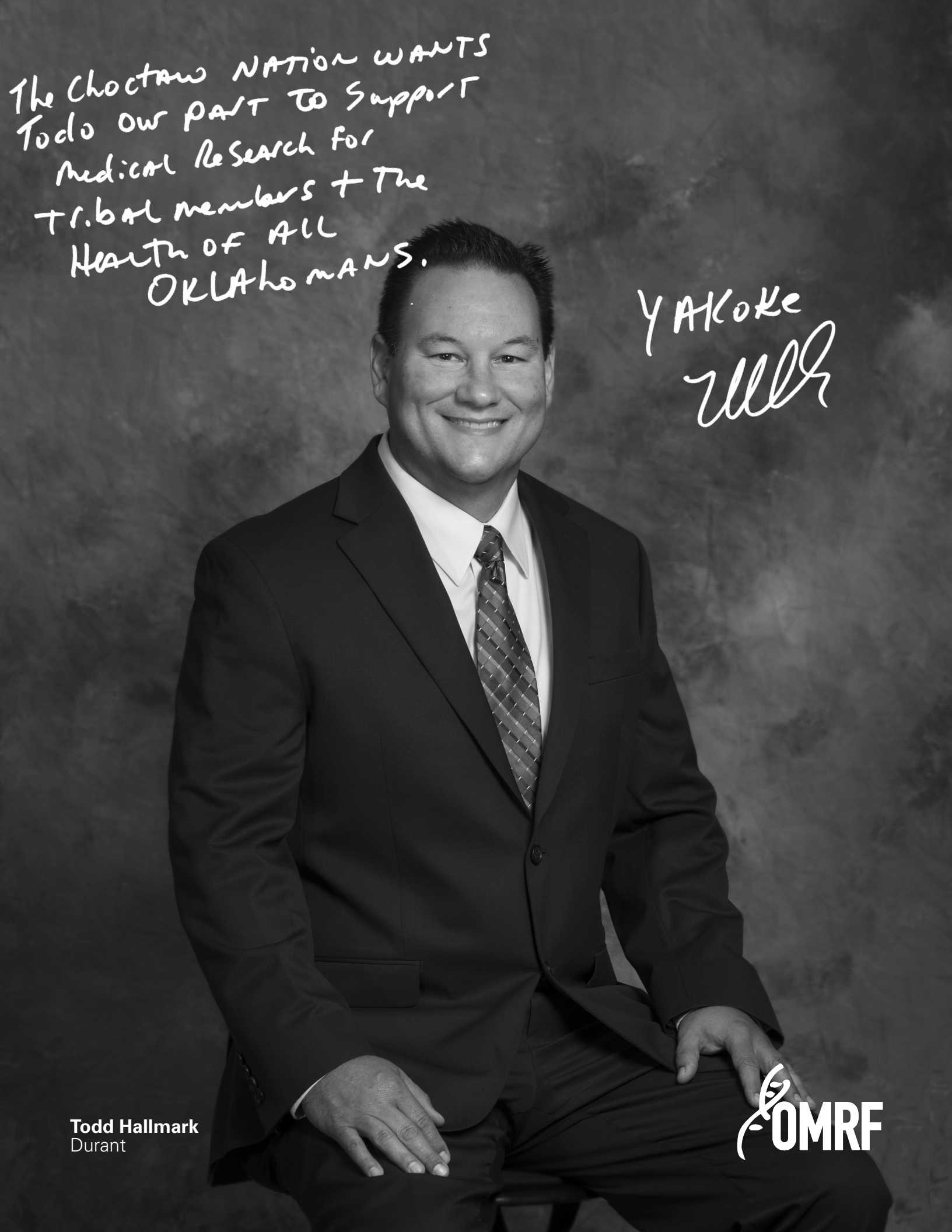
FINDINGS

omrf.org • Summer/Fall 2017

Staying Alive

Can an experimental OMRF drug stop Mike Schuster's brain cancer?



Todd Hallmark
Durant

OMRF

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Summer/Fall 2017

FEATURES

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Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as cancer, diseases of aging, lupus and cardiovascular disease.

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OMRF

Team Jeanne

OMRFers rally around a friend and coworker

The prospect of retirement was looking pretty good to Jeanne Fowler. After 45 years working in OMRF's accounting department, she was counting down the months until she'd spend her days puttering in the garden and taking strolls with her husband, Ed, and their dog.

Then she received a diagnosis of breast cancer.

"Stunned is the only way I can describe it," she says. "The day I got the news was the worst day of my life. The second worst was the day I had to shave my head. My hairdresser and I cried together."

Fowler's hair fell victim to chemotherapy and radiation treatments her doctors prescribed following a lumpectomy. Although the treatments would exact a considerable toll on her body, they came with an unexpected silver lining.

During her first chemotherapy session, Fowler's phone buzzed. When she clicked on the text message, she discovered a photo of 20 coworkers, all wearing pink "Team Jeanne" t-shirts. Even with an I.V. delivering cancer-killing chemicals tethered to her arm, Fowler found herself smiling.

"Jeanne was at her lowest point on that first day of chemo," says Janet Sharpe, a senior accounting clerk at OMRF who, years earlier, had received her own cancer diagnosis. "She needed a big dose of positivity, and we were determined to give it to her."

With Sharpe leading the charge, the effort morphed into an OMRF-wide movement. Sharpe canvassed the hallways, wrangling an ever-growing circle of OMRFers for group and individual photos. Then, on treatment days, dozens of images of pink-clad, smiling colleagues would flood Fowler's phone.

As word spread, more than 100 people bought t-shirts and joined the effort. To keep Fowler smiling, Sharpe had the group take the form of a giant pink ribbon for one photo. For another, she organized a special Bedlam-themed shot for the annual University of Oklahoma-Oklahoma State University football clash.

"I'm almost embarrassed by all the love and support I've had. I feel like the luckiest person in the world."

"Heck, I didn't even know everyone in Team Jeanne personally, but there they were in the photos, smiling and cheering me on," Fowler says. "Somehow, they heard my story and came on board."

Fowler retired from full-time employment in 2017. But she still comes to OMRF occasionally to help out on projects (and go for lunchtime walks with her long-time coworkers).

With her treatments finished, Fowler's hair has grown back. And her doctors have pronounced her cancer-free. Still, Fowler remains understandably cautious. "I'll probably never stop worrying about it," she says. "Now, I'll focus on making the five-year mark."

Although the shadow of cancer may continue to lurk, for Fowler, the disease has been eclipsed by the response it triggered. "I'm almost embarrassed by all the love and support I've had. I feel like the luckiest person in the world."

PINK OUT This Bedlam-themed photo is one of hundreds that OMRF coworkers sent to Jeanne Fowler (right) to cheer her during chemotherapy.

A Cut Above

A powerful, new gene-editing tool is poised to transform medical research and treatment

When Dr. Gaurav Varshney arrived at OMRF in late 2016, the first things he purchased for his new research program were fish tanks. Lots of them.

During a seven-year post-doctoral fellowship at the National Institutes of Health in Bethesda, Md., Varshney developed an expertise in studying developmental biology in paperclip-sized aquatic creatures known as zebrafish. Named for the dark, horizontal stripes that run the length of their silvery bodies, zebrafish provide scientists with a sort of living Petri dish for investigating human diseases. "Approximately 70 percent of human disease genes have a counterpart in these tiny fish," says Varshney. "Because their embryos are transparent and develop outside the body, researchers can easily monitor different stages of embryonic development."

