Gene Therapy Regenerates Functioning Auditory Hair Cells

U-M RESEARCH FINDINGS COULD UNLOCK FUTURE ADVANCES IN THE TREATMENT OF HEARING LOSS

Millions of people with the most common type of hearing loss – caused by aging, infections, drugs, diseases or exposure to loud sounds – are one step closer to an effective treatment, thanks to scientists at the University of Michigan Medical School.

In research published in the March 1 issue of *Nature Medicine*, U-M scientists used gene therapy to grow new auditory hair cells and restore hearing in deafened guinea pigs. This was the first successful restoration of auditory hair cells in an adult animal, and it made international news.

Reporters from around the world sought interviews with Yehoash Raphael, Ph.D., associate professor of otolaryngology at U-M's Kresge Hearing Research Institute. For the last 11 years, Raphael has been searching for a way to regenerate functioning auditory hair cells.

Unlike hair that grows on our bodies, hair cells are the sensory cells of the auditory and balance organs in the inner ear. They get their name from microscopic hair-like projections that grow from each cell. Certain diseases, drugs and exposure to loud sounds can damage or destroy hair cells. This breaks the connection between sound waves and the brain's auditory processing center and makes it impossible to hear.

Raphael used a "pro-hair cell gene" called Atoh1, which normally is active only during embryonic development. "Our goal was to find a way to activate Atoh1 in mature non-sensory cells in the inner ear, causing them to develop into new hair cells," Raphael says.

Masahiko Izumikawa, M.D., a research fellow in Raphael's laboratory, used an adenoviral vector to deliver the Atoh1 gene to non-sensory cells in the deafened inner ears of adult guinea pigs. The animals were deaf because their original hair cells were destroyed by ototoxic drugs. Eight weeks later, the scientists found new auditory hair cells in the Atoh1-treated ears of the research animals.

To find out whether the guinea pigs' new hair cells were working, the scientists used auditory brainstem response tests, similar to hearing tests given to people. These tests measure auditory thresholds – the lowest level of sound

Photo: Martin Vloet

Yehoash Raphael

Photo: Martin Vloet

Masahiko Izumikawa

intensity that generates a response in the brainstem.

"Four weeks after treatment, the threshold levels indicated profound deafness. But at eight weeks, average thresholds in Atoh1-treated ears were lower (better) at all frequencies than in the control ears. This is the most exciting finding of our study," says Raphael.

Restoring auditory threshold levels is an important advance, but Raphael cautions that it is not the same as restoring normal hearing. "At this early stage the structural and functional repairs are incomplete, and the hearing of these animals is likely to be distorted," he says. "For this and other reasons, it will be several years before Atoh1 gene therapy is ready for human testing."

Photo-illustration: Shayne Davidson

A digitally enhanced scanning electron microscope image of a new hair cell generated in the mature guinea pig cochlea by Atoh1 gene therapy.

The research was supported by the National Institute on Deafness and Other Communication Disorders of the National Institutes of Health, a gift from Berte and Alan Hirschfield, a gift from General Motors and the United Auto Workers, the Center for Hearing Disorders, and GenVec Inc., a biopharmaceutical company in Gaithersburg, Maryland. GenVec provided its proprietary adenovector with the Atoh1 gene insert.

—SFP

For an expanded version of this story:
www.med.umich.edu/opm/newspage/2005/haircell.htm

For more information on deafness and hearing loss:
www.nidcd.nih.gov/health

Misfolded Molecules: Key to Diabetes?

University of Michigan scientists may have found a new culprit in diabetes: improperly folded molecules of proinsulin, the precursor molecule for insulin.

Too many misfolded molecules can clog a cell's internal waste disposal system, putting stress on cells and even killing them. If this happens with proinsulin in the pancreatic beta cells that produce insulin, it could be an important factor leading to the development of diabetes, according to Peter Arvan, M.D., Ph.D., the William K. and Delores S. Brehm Professor of Type 1 Diabetes Research.

Photo: Paul Jaronski

Peter Arvan

Pancreatic beta cells make insulin by folding long molecules of proinsulin into a specific shape, so chemical bonds can form, and then chopping them up to make active insulin. If the folding process is defective, the cells must work extra hard to generate additional insulin needed to regulate the amount of glucose in the bloodstream.

According to Arvan, this continual stress on beta cells could explain why people with diabetes make less insulin and why the cells eventually die. Destruction of pancreatic beta cells is the hallmark of both type 1 (juvenile) and type 2 (adult) diabetes.

In a study published in the *Journal of Biological Chemistry*, Arvan's research team found that normal rat and human beta cells produce misfolded, as well as normally folded, proinsulin. But mice with gene mutations that made them prone to diabetes and mice that produced mutant forms of proinsulin had much higher levels of misfolded molecules. Misfolded molecules were much less likely to leave the cell.

