In the Lab

Putting the 'Stem' in Stem Cell

U-M researchers show 'Mof' protein is crucial to cell transformation

ALMOST DAILY, NEW DISCOVERIES about stem cells and their potential to treat disease and repair defects get researchers excited. Yet one great mystery keeps scientists scratching their heads: Exactly what gives stem cells their unique and valuable qualities? They are the only cells, after all, that can keep dividing and renewing themselves indefinitely or rapidly change course and transform themselves into cells with specific functions, such as muscle, blood and bone.

Recent research by Yali Dou, Ph.D., and colleagues reveals that a protein called Mof plays a crucial role in maintaining stem cells' essential traits of self-renewal and pluripotency (the potential to differentiate into a variety of cell types). The discovery may aid research efforts aimed at repairing patients' damaged tissue or organs using their own cells.

Dou, an associate professor of pathology and of biological chemistry, has been fascinated with Mof since her postdoc days at Rockefeller University. Early work pointed to Mof's importance in transcription activation — the process by which a cell's gene-reading equipment gains access to genes and starts turning instructions into tangible products.

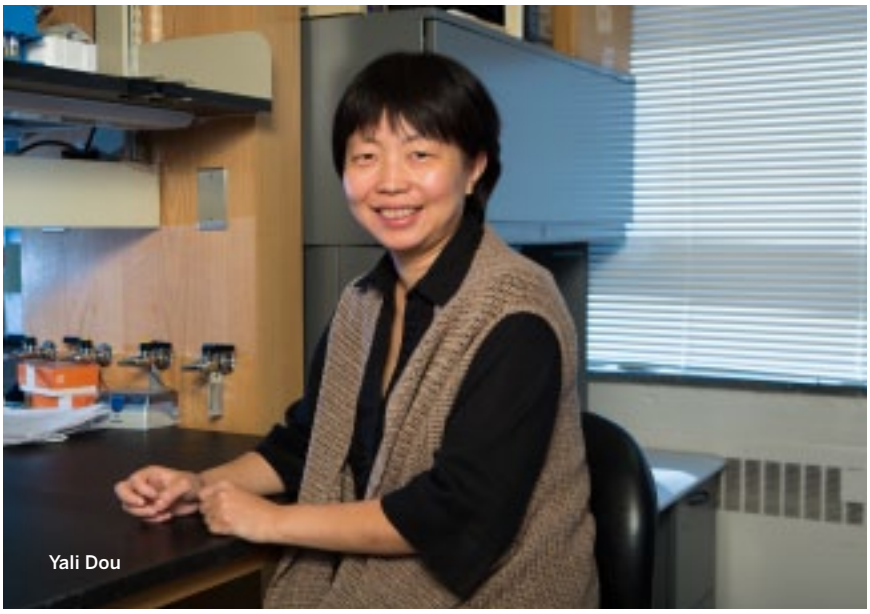
Stem cells are veritable hives of gene transcription, compared to differentiated cells, in which a more limited subset of genes is transcribed. Knowing this, Dou and her colleagues wondered whether Mof might be more prevalent in stem cells than in differentiated cells. In work recently published in *Cell Stem Cell*, they show that is indeed the case.

"That finding almost instantly suggests to us that Mof probably plays an important role in stem cells," Dou says.

To further explore the possibility, the researchers created a mouse model in which Mof was missing from embryonic stem cells. "When we deleted Mof, we saw the stem cells lose their capacity for self-renewal and their ability to develop into different types of cells," says Dou. Then the team delved into the underlying mechanisms and found that Mof regulates several transcription factors (proteins that promote or block transcription of specific DNA sequences) thought to be essential in maintaining pluripotency and self-renewal.

The research could assist efforts to reprogram regular body cells to make them act like embryonic stem cells. These "induced pluripotent stem cells" (iPSCs) offer the possibility of treating patients with stem cells made from their own tissues, a potential boon in repairing diseased or damaged tissues and organs with minimal risk of rejection. In generating iPSCs, scientists use various transcription factors, most of which are regulated by Mof. It's possible that enhancing the function of Mof could facilitate the conversion process, Dou speculates. "That's something we would like to test in the future."

