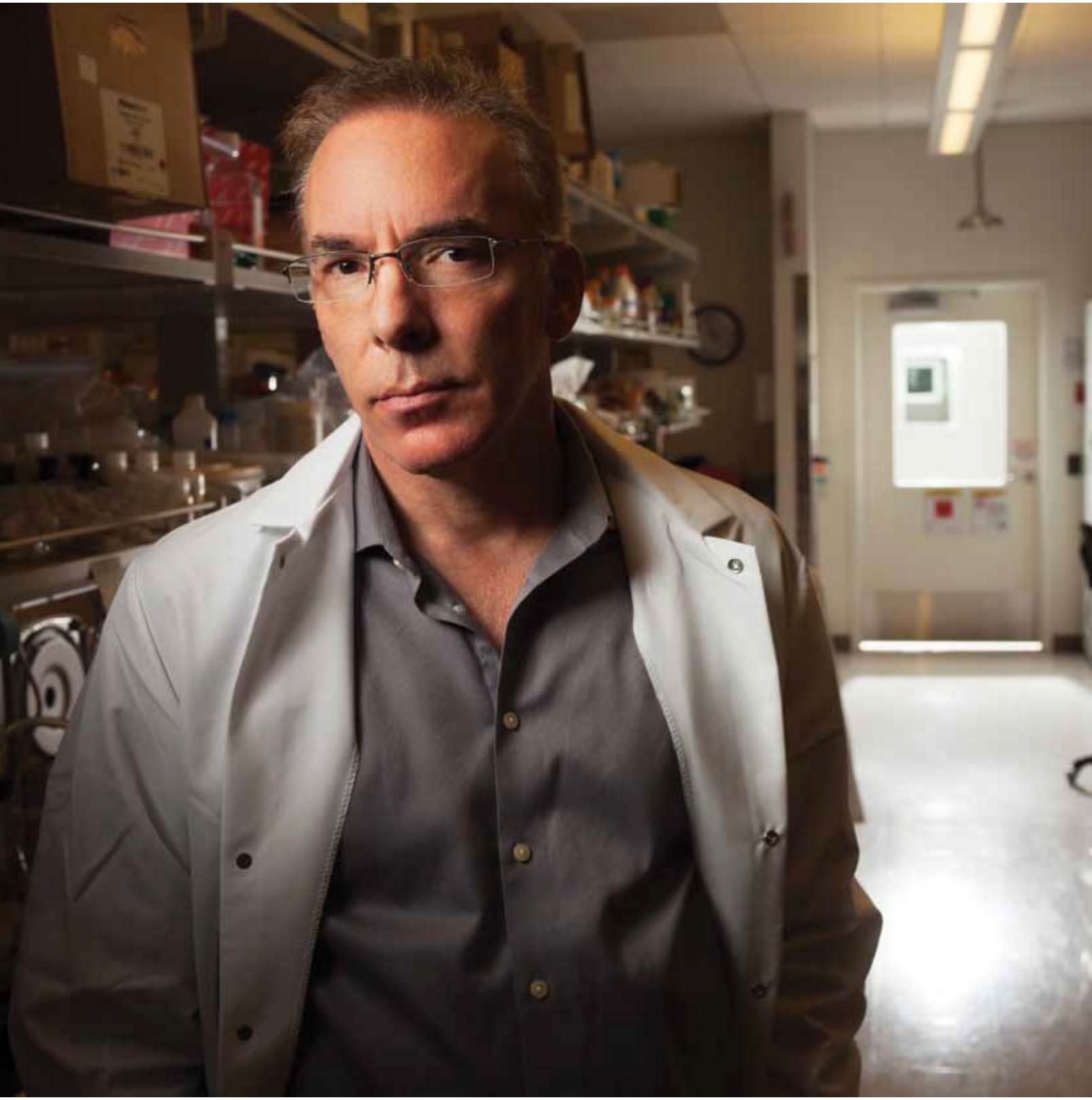


Immunologist Michael Gale Jr., '85, '94, and his team of scientists and students are focusing on a drug-like molecule that triggers a body's innate immunity to fight infection in a range of global pathogens including Zika, hepatitis C and West Nile.

PATRICK DAHMS

ZEROING IN ON ZIKA

One UW lab is RACING to HALT the Zika virus in its spread aROUND the world

EVERY COUPLE OF WEEKS, an eagerly awaited package arrives at a University of Washington research lab in South Lake Union. Inside, nestled in dry ice, are special chemical compounds that Michael Gale Jr. affectionately dubs his "favorite molecules."