"We've shown that misfolded forms of proinsulin are made under normal conditions, and in higher abundance under diabetic conditions," Arvan says. "The next step is to see how they affect cell function."

—KG

Read an expanded version of the story:
www.med.umich.edu/opm/newspage/2005/insulin.htm

For more information on the Brehm Center and U-M diabetes research:
www.med.umich.edu/brehm

Simulation Station

WHERE MEDICAL TRAINEES CAN PRACTICE SURGERY AND OTHER PROCEDURES AGAIN AND AGAIN — WHILE DOING NO HARM TO PATIENTS

Hands-on training at the operating table is invaluable, but it presents distinct limitations. Medical students and residents are restricted to the cases that present themselves. Learning through trial-and-error is not an option when a patient's safety is on the line. And minimal opportunity exists for the repetitive practice needed to master surgical and clinical procedures.

That's why the University of Michigan Medical School has created the Clinical Simulation Center. Established last year, the Simulation Center brings together high-tech teaching tools and innovative curricula to deliver realistic, intensive and risk-free training.

For example, the center is home to a full-size mannequin, known as a human patient simulator, equipped with software and sophisticated electrical, mechanical, hydraulic and pneumatic devices which realistically replicate human physiology. He (or she — the patient simulator has interchangeable genitalia) speaks, blinks his eyes, and has a heartbeat. His pupils dilate and constrict to light, his chest rises and falls with each breath, and his pulse can be felt in his neck, wrists, thighs and feet.

Instructors program the patient simulator to present specific symptoms and create medical scenarios for students to respond to. The mannequin can be intubated, ventilated, anesthetized, catheterized and medicated intravenously — and he will mirror human responses to the treatments. His heartbeat can be set to mimic arrhythmia. If he goes into cardiac arrest, students can perform CPR or use a defibrillator. If his lung collapses, they use a needle to reinflate it. A tube can be inserted into his chest to remove gas trapped in the lungs or fluid around the heart.

"We can create any medical scenario we want. Students respond to the scenario, and the simulator responds to the students' actions," says Pamela Andreatta, an assistant professor in the Department of Medical Education and director of the Clinical Simulation Center. "You can't get that in real life."

Photo: Martin Vloet

Pamela Andreatta in the Clinical Simulation Center, where Jim Cooke, M.D. (Residency 2000), and third-year resident Catherine Bettcher, M.D., are working with an infant mannequin

> "We can create any medical scenario we want. Students respond to it, and the system responds to the students' actions. You can't get that in real life."
>
> —Pamela Andreatta

The Simulation Center also has a full-sized female mannequin which simulates childbirth. Called Noelle, this patient simulator replicates a variety of medical situations, since instructors can alter fetal head descent, cervical dilation, placenta location, the speed of delivery, and fetal heart sounds and heart rate.

The center also is equipped with infant and pediatric patient simulators, mock operating/trauma rooms, and procedural simulators which allow doctors-in-training to practice laparoscopic surgery, hysteroscopy, endoscopy and other clinical procedures. Audio-video equipment records simulations from a variety of angles for review and debriefing.

The goal of patient simulation is to provide medical students and residents the opportunity to

Bexxar:
Effective First-Line Treatment for Lymphoma

Bexxar, a cancer therapy developed by scientists at the U-M Comprehensive Cancer Center, is an effective first-line treatment for patients with advanced-stage follicular lymphoma — a cancer previously considered to be incurable — according to a study published in the February 3 issue of the *New England Journal of Medicine.*

Of 76 patients enrolled in the study, 95 percent responded to the treatment and 75 percent had a complete response, meaning no evidence of cancer remained. More than three-quarters of patients with a complete remission were disease-free after five years.

According to Mark Kaminski, M.D., professor of internal medicine and director of the study, results from a one-week treatment with Bexxar rivaled those of other treatments for follicular lymphoma. Plus, Bexxar treatment took less time and produced fewer side effects. The drug was approved by the U.S. Food and Drug Administration in 2003 for use in patients with follicular lymphoma after other treatments have failed. The new study evaluated Bexxar as a first-line treatment for the disease.

Kaminski and his colleague Richard Wahl, M.D., formerly at the U-M and now at Johns Hopkins University, developed the Bexxar regimen. The University of Michigan holds patents for the Bexxar therapeutic regimen, which is marketed by GlaxoSmithKline under a licensing agreement.

—NF

Read an expanded version of this story:
www.med.umich.edu/opm/newspage/2005/bexxar.htm

For patient information about non-Hodgkin's lymphoma:
www.cancer.med.umich.edu/learn/lymphomainfo.htm

Photo: Martin Vloet

Mark Kaminski

practice critical procedures earlier in their training and more often before performing them on patients, Andreatta says. This helps ensure that the necessary motor skills and cognitive processes become ingrained, which enables trainees to focus on more substantive issues when they treat patients — thereby improving both the quality of care and the learning experience. "We want to provide our students, our faculty and our staff with access to procedures so they can hone their skills to perfection and have complete confidence," she says.

