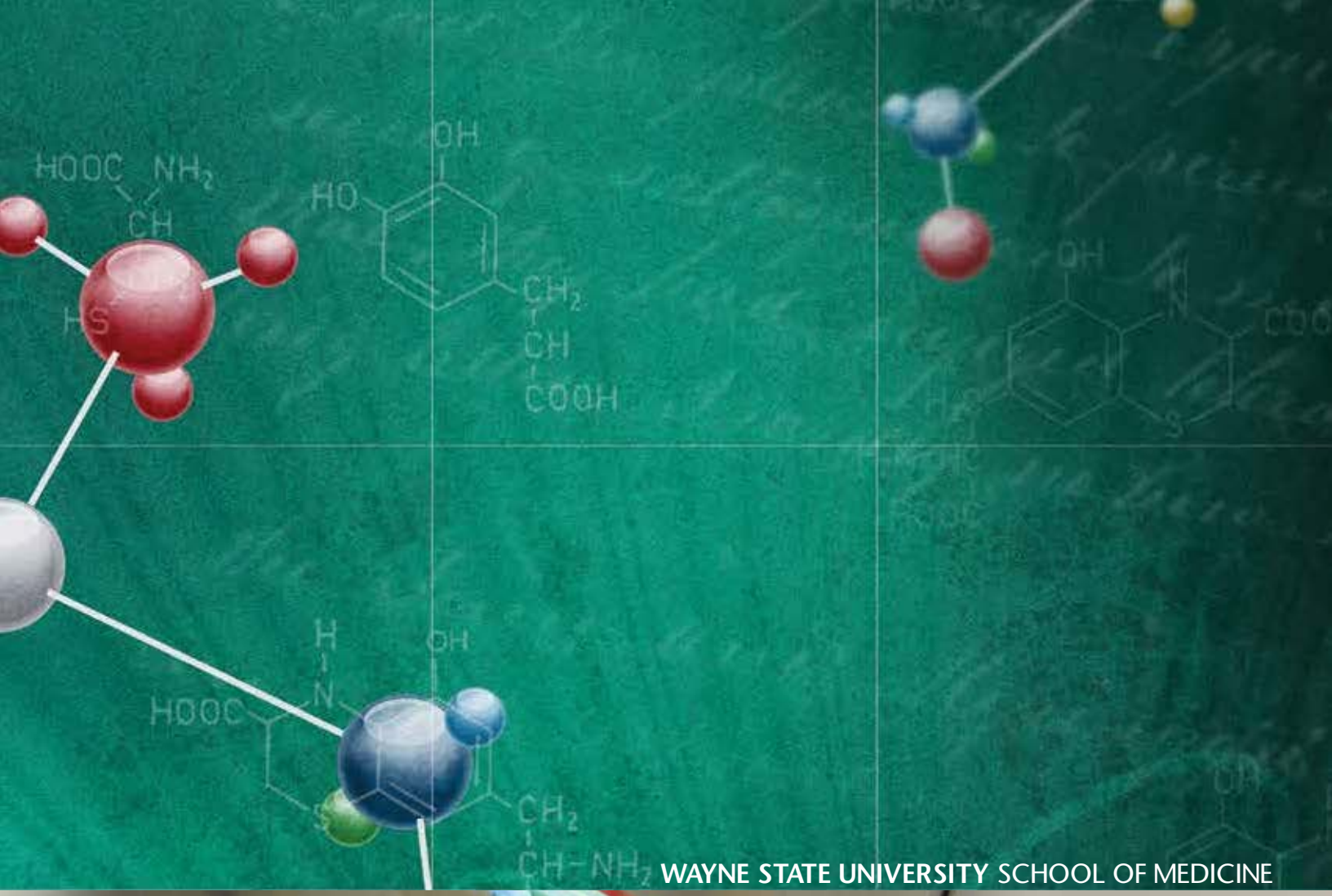

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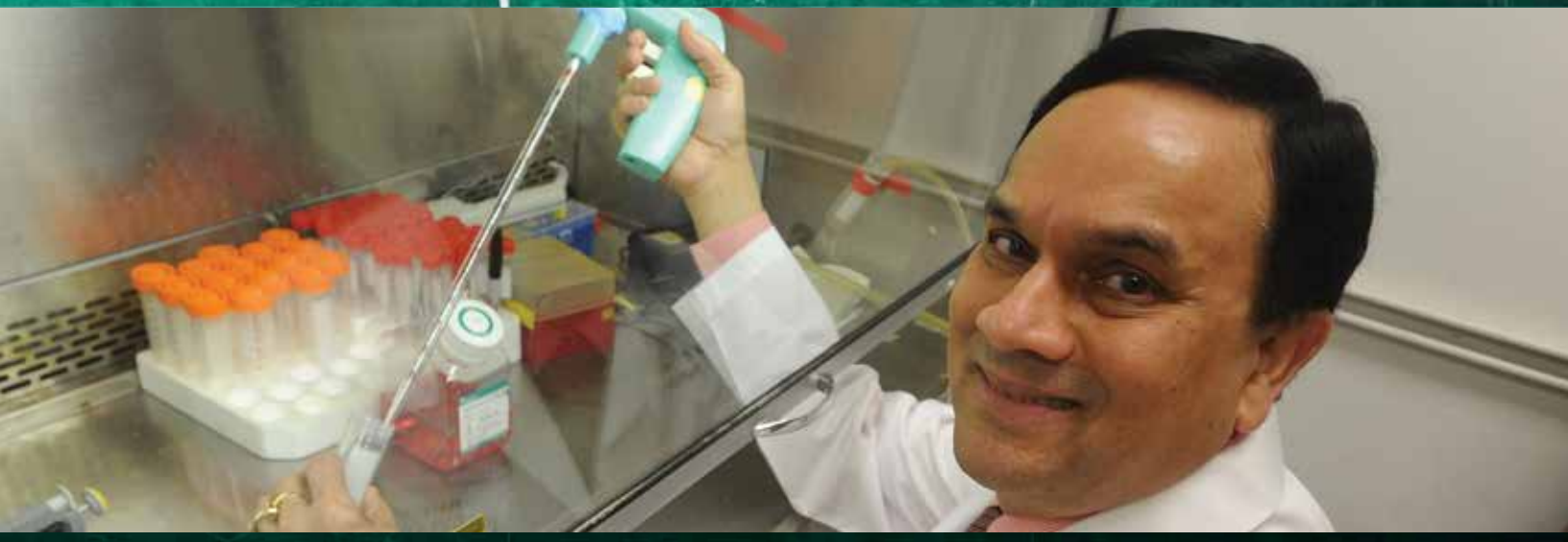

MEDRESEARCH

VOLUME 3, No. 1 FALL 2012


WAYNE STATE

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Behind every bit of research we conduct at the Wayne State University School of Medicine lies a basic driving force: hope.

Research provides hope for improved treatments, hope for a cure, hope for better lives and a brighter future for billions of people around the world.

Diseases such as cancer, diabetes, multiple sclerosis, Parkinson's, cerebral palsy and depression rob people and families of hope. Today, those conditions remain obstacles, but each day our researchers peel back additional layers that edge us ever closer to better therapies and cures.

Medical researchers are akin to the architects who planned the great cathedrals of Europe. Those planners knew that they would not live to see the completion of their work, but carried on with unflagging faith that the project would come to fruition. Today's medical scientists embody similar faith, which enables their drive to solve and eradicate problems.

Carl Sagan, the celebrated American astronomer and scientist, wrote that, "Somewhere, something incredible is waiting to be known." That "something" to which Dr. Sagan referred is what drives research and researchers, especially in academic medical research. Just as astronomers seek to broaden our knowledge by exploring and measuring ever further to the outermost reaches of our solar system and the universe, Wayne State University School of Medicine researchers continue to delve into smaller worlds, working through microscopic and ever smaller levels to reconnoiter the unique universe that is the human body. Researchers have mapped the human genome and now set out to explore what occupies the areas between the stuff of which we are made. Developing new methods to deliver drugs through nanotechnology that may be a catalyst for a cure for cerebral palsy. Genetically modifying cancer cells so that they are fooled into destroying themselves. All of this, and much more, is taking place in our labs. These explorations will lead to new therapeutic targets and new approaches to treating, curing and perhaps avoiding disease altogether before birth in a new world of personalized medicine.

Wayne State University has embarked upon its latest symbol of hope with the construction of a new Multidisciplinary Biomedical Research Building. This cathedral of medical research will set the stage for a new era of studies that will improve the health and lives of generations who come after us. The university's largest building project ever is dedicated to the proposition that research is the foundation to all medicine, today and in the future.

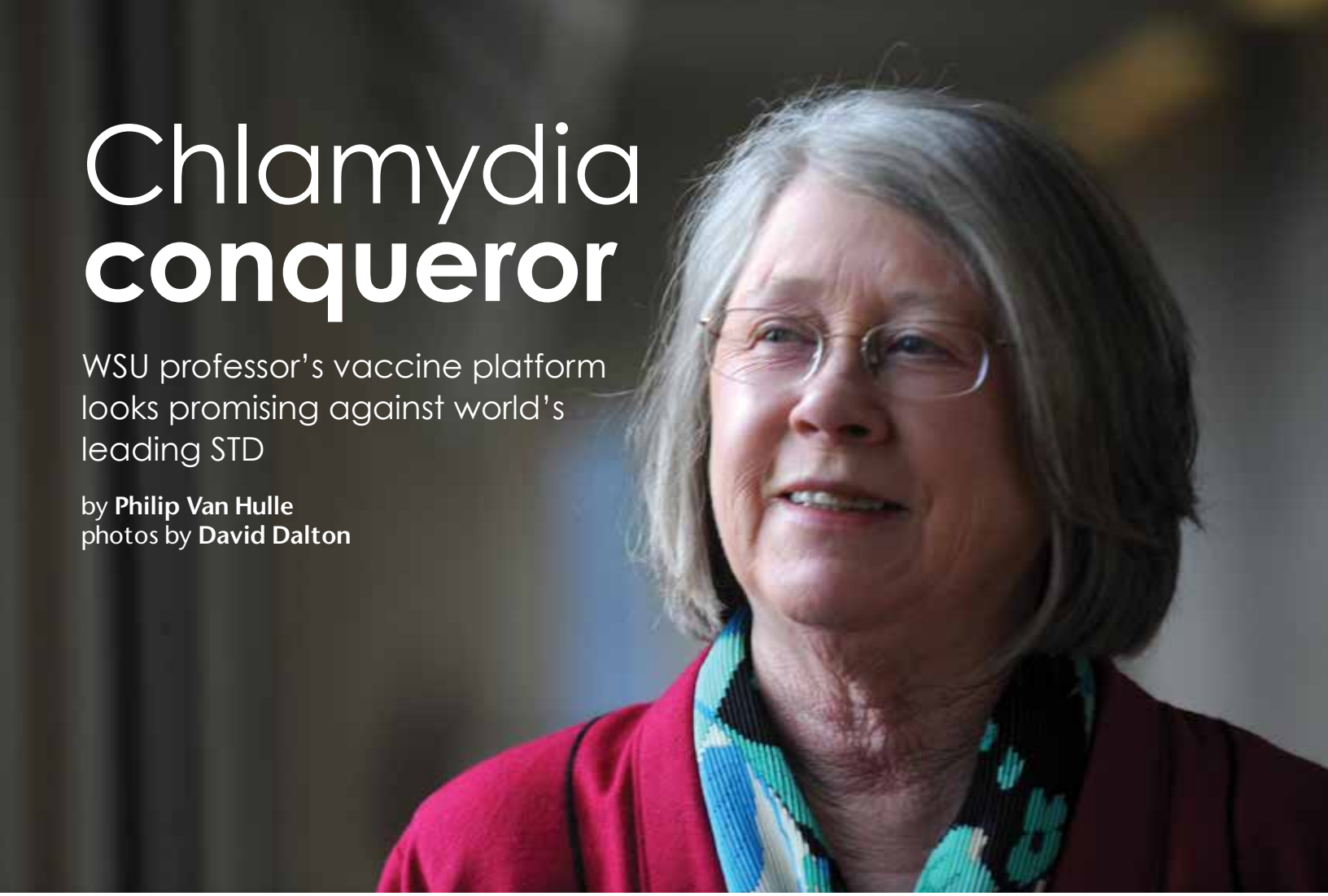
From shaman to scientist hasn't really taken all that long. Physicians who practiced 500, 100 or even 50 years ago — a millisecond in human history — would be astounded at how far research has taken medicine. We have come a long way quickly, and have far to go. Wayne State University School of Medicine researchers are leading us to the newest horizons.

Valerie M. Parisi, M.D., M.P.H., M.B.A.
Dean
Wayne State University
School of Medicine

Chlamydia **conqueror**

WSU professor's vaccine platform looks promising against world's leading STD

by **Philip Van Hulle**
photos by **David Dalton**



Judith Whittum-Hudson, Ph.D., has identified peptides that have demonstrated a vaccine effect to inoculate against Chlamydia. Her research could soon result in a vaccine against the leading sexually transmitted disease.

Chlamydia is the world's leading sexually transmitted disease, and a leading cause of new cases of blindness.

Chlamydia rates among women nationally and in Michigan have been increasing for more than a decade, with the infection rates in Michigan continually outstripping the national rate. In 2002, the rate of women infected with the disease in Michigan stood at 412 per 100,000 women compared to a national rate of 396.3. By 2009, the state's rate had climbed to 666.6 cases for every 100,000 women. Nationally that year, the U.S. Centers for Disease Control and Prevention put the rate at 592.2 cases for every 100,000 women.

The disease far outpaced the reported cases of other sexually transmitted diseases that year in Michigan, with gonorrhea (14,770 cases) and syphilis (1,175) placing second and third respectively.

Chlamydia in particular strikes women and the young disproportionately. In 2011, Michigan reported 50,063 cases of chlamydia. The largest number of cases — 38,303 — were recorded among 15- to 24-year-olds. In fact, the Michigan Department of Community Health says the largest risk factor for Chlamydia is simply being in that age range. The disease hit women 2.8 times more than men.

A Wayne State University School of Medicine researcher has developed a potential vaccine for Chlamydia. Judith Whittum-Hudson, Ph.D., professor of Immunology and Microbiology, Internal Medicine and Ophthalmology, has identified three peptides that have demonstrated a vaccine effect to inoculate against Chlamydia successfully in an animal model. Those findings could soon result in a vaccine for humans.

Wayne State University has filed patent applications on the technology, which has been licensed to a start-up company.

While Chlamydia infection can be readily addressed with a regimen of antibiotics, the treatment does not prevent re-infection. Treatment with antibiotics too early after infection may interfere with the natural development of immunity to Chlamydia, Dr. Whittum-Hudson said, and significant portions of the world lack access to basic health care infrastructure that could offer treatment through antibiotics.

"There is no vaccine and the disease is widely rampant," she said. "Antibiotics, while effective in treatment, offer no protection against re-infection."

The technology Dr. Whittum-Hudson developed consists of novel peptide immunogens selected from a random phage display library by an antibody against a Chlamydial glycolipid exoantigen, or GLXA, or peptides that correspond to antigen-binding regions of an anti-idiotypic antibody mimic of GLXA. The peptides comprising the vaccine would induce antibodies and other immune responses to the entire spectrum of genus-wide Chlamydia. Dr. Whittum-Hudson said colleagues have developed a method to encapsulate the vaccine so that it can be delivered orally rather than through injection, a boon to developing nations that lack the infrastructure to support inoculations through needle injection.

Chlamydial infections are the leading cause of pelvic inflammatory disease, because the disease infects the lower genital track and then may ascend into the fallopian tubes. PID can lead to infertility, ectopic pregnancy and chronic pelvic pain. The CDC estimates that 750,000 women annually in the United States experience acute PID because of Chlamydia infection, and as many as 15 percent of those women may become infertile.

Because an estimated 85 percent of women infected with Chlamydia are asymptomatic, the disease can wreak its permanent damage before they even become aware of the infection. Pregnant women can pass the infection to their infants during birth, leading to eye infections, including conjunctivitis, and bronchial infections.

Chlamydia trachomatis is the leading cause of infectious blindness in humans. Worldwide, according to the World Health Organization, as many as 25 percent of people infected with this form will be blinded permanently. More than 140 million people are infected with C. trachomatis, leaving 6 million blinded in Africa, the Middle East, Asia and Latin America. At least 85 million eye infections annually are attributed to the disease, the WHO estimated. With the lack of access to basic health care in many of these regions, a vaccine would substantially reduce, if not eliminate, blindness due to Chlamydia in these areas.

A vaccine would have significant impact on health care around the world. The WHO estimates that 92 million people are infected with the sexually transmitted disease form of C. trachomatis, and the numbers continue to increase. C. trachomatis is the most commonly reported disease in the United States and since 1994 remains the most prevalent of all sexually transmitted diseases reported to the CDC. The numbers of Chlamydial infections in the U.S. continue to rise. In 2009, the last year for which statistics are available, 1,244,180 cases of Chlamydia infection were reported to the CDC, a 2.8 percent increase over 2008 reported cases.

In rankings of states with the highest number of reported cases in 2009, Michigan placed 13th. Mississippi ranked first (802.7 cases per 100,000) and New Hampshire ranked last (159.7 cases per 100,000). Some studies estimated that in the U.S. alone there are 4 million to 5 million new cases of Chlamydia infection annually.

Dr. Whittum-Hudson reviews lab results with students and assistants. A viable vaccine based on her work could save millions around the world from Chlamydia and related cases of blindness.

Another chlamydial species, Chlamydia pneumoniae, is responsible for 10 percent to 20 percent of community-acquired pneumonia in adults. Chlamydiae also have been associated with arthritis, atherosclerosis, stroke, myocarditis, chronic obstructive pulmonary disease, late-onset Alzheimer's and temporomandibular joint disease.

Dr. Whittum-Hudson noted that animals in which the prototype vaccine has been tested showed a decrease in joint inflammation, reducing the reactive arthritis-inducing effect of disseminated Chlamydia.

She said the vaccine may require boosters delivered at various stages of life. For instance, infants or children may be vaccinated, and then receive a booster immunization as they approach sexual maturity. A booster could be administered as a patient reaches age 40 to assist in warding off the potential cardiovascular effects of Chlamydia. Another booster might prove beneficial at an older age to combat the effects of Chlamydia-associated late-onset Alzheimer's disease.

Another potential benefit of the vaccine lies in the livestock and poultry industries. Cattle, sheep and some poultry can contract Chlamydia, leading to illness and the self-aborting of fetuses, or respiratory infections in poultry. A viable vaccination could save the livestock industry untold millions of dollars, and protect workers in the poultry industry, who can contract the disease from infected animals. ■

Tricking cancer into treatment

WSU researcher creates patented personalized therapy that causes cancer cells to kill themselves

by **Philip Van Hulle**
Image **courtesy of Karli Rosner, M.D., Ph.D.**

Oncologists use an arsenal of technologies to combat cancer, including targeted radiation, chemotherapy and surgery. All the techniques approach cancer as an invader to be slowed or eradicated with outside weapons.

A Wayne State University School of Medicine physician-researcher has developed a personalized therapy to treat a wide range of cancers, a treatment based on a naturally occurring human enzyme that has been genetically modified to fool cancer cells into killing themselves.

The unique concept, patented by Wayne State University, was successfully demonstrated on melanoma cells that are resistant to routine treatments such as chemotherapy or radiotherapy. Melanoma is a perfect model for testing this new therapy because it is considered the most aggressive form of human cancer due to its many defense mechanisms against available treatments. The success of the therapy in killing melanoma suggests a similar outcome in treating other cancers.

Developed by Karli Rosner, M.D., Ph.D., assistant professor and director of Research in the Department of Dermatology, the method uses genetic constructs that contain a genetically modified enzyme — DNase1 protein — to seek out and destroy cancer cells. The novel technology was published in the article "Engineering a waste management enzyme to overcome cancer resistance to apoptosis: adding DNase1 to the anti-cancer toolbox" in the online version of Cancer Gene Therapy, a Nature Publishing Group journal.

Dr. Rosner modified — "hacked," as he puts it — the genetic code for DNase1, a highly potent DNA-degrading enzyme, and altered its genetic composition by deleting a part of the code, mutating another segment and adding an artificial piece of code. Through

In green, firework-like defragmenting nuclei belonging to melanoma cells that commit suicide are shown here. After absorbing **Dr. Rosner's** genetic construct, these cancer cells translated the genetic code into a toxic protein. In turn, this protein destroyed the nuclei of cells that manufactured it. In blue, intact nuclei found within melanoma cells that were not transfected with the genetic construct are shown.

these changes, the altered DNA program is translated into a modified protein. In contrast to the natural protein, the modified protein is not eliminated from the cancer cell, resists deactivation by cell inhibitors and gains access to the cancer cell's nucleus. "If you imagine the cell's nucleus as a computer and DNA in the nucleus as computer software," Dr. Rosner explained, "then the altered, hacked DNA program corresponds to a computer virus.

"To further understand this anti-cancer technology," he continued, "recollect the plot from the movie 'Independence Day.' In this movie, a computer virus is introduced into an alien ship to neutralize its defenses and make it vulnerable to external weapons. We do something similar but much better by introducing the altered genetic code of DNase1 into the DNA of cancer cells alien to the healthy body."

The cancer cell, unaware of the destructive potential of the modified code, translates it into a protein that evades the cell's defense mechanisms and enters the nucleus. In the nucleus, the protein damages DNA by chopping it into fragments without the need for external weaponry, i.e., other medications. Following damage to the DNA, the cell's organelles disintegrate and the cancer cell dies.

In effect, Dr. Rosner's technology leads cancer cells into committing suicide because it fools them into generating the protein that causes their own death.

The beauty of this therapy is that specifically-targeted cancer cells destroy themselves through the physiological mechanism of apoptosis, or cell death, leaving surrounding healthy cells intact. This mode of cancer cell elimination leaves no residual debris to alert the body's immune system to kick in, essentially committing "the perfect crime," Dr. Rosner said. This is important because the many side effects of current anti-cancer treatments are attributed to activation of the immune system. The fact that this therapy does not require participation of the patient's immune system to kill cancer cells is a big advantage over other newly developed technologies, such as a cancer vaccine. Those technologies depend on the patient's immune system to destroy cancer. Unfortunately, they are not effective in the presence of a compromised immune system, which is the case with many cancer patients. In contrast, Dr. Rosner's therapy will be able to treat even the most severely immuno-compromised patients with the same degree of success as in treating patients with a fully functional immune system.

Patients with the same cancer type vary in their response to identical treatment because the biological characteristics of the cancer type usually differ between patients. As a result, the medical field strives to develop treatments that can be adjusted to each patient. The structure of Dr. Rosner's technology is flexible in that it contains Lego-like pieces that together form a genetic construct. Each piece can be replaced by one of several other genetic pieces that perform the same task, but differ slightly in their genetics. The multiple options available for each genetic piece will allow a physician to tailor the finalized treatment to each patient based on the unique characteristics of his or her cancer. In this way, the new technology is a "true personalized therapy," he said. The physician will expose a patient's cancer cells, obtained by biopsy, and refer to various genetic constructs to identify the version of therapy that kills the patient's cancer with the utmost efficiency.

Of particular importance is the potential for this technology to treat a large variety of tumors, such as prostate, lung and breast cancers.

Dr. Rosner likened the therapy to the military's Tomahawk missile platform. The Tomahawk is directed to its target by programming the missile's homing device. Likewise, the destructive genetic construct can be targeted to a particular cancer type by incorporating a genetic segment that specifically identifies the cancer. Multiple genetic homing devices will be at the physician's disposal. The ability to target the therapy specifically to cancer cells will reduce side effects common with today's anti-cancer therapies. Moreover, the ability to target multiple cancers will immensely increase the number of cancer patients who will benefit from the new technology.

The one side effect that Dr. Rosner foresees is the potential for lightening of skin hue at a level that he cannot predict, but that's a tradeoff someone suffering from metastatic cancer and given a limited prognosis may willingly accept in exchange for becoming cancer-free.

To date, Dr. Rosner has demonstrated cancer cell kill rates of 70 percent to 100 percent with his first generation of "gene suicide therapy." To further increase the killing efficiency, he recently designed a second generation of constructs. In the near future he intends to test the therapy in an animal model, an intermediate step required before moving the treatment into clinical trials. ■

Karli Rosner, M.D., Ph.D., works with research assistant **Evangelia Kirou** in his lab.

Beginning a new **era of research**

Multidisciplinary Biomedical Research Building will encourage collaboration across a range of scientific areas

by **Jen Harte and Andrea Westfall**

Wayne State University has launched the birth of the university's newest research hub and its largest-ever construction project will encourage interdisciplinary work across a range of scientific areas with the goal of translating new discoveries to improve human health and society.

Leaders, faculty and students from Wayne State University joined with officials from the city of Detroit, state and federal government to mark the groundbreaking for the new Multidisciplinary Biomedical Research Building during an Oct. 25, 2012, ceremony emceed by WSU School of Medicine Dean Valerie M. Parisi, M.D., M.P.H., M.B.A.

"The MBRB is about everything we want to be as a research university, with key strengths in the health sciences and a commitment to the community," said Wayne State University President Allan Gilmour. "It's about discovery, it's about teaching and it's about economic growth."

A $93 million project, the MBRB will be located at the corner of Woodward Avenue and Amsterdam. The building will feature nearly 200,000 square feet of space to accommodate nearly 70 principal investigators and 500 researchers and staff members. It will include wet and dry laboratories, faculty offices and common areas, as well as clinical space.

Faculty members from across the university will populate the MBRB. The School of Medicine, the College of Engineering, the College of Liberal Arts and Sciences, the School of Social Work, and the Eugene Applebaum College of Pharmacy and Health Sciences will conduct research at the facility. Ninety-three percent of the structure will be occupied by Wayne State University, with the remaining 7 percent housing university partners from the Henry Ford Health System, including its bone and joint research program, and biomechanics motion laboratory.

Hilary Ratner, Ph.D., vice president for Research at WSU, described the MBRB as vital to growing the university's research enterprise. "When you look at how groundbreaking research is accomplished today, you find investigators from multiple disciplines working together to answer questions and solve problems," she said. "The MBRB will provide a dynamic environment that encourages collaboration in both a structured and an organic way."

The multidisciplinary nature of the MBRB will make it the first of its kind at Wayne State and place the university in line with other major research institutions such as Columbia University, the University of Michigan and the University of Rochester. It will be Wayne State's first new biomedical research facility since the opening of the Eugene Applebaum College of Pharmacy and Health Sciences building in 2002 and the first since 1998 with accommodations for researchers from the School of Medicine.

"When we think about what we want to be as a research university and a school of medicine, the MBRB becomes an important step forward in achieving our goals for the future," Dean Parisi said.

Research in the MBRB will be arranged into thematic areas — cardiovascular disease;

A light-filled atrium will greet employees and guests as they arrive at the building.

metabolic disorders such as diabetes, hypertension and obesity; systems biology; biomedical engineering; bioinformatics and computational biology; and translational behavioral science. Dean Parisi described these disciplines as areas of strength at Wayne State. "By strategically bringing researchers together in one place, we have the potential to yield more bench-to-bedside research outcomes and to bring more external funding to Wayne State and the state of Michigan," she said.

