilling to know that today’s findings will, in the very near future, mean the difference between disease and wellness for scores of our citizens, and that yesterday’s breakthroughs are already improving countless lives.

Quite simply, our biomedical research bounty is yielding its fruits in real time.

I invite you to take a moment to read the details in this 2008 edition of *MCG Tomorrow* and ponder how MCG research may very well change your life or the lives of your loved ones. Advances in cancer, cardiology, diabetes/obesity, infection/inflammation and neurological disease are reaping incredible rewards.

Thank you for taking the time to read about and support MCG’s research. I think you will find our progress simply stunning. And we can’t wait to see what tomorrow will bring.

Sincerely,

Frank A. Treiber, Ph.D.
Vice President for Research, Associate Provost and Regents Professor of Pediatrics
Cancer is smart. It’s manipulative.

The key to beating it is being more manipulative—understanding its molecular signature, the way it preys on the body and how it uses our immune system for its protection.

“Why does the immune system allow tumors to persist and kill the host even though the tumor is clearly bad for us?” muses Dr. David Munn, program leader for the Cancer Immunotherapy Program in the MCG Cancer Center and professor of pediatrics. “There are plenty of differences between a tumor and healthy tissue that should signal the immune system that the cancer is bad and it should defend against it. But we know that in everyone who comes into a clinic with a tumor, for some reason, their immune system has refused to do that.”

Instead, Dr. Munn says, it is tricked into tolerating the tumor—to letting it live and grow. For the past decade, he and research collaborator Dr. Andrew Mellor have led research groups trying to dissect the deception.

“It’s not that tolerance is all bad; it’s not a sign of weakness,” he says. “We all depend on our immune system to remain tolerant to our own bodies. But in cancer, tumors manage to sneak in and persuade the immune system that it should use the tolerance that is a benefit to normal tissue and apply that to the tumor. The tumor actively creates that tolerance and that’s what we need to interrupt.”
One likely culprit, MCG researchers discovered in 1998, is an enzyme called IDO. IDO is used by fetuses to help avoid rejection by the mother’s body. But in cancer, IDO strengthens the effectiveness of the regulatory T-cells that cancer uses to protect itself from the immune response.

IDO serves as a sort of linchpin, Dr. Munn says. “It’s a crossroads where a number of mechanisms, some of which are more powerful than IDO itself, come together,” he says. “Regulatory T-cells, for example, are much more powerful than IDO. If you take a mouse and remove IDO, it compensates just fine. If you remove the T-cells, the mouse dies. When tumors use IDO to recruit and activate those T-cells, it becomes a leverage point.”

In addition to the program in cancer immunotherapy, MCG’s immunotherapy research includes clinicians who treat transplant patients as well as researchers studying infectious disease, diabetes and other immune disorders—all conditions where too much or too little immune response is the problem.

“All of these have been related by the same set of molecular mechanisms,” Dr. Munn says. “If we’re going to create a drug or targeted therapy to manipulate that mechanism, whether it boosts or suppresses the immune system, we need to know the normal mechanisms that turn it off and on at certain times.”

But clinical immunotherapy is a small part of a broader approach to finding out how the immune system gets hijacked.

“We know this: the immune system doesn’t want to respond to tumors; we want to persuade it to do so,” Dr. Munn says. “How we do that is the question.”
Even with all the progress in research, immunotherapy trials in cancer treatment have been going on for several decades with only limited success, Dr. Munn says. Scientists first had to realize that single agents don’t work effectively—that no single strategy to activating the immune system is effective. Combination regimens are important. They and others in the field have discovered that chemotherapy, often thought of as immunosuppressive, can actually be a good thing. “It turns out that chemotherapy wipes the slate clean,” Dr. Munn says. “For the years that the cancer has been developing, the immune system has decided that the tumor should be allowed to live. With cancer, the immune system refuses to respond.” Wiping the slate clean may actually create better opportunities to use cancer vaccines such as those Dr. Yukai He is researching.

Dr. He, a member of the Cancer Immunotherapy Program in the MCG Cancer Center, has shown that antigens—proteins on or in all cells—presented to T-cells by cells called dendritic cells can get the attention of the immune system. By modifying those antigens just enough to wake up the immune system, he and his colleagues believe they can use vaccines to trick it into targeting and killing cancer cells. His research focuses on using the lentivector, HIV minus most of the genes, as the basic mode of transportation. The vector, which already does a good job of carrying HIV into the body and allowing it to survive, could be used to help a small amount of cancer cells generate a response that primes the immune system to reject cancer from that point on. “Tumor vaccines work where tumor growth is established,” says Dr. He. “New strategies could include an inhibitor to turn off IDO’s suppression of the immune system and a vaccine to turn on the immune response.”
Bad SIBLINGs

Much like IDO manipulates the immune system, some proteins that are supposed to aid bone formation and cellular repair instead spread oral cancers.

Small Integrin-Binding Ligand N-linked Glycoproteins, or SIBLINGs, are a protein family found in a narrow region of human chromosome 4 that helps mineralize bone by adding calcium. Scientists originally thought SIBLINGs were limited to tissues in bone and teeth, but recent research found them in the soft tissues of the salivary glands, where they repair cells damaged by the high-energy saliva production process.

Unless they’ve gone bad.

“We believe several members of the SIBLING family work in concert with other proteins to break down tissue barriers in the mouth and allow cancer to seep into the connective tissue,” says Dr. Kalu Ogbureke, oral pathologist. “Inside that tissue, the cancer comes into contact with blood and lymphatic vessels, which transport it to distant sites in the body. This becomes the seed for cancer. The irony becomes that in each situation, SIBLINGs are helping everyone do their job. In bone formation and cellular repair, the outcome is desirable, but in cancer it’s not.”

Watching how these SIBLINGs help perpetuate cancer has enabled scientists to use them as biomarkers for oral cancer—an important because pathologists determine whether cancer has been removed by examining the borders of surgically removed lesions.

But those tests aren’t always reliable, Dr. Ogbureke says, and the mortality rate for oral cancer remains around 50 percent.

“Cancer starts at the molecular level, even before it manifests to the trained eye,” he says. “So now, we can test the borders for SIBLING proteins. Because we know that their presence indicates the presence of disease, cutting out lesions until they have a SIBLING-negative margin may help us stop the disease before it spreads.”

Such findings should inevitably lead to better therapies, researchers say. Therapies targeted to the molecular structure of individual cancers stand a better chance of eradicating the disease that kills more than half a million people each year.

continued
Strategy, says Dr. Kapil Bhalla, is the key. “Our plans must be very strategic,” says Dr. Bhalla, founding director of the MCG Cancer Center and Cecil J. Whitaker Jr., M.D./Georgia Research Alliance Eminent Scholar in Cancer. “We have to dream the impossible to make it possible at some point. We have to create a team of people who are in it for the fun of science, and beyond that, making the lives of others better.”