In addition to Dou, the research team included former postdoctoral fellow Xiangzhi Li, Ph.D., now at Shandong University in China, and colleagues at Emory University and the National Institutes of Health. —NANCY ROSS-FLANIGAN



Yali Dou

AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY

Restoring the Sense of Smell


Jeffrey Martens

AS MANY AS TWO MILLION Americans have problems with taste or smell. A subset has never been able to smell a flower or fresh baked bread due to a genetic condition called congenital anosmia. But new research by U-M scientists and collaborators from several other institutions offers a glimmer of hope. In findings published in *Nature Medicine*, the team describes how they were able to use gene therapy to restore a sense of smell in mice born with a defect affecting a protein known as IFT88, which leads to a lack of cilia on cells in the olfactory system and elsewhere in the body.

The researchers infected the mice with a common cold virus carrying normal IFT88 genes. Over the course of two weeks, the mice got fatter (a sign they were eating more) and instruments showed their noses were reacting properly to a pungent odor. "Essentially, we induced the neurons that transmit the sense of smell to regrow the cilia they'd lost," says senior study author Jeffrey Martens, Ph.D., associate professor of pharmacology. —ID MORE ON THE WEB

Breathing Easier

VENTILATORS CAN BE A LIFESAVER FOR CRITICALLY ILL PATIENTS, KEEPING vital organs supplied with oxygen. But the high O_2 concentrations required to keep patients with respiratory failure alive can damage their lungs, sometimes fatally. Megan N. Ballinger (Ph.D. 2007), a clinical lecturer in the Division of Pulmonary and Critical Care Medicine, and her colleagues recently shed new light on the process by which the lungs protect themselves against such injury.

In genetically modified mice, they demonstrated hyperoxia can induce expression of a protein known as IRAK-M, which appears to exacerbate damage by suppressing key anti-oxidant pathways. Mice without IRAK-M had much better survival rates when exposed to high concentrations of oxygen, the team reported in the *Journal of Immunology*.

The findings suggest therapies to limit expression of IRAK-M in lung epithelial cells might improve outcomes for patients requiring ventilation. —ID MORE ON THE WEB

Battling Bacteria in the Blood

RESEARCHERS HAVE LONG studied bacteria growing in films on flat surfaces or in gyrating flasks, but neither accurately simulates the dynamic conditions of the human bloodstream. A team of U-M physicians and scientists, however, has developed a rotating device that mimics forces inside the body, providing a better understanding of how a common health-care associated infection, *Klebsiella pneumoniae*, develops in human hosts. While most people fight off such infections, bacteria in the bloodstream can be particularly dangerous for seniors, cancer patients and others with compromised immune systems.

The researchers found that unlike bacteria grown in shaken flasks, in their apparatus the *K. pneumoniae* quickly formed into small clumps, which increased its resistance to two front-line antibiotics. "The more accurately you can reproduce what bacteria experience inside patients, the better you can understand how they can cause an overwhelming infection," says senior study author John Younger, M.D., M.S., a professor of emergency medicine and a member of the U-M Biointerfaces Institute. —ID

MORE ON THE WEB

AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY

In the School

To Serve and to Learn

Student Run Free Clinic helps uninsured get essential care

Medical students Tani Shtull-Leber, Thomas Filardo, Colin Parker and Chris Eisert at the Student Run Free Clinic

IN A SMALL BRICK STOREFRONT on South Howell Street in Pinckney, Michigan, a simple yet powerful exchange takes place every Saturday afternoon.

A free medical clinic run entirely by U-M medical students is helping to provide critical health care services to uninsured residents of rural Livingston County, just north of Washtenaw County. In turn, students are gaining valuable skills in patient interaction and clinical care as well as the administrative and business sides of medicine.

In addition to handling the many details involved in managing the clinic, known as the U-M Student Run Free Clinic, students schedule appointments, interview arriving patients and enter information into a computerized medical record system. The clinic is housed in the same facility as Faith Medical Clinic, which offers free health care services to uninsured patients on Thursday evenings and Saturday mornings. The student clinic augments that schedule by providing services on Saturday afternoons, under the supervision of U-M faculty physicians. Students handle all aspects of patients' visits except those that require a licensed physician.