The focus of the MBRB will be on team science. Bonita Stanton, M.D., vice dean for Research at the School of Medicine, who is helping to guide the MBRB to fruition, said that a team approach to scientific inquiry is essential to solving complicated health issues. She sees numerous opportunities for team science within the MBRB and referenced obesity, which is among the leading causes of preventable death in the United States, as an example. She explained that solutions to mitigate the obesity epidemic will likely extend from basic science research and behavioral interventions from clinical research. "Wayne State University has investigators in both of these areas who are leaders in their fields," she said. "The MBRB will enable them, and many others, to work together in more deliberate ways."

To support team science, the MBRB will include traditional wet laboratories and dry laboratories for computational and applied mathematical analyses. "Human knowledge has increased dramatically within the past

Wayne State goes for LEED silver

The Multidisciplinary Biomedical Research Building will be designed in accordance with the United States Green Building Council's 2009 LEED Standards for New Construction and Major Renovation.

LEED, or Leadership in Energy and Environmental Design, is an internationally recognized symbol of distinction that honors practical and measurable solutions for eco-friendly building design, construction, operations and maintenance. Wayne State University's Marvin I. Danto Engineering and Development Center is a LEED-certified facility at the silver level. It is Wayne State's first building to receive the honor.

LEED certification is a point-based system, with points awarded for performance in categories such as sustainable site development, water efficiency, energy and atmosphere, materials and resources, indoor environmental quality, innovation in design and regional priority. The goal for the MBRB project is to receive a silver rating. LEED silver projects must earn between 50 and 59 points out of a possible 100. To accomplish this, the MBRB design will incorporate methodologies to mitigate the heat island effect on the roof, enable fuel-efficient vehicle parking, maximize building re-utilization and integrate low-emitting materials and other systems and concepts that support resource management and efficient building systems.

Associate Vice President for Facilities Jim Sears described the initiative to achieve LEED certification for the MBRB as a part of Wayne State's growing focus on sustainability.

"Wayne State is proud of its commitment to sustainability," Sears said. "The MBRB represents another step forward in our application of sustainable building practices and is symbolic of the university's continued dedication to its environment."

Labs in the MBRB will be open, purposefully allowing for expansion or contraction as needed, and encouraging discussion and team science.

decade, and today's research methods are complex," Dr. Stanton continued. "In addition to requiring high-technology equipment, current science demands a bioinformatics infrastructure."

The Human Genome Project, an international effort to sequence the chemical base pairs that make up human DNA, took more than a decade of work before completion in 2003. "Today scientists can sequence your 9,000,000,000 base pair genome in less than a month," Dr. Stanton said. "This kind of scientific advance has major implications for personalized medicine, meaning physicians will one day be able to target therapies based on your individual genetic make-up. But to reach this goal, bioinformatics experts have to be able to work through mountains of data in an efficient way." The MBRB will provide a place for this to happen, consolidating the university's bioinformatics capabilities and becoming the focal point for high-technology data management.

Sylvie Naar-King, Ph.D., professor of Pediatrics, represented WSU faculty during the groundbreaking ceremony. The research she and her colleagues in the Pediatric Prevention Research Center and in other disciplines across the campus work on revolves around behavioral interventions to improve human health, particularly in areas of asthma, HIV, diabetes and obesity in children and teens.

"We know that the complexity of our nation's health problems demands that researchers move beyond the confines of their own disciplines and explore new models of team science," Dr. Naar-King said. "We know that we will need to combine the physical, biological and social sciences to improve the health of our nation in the 21st century. Obesity is a good example of a health care crisis demanding a team science approach. Obesity underlies or exacerbates almost every health condition."

Wayne State's history of interdisciplinary research assisted in Dr. Naar-King securing a $5.7 million center grant from the National Institutes of Health to develop new obesity interventions for African-American families in Detroit. The grant utilizes community health workers as interventionists, boosting the community workforce. The center, she said, incorporates faculty from seven departments and three schools on the WSU campus. However, the team members are housed in varying locations, creating an obstacle to team science that the MBRB will overcome.

Photo by Andrea Westfall

Officials, including Detroit Mayor **Dave Bing**; School of Medicine Dean **Valerie M. Parisi, M.D., M.P.H., M.B.A.**; Wayne State University Board of Governors Vice Chair **Debbie Dingell**; and WSU President **Allan Gilmour**, break ground Oct. 25 for the Multidisciplinary Biomedical Research Building.

"This building will bring teams of researchers together to help to solve our nation's health problems, make us more competitive in bringing funding into the university and the city, and help us better serve the community around us," she said.

Located along the main artery into downtown Detroit, the MBRB will serve as the gateway to the north end of the campus. It will inform visitors' first impressions of Wayne State and the importance of science and research within the university landscape.

The development of the MBRB will include the reconstruction of the Dalgleish Cadillac building on Cass Avenue, a historic Detroit structure designed by renowned architect Albert Kahn. A new 70,000-square-foot addition will be a companion to the Kahn building. While its elegance will be preserved, modern design elements will reflect the state-of-the-art nature of the research taking place inside.

To implement the vision for the MBRB, Wayne State University has commissioned the architecture firm Harley Ellis Devereaux. Jim Sears, associate vice president for Facilities, Planning and Management at Wayne State, described Harley Ellis Devereaux, which also

A neighborhood of partners

The new Multidisciplinary Biomedical Research Building will redevelop 2.75 acres on Woodward Avenue that is now vacant real estate. Revitalizing this section of Midtown will contribute to the growing strength of the neighborhood and the importance of Wayne State's presence within the community.

Once fully operational in early 2015, the MBRB will create both temporary and permanent jobs, and estimates show that it will result in about $40 million in new earnings annually in Michigan, 98 percent of which will be in metropolitan Detroit.

The location will place the MBRB close to Wayne State's main campus and the Henry Ford Health System. The site's footprint includes sufficient adjoining space for future growth and increasing collaborations between the two institutions. The evolving connection between Wayne State and Henry Ford will leverage the collective and compatible strengths of both organizations.

The site also is adjacent to TechTown, the university's business incubator. Laboratory researchers and entrepreneurs will leverage this proximity and easy access for technology development opportunities, further strengthening the university's ultimate vision for the MBRB, which is to move groundbreaking discoveries from the laboratory into practice.

designed the university's A. Paul Schaap Chemistry Building, as especially qualified to bring the MBRB to life. "The architects of Harley Ellis Devereaux know Wayne State and they have spent many hours meeting with our faculty and deans to create a building that will meet the university's research needs and inspire our community with a unique and innovative design," he said.

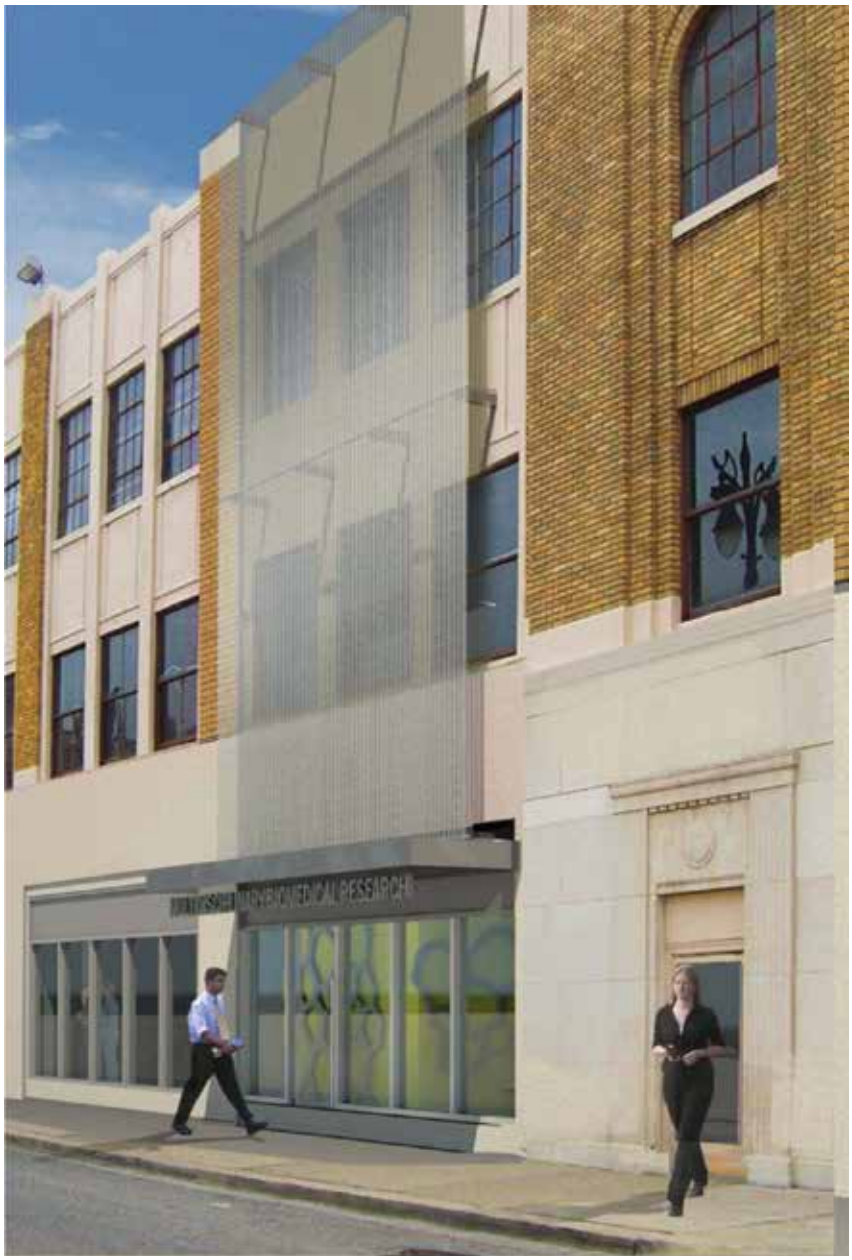
The MBRB will promote collaboration through its interior configuration, following industry research into how, when and where people interact. "We're creating spaces that will encourage the building's occupants to work together," Sears said.

Strategically placed gathering locations and shared resources will help further partnership among research teams.

The main entrance, located in the new addition, will feature a commons area that will be the primary welcome point of the building. A lecture hall will provide high-technology capabilities for formal research presentations, and a lounge will serve as a space for faculty, staff and students to meet informally. There will be offices for principal investigators and accommodations for research faculty, post-graduate fellows and students. A laboratory core will offer wet labs designed for the latest in modern science. Clinical space will allow researchers to interact with patients enrolled in studies.

To construct the MBRB, Wayne State University will employ a combination of state support, university funding and private investment. The state of Michigan will provide $30 million for the construction of the building as a part of its capital outlay for colleges and universities. Philanthropy will play an equally important role.

"Over the years, we are fortunate to have had alumni and friends who contributed to the university's most ambitious projects," President Gilmour said. "As we build the MBRB, we will look to our supporters to embrace our vision for the future as a major research institution dedicated to improving human health through innovative scientific discovery."



The building, while updated, will maintain the original Albert Kahn design.

For more images of the design of the MBRB, and to see how the building looked in the 1930s, visit http://www.flickr.com/photos/waynestateuniversity/sets/72157631776814418/. ■

A giant leap **forward**

Study indicates window to treat cerebral palsy immediately after birth; progesterone application substantially reduces preterm birth

by **Philip Van Hulle**
photo by **Robert Widdis**

About 10,000 babies born each year in the United States will develop cerebral palsy, a disorder of the developing fetal brain that affects motor skills and muscle coordination. Often, the condition is not diagnosed until children reach the age of 2 or 3.

Cerebral palsy, or CP, locks patients into a lifetime of bodies with impaired motor function and loss of muscle control and coordination. There is no known cure.

But in 2012, researchers at the Perinatology Research Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health, housed at the Wayne State University School of Medicine and the Detroit Medical Center, demonstrated that there may be an opportunity immediately after birth for drug treatment that could minimize the effects of CP.

The researchers showed that a nanotechnology-based drug treatment in newborn rabbits with cerebral palsy enabled dramatic improvement of movement disorders and the inflammatory process of the brain that causes many cases of the condition. The study is the first to show that an anti-inflammatory drug delivered with a nanodevice can dramatically improve CP symptoms in an animal model.

A report of the study, "Dendrimer-Based Postnatal Therapy for Neuroinflammation and Cerebral Palsy in a Rabbit Model," was published April 18, 2012, in the prestigious

journal Science Translational Medicine, published by the American Association for the Advancement of Science.

"The key finding of this work is that early identification of neuroinflammation allows postnatal treatment," said Roberto Romero, M.D., D.Med.Sci., chief of the Perinatology Research Branch. "This suggests that there is a window of opportunity to prevent cerebral palsy."

Sujatha Kannan, M.D., is the first author of the study, and Rangaramanujam M. Kannan, B.E., Ph.D., co-wrote the study with Dr. Romero as members of the PRB.

"This is an exciting breakthrough and it certainly points toward new hope for those affected by cerebral palsy," said Dr. Rangaramanujam Kannan, now of the Center for Nanomedicine at the Johns Hopkins Wilmer Eye Institute. "We found that the administration of the anti-inflammatory agent coupled with the dendrimers allowed the drug to not only cross the blood-brain barrier but also to target the cells that cause the neuroinflammation in CP. Of course, this approach and these compounds are not yet approved for testing in humans, and further studies are required to find the optimal dose, duration of treatment and establish safety. More questions need to be answered, but the potential is immense."

Risk factors for CP include low birth weight and premature birth. Children born before the 32nd week of pregnancy are at high risk for developing CP. Intrauterine infection and/or inflammation is a major risk factor for the condition.

Microglia — immune cells in the brain — play an important role in remodeling and growth during fetal and postnatal periods. Activation of these cells can cause an exaggerated inflammatory response, leading to brain injury and CP. Treatment


Photo courtesy of NIH

Research conducted at the Perinatology Research Branch led the state of Michigan to adopt new screening and treatment recommendations to combat premature birth.

is problematic because inflammation and the resulting injury can be spread throughout the brain's white matter. Transporting drugs across the blood-brain barrier also represents a challenge.

The PRB team hypothesized that it was possible to deliver a drug using a tiny device (or nanodevice) that would cross the blood-brain barrier and target the activated cells (microglia and astrocytes) in the brain involved in neuroinflammation.

The researchers used a rabbit model of congenital CP because it replicates the type of neuroinflammation found in human brains and the resulting motor deficits observed in children with CP. The method consisted of exposing fetal rabbits to endotoxin (a component of bacteria). The endotoxin induced inflammation of the fetal brain. When the rabbits were born, they had great difficulties walking or hopping.

The experiment consisted of treating affected rabbits intravenously with either a saline solution, a drug known as NAC (N-acetyl-L-cysteine) or a dendrímer coupled with NAC, also known as a D-NAC conjugate. Rabbits with CP treated with D-NAC on the first day

PRB studies showed that a nanotechnology-based drug treatment in an animal model of cerebral palsy enabled dramatic improvement of movement disorders and brain inflammation. The findings offer hope that there may be a window to treat CP immediately after birth.

of life showed a dramatic improvement and, within five days were able to walk and hop. Rabbits treated with the NAC conjugate also showed a higher neuron count and lower evidence of inflammation compared to untreated animals.

NAC is an antioxidant and anti-inflammatory agent. It is being explored in several ongoing clinical trials to test its potential in autism spectrum disorders, pregnant women for the treatment of maternal and fetal inflammation, and Alzheimer's disease. Dendrimers are synthetic biomimics of globular polymers of the amino acid alanine. Researchers are exploring their use as a vehicle to target drug delivery, a science known as nanotechnology.

The authors believe that conjugating NAC with dendrimers allows delivery of the drug directly to the cells involved, providing greater effectiveness.

"One of the challenges of the 21st century is to rebuild brains injured during fetal or neonatal life, and to prevent not only cerebral palsy, but also other brain disorders," Dr. Romero said.

While still in preclinical testing in animals, the dendrimer-drug conjugate shows promise for postnatal treatment of babies suspected of having CP.

"The use of a rabbit model is a unique aspect of the work, since this model mimics the phenotype of CP as seen in humans. This also illustrates the potential of research collaborations across disciplines in advancing and translating novel technologies for the treatment of debilitating childhood disorders," said Dr. Sujatha Kannan, now a pediatric critical-care specialist at the Johns Hopkins Children's Center.

Dr. S. Kannan said the work was made possible by the development of an animal model of cerebral palsy, the implementation of molecular imaging to detect neuroinflammation at the time of birth and the coupling of the nanodevices (dendrimers) with NAC. The significance of the work is that it opens avenues for the treatment of neuroinflammation, a mechanism of disease not only for cerebral palsy, but for other conditions such as meningitis, encephalitis and multiple sclerosis.

The United Cerebral Palsy Foundation, a national advocacy and support group, estimates that 764,000 children and adults in the United States have CP. A 2009 report by the U.S. Centers for Disease Control and Prevention indicated the prevalence of the condition at 3.3 per 1,000 births. Worldwide, the CDC estimates the prevalence of CP births to range from 1.5 to 4 for every 1,000 births.

The CDC puts the lifetime cost to care for a person with CP at nearly $1 million (in 2003 dollars). The estimated combined lifetime cost for all Americans born with CP in 2000 is expected to total $11.5 billion in direct and indirect costs.

The therapy described by the PRB researchers also holds promise for possible future treatments of neurological disorders, including multiple sclerosis. The brain, for the most part, can be divided into gray and white areas. Neurons are located in the gray area, and the white parts are where the neurons send their axons — similar

to electrical cables carrying messages — to communicate with other neurons or muscles. Oligodendrocyte cells manufacture a cholesterol-rich membrane called myelin that coats the axons. The myelin's function is to insulate the axons, much like the plastic coating on an electrical cable. In addition, the myelin speeds communication along axons and makes that communication much more reliable. Patients with multiple sclerosis display neuronal loss and myelin abnormalities that reduce the myelin coating.

The PRB team found that D-NAC therapy improved the production of myelin and reduced the neuroinflammation associated with the loss of myelin. In fact, by the fifth day after treatment with D-NAC, the CP rabbits demonstrated a significant increase in myelin that nearly matched healthy control animals.

"This is tremendous recognition of the research breakthroughs and the power of the partnership between Wayne State University, the Detroit Medical Center and the Perinatology Research Branch," said Valerie M. Parisi, M.D., M.P.H., M.B.A., dean of the Wayne State University School of Medicine. "This study has the potential to pull back a curtain that has shrouded a medical challenge not just in relation to cerebral palsy, but with other conditions that affect millions around the world."

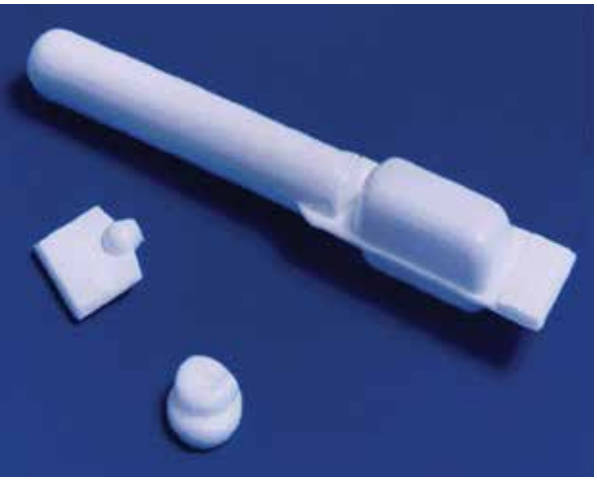
The CP findings were the second groundbreaking maternal-fetal medicine study by the PRB to gain worldwide attention in 2012. The first demonstrated that performing a cervical ultrasound in all pregnant women and treating those with a short cervix with vaginal progesterone reduces the rate of preterm birth and neonatal complications. The study is based on the analysis of all randomized clinical trials of vaginal progesterone conducted worldwide.


Photo by **David Dalton**

Sonia Hassan, M.D., the associate dean for WSU Maternal, Perinatal and Child Health, was the lead author of a groundbreaking clinical study for a new method for preventing premature birth in millions of women each year, published in the medical journal Ultrasound in Obstetrics & Gynecology. The study showed that the rate of early preterm delivery in women less than 33 weeks into their pregnancy can be reduced by 45 percent simply by treating the women at risk with a low-cost gel of natural progesterone from mid-trimester until term.

"Our group has been working on this approach to reducing infant mortality for much of the past decade; it's very exciting to see that the effort is paying off and that

Pregnant women with a short cervix (one that is less than 25 millimeters long) are at high risk for preterm delivery. **Sonia Hassan, M.D.,** says an ultrasound examination is simple to perform, painless and can be performed between the 19th and 24th weeks of pregnancy to identify women who could benefit from progesterone treatment.



Women identified as at risk for preterm delivery because of a short cervix can benefit from a daily self-administered application of progesterone.

mothers and infants will be able to benefit from it," said Dr. Hassan, director of the Center for Advanced Obstetrical Care & Research within the Perinatology Research Branch and a recognized authority in the study of the uterine cervix during pregnancy.

The peer-reviewed research and findings were led by the Perinatology Research Branch of the National Institutes of Health, housed at the Wayne State University School of Medicine and Hutzel Women's Hospital in Detroit. The results published in "Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial" will have substantial impact on the practice of medicine, said the lead author of the three-year clinical trial.

"This study offers hope to women, families and children," Dr. Hassan said. "Worldwide, more than 12 million premature babies — 500,000 of them in this country — are born each year, and the results are often tragic. Our clinical study clearly shows that it is possible to identify women at risk and reduce the rate of preterm delivery by nearly half, simply by treating women who have a short cervix with a natural hormone — progesterone."

Dr. Hassan also pointed out that numerous studies — many conducted by the PRB — over the past decade have shown that ultrasound of the uterine cervix can identify pregnant women who are at high risk for preterm delivery. The ultrasound examination is simple to perform, painless and can be performed between the 19th and 24th weeks of pregnancy. Pregnant women with a short cervix (one that is less than 25 millimeters long) are at very high risk for preterm delivery.

Once a mother at high risk for preterm delivery has been identified she can be offered treatment with the progesterone gel. The inexpensive gel is applied by the mother intravaginally daily. Generally, women are identified as high risk between 19 and 24 weeks of gestation. They apply the progesterone through the 37th week of pregnancy. Of major interest is that progesterone reduced the risk of preterm delivery not only at less than 33 weeks gestation, but also at less than 28 weeks and less than 35 weeks (secondary endpoints of the study). It also reduced the rate of respiratory distress syndrome, the most common complication in premature babies.

"The findings of the study are especially good news for expectant mothers in Detroit," Dr. Hassan said. "Preterm delivery has long been a major health care problem in the city."

In 2008, more than 17 percent of births in Detroit were premature, and they accounted for more than 70 percent of the infant mortality recorded in that year, according to the latest research from the Michigan Chapter of the March of Dimes.

The city's high infant mortality rate, preterm delivery rate, and ethnic and racial disparity in birth outcomes were important considerations in the National Institutes of Health's decision to establish the Perinatology Research Branch in Detroit 10 years ago. The branch allows women in the region to obtain state-of-the-art medical care and join medical studies to improve prenatal diagnosis, monitor fetal growth, predict preeclampsia and prevent premature birth and the potential lifelong difficulties that attend it.

Describing the results, which showed that the rate of preterm birth among women with a short cervix had been reduced by 45 percent, Dr. Hassan, director of the Wayne State/Perinatology Research Branch/Detroit Medical Center Maternal-Fetal Medicine Fellowship Program, noted in the study: "The main implication for clinical practice is that universal screening of women with ultrasound examination in the mid-trimester to identify patients at risk (based on a short cervix) can now be coupled with an intervention — the administration of vaginal progesterone — to reduce the frequency of preterm birth and improve neonatal outcome. This can be accomplished conveniently.

"We're obviously very gratified by these results," Dr. Hassan said. "Based on the findings of our clinical trial, we expect that obstetricians and clinicians will provide expectant mothers with ultrasound screening for cervical length, and to make progesterone therapy available to those who present with a short cervix."

The study was conducted at 44 centers worldwide during the past three years, and included patients from the United States, South America, Europe, Asia and Africa, and screened more than 32,000 women for a short cervix.

Subsequent findings based on an individual patient meta-analysis of all randomized clinical trials of vaginal progesterone conducted worldwide include:

- The vaginal application of progesterone reduces the rate of preterm birth in women at less than 33 weeks of gestation, but also is effective at less than 28, 32 and 35 weeks. Vaginal progesterone reduces both "early" and "late" preterm births. Early preterm births (less than 32 weeks) are associated with a high rate of neonatal complications and long-term neurologic disability. Late preterm births (34-36 6/7 weeks) represent 70 percent of all preterm births, which, although they have a lower rate of complications, are still a major health care problem.
- Vaginal progesterone administration reduced the rate of admission to newborn intensive care units; respiratory distress syndrome; the need for mechanical ventilation; and a composite score of complications that included intracranial hemorrhage, bowel problems, respiratory difficulties, infection and death.
- Vaginal progesterone was effective in women with a short cervix and who had or had not previously given birth prematurely.
- This was the first study to show that vaginal progesterone is effective in reducing the rate of neonatal complications in twin gestations.

One of every eight babies born in Michigan — 295 in an average week — is born prematurely. Michigan's preterm birth rate of 12.7 percent exceeds the national average of 12.2 percent. In Detroit, the rate is even higher.

Previous studies of natural and synthetic progestins have been negative. This study found that progesterone benefits women with a twin gestation and a short cervix.

- There was remarkable consistency of the magnitude of the effect of vaginal progesterone in the prevention of preterm birth among studies conducted in different parts of the world.

The results indicate that it is now possible to offer all pregnant women a method to determine whether they are at risk for preterm birth and prevent a significant number of preterm births in women with a short cervix using vaginal progesterone. Universal implementation of cervical ultrasound and vaginal progesterone is estimated to result in the prevention of approximately 30,000 preterm births at less than 35 weeks in the U.S. per year, with an annual savings of more than $500 million in health care costs.

The study results, and subsequent recommendations to screen all pregnant women for short cervix and recommend the use of progesterone were adopted Aug. 1, 2012, by the Michigan Department of Community Health to combat infant mortality in the state.

With Michigan's 110,000 births annually, the potential cost savings has been estimated to be $19,603,380 (in 2010 dollars) for every 100,000 women screened.

The causes of preterm birth have long been shrouded in mystery, and standard treatments aimed at stopping uterine contractions in women with premature labor have not been successful. Dr. Romero has previously proposed that preterm labor was not simply labor before its time, but the result of pathologic insults that trigger the onset of labor, and now the Perinatology Research Branch is unraveling those mysteries through the development of personalized maternal fetal medicine.

The PRB is strategically located to serve a high-risk population that requires the full spectrum of services the branch offers, including the most advanced three-dimensional and four-dimensional ultrasound for prenatal diagnosis. Since locating at the Wayne State University School of Medicine and the Detroit Medical Center at Hutzel Women's Hospital, the branch has assisted more than 20,000 at-risk mothers, most of them uninsured.

There clearly is a critical need, locally and worldwide, for the services and medical research conducted at the Perinatology Research Branch. In 2005, nearly 13 million babies — about 10 percent of births worldwide — were born preterm, or before 37 weeks gestation. "The Global and Regional Toll of Preterm Birth," a report released by the March of Dimes in late 2009, declared that about 1 million deaths in the first month of life, or 28 percent of newborn deaths around the world, could be traced to a complication of premature birth. While the majority of women (11 million) giving birth prematurely did so in Africa and Asia, the United States and Canada recorded a combined 500,000 premature births. Since the report counted only single births and mothers with no known medical conditions, it is likely the data underestimated the severity of the problem.

