OUT OF THE WOODS

Groundbreaking hepatitis C drug combination saves liver transplant patient Robert Gholston

ALSO:
IVC Filter Recommendations
High-Risk Prostate Cancer
Neuroscience Breakthroughs
Intraoperative MRI
On the cover: Robert Gholston received an investigational drug regimen that resolved his hepatitis C after a liver transplant.

TECHNOLOGY

An app with nerve

What can a gingerbread man teach physicians about nerve pathways and their connection to specific symptoms? A lot, it turns out.

The human-shaped cookie stands in for a real patient in a new app for iPhone and iPad developed by U-M neurologists to teach neuroanatomic pathways.

Enter the symptoms, such as weakness and numbness, and the neuroanatomic pathways are drawn out for you. As you add more signs, Neuro Localizer will show you where the pathways overlap in the central or peripheral nervous system.

ONLINE

The app is free and available in the iTunes app store. Learn more at umhealth.me/neuroloc.

AED EDUCATION

University of Michigan joins nationwide effort to teach proper use of devices

Although more and more schools are realizing the need for AEDs on campus, just purchasing a machine is not enough. Students, teachers and other school personnel need to be prepared to quickly and efficiently respond to a sudden cardiac arrest (SCA). To address this need, the University of Michigan has become an affiliate of Project ADAM, a nationwide initiative named for Adam Lemel, who died of an SCA on a high school basketball court. The project’s goal is to facilitate education about the appropriate use of an AED.

“Over the years, we’ve seen too many children die or suffer neurological impairment from an SCA, who might have been helped if schools were better prepared,” explains Monica Goble, M.D., pediatric cardiologist and medical director of Project ADAM Michigan. “Our goal is to help schools be prepared, not just in athletics, but anywhere on school grounds. By doing this, not only are we preparing for the next emergency, but we empower students and teachers to act if they witness an event outside school or later in life.”

U-M offers a wide variety of support, guidance, training materials and access to resources for community physicians who wish to help facilitate this education in their local schools. “Contact your local school(s), and see where they are in the process of AED education,” advises Goble. “We here at U-M are eager to partner with physicians to bring these resources to the community to help support these important efforts.”

INFORMATION

For more information about Project ADAM, and how U-M can help your community be prepared for an SCA event, visit mottchildren.org/projectadam.

For each minute that passes as sudden cardiac arrest occurs, the chance of survival falls by 10 percent. With an AED on-site, school responders can immediately attempt to save a life.
The mouse on the left received amlexanox and was fed the same diet as the mouse on the right.

OBESITY STUDY
NOW RECRUITING

Researchers are ready to test on humans a drug showing dramatic results in mice

The drug amlexanox, an asthma and canker sore medication, has been shown by U-M researcher Alan Saltiel, M.D., and colleagues, to inhibit two genes that play a role in metabolism and fat-burning in mice. The drug lowered the weight of obese mice and reversed related metabolic problems such as diabetes and fatty liver in both genetic and dietary-induced obese mice. These findings were published this past February in the journal *Nature Medicine*.

To determine if the drug may have the same effect on humans, Elif Oral, M.D., associate professor of Internal Medicine in the Division of Metabolism, Endocrinology & Diabetes (MEND), is seeking 10 people with type 2 diabetes or obesity and evidence of central obesity (belly fat) for phase I of a study.

If the drug works in humans, according to Oral, “This would mean that there is a completely different drug available for people that has a completely different mechanism of action in the body. If this drug can address weight and diabetes — as well as inflammation — without causing major side effects, this would be a huge innovation!”

ONLINE To link to the journal article about the mouse study and for more information about the human study, including eligibility guidelines, visit Colleagues in Care Online at med.umich.edu/cic. You may also contact Adam Neidert at 734-615-0539 or aneidert@med.umich.edu for more information.

RESEARCH

Big Ten big news

Big Ten Cancer Research Consortium formed

In athletics, the Big Ten universities compete against each other, but now many will join together against a common foe — cancer.

Leaders from the University of Michigan Comprehensive Cancer Center and other Big Ten universities’ cancer centers have formed the Big Ten Cancer Research Consortium to transform cancer research through collaborative oncology trials that leverage the scientific and clinical expertise of the Big Ten universities.

“For research to be truly impactful, we must work together. Collaborating with other institutions gives us another opportunity for a broader and deeper brain trust while allowing implementation of novel ideas in a more representative patient population,” says Maha Hussain, M.D., FACP, associate director of clinical research at the University of Michigan Comprehensive Cancer Center.

The clinical trials that will be developed will be linked to molecular diagnostics, enabling researchers to understand what drives the cancers to grow and what might be done to stop them from growing.