In particular, Varshney uses colonies of zebrafish to understand the disease pathology and molecular mechanisms of hearing loss. To do this, he manipulates the DNA of fish embryos, then studies if and how particular genetic changes impact the ensuing development of these "mutant" fish.

The ability to induce genetic mutations has historically served as a major stumbling block in medical research. Laborious and slow, the process of engineering a single genetic mutation could take a dedicated lab many months, even years. Even then, the results were far from guaranteed; altered genes frequently ended up in random locations on the genome or appeared in widely varying numbers.

Due to these limitations, researchers like Varshney constantly search for new and more efficient methods to alter genes. Not long ago, he found one.

Known as CRISPR—short for Clustered Regularly Interspaced Short Palindromic Repeats—the groundbreaking technique consists of two components. The first is essentially a cellular scalpel that cuts DNA. "Think of it like molecular scissors," says Varshney. The second consists of RNA, the molecule that most often transmits biological information in the body. The RNA acts as a guide for the scissors, escorting them past thousands of genes until it finds the precise section of the genome for the scissors to slice.

Although based on a naturally occurring virus-fighting cellular process in the immune systems of bacteria and other microorganisms, scientists realized they could hack the process to construct a powerful new

CRISPR could one day fix genetic errors that cause blindness, blood disorders and countless other diseases.

AQUA MAN Dr. Gaurav Varshney is using CRISPR technology to study hearing loss in zebrafish.

genetic tool. They devised a method to create synthetic versions of the RNA that they could program—enabling the scissors to target any gene they desired. After the scissors did their cutting, the scientists figured out how to "paste" new genetic material into the gap they'd just created.

Now, scientists who wished to perform genetics experiments no longer had to rely on an arduous and arbitrary process. Instead, with CRISPR, they could edit the genome with the sort of precision we've come to expect from the search-and-replace function on a word processor. "It's been a game-changer," says Varshney.

For Varshney, CRISPR has allowed him to test the function of scores of genes in zebrafish in a fraction of the time—and at a fraction of the cost—such studies previously required. In particular, he's focused on the disease progression and mechanisms of hearing loss. His studies center on tiny hair cells in the ear that are central to hearing. "Because zebrafish hair cells are functionally similar to the hair cells found in the human inner ear," he says, "they provide an excellent model system to understand the pathology of hearing loss."

CRISPR's utility, though, spans far beyond fish and hearing loss. Unlike previous techniques, the gene-replacement method seems to work in just about any organism. And it appears to be effective in every cell type, including ones that researchers had previously struggled to modify.

At OMRF, researchers are using CRISPR in mice to study genes that have been linked to colitis, colon cancer and vascular disease. Elsewhere, scientists have employed the technique to tackle autism, cancer and simultaneously alter 62 genes in pig embryos, creating animals that could, at least in theory, grow human organs for transplant.

In August, scientists announced that they had successfully edited genes in human embryos to repair a common and serious disease-causing mutation. The research marked a major milestone; while still far removed from clinical use, the experiment underscored the potential CRISPR holds for intervening against a variety of hereditary conditions in humans.

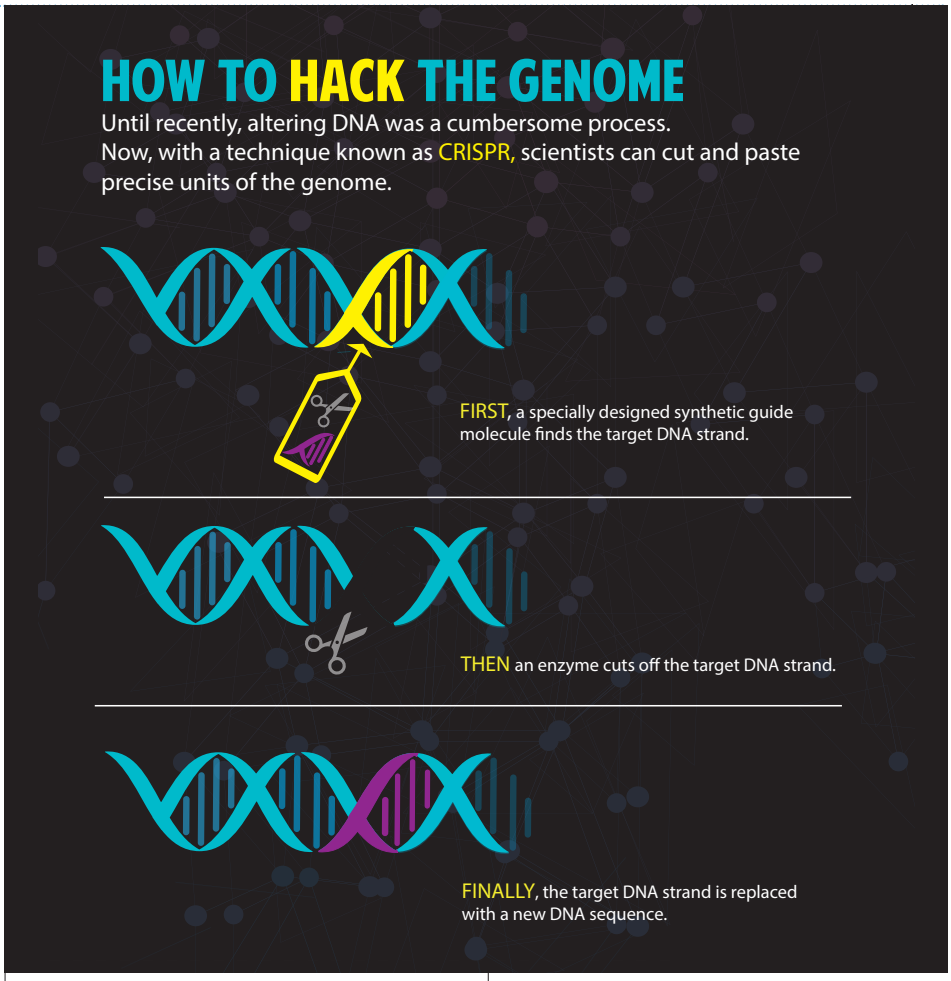
If scientists can master this technique, it could eventually spell the end of genetic diseases. By reprogramming the genetic mutations responsible for gene-based conditions such as cystic fibrosis or Huntington's disease, researchers could protect not only the embryo carrying that damaged DNA but also future generations no longer at risk to inherit the flawed gene.

Human race-altering applications remain a long way off. But clinical trials for CRISPR-based treatments for individual patients loom much closer. Experts predict that in the near future, physicians will begin testing the injection of CRISPR components into, say, the eye to fix a sight problem. Or doctors may remove cells from the body, "fix" them in the lab with CRISPR technology, then re-inject them into patients. This approach might work in a condition such as sickle-cell disease, where CRISPR could prompt a genetic reboot, leading the body to stop producing misformed blood cells.

As treatments approach the clinic, the debate about the ethical implications of gene-editing has also heated up. "The social dangers of creating genetically modified human beings cannot be overstated," the executive director of the Center for Genetics and Society told National Public Radio.