Data compiled by the World Health Organization and used for the 2009 March of Dimes report indicated that 10.6 percent of births in North America (the United States and Canada) are premature, second only to the 11.9 percent rate of Africa. In the United States, premature births have increased 35 percent in the last quarter century.

Wherever trend data are available, according to the March of Dimes, the rates of preterm birth are increasing around the world. In fact, the U.S. consistently records higher infant mortality rates than most other developed countries. The nation currently ranks 43rd in infant mortality rates among industrialized nations. In 2007, nearly seven of every 1,000 American babies died before their first birthday. The U.S. National Center for Health Statistics cited the high rate of premature births as the main reason for the nation's poor ranking of infant mortality rates.

Even though many states improved their rates of premature birth, the March of Dimes still graded the United States with an overall C in its 2011 Premature Birth Report Card. The organization compared the nation's 2009 rate of preterm birth (12.2 percent) with the March of Dimes' new 2020 goal of 9.6 percent. In the most recent report card, only Vermont received an A grade. Sixteen states earned a B grade and 19 states, including Michigan, received a C. Eleven states and the District of Columbia received a D, while three states and Puerto Rico received an F.

One of every eight babies born in Michigan — 295 in an average week — is born prematurely. Michigan's rate of preterm birth (12.7 percent) exceeds the national average of 12.2 percent. The Michigan Department of Community Health reports that for every 1,000 live births in the state, eight infants die before their first birthday. Data compiled in 2009 by the CDC and the Michigan Department of Community Health indicate Michigan's infant mortality rate consistently exceeds the national average.

In addition, there is an alarming disparity in the access to care, quality of care and pregnancy outcome among racial and ethnic groups in Michigan. African-American mothers experience more birth complications, including more premature births, preeclampsia — a sudden and dangerous increase in blood pressure — and babies with low birth weight. Infants born to black mothers in Michigan are 70 percent more likely to be born prematurely than infants of other races, according to a 2010 report by the Center for Healthcare Research & Transformation, a public policy and research organization based in Ann Arbor, Mich. Most babies are delivered between 38 and 40 weeks of gestation. However, 19 percent of babies born to black mothers in the state were born before 34 weeks of gestation, said the report, compared to 11 percent of white and Hispanic newborns. While the state's rate of premature births held stable for births less than 34 weeks of gestation, the rate increased 20 percent among births between 24 and 27 weeks.

Premature births are costly. The CDC reports that preterm births topped the list of the most expensive hospitalizations in Michigan in 2007. Each premature birth in the state costs an average of $102,103 at the time of discharge from the hospital. That is 14 times the cost of a normal birth. Nationwide, the March of Dimes puts the cost of premature birth at $26 billion annually. ■

The power of **D**

Phillip Levy, M.D., M.P.H., believes that vitamin D holds a key to halting and reversing heart disease in African-Americans with high blood pressure.

Study to determine whether inexpensive vitamin therapy can reduce cardiovascular disease in African-Americans with high blood pressure

by **Philip Van Hulle**
photo by **David Dalton**

High blood pressure claims nearly 1,000 lives a day in the United States, according to the U.S. Centers for Disease Control and Prevention. The condition, left untreated, can lead to cardiovascular disease, the No. 1 killer of all Americans.

While nearly one in three American adults has high blood pressure and almost 30 percent register blood pressure readings that place them in the prehypertension category, the condition far and away takes a greater toll among African-Americans, who historically demonstrate greater rates of high blood pressure.

Now, a Wayne State University School of Medicine physician-researcher is utilizing a $1.9 million National Institutes of Health grant to study the role of an inexpensive and commonly available tool in halting and reducing subclinical cardiac damage

in African-Americans suffering from high blood pressure.

Phillip Levy, M.D., M.P.H., associate professor of Emergency Medicine, will use the five-year R01 grant to determine how vitamin D affects cardiac structure and function, and vascular function in African-Americans with hypertension. The research could identify vitamin D as a safe, effective and inexpensive therapy to stop, and even reverse, cardiac ravages caused by high blood pressure.

"This project focuses on a vulnerable demographic subgroup at high risk for hypertension, poor blood pressure control and, consequently, adverse pressure-related cardiovascular complications," Dr. Levy said. "Vitamin D is an inexpensive therapeutic intervention, which, if shown to be efficacious, could greatly enhance the existing approach to secondary disease prevention in a widely accessible, cost-effective manner."

Vitamin D is naturally present in few foods, among them, salmon, tuna and mackerel. Other food products are fortified with vitamin D. Most humans also derive vitamin D from exposure to sunlight. African-Americans, however, have more difficulty in absorbing sufficient vitamin D through exposure to sunlight because of skin pigmentation.

Previous studies, Dr. Levy said, suggest a relationship between the degree of skin pigmentation and thickening of the muscle tissue in the wall of the heart's main pumping chamber — a condition known as left ventricular hypertrophy. Common in those with high blood pressure, left ventricular hypertrophy is a major risk factor for cardiovascular disease, especially heart failure. Importantly, the cardiovascular risks associated with left ventricular hypertrophy start increasing early in the process, often before the appearance of overt symptoms.

Vitamin D deficiency has been linked to high rates of cardiovascular disease in African-Americans, but whether supplementation can reduce this risk is not known. It is thought that vitamin D deficiency may accelerate ventricular changes that occur with high blood pressure, thus serving as a potential point of intervention.

Dr. Levy's study will recruit patients between the ages of 30 and 74 who present to the emergency department at Detroit Receiving Hospital with poorly controlled chronic hypertension but no prior history of secondary cardiovascular disease. Dr. Levy said 267 patients will be screened, with the anticipation that 75 percent will have vitamin D deficiency. Those with vitamin D deficiency will then undergo cardiac magnetic resonance imaging to screen for increased left ventricular mass. Based on earlier work funded by the Robert Wood Johnson Foundation's Physician Faculty Scholar's program, Dr. Levy anticipates that 60 percent of those evaluated by MRI will have left ventricular hypertrophy, resulting in a final sample of 120 patients who will be randomized to receive blood pressure control with additional placebo or vitamin D supplements for an entire year.

Dr. Levy said patients enrolled in the study will receive 50,000 international units of vitamin D3 every other week, an amount consistent with current therapeutic recommendations. The supplement will be provided in a liquid gel capsule. Most people who take vitamin D as an over-the-counter supplement ingest 1,000 IU daily. The federal Recommended Daily Allowance for vitamin D, set in 2010, is 600 IU daily.

Dr. Levy expects to find that study enrollees who receive vitamin D therapy will experience a regression in left ventricular mass beginning 16 weeks after they start taking the supplements. That regression should continue and increase in magnitude over the course of a year. Myocardial fibrosis,

which comprises much of the increase of left ventricle mass in those with hypertension, should decrease. Other expected outcomes include improved vascular function with a decrease in central and possibly peripheral blood pressure.

"Vitamin D's effectiveness in further reducing left ventricle mass would decrease the excess risk of cardiovascular disease complications in African-Americans," he said.

Additionally, if serum markers parallel MRI findings in the study, Dr. Levy said, they could then serve as a screening and assessment tool.

The CDC reports that high blood pressure affects African-Americans in greater percentages than any other racial segment in America. Forty-three percent of African-American men and 45.7 percent of African-American women have hypertension. The rates are 33.9 percent and 31.3 percent, respectively, among white men and women. The condition is a leading factor in cardiovascular disease, and Michigan ranks as the ninth worst state in cardiovascular deaths, with 293.2 deaths for every 100,000 residents, according to the Michigan Department of Community Health. The heart disease death rate for African-Americans in Michigan remains higher than national rates.

Dr. Levy will serve as the principal investigator for the study. His research mentor, John Flack, M.D., M.P.H., professor and chair of Internal Medicine, and Rafael Fridman, Ph.D., professor of Pathology, will be co-investigators.

"There are biologically plausible mechanisms through which vitamin D deficiency can cause or contribute to left ventricular hypertrophy," Dr. Flack said. "Populations, such as African-Americans, who manifest high rates of vitamin D deficiency, also have excessive rates of left ventricular hypertrophy. The test of whether moderate to high dose vitamin D replacement can regress left ventricular hypertrophy is long overdue. Vitamin D is safe, reasonably cheap, and has enormous, but mostly unproven, therapeutic potential."

Dr. Levy, in addition, has found that an overwhelming majority of African-American patients with hypertension also suffered hidden heart disease caused by high blood pressure even though they displayed no symptoms.

His study — "Subclinical Hypertensive Heart Disease in African-American Patients with Elevated Blood Pressure in an Inner-City Emergency Department" — published online in Annals of Emergency Medicine in June 2012, discovered that nine of every 10 patients tested suffered hidden heart damage caused by high blood pressure. While slightly more than 93 percent of 161 patients in the study had a history of hypertension, 90.7 percent tested positive for hidden hypertensive heart disease. None of them knew their high blood pressure was affecting their hearts and did not show any symptomatic signs of heart disease.

"These results present a tremendous opportunity to screen for heart disease before it becomes symptomatic, especially in a population with high rates of hypertension," Dr. Levy said. "If we can detect incipient heart disease early, we have a better shot at treating it before it turns into a full-blown health emergency. Our study is also a strong reminder that emergency patients with chronic disease — in this case, hypertension — are generally a high-risk group."

The patients were enrolled in the study, funded by the Blue Cross Blue Shield Foundation of Michigan, after appearing at the emergency room of Detroit Receiving Hospital. They did not come to the hospital because of heart disease symptoms. Once enrolled in the study, they underwent echocardiograms, which revealed the hypertensive heart disease. Of the total

161 patients, 93.8 percent were inner-city African-Americans; 51.6 percent were male. The mean age of the patients enrolled was 49.8 years.

Most of the patients (93.8 percent) had a history of high blood pressure and were aware that they had the condition. Only 68.3 percent were receiving treatment.

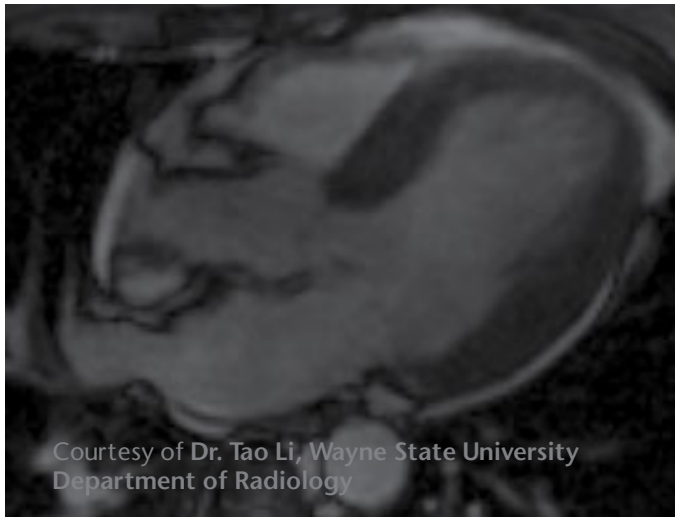
Of those found to have hidden heart disease, the majority were diagnosed with diastolic dysfunction, defined as the heart's inability to adequately pump blood. Dr. Levy said the echocardiograms found the presence of subclinical hypertensive heart disease "ubiquitous."

Statistics kept by the CDC show that 228.3 of every 100,000 Michigan residents 35 and older died of hypertension-related causes in 2009. In African-Americans, the rate was 381.9 deaths for every 100,000; in whites it was 211. All Michigan rates were higher than national statistics. In rates of hypertension hospitalizations of Michigan residents 65 and older who are Medicare beneficiaries, African-Americans had higher rates (14 hospitalizations per 1,000 Medicare beneficiaries) than whites (3.6 per 1,000). Again, both rates were higher than national numbers.

Since subclinical heart disease is unlikely to be detected in such hypertensive patients until the damage manifests in visibly recognized symptoms, the early identification of the condition "has emerged as an important aspect of secondary cardiovascular disease prevention," Dr. Levy said.

Emergency room physicians may underestimate the prevalence of hidden hypertensive heart disease in inner-city African-Americans, who are considered an especially high-risk group and who rely on emergency rooms for treatment because of lack of access to primary care physicians.

"Emergency physicians are uniquely positioned to lessen the overall impact of chronic high blood pressure in at-risk communities," Dr. Levy said. "Blood pressure readings are taken for every patient in the ER. By not just taking in new information but also acting on it, we can substantively contribute to much-needed secondary disease prevention efforts."



This MRI view shows left ventricular hypertrophy of the heart. The condition, a major risk factor for cardiovascular disease, consists of a thickening of the muscle tissue in the wall of the heart's main pumping chamber.

Recognizing the likelihood of previously unrecognized subclinical hypertensive heart disease prevalence in African-Americans holds therapeutic promise that could reduce adverse outcomes, Dr. Levy said. Blacks progress from hidden to symptomatic stages of left-ventricular dysfunction more rapidly than other population groups, and the mean age of blacks admitted to hospitals with heart failure is much lower than that of whites (63.6 years versus 75.2 years).

"While we must recognize the risk that exists for these patients, we should not expect emergency departments to perform the further studies needed to identify subclinical end-organ damage," Dr. Levy said. "Emergency departments should focus on identification of poorly controlled hypertension — whether or not it was the primary reason for the emergency visit — and hospital systems, especially those where a high disease prevalence exists, should have some coordinated mechanism where patients can be referred for follow-up. Moreover, at that follow-up, a mechanism should exist to perform effective intervention, including risk stratification, even if patients lack insurance." ■

Controlled **chaos**

Team sets out to determine whether stress in emergency room doctors affects quality of patient care

by **Philip Van Hulle**
photos by **David Dalton**

Wayne State University School of Medicine doctors **Karin Przyklenk**, **Philip Lewalski**, **Bengt Arnetz** and **Sham Maghout Juratli** (not pictured) are turning the research tables by examining connections between the stress of emergency room physicians and the quality of care they provide.

Decades of television programs such as "ER," "St. Elsewhere" and "M*A*S*H*" have conditioned the public to view emergency room doctors as tough nuts who don't crack under the pressure, juggling multiple cases with swagger and sardonic wit, and thriving in a chaotic atmosphere.

A multidisciplinary team of Wayne State University School of Medicine physicians and researchers are putting that stereotype to the test.

Using a Physician Investigator Research Award from the Blue Cross Blue Shield of Michigan Foundation, the investigators will study the links between the acute cardiovascular stress experienced by emergency room doctors and the quality of patient care they provide.

"The goal of this pilot project is to investigate the critical relationships between acute stress, biochemical markers of cardiovascular risk and quality of patient care among junior physicians (residents) in the high-stress environment of the emergency medicine department," said Karin Przyklenk, Ph.D., professor of Physiology and Emergency Medicine, and director of the School of Medicine's Cardiovascular Research Institute. "It is very possible that residents may believe that they thrive on stress and are unaffected when, in fact, biochemical markers of stress are increased. A second interesting possibility is that stress

markers may be high before a shift in anticipation of the forthcoming stress. Our protocol will allow us to explore these different possibilities."

The study will involve 52 second- and third-year residents in emergency rooms at Sinai-Grace and Detroit Receiving hospitals.

Philip Lewalski, M.D., a co-principal investigator in the study, has been an emergency room attending physician for 19 years at Detroit Receiving Hospital, and is a stroke survivor. While he said that he cannot with certainty attribute his stroke to the chaotic environment of the emergency room, physicians may not recognize the toll such stress takes.

"I did not feel I was stressed. I thought I thrived on being an adrenaline junkie. I worked midnights for 18 years and loved it," said Dr. Lewalski, assistant professor of Emergency Medicine. "But certainly the 'macho' environment contributed to the fact that I hadn't seen a doctor in 25 years because I felt bulletproof and my untreated (undiagnosed) hypertension clearly led to the intracerebral bleed."

He noted that co-workers began checking their blood pressure during busy times and found baseline pressures that were slightly high (140/90) increased significantly (170/105 and higher). "That's why I became interested in the effects of acute stress. Maybe we didn't feel stressed in our conscious mind, but perhaps there is still an effect physiologically," he said.

Many emergency room physicians believe they are immune to the stresses of the job, Dr. Lewalski said. "We do enjoy the chaos, but my suspicion is that the stress affects us more on a subconscious level. The strongest indicator of stress most of us would admit to a colleague is, 'Man, it was crazy last night!' And we do that with a sort of macho grin, as if to say, 'But it didn't bother me, because I love it!'"

Dr. Lewalski said he would like to be able to say that the stress experienced by emergency room physicians has no effect on patient care, but he can't rule it out. "Six gunshot patients are hard because of the volume. One critically ill child is hard for very different reasons. An unexpected death can affect you in different ways," he said. "You try to bury it and approach the next patient with a clear mind, but no one can do that 100 percent of the time."

Blood and saliva samples will be obtained from emergency department residents both before and after eight- to 12-hour shifts. The samples will be processed and analyzed in the Cardiovascular Research Institute labs for established biochemical markers of acute cardiovascular stress, such as fibrinogen, interleukin-6 and C-reactive protein. The team also will use a questionnaire asking residents to indicate their perceived stress before and after shifts in the emergency department.

"We expect to see an increase in stress biomarkers in blood and saliva, and an increase in self-reported perceived stress, after completion of the eight- to 12-hour shift," Dr. Przyklenk said. "In addition, we

expect to see a negative, inverse relationship between stress and quality of patient care."

Team members said that this is the first study they know of that will objectify stress, examine cognitive and biological stress mechanisms, and relate them to top level cognitive demands and performance. The impact of acute work stress is of particular significance among physicians, whose work stress has been linked not only to increased cardiovascular risk but to compromised patient care. While these relationships embody important public health implications, acute physician work stress and its potential consequences have not been examined in a controlled manner. One difficulty in such a study is reproducing a real-life environment — a "stress laboratory" — in which to examine study subjects. Using the experience of residents in Detroit Receiving, Michigan's largest Level I trauma emergency department, provides a stable cohort of study subjects as well as a real stress lab.

The two other investigators working in the study are Bengt Arnetz, M.D., Ph.D., M.P.H., professor of Family Medicine and Public Health Sciences and director of the Division of Occupational and Environmental Health, and Sham Maghout Juratli, M.D., assistant professor of Family Medicine and Public Health Sciences. The study, which brings together experts in Emergency Medicine and experts in stress and Cardiovascular Pathophysiology, exemplifies the type of multidisciplinary collaboration that is the mission of the Cardiovascular Research Institute.

Dr. Przyklenk said the team's long-term objective is to use results from this pilot study as the foundation for subsequent comprehensive and long-term investigations of the relationships among acute and chronic work stress, cardiovascular risk and quality of patient care in Emergency Medicine centers across Michigan. The team plans to conduct future studies with an expanded enrollment that will include attending physicians who are older and more experienced, as well as nurses and other health care personnel serving in emergency departments. "There may be interesting differences in the response to acute stress in these cohorts versus younger and less-experienced residents," she said. ■

Stopping seizures more effectively

Robert Welch, M.D., associate professor of Emergency Medicine, oversaw the Detroit portion of the Rapid Anticonvulsant Medication Prior to Arrival Trial, or RAMPART study, to determine a more effective method for first-responders to patients whose seizures aren't stopping.

WSU researcher reveals improved method for paramedics to stop prolonged seizures

by **Philip Van Hulle**
photos by **Tom Owoc**

Emergency Medical Services and ambulance crews have it tough. Working on cardiac patients who may be dying in front of family members, back strain from lifting obese patients and sometimes seeing firsthand the results of the darker side of humanity are all part of the day's work.

One of the toughest jobs of the paramedic, however, is attempting to establish an intravenous line in a patient suffering prolonged seizures. Standard practice calls for emergency medical crews to get an IV into a seizing patient's arm to administer an anti-seizure medication. Doing so while that patient is jerking about presents a physical, as well as a targeting, challenge.

Drug delivery directly into the thigh muscle using an autoinjector is faster and may be more effective in stopping prolonged seizures, according to a study sponsored by the National Institutes of Health and conducted by a Wayne State University School of Medicine researcher.

The Department of Emergency Medicine at the Wayne State University School of Medicine was one of a number of sites that conducted a trial comparing the effectiveness of two U.S. Food and Drug Administration-approved anti-seizure medications and how they are administered to patients suffering prolonged seizures before they arrive at hospitals.

The Rapid Anticonvulsant Medication Prior to Arrival Trial, or RAMPART, was designed to determine whether midazolam or lorazepam are safer and more effective when paramedics are called to treat patients whose seizures aren't stopping. The study was funded by the National Institute of Neurological Disorders and Stroke, part of the NIH. The prolonged seizures, called status epilepticus, create an emergency situation, said Robert Welch, M.D.,

associate professor of the WSU Department of Emergency Medicine, who oversaw the Detroit portion of the study. Estimates indicate that between 120,000 and 200,000 such cases take place each year in the United States. As many as 55,000 people die from the seizures.

Complications of prolonged seizures, Dr. Welch explained, include impaired ventilation and aspiration into the lungs, which can result in pneumonia. Other issues include heart rhythm problems and direct injury to the nervous system. “Optimal outcomes in patients therefore depend on treatments that lead to rapid cessation of seizure,” Dr. Welch said. “In the pre-hospital setting, it can be difficult to treat this group of patients, particularly since starting an IV to administer medications can be very difficult.”

Emergency medical services crews generally administer anticonvulsant drugs at the scene intravenously as a first-line treatment for seizures. However, starting an IV in a patient experiencing seizures can pose a challenge for paramedics and waste precious time. Applying an intramuscular injection using a device similar to the EpiPen used to treat severe allergic reactions is easier, faster and more reliable, especially in patients having convulsions. The researchers sought to determine whether an intramuscular injection, which quickly delivers anticonvulsant drugs into a patient’s thigh muscle, is as safe and effective as giving a drug directly into a vein. The study, which was carried out by paramedics, compared how well delivery by each method stopped patients’ seizures by the time the ambulance arrived with the patient at the emergency department.

Midazolam and lorazepam are benzodiazepines, a class of sedating anticonvulsant drugs. Midazolam was a candidate for injection because it is rapidly absorbed from muscle. Lorazepam must be given by IV.

The study, published in The New England Journal of Medicine, found that 73 percent of patients in the group receiving midazolam via direct injection into the thigh muscle were seizure-free upon arrival at the hospital, compared to 63 percent of patients who received lorazepam via IV. Patients treated with midazolam also were less likely to require hospitalization than those receiving lorazepam intravenously. Among those admitted, both groups had similarly low rates of recurrent seizures.

“This study demonstrated that giving an intramuscular dose of medication is just as effective in stopping the prolonged seizure as is giving an intravenous medication,” said Dr. Welch, who also serves as director of Clinical Research for the department, as well as principal investigator of the Wayne State University hub of the Neurological Emergencies Treatment Trials Network. "Since it can be very difficult to establish an IV in a patient who is seizing, giving a medication intramuscularly is easier, and may lead to better outcomes. In order to reduce the potential for brain damage, stopping the seizure as soon as possible is the goal of treating status epilepticus. This method is as good, and maybe better, than trying to start an IV and administer medication.”

The study involved 1,024 patients nationwide. The WSU portion of the study consisted of

“In the pre-hospital setting, it can be difficult to treat this group of patients, particularly since starting an IV to administer medications can be very difficult.”

178 enrolled patients, the largest group of patients in the study. Paramedics treated patients in the study who were transported to Detroit Receiving Hospital, Sinai Grace Hospital and St. John Hospital.

Paramedics involved in RAMPART used study boxes with a time-stamped voice recorder. This tool allowed them to make quick decisions, indicate the time treatment began and the time the convulsions stopped, all without having to interrupt patient care to record data. The goal of the study was to control seizures within 10 minutes without having to deliver a second dose of drug.

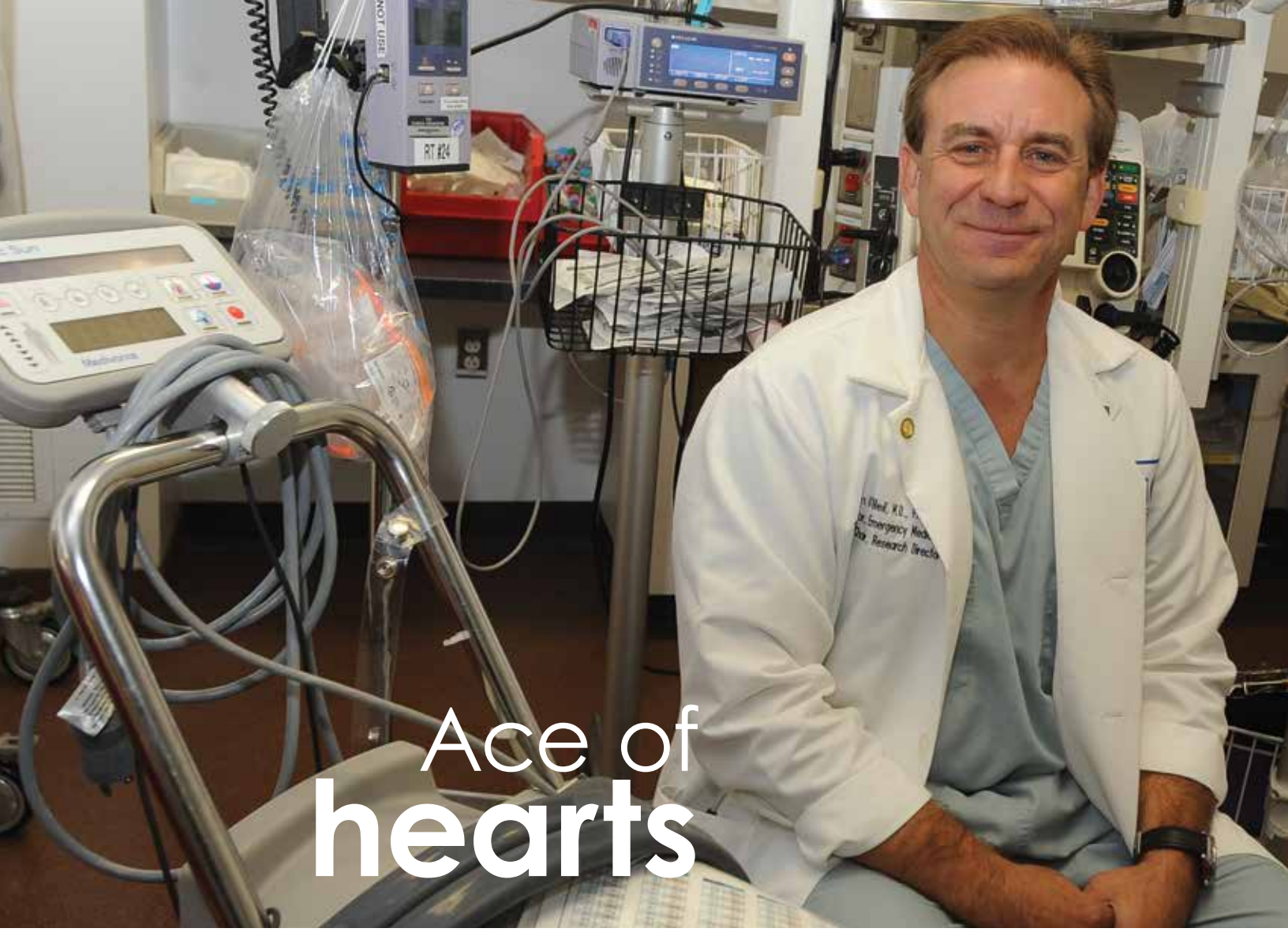
Since the study involved patients who were severely affected and could not make decisions for themselves, the research was given exception from informed consent parameters. If patients were unconscious after they were transported to the hospital and the seizure had subsided, a member of the study team attempted to contact a family member. If patients later determined that they no longer wished to continue participating in the study after initial treatment, they could opt out. Community consultation was held in advance of the study to raise awareness, ensure transparency and gain input from residents.

