

FINDINGS

Fall 2011 • omrf.org



THE QUEST
FOR AN
ALZHEIMER'S DRUG



Don't let Alzheimer's steal someone you love

I never imagined my mother would lose her laughter. Or that she'd one day forget how to swallow and, finally, to draw a breath.

Alzheimer's disease robs more than 5 million Americans of their memories and, eventually, their minds. Here in Oklahoma, we have one of the top medical investigators in the world, Dr. Jordan Tang, leading a team that is working each day to solve this mystery of human health. An experimental drug based on this research is currently undergoing human clinical trials.

Your gift to the Oklahoma Medical Research Foundation ensures that this progress will continue. And that all those who've lost their lives to Alzheimer's will not be forgotten.

Becky Switzer

Becky Switzer



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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 Alzheimer's disease, cancer, lupus and cardiovascular disease.



10

NOT DONE YET In 1999 and 2000, Dr. Jordan Tang made an extraordinary series of Alzheimer's discoveries. More than a decade later, he continues to push ahead in his quest for one of medicine's Holy Grails—an Alzheimer's drug.

DIALOGUE

04 Your Letters

DISPATCHES

05 The Robots Are Coming

06 Taking the Bull by the Horns

07 Don't Sweat It

08 These Are a Few of Our Favorite Things

09 Grants

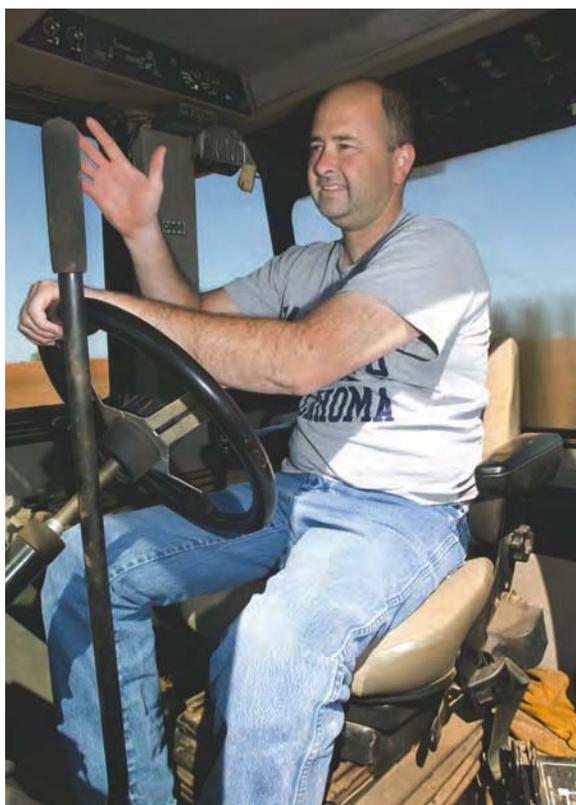
FEATURES

10 Unfinished Business

18 Pioneer Woman

COVER STORY

letters



I thoroughly enjoyed the current edition of *Findings*, especially the article about your researchers' musical composition foray, as I am a professional musician. I also appreciated your story about **John Enns**. He is a man to be admired, and his story struck close to home. My son is hemiplegic after suffering a stroke at the age of 28 while he was in his medical residency. Now, at age 52, he is a practicing physiatrist and lecturer and father of four.

Barbara G. Hardin
Monument, CO

I love the heartwarming stories and the information on research about human disease in *Findings*, and I can relate to some of them. "The Last Lesson" about Debbie Ocker was very interesting, because she was one of my grandsons' teachers. They tell me she was very good for him. "Dr. Moser's Opus" caught my attention because my daughter has lupus. This past year, my wife passed away after suffering many years with Alzheimer's. I have learned a lot about the disease, and part of what I know about Alzheimer's from reading *Findings*. Thank you so much.

Robert McClain
Kimberling City, MO

My grandmother died of Alzheimer's many years ago.

One of the hardest things I ever had to do was tell my mother, who was dying of cancer at the time, that her mother had died. I will never forget her words: "No, Kay, my mother died years ago. That person was not my mother." Perhaps in the not-too-distant future this disease can be eradicated. Strides have been made, but there is so much more to do. I was sorry to read about what Becky Switzer had to go through with her mother, but I want to thank her for telling her story here—both for OMRF and for all of us who have lost loved ones to this terrible disease.

Kay Woods
Norman

I love reading your *Findings* publications when my dad gets them in the mail. What wonderful reading material. It makes me want to finish up my microbiology degree and apply for a position at OMRF!

Erin Jeffries
Norman

WRITE TO US! Send us an email at findings@omrf.org or mail your letters to *Findings*, 825 Northeast 13th Street, Oklahoma City, OK 73104. Please include your name and address, and you'll receive an OMRF T-shirt if we publish your letter.

FOLLOW US ONLINE!



DISPATCHES

THE ROBOTS ARE COMING!