The arguments echo ones that surrounded the first in vitro fertilization in 1978 and the cloning of Dolly the sheep in 1997. With more than five million children born through IVF and not a single human being having been cloned to date, those furors seem to have subsided. If CRISPR helps unravel the mysteries of autism or cures conditions like hearing loss or early-onset Alzheimer's, it's a fair bet today's debates will grow similarly silent.

In the meantime, with all the necessary components to edit a particular gene available to be ordered online and delivered in a matter of days, the science in Varshney's lab and around the globe continues to move forward at breakneck pace. "It is," he says, "an extremely exciting time to be working in the field of genetics."



Joint Interest

Dear Dr. Prescott,

What's the difference between osteoarthritis and rheumatoid arthritis? Are they both caused by inflammatory reactions? And if that's the case, why wouldn't rheumatoid medications also be effective for osteoarthritis?

Ginger Coleman Kelso
Norman

While osteoarthritis and rheumatoid arthritis share inflammation as a common component, the conditions have different causes. That's why some medications that target RA don't work against osteoarthritis.

Osteoarthritis stems from wear and tear that erodes the cartilage between the bones in joints. The most common form of arthritis, it strikes more than 30 million Americans and typically affects fingers, hands, hips, lower back and knees. Pain often worsens with use and improves with rest, and we're more likely to develop osteoarthritis as we grow older. Other risk factors include overuse, obesity and history of traumatic injuries (like an auto accident or a sports injury).

Doctors typically recommend that people with osteoarthritis engage in regular physical activity, which not only strengthens muscles that support the joints and helps control weight, but it also has been shown to reduce pain. They may treat it with nonsteroidal anti-inflammatory drugs like aspirin, ibuprofen (Advil), naproxen (Aleve) and celecoxib (Celebrex). In severe cases, physicians will inject corticosteroids into specific joints to help relieve symptoms. These tactics are aimed at mitigating the symptoms of osteoarthrits. Still, they don't affect the underlying cause of the disease, which has no known cure.

Rheumatoid arthritis is less common than osteoarthritis, affecting a little more than a million Americans. Although researchers have yet to find its origins, they know the disease is caused by a dysfunction of the immune system. Specifically, the immune system perceives something inside the joints as foreign, prompting it to launch an attack. Tissues in the joint become inflamed and swollen, eventually leading to the destruction of cartilage and bone.

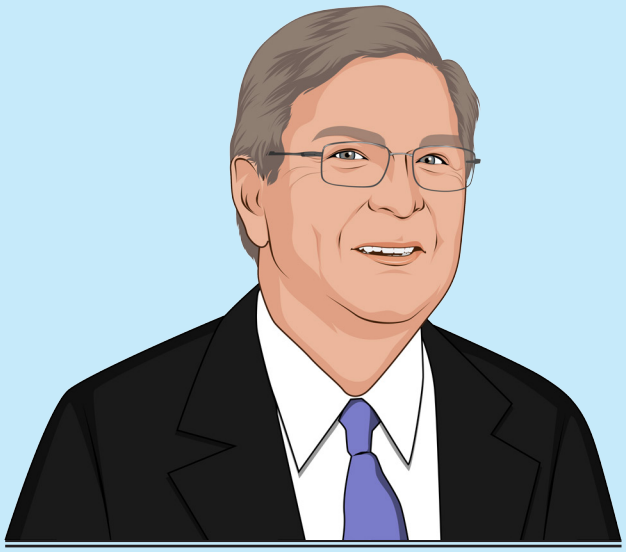
RA displays all the symptoms of osteoarthritis, plus noticeable joint swelling. But unlike osteoarthritis, RA symptoms are often worse in the mornings or after prolonged inactivity and improve a bit with use of the joints. Doctors use a combination of a physical exam, blood tests and X-rays to determine the type of arthritis a person has.

As with osteoarthrits, doctors use non-steroidal anti-inflammatories and corticosteroids to treat the joint pain and stiffness brought on by RA. But rheumatologists have a series of more specific disease-modifying therapies at their disposal for RA that can slow the progressive destruction of the joints. These potent medications use different approaches to alter the course of the underlying illness (although they still do not cure it).

The drugs target the immune system's attack on the joint structures and generally fall into three categories. First, there are older compounds like methotrexate and hydroxycholorquine. Rheumatologists also use newer "biologics" such as Humira and Remicade, which are administered by self-injection or infusion in a doctor's office. Finally, there is Xeljanz, the first of a novel category of oral inhibitors that block pathways involved in the body's immune response.

While these drugs can help control RA, they will have no effect on osteoarthritis. That's because the drugs target mechanisms in the immune system that are crucial to RA but have nothing to do with osteoarthritis.

As is so often the case in medicine, different diseases can have overlapping characteristics and symptoms. However, because their causes are distinct, what works for one condition won't always work for the other.



Tom R. Gray, III
PRESIDENT
PRESBYTERIAN HEALTH FOUNDATION

"As biomedical research grants become exceedingly difficult to receive from the National Institutes of Health and other organizations, it is exciting for Presbyterian Health Foundation to be at the forefront and begin filling that gap. Through grants to OMRF and the University of Oklahoma Health Sciences Center, we can increase the research dollars going to experienced and emerging scientists. The funding will help continue to foster an environment in our state where scientists can pursue innovative research—work that, we hope, will ultimately lead to new therapies for debilitating diseases."

In July, the Presbyterian Health Foundation announced $3.7 million in new funding for more than 30 research and clinical projects at OMRF and OU.

Doctors exhausted conventional treatments for Mike Schuster. Can an experimental OMRF drug stop his brain cancer?

SAVING MIKE

By Shari Hawkins and Adam Cohen
Photos by Brett Deering

In the summer of 2010, Mike and Teresa Schuster took their two boys to Mexico's Yucatan Peninsula. The Schusters live in Norman, where Teresa is an administrative assistant in the University of Oklahoma's Office of Student Affairs and Mike has worked in the restaurant and roofing industries. But whenever they have the chance to hit the road, they do. "Travel is our favorite thing to do together," says Mike.

Mike rented a car in Mexico, as he wanted to bring Teresa and their sons, Parker and Connor, to sites off the well-worn tourist path. In the cities, Mike navigated narrow, traffic-choked roads, dodging pinballing buses and honking cars. "It was terrifying," recalls Teresa. But the urban hurly-burly soon gave way to countryside, and the Schusters found their way to remote villages and Mayan ruins. It was near the remains of one ancient settlement that they discovered their first cenote.

The Yucatan is a flat, thick shelf of limestone. Beneath this layer of rock is a network of water-filled caves, all linked by subterranean rivers. When the roof of one of the caves collapses, it produces a sinkhole known as a cenote.

Because this particular cenote's roof had only partially given way, from the earth's surface, it looked like nothing more than a hole in the ground. But when the Schusters climbed down the hole on a wooden ladder, they found themselves in a massive underground chamber that had no floor—only a pool of water that stretched from wall to wall.

Mike made his way to the edge of a rocky outcropping and peered down. In the cave's dim light, the liquid appeared black as pitch. There was no telling what might lurk beneath its surface, nor how deep it went.

Still, he hadn't come all this way simply to look at the water.