Dr. Welch said that when the autoinjectors are available they should become standard equipment in EMS units and ambulances. Until that time, he recommended that paramedics administer midazolam intramuscularly in the thigh using a traditional syringe.

RAMPART investigators said that while autoinjectors might someday be available for use by epilepsy patients and their family members, more research is required. Because of the strong sedative effect of midazolam, on-site medical supervision is now required to ensure patient safety.

The Neurological Emergencies Treatment Trials Network, funded by the NIH, includes more than 100 emergency departments and EMS agencies in 17 major metropolitan areas. The organization was formed to conduct large trials to reduce the burden of injuries and illnesses affecting the brain, spinal cord and peripheral nervous system. The network, Dr. Welch said, explores the narrow window of opportunity that seems to exist in treating neurologic damage from a variety of conditions, ranging from stroke and traumatic brain injury to seizures and meningitis. The study of rapid interventions by NETTN requires the assistance of paramedics treating patients in the field. ■

Dr. Welch discusses findings of the RAMPART study with a member of the Emergency Medical Services division serving the city of Detroit.



Ace of hearts

Brian O'Neil, M.D., found that those providing CPR were not pushing hard enough or fast enough when performing chest compressions.

WSU Emergency Medicine physician rewrites the CPR guidelines for the American Heart Association

by **Philip Van Hulle**
photos by **David Dalton**

Push harder and faster, and don't stop.

That, in a nutshell, is the new recommendation on how to administer chest compressions when providing cardiopulmonary resuscitation to someone suffering a cardiac episode, according to newly revised guidelines from the American Heart Association.

Brian O'Neil, M.D., F.A.C.E.P., the Edward S. Thomas Endowed professor and interim chair of the Wayne State University School of Medicine's Department of Emergency Medicine, co-wrote the new guidelines, which incorporate a radical change from the CPR rules taught to generations of Americans and Canadians.

The revised guidelines call for those administering CPR to begin chest compressions immediately after notifying emergency response personnel, and to continue doing so until health care professionals can begin treatment.

Previous guidelines taught a simple memory device for assisting someone undergoing

a heart attack — ABC, which stood for checking the victim's airway, blowing breaths into the mouth and then performing chest compressions. However, Dr. O'Neil and his colleagues who wrote the new guidelines found that checking the airway and breathing into the victim wasted vital time before the chest compressions — the key element in treating those who need CPR — were started. The new steps now recommend a CAB process, for compressions, followed by checking the airway and then providing breaths.

The chest compressions keep blood and oxygen flowing to the heart and brain. The new recommendations emphasize continuous compressions without breaks at a rate of 100 per minute. They minimize the importance of checking the victim's pulse. Dr. O'Neil's group noted that hands-only CPR is easy to perform, and that when all adult cardiac incidents were reviewed, survival rates were as good as or better when bystanders provided compressions only as compared to traditional CPR methods.

The most recent recommendations eliminate the traditional mantra of "look, listen and feel" for breathing to prevent any delay in administering compressions.

According to the American Heart Association, about 300,000 sudden cardiac arrests occur outside of hospital settings annually, 80 percent of them in private homes. Nearly 70 percent of Americans may not know how to administer CPR. That statistic may contribute to the fact that less than 8 percent of those who suffer cardiac arrest outside of a hospital survive, resulting in a death every two minutes in the United States. The Sudden Cardiac Arrest Association estimates that CPR performed by bystanders can as much as triple survival rates.

While the former CPR recommendations, adopted in 2005, called for a compression rate of about 100 per minute, the guidelines now recommend at least 100 per minute. The higher number of compressions per minute, Dr. O'Neil said, have been linked with patient survival, and the actual compression rate applied by bystanders is often well below 100 per minute. The American Heart Association now says compressions must push at least 2 inches into the chest as opposed to the previous recommendation of 1.5 to 2 inches. Studies found that the deeper compression is more effective and those assisting victims often do not push hard enough.

"This is one of the fastest growing fields, with large clinical trials continually changing the paradigm," said Dr. O'Neil, who serves on the Emergency Cardiac Care Committee and the International Liaison Committee on Resuscitation, groups that advise the American Heart Association. He also is a member of the writing committee for the AHA, Acute Coronary Syndromes Guidelines and the AHA's Advanced Cardiovascular Life Support Subcommittee and Writing Group. "The biggest thing in this last revision was the need for quality CPR with some monitor of its quality and the need for aggressive post-cardiac arrest care."

Half of acute coronary syndrome patients who die do so before reaching a hospital. Many of those deaths occur because patients, family members and witnesses to someone needing assistance fail to recognize the signs of acute coronary syndrome and fail

"The biggest thing in this last revision was the need for quality CPR with some monitor of its quality and the need for aggressive post-cardiac arrest care."

Brian O'Neil, M.D.

to activate the emergency medical service system. Despite decades of awareness and training programs, Dr. O'Neil and his colleagues said, communities must continue to develop programs that spread the knowledge of prompt recognition of acute coronary syndrome symptoms, how and when to contact emergency health care providers and first-responders, and how to perform high quality CPR. They also recommended that all emergency dispatch personnel be educated in providing CPR instructions over the telephone, and to instruct patients with suspected acute coronary syndrome with no history of allergy to aspirin to chew an aspirin while waiting for EMS personnel. Aspirin has proved valuable in preventing or slowing blood clotting, reducing death in cases of acute coronary syndrome.

Additional recommendations in the revised guidelines, four years in the making and vetted by experts from around the world, include monitoring the quality of CPR with devices like waveform capnography and focusing on providing high-quality CPR and defibrillation. For EMS personnel and physicians, the guidelines recommend no longer using atropine for routine use in the management of pulseless electrical activity and asystole (cardiac standstill), using chronotropic drug infusions as an alternative to pacing in symptomatic and unstable bradycardia, and recognizing adenosine as safe and potentially effective for treatment and diagnosis in the initial management of undifferentiated regular monomorphic wide-complex tachycardia.

Another major emphasis of the new guidelines was the fifth link in the survival chain, post-cardiac arrest care. This care stresses transport to a comprehensive post-arrest system of care, aggressive coronary reperfusion, normoxia not hyperoxia and temperature regulation with an emphasis on the use of therapeutic hypothermia.

Emergency Medical Services crews should continue with or implement the use of 12-lead electrocardiograph devices to monitor patients and transmit information to hospitals. They should also triage patients with ST-segment elevation myocardial infarction to percutaneous coronary intervention hospitals because studies have shown improved rates of survival for STEMI patients at such facilities. ■

Improving MS therapies

Studies conducted at WSU Multiple Sclerosis Center to modify treatment for patients around the world

by **Philip Van Hulle**
photos by **David Dalton**

A global study overseen by a Wayne State University School of Medicine neurologist will likely result in the modification of the preferred treatment regimen for millions of multiple sclerosis patients around the world.

The study findings are expected to see people with relapsing-remitting multiple sclerosis, or RRMS, eventually change from a daily drug injection to just three injections per week.

The Glatiramer Acetate Low-Frequency Administration, or GALA, Phase III study investigated a new dose and frequency of glatiramer acetate, in patients with RRMS. The study found that glatiramer acetate injected in the amount of 40 mg subcutaneously three times a week was significantly better than a placebo in reducing the annualized relapse rate after one year. Another key finding: The drug was just as effective when injected at 40 mg three times a week as when injected daily in a lesser dose.

Omar Khan, M.D., professor and interim chair of the Wayne State University School of Medicine Department of Neurology, showed that glatiramer acetate administered at 40 mg three times a week was highly effective in reducing the relapse rate and brain magnetic resonance imaging evidence of tissue injury in patients with relapsing-remitting MS. He developed the concept of less frequent dosing of the drug without compromising its immunologic, clinical and MRI effects.

"Once we were able to demonstrate that the universal antigenic approach of this peptide therapy did not require

Omar Khan, M.D., professor and interim chair of Neurology, showed that Copaxone administered fewer times per week was effective in reducing the relapse rate in patients with relapsing-remitting MS. He developed the concept of less frequent injections without compromising its immunologic, clinical and MRI effects.

daily exposure to the immune system, the commercial manufacturer, Teva Pharmaceuticals, was willing to conduct an $80 million global study," said Dr. Khan, who served as the principal investigator of the study that involved 1,400 patients in 30 countries.

"At the end of the day, it is a win-win situation for everyone, but most importantly for our patients, who may have a new way of using this treatment," said Dr. Khan, the director of the Wayne State University Multiple Sclerosis Center.

Known commercially as Copaxone, the drug is approved by the U.S. Food and Drug Administration for the treatment of relapsing forms of MS at an injection dose of 20 mg daily. The drug, said Dr. Khan, is the most prescribed medication for the treatment of MS, with annual worldwide sales exceeding $3.5 billion.

The Multiple Sclerosis Society and other health organizations put the number of people with MS worldwide at about 2.1 million. In the United States, 400,000 people live with the condition, with another 200 new cases diagnosed weekly. Estimates of MS patients in Michigan range from 18,000 to 20,000.

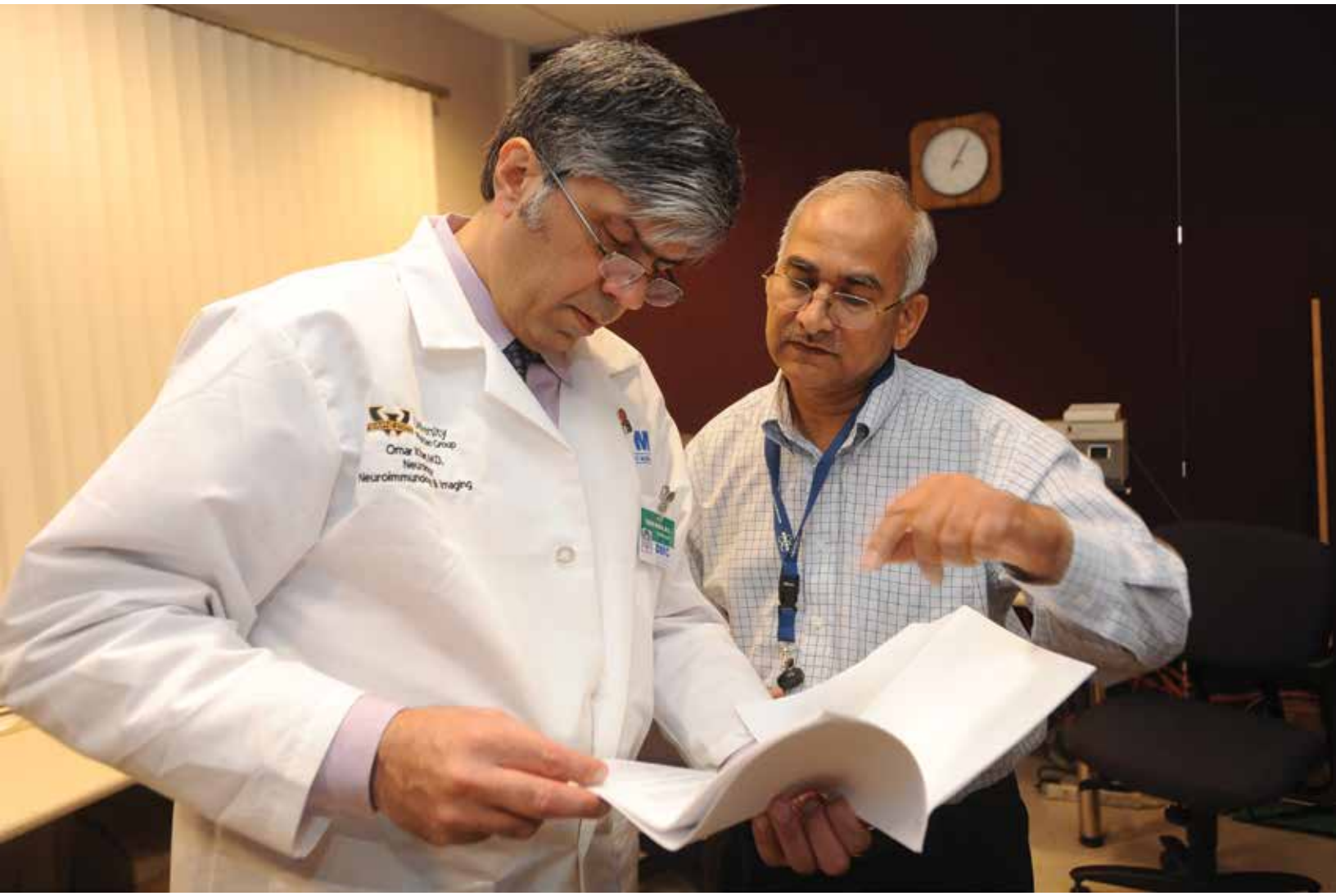
Multiple sclerosis is a progressive disease of the central nervous system characterized by the destruction of the myelin sheath surrounding nerve tissue, damaging the effectiveness of signaling between the neurons in the brain and spinal cord. The brain can generally be divided into gray and white areas. Neurons are located in the gray area, and the white parts are where neurons send their axons — similar to electrical cables carrying messages — to communicate with other neurons and bring messages from the brain to muscles throughout the body. The white parts of the brain are white because a cell type called oligodendrocytes manufactures a membrane called myelin that coats the axons. The myelin's function is to insulate the axons, similar to the plastic coating covering an electrical cable. In addition, the myelin speeds communication along axons and makes that communication more reliable. When the myelin coating is attacked by the body's immune system and degraded, the impulses — messages from the brain to other parts of the body — can "leak" and be derailed from their intended target.

The cause of MS remains unknown and there is as yet no cure. The condition strikes women twice as often as men. The disease is progressive, meaning it worsens with time. Those with relapsing-remitting multiple sclerosis can have bouts in which the condition recurs or temporarily worsens punctuated by periods of recovery.

Copaxone, a polypetide of four amino acids, works by preventing the body from damaging myelin, and can reduce symptoms in patients with RRMS.

"This study provides confirmation of a concept that originated at Wayne State University and will impact the entire field, including patients worldwide," Dr. Khan said. "I take great pride in the fact that work done at Wayne State University led to this large international study, not only confirming our original work but changing the lives of people with MS in

"At the end of the day, it is a win-win situation for everyone, but most importantly for our patients, who may have a new way of using this treatment."



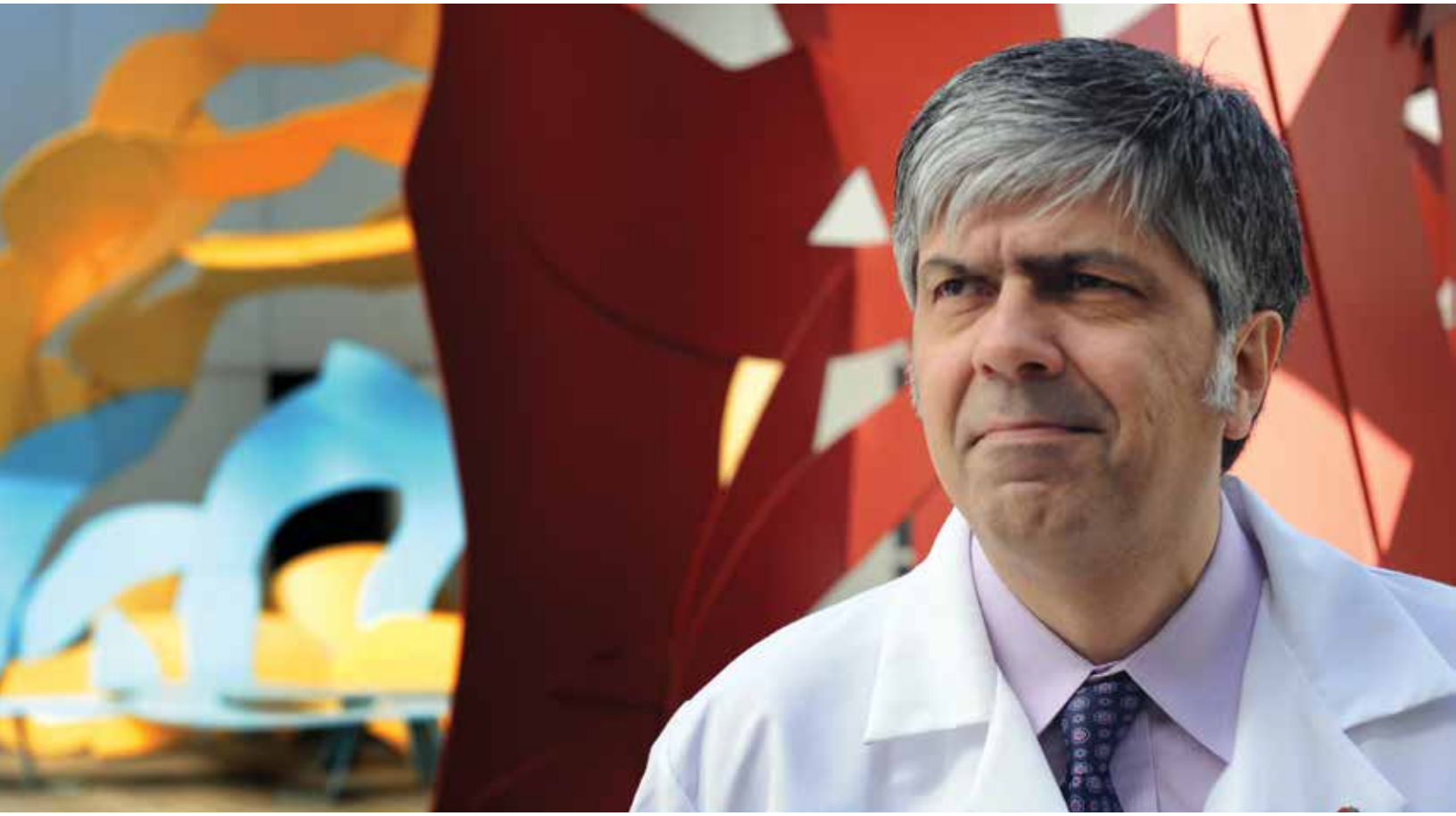
the world. For patients, it is great news, as reduced frequency of injections will improve compliance and tolerability while maintaining efficacy."

Dr. Khan said the study results were to be submitted to seek approval for the new dose and frequency to the FDA in late 2012 or early 2013.

The Wayne State University Multiple Sclerosis Center, one of the five largest MS centers in the United States, also is investigating a new drug to treat RRMS. Dr. Khan has served as the principal investigator and member of the U.S. Advisory Committee on the drug Alemtuzumab since 2002.

"We had several patients participate in the study who have ever since remained stable and free of any further disease activity without receiving any further treatment for their MS," Dr. Khan said. "Alemtuzumab could be the first definitive treatment that may eliminate active disease in relapsing MS patients, meaning no further relapses, no disease progression and no new lesions in the brain. While it may not cure the disease, it may give hope to millions of patients that

Dr. Khan reviews imaging results with **Zahid Latif**, chief MRI research technologist at the MR Research Facility at the WSU School of Medicine. Dr. Khan's studies show that Alemtuzumab reduced the relapse frequency and MRI activity, including brain atrophy, in MS patients.



"I take great pride in the fact that work done at Wayne State University led to this large international study, not only confirming our original work but changing the lives of people with MS in the world," **Dr. Khan** says. "For patients, it is great news, as reduced frequency of injections will improve compliance and tolerability while maintaining efficacy."

early intervention with Alemtuzumab may prevent the fear and stigma of the disease in the form of crippling disability and being in a wheelchair."

Physicians and researchers of the WSU Multiple Sclerosis Center began testing Alemtuzumab in a Phase II trial in 2002 that proved successful and was published in 2008 as a major breakthrough in potential treatment for MS in the New England Journal of Medicine. The study results showed "very convincingly," Dr. Khan said, that Alemtuzumab was more effective than high-dose, high-frequency interferon beta-1a, an FDA-approved therapy for MS.

The Phase II study involved a randomized, blinded trial of 334 patients with previously untreated early relapsing-remitting multiple sclerosis. The patients received either subcutaneous interferon beta-1a three times per week or annual intravenous cycles of Alemtuzumab for 36 months. Alemtuzumab, Dr. Khan noted, significantly reduced the rate of sustained accumulation of disability compared to treatment with interferon beta-1a. In this study, Alemtuzumab demonstrated a 55 percent reduction in the MS relapse rate over high dose interferon treatment, currently considered one of the first line therapies for MS.

Two large multi-center international Phase III trials, published back to back in the Nov. 1, 2012, issue of The Lancet, confirmed the superior efficacy of Alemtuzumab compared to interferon beta-1a (commercially known as Rebif). In both

studies, Alemtuzumab reduced the relapse frequency and MRI activity, including brain atrophy, compared to an active therapy comparator over two years.

"Even disease progression was significantly reduced in the second Phase III trial, which is not an easy outcome to achieve in a short period of time," Dr. Khan said. "These studies provide conclusive data that inflammation drives outcomes earlier in the disease course, including injury to gray matter in the central nervous system. By targeting the inflammatory cascade and preserving regulatory lymphocyte compartment, Alemtuzumab provides a unique approach in which the immune system, after rapid depletion, is reconstituted. While this therapy is setting a new standard of efficacy, long-term safety of Alemtuzumab, especially with respect to secondary autoimmune phenomena, remains to be carefully studied."

Alemtuzumab is administered intravenously three to five days once a year, making it an extremely attractive treatment option for patients. The vast majority of the patients in the Phase II and Phase III trials have not required more than two treatment cycles of Alemtuzumab. In other words, they have not received any further treatment after the first year and have remained disease free since. "For many patients, that is approaching seven years of no clinical or MRI disease activity," Dr. Khan said.

Alemtuzumab, trademarked under the name Lemtrada, is a monoclonal antibody that targets the cell surface glycoprotein CD52, which is highly expressed on T- and B-lymphocytes. Research suggests that the drug depletes the T- and B-cells that may be responsible for the cellular damage in MS, while sparing other immune system cells. The reconstituting immune system after treatment with Alemtuzumab appears to be less autoreactive and destructive toward the immune system.

Alemtuzumab has been granted fast track designation by the U.S. Food and Drug Administration, according to Genzyme, the drug's manufacturer. If the drug wins FDA approval and becomes available in the United States in 2013, there will be demand to switch patients to the new therapy, Dr. Khan said, though he cautioned that each patient's case should be decided individually. At the time of this publication, Alemtuzumab was under FDA review. ■

Stopping cancer cold

Wayne State physicians prove targeted tumor freezing therapy increases survival rates in cancer patients

by **Andrea Westfall**
photo by **Tom Owoc**

"I wish I would have known this existed."

It's a phrase you'll hear often if you keep the company of a certain group of Wayne State University physicians and researchers long enough.

The "this" in question is cryoablation, a medical term for freezing tissue — in this case, tumors. In conversation, the name of the loved one is always different, as is the cancer, but the sentiment is always the same: "Why haven't I heard of this?"

Cryoablation, in its simplest form, is a process that uses extreme cold to kill tissue, like a wart or lesion. Using it to treat cancer is somewhat uncharted territory. That said, a team of Wayne State University School of Medicine researchers has proved that freezing tumors increases survival rates in cancer patients, often giving them several more months, or even years, of quality life.

Cryoablation is performed using a gas-powered, needle-like probe inserted into the tumor through the skin, with imaging technology such as computerized tomography for guidance. The treatment causes minimal pain and results in faster recovery than surgery.

"This is as high-tech as you can get without surgery," said interventional radiologist Peter Littrup, M.D., professor of Radiology for the School of Medicine and director of Imaging Core and Radiological Research at the Barbara Ann Karmanos Cancer Institute, a champion of the technique.

Robin Stone is among the believers. She was diagnosed with stage 3c advanced ovarian cancer Nov. 11, 1994, at age 52. "I thought I would die," she said.

The five-year survival rate for that stage is about 30 percent. Seventeen years later,

Peter Littrup, M.D., with, from left, Research Assistant **Brandt Currier** and **Hyun Bang, M.D.,** displays the icy probes used in cryoablations, framed by a magnetic resonance imaging device at the Barbara Ann Karmanos Cancer Center in Detroit.

though, Stone is still living her life. In the last 17 years, she has had three major surgeries, 55 chemotherapy treatments, and unlike many cancer patients, eight cryoablations, mostly in her abdomen, some in the same spots. Her most recent procedure was Oct. 30, 2012.

She is not "cancer free," but her cancer is in the background of her life. Stone closed her private practice as a clinical psychologist and forensic expert a few years after her diagnosis, but keeps busy with a vintage jewelry business. She is a member and past president of the Karmanos Patient & Family Advisory Council.

Stone can't prove whether it's the cryoablation or making good choices that's keeping her alive. But she can attest that cryoablation has improved her quality of life with cancer exponentially. It gives her "holidays" from chemotherapy, some as long as 36 months, but averaging 14 months each.

"It's not a cure, but it's just extremely helpful," she said. "It's given me more time off chemo; that's how it has improved my life. It's a quick and relatively easy fix."

Besides hair loss, chemotherapy's most life-jarring side effects can include neuropathy (numbness) in the hands and feet, anemia, fatigue, nausea, vomiting and increased chances of bruising, bleeding and infection. With cryoablation, Stone recalled, there was some pain after the anesthesia wore off, but her recovery was usually limited to one or two days of home rest.

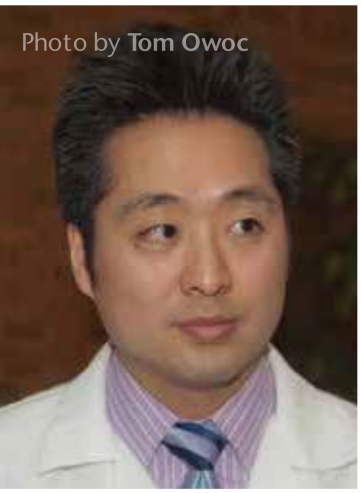
Hyun J. Bang, M.D., a resident in the Wayne State University/Detroit Medical Center Radiology program, presented the research team's findings at the Clinical Interventional Oncology Symposium on Endovascular Therapy in Miami, Fla., in January 2012.

In 98 percent of all tumors treated in the 21 ovarian cancer patients who underwent cryoablation, their survival rate was 57 months, or approximately 4.75 years. In comparison, the majority of women whose tumors aren't successfully removed surgically — some 60 percent, according to studies — survive seven months to 2.5 years. In the study's abstract, the WSU team outlines how they treated 48 tumors in the soft tissues, liver and lungs of 21 women over seven years in an outpatient setting. It also analyzes the cost benefit associated with the treatment, and concludes that costs were an average of $26,806 per life year saved, nearly 75 percent less than the current standard of $100,000.