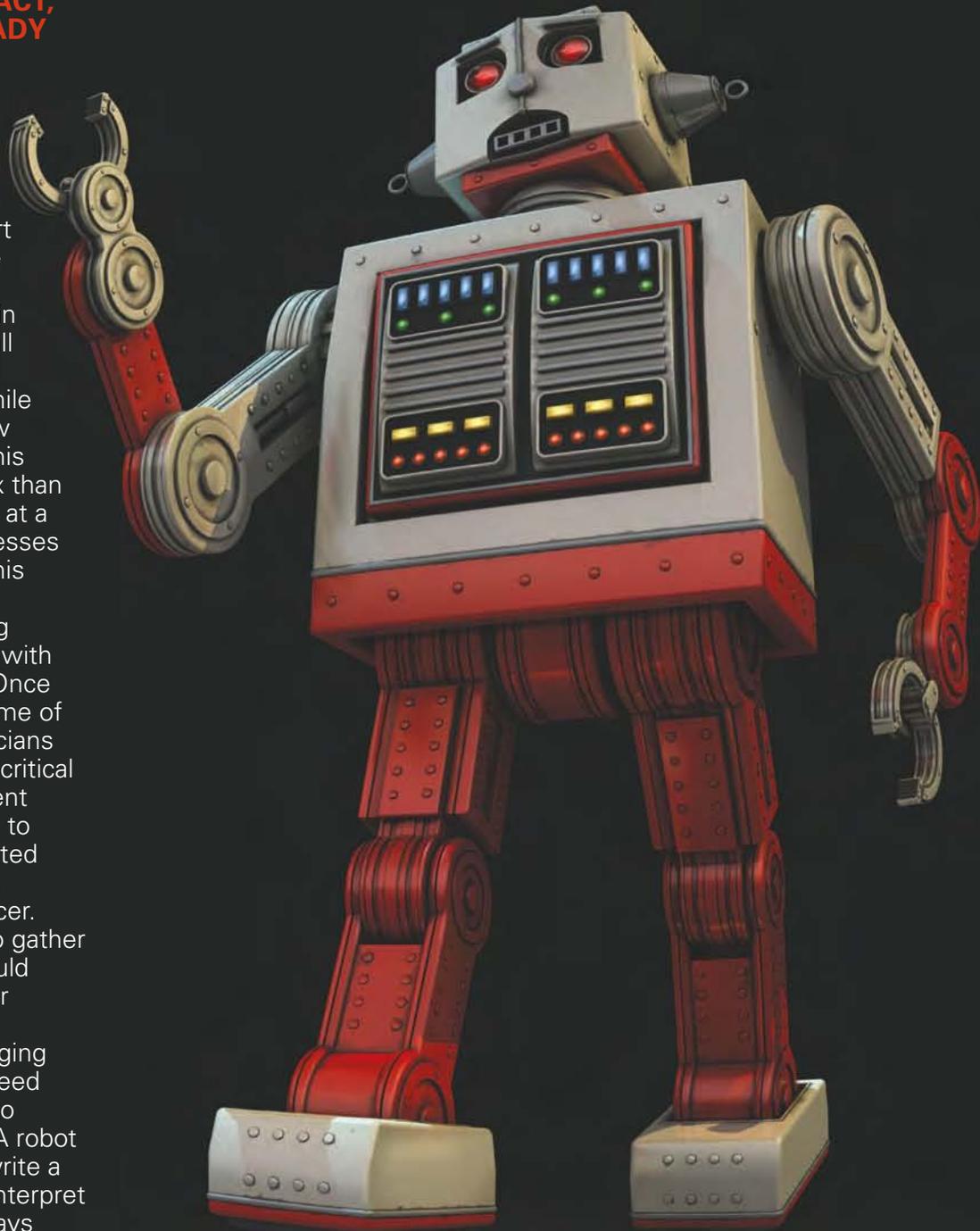
IN SCIENCE FICTION, THE RISE OF THE ROBOTS IS CAUSE FOR ALARM. BUT IN SCIENCE FACT, THE MACHINES ARE ALREADY HERE.

"Robots are simply machines capable of carrying out a complex series of actions automatically," says OMRF's Dr. Patrick Gaffney. In Gaffney's lab, robots have played a key part in identifying genes linked to the autoimmune disease lupus.

For example, a common tool in the labs is a 96-well plate, a small plastic tray that holds 12 rows of 8 biological samples each. While lab technicians must fill each row individually, a robot—which, in this case, looks more like a black box than a humanoid—can fill entire rows at a time. In a lab that routinely processes tens of thousands of samples, this saves valuable time.

"Robots are excellent at doing very repetitive tasks quickly and with few mistakes," says Gaffney. "Once they're set, machines can do some of the tedious work, freeing technicians to do projects that require more critical thinking and creativity." In a recent project, researchers used robots to identify a genetic variant associated with lupus and, potentially, heart disease and certain kinds of cancer. The project took eight months to gather data. "Without the robots, it would probably have taken three or four years," said Gaffney.

Although robots may be changing the face of science, there's no need for flesh-and-blood researchers to worry about their job security. "A robot cannot generate a hypothesis, write a grant, design an experiment or interpret the results of an experiment," says Gaffney. "At least not yet."