Sometimes, he thought, you have to take a chance if you want to experience life in all of its richness. Sure, there are always risks. But without risk, there's no reward.

So Mike took a deep breath. And then he jumped.

ON THE AFTERNOON before Thanksgiving five years later, Mike was not thinking about cenotes or the Yucatan. The clock on his desk in Newscastle, Okla., where he worked as a consultant for a roofing company, said 1:00. Just finish up the numbers for this last job, he told himself, and you can call it quits for the holiday weekend.

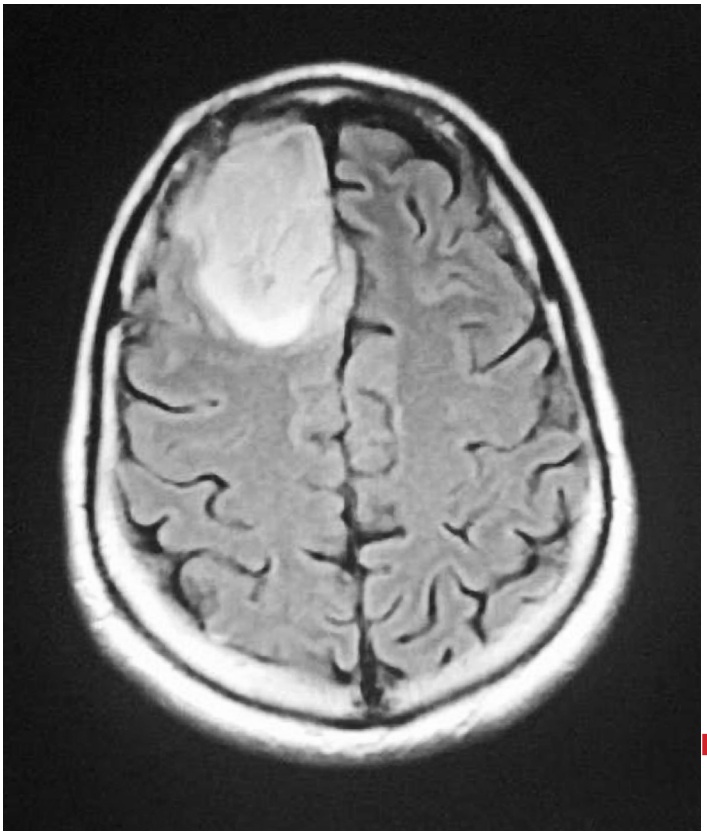
He remembers studying the numerals that filled his computer screen. Then nothing.

He awakened gradually, finding his senses bit by bit. Voices swirled around him. A siren wailed nearby. He opened his eyes and saw he was in the back of an ambulance, atop a stretcher. You've had a seizure, someone told him.

This was a first. Mike, then 50, had never before had a seizure. As far as he could recall, everything had been normal until the moment he pitched out of his desk chair. No headache or dizziness. No warning of any kind.

At the hospital, the doctor ordered an MRI of Mike's brain. When his physician tacked the film to a light box, Mike could see the white outline of his skull. Equally visible was a bright, oval-shaped spot on the right frontal lobe of his brain. About the size and shape of a kiwi, the brain tumor had formed just above his right eye.

"I've been healthy all my life," Mike says. "No medical issues at all. I just couldn't believe that this was happening."



THE ENEMY WITHIN Mike Schuster's MRI revealed an egg-sized cancer in the right, frontal lobe of his brain. (This image is flipped.)

The doctor told Mike his tumor was a form of brain cancer. It has to come out immediately, the doctor said. He scheduled the surgery for the morning after Thanksgiving.

A BRAIN TUMOR is an abnormal growth of cells in or close to the brain. Because the brain controls a multitude of bodily functions, tumors can have a dizzying array of effects, ranging from the seizure Mike experienced to impaired speech, comprehension, memory, vision, balance, judgment, hearing and reasoning. Tumors can also profoundly alter a person's moods, personality and decision-making.

Brain tumors most commonly begin in other parts of the body and then spread to the brain. But in Mike's case, the tumor originated in his brain. These growths, known as primary brain tumors, begin when normal cells acquire errors—mutations—in their DNA. The mutations cause cells to grow and divide at accelerated rates and to continue living when healthy cells would die. Over time, this results in a mass of abnormal cells, which forms a tumor.

Of the more than 120 types of brain and central nervous system tumors, Mike's type, known as a glioblastoma, is the most aggressive. Senator Edward Kennedy died of glioblastoma, as did Beau Biden, son of former Vice President Joseph R. Biden, Jr. Senator John McCain was also recently diagnosed with this form of brain cancer.

Formed from the glue-like supportive tissue inside the brain, glioblastoma cells reproduce rapidly, fueled by the brain's extensive network of blood vessels. The standard treatment regimen involves surgery to remove as much of the tumor as possible, followed by radiation and chemotherapy. Still, the tumor almost always grows back in a year, which typically triggers a second surgery.

Because they keep returning, glioblastomas are rarely cured, and the prognosis is poor. With treatment, the median survival—which means half of patients live longer, and half die sooner—is 12 to 18 months. Only one in 20 patients will survive five years.

FOR THANKSGIVING, Mike opted out of the family celebration hosted by Teresa's grandparents. "There were so many people in town, and I just didn't think I could handle it." Instead, he spent the day at home, watching black-and-white movies. Getting himself centered.

He happened across "The Long, Long Trailer," an old Lucille Ball movie. In the film, Lucy and Desi Arnaz play newlyweds whose honeymoon trip runs predictably amok. Lucy gets frazzled, Desi gets angry, lots of things get broken.

Still, by the time the credits rolled, everything had turned out just fine.

The next morning, in a procedure that lasted six hours, surgeons removed as much of Mike's tumor as they could. When they finished, they screwed in a titanium plate to replace the portion of his skull they had cut away. Then they closed the wavy incision that snaked across the top of his head with dozens of precise stitches.

When Mike regained consciousness, he was, understandably, "a bit woozy." But the essential Mike, he soon discovered, remained unchanged. His faculties seemed unaffected.

On the right side of his head, a tube protruded from his incision, allowing the surgical site to drain. An I.V. dripped into his arm, and a half-dozen different monitors attached to his body tracked his heart rate, oxygen retention, blood pressure and assorted other vitals.

"I was hooked up to so much stuff that I could hardly move," he says. "I had to call for help just to go to the bathroom."

His surgeon explained that he'd succeeded in excising most of the tumor. But, he said, like most glioblastomas, this one had "tentacles." Tiny arms of the tumor had grown into surrounding brain tissue and could not be removed.

Just take it easy for now, said the surgeon. You need to get your strength back. Then we'll focus on getting the cancer that's still inside you.

