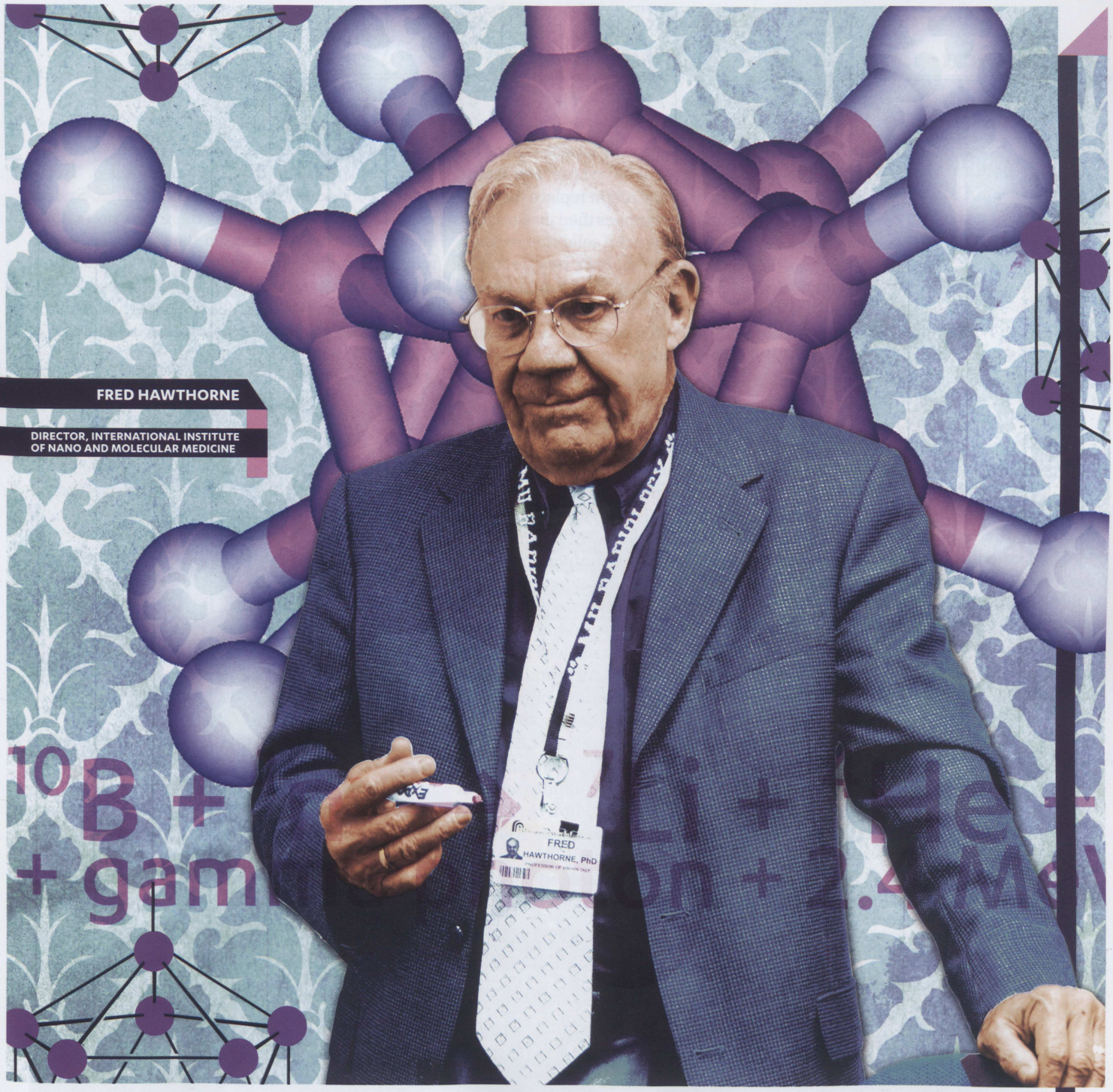
CHRONIC SUCCESS

Researchers at MU are making great strides against chronic diseases that have cost humankind untold misery and countless billions of dollars in health care and lost productivity. When it comes to therapies for cancer, diabetes and stroke, research by **Fred Hawthorne, Habib Zaghouani** and **Zezong Gu** has been spectacularly successful in mice. As their work moves toward human trials, they seek the resources to take their discoveries to the next level.