Clinical simulation is quickly being integrated into the U-M Medical School curriculum across disciplines, Andreatta says, and faculty are conducting research to evaluate the validity and effectiveness of this instructional approach.

—DW

The Clinical Simulation Center is located in the Towsley Center at the U-M Medical School. For more information, call (734) 936-8305 or visit www.med.umich.edu/umcsc.

Photo: Martin Vloet

Kenneth Langa

Help Your Heart, Save Your Brain

HEART ATTACK PREVENTION MEASURES MAY ALSO HELP PRESERVE MEMORY FOR PATIENTS WITH ALZHEIMER'S AND DEMENTIA

Medications and lifestyle changes that help prevent a heart attack or stroke could also prevent or slow the memory loss and confusion of dementia, according to U-M researchers. For some people with a condition called mixed dementia, controlling blood pressure and cholesterol could help more than memory-preserving drugs.

Mixed dementia is a combination of Alzheimer's disease and vascular dementia, caused in part by problems with blood flow in the brain. It may affect as many as 20 percent of the 6.8 million Americans with dementia. Doctors now think that many people with symptoms attributed solely to Alzheimer's — memory loss, confusion, wandering, trouble following instructions — may have mixed dementia.

"The effects of high blood pressure and high cholesterol damage small blood vessels in the brain and can cause death of brain cells over time," says Kenneth Langa, M.D., Ph.D. (Residency 1997), an assistant professor of internal medicine and assistant research scientist in the Institute of Gerontology.

"In addition, the Alzheimer's disease process itself can affect the walls of blood vessels in the brain, making strokes more likely," Langa says. "Strokes can cause dementia through the death of large areas of brain tissue, or through the build-up of damage from multiple small strokes caused by atherosclerosis in small arteries in the brain or the larger carotid arteries in the neck."

Langa and the research team reviewed all recent studies on mixed dementia, vascular dementia and Alzheimer's. They analyzed hundreds of articles, noting any results from drug studies that were relevant to mixed dementia. The researchers concluded that efforts to treat cardiovascular risk factors, especially high blood pressure, may be more effective than memory drugs in protecting brain function.

—*KG*

Read an expanded version of the story:
www.med.umich.edu/opm/newspage/2004/mixeddementia.htm

For patient information on Alzheimer's disease and dementia:
www.med.umich.edu/1libr/aha/aha_alzhdis_crs.htm

Medical School Again in the Top 10

U.S. News and World Report's annual survey of graduate schools ranks the U-M Medical School among the top 10 research-oriented medical schools in the nation for the fifth consecutive year. This year, the school took ninth place.

The school also ranked in six of eight medical specialties: family medicine (fourth), geriatrics (sixth), women's health (seventh), internal medicine (eighth), drug/alcohol abuse (14th) and pediatrics (18th).

Born to Run?

LOW EXERCISE CAPACITY LINKED WITH INCREASED RISK OF CARDIOVASCULAR DISEASE

One of Britton's rats on the treadmill.
Photo: Martin Vloet

If just thinking about exercise makes you tired, perhaps you have something in common with Steven Britton's rats. They have been selected and bred over 11 generations to concentrate genetic differences related to innate aerobic exercise capacity. As a result, the rats differ substantially in their ability to use oxygen efficiently and generate the energy it takes to run for long periods of time.

For example, the high-exercise-capacity rats in generation 11 can run continuously on a treadmill for 42 minutes on average before exhaustion forces them to stop, while low-capacity "couch potato" rats give up after only 14 minutes.

In a study, published in the January 21 issue of *Science*, Steven Britton, Ph.D., and Lauren Gerard Koch, Ph.D. – professor and assistant professor, respectively, of physical medicine and rehabilitation in the U-M Medical School – reported that low-capacity rats had more cardiovascular disease risk factors, including high blood pressure and vascular problems, than rats bred for high exercise capacity.

Scientists from the Norwegian University of Science and Technology, the Medical College of Ohio and Williams College, who collaborated in the study, found a close association between low aerobic exercise capacity and high scores for risk factors linked to metabolic syndrome – physical changes, like insulin-resistance and more abdominal fat, often seen in people who later develop cardiovascular disease and diabetes.

"Essentially we are breeding for genes that code for low levels of proteins involved in mitochondrial function," Britton says. "We think impaired mitochondrial function may be the link between low aerobic capacity and disease."

Photo: Martin Vloet

Steve Britton and Lauren Koch

> "We think impaired mitochondrial function may be the link between low aerobic capacity and disease."
>
> —Steve Britton

Studies with thousands of people have found low aerobic exercise capacity to be the strongest predictor of mortality among all risk factors for cardiovascular disease, Britton adds. So increasing exercise capacity is important for anyone who wants to reduce their risk of dying from a heart attack or stroke.