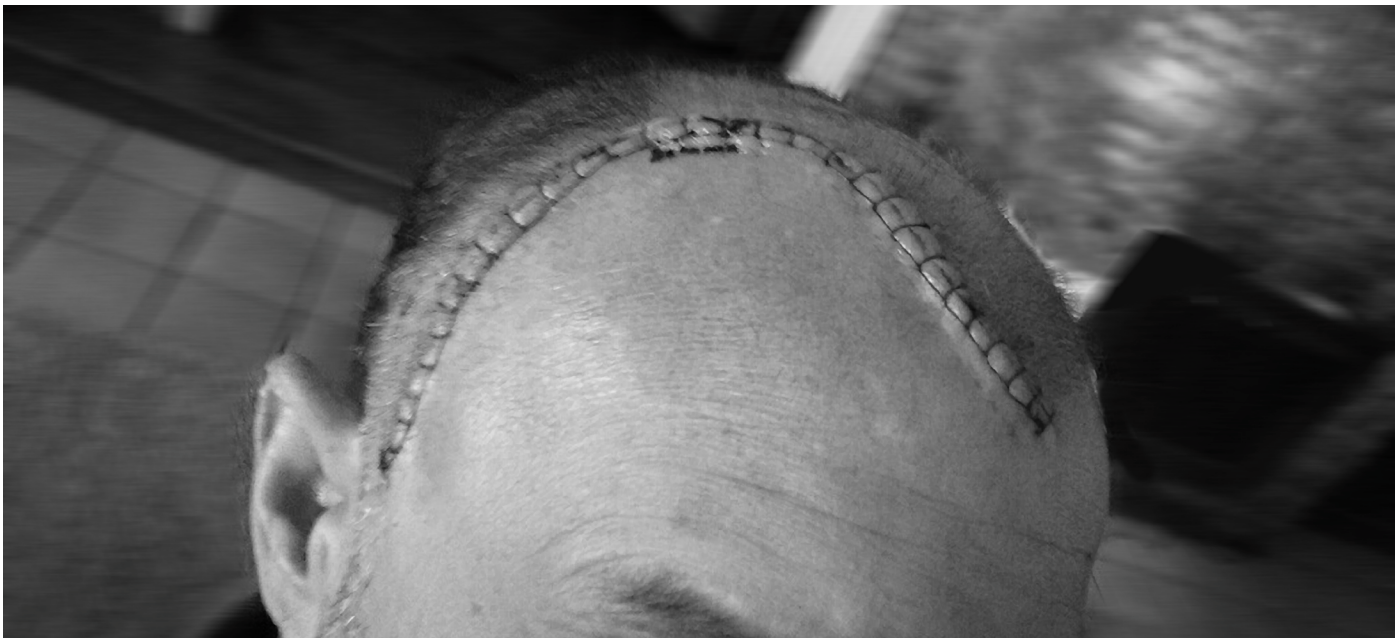
IN A FEW DAYS, Mike's doctor removed the tube from his head—"He yanked it out like he was pulling off a Band-Aid"—and released him from the hospital. At home, Teresa kept a close eye on her husband, watching for any changes. But other than fatigue, which took hold quickly, she saw the same person she'd been married to for more than two decades.

Gregarious and social by nature, Mike wanted to get back out in the world. He liked seeing and interacting with people. But he was self-conscious about the scar on his head, which, he says, looked like "the stitching on a baseball."

When Teresa would take him out, Mike would immediately spot someone he was sure he knew. "I'd say, 'Hey, how are you doin'? I haven't seen you in awhile!'" After a brief, awkward conversation, he'd discover that, indeed, he hadn't seen that person recently. Or ever. Each time, the "friend" would turn out to be a perfect stranger.

One doctor didn't know what to make of the phenomenon. Another had read of such surgery-induced déjà vu. But with Mike's speech and memory fully intact, they didn't worry much about it. And within a week or two, Mike stopped mistaking people he'd never met for long-lost pals.

Life, though, didn't quite return to normal. Mike was unable to go back to work. He did a



A CUT ABOVE To remove his glioblastoma, surgeons made an eight-inch incision along Mike's hairline.

little consulting, writing a computer program for one company. But, otherwise, he found it tough to maintain focus.

Everyone, it seemed, wanted to hear his story. How did it happen? What were the signs? How are you feeling?

Mike appreciated the concern. But he didn't want to be the guy with cancer forever talking about his condition. "Sometimes, I'd tell Teresa I just couldn't handle talking about it anymore."

In December, he traveled to Colorado for his son's college graduation. The journey and extended absence from home was, he says, "tough" on his body. But he was happy to be regaining some sense of normalcy, to be doing the two things he cherished most in life: traveling and spending time with his family.

As he watched his son receive his diploma, Mike thought, this is a moment I wouldn't have wanted to miss for anything. And he hadn't.

Once he'd recovered sufficiently from surgery, he began a follow-up treatment regimen at the Stephenson Cancer Center at the University of Oklahoma. For six weeks, he'd travel each weekday to Oklahoma City, where doctors would focus a powerful beam of radiation into his skull. Even though Mike couldn't feel the electromagnetic waves pulsing through his brain, "you could smell it," he says. He also started chemotherapy, taking a pill called temozolomide. Together, the treatments were intended to kill the tumor cells that remained in the fissures of his brain.

"If you leave even a single cancer cell in the brain, it can regrow," says Dr. James Battiste, the neuro-oncologist who oversees Mike's care at Stephenson. "The brain is fertile soil for these tumors. That's why chemo and other therapies are so important."

Radiation and chemotherapy, though, are blunt instruments, killing much more than cancerous tumor cells. Mike's hair, which had begun to grow back following the surgery, fell out. Ditto with his right eyebrow.

Still, Mike tolerated the therapy well. He maintained his appetite throughout, managing any nausea with medication. By the end of radiation—doctors limited his treatment to six weeks for fear of triggering a secondary cancer—he even decided he liked the Bruce Willis look and continued to shave his head. (He also kept a goatee, which he'd grown during radiation treatments "to have a little hair on my face.")

He stayed on temozolomide. As the months piled up, he became increasingly optimistic; periodic MRIs showed that, while pockets of tumor cells still lurked in his brain, they weren't spreading. By late November, brain scans continued to show no new growth.

Mike was elated. The previous year, he'd spent Thanksgiving grappling with an impending surgery for a lethal brain tumor. The 2016 holiday couldn't have been more different. "I was telling everybody I didn't have cancer. Teresa would say the word, and I'd say, 'no.'" As far as Mike was concerned, he'd beaten the disease.

Four weeks later, an MRI of his brain revealed a new tumor.

AWAKE SURGERY was pioneered decades ago in epilepsy patients; anesthesiologists would keep patients alert enough to ensure surgeons were destroying the brain tissue that triggered seizures. With the advent of sophisticated brain-mapping technology and anesthetics, use of the technique has blossomed in recent years. It's become the go-to surgery for many types of brain tumors, especially ones like Mike's, which was perilously close to tissue that controls motor skills and other sensory abilities.

The advantage of keeping patients awake, says Battiste, is that surgeons can remove more of the tumor and parts of the associated tentacles without the risk of added damage to the brain. And because neurons in the brain don't have any pain receptors, so long as the scalp is numbed properly, patients don't feel anything that surgeons are doing in the brain itself.

In early January of this year, after administering an anesthetic, Mike's surgeons inserted screws in his skull and mounted them to a metal halo to immobilize his head. "I could hear the buzz as they drilled holes in my head," says Mike, "but I couldn't feel anything."

Tumor fragments had attached to his skull, and the surgeons removed them using a chisel. Again, there was no pain, but each blow of the surgeon's hammer resonated in Mike's jaw.

As the doctors worked, a physical therapist kept Mike engaged by having him move pegs around a peg board. At intervals, she'd also ask him to perform other tasks.