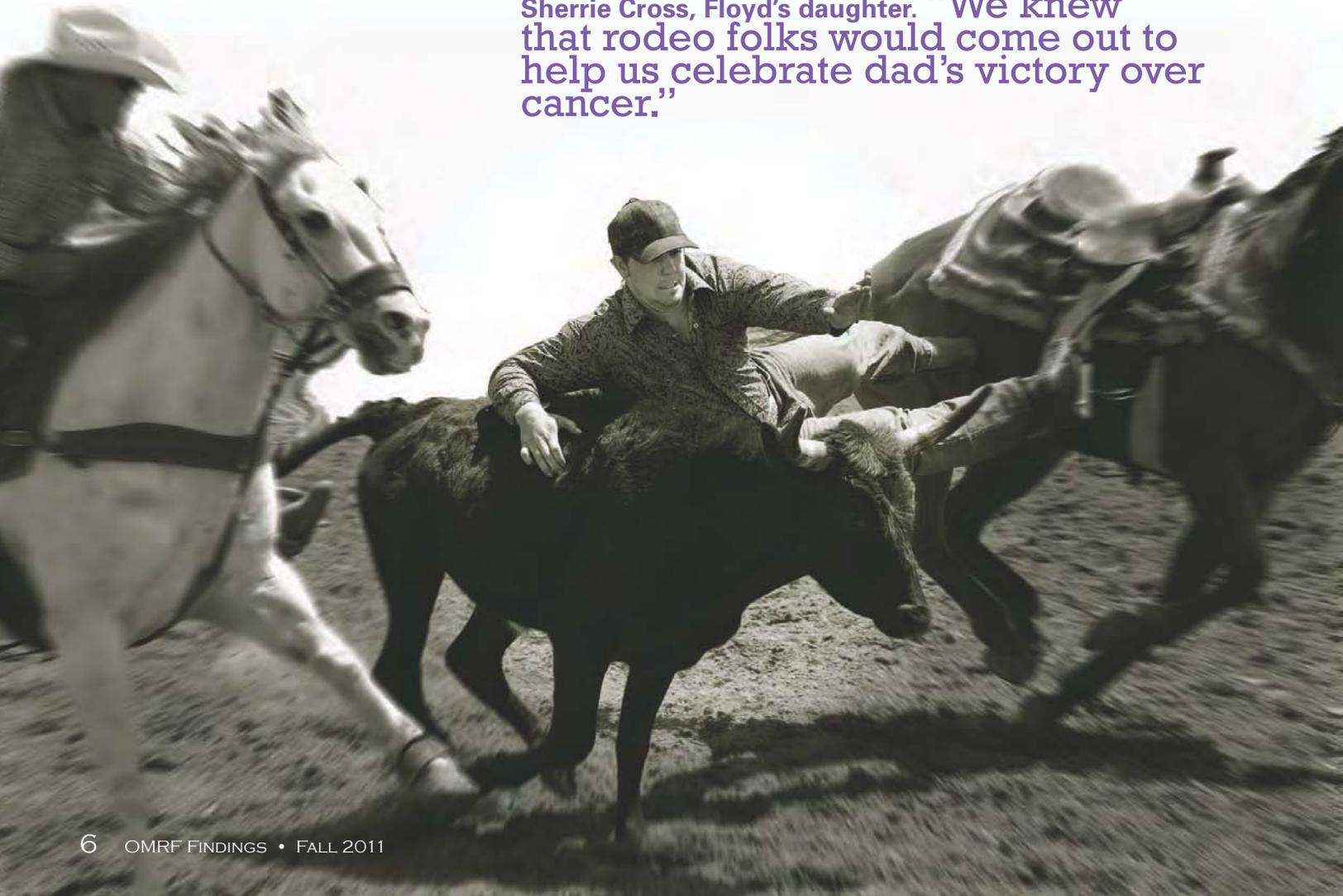
Taking the Bull by the Horns



Floyd Cross was a bulldogger. But, he discovered, taking down a steer is nowhere near as tough as taking down cancer. For 12 years, he lived with the disease. It invaded his colon and liver, threatening his life time and again. But thanks to new treatments developed through research, he is now cancer-free.

To celebrate Floyd's victory, his family organized the first annual "Tough Enough to Wear Purple" steer wrestling competition in their hometown of Kingfisher. On Mother's Day, 15 cowboys, most longtime friends of the Cross family, trekked from Kansas, Texas, Iowa and across Oklahoma to grapple with 500-pound steers in the triple digit temperatures. Their efforts netted more than \$3,000 for OMRF research.

"In rodeo, everybody helps everybody," says Sherrie Cross, Floyd's daughter. "We knew that rodeo folks would come out to help us celebrate dad's victory over cancer."





Send your health questions to Dr. Stephen Prescott at askDrP@omrf.org.

Ask Dr. P

Don't sweat it Actually, on second thought...

Last year, the Oklahoma City Memorial Marathon took place on an unseasonably warm day, and I melted down, running 35 minutes slower than my best. When temperatures were downright chilly this year, I set a new personal record. **What can I do to ensure that I run well, regardless of the weather?**

Penny Voss, Norman

The key to acclimation is to exercise daily. And here's the no-fun part—in the heat. You want to be sure you are sweating profusely. In the summer in Oklahoma, that's no problem. But if you find yourself in cooler climates, you may want to throw on a little extra clothing. Odd as it may seem, the better you're adjusted to the heat, the more you sweat, so you want to teach your body to open those spigots and let flow.

If you're having a hard time dealing with the heat, it's okay to cut back on the intensity of your workouts. On balance, the most important thing is to spend more time exercising in the sweltering temperatures. Better to go slow and long than short and intense.

THE BOTTOM LINE

When the mercury skyrockets, it's important to train in the heat beforehand.

The science of sweat



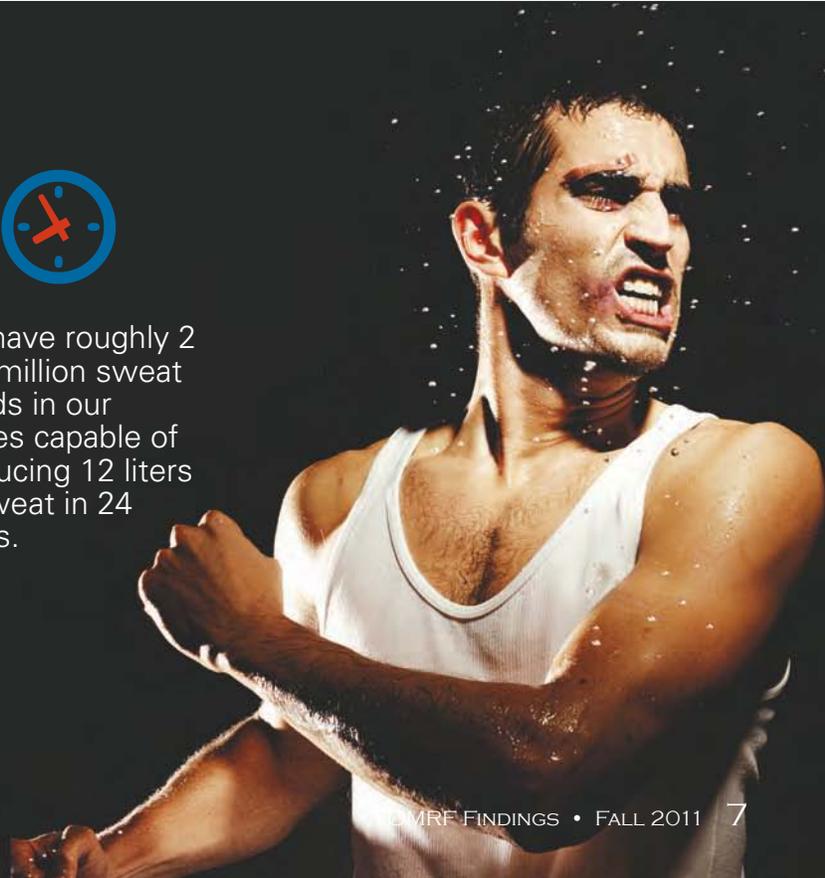
Men sweat 40 percent more than women do, but women actually have more sweat glands.