An average procedure costs about $15,000 per treatment. The additional cost of preliminary and follow-up imaging, approximately $42,000, is commonly covered by insurance.

Cancer patient **Robin Stone's** nine cryoablations have improved her quality of life with ovarian cancer.

The researchers are quick to note this is not a way to avoid chemotherapy or surgery. Cryoablation in the majority of their patients was not used alone, but rather served to improve the standard care of surgery-chemotherapy-radiation therapy. Over the last two years, Dr. Bang has been studying the current treatments for many metastatic cancers in comparison to cryoablation.



Hyun Bang, M.D.

Peter Littrup, M.D.

"I have not seen anything like this. While most patients are unable to receive the benefits of surgery, and with chemotherapy generally offering minimal survival gains, there is a great need for any treatment which can augment the standard care approach. Cryoablation may fill that void," he said.

Cryoablation is an option when the disease is in the late, very advanced stages and is oligometastatic, meaning the tumors are limited in number and location. They must also be seven centimeters or less.

Interventional radiologists like Dr. Littrup use a minimum of two probes simultaneously for each treatment, and up to eight probes depending on the size of the tumor (one probe is needed for each centimeter of tumor). The centers of the probes circulate pressurized argon gas, which expands internally and creates a cooling effect, making the outside of the probe about -20 to -40 degrees Celsius. Over time the probes gradually produce a ball of ice on each probe's tip. The ice from the probes fuses together inside the body, encapsulating the tumor from the inside out. The tumor freezes, dissolves and disintegrates.

Dr. Littrup performs the treatment, usually with fellow radiologist Hussein Aoun, M.D., and nurse practitioner Barb Adam, N.P., by his side. He has cryoablated approximately 1,000 tumors to date in various soft tissues and organs, starting with the prostate in 1992. Each treatment takes an average of 90 minutes. For the majority of patients, treatments are performed in an outpatient setting.

Dr. Littrup credited Dr. Bang for recognizing the presence of long-term, effective data and taking the initiative to prove his technique worked.

The abstract — "Cryoablation of Metastatic Ovarian Cancer for Local Tumor Control: Improved Survival and Estimated Cost-Effectiveness" — focuses on ovarian cancer and brought them to the national stage.

Yet one visit to their lab shows that it's not their only organ system of interest. There are posters outlining cryoablation research related to breast, kidney, lung and colon cancer as well. The studies were partially supported by National Institutes of Health funding. The team has published two papers related to the findings in kidney and lung cancers, with a third submitted regarding colon cancer. Dr. Littrup, Dr. Bang and the research team co-wrote a manuscript discussing the role of percutaneous cryoablation for metastatic lung and kidney cancer treatment. The studies were accepted for publication in the Journal of Vascular and Interventional Radiology in March 2012.

In 2012, about 577,190 Americans are expected to die of cancer, more than 1,500 people a day, according to the American Cancer Society. Cancer is the second most common cause of death in the U.S., exceeded only by heart disease, and accounts for nearly one of every four deaths.

After an initial diagnosis, cancer treatment may begin with surgery, then chemotherapy or radiation. Targeted therapy like cryoablation isn't necessarily part of the standard treatment regimen, but Drs. Littrup and Bang would like to see that change. In the case of every cancer patient they treated, followed up with and analyzed, survival has been shown to be longer than in patients who did not undergo cryoablation. Not all patients get as lengthy of an extension as those in the ovarian cancer study. In the case of lung cancer, for example, survival extension can range from one year to four months, depending on the type of chemotherapy used for comparison, the researchers said.

The "freeze and destroy" technique has existed for at least two decades, but is only considered a standard procedure by insurance companies when patients have kidney or prostate cancer. Stone heard about

the therapy through her oncologist a few years ago. “It was an option offered to me at some point and it sounded great. Compared to being on chemo for six months and having major abdominal surgery, it’s a walk in the park,” she said.

She’s quick to note that Dr. Littrup was extremely cautious whenever considering cryoablation for a new tumor. On at least one occasion, they opted for chemotherapy because of that tumor’s proximity to her bowel.

“I believe I’ve survived because of the choices I’ve made. It’s not a miracle cure but it’s a very effective tool if you have solid tumors. I believe in taking the tumors out as fast as possible. If it’s close to a centimeter, I don’t like it hanging around,” she said.

It is cases like Stone’s, and those of the other men and women in the studies, who might be opening a new paradigm, the researchers said. Does cancer treatment really have to be all or nothing? If it’s a small, new tumor in an advanced patient, could it be frozen and destroyed before it gets out of hand? Can the treatment be effective before another round of chemotherapy or additional surgery?

“It’s amazing how many times patients are told, ‘There’s not a lot we can do for you with a couple of spots,’” Dr. Littrup said. “Do you have only a driver and a putter in your golf bag? No.”

To bring attention to the work, Dr. Bang recommended approaching it from the disease type, not the procedure type. He believes targeted therapy like cryoablation will be part of the treatment plan for many cancer patients in less than 10 years.

“With low complication and recurrence rates, we can see that the procedure can be safely performed in patients who are ineligible for surgery, or simply want more options,” he said. “The cost of cryoablation is considered acceptable given this survival extension when used with systemic therapies, and the patient’s quality of life is preserved.”

The team has been contacted by individuals from as far as California since Dr. Bang’s presentation in January. They are sisters, mothers and husbands of patients who have had multiple surgeries, still have cancer and are told there have no further options. The most recent out-of-state patient arrived in Detroit from Texas in early 2012.

“It’s usually several per year who end up coming here, still, because what we do for patients is so unusual. You have to really know cryoablation to feel comfortable doing what it is we’re doing,” Dr. Littrup said. Interventional radiologists need to understand the technology, the safety risks and the effectiveness related to each tumor, he said.

Another issue, for patients, is cost. Almost all preliminary testing and follow-up imaging is generally covered by “nearly all people’s insurance,” Dr. Littrup said. It’s the actual procedure that is variable. “Some insurance companies already understand this and will reimburse it, because the heat-based ablation codes are in process,” he said.

The first person Dr. Littrup knows to bring up the cost benefit of cryoablation versus other cancer treatments was not an insurance company or a doctor. It was Robin Stone. She read that some of her chemotherapy drugs cost as much as $2,000 to $5,000 a treatment. She could require several in a month. She thought, if one cryoablation costing $15,000 keeps me off chemotherapy for three years, isn’t that a big savings to my insurance?

The road to cryoablation awareness is being paved, as patient awareness drives patient care. If you have enough evidence and proven data, “eventually, people will start listening,” Dr. Bang said. ■

Research Assistant **Brandt Currier** shows off the icy end of a cryoablation probe.

Building a better **cancer model**

The lab of proteolysis expert Bonnie Sloane, Ph.D., gains international attention for distinctive experiments with human breast tissue to predict cancer cell growth and invasion

by **Andrea Westfall**
photo by **Robert Widdis**

Predicting — and preventing — a cancer cell's next move sounds like the stuff of science dreams. But in the lab of Wayne State University School of Medicine Distinguished Professor Bonnie Sloane, Ph.D., it's a reality. And other scientists from across the world have been contacting the Sloane lab to get training on just how they do it.

The Sloane lab uses a variety of cells derived from human breast tissue by Fred Miller, Ph.D., and colleagues at the Barbara Ann Karmanos Cancer Institute to replicate breast cancer in vitro, creating what's inside the human breast outside the human body. It's what the cells do over the next several days and weeks that's making waves in cancer research.

The lab grows the cells for as long as 23 days in a controlled environment in a three-dimensional matrix, then analyzes them under a microscope at intervals, tracking growth and cell interactions, including with the surrounding microenvironment.

The technique has provided visual proof that stromal cells — the connective tissue cells of any organ — contribute to cancer growth and invasion. It strips the veil from tumor growth, allowing the earliest dynamic interactions to be observed and providing a "calendar" for what's occurring when a pre-invasive cell becomes invasive.

If the researchers can define what molecule or process induces invasion, then a clinical team can choose the appropriate drug or drug combinations to stop it in its tracks. The 3D models are being used to test novel drug combinations at the Van Andel Research Institute in Grand Rapids. If these preclinical studies are successful, the combinations will move into Phase I clinical trials at Karmanos.

The WSU researchers are learning quite a bit in the process, perfecting their own science.

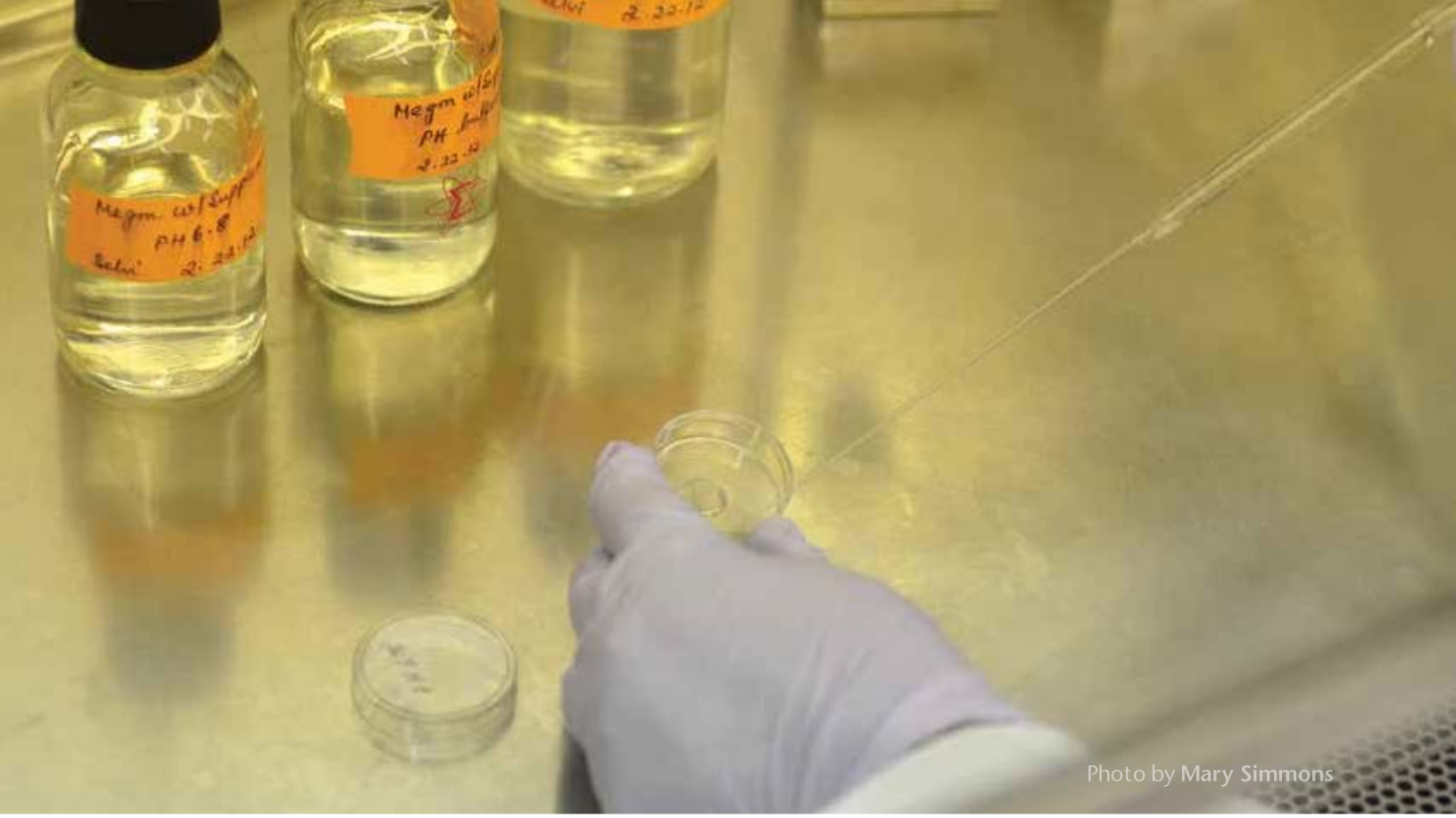
"By adding new cell types to this model, we are improving its ability to replicate breast tissue and to screen drugs," said Mansoureh Sameni, M.S., the research associate who designed the specific model the Sloane lab uses.

It's a tool that intrigues others, taking Dr. Sloane, her staff and her graduate students around the world in the last few years. She traveled to Italy and northern Germany in February to present the model. Other trips have taken them to Dubai, Brazil and Italy. Two of her students talked about their findings using the model at a meeting in California in April 2012.

Dr. Sloane, chair of the Department of Pharmacology, hopes an article and eight-minute video published in the February 2012 edition of the Journal of Visualized Experiments, or JoVE, will help others use the model that she and her team have worked to develop. JoVE is the only peer-reviewed, PubMed-indexed science journal to publish all articles in both text and video format.

Sameni based the technology on one using 2 percent overlay of basement membrane for 3D cultures of breast epithelial cells that Stefanie Mullins, Dr. Sloane's former doctoral student in WSU's Cancer Biology Graduate

Imaging techniques that predict, and could prevent, a cancer cell's next move, are at the forefront of the work of the lab of **Bonnie Sloane, Ph.D.**, distinguished professor and chair of the Wayne State University School of Medicine Department of Pharmacology.



The Sloane lab grows cancer cells derived from human breast tissue for as long as 23 days in a controlled environment in a three-dimensional matrix. Here, **Arulselvi Anbalagan, M.S.**, research assistant, prepares dishes with medium.

Program, learned on an educational visit to the laboratory of Joan Brugge, Ph.D., at Harvard Medical School. The triple layer protocol featured in the JoVE article/video was based on a protocol originally established by Sameni for live-cell imaging and quantification of proteolysis, but with the addition of a 2 percent overlay of basement membrane.

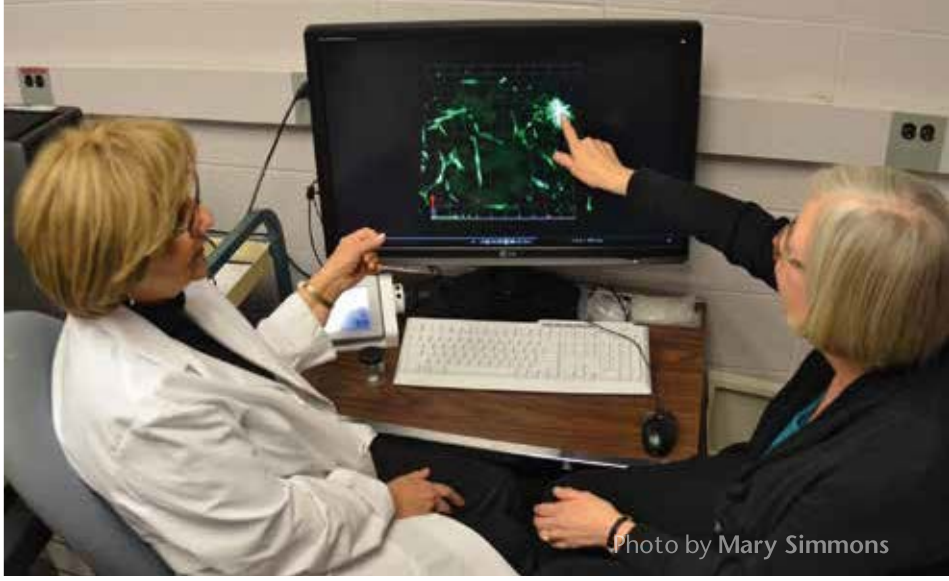
The WSU experiments start with several breast cell types, which are layered in co-cultures at specific intervals by trained lab staff such as Arulselvi Anbalagan, M.S. The initial layering process takes nearly a whole workday. Sameni will review a growing co-culture several times over the next three weeks or longer, monitoring how the cells react at each stage.

"We are trying to analyze tumors as a sum total of tumor cells plus other components of their environment, not just the tumor cells," Sameni said. "We are trying to determine what's in a tumor environment that makes it more invasive."

Besides Dr. Sloane and Sameni, the article authors include Associate Professor of Pharmacology Kamiar Moin, Ph.D.; Associate Professor of Pharmacology Raymond Mattingly, Ph.D.; and research assistants Anbalagan and Mary Olive.

The video demonstrates the assembly of the breast co-culture system, breaking down the layering of the co-cultures step by step, giving viewers the recipe for success, including appropriate carbon dioxide levels, temperature and exact timing. The latter part of the video analyzes the results that follow. The Sloane lab calls its model MAME for Mammary Architecture and Microenvironment Engineering. MAME focuses on the breast, but can be used with appropriate cells to model other tissues, such as prostate.

That adaptability, and the intricacies of the experiment, is why JoVE Senior Science Editor Nandita Singh, Ph.D., felt its inclusion in the journal would be useful to other scientists.



Research Associate **Mansoureh Sameni, M.S.**, left, and **Bonnie Sloane, Ph.D.**, evaluate 3D Live MAME Coculture images.

"It's a methodology that would benefit the community and make it more accessible and more producible in the science community," Dr. Singh said. "Our focus is strictly the methodology. It's strictly how the science is done; the nuances, the tricks. Everyone who has been on the bench realizes it's almost like an art. It's almost like cooking a really difficult meal. You really need a colleague to show you how to do an experiment to start it independently."

JoVE's video team headed to WSU late last year to capture the experiment. "This is a very powerful technique, to be able to monitor the tumor progression in the microenvironment," Dr. Singh said. "More importantly, this enables scientists to set up this experiment easily. They don't have to go and reinvent the wheel again."

The co-culture consists of a layer of human breast fibroblasts in collagen protein below a layer of reconstituted basement membrane (a thin layer of fibers). Ductal carcinoma cells from the breast are added before the entire model is submerged in media, in this case a liquid substance that contains nutrients to promote cell growth.

Sameni views the culture under an eight-laser Zeiss confocal microscope inside the Microscopy, Imaging and Cytometry Resources Core, located in WSU's Scott Hall. From the outside, the MICR looks like an unassuming office on the sixth floor of the School of Medicine's building. Inside are rooms containing the latest computer equipment and cutting-edge confocal microscopes. The door frames are all painted bright pink, a nod to breast cancer research and the partnership with Karmanos.

The 780 Zeiss microscope is attached to a computer. Sameni uses fluorescently labeled cells and maps their movement from all angles, showing when and where the invasive cells start to move away from the primary structure as well as when stromal cells move toward the growing tumor. Special software processes the data. The resulting images and video are analyzed by Sameni.

Dr. Sloane has already given the JoVE video and article to colleagues who inquired about the technique only a week after it was published. "A lot of people have come to our lab over the years to learn the technique, and now they can see it, and that's good for us," she said. "We're hopeful the cultures will be useful as a screening tool for novel anti-cancer therapies."

The work was supported in part by funding from the National Institutes of Health and the Department of Defense Breast Cancer Research Program. ■

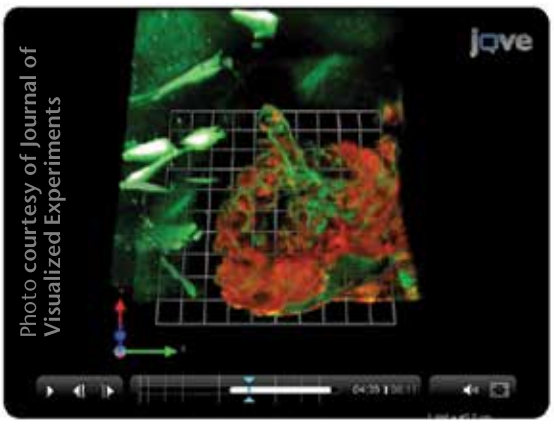


Image of 3D Live MAME Cocultures by Confocal Microscopy.

Beyond gray matter

Investigators exploring link between brain function *in utero* and developmental outcomes later in life

by **Andrea Westfall**
photos by **Rob Widdis**

Tracey Moses was four months pregnant when genetic testing revealed her baby could be born with a severe disability or deformation and might not live past his first birthday.

The Detroiter was older than 40, and up to that point, disappointed with the quality of her prenatal care. She also was determined to enjoy her third pregnancy — her first since giving birth to a son 19 years earlier. "It had been 20 years since I had a child, and I wanted the best care," she said.

Fear of the unknown lingered. She learned about an open-ended, multi-part baby development study being conducted by Wayne State University researchers while attending an appointment at the Center for Advanced Obstetrical Care and Research in the Detroit Medical Center's Hutzel Women's Hospital, part of the National Institutes of Health's Perinatology Research Branch at the WSU School of Medicine. She enrolled in the study, where she would be considered a "typical" pregnancy, serving as a normal community sample but on the "high-risk" end of the healthy spectrum.

"I knew, being involved in the study, no stone would be left unturned. I know I'll be getting the best care for my baby, so that's why I participated; the one-on-one attention," she said. "I couldn't have had such a relaxed pregnancy unless I was in the study."

A multi-disciplinary team of faculty, fellows and graduate student researchers from the School of Medicine, the Merrill Palmer Skillman Institute for Child and Family Development, and the Psychology Department teamed up in 2011 to launch what they dubbed the PINC/PURPLE project — a WSU-funded study officially known as "Perinatal Imaging of Neural Connectivity/ Parent Representations during pre- and postnatal Periods Linked to Early Outcomes."

The PINC portion of the study focuses on recording spontaneous activity in the fetal brain, while the mother is still pregnant, using resting-state functional magnetic resonance imaging. This pioneering work, which began at the School of Medicine's MRI Research Facility in November 2011, will map functional connections in the developing fetal brain.

PINC is directed by neuroscientist Moriah Thomason, Ph.D., an assistant professor of Pediatrics in the School of Medicine and in MPSI. She is also director of the Unit on Perinatal Neural Connectivity at the Perinatology Research Branch and affiliate faculty in the Department of Psychology. She estimates there are fewer than 10 published reports that have used fMRI to study the human fetal brain, and none that have quantified fetal brain functional connections using resting-state MRI.

"Our studies will offer insight into how brain networks become formed in utero, and will also be applied to study the effects of premature birth and pregnancy-related health complications on fetal brain development," Dr. Thomason said.

Before joining the WSU faculty in March 2011, Dr. Thomason spent 12 years at Stanford University School of Medicine, using MRI in children and adolescents for similar purposes. She collected pilot data for the PINC study at Stanford, using adult images to prepare for potential movement corrections needed after processing. But when it came time to look at

The WSU professors leading an open-ended, multi-part baby development study are, from left, infant mental health expert **Ann Stacks, Ph.D.**; neuroscientist **Moriah Thomason, Ph.D.**; and developmental psychologist **Marjorie Beeghly, Ph.D.**, pictured in the courtyard of WSU's Merrill Palmer Skillman Institute.

Dr. Moriah Thomason's study focuses on recording spontaneous activity in the fetal brain, while the mother is still pregnant, using resting-state functional magnetic resonance imaging. This pioneering work, which began at the School of Medicine's MRI Research Facility in November 2011, will map functional connections in the developing fetal brain. Images of a baby at 25 weeks gestational age are pictured behind her.

developing fetal brains, her former employer lacked the components she needed, including a diverse population with a high rate of premature births.

In 2008, more than 17 percent of births in Detroit were preterm, nearly 5 percent higher than the national average, according to one of the latest reports from the Michigan Chapter of the March of Dimes.

"We couldn't do this anywhere else," Dr. Thomason said.

To gauge brain development, the study enrolls a mix of mothers at high risk for premature birth and those expected to carry their babies to full term. "The event of being born premature has an effect on the brain development of these young infants, but we do not know if those effects result from events occurring during the pregnancy, or, alternatively, if the brain is particularly vulnerable to injury as a result of life outside of mother beginning too soon," she said.

The field of obstetrics doesn't have accepted evidence that the brain is developing differently in fetuses that will be born preterm. By using MRI advances, though, "one objective is to map what has not been mapped, to study neural connectivity in the premature brain because it may offer insight into the genesis of developmental disorders that are commonly attributed to early delivery," she added.

For PINC, Dr. Thomason images a variety of pregnant women at different gestational stages to assess fetal structural and functional brain development. Her collaborators and team also assess the mothers' prenatal psychosocial adaptation and stress reactivity, and explores women's mental representations of their fetuses. The fMRI is safe for mother and baby, and the procedure takes only about 45 minutes. During the visit, she also takes salivary cortisol samples to record the mother's stress levels — insight into what the biological environment of the mother is like during pregnancy.

Her goal is to bring brain scans in utero — and WSU's role in that pursuit — to the forefront of what neuroscientists across the world are trying to determine: Even before birth, could the brain broadcast clues to how a child might develop socially and emotionally?

The PURPLE portion of the study is co-directed by Ann Stacks, Ph.D., assistant professor of Research at MPSI and director of the Infant Mental Health Program; and Marjorie Beeghly, Ph.D., associate professor of Psychology and affiliate faculty at MPSI. The importance of parenting and parent-child relationships in shaping children's developmental outcomes is a primary research interest for both.

"Together, we, and the staff on the PINC and PURPLE teams, expect our combined study will shed important new light on the specific prenatal and postnatal bio-psychosocial factors that are most predictive of children's positive developmental and behavioral outcomes in both typical and at-risk groups," Dr. Beeghly said.

"I believe this is truly pioneering work, as no one knows yet what 'normal' fetal brain development looks like at different gestational ages during pregnancy," said Dr. Beeghly, a developmental psychologist with nearly 20 years of experience conducting longitudinal child development and parenting studies in

at-risk, delayed and typical populations of infants and parents. "We don't know, for instance, to what extent typical fetal brains show variation in the timing of when different regions get connected, the extent of the connectivity, denser versus sparser connections, and so on. We also don't know the meaning of such individual differences with respect to infants' later developmental or behavioral outcomes."

"This is especially the case for infants at risk for preterm birth," Dr. Thomason said. "Something may be going on in the uterine environment that alters the way the brain connections are formed." Because of that environmental factor, the fMRI is just the first step in a series of follow-ups that Dr. Thomason believes could help science achieve a clearer understanding of how early brain functional development during pregnancy affects childhood development. And that's where PURPLE comes into play.

The first postnatal assessment infants receive is the Brazelton Neonatal Behavioral Assessment Scale, administered during the infant's first week of life by Dr. Beeghly and PURPLE team staff.

Established research proves the brain is shaped by environment, with important implications for children's later outcomes, especially social emotional functioning. The PURPLE team also places a strong emphasis on postnatal environmental measures in its assessment.

"If you want to predict children's outcomes accurately, you need to consider environmental factors such as maternal well-being and the quality of the child's proximal caregiving environment," Dr. Beeghly said. "Quality of caregiving appears to be especially influential for the outcomes of biologically at-risk children."

In other words, parenting is just as important as the way a baby is pre-wired, and even more so when pre-birth brain scans show a possible developmental delay or behavioral issue could manifest down the road.

"Social interactions with caregivers shape and change their brains," Dr. Stacks added. For example, infants who are maltreated respond differently to stressful situations than infants living in warm, nurturing households, she said. Babies living in what's considered an unsafe environment with a parent classified as "harsh" or "insensitive" develop differently than those with a sensitive parent.

Moriah Thomason, Ph.D., WSU assistant professor of Pediatrics, checks in with 6-month-old Ella and her mother, Rebecca Dorn-Wheeler, before the Still-Face paradigm is administered by Marjorie Beeghly, Ph.D., associate professor of Psychology. Dorn-Wheeler is a WSU doctoral student who also works on the PINC/PURPLE study.