"Recite your ABCs," she'd instruct him. When Mike would dutifully comply, she'd say, "Now count backward from 21." The exercises, which also included seemingly straightforward tasks like touching his fingers together, were more than mere busy work. Mike's steady stream of responses served as a sort of cartographic warning system to the surgeons; when he displayed any sort of difficulty, it would alert the doctors they were probing dangerously close to a region of the brain that controls language or other sensory abilities. Even a nick in such a no-go zone could leave Mike unable to speak or understand language for the rest of his life.

After nearly half a day, the surgeons once again secured the titanium plate that, for the past 14 months, had replaced what had previously been skull. Once more, they had removed the principal tumor. They'd also scraped and dug out many minuscule fragments that had grown in other parts of his brain.

He also had a new addition on the left side of his scalp: a grape-sized bump where doctors had placed a valve under his skin. Connected to a pair of tubes, this shunt system relieved pressure on his brain by draining excess fluid into his stomach.

Late that night, Mike underwent a post-surgical MRI. His doctors wanted to see if any portions of the main tumor had eluded their scalpels. "Waiting for those results was tough," says Mike. Happily, the brain scan showed that the doctors had succeeded in removing all of the primary tumor.

Still, many glioblastoma tentacles had escaped their reach, remaining lodged in his brain.

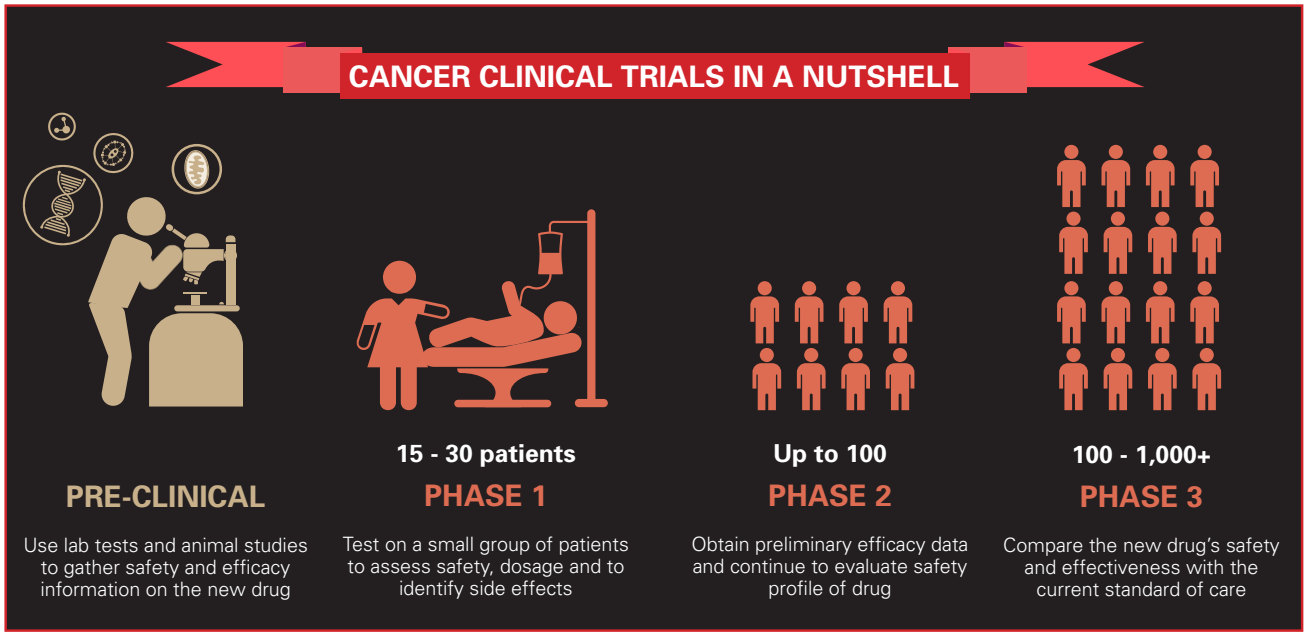
Mike spent five days in recovery. Despite the ostensibly successful surgery, he found his spirits flagging. "I'd thought that I had it beat. And now, I felt like I was starting all over again."

He knew those tentacles were, in essence, seeds that could sprout another full-blown tumor in a matter of weeks. They'd already done it once. What was to stop them from doing so again? And now, having reached his body's limits for radiation and chemotherapy, he could no longer rely on them to keep his cancer in check.

Mike told Battiste he was willing to try anything to beat back the glioblastoma. In particular, he'd read about clinical trials of experimental medications. Was there one of these that might help him?

Stephenson has more than 200 different clinical trials for new cancer drugs underway. Battiste, in fact, was leading a trial that, he says, "just seemed suited for Mike." The trial was designed to test an investigational medication for glioblastoma. Coincidentally, that drug had been born just down the block from Stephenson—in the labs of OMRF.

THE EXPERIMENTAL medication known as OKN-007 was discovered by OMRF's Dr. Robert Floyd. Originally conceived of as a treatment for stroke, the compound attracted the interest of pharmaceutical giant AstraZeneca, which spent years refining and testing the drug. The medication successfully completed the first two phases of human clinical trials, but in the final stage—which involved thousands of stroke patients around the world—it failed to show efficacy. So the company mothballed the drug.



DYNAMIC DUO Dr. James Battiste (left) is leading the clinical trial for OKN-007, an experimental drug that Dr. Rheal Towner (right) helped pioneer to treat brain cancer patients like Mike.

Floyd, though, wasn't prepared to give up on OKN-007. In previous pre-clinical experiments, the compound had shown a significant amount of anti-cancer activity. Dr. Rheal Towner, a colleague at OMRF, had been studying the use of similar compounds as potential cancer therapeutics. For those experiments, Towner had developed a method of implanting and growing glioblastoma tumors in rodents. Based on that work, Towner decided to administer the drug to one of his glioblastoma rats. Within weeks, 90 percent of the animal's tumor melted away.

"We were amazed," says Towner. He repeated the experiment in several different rodent glioblastoma "models," and each time, tumors shrank and survival rates increased. "The compound," says Towner, "was working."

Even three months later, in rodents whose brains had once been riddled with cancer, the scientists found no evidence of recurrence. Testing showed the compound dramatically decreased cell proliferation (spread) and angiogenesis (formation of new blood vessels), and it turned on apoptosis, the process of removing damaged cells so they can't become cancerous. "Those are the three major factors needed in a cancer drug," says Towner. "This compound seemed to do all of them."

Unlike most experimental drugs, thanks to its clinical trials, OKN-007 had an extensive, well-documented history of how it behaved in humans. Although it had not been found to be effective in remedying strokes, it hadn't shown any dangers or side effects. With that safety data in hand, plus the promising results of Towner's rodent experiments, the FDA gave OMRF the green light to begin testing OKN-007 in glioblastoma patients.

IN JULY, Mike sat in an overstuffed chair in the infusion suite at Stephenson Cancer Center. When a nurse approached, he unbuttoned his Hawaiian shirt, and she felt around until she found a raised area on the right side of Mike's chest. This was the end of a port his doctors had inserted to serve as a sort of artificial vein.

