

In the Lab

To Be or Not to Be

Epigenetics explains the fate of baby cells. But what happens when cells grow up?

EVERY CELL IN THE HUMAN BODY contains the same set of genes. But only some of those genes are turned on — or expressed — in any specific cell. Cardiac cells turn on genes required for heart function, for example, while kidney cells express a different set of genes.

Each cell's unique pattern of gene expression is fixed early in an embryo's development. But how do cells maintain their genetic identity over time?

In a new field of science called epigenetics, researchers are exploring how cells know which genes to express. Each cell stores coded instructions for all its genes on long strands of DNA packed into tight bundles called histones. Genes can only be expressed if these bundles relax and unwind the DNA, allowing the genetic instructions inside to be copied and transferred from the nucleus to other parts of the cell. If certain biochemical tags are attached to a section of DNA, the histone will relax and those genes can be expressed. But if different biochemical tags are attached, the DNA remains tightly spooled and those genes stay silent.

Gregory Dressler, Ph.D., the Collegiate Professor of Pathology Research, and Adam Stein, M.D., an assistant professor of internal medicine, wanted to know if the biochemical signals that control histone relaxation were important to adult cells. So Dressler and Stein, a cardiologist, decided to study their effects

on heart muscle cells called cardiomyocytes in adult mice.

Dressler studies kidney development and has spent years working with proteins called H3K4 methyltransferases, which mark genes to be expressed during embryonic development.

To change the normal pattern of histone methylation tags in heart muscle cells, the U-M scientists knocked-out one gene in the H3K4 methyltransferase complex of a strain of research mice and then examined the effects on cardiomyocytes and heart function.

"We found that epigenetic imprinting controlled the expression of genes important for normal heart equilibrium," says

Stein. "Without normal histone methylation, adult mice developed altered potassium channel activity and electrical instability in their cardiac cells. We can't say that defects in histone methylation caused these cardiac arrhythmias, but it's a potential causative factor."

The study was the first to recognize a potential link between defective epigenetic imprinting and heart disease in animals. Previously, Dressler discovered an epigenetic connection to defects in kidney cells. The bottom line is that "epigenetic changes can alter the properties of adult cells in ways that can lead to disease," Dressler says.

In future research, Stein hopes to determine whether mutant methylation affects how the heart responds to stress. Dressler plans to explore how a cell's epigenetic imprint affects how it responds to developmental signals. —SALLY POBOJEWSKI [MORE ON THE WEB](#) ↗



Adam Stein and
Gregory Dressler

STEVE KUZMA

MacArthur Calling

WHEN YUKIKO YAMASHITA, PH.D., answered the phone recently, she had no idea her life was about to change. “Someone you know very well just got a MacArthur award,” said a voice on the other end of the line. “Can you guess who it is?”

“I kept saying ‘I don’t know,’” says Yamashita, an assistant professor of cell and developmental biology. “Finally, they said it was me. I couldn’t believe it.” She called her husband who warned: “If you get another call asking for your bank account and PIN number, don’t give it to them!”

It’s not every day that a young scientist just starting her career gets \$500,000 to spend however she wants. MacArthur award winners are always surprised, because no one ever applies for a fellowship

and the selection process is conducted in total secrecy. Recipients are chosen for their “creativity, originality and potential to make important contributions to the future,” according to MacArthur Foundation officials.

Yamashita is one of 22 MacArthur winners for 2011, and one of 24 U-M faculty members who have received awards since the program was established in 1981.

She says she will use the \$500,000 to explore results from her research that are unexpected and point in an important new direction.

Yamashita is a stem cell biologist who joined the U-M faculty in January 2007 after completing a postdoctoral fellowship at Stanford University. She studies how adult stem cells in the reproductive



Yukiko Yamashita

tracts of male fruit flies divide to form one stem cell and one daughter cell that becomes a sperm. She focuses on centrosomes — structures that help cells form a division apparatus, or spindle, during cell division. If centrosomes don’t line up properly, mitosis can’t proceed normally in these stem cells. As fruit flies get older, centrosome misalignments become more common, which could explain why sperm production declines with age. —SP [MORE ON THE WEB](#) ✦

A Molecular Switch in Action

CELLS DO IT MILLIONS OF TIMES every day: A protein called a G protein-coupled receptor (GPCR) embedded in the cell’s outer membrane detects an incoming signal — such as a hormone or neurotransmitter, from outside the cell. Grabbing hold of the signal, the GPCR latches onto another protein inside the cell membrane to create a molecular switch, which activates a specific intracellular response.

