

In the Lab

Scientists Grow 3-D Mini Lungs From Stem Cells

Model mimics human lungs to allow scientists to study development and disease

UNIVERSITY OF MICHIGAN

researchers, along with a multi-institutional team of scientists, have used stem cells to grow the first three-dimensional mini lungs, called lung organoids. These organoids, the name for artificial structures resembling an organ, simulate the architecture and cellular complexity of human lungs and may serve as a discovery tool for researchers to translate basic science ideas into clinical innovations.

"These mini lungs can mimic the responses of real tissues and will be a good model to study how organs form, change with disease, and how they might respond to new drugs," says senior study author Jason R. Spence, Ph.D., assistant professor in the departments of Internal Medicine and Cell and Developmental Biology.

The team published their study results in the open access journal *eLife*. Their work improves on previous research, which has focused on deriving lung tissue from cell systems that grow on the bottom of tissue culture dishes, or by growing cells on scaffolds of donated

organs. The organoids self-organize into 3-dimensional tissue and possess structures resembling the large airways known as bronchi and small lung sacs called alveoli. However, since the organoids are developed in a dish, the mini lungs lack several components of the human lung, including blood vessels and neurons. Still, scientists can use the organoids to validate findings from animal research, an important step to show, for example, that a drug discovery made in animals will be effective on human tissue.

Researchers at the U-M, along with colleagues from the University of California, San Francisco; Cincinnati Children's Hospital Medical Center; and Seattle Children's Hospital, derived organoids by manipulating several signaling pathways that control the formation of organs. First, stem cells were instructed to form a type of tissue called endoderm, which is found in early embryos and gives rise to the lung, liver and several other internal organs.

Next, the scientists activated two important pathways that caused the flat layer of cells in the dish to organize into

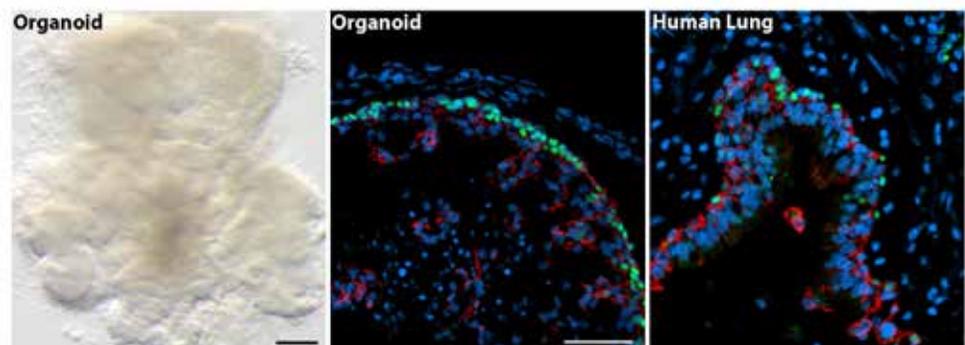
3-dimensional, sphere-like structures. Simultaneously inhibiting two other key development pathways, the endoderm became tissue that resembles the early lung found in embryos.

The organoids were suspended in a protein mixture that enabled three-dimensional outgrowth of the tissue. The next challenge was to make these structures develop into lung tissue. To do this, the team exposed the cells to additional proteins that are essential for lung development.

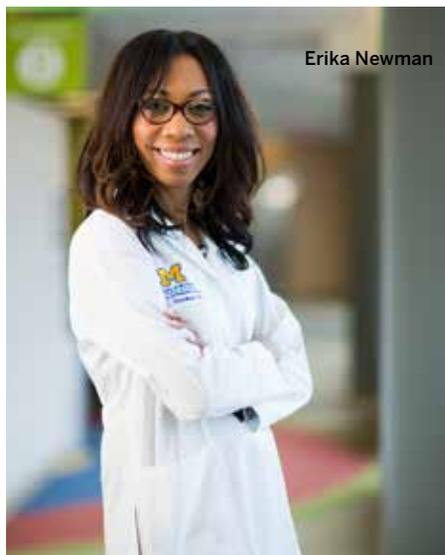
The resulting lung organoids survived in the lab for over 100 days.