"Although health care reform should give more uninsured Americans access to care over the next few years," says Hari Conjeevaram, M.D., an associate professor of internal medicine who is the lead faculty advisor to the clinic team and medical director of the clinic, "services like the Faith Clinic and our student-run clinic provide a vital safety net for non-emergency and preventive care."

For students in their first and second years of medical school, whose studies don't yet bring them into contact with patients, the opportunity to take vital signs and medical histories is especially beneficial. But the U-M clinic is unique in the country in that third- and fourth-year medical students also participate — examining patients, helping review and make recommendations on patient care under the faculty physician's supervision, and mentoring the first- and second-year students.

Not only is the clinic student-run, it was student-conceived. Now in their third year of medical studies, the five founding student directors — Alexander Andrews, Karen Chow, Michael Gao, Alexandra Pulst-Korenberg and Lauren Dennisuk — approached Medical School leaders with the idea in 2010. Funding has been provided by the Dean's Office and Michigan Central Student Government.

"We learned about Faith Clinic's ongoing work, and the unmet needs of the Pinckney community," Dennisuk says, "including a nearby free clinic that had closed recently. Faith had a months-long waiting list for new patients, so we took this as clear evidence of the need in Pinckney."

An advisory committee, medical director and several student directors and coordinators ensure the clinic's smooth and efficient operations. One of those student directors, second-year student Mohamad Issa, cites the value to medical education of business and clinic management, professional relationships and optimizing the patient experience, and emphasizes that students from all four classes have been eager to volunteer.

"The demand is there from the students," Issa says, "and the need is there from the patients. And we know the more practice we get before our third year of medical school, the more opportunities we'll have to improve our bedside manner." —KARA GAVIN/RICK KRUPINSKI

MORE ON THE WEB ↗

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

Guidelines Lacking for Electronic Record Education

ELECTRONIC HEALTH RECORDS have improved health care delivery, but they also present a challenge for medical student training. Cohesive guidelines for medical schools on how to teach and assess student proficiency with electronic records do not yet exist.

"Currently only 64 percent of medical school programs allow students any use of electronic health records, and of those only two-thirds allowed students to write notes within the electronic record," says Maya M. Hammoud (M.D. 1996), associate professor of obstetrics and gynecology at the U-M and the lead author of a recent study on the subject.

"Previously, students were just able to pick up a physical patient chart. Now they need permission to use hospital computers and passwords to access the records," she adds.

The Alliance for Clinical Education, whose research committee Hammoud chairs, offers several recommendations, including: review of students' electronic notes for content and format; practice with order entry; exposure to common accompanying decision-aids; and development by schools of electronic charting competencies. —MM

MORE ON THE WEB

ERIC BRONSON, MICHIGAN PHOTOGRAPHY

INDUCTED: The Class of 2016

THE U-M MEDICAL SCHOOL WELCOMED ITS LATEST CLASS OF physicians-to-be in August as first-year studies got underway. Bright, diverse, and coming from a wide array of undergraduate disciplines, the Class of 2016 comprises students from 26 states. Additional information about class members and the process that brought them here appears below.

- Number applying: 5,392
- Number interviewed: 667
- Students in the class: 177*
- Class average total GPA: 3.78
- Class average MCAT: 34.20
- MSTP students (M.D./Ph.D.): 13

- Female: 49.4%
- Male: 50.6%
- Underrepresented in medicine: 19 (10.7%)
- Average age: 23.8

- Michigan residents: 55.1%
- Non-residents: 44.9%
- Total undergraduate institutions represented: 68
- Michigan undergraduate institutions represented: 14

TOP UNDERGRADUATE FIELDS OF STUDY

- Biology: 23.6%
- Science: 21.3%
- Biochemistry: 13.5%
- Basic medical sciences: 6.2%
- Business/economics: 6.2%

*Data subject to change

In the Clinic

Alone Together

How one U-M researcher is raising global awareness of the *hikikomori* phenomenon

MR. H DIDN'T LEAVE HIS APARTMENT for three years. For the first year, he sequestered himself in a walk-in closet. A housemate supplied him with junk food, and he passed the time surfing the internet and playing video games. And while Mr. H. said disdain for society drove him to seclusion, it was also a source of distress. One day, the 30-year-old reached out to psychiatrist Alan Teo, M.D.