ONLINE The consortium will lead to a larger pool of clinical trials available to U-M Comprehensive Cancer Center patients. Get linked to a list of cancer clinical studies that could benefit your patients at med.umich.edu/cic.
A camera system transmits images to the prosthesis.

**OPHTHALMOLOGY**

**The bionic eye**

Retinal implant restores partial vision and mobility

Physicians now have something to offer patients with end-stage retinitis pigmentosa (RP), a degenerative eye disease that causes slow but progressive vision loss and, ultimately, blindness. The U-M Kellogg Eye Center is one of 13 centers nationwide to offer the Argus® II Retinal Prosthesis System, an FDA-approved retinal implant that allows patients to perceive light and shapes.

The device is an epiretinal (on the inner retinal surface) prosthesis surgically implanted in one eye. After surgery, the patient wears glasses equipped with a camera system that transmits images to the prosthesis, which uses electrodes to relay images to the optic nerve and on to the brain.

“This is a breakthrough for patients with advanced RP,” says Kellogg retina surgeon Thiran Jayasundera, M.D. “The implant will bring light back into these patients’ worlds, allowing them to detect shapes of people and objects in their environment.”

**REAL-TIME RESULTS**

**Intraoperative MRI increases accuracy, decreases risks**

Intraoperative MRI technology that provides real-time patient assessment during surgery is now available for both adult and pediatric patients at the University of Michigan. U-M is the only hospital in Michigan bringing intraoperative MRI (iMRI) technology to the patient on the operating table. This allows for the surgical field to remain intact and avoids the need to move or reposition the patient, which increases accuracy and lowers the risk of injury.

“I-MRI technology is particularly advantageous in brain and spinal cord tumor resections, as this technology can show the exact interface between healthy neurological tissue and a tumor during the surgery,” explains Hugh Garton, M.D., pediatric neurosurgeon at U-M’s C.S. Mott Children’s Hospital. “This can decrease the necessity of performing a partial resection or intentionally leaving tumor tissue behind in efforts to protect vital neurologic structure adjacent to the tumor.”

iMRI uses standard MRI infrastructure that is deployed on rails mounted from the ceiling. These rails surround a stationary operating table, allowing maintenance of the surgical field during the procedure. Patients can be scanned, treated percutaneously or surgically, and scanned again to verify treatment — without ever moving the patient or the operating table.

iMRI technology also has other benefits. For instance, during the removal of large tumors, significant shifts occur in brain tissue, limiting the accuracy of preoperatively acquired images. “The real-time visualization of the operative site with iMRI identifies both residual tumor and its relationship to the surrounding brain, improving our ability to distinguish tumor margins and allowing immediate modification of the surgical plan as needed,” says Garton. “Even with large tumors, this reduces the need for re-operation.”

Although iMRI technology has been available for some years, the first-generation machines were extremely bulky and image quality was often inadequate for the fine detail required when performing brain, spinal cord or other delicate procedures. “This technology at U-M is giving a wide range of surgical specialists — including in neurosurgery, neurology, neuro-oncology, radiation oncology, otolaryngology and ophthalmology — new tools to improve patient outcomes, reduce the risk of injury and eliminate the need for reoperations,” says Garton. “We are already exploring all the ways that the iMRI can help improve patient outcomes in a variety of procedures beyond tumor resection surgery at U-M.”

**WATCH** Learn more about iMRI at U-M and watch a video demonstration at uofmhealth.org/imri.

**CALL** Find out more by calling the Kellogg Eye Center Retinal Dystrophy Clinic at 734-763-2280 or emailing retina-implant@umich.edu.

**WATCH** See a video about the bionic eye and learn about eligibility requirements on Colleagues in Care Online at med.umich.edu/cic.
Out of the woods

Groundbreaking hepatitis C drug combination saves liver transplant patient

"If God wanted to test me, I was ready. I said, let me be the guinea pig for the human race. Put me in a medical journal. Just let me help somebody else."

Robert Gholston
When he was just nine years old, Robert Gholston was in a car accident and received a blood transfusion. It may have saved his life, but likely infected him with a disease that he wouldn’t discover for years.

Gholston was a consistent blood donor until the late 70s, when the Red Cross started screening blood products for the hepatitis C virus. The healthy 29-year-old was shocked to learn he had hepatitis C.

The usual drug treatments for hepatitis C didn’t work too well for Gholston, and by 2011 he got so sick that his only option was a liver transplant.

A NEW LIVER, THEN A NEW LEASE ON LIFE

After receiving that transplant, he met with Robert Fontana, M.D., at the University of Michigan, who had some grim but not expected news: A new liver doesn’t stop the hepatitis C virus. It could come back.