"We expected different cells types to form, but their organization into structures resembling human airways was a very exciting result," says lead study author Briana Dye, a graduate student in the Department of Cell and Developmental Biology.

The research has gained support from the National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the March of Dimes and the U-M's Center for Organogenesis. – SK



The panel on the left is a human lung organoid generated from human pluripotent stem cells, viewed under a microscope. The middle panel is a cross section through an organoid and stained to visualize the lung tissue. Lung tissue in organoids is organized in a similar manner to the adult lung, shown in the right panel.



U-M Researchers Close in on New Treatments for Neuroblastoma

RESEARCHERS AT THE U-M'S C.S. MOTT CHILDREN'S HOSPITAL HAVE

identified a promising target for developing new therapies for kids with high-risk neuroblastoma. Published in *Molecular Cancer Research*, their study found for the first time that components of an alternative DNA repair pathway are highly expressed in neuroblastoma tumors.

“We discovered that high-risk neuroblastoma cells preferentially use an efficient but erroneous DNA repair pathway that gives these cells survival advantage. Importantly, children with neuroblastoma tumors harboring these alternative repair factors have worse overall survival than children with tumors that have low expression,” says Erika Newman, M.D. (Residency 2008), assistant professor of pediatric surgery and surgical director of the Mott Solid Tumor Oncology Program, or MSTOP, who led the study.

Newman says this information could provide a promising treatment option for neuroblastoma patients by developing new therapies that disrupt the ability of cancer cells to repair DNA damage. – MM

Largest Ever Genome-Wide Study Strengthens Genetic Link to Obesity

U-M RESEARCHERS HAVE CONTRIBUTED TO THE LARGEST EVER GENOME-WIDE

study to shed light on how genetics influence people's tendency to gain weight and develop obesity-related diseases. The team analyzed genetic samples for over half a million individuals as part of the Genetic Investigation of ANthropometric Traits consortium, an international collaboration that aims to identify genes that regulate human body size. Researchers found more than 100 locations across the genome that play roles in obesity traits. The large number of genes makes it less likely that one solution to beat obesity will work for everyone but opens the door to ways we could use genetic clues to help defeat obesity.

Learning more about the genes and biological processes may guide the development of weight-loss therapies, and help doctors tailor the health advice they give to patients.

Faculty and staff from the U-M Department of Human Genetics, Department of Epidemiology, Kidney Epidemiology and Cost Center, School of Public Health, Center for Statistical Genetics, Department of Biostatistics, Department of Internal Medicine, Department of Computational Medicine and Bioinformatics, and the Institute for Social Research contributed to the research. – SK

Gut Bacteria May Fight Disease

NEW RESEARCH CO-LED BY U-M

faculty has found that bacteria that aid in digesting bread and beer yeast could enable new treatments for autoimmune diseases.

The study shows how microbes in the human digestive tract have evolved to break down complex carbohydrates that make up the yeast cell wall. Adapted over 7,000 years of consuming fermented food and drink, the ability of a gut bacterium called *Bacteroides thetaiotaomicron* to degrade yeasts is almost exclusively found in humans. The discovery of this process could accelerate the development of prebiotic medicines for people with bowel problems and autoimmune diseases, such as Crohn's disease.

During the study, the U-M team, led by Eric Martens, Ph.D., assistant professor of microbiology and immunology, fed mice a customized food made with bread from Ann Arbor's nationally known Zingerman's Bakehouse. The international research team also included Harry Gilbert, Ph.D., professor of biochemistry at Newcastle University, and Wade Abbott, Ph.D., research scientist at Agriculture and Agri-Food Canada. The findings provide a better understanding of how our unique intestinal soup of bacteria — termed the microbiome — has the capacity to obtain nutrients from our highly varied diet. – SK

In the Clinic

A New Way to Save Lives and Dollars

Stopping drunk drivers from starting their cars pays off

INSTALLING ALCOHOL IGNITION

interlock devices in all new vehicles in the U.S. could prevent more than 59,000 deaths and 1.25 million injuries, plus save \$343 billion in associated costs over 15 years. Those are the findings of a recent study from the University of Michigan Injury Center and the U-M Transportation Research Institute. Published online and in the May issue of the *American Journal of Public Health*, it was the first study to model the potential impact in the U.S. of mandatory technology that tests a driver's blood alcohol level before allowing his or her car to start.

