In the Lab

Potential Options for Triple-negative Breast Cancer

Study sheds light on link between cancer stem cells and inflammation


Max Wicha

NEW RESEARCH FROM COLLABORATING scientists at the U-M Comprehensive Cancer Center and Georgia Regents University Cancer Center finds that a protein that fuels an inflammatory pathway doesn't turn off in breast cancer, resulting in an increase in cancer stem cells. The finding provides a potential target for treating triple-negative breast cancer, the most aggressive form of the disease.

The researchers identified SOCS3, a protein highly expressed in normal cells but undetectable in triple-negative breast cancer. They showed that this protein is degraded in cancers, blocking the cellular off-switch of a feedback loop involving the inflammatory protein interleukin 6, or IL-6. When the switch doesn't get turned off, it enables cancer stem cells to grow.

"We've known for a long time that there are important links between inflammation and cancer, including similar pathways that regulate normal and cancer stem cells," says study author Max S. Wicha, M.D., Distinguished Professor of Oncology and director of the Comprehensive Cancer Center. The study appears in the journal *Oncogene*.

"This work helps explain why these pathways shut off in normal tissues after injury but remain active in cancers, resulting in an increase in cancer stem cells. Furthermore, they suggest that blocking these inflammatory loops may be a means of targeting cancer stem cells, improving patient outcome," Wicha says.

Currently, there are no molecularly targeted therapies aimed at triple-negative breast cancer, which is a type of cancer negative for estrogen receptor, progesterone receptor and the HER2 protein — all key targets for current therapies. Patients with this form of disease tend to have worse outcomes.

The researchers tested a drug, bortezomib, in mouse models of triple-negative breast cancer and found that it stops the protein degradation, resulting in the inflammatory loop shutting off. This reduces the cancer stem cells, thereby blocking metastasis. Bortezomib is currently approved for treatment of the blood cancer multiple myeloma.

The research team previously showed that IL-6 can stimulate breast cancer stem cells in HER2-positive breast cancers, and they're designing a clinical trial which uses an IL-6 blocker. The new research suggests that adding bortezomib to the IL-6 inhibitor may be a way to target stem cells in triple-negative breast cancer.

Understanding how inflammation is regulated in triple-negative breast cancer should facilitate translation into clinical care, since drugs used to block these chemical messengers are already approved for the treatment of rheumatoid arthritis and other inflammation-related diseases. More laboratory testing is needed before a clinical trial can begin. The researchers further suspect that this pathway may apply to other cancers as well and also are investigating that potential.

According to the American Cancer Society, 235,030 Americans will be diagnosed with breast cancer this year and 40,430 will die from the disease. —NF

MORE ON THE WEB

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

Decoding Dengue and West Nile

DENGUE FEVER AND WEST NILE FEVER ARE MOSQUITO-BORNE DISEASES that affect hundreds of millions of people worldwide each year, but there is no vaccine against either of the related viruses. A team of scientists at the U-M, along with colleagues at Purdue University, has discovered a protein key to the viruses' replication in the cells of their host and manipulation of the immune system as they spread. The findings supply a target for a potential vaccine or treatment of the viral diseases.

"Seeing the design of this key protein provides a target for a potential vaccine or even a therapeutic drug," says Janet L. Smith, Ph.D., the Margaret J. Hunter Collegiate Professor of Life Sciences in the Medical School's Department of Biological Chemistry and a faculty member in the U-M Life Sciences Institute, who led the team whose paper was published online in *Science*.