The hypothalamus area of the brain controls perspiration, sending signals to glands to produce sweat.



We have roughly 2 to 4 million sweat glands in our bodies capable of producing 12 liters of sweat in 24 hours.



What I'm...

At OMRF, scientists spend long hours designing experiments and investigating the inner workings of disease. But they don't live their entire lives behind a microscope. Here's what they're doing when they're not in the lab.

Doing

Dr. Jana Barlic-Dicen



"When I moved to Oklahoma two years ago, I bought a house in the right location and with the right floor plan but not much else. Since then, I've renovated the inside almost all by myself, with some help from professionals on electrical and plumbing systems. It's starting to look exactly the way I want it. With the insides taking shape, I'm now focusing on the outside, especially the flower beds."



Reading

Dr. Linda Thompson



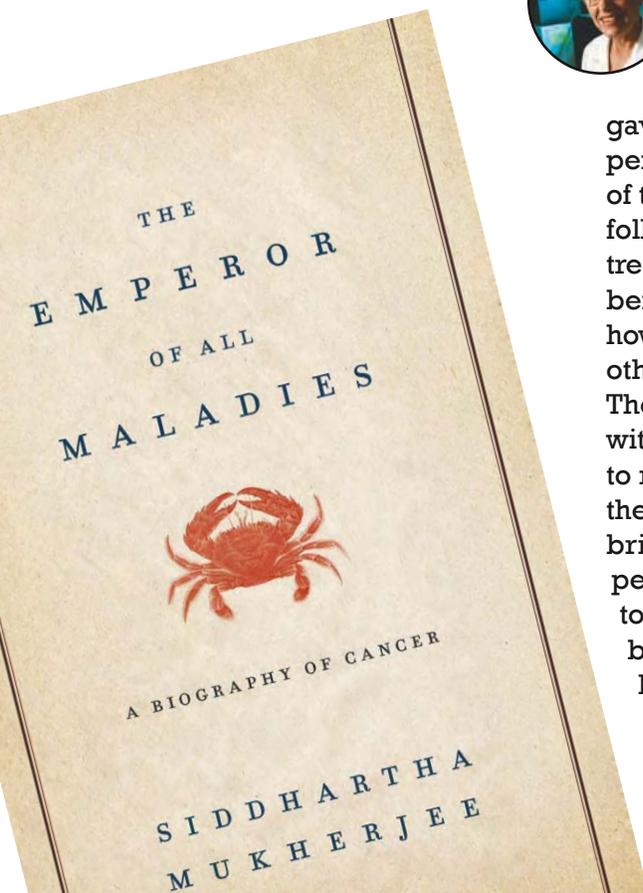
"I study cancer in the lab, but the book *The Emperor of All Maladies: A Biography of Cancer* by Siddhartha Mukherjee

gave me a whole new perspective on the history of the disease. The author follows stories of cancer treatment in its early days before chemotherapy and how it developed along with other modern treatments. The book includes interviews with people who were the first to receive game-changing therapies. Their stories really bring the subject to life. It's perfect for people who want to learn more about cancer but don't have a scientific background."

Watching

Dr. Kenneth Humphries

"If the TV is on at my house, I'm not really in charge. More often than not, it's tuned to *Mickey Mouse Clubhouse*, *Yo Gabba Gabba* or *Ni Hao Kai-Lan*, my two-year-old son Liam's favorite cartoons. But when I get a turn with the remote control, I'm a big fan of *Mythbusters*. It's not the best science in the world, but I appreciate that they look at a problem, come up with a hypothesis and try to test it. Besides, **I really like watching people blow things up—for science!**"



Grants Awarded

Dr. Marta Alarcon-Riquelme, *Identification of Susceptibility Genes for SLE of Amerindian Origin in Hispanics*, National Institute of Arthritis and Musculoskeletal and Skin Diseases; *An Analysis of the Novel Gene Bank1 on B-cell Function*, Oklahoma Center for the Advancement of Science and Technology

Dr. Jana Barlic-Dicen, *The Role of the Chemokine Receptor CXCR4 in Obesity*, Oklahoma Center for the Advancement of Science and Technology

Dr. Robert Barstead, *A Gene Knockout Resource for C. Elegans*, National Human Genome Research Institute

Dr. Hong Chen, *Epsin in Angiogenesis and Vascular Remodeling*, National Heart, Lung and Blood Institute; *Inhibiting Epsin: A New Anti-Cancer Strategy*, Oklahoma Center for the Advancement of Science and Technology

Dr. Mark Coggeshall, *Molecular and Immunologic Analysis of the Pathobiology of Human Anthrax*, National Institute of Allergy and Infectious Diseases

Dr. Dean Dawson, *Meiotic Centromere Behavior in Yeast*, National Institute of General Medical Sciences

Dr. Robert Floyd, *Pre-Clinical Study of Combination Oral Treatment for Acute Acoustic Trauma*, Office of Naval Research