Within six months, hepatitis C was aggressively attacking Gholston’s new liver. But Fontana, professor of Internal Medicine and medical director of Liver Transplantation, offered Gholston some hope: a new oral drug regimen never tried before.

Fontana wanted to pursue using a combination of sofosbuvir and daclatasvir combination therapy, an interferon-free, all oral regimen. The drugs were co-administered for 24 weeks. Within four weeks of initiating the treatment, serum HCV RNA levels were undetectable and liver biochemistries normalized.

Gholston is now hepatitis C-free. He is 59, lives in Troy, Mich., with his wife, and works as a durability test driver/trainer at General Motors. He’s a father of eight, grandfather of eight and walks five miles a day.

“I hope this provides hope for others in this situation,” says Gholston, who also has had diabetes and coronary artery disease. “I feel great.”

Fontana says it definitely does. The case was published in the American Journal of Transplantation in January 2013.

GREAT PROMISE

“The rapid and sustained suppression of hepatitis C in Mr. Gholston provides great promise for the use of these combination oral antiviral regimens in other transplant recipients,” says Fontana. “Recurring hepatitis C is very challenging to manage and this shows there is a safer and more effective treatment option.”

Hepatitis C is the leading indication for liver transplantation in the United States and many parts of the world. However, patient survival is significantly lower in patients with hepatitis C compared to other recipients, due in part to the inevitable recurrence of hepatitis C infection.

“This case illustrates that the use of potent oral antiviral agents such as daclatasvir and sofosbuvir, even early after transplantation, offers great promise to the many HCV patients worldwide who are experiencing reduced quality of life and survival because of recurrent infection,” Fontana says.

There’s an urgent need to develop better therapies for liver transplant recipients to combat the recurrence of hepatitis C. According to the Annals of Internal Medicine, by 2007, hepatitis C had superseded HIV as a leading cause of death in the United States, and deaths from hepatitis C and hepatitis B disproportionately occurred in middle-aged persons. It is a growing, serious health problem among aging baby boomers.

A THANKFUL PATIENT

Gholston is thankful for yet another second chance at life. He said he was never too anxious about trying a new drug combination: “Dr. Fontana said no one else has ever taken it, but I knew I didn’t have another choice. But with every step, Dr. Fontana was so calm with it. And me being a man of faith, I think what God is going to do, God is going to do. I really had peace with it.”
Marie Janus wasn’t supposed to get this sick. She was just 22 years old and had a newborn along with an active two-year-old.

But she got news she never expected: Her liver was failing fast, and she ended up at U-M, needing a liver transplant. Janus represents a milestone for U-M, as the 2,000th liver transplant recipient for the program, which began in 1985. No other hospital in Michigan, and only a handful in the country, has done that many liver transplants.

“We are proud of this milestone, but even prouder that we were able to help Marie get back her health and return to her family. Her case illustrates the amazing team effort it requires to take a critically ill patient quickly from a life-threatening illness through transplant and back to health,” says Christopher Sonnenday, M.D., surgical director of Liver Transplantation at U-M and the surgeon who performed Marie’s operation.

Watch a video about Marie’s experience at Colleagues in Care Online at med.umich.edu/cic.

Gholston is trying to give back, and has established a close relationship with the family of his donor, playing Santa Claus to the donor’s son and planning for camping trips. Gholston, who is African-American, has been active with promoting organ donation awareness among minorities through Gift of Life Michigan and its Detroit Minority Organ Tissue Transplant Education Program (MOTTEP).

“Every single day I think about that donor, and I am grateful for that gift and the chance to be healthy that this treatment gave me. I really hope it helps others,” says Gholston.

Worldwide, more than 170 million people are estimated to have hepatitis C, most without yet knowing it.
More inferior vena cava filters, cage-like devices that catch blood clots and prevent them from reaching the lungs, are being implanted in patients than ever before. Some patients will require the long-term protection provided by the filter from potentially deadly pulmonary embolisms, but others only require a short-term safeguard. It is for treatment of the latter group that retrievable filters were developed. They can be removed when the patient no longer needs the protection the filter provides.

John Rectenwald, M.D., M.S., associate professor of surgery and radiology at the University of Michigan Medical School, led the creation of the first prospective national IVC filter registry and offers recommendations about the ongoing care of the thousands of patients implanted with IVC filters each year.

“There’s concern that these IVC filters, intended for retrieval, are not always removed once a patient’s risk for PE is over,” Rectenwald says. “In real-world use, much less than 50 percent of retrievable filters are actually removed as intended.”