The Cancer Center supports basic science research and translates discoveries into the clinic as new treatment, prevention and screening strategies. That requires three things, Dr. Bhalla says: large numbers of investigators; an infrastructure that supports basic science, translational and clinical programs; and a strategic vision.

His plan includes:

- Cultivating existing research programs in cancer immunotherapy, epigenetics, chaperone biology, cancer cell signaling and developmental therapeutics
- Building a translational research infrastructure, including a tumor bank that allows physicians to study the molecular signatures of individual cancers and move toward developing personalized therapies
- Developing a phase I/II clinical trials unit to help implement trials of cutting-edge, novel therapeutics based on basic science discoveries
Cancer Research at a Glance

- MCG has been re-designated a Minority-Based Community Clinical Oncology Program by the National Cancer Institute, ensuring better access and treatment for cancer patients, particularly minorities.

- Cancer Center Director Kapil Bhalla and postdoctoral fellow Warren Fiskus developed a cell line that resists conventional treatment but is highly sensitive to heat shock protein 90, an emerging cancer treatment.

- Dr. Bhalla and postdoctoral fellow Yonghua Yang are determining how environmental stress can cause cancer by reducing the activity of an enzyme that causes cell death.

- Associate Cancer Center Director John K. Cowell is probing genetic mutations that lead to cancer.

- Geneticist Hernan Flores-Rozas has identified genes that protect cells from the chemotherapy drug doxorubicin, a finding that should also help prevent the heart damage commonly caused by the drug.

- Hematologist-oncologist Teresa A. Coleman is studying a drug called vinflunine to treat advanced bladder cancer in patients whose kidney problems preclude conventional treatment.

- Cell biologist Quansheng Du is studying the role of the mitotic spindle in cell division. Understanding the mechanism should provide clues for targeted cancer therapy.

- Cell biologist Patricia V. Schoenlein is probing the survival mechanisms of breast cancer cells that don’t respond to hormone therapy.

- School of Dentistry faculty Jill Lewis, Regina Messer and John Wataha are working with student Alpesh Patel in determining how the blue curing light used to harden dental fillings seems to stunt tumor growth.

- Molecular biologist Zixuan Wang is studying a new test, the GeneSearch Breast Lymph Node Assay, that examines large sections of the sentinel lymph node for genes expressed by breast cancer.

Visit www.mcg.edu/news/cancer for in-depth information about our cancer research.
Dr. John Catravas makes cardiovascular research sound like the most elegant of Agatha Christie plots: The mystery is baffling and inscrutable at the outset, but once the pieces fall into place, the denouement makes perfect sense.

He lives for the “aha” moments, and he’s had a gracious plenty of them.

When he and his colleagues identify an area for study, “it starts as a surprise,” says Dr. Catravas, director of MCG’s Vascular Biology Center. “Before we understand the mechanism, we’re operating in the dark. But once we understand it, it makes such beautiful sense. We start with a surprise and end with amazement of how logical it is.”

The heart—that tireless muscle that pumps blood throughout the body—has long been a source of intense study, particularly considering heart disease is a leading cause of death and disability in America. But the heart can’t be studied in a vacuum.

Most heart disease results when vessels that carry oxygen and other nutrients back to the organ are blocked or otherwise impeded, in effect starving the heart. MCG has made tremendous strides in understanding just exactly what happens in the vessels to cause the breakdown.

“We know so much more than we did even a decade ago about how the cardiovascular system works,” Dr. Catravas says.
Laying the Groundwork

Their expertise, he says, builds on an astonishing body of research that distinguishes MCG as one of the foremost universities in cardiovascular research.

For example, it was Dr. William F. Hamilton, longtime chair of the MCG Department of Physiology, who in the 1940s invented a manometer to measure intravascular pressures. Dr. Andre Cournand, who with Drs. Werner Forssmann and Dickinson W. Richards received a 1956 Nobel Prize for their innovations in cardiac catheterization, stressed their work would not have been possible without the manometer and said in accepting the award that Dr. Hamilton should have shared the award.

In the same era, Drs. Raymond Ahlquist and Philip Dow were revolutionizing cardiovascular treatment in the areas of pharmacology and physiology, respectively. Dr. Ahlquist, for instance, laid the groundwork for beta-blocking drugs, which block the action of the involuntary nervous system on the heart.

Their successors carried the torch both at the bench and bedside. Dr. Robert G. Ellison, the late Chief of the Section of Thoracic and Cardiac Surgery Emeritus, studied with the Nobel laureates and performed Georgia’s first open-heart operation in 1956, among many other accomplishments in the field. His wife, Dr. Lois T. Ellison, helped develop MCG’s cardiopulmonary laboratory for cardiac catheterizations and pulmonary function studies.

“Present-day cardiologists would find it difficult to believe the methodology and equipment available in these early catheterizations,” says Dr. Lois Ellison, who today serves as MCG’s Medical Historian in Residence.
In the publication, *Moments in MCG History*, she describes a dizzying but precision-filled process of manually calibrating the manometer, rolling a heavy, unwieldy fluoroscope unit into the cath lab, positioning it over the patient’s chest and controlling it with a foot switch, bending over the screen to see the real-time X-ray images (“difficult and tiring,” she recalls, “especially with the lead aprons that were worn”), capturing the manometer’s measurements on photographic paper with a light beam, then rushing the paper from the hospital to the Dugas Building to develop it in the dark room.

**Science Sees the Light**

The technology was primitive by today’s standards, but the implications were breathtaking: It was finally possible to visualize and assess heart function. Medical science wasted no time capitalizing on the wellspring of information to prod sluggish hearts to stay the course. Advances included electrical impulses such as pacemakers to shock it back into action, surgery to clear or reroute clogged arteries, surgery on the heart itself and drugs such as beta-blockers to reduce stress on the heart.

But all these lifesaving procedures reflect damage control. The Vascular Biology Center’s goal isn’t just to optimize the function of a diseased system, but to restore the system to health.

“We have two uncommon but key factors: a high degree of collaboration..."
and interaction and a critical mass of investigators with similar interests,” says Dr. Catravas of his 13-member team. The synergy is yielding remarkable results. Last year, Dr. Catravas and his colleagues reported their finding that heat shock protein 90 inhibitors show great promise in calming vascular inflammation.

“HSP 90 is a chaperone that activates other proteins and keeps them mature,” Dr. Catravas says. “Lots of proteins contribute to inflammation, so if you degrade them by inhibiting HSP 90, you reduce the inflammation associated with them.” Less inflammation means smoother blood flow to and from the heart. Hypertension, or impeded blood flow, is the chief cause of heart disease and a factor in many other diseases, including type 2 diabetes and stroke.

**Exceeding Expectations**

HSP 90 inhibitors are already showing success in cancer treatment, which also requires inflammation control. In fact, clinical cancer trials and MCG’s animal studies in inflammation are finding that HSP 90 inhibitors exceed expectations.

“Not all proteins (associated with inflammation) are bad, and when you block the good ones, you may have side effects,” Dr. Catravas says. “But HSP 90 inhibitors don’t have as many side effects as we would have predicted. In cancer treatment, for instance, the inhibitors tend to concentrate mostly on the cancer cells for reasons we’re just starting to understand.”