Dr. Patrick Gaffney, *Molecular Mechanisms and Genetics of Autoimmunity*, National Center for Research Resources; *Candidate Causal Variants in Systemic Lupus Erythematosus*, National Institute of Arthritis and Musculoskeletal and Skin Diseases; *TNFAIP3 (A20) and Susceptibility to Systemic Lupus Erythematosus*, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Gary Gorbsky, *Chromosome Movement in Prometaphase*, National Institute of General Medical Sciences

Dr. Courtney Griffin, *ATP-Dependent Chromatin-Remodeling Complexes and Vascular Development*, National Heart, Lung and Blood Institute

Dr. Timothy Griffin, *Stimulating Endogenous Cartilage Antioxidant Capacity*, Oklahoma Center for the Advancement of Science and Technology

Tim Hassen, *OMRF GAIIX Equipment*, Health Resources and Services Administration

Dr. Kenneth Humphries, *Mitochondria in Cardiac Ischemic Preconditioning*, Oklahoma Center for the Advancement of Science and Technology

Dr. Rita Issa, *Biomedical Regulation of Oxidative Homeostasis in Articular Cartilage*, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Judith James, *Oklahoma Rheumatic Disease Research Core Centers*, National Institute of Arthritis and Musculoskeletal and Skin Diseases; *Predicting Systemic Autoimmunity Through Follow-Up of Blood Relatives*, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Susan Kovats, *Regulation of Dendritic Cells by Estrogen Receptors During Influenza Infection*, National Institute

of Allergy and Infectious Diseases; *Sex Differences and Estrogen Receptors Regulate Dendritic Cells in Inflammation*, National Institute of Allergy and Infectious Diseases

Dr. Florea Lupu, *Validation of Extracellular Histones as Biomarker and Therapeutic Target in Sepsis*, National Institute of General Medical Sciences; *Fluorescence Life Time Imaging Instrument*, Oklahoma Center for Adult Stem Cell Research

Dr. Kenneth Miller, *Forward Genetic Analysis of the Synaptic GS Pathway*, Oklahoma Center for the Advancement of Science and Technology

Dr. Courtney Montgomery, *African American Sarcoidosis Genetics Resource*, National Heart, Lung and Blood Institute

Dr. Kevin Moore, *Identification of Tyrosine-Sulfated Proteins in the Male Genital Tract*, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Dr. Kathy Moser, *Lupus Multiplex Registry and Repository*, National Heart, Lung and Blood Institute; *Susceptibility Genes in Primary Sjögren's Syndrome*, National Institute of Dental and Craniofacial Research; *Genetic Basis of Human Sjögren's Syndrome*; Sjögren's Syndrome Foundation

Dr. Swapan Nath, *SLE Susceptibility and Clinical Significance at 2q22-24 Across Multiple Ethnicities*, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Roberto Pezza, *MND1 and HOP2 in Homologous Recombination*, Oklahoma Center for the Advancement of Science and Technology

Dr. James Rand, *Regulated Splicing of the Cholinergic Gene Locus*, National Institute of Neurological Disorders and Stroke; *Synaptic Mutations and Oxidative Stress*, Oklahoma Center for the Advancement of Science and Technology

Dr. William Rodgers, *RAfT Protein Clustering by the Actin Cytoskeleton*, Oklahoma Center for the Advancement of Science and Technology

Dr. Xiao-Hong Sun, *Notch-Induced Protein Degradation in Lymphopoiesis*, National Institute of Allergy and Infectious Diseases

Dr. Luke Szweda, *Modulation of Mitochondrial Function by Pro-Oxidants*, National Institute on Aging

Dr. Linda Thompson, *The Regulation of Inflammatory Responses by CD73*, National Institute of Allergy and Infectious Diseases

Dr. Lijun Xia, *The Role of Mucin-Type O-Glycans in Intestinal Inflammation*, National Institute of Diabetes and Digestive and Kidney Diseases; *Glycoengineering EPCS for Therapeutic Neovascularization*, Oklahoma Center for the Advancement of Science and Technology

Dr. Jane Yaciuk, *Role of PTPRkappa in Lck Regulation During T Cell Development*, National Institute of Allergy and Infectious Diseases



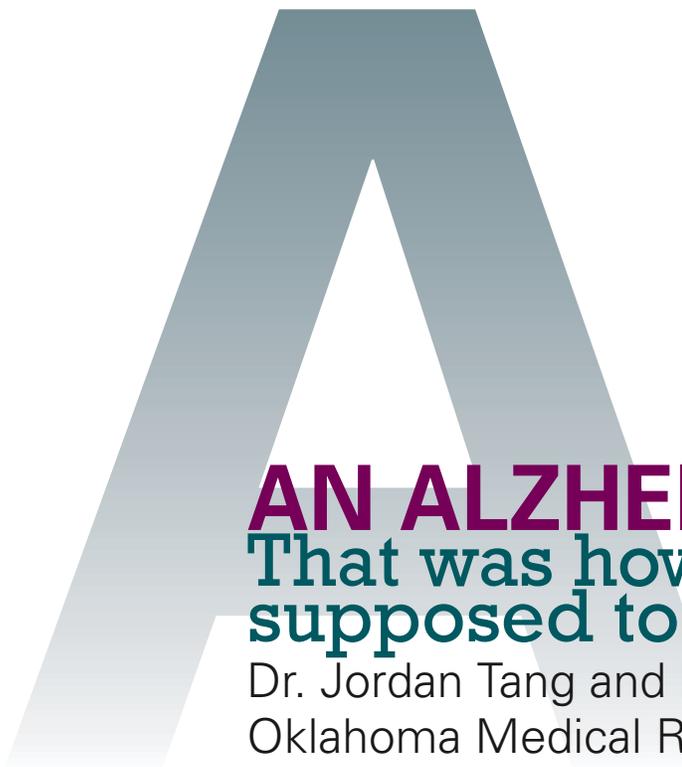
Unfinished
Jordan Tang
BUSINESS
Is Not Done With

By Adam Cohen • Photos by John Jernigan



Research

Alzheimer's Yet



AN ALZHEIMER'S DRUG.