Aside from analyzing a baby's development, Dr. Thomason wants to use the fetal brain data collected in PINC to map, as early as possible, the order, timing and patterning of brain functional development. This effort aligns with the National Institutes of Health's Human Connectome Project — a $40 million initiative to map the neural pathways that underlie all human brain function, launched in 2010.

Dr. Thomason believes she will prove that a default mode network — a "very critical and essential foundational network" — exists in fetuses earlier than previously thought. The default mode network is a network of brain regions that are active when an individual is awake but resting. According to the Society for Neuroscience, it is thought to be responsible for internal tasks such as daydreaming, retrieving memories, thinking about the future and gauging others' perspectives, and according to several published reports, may be relevant to Alzheimer's disease, schizophrenia and autism.

Assistant Professor of Pediatrics **Moriah Thomason, Ph.D.**, reviews with WSU students **Amy Anderson**, right, and **Maya Dassanayake**, left, images of a fetus taken with magnetic resonance imaging while the mother was 25 weeks pregnant.

The presence of a pre-birth default mode network suggests its existence is foundational to the development of other networks. This conclusion is unanticipated, as the default mode network is most often conceptualized as a cognitive network, and more primitive networks would be expected to emerge earliest in development. "Increasingly, research is indicating it's really the early life events that foretell later outcomes," Dr. Thomason said. "There is nothing sooner than this (in utero) period."

For children at risk for poor developmental outcomes, the brain can still be shaped by a nurturing environment, which includes sensitive parenting, Dr. Stacks said. Her research focuses on the impact that the caregiving environment has on children's social and emotional development, specifically their attachment representations and behavior at home and school. She poses the question, "What happens if you take two infants whose development is known to be at-risk but they are raised in homes with two different parenting styles?" It is likely that their attachment representation will be different, which can either protect them from risk or become an additional risk factor. Humans are hard-wired to form an attachment. But the form of attachment — secure, insecure or disorganized — is key. Children with a secure attachment tend to be more socially competent, whereas children with a disorganized attachment are at higher risk for emotional and behavioral disorders. Children with disorganized attachment at 12 months old are more likely to exhibit severe behavioral problems at age 2. These behavior problems can persist into adulthood.

When infants are 4 and 9 months old, the PINC staff calls mothers to complete a brief developmental screening over the phone to find out whether infants are showing developmental delays relative to published

norms. At 7 months old, mother and infant come to the play lab at WSU for a formal evaluation of the child's developmental skills, mother-infant social interaction and maternal interviews by the PURPLE team. The infants' cognitive, language and motor skills are evaluated using the Bayley Scales of Infant Development III, a widely used age-referenced developmental assessment. Then, individual differences in parent-infant interactive behavior and stress reaction are evaluated during the Still-Face paradigm, a videotaped observation during which the mother interrupts her normal behavior with the baby by briefly holding a non-responsive "still-face" while continuing to look at the baby. Dr. Beeghly said behavioral and physiological reactions during the Still-Face paradigm suggest that infants find their mother's still-face stressful, perhaps because it violates the child's expectation based on usual behavior or breaks the rules of what is supposed to happen during typical infant-mother interactions. Like Dr. Thomason, the PURPLE team also collects salivary cortisol samples from the mother and infant before and after the Still-Face paradigm to measure variations in maternal and infant physiological reactivity to this social stressor. The maternal cortisol measures will be combined with the cortisol measures collected by the PINC team during pregnancy to evaluate stability and change in maternal stress over time.

At 15 months old, infant and mother visit the play lab again, this time to evaluate parent-infant attachment, reassess maternal and infant stress levels, and check that developmental milestones are being reached.

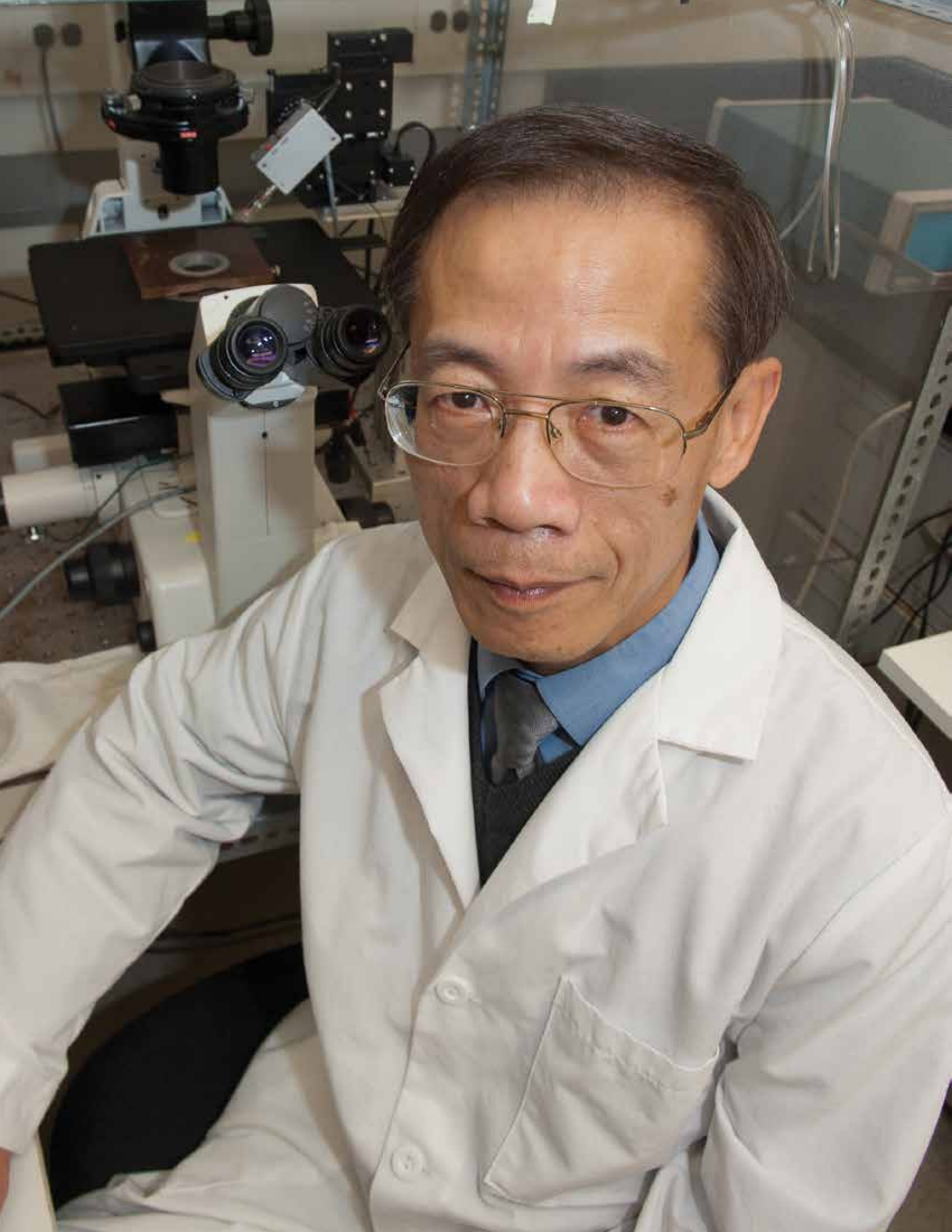
"The eventual product of our work will be data that can be used to make predictions about sound courses for treatment. People wonder about prenatal stress and how that affects the brain," Dr. Stacks said. "Is there something we can do prenatally to help put kids on the right course?"

Dr. Beeghly asked, "Can positive parenting attenuate the possible harmful effects of compromised fetal brain development and/or high-risk birth on children's outcomes? The rich longitudinal data we are collecting in the PINC/PURPLE study have the potential to address these questions."

As for Tracey Moses, she decided she would put her faith in God, but with a caveat: "There's nothing wrong with having a little insight with technology," she said.

The MRI revealed all was developing normally. "I was really pleased, because when the results came back it was everything I expected. I thought it was a blessing. I thought, 'Now I know we can get down to business,'" she said.

Rebrick Copeland Jr. was born Dec. 14, 2011. He is meeting all of his expected developmental milestones, sometimes earlier than normal. "He's doing fine," she said. "I think he's going to be our little brainiac. Our genes are going to do well." ■



Seeing green

A team of scientists led by Zhuo-Hua Pan proves that algae may hold the key to vision restoration

by **Andrea Westfall**
photo by **Tom Owoc**

A possible cure for blindness has been discovered in the labs of the Wayne State University School of Medicine.

The work of researchers led by Zhuo-Hua Pan, Ph.D., has proved in animal models that inserting a light-sensitive protein from green algae into a "dead" retina may hold promise in restoring vision in patients with Dry Age-Related Macular Degeneration and Retinitis Pigmentosa. Both disorders are considered incurable.

The protein is derived from an algae — not necessarily pond scum but a close cousin — and is called Channelrhodopsin-2, or ChR2.

Phase I clinical trials using ChR2-based gene therapy could start as early as 2013. Dr. Pan predicts that the technology could be used on patients in less than 10 years.

Algae, no matter what type, uses light for energy. Dr. Pan's team determined the protein could be carried into the retina by a harmless virus known as adeno-associated virus, or AAV. The retina is a layered neural tissue lining the back of the eye. It converts light images to nerve signals and sends them to the brain.

"If this works, if it does turn out this Channelrhodopsin-2 does respond to light in a manner that will send coded information to the brain to give clear vision, this will be Nobel Prize-area work. But there's a lot of 'ifs' in that," said Gary Abrams, M.D., founding director of the Ligon Research Center of Vision at the Kresge Eye Institute and professor of Ophthalmology at WSU.

According to the U.S. Centers for Disease Control and Prevention, an estimated 1.8 million Americans 40 and older are affected by Dry AMD, and that number is expected to reach 2.95 million in 2020. The condition is the leading cause of permanent impairment of reading and fine or close-up vision among people 65 and older. British actor Dame Judi Dench, 77, announced in early 2012 she is going blind from the disease, and reportedly has friends read her scripts aloud.

Retinitis Pigmentosa is one of the most common inherited diseases of the retina, affecting as many as one in 4,000 people worldwide.

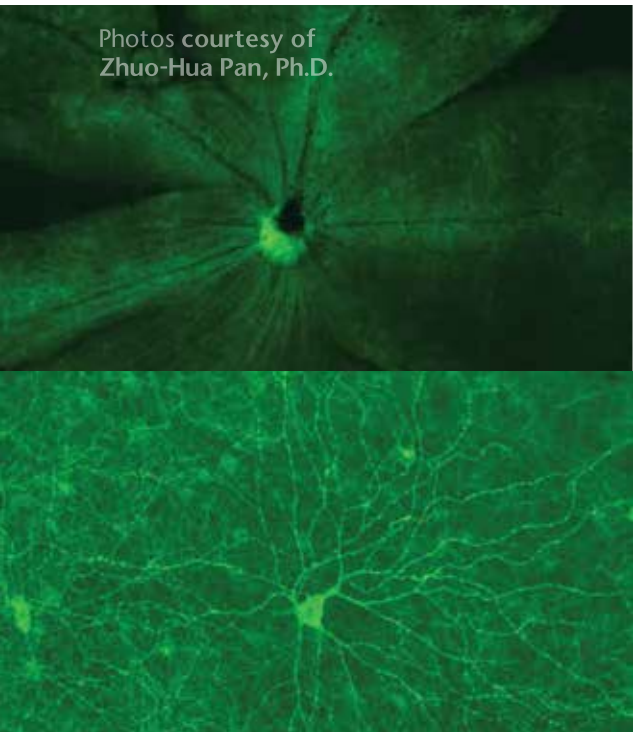
Dr. Abrams credited Dr. Pan as one of the first scientists to use the algae technique. "He was one of the pioneers in being able to research this in gene therapy. His technique is going to be the one that is used," he said.

Wayne State University has applied for two patents related to the technology, and there will be more, Dr. Pan said.

"This is one of the most exciting things I've worked on," said Dr. Pan, professor of Anatomy/Cell Biology and scientific director of the Ligon Research Center of Vision at the Kresge Eye Institute and the Edward T. and Ellen K. Dryer Endowed Professor in Vision and Blindness Research for the WSU Department of Ophthalmology.

Vision normally begins when rod and cone cells, called photoreceptors, respond to light and send signals through other retinal neurons, called inner retinal neurons

Dr. Zhuo-Hua Pan's work focuses on a cure for blindness using a light-sensitive protein from green algae.



Photos courtesy of Zhuo-Hua Pan, Ph.D.

TOP: This 75x microscope image shows the expression of ChR2 in a retina flattened to fit on a slide and tagged with a green fluorescent protein from jellyfish so the algae shows up under the microscope.

BOTTOM: This 250x microscope image shows the magnified expression of ChR2 in a retina flattened to fit on a slide and tagged with a green fluorescent protein from jellyfish for illustration.

(interneurons), and the optic nerve to the visual cortex of the brain, where visual images are formed. "When the photoreceptors die, people become blind," Dr. Pan said.

Dr. Pan came to WSU from Harvard Medical School in 1999, quickly forming a team to tackle blindness with Alexander Dizhoor, Ph.D., a molecular biologist in the Department of Ophthalmology. Until then, the two approaches to restoring vision were cell transplantation and device implant. Both faced enormous challenges to make them technically feasible, Dr. Pan said. But researchers knew that many inner retinal neurons still survive and retain physiological function after the death of photoreceptors. They hypothesized that if they could make these inner retinal neurons respond to light, or in other words, convert them to new photoreceptors, it would be a better way.

But just how to do it was the question. "We have this fancy idea but we don't know how to implement it," Dr. Pan said, recalling his first discussions with Dr. Dizhoor, now a professor of Pharmacology at Salus University in Elkins Park, Pa.

They knew they would have to find the right molecule, a kind of "light sensor," for the job.

In November 2003, while searching for a potential light sensor, Dr. Pan found a paper reporting that the insertion of ChR2 molecule from green algae into frog eggs and a human kidney cell line made them directly respond to light. "I was so excited because I thought, 'Wow, that's the molecule we are looking for!'" he said.

He ran to the lab next door to share his excitement, then quickly called his colleague. "We have the solution," he told Dr. Dizhoor.

Dr. Pan tried to request the ChR2 gene from the paper's author but determined they had to synthesize the DNA, which cost about $3,000 then. Linda Hazlett, Ph.D., professor and chair of the Department of Anatomy and Cell Biology, quickly recognized the importance of the work and provided the money for making the gene.

"I am pleased that the early investment by me and the department was well worth it and that his work provides hope and real promise for curing blinding eye diseases," Dr. Hazlett said.

The next task for the team was to insert the ChR2 gene into retinal neurons. After trying a number of methods, they determined the AAV was the best carrier for delivering the ChR2 into mammalian retinal neurons. By early fall 2004, they had succeeded in inserting the functional ChR2 in retinal neurons in live rats and mice, likely well before anyone else had achieved that in the mammalian central nervous system. Later, they showed the ChR2 protein can stay in the retinal neurons the entire lifespan of the animals.

"You can pack ChR2 DNA in the virus, and the virus will infect the cell and carry the DNA into the cell. Also, you only need to do one injection of the virus into the eye to get a lifetime expression of ChR2 in the retina,"

Dr. Pan said. "Once we succeeded in that, we next used different ways to demonstrate both in normal and photoreceptor-deficient blind mice that indeed the inner retina neuron was becoming light sensitive, and that this signal can transmit to the visual cortex."

The research was published in the April 2006 issue of Neuron, a highly-regarded peer-reviewed journal.

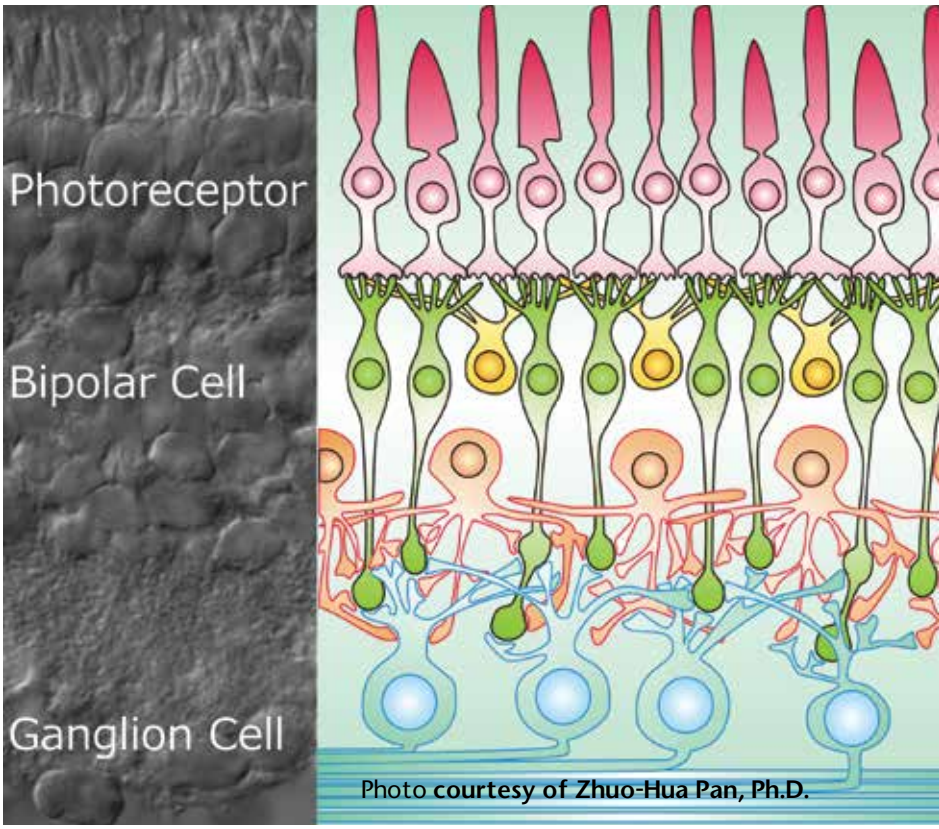
In the meantime, the team secured a pilot grant for the project in 2004 from the National Eye Institute of the National Institutes of Health. Dr. Pan continues to renew the grant.

In 2009, Sean Ainsworth founded RetroSense Therapeutics in Ann Arbor, Mich., to develop Dr. Pan's technology for clinical applications. The company licensed the technology from WSU and Salus University, with the intent to begin the first phase of trials for testing the technology in humans. The therapy has performed well thus far in unrelated vision-restoring clinical trials of gene therapy for people with Leber congenital amaurosis, or LCA, Dr. Abrams said. LCA is a rare, inherited eye disease that begins in infancy and worsens over time.

The Maryland-based Foundation Fighting Blindness provided RetroSense $250,000 in February 2012 to further the technology.

"That's a pretty good endorsement for the work," Dr. Abrams said. "They're very selective who they fund. It's tough to get that. They have a tough scientific board."

The technology has the potential to be a real game-changer in the clinical setting, said FFB's Chief Research Officer Stephen Rose, M.D. "This has the potential for restoring functional vision," he said.



A scientific diagram of the eye. The retina includes the photoreceptors, where vision begins and ends, and the ganglion cells, in which the algae is injected to revive sight.

While RetroSense aims to move the technology to clinical trials, Dr. Pan's team continues to focus on developing and fine-tuning the technology, including modifying the light response properties of ChR2 or other light-sensitive proteins, inserting them into the right inner retinal neurons in the right places and testing them in animal models.

Right now, the algae protein-injected retina responds to extremely bright light. Researchers don't know whether this will produce a recognizable image, or whether Dr. Pan will come up with ways that he can eventually use natural, ambient light, Dr. Abrams said.

In other words, keep watching. ■

Saving preemies

A team of neonatologists at Wayne State University on staff at Hutzel Women's Hospital, led by **Lilia DeJesus, M.D.**, determined the risk factors for infants who die after leaving the NICU healthy include race, length of stay and insurance status.

Neonatologists identify why some babies die after leaving the Neonatal Intensive Care Unit healthy

by **Andrea Westfall**
photos by **Tom Owoc**

On one side of a brightly lit, narrow and unassuming corridor on the Hutzel Women's Hospital's third floor is a trio of dim but busy rooms. Grandparents and parents peer in on their little ones, nestled within layers of blankets in a temperature- and humidity-controlled, closed environment. Some of their newest family members are being bottle fed by nurses outside their incubators, or gently held by a mother or father. Others have just arrived and are getting settled in for what could be a long journey ahead.

These are the nurseries of the Neonatal Intensive Care Unit.

Inside, dozens of babies weighing as little as 520 grams, or just over one pound, are being cared for by neonatologists, nurses and other caregivers. The mood is upbeat and comforting despite the task at hand. The tiniest of babies one Friday was Jaslynn, a girl born at just 24 weeks gestational age — four months shy of full term — on Feb. 13, 2012. Jaslynn appeared almost lost within all the medical equipment. Her body

looked barely longer than the average human hand from fingertip to wrist. She lay in an incubator within the NICU, where staff estimated she would remain for at least four months.

Infants like Jaslynn — called micro-preemies by their caregivers — were the focus of a large, 16-site, two-year study conducted by a team of Wayne State University School of Medicine researchers on staff at the Detroit Medical Center's Hutzel Women's Hospital from 2009 to 2011.

The team discovered that babies who die after discharge from a NICU are more often African-American, have had longer stays in the NICU than other preterm babies and have unknown or no health insurance.

The data was collected through the 16 academic research sites within the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Neonatal Research Network. The network includes Hutzel Women's Hospital. From 2000 to 2007, Hutzel had a post-NICU infant death rate of 5.4 percent, the highest among all the centers in the network despite advanced, world-class neonatal care, making a strong case for the study itself.

Reducing Michigan's infant mortality rate is one of Gov. Rick Snyder's two main health initiatives. Wayne State University School of Medicine Dean Valerie M. Parisi, M.D., M.P.H., M.B.A., was a keynote speaker during Michigan's Call to Action to Reduce and Prevent Infant Mortality Summit, held Oct. 17, 2011, in Ypsilanti. Gov. Snyder called for, and hosted, the event.

The state's infant mortality statistics are alarming. For every 1,000 live births in the state, approximately eight infants die before their first birthday, according to the Michigan Department of Community Health. Data compiled in 2009 by the U.S. Centers for Disease Control and Prevention and the MDCH indicate Michigan's infant mortality rate consistently exceeds the national average.

The disparity is even more shocking in the state's largest city. In Detroit, nearly 15 babies per 1,000 live births will die before their first birthday, according to 2009 statistics, nearly twice the national average. Detroit is located in Wayne County, which, excluding Detroit, has an overall infant death rate of 12.2 deaths per 1,000 live births for African-American babies and 5.6 deaths per 1,000 births for white babies, according to the MDCH.

The WSU study, "Risk Factors for Post-NICU Discharge Mortality Among Extremely Low Birth Weight Infants," was published in the Feb. 9, 2012, edition of The Journal of Pediatrics. Wayne State University School of Medicine Assistant Professor of Pediatrics Lilia DeJesus, M.D., lead investigator; Assistant Professor of Pediatrics Athina Pappas, M.D., the study's follow-up director; and Professor of Pediatrics Seetha Shankaran, M.D., the National Institute of Child Health and Development Neonatal Research Network site principal investigator and division chief of Neonatal/Perinatal Medicine at Children's Hospital of Michigan and Hutzel Women's Hospital, are among the researchers who worked on the study.

According to the CDC, a premature birth is one that takes place before 37 weeks of pregnancy. Premature births account for 12 percent of all pregnancies in the U.S. and are one of the top causes of infant death. For infants who do survive, life can pose additional health obstacles, including breathing problems because of underdeveloped lungs, underdeveloped organs, risk of life-threatening infections, cerebral palsy, and learning and developmental disabilities.

The MDCH reports that the risk of infant mortality is higher if a baby has a low birth weight, was exposed to the effects of smoking and if the mother is younger than 20 or older than 40, unmarried or lacks adequate prenatal care.

The rate of premature birth increased more than 10 percent between 1998 and 2008 in Michigan. One of every eight babies born — 295 in an average week — is born prematurely. And Michigan's rate of preterm birth of 12.7 percent exceeds the national average of 12.3 percent.

Dr. DeJesus and the WSU team conducted an exploratory study and used logistic regression models to identify risk factors associated with infant death after babies go home from the NICU. They examined 5,364 preterm infants who were born between 2000 and 2007 at or before 27 weeks of gestational age (seven months of pregnancy), and had a birth weight of less than 2.2 pounds. Of the 4,807 infants the study successfully followed until 18 to 22 months of age, 107 died after discharge. The team discovered that the odds of death after NICU discharge were double in African-American infants compared to other racial groups, three times higher in infants who were in the NICU for more than 120 days and 15 times higher if the mother's insurance status was unknown.

For the investigators, the insurance status was actually the most astounding discovery. It indicated the mothers likely had poorer access to health care, including appropriate follow-up care.

"Initially it was a surprise. We were expecting the same risk factors for in-hospital and for post-NICU discharge death. What we learned is that post-NICU discharge death is not only associated with a longer duration of hospital stay (which indicates severity of illness) but was also associated to certain socio-economic factors," Dr. Shankaran said.

The findings are no surprise to Mouhanad Hammami, M.D., Wayne County's chief of Health Operations and acting health officer. The Wayne County Health and Human Services Department asserts in its 2011 White Paper "Already Broken" that infant mortality in Wayne County is directly related to lack of prenatal education and care, lack of transportation to health care appointments and the mothers' environment, specifically the lack of a sound support system.

The WSU team wanted to study the infant deaths because of the disproportionately high post-NICU discharge infant death at Hutzel Women's Hospital. Fellow researcher Yvette Johnson, M.D., assistant professor of Pediatrics at Baylor College of Medicine and Texas Children's Hospital in Houston, first raised this issue in 2001 while she was working in Detroit.

"We are spending millions of dollars each year to improve the survival rate and overall outcomes of these extremely low-birth weight infants. However, despite our best effort, some of them will not survive after discharge from NICU," Dr. DeJesus said. "Therefore, identifying these risk factors will help us formulate interventions on how to care and follow these high-risk infants after discharge from NICU."

The NRN was established in 1986 to improve the care and outcome of neonates, especially very low birth weight infants. The network, funded through the NICHD, includes 18 academic centers and a data coordinating center. These sites include research centers at universities and medical centers across the nation, including Duke University, Stanford University, Case Western Reserve University and University of California, Los Angeles.

The hospital had already launched a pro-active role in the babies' post-NICU lives. Before a baby leaves the nursery, Hutzel's discharge coordinators talk to parents to prepare them for life at home with their infant, Dr. DeJesus said. Intervention begins about a week before actual discharge. Coordinators help parents find a pediatrician, identify necessary equipment and supplies the baby will need at home, and arrange all follow-up appointments to ensure attendance.

"Some of these infants will need multiple appointments and it can be overwhelming to the mother or caregiver sometimes," she said.

But for Dr. Hammami, the solution to these issues should start before the appointments ever need scheduling. According to "Already Broken," more than 20 percent of pregnant women in Wayne County get no prenatal care during the crucial first trimester, as they may lack insurance, education and employment. "All that can be traced to different levels upstream. It all falls back into how healthy the mother is," Dr. Hammami said.