His studies suggest the inhibitors will be equally accommodating in treating inflammatory disease. “We’ve been successful in animal studies, but can it be translated to humans? That’s what we want to find out.” If successful, he hopes the drugs will supplement other medications such as ACE inhibitors, which block the synthesis of the inflammation-causing peptide, angiotensin.

As his research seeks a way to degrade proteins in general, Department of Physiology Chair R. Clinton Webb is principal investigator of an $11 million National Institutes of Health Program Project grant targeting a specific class of proteins called cytokines, which facilitate communication among immune system cells. He hopes to manipulate these cytokines to thwart the immune system’s inflammation response in blood vessels.

**Drilling it Down**

While the Vascular Biology Center pursues these and many other studies, the MCG Department of Pediatrics’ Georgia Prevention Institute is teasing out cardiovascular disease at an even more basic level. Why, for instance, do vessels become inflamed in the first place?

The GPI was established some 30 years ago to determine risk factors for adult-onset diseases, including cardiovascular disease. But the mission took on new urgency when the adult diseases, before the researchers’ eyes,
“High blood pressure affected about 1 percent of children a generation ago. Now, it’s up to 9 percent.”

DR. GREGORY HARSHFIELD

began getting a foothold in childhood. “High blood pressure affected about 1 percent of children a generation ago,” says Dr. Gregory Harshfield, director of the GPI. “Now, it’s up to 9 percent.” Heart disease and type 2 diabetes are also showing up in childhood.

Such a sudden surge obviously implicates environmental factors, and the GPI Echoes the now familiar refrain that high-fat diets and sedentary lifestyles are dooming many children to poor health. Many GPI researchers’ studies are quantifying the effects, including Dr. Catherine Davis’ study putting overweight children on a vigorous daily exercise routing and measuring the resulting improvements in areas including weight, blood pressure and cognitive skills.

Other GPI projects are probing genetic variations that may predispose people to hypertension and related diseases. For instance, Dr. Harshfield, principal investigator on a $10.5 million NIH Program Project grant renewal, has identified the tendency of some people to retain salt after stress—a primary reason, he believes, that blood pressure remains elevated during sleep for those with the problem.

Dr. David Pollock, a renal physiologist in the Vascular Biology Center who conducts animal studies on the subject with wife Jennifer, suspects a defect in the kidneys that keeps them from excreting salt normally. MCG researchers also have identified a variation of the angiotensin receptor gene that they believe exacerbates salt retention.
One Size Does Not Fit All

Abnormal salt retention seems to disproportionately target African-Americans, one of many ethnic variations scientists are exploring.

For instance, Dr. Sunita Dodani, assistant dean for research in the School of Nursing, a cardiologist and cardiovascular epidemiologist, is exploring the disproportionate risk of heart disease and diabetes among African-Americans and south Asian immigrants.

Dr. Dodani is determining that high-density lipoprotein—the so-called “good” cholesterol—may not protect the hearts of high-risk south Asians. That genetic strike is often exacerbated by strikes two and three when they face the stress of assimilating into American life and adopt American lifestyles including high-fat diets.

“South Asians tend to have low obesity and smoking rates, and most of them don’t eat red meat,” she says. Reports of south Asians with low cholesterol levels having heart attacks at young ages, therefore, suggest untraditional risk factors that she is trying to tease out.

Dr. Dodani also has a $3.7 million NIH grant to assess a faith-based program, Fit Body and Soul, offering information and support about healthy lifestyles, including diabetes prevention, in 20 African-American churches. Her over-riding premise is that one size of cardiovascular disease treatment does not fit all.

She hopes her research will encourage health care providers to consider individualized approaches to cardiovascular treatment. She also wants to sound the alarm to parents everywhere: Prevention is the key, so healthy lifestyles are vital.

“What happens in childhood,” she says, “will affect your whole life.”

Cardiovascular Research at a Glance

- Vice President for Research Frank Treiber is continuing his long-term study of 523 pairs of twins to determine how environmental stress contributes to cardiovascular disease and type 2 diabetes.

- Cardiologist Vincent J.B. Robinson and internal medicine resident Dineshkumar Patel demonstrated that a nuclear stress test can effectively diagnose diastolic dysfunction as well as coronary disease.

- Dr. Robinson and research assistant Rakesh N. Patel have developed algorithms to individualize diagnostic techniques for heart disease.

- Physiologist Adviye Ergul is probing the interaction of receptors for a blood vessel constrictor called endothelin-1 in hopes of harnessing its potential in hypertension and heart disease treatment.

- Physiologist Edward W. Inscho is studying a molecule called ATP, particularly in the kidney’s filters, in better understanding blood vessel constriction.

- Nurse researcher Martha S. Tingen is determining whether school and family intervention can prevent smoking in African-American children.

- Patricia Sodomka, director of the MCG Center for Patient and Family Centered Care, is probing the use of electronic personal health records to help patients better manage hypertension.

Visit www.mcg.edu/news/cardio for in-depth information about our cardiovascular research.
She sees her study subjects every day after school.

Children pile off the bus and into the gym at the Georgia Prevention Institute to do what most of them wouldn’t be doing at home: passing balls, running around, maybe doing a few calisthenics or gyrations with a hula hoop.

“That is how kids naturally exercise when they do spontaneously exercise. There is a burst of activity, they catch their breath, then run again,” says Dr. Catherine Davis, clinical health psychologist. The problem is many children aren’t doing that these days. The result is an epidemic of obesity and weight-related problems such as type 2 diabetes, which not long ago was considered an adult disease.

The kids in her studies are still healthy but overweight and largely inactive on their own. She’s shown that with relatively little effort, 20 or 40 minutes a day, the children can reduce their weight and insulin resistance (a risk factor for diabetes) and improve their cognitive ability. From the typical shrieks and laughter, it seems the kids have fun as well. “You can sometimes see the difference. They feel better about themselves,” Dr. Davis says.
Healthy Bodies, Healthy Minds

When she presented her research at the 2007 Obesity Society’s Annual Scientific Meeting, the documented cognitive improvements alone caused quite a stir. It endeared her to exercise guru Richard Simmons and ideally helped provide the kind of ammunition schools need to again find time for regular, vigorous physical activity in students’ jam-packed days.

Schools are doing a great job trying to meet kids’ educational needs, but cramming more learning into a day at the expense of physical activity may not serve schools or the kids well, the researcher says.

“Having the kids in better health because they are active and maybe even because they are enjoying themselves could be more effective in helping these children in school,” says Dr. Davis. She suspects the fact that physical activity enables better sleep may be part of the magic. “My hunch is they may be able to think better because they sleep better.”

Dr. Davis is starting another study to examine the relationship between hard-working bodies and better brains.