That was how the story was supposed to end.

In 1999 and 2000, Dr. Jordan Tang and his team of researchers at the Oklahoma Medical Research Foundation made an extraordinary series of Alzheimer's breakthroughs. First, they identified the enzyme believed responsible for the disease and cloned it. Then they developed an inhibitor that stymied the enzyme.

Understandably, the work created sky-high expectations. The reasoning went something like this: Here is a deadly, memory-robbing disease with no effective treatments, and Tang seems to have figured out a way to stop it. His fix worked in a test tube. But how long would it be until he transformed his work into an effective drug to treat people suffering from Alzheimer's?

Stories ran everywhere from the *Los Angeles Times* to CNN. Tang even appeared on "The Early Show" on CBS. In 2001, OMRF's then-president told a magazine, "These are monumental discoveries. I will be stunned if a decade from now, corner drugstores are not selling a drug to inhibit Alzheimer's disease that came out of this foundation." Well, that decade has passed. The Alzheimer's treatment landscape looks about as bleak as it did ten years ago. The few available drugs are, at best, band-aids for a disease that cries out for much, much more in the way of treatment.

And what of a drug based on Tang's discoveries? No, you can't find it on the shelves of your local pharmacy. As is so often the case, reality proved far more complicated than first imagined. **But the dream of an Alzheimer's drug is far from dead.**

Asking Tang about Alzheimer's research feels a little bit like talking to Neil Armstrong about the moon landing. Or discussing Harry Potter with J.K. Rowling. Surely, his eyes say, there must be something else we can discuss. But as the state's best-known Alzheimer's researcher, he understands the role that's been thrust upon him: educating the public about the disease that has defined the last 12 years of his scientific life.

"I know the magnitude of tragedy that's involved when people find out their loved ones have this terrible disease," says Tang. He speaks softly, his voice just above a whisper. "But when people turn to me for answers, I feel powerless, because we don't yet have a treatment."

He's just come from a lunch where he'd given a talk about Alzheimer's disease. With 5 million Americans, including 1 in 2 people over the age of 85, suffering from the illness, Tang receives frequent requests to speak on this topic. "I know how desperate the situation is. I have personal acquaintances with the disease. People in my lab—two of their parents had Alzheimer's." He grows quiet, his dark eyes seeming to search the room for a delicate way to express this next thought. "But you can't get emotional about it. Because if you do, it will interfere with your work."

Tang is an unlikely standard-bearer in the quest to stop Alzheimer's. For more than four decades, his work had nothing to do with the human brain. Rather, he focused his research on a group of cutting enzymes known as proteases.

Proteases play roles in many different processes in the body. But their essential function is to act as a sort of biological scissors, breaking complex proteins down into simpler constituent parts. In his early work, Tang discovered a previously unknown protease in the stomach. He then spent the better part of a decade unlocking the chemical structure of a similar protease that plays an important role in the digestive process.

When scientists discovered that this stomach enzyme was quite similar to a protease that controls blood pressure, Tang moved his work into the field of hypertension as well. In particular, using techniques he'd developed when working with stomach proteases, he created an inhibitor he hoped could form the basis of a drug to lower blood pressure. He developed a molecule that acted as a sort of chemical chewing gum that stuck to the enzyme's scissor-like blades, thus preventing their cutting mechanism. But while the inhibitor fared well in laboratory tests, the results did not play out in human clinical trials; the inhibitor proved too large and interfered with the cutting mechanisms of other vital enzymes in the body.

Tang's work took an unexpected turn in the 1980s, when research revealed that the ability of the AIDS virus to replicate itself hinged on the action of a protease. For the next decade, tapping on the knowledge he'd acquired working with the proteases involved in digestion and regulating blood pressure, he laid the scientific groundwork for inhibitors that

would stop the AIDS virus from replicating. These inhibitors became key ingredients in potent HIV-fighting therapeutics that have added years to the lives of people suffering from the disease.

In the late 1990s, scientists assembled the first rough sequences of the human genome. Dr. Gerald Koelsch, a researcher in Tang's lab, suggested they search the data for new proteases. In 1999, Tang's team discovered a previously unknown protease. The enzyme, which Tang named memapsin 2, was present in several organs throughout the body. Most puzzling of these sites was the brain.

"Why would there be a cutting enzyme in the brain?" Tang remembers asking himself at the time. "Is it possible this enzyme might play a role in Alzheimer's disease?"

Researchers had known that the brains of Alzheimer's patients contained an abundance of plaques, clumps of protein and cellular material that cannot dissolve and pile up like garbage. Using the expertise they'd developed in many years of working with proteases, Tang's team synthesized memapsin 2 and "fed" larger brain proteins to the enzyme in a test tube. They found that this newly discovered protease sliced a particular protein and created the same fragments that, when clumped together, formed plaques in the brains of Alzheimer's patients. These fragments, most experts agree, disrupt and destroy brain cells, leading to memory loss and dementia.