Exactly how does this molecular switch work? Biologists and biochemists have been trying to figure it out for decades. Now, three teams of scientists — led by researchers at the

U-M, the University of California, San Diego and Stanford University — have taken a major step toward solving the puzzle.

In papers featured on the cover of *Nature*, the international research collaboration published the first high-resolution images showing the molecular structure of a G protein-coupled receptor caught in the act of binding to a G protein inside the cell.

Virtually every type of cell activity depends on these molecular switches. Without them, cells couldn’t respond to changes in their environment. Hearts would stop beating. Nerves

would stop firing. It would be impossible to see, hear or smell.

Defects in the GPCR signaling complex have been linked to many diseases. Nearly half of all therapeutic drugs are designed to target different GPCRs. But drug discovery has been limited by an incomplete understanding of exactly how the complex works.

“Now we know how the signaling complex is assembled and how the receptor turns G proteins on,” says Roger Sunahara, Ph.D., an associate professor of pharmacology who led one of the research teams. “This will help scientists design new and more effective drugs.” —SP

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In the School

Maintaining the Edge

Computational medicine and bioinformatics, cardiac surgery gain stature as independent departments

NOT SINCE THE DEPARTMENT OF Emergency Medicine was created in 1999 has the Medical School established a new department. Recently, however, the U-M Regents approved two.

The departments of Cardiac Surgery and of Computational Medicine and Bioinformatics join more than two dozen other clinical and basic science departments which comprise the Medical School. The move signifies the growing

importance, evolution and contribution to clinical medicine and biomedical science represented by the two fields, and the Medical School's commitment to remain on the competitive edge of medical education, patient care and medical research.

Cardiac surgery at the U-M continues to be a leader in treating the wide range of cardiac diseases, from congenital abnormalities to problems

of the elderly. One of the first pediatric open-heart operations in the nation was performed at the U-M in 1960; today U-M surgeons perform more than 2,000 heart operations a year. Cardiac surgery programs housed at the U-M Cardiovascular Center and the U-M C.S. Mott Children's Hospital are consistently ranked among the top in the nation. Beyond its clinical significance to the Health System, cardiac surgery's



research programs are expected to expand in the areas of health outcomes research and clinical trials.

The Center for Computational Medicine and Bioinformatics was created in 2005 as a campus-wide, interdisciplinary center financed within the Medical School. The center distinguished itself as a distinct discipline with highly regarded research and graduate training programs. Now, the Medical School is one of the first in the country to establish a comprehensive department of computational medicine and bioinformatics. The department will continue to support the collaborative environment that has successfully built bridges to faculty across the university in research and training.

Computational biology is the process of analyzing and interpreting data, and bioinformatics is the science where biology, computer science and technology combine to achieve new biological insights. It involves data such as nucleotide and amino acid sequences, protein domains and protein structures. Clinical informatics involves managing and analyzing clinical data from electronic health records for patients being treated and participants in clinical and translational research.

“Establishing these new departments is critical to sustaining and enhancing the university’s excellence in the fields of cardiac surgery and computational medicine and bioinformatics,” says James O. Woolliscroft, M.D. (Residency 1980), dean of the Medical School and the Lyle C. Roll Professor of Medicine. Both departments will expand academic growth and research potential. —RICK KRUPINSKI

Alumnus to Lead Ophthalmology at the U-M

PAUL LEE, WHO EARNED HIS M.D. AT THE U-M IN 1986, WILL RETURN TO THE Medical School on February 1, 2012, to become chair of the Department of Ophthalmology and Visual Sciences and the F. Bruce Fralick Professor of Ophthalmology.

Currently vice chairman of the Department of Ophthalmology at Duke University, Lee also serves as director of Applied Health Systems Research and as the senior advisor to the chancellor. Additionally, he chairs the finance committee of the physician practice and is a member of the executive management committee of the Duke University Health System. Lee serves on the board of directors of the American Board of Ophthalmology, and has held leadership positions with numerous national and international organizations.

Lee has a significant scholarly background, with extensive publications and research funding in assessing and improving quality of care, quality of life and outcomes, and health systems utilization and policy. Clinically, he specializes in glaucoma and complex glaucoma surgery. In addition to his Michigan M.D., Lee completed his residency at the Wilmer Eye Institute at Johns Hopkins University, a fellowship in glaucoma at the Massachusetts Eye and Ear Infirmary, and a law degree from Columbia University.