Georgia Prevention Institute colleague Dr. Yanbin Dong has found what can happen to children who don’t get such intervention. Key indicators of cardiovascular health, such as blood pressure and arterial stiffness, suffer even in mildly overweight adolescents, he has shown. The health risks worsen as weight increases.

continued
“This is a wakeup call to parents and physicians to pay more attention to children who fall somewhere in the middle because they likely are headed toward being fatter and at increased risk of cardiovascular disease,” says Dr. Dong. In fact, many of the children running around the GPI gym for Dr. Davis’ studies probably fall into this category: kids you might not pick out of a crowd as heavy but whose health indicators are creeping in the wrong direction.

“Almost everything was in between,” Dr. Dong says of study participants. For example, the whites had about a 2-mmHg increase in casual and ambulatory systolic blood pressure (the top number taken when the heart is contracting) as he looked across the three categories of kids from thinnest to heaviest. Although such incremental increases don’t guarantee eventual hypertension, it’s not a good sign, says Dr. Dong. “If you become hypertensive when you are 42, it doesn’t go up just like that,” he says, snapping his fingers. “Blood pressure in your adolescence will track to your adulthood, so it’s likely there will be amplification when you get older.”

Improved fitness will no doubt help these children; losing weight would as well, he says. Still, as a pragmatist, he knows weight loss is seldom permanent, and as a geneticist, he also knows obesity risk is programmed into the DNA of some of these children. So he is teaming up with vascular biologists to also look at genetics and environment and find what they can do about both.
The Diabetes/Stroke Link

The bench science of Dr. Adviye Ergul reflects a human bottom line.
She studies mice bred to be diabetic under as natural conditions as possible, most closely reflecting the health of human type 2 diabetics.

The realistic model is providing insight into diabetics’ increased stroke risk and poorer prognosis. In fact, she has documented the thickening of blood vessel walls in her lab animals by the time they are just 10 weeks old.

The physiologist is an expert in endothelin-1, a protein that constricts blood vessels and remodels their walls. Higher blood glucose increases endothelin levels, and she wants to know how endothelin contributes to vascular damage to the brain. The role appears significant: When her laboratory mice received endothelin antagonists, the damage abated.

Because diabetes can modify blood vessels in such short order and knowing diabetics’ increased stroke risk, she decided to pursue her hypothesis that their strokes would be bigger. She was surprised to find that is not the case; rather, diabetes causes more bleeding—and consequently more brain damage—following a stroke. The nature of the stroke is different as well, she says, citing hemorrhagic transformation linked to an ischemic stroke caused by a clot. Now she is trying to find out why.

“We think what is happening is the animal, like a human, is chronically exposed to a high blood glucose level and somehow the brain senses that and tries to revascularize to make new blood vessels,” she says. A similar thing happens in diabetic retinopathy: the body’s well-intentioned rescue of a retina starving for oxygen ends up producing excessive, leaky blood vessels that cause blindness.

Interestingly, about 60 percent of stroke patients—both with diabetes and without—have elevated blood glucose levels when they arrive at an emergency room. And a major side effect of the only FDA-approved medication for stroke, tPA, is bleeding.

“The higher the blood glucose level, the more likely they are going to bleed with tPA,” says Dr. Ergul. “There is a lot of interest among stroke specialists here and nationally about how you manage blood glucose in this situation.”

Of Mice and Men?

For example, Drs. David Stepp and David Fulton, colleagues in the Vascular Biology Center, are looking at why eliminating a single gene—PTP1B—that contributes to insulin resistance appears to prevent much of the cardiovascular damage typically associated with obesity.

Cardiovascular disease is the biggest health threat of obesity. In the researchers’ efforts to find out why, they eliminated protein tyrosine phosphatase 1B, or PTP1B, in genetically fat mice that get diabetes. Now they want to know the “why” of PTP1B, which is over-expressed in obesity.

They suspect swings in blood glucose levels that begin long before diabetes is officially diagnosed produce superoxides that block nitric oxide, a powerful dilator of blood vessels. Decreasing insulin resistance by blocking even one responsible gene appears to steady fluctuating blood glucose levels and reduce cardiovascular damage, at least in mice. Acknowledging that what works in mice may not work in man, Dr. Dong will look at PTP1B variations in humans and how they correlate to obesity.

“I don’t know what is the normal variation of the abundance or activity of that gene in the human population,” says Dr. Stepp. “Yanbin can get that. He can say this group of children has a genetic variation that makes PTP1B less effective, and look: they don’t develop insulin resistance or cardiovascular damage that is as bad.”

“I think we are far away from being able to fix a gene,” says Dr. Dong. “But if we can look at your genes and say you have a bad form of this gene, not me, not him, but you have to be more mindful in monitoring your weight and blood glucose.”

Still, a gene is only part of the story; typically there are environmental triggers as well that, like genes, can vary from one person to the next.

“If I have the bad gene, mental stress may trigger me to develop hypertension, obesity and diabetes,” says Dr. Stepp. “For another person who has that gene, maybe eating fast food triggers the same thing. What we need to dissect in humans is what set of genes and what environmental interactions really make you hypertensive, diabetic and obese.”
Want to avoid diabetes?
A healthy lifestyle is your best bet to steer clear of the type 2 form of the disease, characterized by the body's inability to effectively use insulin.

But the type 1 form of the disease—in which the body inexplicably attacks its insulin-producing cells—involves factors largely beyond your control.

What exactly are those factors?
Dr. Jin-Xiong She, director of the MCG Center for Biotechnology and Genomic Medicine, is trying to find out. He is a principal investigator on an international effort looking at thousands of babies with genes that put them at high risk for diabetes, then following them for years to see how genetics and environment work together to cause the disease. His laboratory studies include identifying additional high-risk genes as well as biomarkers for children at risk.

As he and his colleagues work to predict who will get the disease, the race is on to try to prevent it. Here are a couple of examples:

**No-Go Zone**

Dr. Andrew Mellor, director of MCG’s Immunotherapy Center, and his colleagues are seeking to create a “no-go zone” in their efforts to forestall type 1 diabetes.

They will try to delay or prevent the disease in laboratory mice by boosting levels of the immune-suppressing enzyme, IDO, or by packaging islet cell antigens, which get the immune system's attention, with this suppressor. Dr. Mellor believes T-cells, which decide whether to attack or ignore an antigen, will ignore insulin-producing cells if they see them for the first time with IDO.

He and his colleagues, funded by the Juvenile Diabetes Research Foundation International, suspect that a defect in dendritic cells hinders IDO expression. Dr. Mellor's research partner, Dr. David Munn, collaborated with Dr. Jonathan Katz of the Cincinnati Children's Hospital Medicine Center to demonstrate that diabetes worsens in mice when dendritic cells and IDO are depleted.

“That was formal evidence that the dendritic cells with IDO were putting the brakes on the disease,” Dr. Mellor said. “It leads to the hypothesis that by reinforcing the IDO mechanism in these mice, you can slow or even prevent the disease.”