"You may have to work harder, and you'll never reach the level of a professional athlete, but almost everyone can improve their aerobic capacity and health status with regular exercise," Britton says.

—SFP

For an expanded version of this story:
www.med.umich.edu/opm/newspage/2005/borntorun.htm

Photo: Martin Vloet

Eva Feldman

U-M Health System Designated as a National Neuropathy Center

The U-M Health System has been designated by the Neuropathy Association — a public, charitable, nonprofit organization established in 1995 — as one of four neuropathy centers in the United States. Neuropathy is a painful nerve disorder affecting up to 20 million Americans. Its tingling, numbness and pain in the hands and feet affects half of all patients with diabetes, as well as people with other conditions that cause nerve inflammation and damage.

As a national center, the U-M will receive funding to coordinate the care and support of neuropathy patients, educate doctors about the best diagnostic and treatment options, raise public awareness and pursue research on neuropathy. The center will bring together many of the neuropathy-related research and clinical efforts already underway at Michigan. "We look forward to offering patients more coordinated diagnosis and care, and access to clinical trials of promising treatments," says Eva Feldman (Ph.D. 1979, M.D. 1983) the Russell N. DeJong Professor of Neurology, who will direct the center.

—KG

For patient information about neuropathy:
www.med.umich.edu/1libr/aha/aha_perineur_crs.htm

For more information on the Neuropathy Association:
www.neuropathy.org

Women Wait Longer for Angioplasty

After a heart attack, time is vital. An emergency angioplasty to re-open clogged blood vessels and restore blood flow to heart muscle can reduce the risk of death by 50 percent, but only if it's performed within 90 minutes of the patient's arrival in the emergency room.

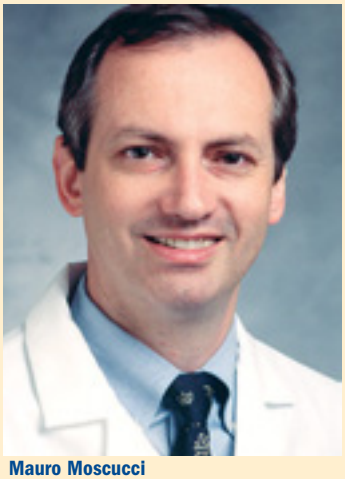
Unfortunately for women, they receive this life-saving procedure an average of 13 minutes later than men, according to a study of 1,511 Michigan heart attack patients conducted by Mauro Moscucci, M.D., associate professor of internal medicine in the U-M Cardiovascular Center. Add the extra 20 minutes that it took for the average woman to reach the ER, and the result is an additional 33 minutes of wasted time and damaged heart muscle, compared to male patients.

The reasons for these gender differences in emergency treatment aren't clear, but may be related to the fact that women are less likely to have the "typical" symptoms of heart attack, such as crushing chest pain and left arm pain. Also, women may be more likely to attribute their symptoms to something other than a heart attack, because they don't realize their own risk for a heart attack.

"Heart attacks happen to women, as well as men," Moscucci says. "Both men and women must recognize and react to symptoms as quickly as possible. Emergency medical professionals must work harder to ensure that women receive the same immediate diagnosis and treatment as men."

The study is part of the Blue Cross Blue Shield of Michigan Cardiovascular Consortium, a multi-hospital initiative to study and improve angioplasty care.

—KG



Mauro Moscucci

Read an expanded version of this story:
www.med.umich.edu/opm/newspage/2004/womenheart.htm

For patient information on heart attack in women:
www.med.umich.edu/1libr/wha/wha_svmyoinf_car.htm

Understanding Depression

GENETIC BRAIN DIFFERENCES COULD SHED LIGHT ON TREATING DEPRESSIVE DISORDERS

Individuals with severe clinical depression who died while they were depressed had lower levels of molecules called fibroblast growth factors, and associated receptors, in their brains than people without the disease, or those with the bipolar form of depression, according to a study by U-M researchers.

Since fibroblast growth factors have never been associated with psychiatric illness before, the discovery suggests a whole new direction for understanding depression and developing new depression treatments. It may even help scientists understand how some antidepressant medications work in the brain to ease symptoms, and why there is wide variation in how depressed people respond to different antidepressants.

The results of the study were published in the *Proceedings of the National Academy of Sciences* by researchers from the Pritzker Neuropsychiatric Disorders Research Consortium. The research team consisted of scientists from the University of Michigan Molecular & Behavioral Neuroscience Institute, formerly known as the Mental Health Research Institute, and researchers from the University of California and Stanford University.

"This finding comes from an unbiased search to find which genes best differentiate major depression brains from normal and bipolar brains," says senior author Huda Akil, Ph.D., the Gardner C. Quarton Distinguished Professor of Neurosciences in Psychiatry. "The family of genes that was most different and showed the highest significance as a coherent group was the fibroblast growth factor family."