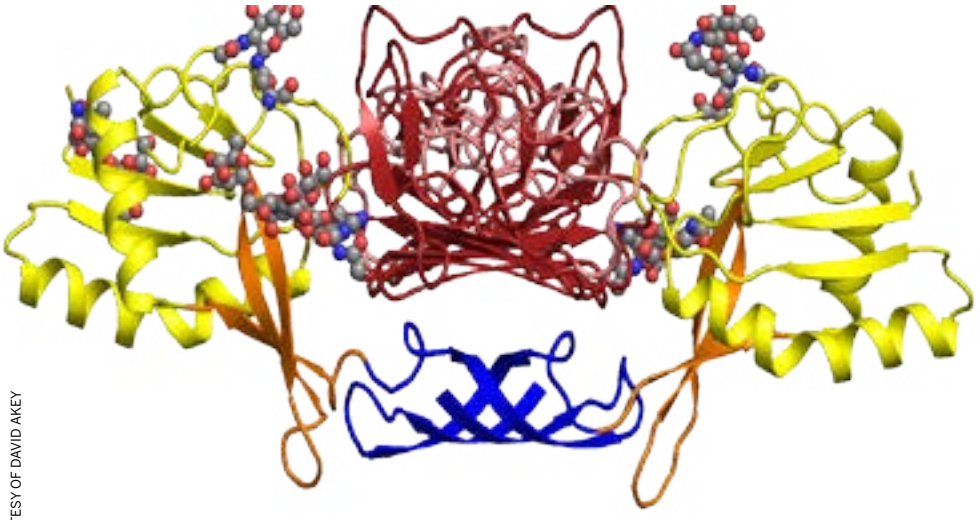
The protein, NS1, is produced inside infected cells, where it plays a key role in replication of the virus. NS1 is also released into the bloodstream, where it may help disguise the infection from the patient's immune system.

Smith and her colleagues created images of the protein using X-ray crystallography, a technique that uses X-ray beams to map the positions of atoms in a crystal.

"We're now collaborating with the Purdue virologists to understand exactly how NS1 helps the virus survive and thrive in patients," she said. "These studies are the next steps toward a vaccine or an antiviral drug."

Dengue and West Nile viruses are members of the flavivirus family, which includes yellow fever and several encephalitis viruses. —KG/LW

MORE ON THE WEB



COURTESY OF DAVID AKEY

NS1 Protein

Quieting Tinnitus' Ring

FOR 50 MILLION AMERICANS there's no such thing as the sound of silence. Even in a quiet room, they hear a constant ringing, buzzing, hissing or humming in their ears. Called tinnitus and caused by hearing damage often associated with excessive noise, the condition can be debilitating and life-altering.

Recent findings published online in *The Journal of Neuroscience* confirm that a process called stimulus-timing dependent multisensory plasticity is altered in animals with tinnitus — and that this plasticity is "exquisitely sensitive" to the timing of signals coming in to a key area of the brain.

Susan Shore, Ph.D., a senior author of the paper and a researcher at the U-M Kresge Hearing Research Institute, explains that in tinnitus, some of the input to the brain from the ear's cochlea is reduced, while signals from the somatosensory nerves of the face and neck, related to touch, are excessively amplified.

Shore — a professor of otolaryngology, of molecular and integrative physiology and of biomedical engineering — and colleagues are working on a device to normalize neural activity in the auditory pathway.

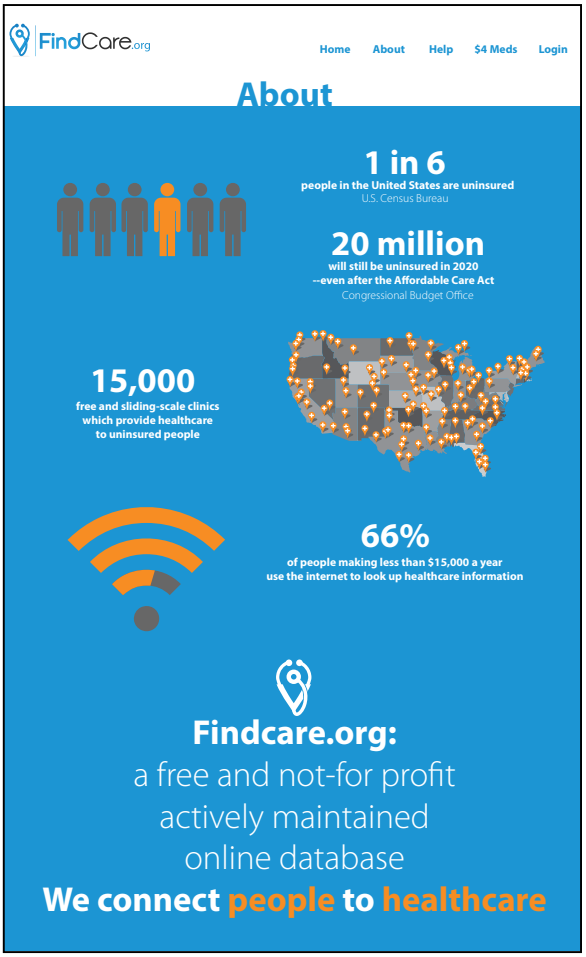
"If we get the timing right, we believe we can decrease the firing rates of neurons at the tinnitus frequency, and target those with hyperactivity," says Shore. —KG

MORE ON THE WEB

In the School

Helping the Uninsured Find Low-cost Care

Students create vital community resource



FINDCARE.ORG — A WEBSITE conceived and created by U-M medical students — went live in mid-April, connecting uninsured Americans with the free and sliding-scale clinics that exist to serve them.