He will study more methods to eliminate IDO in the mice to observe what happens. He will also treat mice with a rheumatoid arthritis drug found to enhance IDO expression. “If you have the IDO come on earlier and stronger,” he said, “maybe you can slow or halt disease progression or even prevent it.”
A Sip of Serendipity

Dr. Stephen Hsu, a molecular/cell biologist in the School of Dentistry, recently stumbled onto the serendipitous finding that EGCG, an antioxidant found in green tea, may be a powerful new tool in the fight against type 1 diabetes.

He and his colleagues were testing EGCG's ability to prevent Sjogren's syndrome in laboratory mice. The syndrome damages moisture-producing glands, causing dry mouth and eyes.

“Our study focused on Sjogren’s syndrome, so learning that EGCG also can prevent and delay insulin-dependent type 1 diabetes was a big surprise,” says Dr. Hsu.

Both type 1 diabetes and Sjogren’s syndrome are autoimmune diseases, which cause the body to attack itself. Autoimmune disorders are the third most common group of diseases in the United States and affect about 8 percent of the population.

Researchers treated a control group of mice with water and a test group with a purified form of EGCG dissolved in the drinking water. At 16 weeks, the EGCG-fed mice were 6.1 times more likely to be diabetes-free than the water-fed group, and 4.2 times more likely at 22 weeks.

Visit www.mcg.edu/news/diab for in-depth information about our obesity/diabetes research.

Diabetes/Obesity Research at a Glance

- Bone biologist Xingming Shi has linked the protein GILZ to increased bone growth and decreased fat production.
- Retinal cell biologist Sylvia Smith is investigating the (+)-form of the drug pentazocine in preventing diabetes-related retinal damage.
- Dr. Robert K. Yu, director of the Institute of Molecular Medicine and Genetics and the Institute of Neuroscience, has linked a key ingredient in rice germination to a reduction in diabetes-related nerve and vascular damage.
- Below: Biologist Jeff S. Mumm is working with his wife, Dr. Meera Saxena, founder of Luminomics Inc., in studying zebrafish cell regeneration in better understanding diseases such as diabetes and Parkinson’s.
The human species wages a daily war it can never win but can’t afford to lose.

The enemy? Bacteria, viruses and other disease-causing pathogens. But the body paradoxically relies on some of these bugs; for instance, bacteria in the digestive tract help break down food. The gatekeeper is the immune system, which gives a pass to the good bugs and a boot to the bad ones.

But the system is imperfect. The immune system can unwittingly fling the door open to bad bugs or declare war on healthy tissue. And even when it does its job optimally, pathogens grow sneakier and more sophisticated in an attempt to elude an immune response. “It’s an arms race that will never end,” says Dr. Andrew Mellor, director of MCG’s Immunotherapy Center.

Dr. Richard Sattin, professor and research director for the Department of Emergency Medicine, concurs. “Bugs are smart. They’re small, they mutate quickly, they reproduce quickly. . . . The extent and rapidity of infectious disease is the difficult part to get a handle on.”

He cites HIV, the virus that causes AIDS, as the ultimate quick-change artist, mutating continuously to outsmart the immune system. Only the recent advance of antiretroviral drugs has transformed the disease from a death sentence to a chronic but manageable disease.

That’s the goal of infection control: staying one step ahead of an unstoppable opponent, and learning to co-exist peacefully if necessary.
MCG researchers such as Drs. Mellor and Sattin have devoted their careers to doing just that. Dr. Mellor and his colleague, pediatric hematologist/oncologist David Munn, have a whole new line of attack, thanks to their groundbreaking discovery in the late 1990s of the role of the enzyme indoleamine 2,3 dioxygenase, or IDO, in fetal survival.

Their finding—that IDO helps stave off an immune response to the 50 percent of a fetus’s DNA that is genetically “foreign”—promises applicability to a host of disease treatments.

“IDO, particularly at mucosal surfaces such as the gut and the lungs, seems to have an anti-inflammatory effect when the body must be in contact with pathogens,” in effect holding the immune system at bay, Dr. Mellor says. So in healthy states such as pregnancy and food digestion, IDO is the body’s best friend. But is it its worst enemy in some disease states such as HIV, giving the immune system an all-clear signal when an attack is clearly warranted?

Studies are under way to try to find out, and to manipulate IDO to treat conditions in which it is implicated. In addition to HIV, these include autoimmune diseases such as rheumatoid arthritis and type 1 diabetes, in which the body inexplicably attacks its own tissue, and organ transplantation, in which the immune system must be prodded to accept the foreign tissue of a transplanted organ.

In autoimmune diseases, Dr. Mellor suggests that “IDO is like a firefighter trying to put out a fire. It may not succeed, but it still slows the disease.”

IDO is also active in a condition few people outside the medical community associate with inflammation: cancer.

“Cancer is a chronic inflammatory disease,” says Dr. Mellor, explaining that the inflammation begins as soon as abnormal cells begin multiplying. “Sometimes fully half the weight of a tumor is inflammation, and it can be a significant barrier to treating the tumor itself.”

Inflammation is healthy when the body uses it to ward off an infection, but increasing evidence suggests a sinister role in cancer. “We used to think inflammation was helpful,” Dr. Mellor says. “Now, we realize the inflammatory response actually protects the cancer cell.”

Why? Back to war games. “Rather than destroying a tumor, inflammation enables the immune system to kind of cocoon it (seemingly via IDO’s modulating effect),” Dr. Mellor says. “It’s a standoff, as if the tumor and immune system call a truce.”

But tumors and pathogens such as HIV can be as unreliable as the most nefarious enemy combatant when it comes to keeping their end of the bargain: staying put and leaving the rest of the body alone. “Tumors seem to be able to exploit some mechanisms designed to contain them, allowing these agents of disease to thrive, to the detriment of patients,” Dr. Mellor says.
The immune system will mount a response that primes it to forever after oust any trace of the real invader.

Today, vaccinations have virtually wiped out many deadly diseases in the developed world, “but allergies seem to be a consequence of us not being exposed to the pathogens our bodies were meant to deal with,” Dr. Mellor says.

Likewise, our hygiene-obsessed society seems to prime children to develop relatively puny immune systems. Dr. Dennis Ownby, MCG chief of allergy/immunology, published the finding several years ago that children who grow up with multiple pets, and therefore gain early exposure to allergens that their bodies can then mount immune responses to, are at lower risk for asthma and allergies than other children.

“This was exactly the opposite of what we would have predicted,” Dr. Ownby says. “This contributes to the mounting evidence that the things allergists have believed for years and things parents have lived by are wrong.”

Also defying conventional wisdom is the public’s newfound understanding of the downside of antibiotics. An over-reliance on the drugs have created superbugs, those most adept at outsmarting the drugs and therefore most likely to survive and reproduce. “We’re starting to worry we’re at the end of the line with antibiotics,” says Dr. Mellor. “The bugs keep getting sturdier, and we’re running out of weapons in our armory to fight this.”

But no rational person would argue that the law of unintended consequences makes a case for letting nature take its course. Just a scant century ago, life expectancy for white males was a measly 50 years old, largely due to an unhygienic environment and inadequate infection control. Modern medical breakthroughs have made a huge difference both in quality and quantity of life, and the pace of research in infection and inflammation has never been brisker.