Fibroblast growth factors stimulate cell growth in many areas of the body and are involved in the growth of multiple tissues at various stages of life. They have potent effects during embryonic, fetal and child development, and can modify the size and structure of particular brain regions. They are also involved in the repair of adult tissues after injury and may mediate the cross-talk between different cell types in the brain.

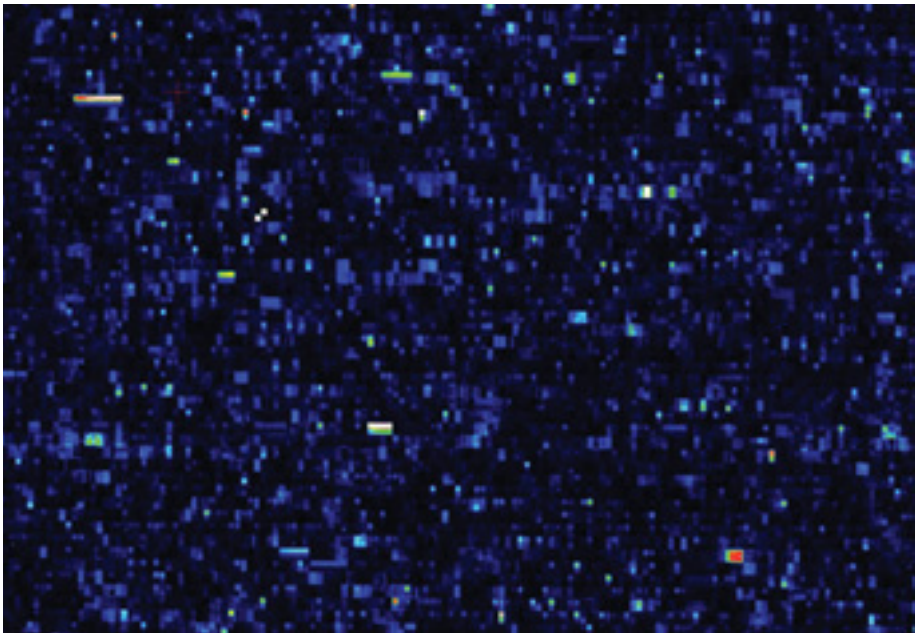


Photo: Simon Evans, U-M Molecular & Behavioral Neuroscience Institute

The intensity of colors in this microarray data from the Pritzker Consortium study represents the level of activity of specific genes in brain tissue.

As a result, they can be seen as mediators of a property that neuroscientists call "neural plasticity" – the ability of the brain to adapt to stress, experience, disease and the effects of drugs.

"We can't say whether these growth factor gene expression changes are a predisposing factor for depression or a consequence of the disease process itself," says Simon Evans, Ph.D., U-M research investigator. "There may be people out there with compromised fibroblast growth factor systems, but if they don't experience stressful life events they may never develop major depression. We need to study the system further to unravel the answer to this question."

–KG

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2004/depressedbrains.htm

For patient information about depression:
www.med.umich.edu/depression

Vitamin D Gains Respect

ONCE REGARDED AS JUST ANOTHER NUTRIENT, VITAMIN D IS VITAL FOR GOOD HEALTH AND HOLDS PROMISE FOR THE TREATMENT OF DISEASE

Everyone knows that vitamin D builds strong bones by helping the body absorb calcium. But new research indicates that it's essential for nearly every other part of the body, too.

Vitamin D deficiency is now recognized as a significant problem in developed countries like the United States. Clinical studies have found intriguing associations between low levels of vitamin D and diseases like diabetes, cancer, depression, hypertension, osteoporosis, muscle disorders, multiple sclerosis, arthritis and heart disease. These associations have made this essential nutrient the subject of many basic science research studies.