In 2009, Teo, a Robert Wood Johnson Foundation Clinical Scholar at the U-M, was the first physician to publish a review in English medical literature of *hikikomori*, a phenomenon of severe social withdrawal gaining prevalence among young adults in Japan; government estimates place the number of *hikikomori* in the island nation around 700,000 — more than the population of Seattle, Washington. Mr. H. had come across Teo's work and sought his help reentering society.

This chance encounter led this year to the publication of a report about Mr. H., who became the first documented case of *hikikomori* in the Americas. Others have been reported in Spain, Italy, Oman and Korea.

Factors in Japanese society and family structure are often highlighted as major contributors to the disorder, but whether it's unique to the Japanese culture is not merely an academic question, says Teo. "It's clearly most prevalent in Japan, but there's growing evidence that *hikikomori* exist all over the world," he adds, noting that social isolation can be as deadly as smoking or excessive alcohol consumption. In May, Teo participated in a symposium at the Japanese Society of Psychiatry and Neurology's 108th annual meeting that explored the international nature of the disorder.

Becoming a recluse is nothing new, but it's a question of prevalence and degree, says Teo. "We're not pathologizing or creating illnesses," he says. "These are people who are no longer able to function in their daily lives, and who are extremely troubled by their isolation and loneliness. Everyone goes through periods of relative withdrawal, but for these individuals it becomes a way of life." A 2010 epidemiologic study found that one out of every 100 Japanese adults between the ages of 20 and 49 reported experiencing a *hikikomori* episode — defined as withdrawal lasting at least six months — with about half of them showing no indication of additional mental health conditions.

Some scientists hypothesize that the isolating effects of modern technology may be driving the phenomenon, at least in part. "Researchers in Korea have found a link between *hikikomori* and Internet addiction, which the national government is already treating as a significant public health problem," says Teo.

Internet addiction is just one of the areas Teo and colleagues from India, Japan and Korea are examining in an ongoing study that will for the first time analyze the disorder cross-culturally.

By raising awareness about *hikikomori*, Teo hopes people like Mr. H. may be able to get help earlier. "The data indicate that people don't come in for treatment until they have been suffering for a year or more," he says. "It's like if a person waits until they're 300 pounds before they try to lose weight; it's going to be really hard to get back to a healthy state. We need the public to keep an eye out for their loved ones and friends, so that they're able to recognize a problem before months or years have gone by."

—IAN DEMSKY

ISTOCKPHOTO/THINKSTOCK

Hospitals Eye U-M Program for Patients on Ventilators

JUST BECAUSE A PATIENT IS ON A VENTILATOR DOESN'T MEAN SHE should be confined to bed. The U-M Health System's Early Mobility Program has been helping to get critically ill patients up and about sooner — a countermeasure against ills of extended immobility like bed sores, pneumonia and weakness.

"Bed rest orders have been replaced with progressive mobility orders," says Sharon Dickinson, a critical nurse specialist in the Surgical Intensive Care Unit. As a result of the protocol, which Dickinson has dubbed "moving and grooving," pressure ulcers have been drastically reduced. And at the Critical Care Medical Unit, patients spent an average of a day and a half less on the ventilator, while the length of their typical hospital stay dropped by six days — from 22.3 to 16.4.

These successes have led to the program's expansion to units across the Health System. Other hospitals are taking note as well. Beaumont Hospital and the Detroit Medical Center have made site visits to the U-M to learn about the program, and the "lean thinking" approach has been shared at national conferences.

"It may look awkward, but it works," says physical therapist Don Packard, a lecturer in the Department of Physical Medicine and Rehabilitation. "Many patients actually prefer it. They don't want to be tied down." —ID

MORE ON THE WEB

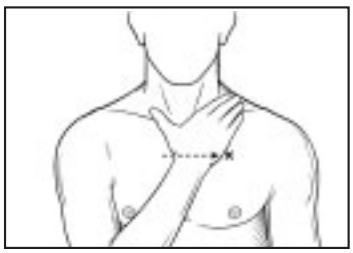
RIGHT: REPRINTED FROM *THE JOURNAL OF EMERGENCY MEDICINE*, VOLUME 43/ISSUE 4, MICHAEL H. LEHMANN, AIMEE M. KATONA, "PROPOSED BEDSIDE MANEUVER TO FACILITATE ACCURATE ANATOMIC ORIENTATION FOR CORRECT POSITIONING OF ECG PRECORDIAL LEADS V1 AND V2: A PILOT STUDY," PAGES 584–592, COPYRIGHT 2012, WITH PERMISSION FROM ELSEVIER.