Students Michael Gao, Elizabeth Haworth-Hoeppner and Sarah Akkina began to develop FindCare.org in 2012, when Gao and four of his classmates were in the midst of founding the Medical School's Student Run Free Clinic in Pinckney, Michigan. While researching the need for free clinics and additional health care for people without health insurance, Gao noticed something surprising.

"It took five very Google-savvy medical students two weeks to find all the existing resources in Washtenaw County," he recalls. People who are sick — or harried emergency room physicians and overworked social workers — don't have that kind of time. Gao, Akkina and Haworth-Hoeppner decided to do something about it.

The team was awarded a competitive and coveted Medical Student Service Leadership grant from Alpha Omega Alpha, the national medical honor society. Since then, FindCare.org has grown to involve 30 students and advisory faculty from the U-M schools of Public Health, Information, Social Work and Business, and colleges of Engineering and Pharmacy.

Currently, the site lists 500 clinics in Michigan and another 1,500 in surrounding states. Patients — or referring physicians or social workers — type in their location and a map and list appear showing nearby clinics with contact information, address, hours of operation and services offered. The database of clinics is kept up-to-date through an innovative combination of Wikipedia-like contributions and automated web page monitoring.

The goal is to expand nationwide, constantly updating information, while remaining a not-for-profit entity.

Cyril Grum, M.D. (Residency 1983), sponsored the group's AOA grant application and has watched the project grow from an idea to powerful fruition.

"It's a terrific example of the type of innovation and leadership we see in our students," says Grum, a professor of internal medicine. "We think this is going to be huge — not just for patients locally, but nationally."

The students conducted a survey to determine such a site's potential and found that 63 percent of Americans earning less than $11,500 annually are willing to use the Internet for health care purposes.

Now that the site is live, the students are reaching out to clinics, emergency departments, homeless shelters, public libraries and food banks — organizations often on the front lines of aiding and educating people who have no health insurance. They're hoping FindCare.org becomes an indispensable part of these organizations' interaction with the public.

"It's always been a goal of mine to work for the uninsured and under-represented," says Haworth-Hoeppner. "I'm grateful to the Medical School for the opportunity to help develop this program."

What will happen to FindCare.org when its creators graduate and move on to the rigors of residency? Second-year students Michael Huarng and Sanjana Malviya are already in place and prepared to take the site to the next level and beyond. —WHITLEY HILL

COURTESY OF FINDCARE

AMA-UM Conference Spotlights Medical Education

Left to right:
From the Medical School: Associate Dean for Medical Student Education Rajesh Mangrulkar ; Senior Associate Dean for Education and Global Initiatives Joseph Kolars; Dean James Woolliscroft. From the AMA: Susan Skochelak, group vice president, Medical Education; Richard Hawkins, vice president, Medical Education Programs; Mark Quirk, vice president, Medical Education Outcomes.

ANN ARBOR BECAME THE epicenter for innovation in medical education in April, when dozens of leaders from top medical schools around the country, and from the American Medical Association, joined the U-M's own medical education leaders for a unique conference.

Topics ranged from massively open online courses (MOOCs) to teaching students about health policy and patient safety. Inter-professional education — an approach that brings medical students, nursing students and other health professions students together in the same types of teams they will work in as professionals — featured prominently.

Jointly sponsored by the AMA and the Medical School, the meeting brought together representatives from the 11 schools that have won $1 million grants under the AMA's Accelerating Change in Medical Education challenge. The schools were selected based on their proposals to change medical education through real-world practice and assessments of medical student competency.

The U-M is using its grant to help formulate and implement a new curriculum. Details of the work are online at: curriculum.med.umich.edu. Incoming medical students will begin their education with two years of integrated scientific and clinical experiences, then branch off into their own individualized professional development tracks to cultivate advanced skills in a clinical setting at their own pace. This may allow some students to graduate from medical school sooner. All will receive dedicated leadership training in order to graduate with the capabilities to lead change in health and health care.