After the nurse hooked an I.V. bag to the port, Mike re-buttoned his shirt and reclined in the chair. For the next hour, clear liquid—OKN-007—dripped through the tubing into Mike's chest, where it was distributed through a large vein near his heart into his bloodstream. From his circulating blood, it passed through a semipermeable membrane into his cerebrospinal fluid, which then delivered the medication to his brain. There, it provided a sort of chemical marinade for the remaining tumor cells, immersing them in a powerful bath of anti-cancer agents that would prevent growth and spreading.

At least that's what Towner and Battiste hoped was happening. With this clinical trial, they'll find out if this is, indeed, the case.

Clinical trials are the FDA's process for evaluating new drugs. For safety purposes, testing starts with small groups of patients to find out whether a drug causes any harm. In later phases, researchers learn more about the compound's risks and benefits.

OKN-007 is now in the first phase of its clinical trial, which primarily focuses on the drug's safety. "We look at potential side effects and learn what dosage levels might cause problems," says Battiste. But they're also examining efficacy, studying each MRI to determine "How is the brain doing?"

Trials represent a significant time commitment for patients like Mike, who comes to Stephenson up to three times a week for infusions. He also receives regular blood work and MRIs, which means his visits to the cancer center can last for up to five hours. "You can't work a regular job" around this regimen, Mike says. Still, he says the experience is "almost like a spa day. Everybody at Stephenson is so nice. They feed you. And you even watch TV while you get your infusion."

So far, Battiste is cautiously optimistic about the performance of OKN-007 in his patients. "We've gone to the highest dosage levels the FDA would allow, and we haven't seen any negative effects from the drug." And while evaluating the medication's effectiveness in controlling the regrowth of tumors is only a secondary endpoint at the moment—later trial stages focus on efficacy—"it's helpful to see things looking good" on this front, too, he says.

Given the relatively rare incidence of glioblastoma, which strikes 2 to 3 out of every 100,000 people, recruiting study participants has proven slow. Although the trial opened four years ago, Mike is one of only about a dozen patients who have taken part. With such small numbers, Battiste says, determining the statistical significance of results can be challenging.

What comes next will be up to Oblato, a Korean biotechnology company that acquired the rights to OKN-007 last year. One path would be to petition the FDA to move to a phase II trial. This would shift the focus of testing from safety to effectiveness and involve more patients, likely at multiple clinical centers (currently, Stephenson is the only trial site).

Another approach, says Battiste, would be to seek FDA approval to increase dosage levels. "In oncology, the thinking is that if one dose is good, a higher dose must be great. And at the current dosage levels, we haven't seen any side effects." Or the company could initiate a new phase I trial using an oral formulation of the drug. "A pill would make it more convenient for patients," increasing usage. Plus, it would provide a more constant level of medication in the body. "If you soak the brain in something, it can be more effective."

ON AUGUST 8, Mike celebrated his 52nd birthday. A couple of weeks earlier, he'd also marked another significant milestone: at 20 months and counting since his diagnosis, Mike had exceeded the life expectancy for the average person with glioblastoma.

When he sees other patients with brain tumors, he says, they appear thin and frail. Mike, on the other hand, has added 15 pounds since he began OKN-007 infusions. "So far, I've had no side effects at all," he says. "I'm never tired, never feel sick."

Mike can't say enough good things about the care he's received at Stephenson. "Everybody has been so great. It's the place to go if you're unfortunate enough to get cancer."

His faith, he says, has also buoyed him throughout this process. "The power of prayer and my faith in God have helped sustain us."

He's grown strong enough to drive himself to appointments and to take Teresa out to dinner. "I've been able to get back to the gym and am doing some yard work. I feel really good." Best of all, he says, "My MRIs are looking good."

He's even begun to think about travel again. If all continues to go as planned, once he finishes the phase I trial in the fall, he'd like to take his family to Cuba.

Of course, neither Mike nor his doctors can know for sure if the drug is responsible for keeping his cancer at bay. Nor can they say if, or when, the disease might recur. "I can't worry about stuff," says Mike, "that's out of my control."

Still, he feels certain he made the right decision when he opted to participate in the clinical trial. Yes, there were—are—perils to receiving treatment with an experimental drug. But, just like that time he took the plunge into the cenote in the Yucatan, without risk, there was no possibility of reward.

Mike believes he's receiving that reward with each new day. "Let's just say I've been very blessed. It's pretty cool how this stuff is working."

Right about then, a monitor beeps. Mike's infusion treatment for the day is finished. A nurse arrives and detaches the drip line. Mike buttons his shirt.

Telling your story is fine when you're hooked to an I.V. and your only other option is to watch TV. But now Mike has a choice to make: he can either keep talking about his cancer, or he can go and live his life.

Mike gives his interviewer a hug. Then he picks up his keys and heads for the door.

MAN IN MOTION Since he began receiving infusions of OKN-007, Mike has grown strong enough to take his wife, Teresa, to dinner and to start working out again. "I feel really good," he says.

Paul Kincade Thinks the Future Is Almost Here

Dr. Paul Kincade *can't recall a more exciting time for stem cell research. And with a 50-year career as a stem cell biologist, he has a vantage point that's second to none.*

Earlier this year, after more than three decades heading a lab and research program at OMRF, Kincade retired as the foundation's vice president of research. But he continues to serve as scientific director of the Oklahoma Center for Adult Stem Cell Research (OCASCR), which he helped to found in 2010. Funded by the Oklahoma Tobacco Settlement Endowment Trust, OCASCR represents a close collaboration among Oklahoma State University, the University of Oklahoma Health Sciences Center and OMRF. The organization has twin missions: to support adult stem-cell research in the state and to promote public understanding of the field.

Kincade recently attended the 2017 annual meeting of the International Society for Stem Cell Research, where stem cell researchers from around the world shared the latest advances in the field. Afterward, he sat down with Findings.

There's been a lot of excitement and discussion over the past 20 years or so about the promise of stem cells for developing new treatments. Give us a quick reminder what a stem cell is.

It's a cell that can self-renew. When it divides, it can either make an exact copy of itself or become another type of cell with a more specialized function, like a muscle cell, a blood cell or a brain cell.

How could stem cells be harnessed to develop new treatments for disease?

As one example, you can now take a sample of blood or skin, engineer it to make stem cells, then reprogram those cells to make any type of cell in a patient's body. The science is progressing to the point that we now have the capacity to make what are basically replacement parts for any damaged cell in the body.

There was a big debate surrounding the use of so-called embryonic stem cells, but I haven't heard much about that topic in recent years. How come?

Because of an extraordinary breakthrough [which won a Nobel Prize in 2012]. We have over 500 cell types in the body, and they normally behave themselves. They stay what they are. That's good, because you wouldn't like for the

AGE: 72

OCCUPATION:
STEM CELL BIOLOGIST

HOMETOWN:
MOORHEAD, MISSISSIPPI

HIS TOP 5 HOPES FOR NEW STEM CELL TREATMENTS
1. PARKINSON'S DISEASE
2. BLINDNESS
3. SPINAL CORD INJURY
4. HEART DISEASE
5. DIABETES

brain to start making blood cells. But scientists discovered this stability can be taken away, that the cells can become flexible. Today, all you need is an "adult" cell—a skin or blood sample from a research volunteer or patient—to make any cell you want. So there's really not much need for embryonic stem cells anymore. To my knowledge, all of the stem cell research in Oklahoma has used adult cells.