Using data from the Fatality Analysis Reporting System and the National Automotive Sampling System's General Estimates System, researchers analyzed alcohol-involved crashes that resulted in injury or death and estimated that 85 percent of fatalities and up to 88 percent of non-fatal injuries could have been prevented. Based on known societal costs, they determined monetary savings — and found that a universal policy would hit the break-even point after only three years.

Given the study's results and that it modeled a mandatory policy, it garnered attention from a number of media outlets including *Forbes* and *Bloomberg.com*, plus various auto and medical websites and blogs, but some people have misinterpreted the study, researchers say.

"The research shows that widespread adoption of technology that can prevent a vehicle from being driven by a drunk driver could have enormous benefits," says Jonathan D. Rupp, Ph.D., a co-author

and research associate professor in the Department of Emergency Medicine and in the Biosciences Group of the U-M Transportation Research Institute and director of UMTRI's Center for the Management of Safe and Sustainable Transportation. "But we're not advocating for a policy that these devices should be required in new vehicles. The study was meant to draw attention to and inform a conversation about interlocks by characterizing potential benefits as these devices phase into the vehicle fleet."

Although interlocks provide a unique solution to drunk driving, they're not widely deployed. All 50 states currently have some type of device that is either DMV-mandated or judicially mandated, usually for people with multiple drunk-driving convictions, says Patrick Carter, M.D. (Residency 2009), lead author and a U-M assistant professor of emergency medicine. However, new technology may enable interlock devices to be used as a preventative measure. An initiative called the Driver Alcohol Detection System for Safety through the National Highway Traffic Safety Administration and Alliance of Automobile Manufacturers is developing technology that could be integrated into cars during manufacture and require no perceptible testing step before you start — or are blocked from starting — your car.

But even with unobtrusive technology (which may be 8 to 10 years away, Carter says), it's unlikely lawmakers would require them in all cars. Instead, they might explore other options, such as making interlocks compulsory for drivers



16 to 21 years old, who are under the legal drinking age. This group is responsible for 15 percent of all preventable alcohol-related fatalities and injuries, according to study data. Or, insurance companies or the federal government may grant drivers insurance breaks or tax credits for purchasing vehicles with interlocks installed at the point of construction.

"My speculation is that interlocks will be implemented as part of a technology package," Rupp says. "We've seen safety technologies become increasingly accepted and preventing drunk driving is one of the most important safety steps we can take."

Exploring effective interlock implementation approaches is the goal of the next generation of research, and the subject of a student-driven follow-up study that recently kicked off at U-M. This is just one of several collaborations between the Injury Center and UMTRI, including one examining the repeal of Michigan's helmet law and studies on how to train young drivers to reduce the risk of injuries. — BETH JANES

Majority of Parents Would Test Kids' DNA for Disease Risks

A NATIONALLY REPRESENTATIVE STUDY FROM THE U-M

recently found that the majority of parents would use whole genome sequencing to find out disease risks for themselves and their children. The study found that 59 percent of the total population, including both parents and nonparents, were interested in genome sequencing. More than three-fourths of parents also showed the same interest in genome sequencing for themselves as they did for their kids. Mothers as a group and parents whose youngest children had more than two health conditions had significantly more interest in the testing for themselves and their youngest children. Those with conservative political views had considerably less interest.

Authors note concern for how accurately the DNA results would be interpreted. Additionally, parents could learn risks of diseases that wouldn't affect their children until they were adults, such as breast cancer. The research team, led by senior author Beth Tarini, M.D., assistant professor of pediatrics and communicable diseases, hopes their data will help clinicians educate their patients regarding this technology, and partner with patients in making well-informed health decisions. — BM



Beth Tarini

Researchers Look at Patient Perceptions of Physicians' Attire

U-M HAS RELEASED A

comprehensive analysis of studies on physician attire and its influence on patient perceptions. Reviewing data from 30 studies involving more than 11,500 adult patients in 14 countries, researchers found that patients generally prefer formal physician attire, but perceptions can vary greatly by age, locale, setting and context of care. Doctors of either gender in suits or white coats are more likely to inspire trust and confidence. But fashion takes a backseat when it comes to emergency, surgical or critical care, where patients may even prefer to see doctors in scrubs.