These "small molecules" have the potential to stop the Zika virus in its tracks. At the UW's Center for Innate Immunity & Immune Disease, Gale, '85, '94, who is the director, is on the hunt for the right one to constitute a drug to sideline the mosquito-borne illness that has dominated headlines this year, as well as other related viruses.

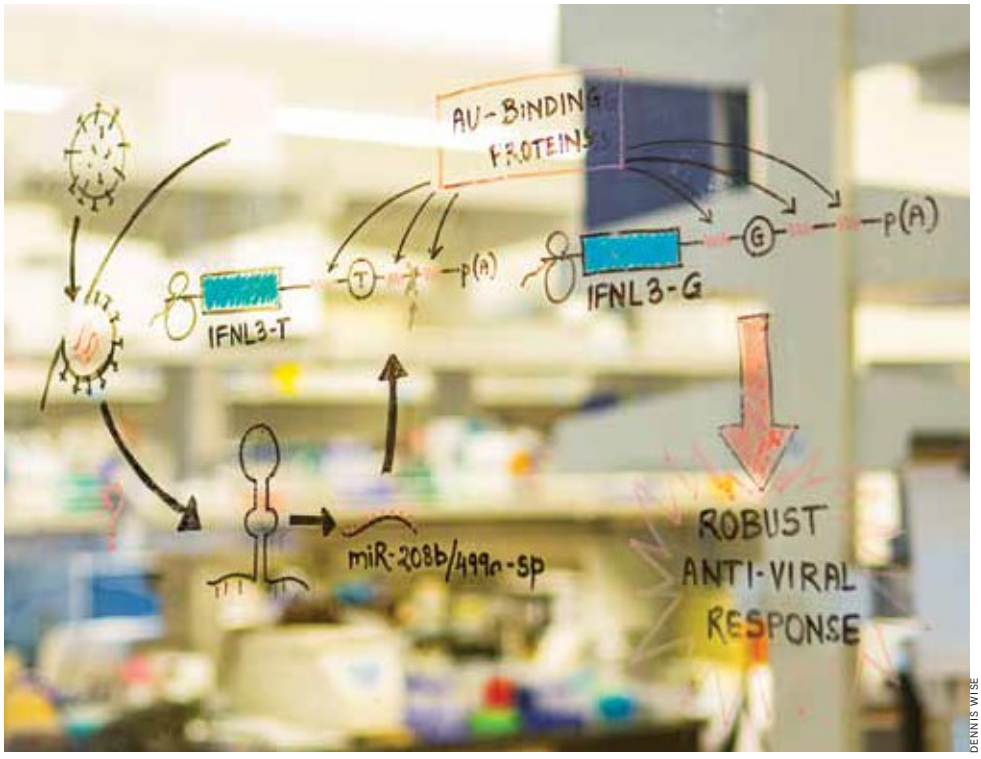
His ace in the hole may be RIG-I, aka retinoic acid-inducible gene I, which was identified in 2005 when he was an assistant professor at the University of Texas Southwestern Medical Center in Dallas. The discovery emerged as Gale and his colleagues were trying to discern how the body triggers an immune response to hepatitis C. RIG-I, they realized, functioned as an "on-off switch" for immunity against the virus. Over a period of years, the researchers figured out that RIG-I kicks into gear

BY BONNIE ROCHMAN

when it recognizes and binds to viral RNA, triggering the immune response. Hepatitis C and Zika virus are both RNA viruses (viruses with an RNA genome, as opposed to DNA viruses); so are West Nile, which like the Zika virus infects the brain, and Ebola, which causes deadly hemorrhagic fever—not to mention the common cold and influenza viruses.

Gale and the 34 researchers in his lab, in collaboration with Kineta, a local biotech company in which Gale is a founding scientist, are now in the process of testing various small molecules—organic compounds that are tiny enough to infiltrate cells and comprise most drugs—to nail the right formulation to attack these RNA viruses. They've screened thousands of molecules to identify a few that activate RIG-I and subsequently induce an immune response that stops the viruses.

First, scientists at Kineta dehydrate the molecules so that they're virtually indestructible. When I expressed surprise that this works, Gale explained that it's not so unusual: "You can literally turn the human body into a powder." The molecule du jour is placed in a test tube. Centrifugal force anchors it at the bottom of the tube, and a vacuum pump sucks out all the water. Within two hours, only a powdery residue remains. That dust is then transferred to another test tube and whisked four-tenths of a mile to Gale's lab, with its specialized biosafety containment facility.



A window into Gale's UW lab illustrates a process for activating an anti-viral response. The scientists are accelerating their efforts to stop the current outbreak of Zika virus.