"We are committed to paving the way for a new and better health care system in our country by changing the way we educate our medical students," says Joseph Kolars, M.D. (Fellowship 1989), senior associate dean for medical education and global initiatives and Josiah Macy, Jr., Professor of Health Professions Education. —KG

MORE ON THE WEB

Two Medical School Faculty Elected to Institute of Medicine

MEDICAL SCHOOL DEAN JAMES O. Woolliscroft, M.D. (Residency 1980), and cancer genetics expert Eric R. Fearon, M.D., Ph.D., have been elected to the prestigious Institute of Medicine (IOM) of the National Academies, one of the highest honors in the health and medical fields.

Woolliscroft, the Lyle C. Roll Professor of Medicine, is an internist and internationally recognized medical education leader who has devoted his career to improving physician education, and as dean has emphasized education at all levels. A pioneer of rigorous medical education programs in outpatient health care settings, he has published many influential papers about medical student and resident assessment and skills development.

James Woolliscroft

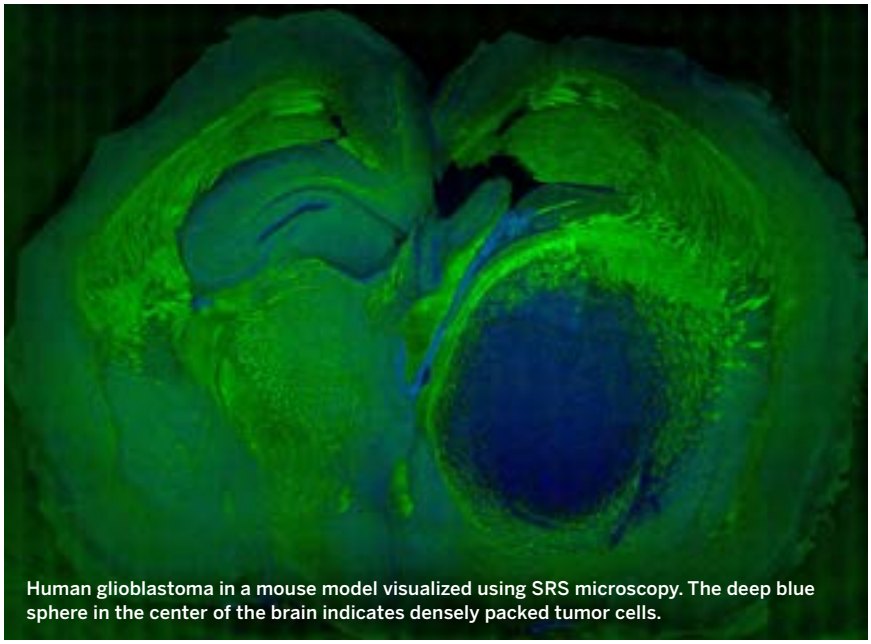
Eric Fearon

Fearon, the Emanuel N. Maisel Professor of Oncology and professor of internal medicine, of human genetics and of pathology, focuses his reasearch on how cancer gene defects contribute to the development and progression of colorectal and other cancers. Fearon is deputy director and associate director for basic science research at the U-M Comprehensive Cancer Center.

With Woolliscroft and Fearon, the U-M claims 53 past and present IOM members. —KG

MORE ON THE WEB

TED GRUDZINSKI, AMA



Human glioblastoma in a mouse model visualized using SRS microscopy. The deep blue sphere in the center of the brain indicates densely packed tumor cells.

COURTESY OF DANIEL ORRINGER

In the Clinic

A New View

A U-M doctor has developed a way to distinguish between tumors and healthy cells

WHEN NEUROSURGEONS OPERATE on malignant brain tumors, the last thing they want is to leave cancer cells behind. Yet to the naked eye, tumor tissue can resemble healthy tissue, and the boundary between them is nebulous. With each millimeter of healthy brain potentially crucial for speech, movement and thought, the stakes couldn't be higher.

A new tool may soon solve the dilemma. Stimulated Raman scattering (SRS) microscopy provides the neurosurgeon with a clear view of the microarchitecture of brain tissue, displaying a stark contrast between tumor and healthy brain. It's harmless, works in real time and doesn't require slides, stains, dyes or MRI.

Daniel Orringer, M.D., (Residency 2011), a clinical lecturer in neurological surgery, introduced human cancer cells into the brains of experimental mice. His team used glioblastoma, a deadly form of brain cancer known for its ragged borders. Using SRS microscopy on mice, they obtained vivid images of individual cells along the tumor margin, making it clear where tumor ended and healthy brain began. They published their results in *Science Translational Medicine*.