A Helping Hand

ELECTROCARDIOGRAPHY routinely is used in clinics and hospitals, yet the ECG's central leads can easily be placed incorrectly, potentially resulting in false findings of ischemia and infarction. Misdiagnoses can have consequences for patients, like delaying surgery or botching preemployment health screenings.

A simple technique to ensure correct placement of the V1 and V2 leads was successfully piloted by Michael Lehmann, M.D., a professor of internal medicine in the Division of Cardiovascular Medicine, and U-M physiologist Aimee M. Katona. Their three-step maneuver ("Hand-down-2 for V1V2") starts with the patient placing his hand around the base of his neck; one then counts downward from a spot near the patient's wrist to locate the correct intercostal space for placement. A detailed description of the method was made available online ahead of print publication in the *Journal of Emergency Medicine*. —ID

MORE ON THE WEB



In the Clinic

Longer CPR Attempts May Benefit Some Patients

ONLY 1 OF EVERY 5 HOSPITALIZED PATIENTS WHO GO INTO CARDIAC ARREST survives to be discharged. For physicians, the challenge becomes one of assessing the point at which resuscitation efforts cross the line into futility.

When it's effective, CPR often restores circulation fairly quickly, with a median duration of 12 minutes, according to a U-M analysis of data from 435 U.S. hospitals. However, the study of more than 64,000 patients found that hospitals where resuscitation efforts are generally continued for longer periods of time had better outcomes than those making shorter attempts, suggesting there may be some benefit in continuing efforts under certain circumstances.

Concerns about harming patients with long efforts were also considered. About 15 percent of survivors needed at least 30 minutes to restore their pulse, according to the findings, which were published in *The Lancet*, and importantly, they did not have substantially worse neurological function at discharge than those who survived less prolonged efforts.

The study, however, does not pinpoint an optimal length for CPR efforts, says senior study author Brahmajee K. Nallamothu, M.D., M.P.H. (Fellowship 2004), an associate professor of cardiology.

Co-author Steven L. Kronick, M.D., M.S. (Residency 1989), an emergency physician who heads U-M's CPR committee, says that while care for individual patients should remain a bedside decision based on clinical judgment, the analysis suggests opportunities for system-level improvements.

Steven Kronick and Brahmajee Nallamothu

The study indicates that extending the minimum duration of CPR efforts by 10 or 15 minutes might save lives with only a minimum investment of additional resources, the authors say, cautioning that further study is still needed. —ID

MORE ON THE WEB

Health Briefs

Often pregnant women are reluctant to take medication for depression, but doctors at U-M may have an alternative to recommend. A 10-week mindfulness-based yoga intervention significantly reduced symptoms in psychiatrically high-risk women, a recent pilot study found. Mindfulness-based yoga incorporates exercise with meditative awareness of the body.

MORE ON THE WEB

A small group of glaucoma patients accounts for a large percentage of care expenditures, according to a new study by researchers at the U-M Kellogg Eye Center and colleagues. Analyzing data from a large U.S. managed care network, they found that a 5 percent subset of patients accounted for 24 percent of spending. Better understanding of patient characteristics may help lower overall costs.

MORE ON THE WEB

When a patient's blood pressure remains uncontrolled, it may indicate the current treatment isn't aggressive enough, but it also can mean the patient isn't taking his medicine as prescribed. A study by researchers at the U-M and VA Ann Arbor Healthcare System found providers recognized non-adherence less than half of the time in patients with significant refill gaps, and frequently chose to intensify their medications. Incorporating objective measurements of drug adherence into patient visits could help providers make better decisions, the authors report. —ID

MORE ON THE WEB

STEVE KUZMA