There, the molecules are rehydrated and applied to cultured cells that are infected with viruses such as Zika and West Nile to see which, if any, can knock out the viral villains. "So far, our molecules are very effective against Zika and other viruses," says Gale. "In particular, these molecules can shut down Zika virus infection."

This is a powerful statement, because there is currently no treatment for Zika virus infection. In fact, there are no antivirals for most RNA viruses. Gale's hope is that his team will be able to bring to market a broad-spectrum antiviral drug.

It stands to reason that any resulting pharmaceutical could be a game-changer, which is critical particularly for a disease such as Zika that has already wreaked havoc on pregnant women, who can pass the virus to their fetuses. Zika virus is transmitted by the bite of an infected Aedes species mosquito; it can also be spread through sex. Most infected people don't feel very sick, or they suffer mild symptoms such as fever, rash, joint pain or red eyes. But pregnant women are considered far more vulnerable. Zika virus invades placental cells and increases infected women's risk of giving birth to babies with abnormally small heads, a condition known as microcephaly that causes irreversible brain damage. Newborns may also emerge with hearing loss, eye damage, nervous system disorders and abnormally small bodies.

Although Zika virus is new to the American consciousness, it isn't new amid the landscape of global disease. It was first documented in 1952, a few years after scientists stuck a monkey in a cage inside the Zika Forest in Uganda as part of a research project involving virus surveillance. The monkey became feverish and the researchers succeeded in isolating a virus that they named "Zika," which means "overgrown" in Luganda, a local language. In 1954, Zika virus was isolated from a human in Nigeria, more than 1,500 miles away.

For years, the virus appeared sporadically, confined to Africa and Southeast Asia. Then in 2007, an epidemic occurred in Micronesia, followed by outbreaks in Polynesia, Easter Island, the Cook Islands and New Caledonia, followed by a rash of 2015 cases in Brazil, which brings us to today. The virus, apparently spread from country to country by travelers who had been bitten in areas where Zika virus was rampant, unfurled throughout South and Central America and the Caribbean and has now creeped into the United States. As of the time this article was written, Washington had registered 41 Zika virus cases, although the mosquito that carries the virus does not call this state home.

• • •

Michael Gale can pinpoint exactly when science cast a spell on him. He was 8, a year younger than his sister, who was one of several people who caught hepatitis A from eating tainted food at Wildwood Elementary School in Federal Way. A teacher and student died from the outbreak. His sister was out of school for weeks.

"I didn't know how sick she was until I talked to my parents about it later," says Gale, who adds that she was "on her deathbed." Gale had eaten the same food at the same time, but he didn't fall ill. "I was lucky," says Gale, a professor in the Department of Immunology. "I wondered why I was not infected. I have been a science geek ever since. Remember those Scholastic books you could order? I ordered 'Fun with Chemistry,' 'Fun with Science.' I still have them. I would set up these experiments in my bedroom to try to figure stuff out."

Born in Burlington, Gale grew up in Federal Way and Monroe, then attended the UW as an undergraduate. He got his first job after graduation as a research associate in the Department of Microbiology, working at the Center for AIDS Research. Gale was part of the team that developed one of the first nonhuman primate models for HIV/AIDS. He continued with graduate studies at the UW, earning his Ph.D. in pathobiology and setting out to work on hepatitis C virus, which had

recently been discovered. Hepatitis C is a distant cousin of Zika; both viruses replicate in the same way, although they infect different cells.

Gale and his team are now trying to get a better handle on how and why these viruses sometimes spread unchecked but at other times are stopped dead in their tracks. In particular, they're curious about how the body deploys innate immunity against virus infection. In practical terms, that translates to figuring out how the body knows it's been invaded by a virus. "It all boils down to the major principle of immunology: how does a body know it's infected with a virus and what happens right after to turn on an immune response to protect us?" says Gale.

He takes me on a tour of the Center for Innate Immunity & Immune Disease, which includes a biocontainment facility. It's rated biosafety Level 3, enhanced, a half-step beneath Level 4, which is reserved for deadly, airborne viruses such as Ebola and Lassa. The facility contains more than half a dozen animal suites that house rodents for studies of Level 3 pathogens such as avian influenza virus, or "bird flu," Japanese encephalitis virus, and tuberculosis. Technicians must first enter through a specialized changing room where they shower before donning a spacesuit to ensure they don't carry in any pathogens. To make doubly certain, the rooms maintain negative pressure, hovering a bit beneath the 14.4 pounds per square inch that characterize standard atmospheric pressure. This ensures that if a pathogen is spilled accidentally, it can't leak out of the room because the pressure inside is less than the pressure outside. Negative pressure is the basic component of biocontainment. "It works very well," says Gale.