Researchers say that because doctors and hospitals now get paid in part based on patient satisfaction, doctors' attire could start mattering to the bottom line. The team will launch their own international study of the impact of physician clothing choices to quantify how patients' views of physicians change based on what they're wearing and where they're providing care. They will also evaluate how attire might affect patients' trust in what that doctor says or recommends. — KG



Patient-Safety Research Team Reports on DVT Risks from Common in-arm IV Devices

U-M AND VA PATIENT SAFETY RESEARCHERS HAVE SHED LIGHT ON

which factors put hospitalized patients at the highest risk for developing deep vein thrombosis, or DVT, clots from intravenous PICC lines.

Vineet Chopra, M.D., assistant professor of internal medicine, and his colleagues at U-M and the VA Center for Clinical Management Research and Patient Safety Enhancement Program looked at records from 909 hospital patients who received PICCs at U-M in 2012 and 2013. In all, 268 patients developed a clot associated with their PICC. Most of the clots developed in the first 10 days after the PICC went in.

The narrower the PICC line a patient received, the lower their risk of a DVT. Patients who were taking aspirin and cholesterol-lowering drugs before they got their PICC also had a lower risk. Patients who had any kind of surgery during their hospital stay, or had had any kind of deep clot in their medical history, were more likely to get a DVT.

The results, Chopra says, suggest doctors should tread carefully when considering PICCs for certain patients, monitor for clots, ensure patients continue taking aspirin and statins, and take the PICC out before any operation. The team also put together two new guides to help physicians decide which patients should receive a PICC or other, less-risky IV device, and prevent and detect clots in patients with PICCs. — KG

In the Clinic

Exposure to Mercury Associated With Risk Factor for Autoimmune Disease



ONE OF THE GREATEST RISK

factors for autoimmunity among women of childbearing age may be associated with exposure to mercury such as through seafood or other ways, a U-M study finds. Analyzing data among women ages 16-49 from the National Health and Nutrition Examination Survey from 1999-2004, researchers found that mercury – even at low levels generally considered safe – was associated with

autoimmunity.

Greater exposure to mercury was associated with a higher rate of autoantibodies, a precursor to autoimmune disease. Most autoimmune diseases are characterized by autoantibodies, proteins made by a person's immune system when it fails to distinguish between its own tissues and potentially harmful cells.

The research team, led by Emily

Somers, Ph.D., Sc.M, an associate professor in the departments of internal medicine and obstetrics and gynecology, as well as the Department of Environmental Health Sciences in the School of Public Health, note there are many health benefits to seafood, a lean protein packed with vital nutrients. However, the findings provide further evidence that women of reproductive age should be mindful of the type of fish they're eating. — BM

U-M Study: Religion and Support for Birth Control Health Coverage Can Mix

NEW RESEARCH DEBUNKS THE

assumption that a woman's religion predicts her views on policies affecting reproductive health care, according to a nationally representative study by the U-M.

Researchers found that religious women's opinions are mixed — even when it comes to policies that have sometimes been characterized as going against Christian views, such as the Affordable Care Act mandate for employer-provided contraception coverage.

Protestants and Catholics were most likely to agree that employer health

plans should cover contraception (66 percent and 63 percent respectively) — even ahead of non-religious women (59 percent) and women of non-Christian religious affiliation (59 percent). Least likely to support the ACA requirement were Baptists (48 percent) and other Christians (45 percent). Fifty-six percent of women overall supported mandated health coverage of contraceptives and less than one-fourth believed employers should be exempt from the law due to religion.

Researchers analyzed data from the

Women's Health Care Experiences and Preferences Study, conducted by the Program on Women's Health Care Effectiveness Research in the U-M Department of Obstetrics and Gynecology.