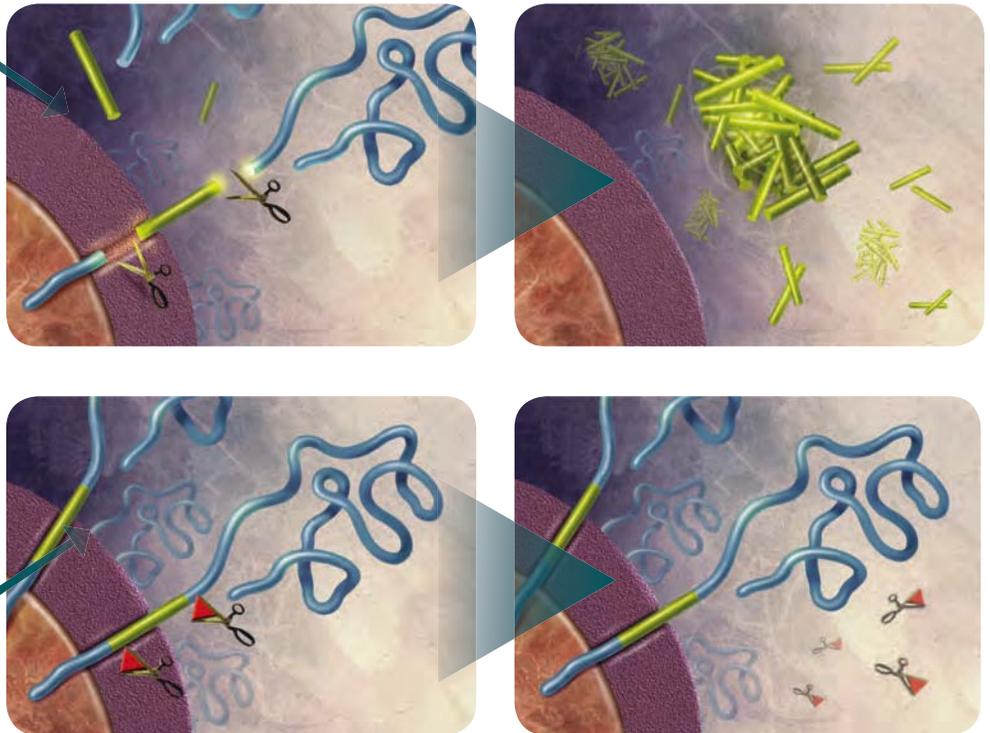
Tang's team had, it appeared, discovered the culprit behind Alzheimer's disease.

If the researchers could figure out a way to prevent the enzyme from cutting, they realized, they could halt the creation of fragments and the build-up of plaques. And if they could do that, they might be able to stop Alzheimer's.

In Alzheimer's, **SCISSOR-LIKE ENZYMES** attack proteins in the human brain to create protein fragments believed to cause the disease.

Inside The Alzheimer's Brain

Dr. Jordan Tang has created **INHIBITORS** that stop the enzymes from cutting and leave brain proteins intact.



W

Within months of this breakthrough, Tang's team took another major step forward. Working in collaboration with Dr. Arun Ghosh, a synthetic chemist then at the University of Illinois-Chicago, the researchers designed a chemical inhibitor that stopped memapsin 2's cutting mechanism. "From our work in blood pressure and HIV, we knew a great deal about designing protease inhibitors," says Tang. "That gave us a big advantage."

In a test tube, the inhibitor acted as a sort of "chemical chewing gum," says Tang. It enticed memapsin 2 to take a bite out of it, but when the protease chomped down, the inhibitor stuck to its scissor-like "jaws," preventing it from making any further cuts. If the protease couldn't slice, then plaques couldn't form. And this, many researchers hypothesized, could delay or even prevent the progression of Alzheimer's disease.

In other words, Tang's inhibitor had all the hallmarks of a promising drug candidate for Alzheimer's disease.

But the key word here is "candidate." Although the inhibitor worked splendidly in a test tube, a test tube is not a human being. "What we had was potent, but it was nothing like a drug," says Tang. "If you put it into the body, it wouldn't get to the brain. It wouldn't stick around long enough to do the job."

Even if the molecule Tang and his collaborators had created could be transformed into a so-called biologic that would remain in the blood—rather than immediately being broken down by the body—and eventually penetrate the brain, that would not be the end of the story. Trials would then take place in lab animals to determine whether the drug was effective and safe in slowing or stopping the progression of Alzheimer's-like conditions.

Success in these "pre-clinical" phases would open the door for filing an investigational new drug application with the US Food and Drug Administration. If the FDA okayed the application, this would initiate a new chapter: human clinical testing. This multi-phase process entails administering the drug to progressively larger groups of people to assess the drug's safety and effectiveness. For a disease as prevalent as Alzheimer's, the final phase of this process would involve thousands of patients at hospitals and clinical sites on multiple continents. Only after the drug had successfully completed all of these steps would its manufacturer seek final marketing approval from the FDA.

"Transforming a laboratory discovery into a drug that works in people is like trying to scale Mount Everest," says OMRF President Stephen Prescott, who has worked extensively in the area of drug development. "The process involves incredible amounts of hard work, endurance and luck, and the odds of any discovery making it to the top are extremely slim."

Indeed, the vast majority of promising drug candidates ultimately fail. According to a study from the Tufts Institute of Drug Development, of every 5,000 potential new drugs tested in animals, only five are promising enough to be tested



WINNING TEAM In 1999 and 2000, Dr. Jordan Tang led a group of OMRF researchers that made groundbreaking advances against Alzheimer's. Pictured (clockwise from left forefront): Drs. Lin Hong, Robert Turner, Jacques Ermoleiff, Jeff Loy, Gerald Koelsch and Tang

in humans. Of those five that begin human testing, only one earns FDA approval for marketing. For those few drugs that do reach the market, the climb is long and expensive; the Tufts researchers found the process averages a dozen years and costs close to \$1 billion.

Nonprofit research institutes like OMRF do not have \$1 billion—or anything close to that amount. With limited resources, they must focus their efforts on limited areas. In OMRF's case, that means discovery science.

"We take the first steps toward creating treatments," says Prescott. "But then we have to find partners capable of helping shoulder our discoveries to the summit." In the world of drug development, those partners are typically pharmaceutical companies.

When Tang published his early work in scientific journals, more than a dozen drug makers beat a path to OMRF's door. "Their goal was to make as much money as they could," says Tang. And they wanted to do the drug development without us." Those aims, he says, "weren't the ideas we had."