He said the scenario often plays out like this: If a young minority mother is employed, her employer may not provide health insurance. She didn't get insurance because she doesn't have a career that typically offers insurance to its employees. And she didn't get a good job because the public schools in her neighborhood didn't provide a good education. She also likely lives in a neighborhood where reliable transportation isn't available, or it just isn't safe for her to go out.

"Her ZIP code is dictating how healthy she can be and how healthy her baby is going to be," he said.

Wayne County is one of 21 counties in the country whose public health leaders, including Dr. Hammami, are part of a W.K. Kellogg Foundation-funded national committee called Place Matters. Participating counties include Cook County, Ill., and Alameda County, Calif. The effort seeks to improve the health of participating communities by addressing social conditions that lead to poor health. Before his work in government, Dr. Hammami was a neonatal research associate in WSU's Department of Pediatrics, working at Hutzel Women's Hospital from 1995 to 2006. He believes health and state workers need to be educated

"We are spending millions of dollars each year to improve the survival rate and overall outcomes of these extremely low-birth weight infants. However, despite our best effort, some of them will not survive after discharge from NICU," **Dr. DeJesus** says.

on how to eliminate these disparities before an infant even enters the NICU. Place Matters identifies the five social determinants of health as education, employment, social isolation, social perception of girls and women, and structural racism.

"It should start from the day a girl is born, to provide her with the chance to be healthy," he said.

Educating parents about safe sleeping habits is one of many initiatives both Dean Parisi and Dr. Hammami agree needs to happen on a community level as well. A 2008 state report, the most recent of its kind available, indicates that safe sleeping habits, or lack thereof, are one reason African-American babies may be at a greater risk. The 2008 Michigan Pregnancy Risk Assessment and Monitoring report showed that 75 percent of white mothers reported placing infants on their backs to sleep, compared to 56.1 percent of African-American mothers. In the same report, 45 percent of white mothers reported never sharing a bed with their infants. Only 19.3 percent of African-American mothers reported never sharing a bed with their infants.

The investigators are planning another study that will look at the causes of death among preterm infants who died after discharge from

NICU. “We can formulate better interventions or discharge plans once we have better idea of the cause of death,” Dr. DeJesus said.

In other parts of the country where the mortality rate is lower than Detroit, a comprehensive follow-up care program is in place. Physicians skilled in management of the common problems of a premature infant also serve as their primary caregiver. This person may be a neonatologist or a pediatrician.

Dr. DeJesus isn’t certain whether that’s practical or financially feasible in Detroit, but it may be worth looking at, she said. A colleague in her neonatology group has plans to explore it locally. The Infant Mortality Summit, the Place Matters national committee and the eye-opening socio-economic results of the NICU study at WSU are all major steps forward, Dr. Hammami said. “Social determinants are being talked about more frequently. (But) if this effort of ensuring social justice in medicine and health care is going to happen, it requires more than health professionals,” he said. “Those issues require truly a whole community.”

There is hope however. On Aug. 1, 2012, the Michigan Department of Community Health unveiled the state’s Infant Mortality Reduction Plan, a strategy that includes the implementation of measures to prevent prematurity derived from medical research conducted by the Perinatology Research Branch of the Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, at the Wayne State University School of Medicine and the Detroit Medical Center. The plan promotes safe infant sleep practices to prevent suffocation, expanding home-visiting programs to support vulnerable women and infants, programs to reduce unintended pregnancies, and weaving social determinants of health into all its strategies to reduce racial and ethnic disparities in infant mortality.

For Jaslynn’s mother, an uncertain future could lie ahead for her and her daughter. Recently, she wanted a copy of a photo a professional photographer took in the NICU — with permission — as a memento. The photographer offered to mail a print. She paused, not sure how to respond. A doctor quickly volunteered to bring the prints to the NICU instead.

Jaslynn’s mother didn’t have a permanent address. ■

Natural **fighters**

Researcher finds vegetable compounds pack a punch in the fight against cancer

by **Philip Van Hulle**
photos by **David Dalton**

Mom really was on to something when she admonished us to eat our vegetables because they were good for us.

While millions of mothers have cajoled their children to dig into the veggies on the basis of good nutrition, a Wayne State University School of Medicine researcher is taking that advice more than a few steps further by developing compounds from them to make the fight against cancer more efficacious.

Fazlul Sarkar, Ph.D., Distinguished Professor of Pathology and Oncology for the School of Medicine and the Barbara Ann Karmanos Cancer Institute, studies natural agents found in a variety of vegetables and a spice that can decrease tumor growth and greatly enhance the effectiveness of chemotherapy or radiation therapy treatments. Dr. Sarkar's research stemmed from many years of research on the development of active agents against cancer discovered from the bounties of nature. However, what nature can offer in terms of novel chemotherapeutic agents has not been fully exploited.

The Natural Products Repository at the National Institutes of Health's National Cancer Institute houses some 170,000 extracts from samples of more than 70,000 plant and 10,000 marine organisms collected from more than 25 countries, as well as more than 30,000 extracts of diverse bacteria and fungi. This repository is considered to be the source of novel compounds to add to the 500,000 compounds envisaged for the NIH Roadmap Molecular Library.

After more than 40 years of screening these extracts, a critical arsenal of cancer drugs has been developed. That arsenal was led by the flagship drug Taxol, which has been approved by the U.S. Food and Drug Administration for the treatment of several human malignancies. Many other drugs originally discovered from nature have also been approved by the FDA, including camptothecin and its analogs (topotecan and irinotecan), vinblastine and vincristine, and microbial-derived anthracyclines such as doxorubicin and the bleomycins. Several other promising compounds are in testing in clinical trials against cancer and other diseases such as AIDS. Interestingly, it has been estimated that more than 60 percent of approved anti-cancer drugs are derived in one way or another from natural sources, and thus far, natural products chemistry has proved superior to that of combinatorial chemistry, Dr. Sarkar said.

The large proportion of natural products in drug discovery has stemmed from the diverse structures and intricate carbon skeletons of natural products, especially flavonoids, coumarins and indoles. Increasing evidence suggests that natural compounds are superior for further drug development. Agents derived from natural sources could be very useful for the treatment of human malignancies either alone or as an adjunct to conventional therapeutics, including chemotherapy and radiation therapy.

Keeping abreast of emerging and rapid advances in the synthesis, characterization and testing of many such agents that are coming through the drug pipeline through exploitation of natural sources became important for Dr. Sarkar's focused research on specific and novel classes of compounds. The compounds are derived from both natural resources and the tables of synthetic medicinal chemicals, which could become newer arsenals for fighting the battle against human malignancies.

The compounds so far examined by Dr. Sarkar are found in soy, leafy vegetables, cruciferous vegetables like broccoli and Brussels sprouts, hot peppers and curcumin, an ingredient in the spice turmeric. They work by making cancerous tumors more sensitive to the attacks of chemotherapy and radiotherapy and, in most cases, cause cancer cell death while protecting normal cells.

Dr. Sarkar, whose research is funded by six NIH-R01 grants, has demonstrated that combining genistein (isoflavones), a component of soy, with the chemotherapy drug oxaliplatin causes pancreatic cancer cells to react more sensitively to chemotherapy. The finding is exciting because pancreatic cancer, a malignant tumor within the pancreatic gland, is often considered the most deadly form of cancer. Depending on the extent of the tumor at the time of diagnosis, the prognosis is generally regarded as poor. Few victims are still alive five years after diagnosis, and complete remission remains extremely rare.

According to the NCI, 43,140 Americans were diagnosed with pancreatic cancer, and 36,800 died from the disease in 2010. Pancreatic cancer remains the fourth leading cause of cancer deaths in men and the third leading cause of cancer deaths in women in the United States. Only 15 percent of pancreatic tumors are surgically removable. About 15 percent to 20 percent of patients who undergo surgery survive five years after the treatment. The average survival of patients with a more advanced stage of the disease is only six months.

The rates of incidence and mortality related to pancreatic cancer have remained relatively constant over the last 30 years. The NCI says that one in every 71 Americans born today will be diagnosed with cancer of the pancreas. Only about 4 percent of those diagnosed survive. Chemotherapy remains a standard of treatment despite the dire outcomes.

Dr. Sarkar's research with genistein shows promise in making chemotherapy more effective in combating the tumors, and not just in pancreatic cancer. Breast, prostate and other types of cancer cells have also demonstrated sensitivity to the compound.

The soy derivative, he explained, works by limiting the cancer cell's ability to mutate in an attempt to battle chemotherapy drugs. In effect, it weakens the cancer cell's defensive mechanisms. In an animal model, pre-treating pancreatic cancer cells with genistein and then with oxaliplatin increased cancer cell death and reduced the spread of the cancer into lymph nodes.

Dr. Sarkar does not claim these naturally-occurring compounds and their synthetic variations have the ability to cure cancers. Instead, they appear to have an adjuvant characteristic that assists chemotherapy treatments by inhibiting a cancer cell's ability to mutate to fight treatment. Similar observations on isoflavones have also been made with radiotherapy in prostate and renal cancer models.

"Think of it in terms of a flood," he said. "The chemotherapy is the water and it seeks to flood the cancer cells. The cells, in reaction, throw up sandbags (mutate) to

block the flow, and they are very good at setting up those sandbags. Water, however, will continue to seek openings in the sandbag wall, and if these compounds can knock down enough sandbags, then the chemotherapy chemicals can become more effective."

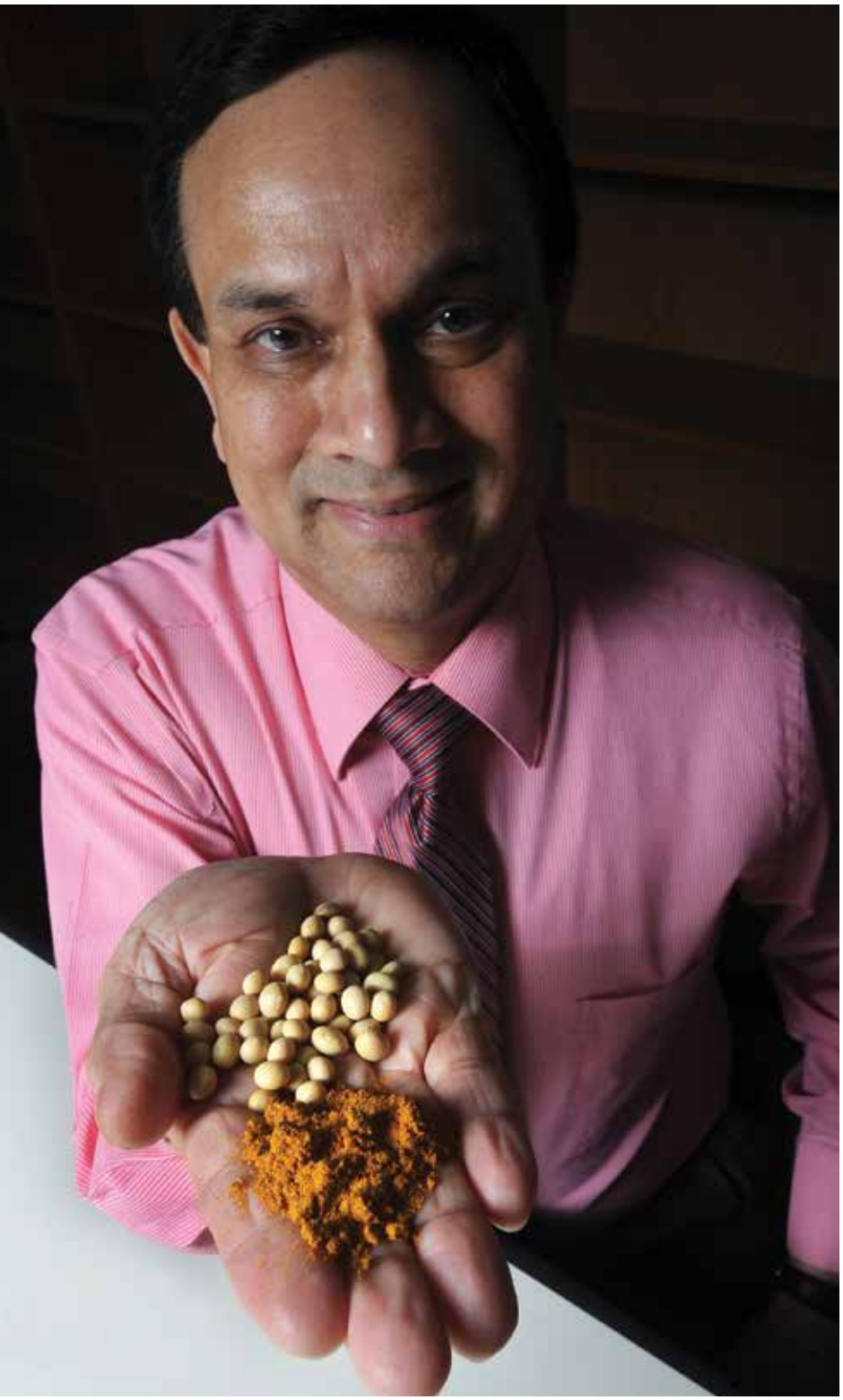
Dr. Sarkar also has tested soy isoflavones in sensitizing prostate cancer cells to radiation therapy. The isoflavones works by inhibiting cell survival pathways activated in response to the attack by radiation. Simultaneously, the isoflavones from soy showed antioxidant and anti-inflammatory characteristics, which can help prevent or diminish the adverse side effects of radiation therapy on normal cells.

In a clinical study, 42 patients with localized prostate cancer were selected to randomly receive 200 milligrams of soy isoflavones or a placebo daily for six months starting on their first day of radiation therapy. At each point during the study, the men who received the isoflavones reported decreased urinary, bowel and incontinence side effects, and better erectile function, than their counterparts who received the placebo.

"I really think that we are only scratching the surface as to the potential compounds in plants that can assist us in winning the battle against cancers," said Dr. Sarkar, who has been engaged in this field of research for more than 20 years.

His research using compounds derived from green leafy vegetables called Indole-3-Carbinol (I3C), which is readily converted to its self-dimerized compound, 3,3'-diindolylmethane (DIM) in the stomach, showed dramatic effects in preclinical studies. Since then, Dr. Sarkar, in collaboration with BioResponce LLC and Elisabeth Heath, M.D., associate professor of Oncology for the Wayne

The compounds so far examined by **Dr. Fazlul Sarkar** — found in soy, leafy vegetables, cruciferous vegetables like broccoli, and curcumin — work by making cancerous tumors more sensitive to the attacks of chemotherapy and radiotherapy and in most cases cause cancer cell death while protecting normal cells.



Dr. Sarkar's research with genistein shows promise in making chemotherapy more effective in combating tumors. Prostate, breast and other types of cancer cells have demonstrated sensitivity to the compound.

State University School of Medicine and director of Prostate Cancer Research at the Karmanos Cancer Institute, has developed an improved formulation of DIM, which he has tested in a Phase I clinical trial in prostate cancer patients. Based on non-toxic dose calculation, he also has initiated a Phase II clinical trial at Karmanos Cancer Institute in collaboration with the Urology Department at Henry Ford Health System in patients diagnosed with prostate cancer. The preliminary results are "very encouraging," Dr. Sarkar said.

He and his research colleagues have also tested extracts from a number of peppers and found that capsaicin too induced significant growth arrest and cell death in human breast and leukemia cancer cell lines, with no significant effect on normal cells.

Capsaicin, the active component of peppers such as jalapenos and habaneros, is found mainly in the white pith that surrounds the internal seeds of such peppers. The compound can irritate and burn the skin, mucous membranes and eyes — hence its use in pepper sprays used by police departments. The rate of cancer cell inhibition and death, Dr. Sarkar found, correlated with the capsaicin content, based on the Scoville scale — a measurement of the hotness of peppers. The hotter the pepper from which the capsaicin is extracted, the more potent in knocking down the defensive mechanisms of the cancer cells. The results, he said, warrant additional research into the potential use of pepper extracts as anti-cancer agents.

Another compound showing promise in the fight against cancer can commonly be found in Indian cuisine. Curcumin, the major

active ingredient in the spice turmeric, Dr. Sarkar has found, also arrests the growth of cancer cells and promotes cancer cell death. However, the compound in its natural state is rapidly processed by the body, so its ability to remain and engage in the fight is relatively weak.

To overcome that weakness, Dr. Sarkar's lab synthesized a novel curcumin analogue called CDF, which remains in the body longer, is absorbed more readily into the blood stream, and demonstrates a greater efficacy in diminishing the defensive mechanisms of cancer cells and causing cancer cell death when used in conjunction with chemotherapy treatments. He is now working to have CDF further synthesized into a drug to be taken in conjunction with chemotherapy for pancreatic, prostate and colon cancer. His research on CDF has been published in many high-impact journals, and he secured a five-year NIH-R01 grant that began July 1, 2011.

Dr. Sarkar, in collaboration with Adhip Majumdar, Ph.D., professor of Internal Medicine at the School of Medicine and the Karmanos Cancer Institute, and senior research career scientist at the Veterans Administration Medical Center, recently published findings in the journal Translational Oncology and Pharmaceutical Research that show the use of curcumin or CDF, either alone or in combination with standard chemotherapy in chemotherapy-resistant colon cancer cells, resulted in the killing of cancer cells that have a cancer stem-like cell quality. The findings are similar to those he published using pancreatic cancer cells. The colon cancer cells resist conventional chemotherapy and have the ability to renew themselves. They also provide a path for malignant cells to propagate and spread. Knocking out the stem-like cancer cells with a curcumin analogue, however, requires developing a compound that remains in the blood stream longer. He said that while curcumin has good absorption rates in the gastrointestinal system, it has very low absorption rates in the blood stream, with levels peaking and then disappearing within 30 minutes to an hour. His newly developed CDF compound raises hope in the fight against human malignancies.

While the produce aisle appears to hold plenty of promise for combating cancer — Dr. Sarkar said he and his wife have added to their own diet some of the vegetables that are the originators of the compounds he studies — he cautioned that fighting cancer isn't as simple as ingesting massive amounts of soy, spinach and turmeric.

"You'd have a very difficult time eating as much curcumin in your diet as the amounts we synthesize for the compounds we are testing to facilitate the development of natural agents or their synthetic derivative as newer drugs that could be used alone as chemotherapy or could be an adjunct to other conventional therapeutics," he said.

But adding more vegetables to your diet can't hurt and definitely has its benefits. Just ask Dr. Sarkar — and Mom. ■

Wired that way

Vaibhav Diwadkar, Ph.D., associate professor of WSU's Department of Psychiatry and Behavioral Neurosciences, discovered stark developmental differences in the brain network function in children of parents with schizophrenia when compared to those with no family history of mental illness.

Vaibhav Diwadkar's team discovers distinctive brain network functions in children and adolescents with a pre-disposition for mental illness

by **Andrea Westfall** photos by **Tom Owoc**

As with the most fascinating of literary characters — Hamlet, Captain Ahab, Holden Caulfield — the motivation for certain behaviors is often rooted deep below the surface.

The same can be said for patients struggling with mental illnesses such as schizophrenia, attention deficit hyperactivity disorder, depression and obsessive compulsive disorder.

That's what drew third-year medical student Sunali Wadehra to study brain network function of children and adolescents at the Department of Psychiatry and Behavioral Neurosciences at the Wayne State University School of Medicine.

Wadehra, an English major in her undergraduate years, was always fascinated by what lies within. What motivates a character? What causes a person to act the way they do?

"I've always been curious about people," Wadehra said. "It's a different way of working through a character's mind."

Wadehra is the second author of a major paper published in the March 2012 issue of the American Medical Association journal Archives of General Psychiatry. Her mentor

and the lead author, Vaibhav Diwadkar, Ph.D., is an associate professor in WSU's Department of Psychiatry and Behavioral Neurosciences and co-director of the Department's Division of Brain Research and Neuroimaging, or BRAIN. Their paper, "Disordered Corticolimbic Interactions During Affective Processing in Children and Adolescents at Risk for Schizophrenia Revealed by Functional Magnetic Resonance Imaging and Dynamic Causal Modeling," explains their discovery of stark developmental differences in brain network function in children of parents with schizophrenia when compared to those with no family history of mental illness.

According to the National Institute of Mental Health, 1 percent of the entire population of the world is schizophrenic, but 10 percent to 20 percent of children with parents who have schizophrenia will develop the illness.

The study results provide significant insight into plausible origins of schizophrenia in terms of dysfunctional brain networks in adolescence, demonstrate sophisticated analyses of functional magnetic resonance imaging data and clarify the understanding of developmental mechanisms in normal versus vulnerable brains. The results can provide unique diagnostic tools for psychiatrists.

The paper, and the attention it is attracting in the science world, is well-deserved, said Stephan Taylor, M.D., co-director of the Psychiatry Affective Neuroimaging Laboratory at the University of Michigan Medical School's Department of Psychiatry. Dr. Taylor's main interest is in the same wheelhouse as the Diwadkar group: clinical translational work in psychosis, OCD and depression, seeking to understand brain circuits underlying these disorders and using brain stimulation techniques to treat the disorders.

"(Dr. Diwadkar's) work has impressed me because he focuses on this vulnerable state, in which people who have a parent with schizophrenia are at a considerable risk of developing the illness themselves," Dr. Taylor said.

Typical neuroimaging studies focus on specific regions of the brain to identify where activity is abnormal, usually considering these regions in isolation from others.

"Technically, the work is impressive because he uses cutting-edge analytic approaches in this high risk population — one of the first studies to take this approach with this population," Dr. Taylor said. "Anything that we can do to identify those at higher risk has a potential role in preventing the onset of the illness."

The team gets plenty of support within WSU as well.

"Dr. Diwadkar's work is ground-breaking and sets the standard for the kind of translational work our department is doing," said David Rosenberg, Ph.D., chair of WSU's Department of Psychiatry and Behavioral Neurosciences. "What sets him apart is that his functional magnetic resonance imaging studies use a novel circuit/neural network approach to developmental neuropsychiatric disorders and those at risk for developing these disorders."

Rather than look at a single area of the brain, Dr. Diwadkar explores the neural networks and underpinnings of genetic risk for psychiatric disorders. His work also bridges various disciplines.

"No neuron, or area of the brain, is an island," Dr. Taylor added. "But the techniques that really recognize this fact are difficult to use. Dr. Diwadkar and his team have employed an approach that reveals abnormal network properties in these at-risk youth. Ultimately, I believe that if we are going to use neuroimaging tools to predict things like who will develop a psychotic disorder, we will use analyses of the interacting networks, not single regions. Thus, I think his work breaks new ground in this direction."

Mental illnesses are considered medical conditions that disrupt a person's thinking, feeling, mood, ability to relate to others and daily functioning, often resulting in a diminished capacity for coping with the ordinary demands of life, according to the National Alliance on Mental Illness, an Arlington, Va.-based advocacy group with chapters in Michigan. Dr. Diwadkar was the guest speaker at a September 2011 NAMI-Oakland County event, talking about his work to discover the causes of mental illness through brain imaging research. He also spoke at select symposia and workshops at the annual meeting of the Society for Biological Psychiatry in San Francisco in 2011 and most recently at the annual meeting of the Organization of Human Brain Mapping in Beijing in June 2012, about the advances, and received a $60,000 Young Investigators research grant from the National Alliance for Research on Schizophrenia & Depression to develop a better understanding of the neurochemical and functional basis of schizophrenia.

"(His work) is going where no one has gone before and is relevant to my area of study in children with OCD, depression and also to other childhood onset neuropsychiatric disorders, including bipolar disorder, ADHD and more," Dr. Rosenberg said.

Jeffrey Stanley, Ph.D., co-director of BRAIN, said the novel approach is significantly elevating science. "Investigating brain function by assessing brain activation differences is inefficient, but to model the data from a network perspective is a big jump forward," said Dr. Stanley, associate professor of Psychiatry and Behavioral Neurosciences.

Dr. Stanley believes it is the dynamic causal modeling, or DCM, that sets the group's work apart from other models in the world of psychiatric research.

"DCM, for now, is ahead of the curve," he said. "(The way) we view and study function has dramatically changed because we are now well beyond the point of saying that this region is involved for function A and that region for function B, and (can) focus our questions on how regions A, B and C function together as a network."

The schizophrenia study took place over three years, using MRI equipment at Harper University Hospital in Detroit. The researchers, including Wadehra and Dr. Diwadkar, studied brain function in individuals 8 to 20 years old after they observed photographs of human faces depicting positive, negative and neutral emotional expressions. Because children of patients with psychiatric illnesses demonstrate a higher risk for conditions such as schizophrenia, the team was interested in emotional processing and the relevance of impaired network function as a potential predictor.

Subjects lay in the MRI machine for 60 to 75 minutes while their brain is mapped on both the structural and functional level. A structural scan is one used to pinpoint the location of a brain tumor or stroke damage, but doesn't give blood flow data. Dr. Diwadkar described a functional MRI scan as a movie of the brain because it measures brain activity by detecting associated changes in blood flow.

The study demonstrated that children at risk for the illness are characterized by reduced network communication and disordered network responses to emotional faces. This suggests that brain developmental processes are going awry in children whose parents have schizophrenia, indicating this is a subgroup of interest to watch in future longitudinal studies.

"Brain network dysfunction associated with emotional processing is a potential predictor for the onset of emotional problems that may occur later in life and that are in turn associated with illnesses like schizophrenia," Dr. Diwadkar said. "If you clearly demonstrate there is something amiss in how the brain functions in children, there is something you can do about it. And that's what we're interested in."

The results don't show whether schizophrenia will eventually develop in the subjects. "It doesn't mean that they have it, or that they will have it," he said. "The kids we studied were perfectly normal if you looked at them. By using functional brain imaging we are trying to get underneath behavior.

"We are able to do this because we can investigate dynamic changes in brain network function by assessing changes in the fMRI signal. This allowed us to capture dramatic differences in how regions in the brain network are interacting with each other," Dr. Diwadkar added.

In addition to Wadehra, colleagues at Harvard Medical School and the University of Pittsburgh School of Medicine, and global collaborator Simon Eickhoff, Dr.Med., of Research Center Jülich and the Institute of Clinical Neuroscience and Medical Psychology at Heinrich-Heine University Düsseldorf, in Germany, also provided significant insight. The latter partnership was supported by a Faculty Global Grants award from WSU's Office of International Programs.

Dr. Diwadkar has used the same modeling in adult schizophrenia, and can study most mental illnesses using the technique. His work has been supported by the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, and the Children's Research Center of Michigan. Together, Drs. Diwadkar and Stanley submitted an R01 grant application to the National Institute of Mental Health as co-principal investigators aimed at tracking functional brain development in children and adolescents with and without ADHD to assess the impact of the condition on development. They'll use dynamic causal modeling to investigate.

Wadehra is one of many students in the Division of Brain Research and Imaging Neuroscience getting attention for their own work. Several of the department's students have published or presented papers on other mental disorders, with many receiving their own research funding from WSU.

"They've done extremely well on their own. That is part of the mission of our division. We are very proactive about that," Dr. Diwadkar said. ■

Medical student **Sunali Wadehra** came to WSU to study brain network function of children and adolescents with **Vaibhav Diwadkar, Ph.D.** Their paper was published in a 2012 issue of the American Medical Association journal Archives of General Psychiatry.