"Debates surrounding reproductive health care have often been framed as religious versus non-religious but that's not an accurate narrative," says lead author Elizabeth Patton, M.D., clinical lecturer in obstetrics and gynecology and research fellow in internal medicine. "We need to be aware of the complexity of how religion affects women's views so we can design reproductive health policies that truly reflect the beliefs and desires of most women in our country."

— BM

How to Fight Superbugs in Nursing Homes

RESEARCHERS AT THE U-M AND VA ANN ARBOR HEALTHCARE SYSTEM

recently found that a targeted infection program, or TIP, may be the key to preventing the spread of “superbugs” and reducing infections in nursing homes.

The authors examined the effect of a TIP to reduce the prevalence of multi-drug resistant organisms, or MDROs, in patients who rely on devices — such as urinary catheters and feeding tubes — that carry a high risk of infection. The TIP intervention included surveillance for infections and MDRO colonization; extensive staff education about key infection prevention practices and hand hygiene; and the use of gloves and gowns when providing assistance to patients for high-risk activities such as bathing and grooming.

Researchers found that MDROs were reduced by 23 percent among 418 residents in 12 southeast Michigan nursing homes who participated over the course of the three-year study. The numbers of new catheter-associated urinary tract infections and new MRSA acquisitions also decreased, by 46 percent and 22 percent respectively.

With the move toward integrated health care systems and reducing hospital length of stay, over 20 percent of Medicare beneficiaries who have a hospital stay now head to a nursing home first. As a result, today’s nursing home population is sicker, making it increasingly important to enhance evidence-based infection prevention practices. Many nursing home residents will need hospitalization again, raising the possibility that MDROs could travel with them and spread to others.

“Reduction in MDROs among the high-risk short-stay and long-stay nursing home population will decrease transmission of these superbugs between institutions,” says Lona Mody, M.D. (Fellowship 1999), an associate professor of internal medicine and research associate professor at the U-M Institute of Gerontology. “This study provides a strong argument to reconsider MDRO management in nursing homes and devote more resources to infection prevention programs in nursing homes.” — MBR



Lona Mody

TOP RIGHT AND BOTTOM LEFT: SCOTT C. SODERBERG, MICHIGAN PHOTOGRAPHY



U-M Comprehensive Cancer Center

Antacids Linked to Cancer Survival

PATIENTS WITH HEAD AND NECK

cancer who take antacids for acid reflux may have better overall survival, finds a new study from the U-M Comprehensive Cancer Center.

Doctors often prescribe proton pump inhibitors or histamine 2 blockers to treat reflux, a common side effect of chemotherapy or radiation treatment for head and neck cancer.

The researchers looked at 596 patients treated for head and neck cancer. Patients who took antacids had significantly better overall survival than those who didn’t take them. Proton pump inhibitors, which include drugs like Prilosec, Nexium and Prevacid, had a 45 percent decreased risk of death, compared to patients who didn’t take antacids. Patients taking histamine 2 blockers, such as Tagamet, Zantac or Pepcid, saw a 33 percent decreased risk. The researchers, led by Silvana Papagerakis, M.D., Ph.D., research assistant professor of otolaryngology-head and neck cancer, have begun additional work to understand why the cancer is affected and if using antacids in people with reflux disease or people with precancerous lesions might reduce their risk of developing head and neck cancer. — NF

In the School

Internet Connections

Massive open online course creates new learning opportunities for medical students

THE MEDICAL SCHOOL HAS EXPANDED

its curriculum to include a massive open online course, or MOOC, that offers students more exposure to health policy education and inter-professional learning. "Understanding and Improving U.S. Healthcare: Special U-M Student Edition," launched in January and was the university's first residential MOOC. It was offered exclusively to U-M students instead of the global audience of MOOCs offered through Coursera, an online education platform that partners with top universities to offer free courses. U-M was one of the first universities to offer courses on Coursera upon its 2012 launch.

Though the U-M MOOC is now required for medical and dental students, it was open to students in every discipline across all three U-M campuses at no cost. More

than 800 students enrolled in the six-week course, adapted from a successful global MOOC created by Matthew Davis, M.D., professor of pediatrics and communicable diseases and of internal medicine.