SRS microscopy may represent a sea change for neurosurgery, says Oren Sagher, M.D., professor of neurological surgery, Orringer's former mentor, and co-author of the paper. "The potential here is for something that will totally change how we look at our patients in the OR and how we treat them," Sagher says.

SRS microscopes direct laser light at the tissue, which it absorbs in a unique way, depending on its chemical makeup. Proteins and lipids absorb energy at slightly different wavelengths. With tightly packed cells containing relatively large nuclei, cancerous regions are rich in protein, while healthy brain tissue is relatively lipid-rich. Color-coding these spectral differences results in stunning images.

Without magnification to reveal the telltale traits of tumor cells, surgeons have traditionally had to rely on fuzzy visual cues like texture and vascularity to decide where to cut. "To your eye, to my eye, everything looks like tan bits of tissue," Orringer says. "I really felt uncomfortable with the lack of precision."

Using MRI to map the tumor revolutionized neurosurgery in the 1990s. Still, that map loses accuracy as surgery proceeds and brain tissue shifts. Another method is to dye the tissue, but that, too, can be problematic.

So, Orringer looked for a better way. In 2009, he accompanied Martin Philbert, dean of the U-M School of Public Health, to a conference in Stockholm. Orringer was then experimenting with nanoparticles to delineate tumor borders. As luck would have it, his poster stood beside that of Harvard physicist Christian Freudiger, who had recently refined SRS microscopy and was on the lookout for "killer apps." The two got to talking and soon agreed to collaborate. For Orringer, looking at the first SRS images of a tumor margin was a "Eureka!" moment.

Funded by the Michigan Translational Research and Commercialization Program, Orringer's group is working with Freudiger's startup company, Invenio Imaging, Inc., to miniaturize SRS microscopy. The team envisions a pen-sized device that a surgeon can touch to brain tissue; its images will appear in real time on an operating-room screen.

The promise of SRS microscopy goes beyond illuminating malignant brain tumors. It should also help demarcate head and neck, gynecologic and other cancers where precision is crucial, as well as guiding local chemotherapy or radiation. In a fiber-optic version, it may make biopsies more precise. And it should allow for more robust research into the poorly understood tumor margin.

The team expects to test a prototype in the U-M's operating rooms by the end of 2014. In the meantime, word is getting around. "The enthusiasm for this technology is palpable," Orringer says. "There's not a surgeon who I've spoken to who says that they wouldn't want something like this." —JENNY BLAIR

Blood Transfusion Overuse Ups Infection Risk

BLOOD TRANSFUSIONS ARE ONE of the most common procedures in hospitals, but the more red blood cells patients receive, the greater their risk of infection, according to a study led by the U-M Heath System and VA Ann Arbor Healthcare System.

Researchers analyzed 21 randomized controlled trials for the study that appeared in the April 1 edition of *The Journal of the American Medical Association*. The authors evaluated all health care-associated infections that were reported after receiving donor blood in the randomized trials. These included serious infections such as pneumonia, and bloodstream and wound infections.

"The fewer the red blood cell transfusions, the less likely hospitalized patients were to develop infections," says lead author Jeffrey M. Rohde, M.D., assistant professor of internal medicine in the Division of General Medicine. "This is most likely due to the patient's immune system reacting to donor blood, known as transfusion-associated immunomodulation. Transfusions may benefit patients with severe anemia or blood loss; however, for patients with higher red blood cell levels, the risks may outweigh the benefits."

Elderly patients undergoing hip or knee surgeries were most susceptible, with a 30 percent lower risk of infection when fewer transfusions were used. Overall, for every 38 hospitalized patients considered for a red blood cell transfusion, one patient would be spared a serious infection if fewer transfusions were used. —BM

Finding a Michigan Physician — Anywhere

SOMETIMES, YOU DON'T JUST WANT A DOCTOR; YOU WANT A U-M doctor, someone who earned a medical degree or trained here in a specialty. Sharing a common experience — like the U-M — can be especially important when it comes to matters of health.

Until recently, Michigan alumni had no reliable way to search for a Michigan-trained physician near them. But in 2012, Medical Center Alumni Society president Stephen Papadopoulos, M.D. (Residency 1988), changed that with the help of a physician-networking website known as Doximity.