Mapping new territory

From left are lab technician **Becky Cai**, Molecular Biology and Genetics Graduate Program doctoral candidate **Emily Wood**, WSU Assistant Professor and ENCODE project co-investigator **Leonard Lipovich, Ph.D.**, and postdoctoral fellow **Hui Jia, Ph.D.**

The Genome Project's next generation proving 'junk' RNA has therapeutic value

by **Andrea Westfall**
photos by **Robert Widdis**

If the Human Genome Project was science's Columbus voyage of discovery, then researchers like the Wayne State University School of Medicine's Leonard Lipovich, Ph.D., are the genome generation's Lewis and Clark.

Dr. Lipovich and hundreds of researchers in dozens of labs around the world are working collaboratively on the National Human Genome Research Institute's "Encyclopedia of DNA Elements Consortium," or ENCODE, launched in 2003 as one of two large-scale research follow-ups to the Human Genome Project.

The HGP gave science the ability to read the complete genetic blueprint for building a human being. ENCODE takes it thousands, maybe millions, of steps further. The goal is to produce an expansive atlas of functional elements in the human genome, making it the Google Maps of genetics.

"Simply by selecting the magnification in Google Maps, you can see countries, states, cities, streets, even individual intersections, and by selecting different features, you can get directions, see street names and photos, and get information about traffic and even weather," said Elise Feingold, Ph.D., an NHGRI program director who helped start the ENCODE Project. "The ENCODE maps allow researchers to inspect the chromosomes, genes, functional elements and individual nucleotides in the human genome in much the same way."

Dr. Lipovich, assistant professor of Molecular Medicine and Genetics and of Neurology, and members of his lab at WSU, are among the topographers. In September 2012, after nearly a decade of research, the ENCODE project's Phase II results describing an analysis of the entire human genome (following a 2007 Phase I pilot that analyzed 1 percent of the genome) were published collectively in the scientific journals Nature, Genome Biology, and Genome Research — the latter considered the genetics and genomics fields' leading peer-reviewed journal. Two papers in Genome Research featured work from Dr. Lipovich's lab at the School of Medicine's Center for Molecular Medicine and Genetics. The publications have pushed him, and his lab personnel, into the science spotlight.

The Lipovich-led group's overall work on long non-coding ribonucleic acids, or lncRNAs, could lead to new therapeutics for cancer and other diseases. And their determination to prove this genetic matter once deemed "junk" has a place in clinical medicine is bringing the School of Medicine to the forefront of a burgeoning field occupying genome enthusiasts in the United States, Asia and Europe. "Long non-coding RNA genes comprise half of human genes. Most medical, therapeutic work so far has focused on normal, protein-coding genes. So, we — working as part of a multinational team of scientists — have just expanded, twofold, the set of genes that can be therapeutic targets," Dr. Lipovich said.

The findings bring into much sharper focus the continually active genome in which proteins routinely turn genes on and off using sites that are sometimes at great distances from the genes they regulate; where sites on a chromosome interact with each other, also sometimes separated by great distances; where chemical modifications of DNA influence gene expression; and where various functional forms of RNA, a form of nucleic acid related to DNA, help regulate the whole system. That includes long non-coding RNAs.

Hui Jia, Ph.D., contributed one of the initial computational investigations needed to analyze lncRNA data in the current phase of ENCODE.

The Genome Research paper, "Long noncoding RNAs are rarely translated in two human cell lines," presented the results of whole-genome translation testing of human lncRNAs, and set a new standard for how to integrate RNA data with protein data in a way that had never been done. Dr. Lipovich was the last co-principal author of the paper, along with his University of California, Berkeley, colleague, James Brown, Ph.D.

"For many years people pooh-poohed our field, saying that our long non-coding RNAs are either junk, or conventional protein-coding messenger RNAs that we failed to properly understand. We now demonstrate, using an experimental approach, that they are really non-protein-coding (never translated into protein) RNAs in human cells," Dr. Lipovich said.

"My lab, through its computational work here at Wayne, did a vital part of the integration, developing a method that can be used in any future studies that intersect protein and RNA data genome-wide," he added. "Unusual, rare lncRNA-encoded proteins, such as those we found in the ENCODE cancer cells, could be the result of incorrect lncRNA processing by cells that occurs specifically in diseased tissues, and hence a huge resource of biomarkers for diagnostics."

Lab technician **Becky Cai** performs lncRNA experiments in the Lipovich lab.

Three weeks after the initial ENCODE project results were published, Dr. Lipovich learned he would contribute to the next generation of the work, this time as part of an NHGRI-funded $1,341,270 project in collaboration with UC-Berkeley researchers.

The project is one of 15 totaling $30.3 million in grants, and will expand the work of ENCODE to become an even more comprehensive catalog of functional elements that control the expression of genetic information in a cell. The project's long-term goal, which this next phase endeavors to fulfill, is to provide the scientific community with information needed to better understand the role that the genome plays in health and disease. The ENCODE grant — WSU's first — places the university into an elite group that includes UC-Berkeley, Stanford University, the Massachusetts Institute of Technology, University of Chicago, The Broad Institute of MIT and Harvard University, and the Sloan-Kettering Institute for Cancer Research in New York City.

As a co-investigator on the project "Removing Statistical Bottlenecks in Data Analysis for the ENCODE Consortium," Dr. Lipovich, supported by his lab staff, will spend the next three years working with UC-Berkeley Professor of Statistics Peter Bickel, Ph.D., and his UC colleagues to develop and validate new statistical and computational approaches to reduce the complexity of ENCODE data, and to allow comparisons involving many ENCODE datasets at once.

The total WSU portion of this grant comprises $390,683. The funds will help support the necessary lab consumables, along with salaries and required travel costs, for Dr. Lipovich, his lab technician Becky Cai, who will conduct the experimental

portion of the project, and Wood, a third-year doctoral candidate in the School of Medicine's Molecular Biology and Genetics Graduate Program.

"Long non-coding RNAs are emerging as a huge part of primate-specific, including human-specific, complexity, including — potentially — human phenotypic uniqueness. Yet, they play a critical role in regulating the conserved part of the genome," said Wood, who served as a second author on the lncRNA translation paper. "It's really on the edge of what's known," she added, calling the lncRNA field "the wild, wild West" right now.

Wood's new computational method to analyze the experimental data will be used in the first year of the project. "There is no unified model of how lncRNAs work," she said. "We're really interested in therapeutics in this lab. We're also not working on a model organism. We're looking at the activity of the human genome in actual human tissues."

Hui Jia, Ph.D., a postdoctoral fellow in the Lipovich lab, contributed one of the initial computational investigations needed for the team to analyze ENCODE data. As a result, he was a joint-first author of "Long noncoding RNAs are rarely translated in two human cell lines," the Lipovich-led paper published in Genome Research as a part of the collection of ENCODE academic papers. Abnormal translation — the unusual expression of proteins from RNAs that are not supposed to be protein templates — has the potential to emerge as a key trend in cancer and autoimmunity research soon, Dr. Lipovich said, and major genomics labs at Harvard Medical School and other top universities are working on complementary aspects of this biological problem.

The UC-Berkeley/WSU team will use one of six ENCODE computational analysis grants recently awarded. The ENCODE Data Coordination and Analysis Center will be responsible for applying techniques to examine all consortium data, per the direction of ENCODE's Analysis Working Group. The ENCODE AWG — in which Dr. Lipovich's lab participated and provided computational analysis for the previous phase of ENCODE — is open to all academic, government and private sector scientists interested in participating in an open process to facilitate the comprehensive identification of the functional elements in the human genome sequence and who agree to a variety of criteria.

Dr. Lipovich now joins a smaller group of ENCODE Consortium grant recipients and co-investigators who will implement the effort's next phase. ENCODE is one of two major collaborative groups to succeed the completion of the Human Genome Project in 2001.

Dr. Lipovich also is a member of the Japan-based international research consortium Functional Annotation of the Mammalian Genome, the other leading post-genome effort. FANTOM, headquartered at the RIKEN (Japan's "Institute of Physical and Chemical Research") Omics Science Center in Yokohama, analyzes the mammalian

"We're really interested in therapeutics in this lab. We're also not working on a model organism. We're looking at the activity of the human genome in actual human tissues."

Leonard Lipovich, Ph.D., is assistant professor of Molecular Medicine and Genetics, and of Neurology, at the School of Medicine. His group's work on long non-coding ribonucleic acids, or lncRNAs, could lead to new therapeutics for cancer and other diseases.

transcriptome — the complete set of all RNA molecules produced in one or a population of cells — using next-generation sequencing. The FANTOM participation exposed Dr. Lipovich to other valuable collaborations — such as ENCODE.

For FANTOM, he contributes computational analysis of complex loci and lncRNA network validations. Other member institutions working with RIKEN — and WSU — on this project include Harvard, UC-Berkeley, Sweden's Karonlinska Institutet, The Roslin Institute at the University of Edinburgh, Scotland, and the United Kingdom's Medical Research Council. Dr. Lipovich's RIKEN collaboration started in 2004, when he joined FANTOM while a postdoctoral fellow at the Genome Institute of Singapore. The Lipovich lab is the only laboratory in Michigan to participate in both FANTOM and ENCODE. "The energy in the lncRNA community is phenomenal," Wood said. "It's a really exciting time to be part of that community. It's really fun to be a student and be a part of it."

An additional paper in September's Genome Research co-written by Dr. Lipovich, "The GENCODE catalogue of human long non-coding RNAs: Analysis of their gene structure, evolution and expression," presented the most authoritative reference catalog of long noncoding-RNA genes ever constructed. "It will be used by the entire international ENCODE Consortium as a foundation for functional studies linking this exciting new class of RNAs to human health and disease," said Dr. Lipovich, who — along with UC-Berkeley's Dr. Brown — was a middle author on this large, international effort from ENCODE's Analysis Working Group.

In the wake of the Genome Research articles and the co-investigatorship on an ENCODE grant, the Lipovich lab is keeping up the energy and momentum that it has become known for — both within and outside of ENCODE. Dr. Lipovich and Wood presented two talks about lncRNAs at the fifth annual Research in Computational Molecular Biology Conference on Regulatory and Systems Genomics, Nov. 12-15, 2012, in Redwood City, Calif., an official conference of the International Society for Computational Biology. Conferences at this level are as high-profile as they are competitive, with many fine abstracts being relegated to poster sessions, so the talks are quite an honor, Dr. Lipovich said. He delivered a talk on lncRNA genes from in vivo human brain regulatory networks, work that he and Jeffrey Loeb, M.D., Ph.D., associate director of the Center for Molecular Medicine and Genetics and professor of Neurology, recently published. Wood discussed lncRNA networks in human breast and skin cancer. ■

Molding tomorrow's scientists

For those seeking a career in medical research, there are no better training grounds than Wayne State University's School of Medicine for living, breathing, learning and furthering laboratory science.

Wayne State University is a nationally recognized center of excellence in research and one of only two urban public universities holding both the Carnegie "Very High Research" and "Community Engagement" designations. The Cancer Biology Graduate Program at the School of Medicine, in partnership with the Barbara Ann Karmanos Cancer Institute, immerses students in a curriculum that allows for original and critical thinking, with a faculty that mentors each student and encourages a passion for scientific discovery. The program provides outstanding training experience in the evolving field of cancer research, using an interdisciplinary graduate curriculum that offers regular interactions with clinicians engaged in cancer diagnosis and treatment.

Five Cancer Biology Graduate Program students were honored late last year with the prestigious Ruth L. Kirchstein National Research Service Award, or T32, training grant, from the National Cancer Institute of the National Institutes of Health. The students are studying various types of cancer under several of WSU's accomplished faculty members.

Elizabeth Tovar, like nearly all of the awardees, has very personal reasons for entering the program and joining the fight to cure cancer.

Just a few years ago, Tovar's Aunt Thea was lying in a hospice bed, covered by a thin white sheet that seemed too heavy for the cancer patient. She was in the last stages of the disease. She labored to breathe. She grabbed Tovar's hand, and tried to speak, but couldn't. Tovar had just told her she loved her, and would come see her again soon.

"The woman in the bed that day was not my Aunt Thea. Cancer had taken her," Tovar said.

At that moment, Tovar's career path — and her future — became clear.

"I decided to focus my efforts on changing those sorrows of the world … in the best way I knew how — continue on with school and contribute to the fight against cancer," she said.

Tovar is one of five Wayne State University School of Medicine Cancer Biology Graduate Program students awarded the T32 in late 2011, and again this year. Students Aimalie Hardaway, Jonathan Irish, Shermaine Mitchell-Ryan and Angela Sosin, who defended her dissertation in August, also received the grant for pre-doctoral students, worth more than $22,000 each.

"I was honored to learn I had received a spot on the T32 Training Grant. I'm proud of myself for what I have accomplished thus far, and with this funding I'm confident I will transition from my Ph.D. into a career in the science field," Tovar said.

Her dissertation mentor, Kenneth Honn, Ph.D., distinguished professor of Pathology, has long been interested in lipid signaling in cancer. Lipid is a fat, or a fatlike substance. Signaling essentially means how one's diet affects these fats. In her research focus, "Eicosanoid Regulation of Prostate Cancer Progression — Disruption of hemidesmosomes and collaboration in tumor invasive growth," Tovar hopes to determine how cancer cells in the prostate develop the

Cancer Biology Graduate Program doctoral students use national training grants to carve out their own cancer research projects at Wayne State

by **Andrea Westfall**
photos by **Robert Widdis**

Elizabeth Tovar, a fourth-year Cancer Biology Graduate Program doctoral candidate and second-year T32 training grant award winner, hopes to determine how cancer cells in the prostate develop the ability to migrate from one tumor to another site.

Angela Sosin recently defended her dissertation, "Targeting MDM2 for therapeutic intervention in B-cell lymphoma."

ability to migrate from one tumor to another site, or, metastasize, studying the essential reasons cancer cells can do what they do. Control of cell migration is a key to understanding how cancer cells work. Once cancer cells metastasize, patient prognosis is poor, she said.

The Farmington Hills resident is now a fourth-year student in the Cancer Biology Graduate Program and the first person in her immediate family to earn a degree in higher education. She chose the WSU School of Medicine for her doctoral training because of its prestigious standing and long history of developing budding scientists into top scientific researchers.

While Tovar's aunt directed her path, for Angela Sosin, it was a group of friends who shaped her future. The recent graduate moved to Michigan's Macomb Township when she was 8 years old. She made quick friends with three girls in her new neighborhood. They were inseparable for the next decade, until each went off to different universities. They grew up together, and became part of each other's families.

"Their parents were, and still are, very much like my own parents," Sosin said.

As an undergraduate, Sosin learned that the mother of one of her friends had been diagnosed with breast cancer.

"Nothing seemed to make any sense, and answers to questions simply led to more questions. I had a hard time grasping how this could happen to someone close to my parents' age," she said. "I couldn't even imagine losing a parent that wasn't 'old.'"

The Birmingham resident was always inquisitive, she said, so it was like her to question the diagnosis of someone close. "I felt that there was always a reason for anything and everything, and can remember frustrating some of my teachers in elementary and middle school by asking so many questions," she said.

In retrospect, the experience drove Sosin to get involved in cancer research, although she didn't realize it until years later.

Sosin renewed her grant for a second consecutive year in 2011. Her dissertation mentor is Ayad Al-Katib, M.D., professor of Internal Medicine, Division of Hematology and Oncology, and her project is titled "Targeting MDM2 for therapeutic intervention in B-cell lymphoma."

She was working as a molecular biologist at a contract research company in Wheeling, Ill., before deciding to pursue her doctoral degree. She chose WSU because she was offered some financial support, liked the idea of being near her family and friends, and appreciated its affiliation with the Karmanos Cancer Institute.

"To me, it meant a broad, in-depth multidisciplinary training experience that would extend well beyond the laboratory," she said.

Sosin developed a strong interest in hematological malignancies — cancers of the blood, bone marrow and lymph nodes — during her first year of graduate school. Her research interests now include developmental therapeutics and their translation into clinical relevance.

Shermaine Mitchell-Ryan, a fourth-year doctoral candidate, examines the disproportionate morbidity, mortality and incidence rates of certain cancers in African-Americans.

Shermaine Mitchell-Ryan's desire to understand the "hows" and "whys" of science also drove the fourth-year Cancer Biology Graduate Program student's career in academic research. It's the city of Detroit that moved her to choose the Wayne State University School of Medicine.

Mitchell-Ryan grew up in the northwest quadrant of Washington, D.C., and now lives in midtown Detroit, overlooking the Karmanos Cancer Center. The work at Karmanos, and the make-up of the surrounding population, are the main reasons she's at the School of Medicine.

"The Cancer Biology Program at Wayne became a clear choice because of their very close partnership with Karmanos. I believe in the Karmanos' commitment to serve Detroit and surrounding communities — a community that looks very much like my Washington, D.C., community, with a very heavy African-American presence," she said.

She also is the first person in her immediate family with a higher education degree.

"I hope that this training will prepare me to be a competitive, prolific and successful academic scientist who makes an impact on my community in the lab, at the bedside and in the neighborhoods," she said.

Her research examines the disproportionate morbidity, mortality and incidence rates of certain cancers in African-Americans. Her dissertation mentor is Larry Matherly, Ph.D., professor of Pharmacology and director of the Cancer Biology Graduate Program. Her lab training focuses on the development of novel anti-folate therapeutics that target tumors expressing the folate receptor alpha — a protein in human DNA. Folate is an essential B vitamin that we must acquire through diet.

Folates are required for the building blocks of DNA and eventually, cell division. Cancer cells are rapidly dividing cells and must make copies of their DNA before they can divide. This means they need plenty of folate. Some cancers will over-express the folate receptor alpha for survival. This gives the tumor an advantage over other cells in an environment where concentrations of the B vitamin are fixed or limited, especially in ovarian cancers. According to the U.S. Centers for Disease Control and Prevention, African-American women are less likely to have ovarian cancer than other racial and ethnic groups, but are less likely to survive it. Dr. Matherly's lab members believe that by targeting the folate receptor alpha protein they can decrease the toxicity of the tumor in patients with this protein and increase treatment options for those in the later stages of the disease.

Mitchell-Ryan used the T32 grant until she was recently awarded an individual F-31 from the National Institutes of Health — a Ruth L. Kirschstein National Research Service Award for individual pre-doctoral fellowships to promote diversity in health-related research.

"I am confident that my training in the Matherly lab will open many doors for me as a professional in science," said Mitchell-Ryan, who joined the Cancer Biology Graduate Program in 2009. "The training I have received thus far has already given me far more than just laboratory training. It has, and continues, to teach me to think critically and

Jonathan Irish, a fourth-year WSU Cancer Biology Graduate Program doctoral candidate, used the T32 award to study the role epigenetics play in breast cancer.

believe in myself and to know that I, too, have a place in research."

Jonathan Irish, like Mitchell-Ryan, was also quite a curious child, and visited his uncle's physics lab in his earlier years. He helped set up a few basic experiments for fun, and watched a superconductor sample float above a magnet cooled with liquid nitrogen.

"Seeing it levitate and remain there in front of me, above a bench? That hooked me," he said.

The visit was only a few hours, but it made a lasting impression. It was his first glance at laboratory science, and he remained fascinated throughout elementary and secondary school thanks to great teachers, he said.

Irish, a fourth-year student in the program, uses the award to study the role epigenetics play in breast cancer. He is co-mentored by Zengquan Yang, Ph.D., assistant professor of Oncology, and Stephen Ethier, Ph.D., voluntary professor of Oncology. Dr. Yang took a position out of state earlier this year. Irish joined him, but continues to study as a Wayne State University student, and will earn his doctoral degree from WSU upon completing the Cancer Biology Graduate Program.

"My motivation for studying cancer is both humanitarian and personal, although on a personal level the motivation comes from a natural curiosity in something so complex as the field of cancer research," Irish said.

The lab he trains in studies oncogenes in breast cancer. Oncogenes are those that cause cancer to become malignant. "It is incredibly interesting, and because it affects most of us, or will at some point in our lives, it is important," he said.

According to the American Cancer Society, 1,596,670 new cancer cases and 571,950 deaths from cancer were projected in the United States in 2011.

Irish's project is titled "Epigenetic Mechanisms of Transformation for the NSD3 Oncogene in Human Breast Cancer Cells With the 8p11-p12 Amplicon." He is driven by studying oncogenes that have not yet been characterized and successfully targeted therapeutically. He appreciates that the T32 training grant confirms his questions are an important part in the lab's overall research focus.

"To me, being awarded a position on the training grant was confirmation that someone thinks I can do a good job, coupled with the expectation that I go ahead and get the job done. So it's a great motivator for both of those reasons," said Irish, a Lansing, Mich., native. "To make even a small contribution toward understanding even one type of cancer better, in order to better prevent or treat it, would mean a lot to me."

Aimalie Hardaway didn't visit science labs as a child, but, as a young girl, she probably never received a doll from her grandmother at Christmas either. Instead, her grandmother, a nurse, always gave her some type of science book, likely in the hopes that her granddaughter would pursue a career in medicine.

Her grandmother's tactics paid off. The books did indeed get Hardaway interested in science. But it was a stint in the Minority Access to Research Careers program as an undergraduate at Wayne State University

that introduced the Detroit native to a possible future in medical research. MARC is directed by Joseph Dunbar, Ph.D., professor and associate vice president for Research in the Department of Physiology.

Hardaway, a fourth-year student in the Cancer Biology Graduate Program, is mentored by Izabela Podgorski, Ph.D., assistant professor of Pharmacology and Oncology. Like Tovar, she recently successfully renewed the T32 grant to continue her study, "Investigating the Role of Bone Marrow Adipocytes in Prostate Tumor Progression in the Bone," for a second year.

"Aimalie is a very driven and resilient student who has a great deal of determination to excel," Dr. Podgorski said. "She is very passionate about pursuing her future career in cancer immunology. She really wanted her dissertation project to focus in some way on the link between inflammation and cancer, and we were able to combine her interests with the research direction in the lab."

Hardaway has a passion for learning more about prostate cancer. About a year before she was accepted into the graduate program, her grandfather died of the disease. She was devastated. "He was a very important male figure in my life and losing him was really hard on me," she said.

Shortly after, her aunt, who was also her godmother, died of a brain tumor at age 51. Her aunt's daughter asked Hardaway why this was happening to their family. "I said, reluctantly, 'I don't know,'" she said. "That was so inexcusable that I felt the need to find out why."

She sought out Dr. Dunbar, who told her about the cancer biology program. Later, she became even more captivated by the idea of researching prostate cancer after hearing Dr. Podgorski speak. "I liked the fact that she integrated prostate cancer metastasis and the link with obesity," Hardaway said. "She went on to describe the difference in disease progression as a result of obesity in conjunction with race."

According to the CDC, men have a greater chance of getting prostate cancer if they are 50 or older, are African-American, or have a father, brother or son who has had prostate cancer. The CDC also reports that an African-American male has a one in five, or 19 percent, chance of being diagnosed with prostate cancer. One in 20 will die from the disease.

"I hope that my research will shed some light on the important role of inflammation in prostate cancer metastasis in the bone. With metastasis, the chance of a five-year survival is less than 30 percent," Hardaway said. "If our lab can at least bring more attention to the need for more research and volunteers for prostate cancer research, then more lives can be saved as a result."

Dr. Podgorski said, "Aimalie is very excited about her novel thesis project that was developed based on her preliminary findings. She hopes that her work will unravel new molecular mechanisms that predispose prostate cells to metastasize to bone."

Hardaway's grandmother, and certainly her grandfather, would be proud. ■

Fourth-year doctoral student **Aimalie Hardaway** is hopeful her research will shed light on the important role of inflammation in prostate cancer metastasis in the bone.

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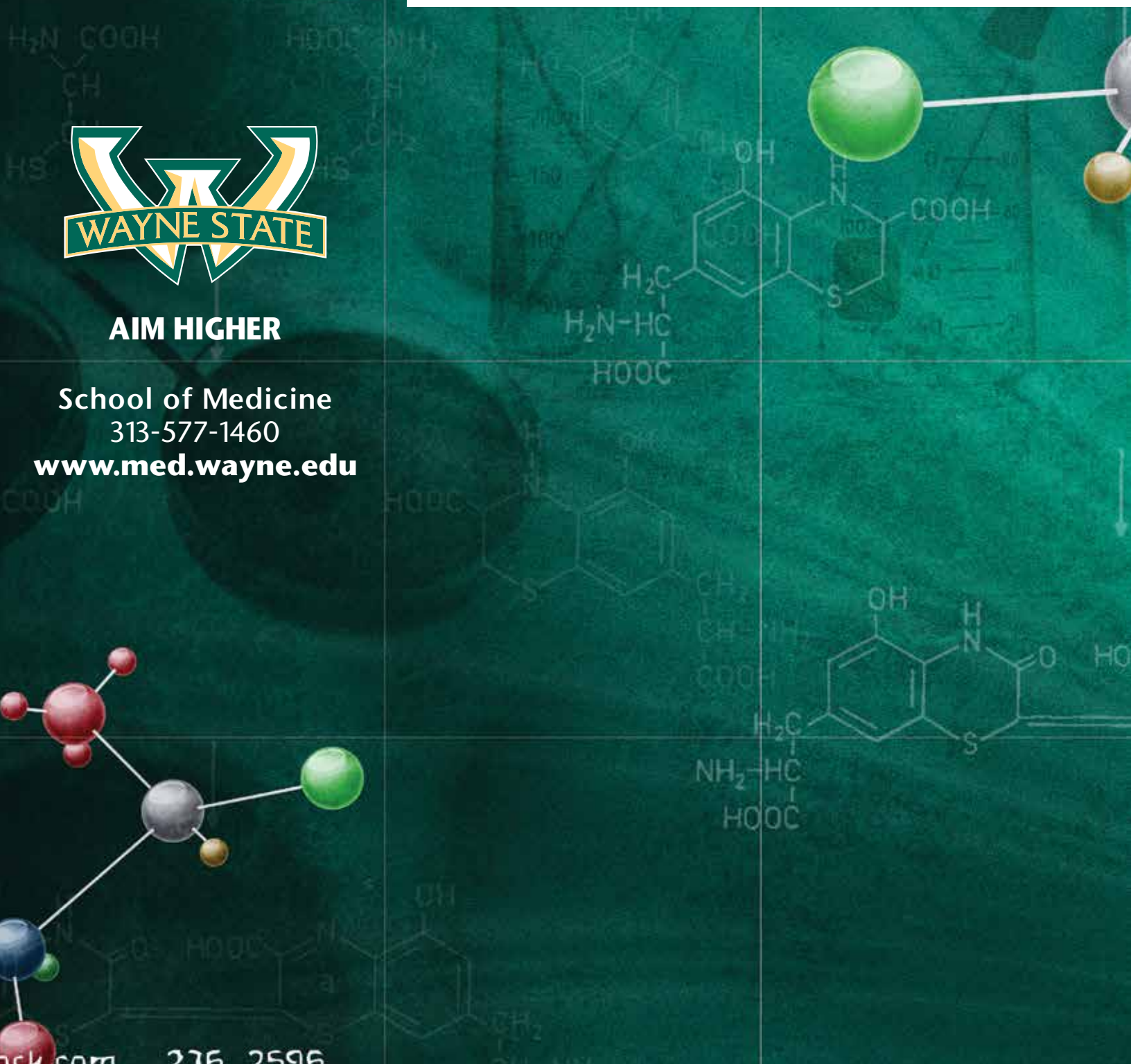

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