Stem cells were first talked about as potential treatments for nearly every condition imaginable. What are the most promising targets today?
Bone marrow transplantation has been used for leukemia and blood cancers for a long time, and that remains the only thing that's standard of care. But that's going to change. Animal studies and early-stage human trials are showing promise in macular degeneration. We're seeing progress in treating burns, and we also believe it's going to be possible to treat spinal cord injuries. There have been exciting advances in Parkinson's and heart disease, too.

Why these particular conditions?
The ones that will be most amenable to stem cell treatments are conditions affecting one cell type. The idea is that we can make that one type of cell from stem cells in large numbers, then transplant them into a patient. But that approach won't work in diseases affecting multiple cell types.

Most stem cell therapies are still in experimental phases. What hurdles still remain for them?
Right now, the process is too time-consuming and expensive to work on a large scale. We need to figure out ways to do it much more quickly and cheaply. In early tests, scientists were re-engineering patients' own cells. But for the treatments to become standard of care, we probably can't do this on an individual basis. We'll have to prepare banks of stem cells that include suitable matches between donor and patient. And we'll have to overcome the problem of cancer-causing mutations that can arise when we reprogram cells. We already know these treatments are possible, but it's going to require patience to make them safe and practical.

What are your biggest concerns about the future of stem-cell-based treatments?
Bad science. The thing that kills a field is something that's done before it's been carefully vetted. Gene therapy is a perfect example.

What happened there?
Scientists tried to cure a teenage patient suffering from a mild form of a metabolic disease, and he ended up dying from unanticipated side effects of the treatment.

Has the potential of stem cells been overhyped?
Yes. And misunderstood. The public and even a lot of physicians didn't understand that. There isn't sufficient evidence to suggest that a lot of so-called stem cell treatments should work.

Yes, I've noticed ads for clinics offering "stem cell therapy" for a variety of illnesses. Is this a viable option for people suffering from conditions like arthritis, multiple sclerosis and neurological diseases?
There are more than 500 such clinics in the U.S., but there's little reason to believe their treatments are effective. They haven't been subject to rigorous scientific analysis.

How do they work?
At the moment, the FDA allows them to operate if they take a cell out of your body and put it back in without much manipulation. They use phrases like "may benefit" or refer to how many patients they've treated—with no reference to whether those treatments succeeded. It's not false advertising per se. But to someone who's desperate, you hear what you want to hear.

But people swear by these treatments…
Yes, you have athletes claiming they've gotten relief from injuries or joint problems. Who knows? There may be some benefits. In a lot of conditions, especially ones involving chronic pain, the placebo effect is 45 or 50 percent. Diseases like MS wax and wane, so after a treatment, you may just get better anyway.

How have stem cells impacted research?
They let scientists model diseases in a test tube. You can study a cell that's misbehaving and figure out exactly what is causing that disease. Then you can design drugs to treat it or screen thousands of compounds, many of which have been used as drugs for something else. This is a rapid way to develop new treatments. These are things you could never do in a patient.

Would you have imagined this 50 years ago?
No way. The pace of discoveries is what astonishes me.

How about Oklahoma—what's happening here?
Before OCASCR, Oklahoma only had a couple of researchers who had stem cell grants. Thanks to the vision and support of TSET (the Oklahoma Tobacco Settlement and Endowment Trust), we now have about 40 scientists whose work pertains to stem cells. They're working on a broad spectrum of problems: leukemia, blindness, respiratory diseases, diabetes and more. In seven years of operation, OCASCR has awarded 100 grants to researchers to support this work, and we've purchased 29 pieces of scientific equipment for shared use by stem cell researchers at institutions throughout Oklahoma. We've helped recruit 10 new scientists to the state. Our goal was to get Oklahoma scientists to start thinking about and working in this hot area. I think we're succeeding.

A Few Good Men and Women

John H. Saxon, Jr., built a successful textbook publishing company around a teaching philosophy that emphasized incremental learning through the completion of problem sets. Given Saxon's life experiences, it's not surprising he took a drill-oriented approach to scholarship: a West Point graduate, he taught for five years at the U.S. Air Force Academy. He also served as an Air Force pilot, flying 55 missions during the Korean War.

Following Saxon's death, his son, Dr. John Saxon, III, wanted to do something to honor his father's military service. But he also wanted to do something to benefit OMRF, where the Muskogee physician has been a board member since 2000. So, he decided to combine the two goals. "Some people may not think of basic science and the military as linked," says Saxon. "But I thought that I could use OMRF's work as an opportunity to stimulate some basic bench science interest with cadets at service academies."

With a gift of $250,000, Saxon established the John H. Saxon Service Academy Summer Research Program at OMRF. Through this initiative, students from the U.S. military academies come to the foundation each summer to work side-by-side with senior scientists. The program aims to expand the students' knowledge base and strengthen the scientific abilities of service academy members who go on to serve as medical officers or in other technical capacities.

Dr. John Saxon, III, created a program at OMRF that honored his father's military roots and introduced service academy members like Lieutenant Connor Fullenwider (now a Navy flight surgeon) to medical research.

Since its establishment in 2009, it has trained more than two dozen students from the U.S. Naval, Air Force and Military Academies. According to Dr. Chris Kinter, a chemistry professor at the U.S. Naval Academy who helps select the Navy students each year (and is also the brother of OMRF scientist Mike Kinter), the Saxon program offers students interested in medicine, chemistry or biochemistry a unique hands-on look at independent laboratory research. "It's invaluable for them to get that experience in a research setting," says Kinter. "Most come back to us saying it really opened their eyes to the scientific process, and some look for other lab experiences as a result."

Projects have covered a wide range of topics. For example, this summer one Saxon student examined the role that a particular protein plays in the hearts of those suffering from diabetes. Meanwhile, Matthew Lerdahl, a cadet at the U.S. Air Force Academy, spent his time at OMRF studying chromosomal segregation, a process that's crucial to preventing birth defects. "The experience was more intense than I thought it would be, and that's a good thing," says Lerdahl. "The mentors give you the freedom to make mistakes and learn on your own. It's made me a better scientist and researcher."

This summer, OMRF cardiovascular biologist Dr. Courtney Griffin mentored Jocelyn Rodriguez, a midshipman at the U.S. Naval Academy. Rodriguez was the fifth Saxon student Griffin has had in her lab. She investigated how blood vessels develop in embryos. And like the first four who'd come before her, Rodriguez did a bang-up job on her research project, says Griffin.

"The Saxon students are always ready to soak in everything we throw at them," says Griffin. "I have so much respect for them. They're academically impressive and simply fearless. Every year, it reminds me that we're in good hands if they represent the future leadership of our country."

SUMMER SCHOOL 2017 Saxon students Erin McShane, Matthew Lerdahl and Jocelyn Rodriguez

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Little Patients, Big Advances

Until the 1950s, children with cancer received only palliative care, which was designed to ease their symptoms but didn't stop the disease. When OMRF opened its research hospital in 1952, it took a decidedly different approach: Dr. Paul Condit and his fellow OMRF physicians used then-experimental treatments like chemotherapy as weapons against leukemia and other childhood cancers. For many young patients, therapies they received at OMRF spelled the difference between life and death.