Lee’s leadership follows that of another alumnus, Paul R. Lichter (M.D. 1964, Residency 1968), who has successfully guided the department and its growth for more than 30 years. Lichter will remain on the faculty after the leadership transition. —RK



Paul Lee



James Woolliscroft, M.D. (left), dean of the Medical School, met in Beijing in September with Michigan Governor Rick Snyder and Yang Ke, M.D., executive vice president of Peking University and Peking University Health Science Center. Woolliscroft and Ke led a symposium hosted by Peking University, for the two universities’ Joint Institute for Translational and Clinical Research. The governor was on a trade mission to Beijing at the same time. For more on the institute and the symposium, visit www.medicineatmichigan.org/magazine.

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In the Clinic

One Size Doesn't Fit All

Using real-world injuries to build safer cars

HUMAN BODIES COME IN ALL

shapes and sizes, but crash test dummies used for vehicle safety tests are built to represent an “average” person. In real car crashes, human variation can mean the difference between walking away from a crash and a trip to the ER.

“Crash test dummies are designed to match the 50th-percentile male,” says Stewart C. Wang, M.D., Ph.D. — a trauma surgeon, Endowed Professor of Burn Surgery and director of the U-M International Center for Automotive Medicine. “Safety features work really well if you’re a 5-foot-10-inch, 170-pound male, but you’re not going to get the same protection if you’re a 300-pound linebacker or a 90-pound grandmother.”

Wang and his colleagues are creating a new research tool to bridge the gap between the data-driven world of automotive engineering and the all-too-human world of trauma medicine.

Using tens of thousands of information-rich computed tomography (CT) scans from crash victims and control subjects, they are building a three-dimensional encyclopedia of the human body — and what crashes do to it.

“It turns out that the categories medicine tends to use — age, gender, height, weight — still leave a lot of room for variation,” explains Wang, who first started bringing car engineers and medical professionals together to review individual cases in 1998. “What we’ve seen is that the factors that really matter are things like how strong and dense your bones are, and how much muscle you have.”

With the help of advances in computing power, and software similar to what scientists used to decode the human genome, Wang and his colleagues can pinpoint where, in a particular crash scenario or population, ribs tend to snap or pelvises buckle.

“Obviously we can’t go out and conduct experiments that intention-

ally put people in car crashes, but there are thousands of these ‘natural’ experiments between bodies and physical forces happening all the time,” Wang says. “In the last decade, crash victims who come through emergency rooms started routinely getting CT scans, and people happily let us use their scans because we’re using them to save lives.”

The ultimate goal is to make car safety systems more robust. The wealth of CT-derived data on body characteristics can one day be used



Stewart Wang

to create virtual crash test dummies that span the spectrum of body types and provide information automotive engineers need to protect more than just the average Joe.

“They will eventually be able to take this data and adjust the power and timing of the airbag or tune seatbelt tension so that the car can protect differently depending on who’s behind the wheel,” Wang notes.

“I always tell engineers the vehicle is important,” he adds, “but the patient is more important.” —IAN DEMSKY

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Spiritual Retreat Promotes Hope in Patients

A RECENT U-M CLINICAL STUDY found that attending a non-denominational spiritual retreat helped patients with serious heart disease feel less depressed and more hopeful about the future. The retreat included meditation, guided imagery, drumming, journal writing and outdoor activities. Patients showed immediate improvement on standardized tests measuring depression and hopefulness that was still evident at three- and six-month follow-up testing.

“Retreats may be of interest to patients who don’t want to take antidepressants for the depression that often accompanies coronary heart disease and heart attack,” says Sara Warber, M.D. (Residency 1997), associate professor of family medicine and lead author of the study. —SP [MORE ON THE WEB](#) ✦



Breathing Easier with COPD

A COMMON ANTIBIOTIC CALLED AZITHROMYCIN (TRADE NAME ZITHROMAX) reduced the number of attacks of coughing, wheezing, and labored breathing in patients with chronic obstructive pulmonary disease (COPD), according to results from a national clinical trial.

The U-M Health System and the VA Ann Arbor Healthcare System participated in the clinical trial, along with nine other research centers. The trial was funded by the National Heart, Lung, and Blood Institute.

COPD is a progressive lung disease that affects more than 12 million people in the U.S. and is now the third leading cause of death in this country. There is no cure, but a combination of drugs and lifestyle changes can help manage symptoms and slow progression of the disease.