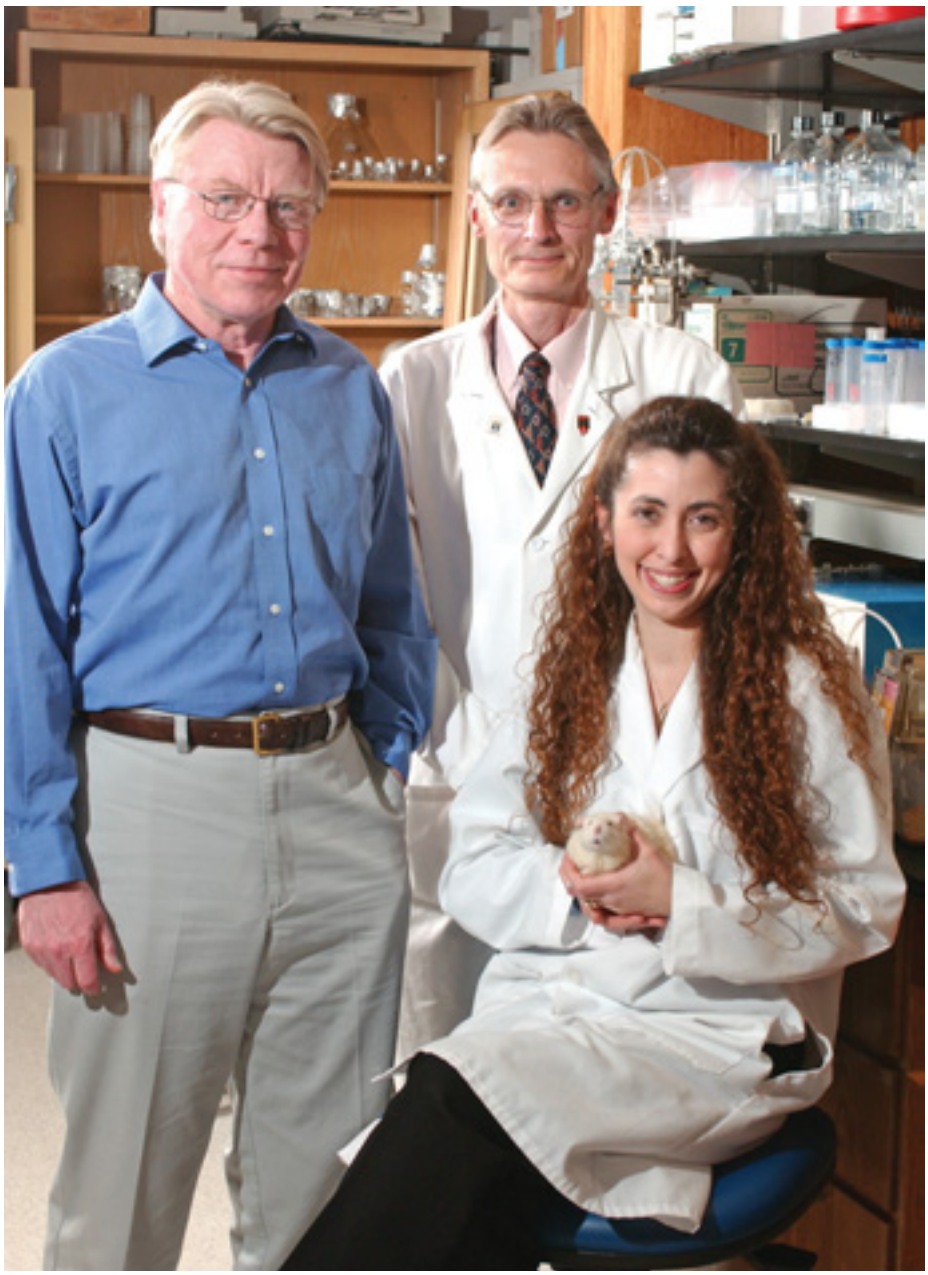
"People used to think vitamin D was just one in a long list of nutrients in your morning multivitamin pill, but now we know how important it is, and how much promise it holds for developing future therapeutic drugs," says Robert Simpson, Ph.D., a professor of pharmacology in the Medical School.

Simpson has spent 25 years studying the secrets of vitamin D, and he says it's gratifying to see it finally getting the respect it deserves from the scientific community.

"Vitamin D isn't really a vitamin at all," Simpson says. "It's a substance the body converts into a hormone called 1,25 dihydroxyvitamin D or calcitriol. The process begins with sunlight. When ultraviolet light from the sun hits your skin, it reacts with a steroid molecule in skin cells to create vitamin D. It's transferred from the skin to your liver and kidneys where it is metabolized into calcitriol, the activated form of the vitamin."

Simpson was the first scientist to identify the docking site, or receptor, calcitriol uses to affect heart muscle cells called cardiomyocytes. He and other scientists have found the same receptor on many other types of cells. When calcitriol binds to the vitamin D receptor, it sends a signal to the cell's nucleus telling it

Photo: Martin Vloet



Robert Simpson, Ph.D., Stephen Hershey, M.D., and Dina Bauer, Ph.D., who is holding one of the lab's spontaneous hypertensive heart failure rats

to turn on, or turn off, certain genes. This makes calcitriol one powerful hormone, because it can alter gene activity in most cells and affect the function of many organs in the body.

Simpson believes that the ability of our cells to respond to vitamin D's signal developed early in human evolution as a sort of internal "wake-up call" triggered by exposure to sunlight. After all, our ancestors didn't just hang around the cave all day. They were outside hunting and gathering food, in a dangerous environment where survival could depend on every organ in the body operating at peak performance.

In 2004, Simpson received a $1.2 million grant from the National Institutes of Health to study the relationship between the vitamin D hormone and a condition called cardiac hypertrophy, or progressive heart failure, which affects nearly 5 million Americans.