"Medical School leadership asked me to think about how to expand the health policy education experience for students in response to students' requests for more exposure to these topics," says Davis, also a professor of health management and policy at the School of Public Health and professor of public policy at the Gerald R. Ford School of Public Policy. "Providing the course online allowed us to bring additional content into the curriculum in an asynchronous learning format that gives students more flexibility in the amount of time they spend with the material and when."

Davis developed the course in partner-

ship with Michael Rubyan, a School of Public Health doctoral student with experience in documentary filmmaking. To create the course content, they filmed brief lectures, and produced mini documentaries on policy reform and newsmagazine-style Web episodes featuring interviews with faculty from the Medical School, School of Public Health, School of Dentistry, School of Social Work and the School of Public Policy. The students had an hour of materials to view online each week, and an additional hour of reading, reflection on course material and posting commentary in the online discussion forums. They also adapted a simulation game developed by Susan Goold (M.D. 1987, Residency 1990, Fellowship 1992), professor of internal medicine, in which students design their own health plans. Additionally, students met for a 90-minute in-person session during week five of the course.

"Usually a MOOC would not include an in-person session," Davis says. "But we wanted to make this a uniquely U-M experience for the students to meet other students from many different schools and colleges at U-M."

Students who completed the residential MOOC reported high engagement with the online learning materials and the in-person classroom session.

"We know from surveys the students completed before and after course, that they were substantially more confident in their knowledge of core principles of the U.S. health care system and more optimistic about the possibility of positive changes to the system occurring in the future," Davis says.

Davis will continue to deliver the residential MOOC during the 2015-2016 academic year. — ALLISON WILSON



U-M Helps Career Changers Apply for Medical School

A NEW PROGRAM AT THE MEDICAL

School offers college graduates from non-science disciplines the training to become strong candidates for medical school.

This 14-month, non-degree post-baccalaureate program, called Postbac MEDPREP, launched in May with a pilot cohort, and will begin accepting applications in August for the 2016 entering class. It provides science coursework from U-M faculty, taken with a group of peers; dedicated faculty advisors and support for application to medical school; and experiential learning opportunities in the U-M health care environment. MEDPREP also includes a “Foundations for Aspiring Physicians” course and in-depth preparation for the MCAT and admissions process. Every participant will come out of the program ready to apply to U-M or other top medical schools nationwide, says program director Matthew Wishart, Ph.D. High-performing participants may even be chosen to apply for accelerated “linkage” admission to medical school while still taking part in Postbac MEDPREP, allowing them to become medical students soon after completion.

“This is the ideal program for a motivated non-science graduate who is ready for an intensive program at a high level,” Wishart says. “We’re especially interested in those who have already sought experiences to help and serve others, and who are committed to begin formal preparation for a career in medicine.” — KG



U-M Part of National Program to Train Doctors and Nurses Together

THE U-M IS ONE OF FOUR UNIVERSITIES LAUNCHING AN INITIATIVE TO educate nurses and physicians together to lead policy-relevant health services research and encourage partnerships to improve health care.

The U-M joins the University of California, Los Angeles, the University of Pennsylvania and Yale University in the National Clinician Scholars Program. At U-M, the program will be based in the Institute for Healthcare Policy and Innovation and will be called the IHPI-CSP Program. The program fills the gap left after the Robert Wood Johnson Foundation, or RWJF, announced in 2014 that it will end its Clinical Scholars program for physicians.

The IHPI-CSP Program expands on the RWJF program by including nurse scientists, in addition to physicians, to address new and emerging issues related to health care delivery and improving community health.

The program will include those who have completed their medical degree and residency training, Doctor of Nursing Practice training, or Ph.D. in nursing. The first cohort will begin the program on July 1, 2016. — KG

Alan Alda visits U-M

ACTOR, WRITER AND DIRECTOR ALAN ALDA RECENTLY VISITED THE MEDICAL School to present a pilot communication workshop to a crowd of U-M physicians, medical students, scientists and other clinicians. Through the Alan Alda Center for Communicating Science at Stony Brook University in New York, Alda and the center’s staff work with medical schools around the country to help scientists and health professionals communicate more effectively with the public. The U-M workshop featured interactive sessions focused on crafting a story and using improvisational techniques to inspire effective communication.