STORY BY DALE SMITH  ILLUSTRATIONS BY BLAKE DINSDALE



Wanted: A Human Beam

Can National Academy of Sciences chemist Fred Hawthorne cure cancer?

Chemist Fred Hawthorne had just finished a postdoctoral appointment at Iowa State in 1954 when he arrived in the Alabama hamlet of Huntsville, population 15,000, which billed itself as the watercress capital of the world. The Cold War was on, and Huntsville's Redstone Arsenal was a research center working out better weapons for the U.S. Army. Hawthorne joined the likes of scientist Wernher von Braun, who became a dinner companion, and other top researchers who were developing rocket engines. Their rockets eventually propelled the first U.S. satellite into orbit during the Cold War and put astronauts on the moon.

As it turned out, Hawthorne's work at Redstone Arsenal also launched his half-century quest to develop a therapy for cancer — a journey that led in 2013

to curing mice of the disease without side effects.

By 1959, Hawthorne led a lab whose task was to discover how solid boron fuel might replace the modestly energetic liquid hydrocarbons then in use and so produce safer and more powerful solid-fuel rockets.

Scientists had discovered boron's unique nuclear properties, Hawthorne says, "But I didn't know much about the chemistry of boron, and nobody else did either." He set out to map the new chemical field and discover ways boron could be used in compounds that had predictable and useful properties, such as in pharmaceuticals. In so doing, Hawthorne became the father of modern boron chemistry, a member of the National Academy of Sciences and winner of the National Medal of Science.

Using boron's nuclear properties to cure cancer was on his mind back in Huntsville. The isotope boron-10 showed the most promise. The idea is to inject a cancer patient with a compound including boron-10 in such a way that it aggregates in tumor tissue. Next, direct a low-energy neutron beam at the tumor. When the beam hits boron-10 nuclei, it sets off millions of tiny nuclear reactions that kill the tumor cells. Ideally, surrounding cells do not take up boron and so remain intact. This is called boron neutron capture therapy, or BNCT.

After Redstone, Hawthorne landed at the University of California where his distinguished career included decades of work chipping away at facets of BNCT and exploratory boron chemistry. Others were working on the therapy as well, but their compounds sent boron to nontumor tissues, so the neutron capture reaction caused collateral damage. Eventually, funding to refine BNCT became scarce due to lack of clinical progress.

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But Hawthorne still believed that, done properly, BNCT would work. Consequently, he explored new chemistry and conducted research to develop better boron compounds, including the two he uses now, and the liposome vehicle to carry the compounds to tumors. Liposomes are nanoscale spheres with a fatty shell and watery core. The fat carries one compound and the water the other, a "double whammy," Hawthorne calls it. Liposomes slip into growing tumors through their leaky blood vessels, and once inside they selectively invade the cancer cells, where they degrade and unleash the boron where it can work best.

Despite Hawthorne's accomplishments over the decades, his work on BNCT was unfulfilled. "In the whole wonderful University of California System with all its medical facilities, there was no neutron beam," he says. No beam, no therapy. So, when he retired from the University of California in 2006, he came to Mizzou as a Curators Distinguished Professor of Chemistry in the College of Arts and Science, and Radiology in the School of Medicine. "Here at Missouri, I've got one." Modifications to the University of Missouri Research Reactor produced a beam suitable to demonstrate the promise of BNCT in mice.

In 2013, Hawthorne published a study using BNCT therapy with 600 mice that had one of three cancers: colon, squamous cell or adenocarcinoma. After injecting the boron-filled liposomes and waiting 30 hours, the mice were given 30 minutes of neutron therapy. The therapy was repeated a week later. Although Hawthorne expected the therapy to work, the results were beyond what he could have hoped. All the mice went into remission, and none showed side effects. Cured.