The researchers are pleased with the progress and their ever-growing understanding of how to bolster the body’s self-defense mechanisms. “We have medications that work really, really well and they’re constantly being improved,” says Dr. Sattin.

But they’ll never let their guards down. “We’re just waiting for the next big infection, and that will always be the case,” Dr. Mellor says. “We’ll never live in a pathogen-free world.”
Infection/Inflammation Research at a Glance

- **Dr. Anatolij Horuzsko**, a reproductive immunologist, and his colleagues are learning how to manipulate the immune response inhibitor, HLA-G dimer, in treating autoimmune disease, cancer and organ transplantation. “This is a molecule with huge potential to regulate the immune response,” Dr. Horuzsko says.

- **Dr. David Hess**, chair of neurology, is principal investigator of a clinical trial studying the unlikely role of a long-used antibiotic, minocycline, to reduce stroke damage. “It’s a safe drug that is easy to give and tolerate, that gets into the brain well, and that may reduce bleeding,” Dr. Hess says.

- **Dr. Krishnan Dhandapani**, a neuroscientist, is working with second-year medical student Jay McCracken to learn how curcumin, the active ingredient of the Indian curry spice, turmeric, may help treat stroke and lower the risk of diseases such as Alzheimer’s and cancer by reducing inflammation.

- Pharmacologists Jerry J. Buccafusco and Dr. Alvin J. Terry Jr. have found elevated levels of certain antibodies in the blood of Alzheimer’s patients, bolstering their theory that autoimmunity and the resulting inflammation are strongly linked to the disease. Says Dr. Buccafusco, “We don’t yet know if it’s a side issue or is directly related to the disease, but it may be a sufficient phenomenon that can be used for early warning.”

- **Dr. Sally Atherton**, chair of cellular biology and anatomy, has documented the virologic and immunologic mechanisms of ocular and central nervous system infections caused by members of the herpesvirus family.

- **Dr. Scott Martin**, a physician assistant, helped document the importance of probiotics—using live, healthy bacteria to combat intestinal disease. “The good bacteria out-compete the bad and bind to the intestines to keep the bad from attaching and causing illness,” he explains. “Consequently, the bad organism—the virus or bacteria—gets flushed out of the gastrointestinal tract.”
Infection control involves practicing medicine at its most microscopic level, but MCG researchers are interested in the big picture as well. Many infectious diseases are contagious, so humans lack the luxury of considering good health to be a solitary pursuit. Some of the most infamous health scourges of the past—yellow fever, dengue, influenza, AIDS—have placed strangleholds on entire civilizations. Yet society still drags its feet on preventive medicine, laments Dr. Richard Sattin, professor and research director of the Department of Emergency Medicine. “I hope people see the benefits of public health prevention,” he says. “It benefits not only the patient, but society as a whole.”

Dr. Frank Rumph, one of the first two African-American graduates of the MCG School of Medicine, was tireless during his tenure in Georgia’s Division of Public Health in promoting preventive public health. “Once I got into public health, I became emotionally tied to it,” he says. “I remember my mentor saying, ‘Here, you can help more people by a few good decisions than a practicing physician could help in his whole lifetime. But nobody will know it and you’ll get no pats on the back.’ That didn’t matter to me, as long as I knew it.”

The timing ensured Dr. Rumph’s lasting legacy: America’s AIDS epidemic hit shortly before he began his job. He held weekly community meetings about AIDS and oversaw the distribution of funds devoted to the disease. He sank his teeth into teen pregnancy and cancer prevention. When he moved on to become director of Georgia’s East Central Health District, he recalls going door to door to warn residents when toxins from a local plant threatened the well-being of nearby residents.

Dr. Sattin applauds such initiatives—and oversees many of his own, including offering HIV testing to MCG Medical Center emergency room patients—but stresses that society as a whole must support such efforts, chiefly through funding. “More resources are needed,” he says. “We need more funding for prevention and public health research.”

Such an investment reaps massive rewards, he says. “Preventing disease is clearly cheaper than treating it. And if prevention isn’t possible, early diagnosis is the next step. The earlier you diagnose an infectious disease, the better you can treat it and reduce transmission.”

He acknowledges that disease prevention isn’t always easy, but it should always be the objective. “I believe what’s thinkable is doable.”

HPV Vaccine:

Dr. Daron Ferris never thought he’d see the day. “I’ve spent my whole career trying to prevent cervical cancer,” says Dr. Ferris, professor of family medicine and obstetrics/gynecology, acknowledging he assumed the goal was out of reach during his lifetime. He was wrong.

The disease—the most common cancer among women of reproductive age in many parts of the world—is generally the last-stage manifestation of human papillomavirus infection, a sexually transmitted condition. There are many types of HPV, some of which can cause genital warts and/or lesions that can lead to cervical cancer.

Cervical cancer is well-controlled in developed countries thanks to Pap smears, which offer early warning and prompt treatment. “But cancer is simply the tip of the pyramid in terms of the problems caused by HPV infection,” Dr. Ferris says. The toll on women’s health, he says, is enormous.
MCG has received a $100,000 Grand Challenges Explorations Grant from the Bill & Melinda Gates Foundation to work toward an HIV vaccine.

The project is one of 104 selected for the first funding round of a five-year, $100 million initiative to forge bold solutions for health challenges in developing countries. The grants represent all levels of scientists in 22 countries and five continents.

The MCG project, overseen by Dr. Pandelakis A. Koni, targets the sugar coating of HIV, the virus that causes AIDS. Dr. Koni is trying to develop antibodies to segments of the coating in hopes that degrading the coating will strip HIV of the armor that protects it from the immune system.

“An idea is that these areas [of the coating] are always conserved and are consistent for a reason,” Dr. Koni said.

As for some parents’ concern that the vaccine may promote or imply promiscuity? “I often make the point that getting a tetanus vaccine doesn’t encourage people to play with rusty nails,” Dr. Ferris says. “And hepatitis B is sexually transmitted, and that vaccine is given to babies. Nobody worries about that.”

His over-riding take is that “this is a golden opportunity. I hate for people to get a disease that can be prevented. It just disturbs me greatly.”

The outlook for the vaccine is only getting brighter. The vaccine is currently limited to girls and young women, but Dr. Ferris is testing it on women up to age 45. “The results are very encouraging,” he says. “We’re also testing it on boys. The more people who are immunized, the less the risk of transmission. It’s known as herd immunity.”

Another bonus? Dr. Ferris thinks young girls who receive the HPV vaccine may in the future need a Pap smear only once every five years, or possibly even once a decade.

“MCG may have done more HPV studies than any site in the world,” Dr. Ferris says, “and it’s clear that this vaccine is one of the most robust and effective ever made.”

Visit www.mcg.edu/news/inf for in-depth information about our infection/inflammation research.
The brain – the human body’s most complex and mysterious organ – is also the focus of some of the most compelling research at the Medical College of Georgia.