Known potential complications of IVC filters are recurrent deep vein thrombosis and pulmonary embolism, filter migration, caval perforation, wire entanglement, and device fatigue and fracture.

DATA IS LACKING

“Retrievable filters are designed for retrieval and may be at increased risk for fracture and migration,” says Rectenwald, a vascular surgeon at U-M Frankel Cardiovascular Center. “All retrievable filters were first approved for permanent placement, but data on these filters’ long-term performance is lacking.”

Implanting physicians and clinicians responsible for the ongoing care of patients with IVC filters, including interventional radiologists, interventional cardiologists, vascular surgeons, emergency room physicians, bariatric surgeons, orthopedic surgeons and primary care physicians, are urged to take a second look at their use of IVC filters and avoid the use of prophylactic IVC filters whenever possible.

IVC filter use has skyrocketed since 1979 when 2,000 of them were implanted. By 2007, almost 167,000 filters were implanted and the market for filters is only expected to increase. Today an estimated 267,000 IVC filters are deployed annually.

PERMANENT OR RETRIEVABLE?

“Retrievable IVC filters are attractive in the patient with a well-defined, short-term risk for VTE who cannot tolerate anticoagulation,” says Rectenwald. “But if the responsible physician does not intend to remove a filter, then I believe a permanent filter should be placed.”

More than 10 permanent and retrievable IVC filters are on the market in North America, and their use is intuitive, he says. The filters are intended to be used in patients who have deep venous thrombosis or PE and have a contraindication to anticoagulation, or in patients who hemorrhage while anticoagulated for DVT.

He notes that filters are useful for preventing pulmonary embolisms — risk factors include history of DVT, having surgery or certain orthopedic fractures, certain diseases or conditions such as hemorrhagic stroke, profound paralysis, right heart failure or severe pulmonary hypertension — but the devices do not treat the underlying DVT.

“The spirited debate concerning which patient should get which type of filter is just beginning,” says the UM vascular surgeon. “More prospective, randomized trials evaluating optional retrievable filters are needed to answer these important questions.”

John Rectenwald, M.D., M.S., FACS, led the creation of the nation’s first IVC filter registry.
Targeted treatment

New ‘high-risk’ prostate cancer clinic

The U-M Comprehensive Cancer Center has started a new clinic focused on men with “high-risk” prostate cancer.

The clinic brings together experts in urology, medical oncology, radiation oncology and pathology to review cases together, discussing each patient’s unique factors and agreeing on the best treatment plan. Patients also receive free cancer genome sequencing along with several recently-introduced predictive genetic tests. Clinical trials are offered when appropriate.

“While prostate tumors may look the same from one patient to the next under a microscope, they may behave quite differently. This kind of behavior is driven largely by the genetic sequence of the cancer,” says Ganesh Palapattu, M.D., FACS, director of Urologic Oncology and director of the new High-Risk Prostate Cancer Clinic at the U-M Comprehensive Cancer Center.

The clinic also offers survivorship services to help patients and their families deal with the challenges that go along with a cancer diagnosis.

M-LINE To refer your patient for an appointment with the High-Risk Prostate Cancer Clinic, call M-LINE at 800-962-3555.

New clinical trial tests targeted genetic prostate cancer treatment

A new randomized phase 2 clinical trial will test whether targeting treatments to a genetic anomaly can lead to more successful treatment for prostate cancer. The trial, led by investigators at the University of Michigan Comprehensive Cancer Center, is being conducted at 12 sites throughout the country. The trial is focused on patients with castration-resistant metastatic prostate cancer.

Patients must undergo a biopsy of a metastatic site as the first step in participating, so researchers can test the tumor for the TMPRSS2:ERG gene fusion, a genetic anomaly in which two genes fuse together to create a hybrid gene. This fusion, which occurs in more than half of all prostate cancers, is believed to cause the cancer.

Trial participants will be stratified based on their gene fusion status. All participants will receive the standard hormone-based therapy abiraterone.

Each group — gene-fusion-positive and gene-fusion-negative — will then be randomized so half of participants will also take an experimental PARP-1 targeted therapy called ABT-888, in addition to abiraterone.

“We hope this study will help us understand why certain patients respond to therapy and certain patients do not,” says the study’s principal investigator, Maha Hussain, M.D., professor of Internal Medicine and Urology, and associate director of Clinical Research at the U-M Comprehensive Cancer Center.

M-LINE To refer your patient for an appointment with the High-Risk Prostate Cancer Clinic, call M-LINE at 800-962-3555.