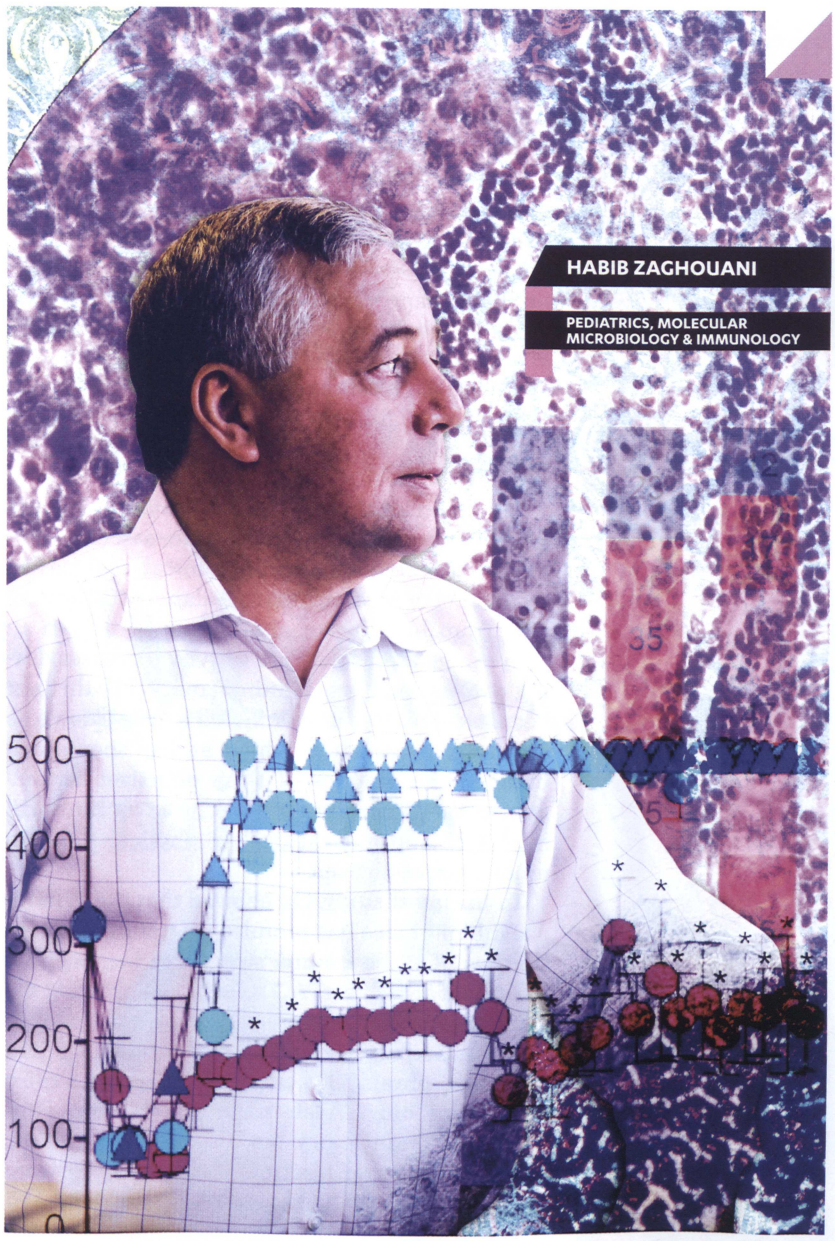
The next step requires a more powerful neutron beam that can reach into larger animals, in this case dogs. He found such a beam at Washington State University. Collaborators there will treat about a dozen dogs with naturally occurring tumors, which vary more than lab-induced malignancies and can prove more stubborn. All in all, it's a higher bar for BNCT than the mouse study, says BNCT expert George Laramore, professor of radiology at the University of Washington. Businessman Mark McAndrew, BS BA '75, of McKinney, Texas, donated $400,000 for this phase of Hawthorne's work. By summer 2015, the dogs will have been treated and followed for about 12 months. If the study goes as Hawthorne predicts, BNCT will be ready for human trials.

Studies in humans will require building a more penetrating medical neutron beam at MU that is situated in a medical setting. When that facility is ready, the study will take about two years and cost an estimated $6 million, including the cost of a human-qualified neutron beam. Although Hawthorne is grateful to his supporters, at 85, he feels a great sense of urgency about these final stages of his life's work.

"If Dr. Hawthorne's compounds work as we anticipate," Laramore says, "It'll break the field wide open."

Caring for Collateral Damage

Can Habib Zaghouani cure diabetes?