The center's crown jewels are high-powered microscopes and cell sorters that can analyze blood cells, including cells from infected human samples. Cell sorters use light refraction to sort cells into separate test tubes; lasers then illuminate the cells to reveal patterns of scattered light and fluorescent light coming from molecular tags that researchers use to define immune cell types.

The collection of cell sorters housed at the center are worth well over $2 million. "This is like being a kid in a candy store," says Gale. "Not many places in the country have such extensive cell analysis facilities."

Gale's passion for tinkering with gadgets goes way back. In high school, he puttered with his green 1968 Mustang, a high-performance iteration of Ford's classic car. He still owns it. "He's a natural mechanic, fix-it type of person," says Edward Clark, professor of microbiology and immunology. When Gale began working in Clark's lab in 1985, he took charge of the cell sorter. Fairly new at the time, cell sorters were finicky and unreliable, but Gale coerced Clark's into functioning. "He was getting really nice data," says Clark. "Everything he did worked."

• • •

It can help to think of viruses as invading combatants and the human body as their battleground. When viruses start to replicate within cells, a body's innate immune response flips on hundreds of genes, which spring into gear and shut down the virus so that it can't spread beyond that cell. "It works well most of the time, otherwise we wouldn't live out of infancy," says Gale.

The problem is that viruses are wily, so they know all about this mechanism and they've developed ways to defeat it. When they're victorious, viruses directly target activated genes and shut them down or trick them into generating an overactive immune response. It's a phenomenon that sounds like it could be the name of a fight-or-flight video game: "viral evasion." If a virus has evolved to skirt the body's innate immune response, a person gets sick.

Gale's mission is to develop drugs to consistently turn on those genes that jump-start the innate immune response. This approach contrasts with the modus operandi of the small family of existing drugs that directly target individual RNA viruses such as influenza, hepatitis C and HIV. Those drugs home in on proteins that can transform as a virus changes, rendering the drugs ineffective. But Gale's emphasis on innate immunity focuses on the actual person who is infected, not the virus. "When innate immunity turns on, hundreds of antiviral genes are turned on. They are warrior genes. It's like attacking the virus with hundreds of drugs."

He is currently working to harness derivatives of KIN1400, an especially effective small molecule that signals cells to launch the innate immune response to attack a viral invader and stop it from replicating. Replication is a virus' bread and butter. No replication, no virus, no illness.

"There is a tug-of-war between viruses and the innate immune response over who is stronger," says Shawn Iadonato, '98, CEO of Kineta. Much of the drug-formulation research focused on RIG-I is carried out on human cells at Kineta's South Lake Union headquarters.

The most potent small molecules are being tested in mice and monkeys to determine how long they stay in blood and how much they're excreted in urine, part of the process in developing appropriate dosages.

> "WHEN INNATE IMMUNITY TURNS ON, HUNDREDS OF ANTIVIRAL GENES ARE TURNED ON. THEY ARE WARRIOR GENES. IT'S LIKE ATTACKING THE VIRUS WITH HUNDREDS OF DRUGS."—MICHAEL GALE JR.

This testing is a precursor to human clinical trials. Although the need for a drug is immediate, it's likely that it would take at least five more years for a lead small molecule to be transformed into a commercially available drug. Clinical trials designed to test safety and efficacy could be rolled out sooner, in accordance with a rigorous pharmaceutical approval process overseen by the federal Food and Drug Administration. The stakes are high because there are no broad-spectrum antivirals as there are with antibiotics. "We only have single drugs that treat sin- gle viruses," says Iadonato. One reason is because viruses are so special- ized that it's hard to develop effective treatments. Bacteria, on the other hand, have larger genomes with more pathways that can potentially fall prey to antibiotics. "Viruses are very small and very lean," he says. "There are fewer pathways to target."

Whether antibiotic or antiviral, drug development is not for the weak. It takes a long time. Gale has been working on this particular project for nearly a decade. His dream is that one of the small molecules he's working on will eventually become an effective treatment for viruses like Zika. "I would love to see a successful drug come out of this," he says.

If that indeed plays out, the term "small molecule" might need a makeover. It will be an underwhelming description for a treatment with big implications. n *—Bonnie Rochman is the author of "The Gene Machine: How Genetic Technologies Are Changing the Way We Have Kids—And the Kids We Have," to be published in February by Scientific American/Farrar, Straus and Giroux.*