And with neurological diseases striking nearly 50 million Americans a year from all walks of life, the new treatments and therapies developed at MCG could have a widespread impact on the nation’s health.

“As the population ages, neurological diseases become a bigger burden,” said Dr. David Hess, chair of the Department of Neurology in the MCG School of Medicine.

Neurological disease is one of the university’s five thematic areas of research. Stroke, the most common neurological disease – and the greatest debilitator of adults over age 45 – is a disease in which MCG researchers have made many advances.

MCG neuroscience researchers such as Drs. Hess, James Carroll, William Hill and others have decided to zero in on acute stroke treatment and recovery rather than prevention, where lifestyle choices play a bigger role than science.
REACHing Out

On the treatment side, MCG’s REACH program has enabled rural hospitals to diagnose ischemic stroke with the help of specialists via the Internet. This allows the rural physicians to administer the only approved stroke treatment, a clot-busting drug called tPA, within its three-hour window of effectiveness. MCG researchers are now performing clinical tests on whether administering the antibiotic minocycline to stroke patients treated with tPA inhibits the hemorrhaging that tPA sometime causes. Researchers hypothesize the minocycline-tPA therapy may be more effective than tPA alone.

As for stroke recovery, investigators are pursuing regulatory approval for clinical trials to test whether stem cell therapy can help rebuild damaged synapses and new brain cells in patients who were not given tPA and those whose tPA treatment was unsuccessful. Dr. Hess, an investigator in the study, said cell therapy proved successful during animal tests and could even be used to treat pediatric ischemic brain injury, which can result in cerebral palsy, a condition with no FDA-approved therapy.
After stroke, Alzheimer’s disease is the leading cause of neurological debilitation among older adults and the number-one reason older adults seek nursing home care. At MCG, the bulk of clinical research centers on characterizing the biological markers for Alzheimer’s disease in humans.

Drs. Shirley Poduslo and Suzanne Smith are trying to identify new genes that increase the risk for Alzheimer’s disease. Basic science research by Drs. Jerry Buccafusco and Alvin Terry Jr. focuses on memory loss and cognitive disruptions in aging primates to develop drugs that could help humans ward off the effects of Alzheimer’s, Parkinson’s and other neurodegenerative diseases. More than 5 million people in the United States—nearly 13 percent of all those age 65 and older—have Alzheimer’s. Without an effective treatment or prevention, by 2050, the number of Americans with this disease could reach 16 million.
Unforgettable Findings

Most neurological diseases affect cognition and memory, two of the most basic and most important functions of the human brain. Those processes are at the heart of Dr. Joe Z. Tsien’s research.

The Georgia Research Alliance Eminent Scholar in Cognitive and Systems Neurobiology has garnered international attention for his research involving mice, specifically his genetically engineered “smart mouse” named Doogie.

By manipulating the genetic expression of certain proteins critical to brain cell communication, Dr. Tsien’s team has created a mouse that can’t form new memories and has selectively and safely removed memories from another mouse. His findings are currently difficult to translate to humans, but one day they might help clinicians treat patients with cognitive and memory disorders.

“While memories are great teachers and obviously crucial for survival and adaptation, selectively removing incapacitating memories, such as traumatic war memories or an unwanted fear, could help many people live better lives,” he said.

“Our work reveals a molecular mechanism of how that can be done quickly and without doing damage to brain cells.”

Suppressing Seizures

Epilepsy is less common than stroke and Alzheimer’s, but it nonetheless causes debilitating seizures in 1-2 percent of Americans. MCG has long been a leading center for epilepsy surgery, and its Comprehensive Epilepsy Program, operated by clinical partner MCGHealth, has been a nationally recognized referral center by the National Association of Epilepsy Centers since 1977.

The program is currently involved in three clinical trials for new epilepsy drugs and a fourth for an implantable device – the highly-publicized NeuroPace RNS System, a battery-powered computer chip that identifies and suppresses seizure activity by delivering controlled electrical signals to the brain via electrodes.

“Unlike a pacemaker that would continually fire, this is a responsive neurostimulator,” said Dr. Patty Ray, an assistant research scientist in the Department of Neurology and coordinator of the local trials.

The device could change the way acute epilepsy is treated if the 29-site, 240-patient trial proves successful.

“We’re constantly investigating new methods of treatment,” Dr. Ray said. “It’s an ongoing process.”

MS Milestones

MCG is also a major player in investigational drug studies for multiple sclerosis, a leading cause of neurological disability for people under age 45. The autoimmune disease causes the body’s own defense system to attack myelin, the fatty substance that surrounds and protects nerve fibers.

The MCG Augusta Multiple Sclerosis Center, which is recognized by the Multiple Sclerosis Society’s Georgia and Mid-Atlantic chapters, is known nationally for its skilled clinicians and large patient base.

Current FDA-approved MS treatments are given by injection and are only partially effective. The center is doing clinical trials for two pills and one long-lasting intravenous drug that all focus on novel immunological targets. A fourth trial is under way for a drug that essentially acts like a vaccine, said Dr. Mary Hughes, medical director of the Augusta MS Center.

“That’s a very exciting option,” said Dr. Hughes, who is also an associate professor of neurology. “We’re always looking at newer, safer and more effective regimens to increase the quality of life. Our goal is to have MS treatment interfere only minimally with people’s day-to-day lives.”

Bridging the Gap

Neuromuscular diseases, such as muscular dystrophy and myasthenia gravis, are less common but are the focus of a novel research project headed by Dr. Lin Mei, a professor with the MCG Institute of Molecular Medicine and Genetics.

Dr. Mei and his team recently identified a low-density lipoprotein receptor called LRP4 that helps agrin, a protein used by neurons to build synapses, and MuSK, an enzyme receptor in muscle cells that is activated by agrin, build the junctions between nerves and muscle.

In his recently published article in Neuron magazine, Dr. Mei hypothesizes a mutation or autoimmune response to LRP4 may cause muscular dystrophy, a group of genetic diseases that impair muscle control because of disruptions at the neuromuscular junction.

“We believe we have identified the missing link,” said Dr. Mei, whose research on LRP4 was funded by the National Institutes of Health and the Muscular Dystrophy Association.

Dr. Hess eventually hopes to expand his department’s basic science program to include amyotrophic lateral sclerosis, or Lou Gehrig’s disease, a progressive neurodegenerative disease that ultimately results in total paralysis.

“ALS is a very tragic disease and we know little about its cause,” Dr. Hess said. “It’s a disease that is a total mystery.” continued
“It is not the possession of truth, but the success which attends the seeking after it, that enriches the seeker and brings happiness to him.”

Max Planck
German Physicist
1858–1947

A Window into the Brain

All neurological research at MCG benefits from the Human Brain Lab, one of only a handful of facilities in the world where scientists can study living human brain tissue dissected from epilepsy patients who undergo surgery to remove seizure-causing sections of the brain. The tiny slices of tissue can be subjected to therapies and drugs that would otherwise be impossible to test in actual patients.