'You might have a child who is playing and suddenly faints, and then you realize they have Type 1 diabetes. By then, the disease is already there.'

Diabetes affects 347 million people worldwide and costs an estimated $245 billion a year in the U.S. alone. Researchers have long searched for a cure. Investigators had approached diabetes as a disease in which the immune system destroys pancreatic beta cells that produce insulin. That's true enough. Another thread looks at vascular damage the disease causes over time, which can lead to blindness, amputation, kidney failure and a host of other problems. Also valid. Recent research by Habib Zaghouani has brought those threads together in a new way, and he has cured diabetes in mice.

"Everybody, including us, thought that if you stop the immune system attack, the beta cells will regrow, and therefore the disease will be cured," says Zaghouani, J. Lavenia Edwards Chair in Pediatrics and professor of molecular microbiology and immunology in the School of Medicine. Using a tolerogen (a specific inhibitor of aggressive immune cells) at the onset of diabetes, he was able to stop the "rogue" immune cells that were destroying beta cells. That was a success of sorts, except that, "In real life, that's not how things happen," he says. "You might have a child who is playing and suddenly faints, and then you realize they have Type 1 diabetes. By then, the disease is already there." So he tried the tolerogen to stop existing diabetes. It didn't work.

Maybe, he thought, too few beta cells survived the immune system attack to reproduce and to create sufficient insulin. So, in addition to the tolerogen, he gave diabetic mice a range of stem cells from bone marrow, in hopes they would regenerate beta cells. Lo and behold, the mice recovered. But when he analyzed the pancreatic tissues using confocal microscopy, he got another surprise. "The stem cells didn't grow any beta cells at all. Instead, they grew new blood vessels." He had discovered that the immune system attack destroys not only beta cells but also nearby blood vessels, which feed the beta cells and carry insulin to the body. What's more, beta cells and their surrounding blood vessels are symbiotic — they each produce substances that the other needs to survive.

The technology is patented, and fundraising is underway to raise $6 million to create a human version of the tolerogen compound and test its safety. Then, if all goes as planned, it would be ready for human trials. Zaghouani expects that taking the medicine would be as simple as receiving an injection or sitting a few minutes for an intravenous drip. The approach could also work for Type 2 diabetes.

A Wider Window for Stroke Treatment

Can Zezong Gu protect the brain from stroke and traumatic brain injury?

'For a stroke victim, time is a matter of life and death.'

Stroke is a leading cause not only of death — one American dies every four minutes of the disease — but also of disability, costing $39 billion a year in health care services, medicine and missed work. Doctors have a drug to treat ischemic strokes, in which a clot blocks a blood vessel. But tissue plasminogen activator (tPA) only works if given in the first three hours after a stroke begins. After that, tPA causes problems of its own. Three hours is a small window of time to experience stroke symptoms, call an ambulance, go to a hospital, receive a diagnosis and start the treatment. Only 3 percent of stroke victims make it in time to use tPA to dissolve the blockage. And the drug cannot be used with hemorrhagic, or bleeding, strokes.

"For a stroke victim, time is a matter of life and death," says researcher Zezong Gu, associate professor of pathology and anatomical sciences in the School of Medicine. Stroke damage comes not only from bleeding or clotting but also from an enzyme (gelatinase) whose activity increases during strokes and causes brain damage. For the past decade, he has been working on a drug known as a gelatinase inhibitor, which he has shown can broaden the window of tPA's effectiveness and control the harmful enzyme. The extra time will save lives and a great deal of physical function among stroke victims.

In his latest study, Gu showed that the gelatinase inhibitor also has promise for traumatic brain injuries. "On the trauma side, there has been no treatment at all like tPA," he says. But by using the gelatinase inhibitor in mice with traumatic brain injuries, he protected against brain damage and preserved physical function. His work with mice shows not only much-improved walking after traumatic brain injury but also better cognition. For instance, after treatment, injured mice were much quicker at solving a maze.

Gu's current version of the inhibitor, injected into the abdomen, performed well in the mouse studies, he says, but he is at work on a new version that will reach the brain more quickly via an IV drip and protect against ischemic and hemorrhagic strokes. When the new compound is prepared, it will be ready for studies in humans. **M**