U-M physicians Fernando Martinez, M.D., and Jeffrey Curtis, M.D., both professors of internal medicine, led the U-M’s participation in the study. They also provided preliminary research data indicating that azithromycin might reduce exacerbations of COPD, which are often caused by bacteria or viruses.

In the study, one group of 570 patients took 250 mg of azithromycin daily for a year in addition to their usual treatment regimen, and averaged 1.48 acute COPD exacerbations during the year. A second group of 572 patients who did not take the antibiotic averaged 1.83 exacerbations. Study participants who took azithromycin responded more favorably on questionnaires that asked them to assess their breathing ability and overall well-being. Side effects were minimal, but a few patients reported some hearing loss.

“This important research is just one of many efforts — both at the U-M and around the country — aimed at helping people with COPD breathe easier and enjoy a better quality of life,” says Martinez.

More research will be required to determine the long-term effects of azithromycin treatment and to identify which COPD patients are most likely to benefit, adds Martinez. Results of the trial were published in the *New England Journal of Medicine* on August 25. —SP [MORE ON THE WEB](#) ✦

In the Clinic

Screening for Prostate Cancer

A NEW CLINICAL STUDY OF A URINE TEST DEVELOPED BY U-M CANCER CENTER

researchers shows that it detects prostate cancer more accurately and with greater specificity than current screening tests for prostate-specific antigen, or PSA, alone.

“Many more men have elevated PSA than actually have cancer, but it can be difficult to determine this without a biopsy,” says Arul Chinnaiyan (M.D. and Ph.D. 1999), the S.P. Hicks Professor of Pathology.

The test detects a specific anomaly found in about half of all prostate cancers — a gene fusion called TMPRSS2:ERG, caused by two genes that change places and fuse together. Previous studies found that this gene fusion almost always indicates prostate cancer. But because it is present only half the time, U-M researchers included another marker, PCA3, in the urine test. The combination of both markers was more predictive of cancer than either marker alone.

In the new study, Chinnaiyan’s research team analyzed urine samples from 1,312 men at three academic medical centers and seven hospitals. All the men had elevated PSA levels and had received either a biopsy or prostate-removal surgery. The researchers tested the urine samples for TMPRSS2:ERG and PCA3. Based on results, they divided patients into low, intermediate or high risk groups and then compared this to biopsy data.

Biopsies had detected cancer in 21 percent of men from the low-score group, 43 percent in the intermediate group and 69 percent in the high group. Only 7 percent of men in the low-score group had an aggressive tumor while 40 percent of those in the high-score group did. Researchers believe the new test could one day help some men delay or avoid a needle biopsy, while identifying those at highest risk for aggressive forms of prostate cancer. —SP

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The Lifetime Dose Matters Most

OBESITY IS A KNOWN RISK FACTOR FOR TYPE 2 DIABETES, but it hasn’t been clear whether the “dose” of obesity — how much excess weight a person has, and for how long — affects the risk of diabetes.

A new University of Michigan study of about 8,000 adolescents and young adults shows that both the degree and duration of obesity are cumulative risk factors for developing type 2 diabetes in adulthood. “We found that the relationship between weight and type 2 diabetes is similar to the relationship between smoking and the risk of lung cancer,” says Joyce Lee, M.D. (Fellowship 2006), M.P.H., an assistant professor of pediatrics. “It’s not just the amount of excess weight you carry, it’s the number of years you carry it.” —SP



Joyce Lee

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Health Briefs

No one should have to face cancer alone. Cancer patients, survivors and family members can share experiences and get needed support at MCancerTalk.org — a new blog provided by the U-M Cancer Center. The site includes information from cancer specialists and open forums for patients and caregivers. U-M oncology nurses, physicians and care providers will answer questions posted on the website.

A new U-M research study finds that menopause — whether natural or surgical — does not raise a woman’s risk for diabetes. Being on hormone replacement therapy had no effect on post-menopausal women’s risk for diabetes. Researchers also found that lifestyle changes, like losing weight or starting an exercise program, helped all women lower their risk of diabetes. [MORE ON THE WEB](#) ↗

An older patient who needs carotid artery stenting to reduce the risk of stroke is more likely to have a better outcome if an experienced physician does the job. In fact, new U-M research shows that patients aged 65 and older were nearly twice as likely to die within 30 days if their stent was inserted by a doctor who did fewer than six procedures per year. —SP

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