The lab’s director, Dr. Sergei Kirov, an associate professor of neurosurgery, also uses his Multiphoton Imaging Laboratory to monitor real-time brain activity in human tissue and mice using...
two photon microscopes to “see” a stroke as it occurs, giving researchers a window into potential therapy options.

“The lab is very unique because it is at the cutting edge of live imaging for cellular neuroscience,” Dr. Kirov said of his Multiphoton Imaging Laboratory.

Neurological research will also benefit from the recently created Brain & Behavior Discovery Institute, one of six in the School of Medicine that were created to improve multidisciplinary translational science in MCG’s thematic areas of research. The BBDI, co-directed by Drs. Hess and Tsien, will create a more “team-based” approach to unlocking the mysteries of four specific areas:

- Neurovascular disease, such as stroke
- Neurodegenerative disease, such as Alzheimer’s
- Regenerative neuroscience, or repairing brain damage caused by severe head injuries, stroke and other diseases – the “Holy Grail of neuroscience,” Dr. Hess said.
- Cognitive and behavioral disorders, a program that Dr. Hess said could eventually be divided into two—one focusing on memory and the other on psychiatric disorders such as schizophrenia.

Stem Cell Success

Dr. Peter F. Buckley, chair of the Department of Psychiatry & Health Behavior, said clinical and basic science research in neurological disease is coalescing through the BBDI.

“This provides us the opportunity to reach outside this building and really get into translational neuroscience, bringing the talent on campus under a broad umbrella,” he said.

One of several examples of cross-departmental cooperation, he said, is Dr. Anilkumar R. Pillai, an assistant professor in his department, joining Dr. Mei of MCG’s Institute of Molecular Medicine and Genetics as a co-investigator for a federally funded study of the role genetics play in schizophrenia.

Research partnerships also extend beyond the boundaries of campus. One of the more exciting developments in neurological research at MCG is a potential partnership with the University of Georgia to perform research with induced pluripotent stem cells, a type of stem cell derived from skin cells by forcing the expression of certain genes. Though artificially created, the iPS cells, as they are known, are identical to natural stem cells, eliminating the controversial use of embryos.

The cells were first produced in 2006 by Japanese researcher Shinya Yamanaka. U.S. researchers, including molecular biologists at UGA, are now working with iPS cells. Dr. Hess said that skin taken from an Alzheimer’s patient, for example, could be reprogrammed into an embryonic-like stem cell.

“We could watch the cell develop and see what’s wrong with it. We could potentially do test runs on it. We could potentially correct the defect and put those cells back in the patient,” he said.

If a partnership is developed, UGA would create iPS cells based on tissue provided by MCG researchers, who would then take the re-engineered cells and determine if they can correct defects in animals genetically engineered with diseases such as Alzheimer’s or Parkinson’s. Dr. Hess said he hopes a partnership materializes because the potential for discovery is immense.

“I think iPS cells are going to transform medicine,” Dr. Hess said.
Schizophrenia Research More PROACTIVE Than Ever

A study by Dr. Buckley and Dr. Anilkumar R. Pillai, an MCG neuroscientist, is determining if changes in growth factors in the blood of schizophrenia patients can predict a relapse. Relapses usually occur when patients stop taking their antipsychotic medications, but the researchers believe a drop in brain-derived neurotrophic factor, or BDNF, indicates medications are becoming less effective and that a relapse is imminent.

Dr. Lin Mei, chief of development neurobiology in the Institute of Molecular Medicine and Genetics, has identified novel functions of neuregulin 1 and ErbB4, two genes whose mutation has been implicated in schizophrenia. Their abnormal function disrupts normal brain cell communication and causes an imbalance of brain activity that may explain the cognitive problems, hallucinations and social disconnection in schizophrenia patients.

Dr. Brian Miller, a psychotic-disorders fellow in the Department of Psychiatry & Health Behavior, is investigating the effect of paternal age on mortality risk in offspring. Through his collaboration with the University of Oulu in Finland, he has found that advancing paternal age – a risk factor for schizophrenia, autism and other conditions – is associated with increased risk of suicide among women in the general population in northern Finland. A second study involving a cohort from Helsinki, Finland showed that advancing paternal age was a risk factor for suicide in men with psychosis.

Dr. Brian Kirkpatrick, vice chair of the Department of Psychiatry & Health Behavior, is studying the role adult stem cells may play in patients with schizophrenia and related psychotic disorders. Adult stem cells circulate in the blood and are involved in the body’s normal repair processes, such as recovering from a bone fracture or heart attack. Dr. Kirkpatrick and his team found that newly diagnosed patients with schizophrenia had a decrease in the amount of stromal cell-derived factor 1-alpha (SDF-1α), the major chemical messenger for adult stem cells.

MCG’s recent participation in one of the largest-ever schizophrenia studies is an indicator of the university’s growing reputation as a hot spot for schizophrenia research. Schizophrenia, considered one of the most serious mental illnesses, affects 2.4 million Americans. Symptoms included a distorted sense of reality, hallucinations and abnormal thoughts, moods and actions.

The $11 million National Institute of Mental Health-funded trial, PROACTIVE, could change the way schizophrenia patients receive antipsychotic medication. MCG, one of eight sites in the 304-patient study, is helping determine whether patients are more likely to adhere to treatment by receiving long-lasting injectable medication every two weeks in a clinical setting instead of the traditional daily pill regimen.

Treatment noncompliance is high among schizophrenia patients because their distorted sense of reality leads them to believe they have been “cured,” causing them to relapse into psychosis. Relapses disrupt family life and employment and sometimes require the patient to be hospitalized.

The PROACTIVE project is only one of several grant-funded schizophrenia research projects involving MCG researchers across several academic departments.

Visit www.mcg.edu/news/neuro for in-depth information about our neurological research.
As we hope you’ve gleaned in this edition of MCG Tomorrow, MCG research is yielding fruits in real time, thanks to the university’s emphasis on translational research and the exceptional dedication of our researchers.

This offers unique and thrilling opportunities from an advancement perspective. Too often, those of us in the gift-planning profession must compel supporters to use their imaginations. “The results of your generosity may not be apparent in your lifetime,” we tell them, in effect, “but trust us that great things are coming.”

At MCG, we can tell them that great things are already here, and that greater things are just around the corner—not a century from now, a generation from now or even a decade from now. Many of today’s biomedical discoveries will help scores of citizens imminently.

So we ask you to peer into the future, but not too far. Partnering with MCG will enable you to help today’s citizens, today’s society, today’s state of wellness. Tomorrow’s too, of course. But that’s just icing on the cake.

Please contact me so I can help you set this in motion. Together, we can accomplish incredible things.

Sincerely,

Tony Duva
Associate Vice President for Gift Planning
800-869-1113
aduva@mcg.edu
“Experimental confirmation of a prediction
is merely a measurement.
An experiment disproving a prediction
is a discovery.”

Enrico Fermi
Italian Physicist, 1901–1954