"Doximity is like LinkedIn, but just for physicians," explains Papadopoulos, chief medical officer and executive vice president at the Barrow Neurological Institute in Phoenix, Arizona. "The site has spent a lot of effort aggregating physician profiles from public information. It occurred to me that they had the best database of American physicians anywhere."

With the cooperation of the Alumni Association of the University of Michigan, Papadopoulos approached Doximity about developing a way for U-M alumni — about 500,000 strong — to search for Michigan physicians near them. Today, a link on the Alumni Association website allows members to find basic background and contact information for Michigan doctors in all specialties who practice in their geographic area.

Papadopoulos says his idea sprang from a reality many physicians share: friends and family members calling him for referrals in their area. Whenever possible, he skews Blue. "You meet a new doctor and you immediately have something in common," he says, "and that's Michigan."
—WH


Stephen Papadopoulos

COURTESY OF STEPHEN PAPADOPOULOS

MORE ON THE WEB

In the Clinic

Device Helps Essential Tremor Patients

FOR PEOPLE WHOSE HANDS SHAKE UNCONTROLLABLY DUE TO A MEDICAL condition, just eating can be a frustrating and embarrassing ordeal — enough to keep them from sharing a meal with others.

But a new study conducted at the U-M suggests that a new handheld electronic device can help such patients overcome the hand shaking caused by essential tremor, the most common movement disorder. In a clinical trial involving 15 adults with moderate essential tremor, the device improved patients' ability to hold a spoon still enough to eat with it.

The results are published online in the journal *Movement Disorders* by a research team that includes U-M neurologist and essential tremor specialist Kelvin Chou (M.D. 1998) who is the Thomas H. and Susan C. Brown Early Career Professor of Neurology, as well as three scientist-engineers from the small startup company Lift Labs, which makes the device. The company's CEO, Anupam Pathak, Ph.D., received his doctorate from the U-M College of Engineering.

The concept behind the technology is called ACT, or active cancellation of tremor. It relies on tiny electronic devices that work together to sense movement in different directions in real time, and then make a quick and precise counter-motion.

The trial, Chou says, showed that the amplitude of movement due to the tremor decreased measurably. "Compared with other devices designed to limit tremor by weighting or constraining limbs, this approach allows movement and is easier to use." —KG

MORE ON THE WEB

Smaller, Smarter Cardiac Monitoring

THE U-M SAMUEL AND JEAN FRANKEL CARDIOVASCULAR CENTER IS ONE OF THE first hospitals to use the Medtronic Reveal LINQ Insertable Cardiac Monitor (ICM) System, the smallest implantable cardiac monitoring device available. The wireless device provides long-term remote monitoring to help diagnose and monitor irregular heartbeats.

Conventional monitors attach to the outside of the body for between 24 hours and 30 days, have visible wires and are often associated with skin irritation and rashes — limiting compliance. Smaller than a key, the new Reveal LINQ ICM is inserted just beneath the skin in the upper chest area, and continuously records heart rhythms over long periods of time.

"The amount of data generated by the device allows us to more accurately correlate what a patient describes they are feeling with their specific rhythm," says Eric Good, D.O., assistant professor of internal medicine and electrophysiology specialist at the U-M. "As a result, it improves our ability to tailor a treatment plan to address their unique heart issue."

MORE ON THE WEB

Second Baby Saved by 3-D-printed Device

IN HIS 18 MONTHS OF LIFE, Garrett Peterson has never gone home, spending his days in hospital beds tethered to ventilators that even at the highest settings couldn't prevent his breathing from periodically stopping. His condition, known as tetralogy of Fallot with absent pulmonary valve, was so tenuous that often his parents could not hold him for fear of compromising his breathing.

But after surgeons at the University of Michigan's C.S. Mott Children's Hospital implanted 3-D printed devices to open Garrett's airways, his parents are now planning to take their son home to their house in Utah for the very first time.

Garrett is just the second person whose life was saved with a new, bioresorbable device developed at the University of Michigan by Glenn Green (M.D. 1991), associate professor of pediatric otolaryngology and Scott Hollister, Ph.D., professor of biomedical engineering and mechanical engineering and associate professor of surgery at U-M. —MM

MORE ON THE WEB

Scott Hollister (left) and Glenn Green (right)

TOP: COURTESY OF LIFT LABS
BOTTOM: JULIET FULLER, UMHS