Heart failure can develop when damage from a heart attack or chronic high blood pressure makes the heart work harder than it should for long periods of time. As a result, the heart gets larger, and its cells don't contract and relax together. This makes the heart less efficient at pumping blood. Over time, cardiac muscle dies, scar tissue forms and the heart gets weaker. Although drugs can help slow the process, doctors currently have no way to stop the heart's gradual deterioration.

"In our laboratory, we study rats and mice that either can't make enough vitamin D hormone or lack the vitamin D receptor," Simpson says. "These animals have abnormally large hearts and cardiac muscle cells, similar to what physicians see in people with heart failure. We think that a lack of vitamin D hormone leads to defects in the heart's extra-cellular matrix resulting in inefficient contractions."

In studies conducted by other researchers, patients with heart failure were found to have vitamin D levels as much as 50 percent lower than similar patients without the disease.

Ultimately, Simpson hopes his research will lead to new drugs for heart failure. He's trying to identify genes that are active in cardiomyocytes and figure out how they are regulated by the vitamin D hormone. He's also looking for slight genetic differences in the human gene for the vitamin D receptor to see if these differences are more common in people diagnosed with heart failure.

Because it is so vital for good health, Simpson says it's important to make sure you get enough vitamin D. The federal government recommends adults get 400 international units of vitamin D every day. The recommended amount for adults over age 55 is 800 international units. Since only a few foods — like fortified milk, egg yolks and salmon — contain vitamin D, Simpson says it's difficult to get an adequate supply through diet alone.

"Sunlight is the best source," he says. "Fifteen minutes of direct exposure without sunscreen several times a week is enough to allow your skin to produce the recommended dose."

Of course, if you are at high risk for skin cancer, you need to check with your doctor and weigh the risks and benefits of sun exposure carefully. Born and raised in sunny southern California, Simpson includes himself in this category. "I've had several pre-cancerous lesions removed from my face," he says. "So I follow my dermatologist's recommendation and use sun-blockers. But I also take vitamin D supplements every day."

If you have dark skin, live in a northern climate where it's cloudy much of the winter, have a history of skin cancer, or spend more time indoors than outside, taking daily vitamin D supplements can help, according to Simpson. "But too much can be toxic," he warns. "So don't take more than the recommended dose without consulting your physician."

—SFP

For more information on sources and recommended amounts of vitamin D:
http://ods.od.nih.gov/factsheets/vitamind.asp

In studies conducted by other researchers, patients with heart failure were found to have vitamin D levels as much as 50 percent lower than similar patients without the disease.

Caring for the Whole Patient

U-M'S PSYCHONCOLOGY PROGRAM ADDRESSES THE PSYCHOLOGICAL AND SOCIAL ASPECTS OF BEING A PATIENT WITH CANCER

Bill Howe calls them his "dark times," the days when concerns about his cancer diagnosis and treatment overshadowed everything positive and pleasant in life.

On days like those, "you're vulnerable to your worst thoughts," says Howe, 58, who was diagnosed with aggressive prostate cancer four years ago. "You worry about how you're going to arrange treatments, pay for treatments, deal with the insurance company, support your family. At its worst, it's like trying to draw a map of an underground cave without a light. You're kind of lost."

Howe found his way to brighter days with help from the U-M Comprehensive Cancer Center's PsychOncology Program, headed by Michelle Riba, M.D., a clinical professor of psychiatry in the Medical School and current president of the American Psychiatric Association. With a staff that includes psychiatrists, psychologists, social workers, child and family life therapists, nurses, physician assistants, art therapists and complementary therapy professionals, the program is committed to helping patients — and their families — deal with the social and psychological effects of cancer, cancer treatment and cancer survivorship.

"People think of the cancer diagnosis as the most stressful event, but there are, unfortunately, many other situations and reasons for patients and families to become distressed during the course of cancer treatment and afterward," says Riba. "A new MRI scan, the results of various tests, three-month or six-month checkups all become additional stresses." Certain treatments can even affect mental functioning, and the effects can be devastating, as Howe discovered.

Michelle Riba

"You start to lose your ability to multitask, your mental sharpness, your energy," he says. "You're at the top of your game, in your most productive years, and all of a sudden you can't do it any more. Your confidence is smashed, and you think, what is going on with me?"

Photo: Martin Vloet

Bill Howe

PsychOncology, says Riba, looks at this whole range of mental and emotional issues related to cancer, in the context of the patient's life before, during and after diagnosis and treatment. And with a new PsychOncology Clinic located in the Cancer Center, patients can get quicker, more convenient access to mental health professionals, often the same day as their oncology appointment.

Helping clinicians to know when patients need emotional support is another part of PsychOncology's mission. "We would love to see all patients and families evaluated for distress at the very beginning of their care and then on a regular basis," says Riba. With that goal in mind, she helped develop the National Comprehensive Cancer Network's guidelines on psychological distress, which include screening tools and answers to such questions as, "How do you know when distress is normal — or more serious?"