REFER For information about referring your patients to this trial, “A Randomized Gene Fusion-Stratified Phase 2 Trial of Abiraterone with or without ABT-888 for Patients with Metastatic Castration-Resistant Prostate Cancer,” call M-LINE at 800-962-3555.
The findings were made using a technique that could be called “epilepsy in a dish.” By turning skin cells of epilepsy patients into induced pluripotent stem cells, and then turning those stem cells into neurons, the team created a miniature testing ground for epilepsy research.

In neurons derived from the cells of children who have the infantile-onset form of epilepsy called Dravet syndrome, measurements showed abnormally high levels of sodium current activity — including spontaneous bursts of communication and “hyperexcitability” that could potentially set off seizures. Control neurons made showed none of this abnormal activity. The work is published in *Annals of Neurology*. Further work in progress will create stem cell lines for other genetic forms of epilepsy.

Because the cells came from patients, they contained the hallmark seen in most patients with Dravet syndrome: a new mutation in SCN1A, the gene that encodes the crucial sodium channel protein called Nav1.1. That mutation reduces the number of channels to half the normal number in patients’ brains.

“With this technique, we can study cells that closely resemble the patient’s own brain cells without doing a brain biopsy,” says senior author Jack M. Parent, M.D., professor of Neurology. “It appears that the cells are overcompensating for the loss of channels due to the mutation. These patient-specific induced neurons hold great promise for modeling seizure disorders and potentially screening medications.”

**ROOTS OF FRAGILE X ATAXIA FOUND**

A bizarre twist on the usual way proteins are made may explain ataxia symptoms in the grandparents of some children with mental disabilities, according to U-M research recently published in the journal *Neuron*.

The condition, called fragile X-associated tremor ataxia syndrome (FXTAS), causes Parkinson’s-like symptoms, and was first described only a decade ago. It most commonly affects adults who have grandchildren with fragile X syndrome, a genetic
cause of intellectual disability and autism-like symptoms.

The common element in both conditions is a repeated DNA sequence in the FMR1 gene. Now, a U-M research team has discovered that a toxic protein they’ve named FMRpolyG contributes to the death of nerve cells in FXTAS — and that this protein is made in a very unusual way. The FXTAS mutation is a repeated DNA sequence that is made into RNA but normally is not made into protein because it lacks a start codon. However, the investigators discovered that when this repeat expands, it can trigger protein production by a new mechanism known as RAN translation.

Says neurologist and researcher Peter Todd, M.D., Ph.D., “Essentially, we’ve found that a sequence of DNA which shouldn’t be made into protein is being made into protein — and that this causes a toxicity in nerve cells,” he explains. “We believe that the protein forms aggregates, and that this is a contributor to toxicity and symptoms in FXTAS.”

The team also demonstrated that blocking RAN translation prevents the repeat mutation from producing toxic results, suggesting a new target for future treatments. Their discovery could also have significance for other diseases such as amyotrophic lateral sclerosis and certain forms of dementia that are caused by DNA repeats.

Peter Todd, M.D., Ph.D., found a faulty sequence of DNA is made into protein, causing toxicity in the nerve cells.

U-M Neurogenetics clinics

At their heart, many neurological disorders stem from genetic factors. Most can be diagnosed and managed using standard techniques that don’t require genetic testing. But for patients with unusual symptoms or conditions that affect multiple generations of their family, U-M’s Neurogenetics clinics can offer added assistance.

Physicians in U-M’s Neurogenetics Clinic for adults and the Pediatric Genetics Clinic at U-M’s C.S. Mott Children’s Hospital routinely work together to address the needs of families with known and suspected conditions with neurogenetic roots.

U-M’s John K. Fink, M.D., is a world expert on many of these conditions, and has led a number of studies on hereditary spastic paraplegia, a degenerative condition affecting the lower limbs. U-M’s multidisciplinary ataxia Clinic, headed by Vikram Shakkottai, M.D., Ph.D., and Peter Todd, M.D., Ph.D., gives patients with inherited and sporadic genetic conditions caused by cerebellar dysfunction access to the resources of a national clinical research consortium. U-M’s Fragile X Clinic also gives patients access to advanced clinical trials for that family of disorders.

The team offers in-house DNA sequencing, advanced genetic test interpretation, time-intensive symptom evaluation, advanced disease management, customized physical therapy, genetic counseling and social work support. Understanding the inheritance pattern can also help unaffected family members with their own testing and reproduction decisions.

RESEARCH Get linked to more information about these studies, including journal articles, at Colleagues in Care Online at med.umich.edu/cic.

STUDY Find out about neuroscience clinical studies that could benefit your patients at umclinicalstudies.org.

ONLINE For information on U-M Neurogenetics care, visit umhealth.me/neurogenetics