Sometimes, without meaning to, physicians add to patients' distress, so another aim of the PsychOncology Program is to educate doctors about avoiding that. For example, Riba recently lectured hematology-oncology fellows on how to break bad news.

Hearing that doctors are getting that sort of training is *good* news to Howe, who'll never forget the way one physician — not from the U-M — delivered the news that his cancer was worse than the doctor had initially thought.

"He called me on the phone and, in about a five-minute conversation, said I'd have to come in and get radiation. It was so matter-of-fact — like a conversation in the Meijer checkout lane."

His experience at the U-M, on the other hand, has been far more empathic, Howe says, and he credits Riba and the PsychOncology Program for much of that difference. "When you have someone to talk to who deals with cancer patients every day and who understands the cancer patient's perspective," he says, "you know they understand what you're telling them — your thought processes, your anger, your resentment. Having someone tell you that the thoughts you're having are normal is such a relief.

"If you are a cancer patient and ask yourself 'Should I reach out to someone?' ... you probably have your answer."

—NR-F

Second Opinions Help Radiologists

COMPUTER-AIDED DIAGNOSIS IMPROVES CANCER DETECTION RATES

Not all lumps, nodules and masses are cancer. To determine whether a lump is malignant or benign, radiologists study its texture, border and shape when they review the CT scan. Researchers at the U-M Comprehensive Cancer Center are developing computer-aided diagnosis methods to make that assessment easier.

"Our system is designed to help the radiologist," says Lubomir Hadjiyski, Ph.D., a research assistant professor of radiology in the Medical School. "From our experiences in evaluating computer-aided diagnosis for breast cancer, we know that radiologists with computers are able to detect more cancers than radiologists by themselves. We expect that computer-aided diagnosis for lung cancer will produce similar results."

In Hadjiyski's diagnostic system, current and previous scans are fed through a computer program designed by U-M researchers to evaluate the size, texture, density and change of nodules over time. The computer analyzes the images with computer-vision techniques specifically designed for a given type of cancer or disease. Based on all the information, the computer determines how likely it is that the nodule is cancerous.

At the same time, the radiologist examines the images and evaluates the likelihood of cancer. The radiologist then compares the two results and makes a final decision.

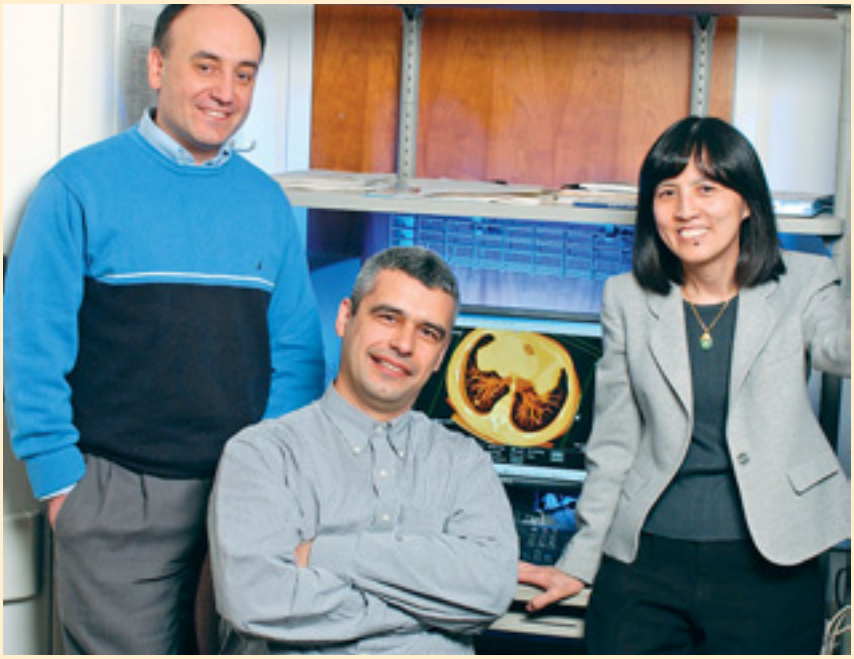


Photo: Martin Vloet

Berkman Sahiner, Ph.D., associate professor of radiology, Lubomir Hadjiyski and Heang-Ping Chan, Ph.D., professor of radiology

"The radiologist is not perfect and the computer is not perfect, but working together they detect more cancers," Hadjiyski says.

Hadjiyski's computer-aided diagnosis programs for lung and breast cancer need Food and Drug Administration approval before they can be offered clinically.

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Read an expanded version of the story at: www.med.umich.edu/opm/newspage/2004/computer.htm

For patient information about lung cancer: www.cancer.med.umich.edu/learn/lung.htm