"Our concern was not money. We simply wanted to get a treatment for Alzheimer's to patients as fast as possible," says Tang. Plus, he says, with a long track record of developing protease inhibitors, "we felt we had the knowledge and experience to help." But Tang and OMRF recognized that drug development was so expensive that it couldn't be funded through the typical channels available to a nonprofit research institute: competitive research grants from agencies and philanthropic support. So OMRF opted to go a different way. "We decided to form a company of our own to compete with big pharma," says Tang.

OMRF started a company that it named Zapaq. "The

name was short for ‘zap the plaques,’” says Tang with a little laugh. “Because that’s what the goal was”—preventing the accumulation of Alzheimer’s-causing plaques in the brain. The company would take the basic inhibitor designed by Tang and his collaborators and begin the time-consuming, expensive process of transforming it into a drug for people. As a for-profit business, Zapaq could attract capital in a way that a nonprofit like OMRF could not. And it did, drawing investments from the Oklahoma Life Science Fund and New York’s Institute for the Study of Aging. Still, with the investors’ total stake topping out at slightly over \$1 million, Zapaq didn’t seem to stand a chance against behemoths like Merck and Pfizer, which had billions of dollars of cash on hand to bankroll such projects.

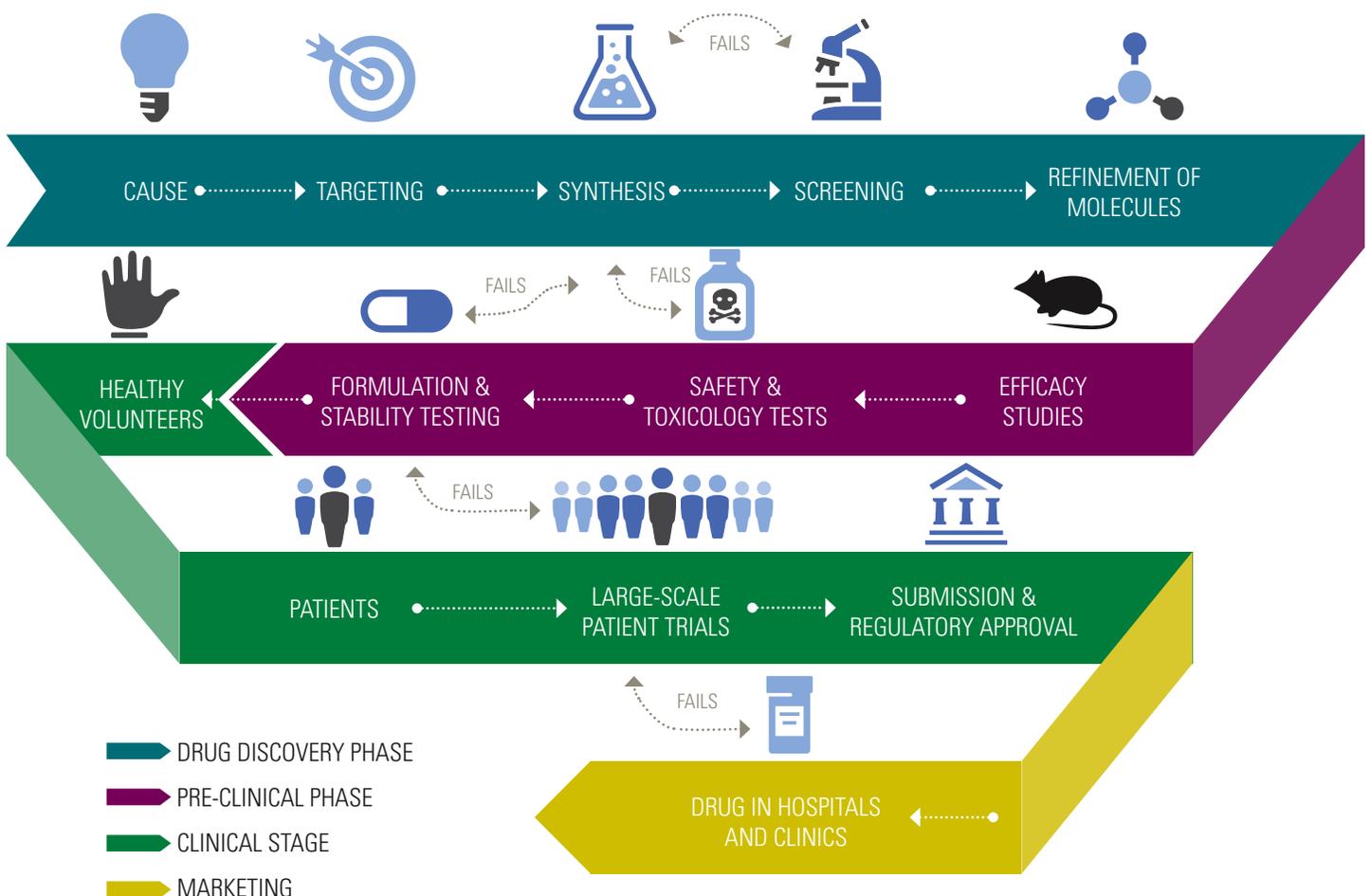
“With start-up companies, your initial goal is not to reach the summit,” says Prescott. “Your aim is simply to make as much scientific progress as possible. And, you hope, by the time you’ve exhausted that first round of funds, you’ve moved far enough down the path to attract more investment.” In other words, it’s a sort of pay-as-you-go proposition. As might be expected, such ventures are risky and come with a low probability of success. “That’s why,” he says, “investors in early-stage companies are known as ‘angels.’”

Zapaq shied away from big capital investments, rationing precious funds so as to focus on a pair of key scientific projects. First, a team of chemists synthesized new variations of the basic inhibitor pioneered at OMRF. Then researchers studied the biochemical and crystallographic properties of these newly created molecules.

“We made several hundred new compounds and evaluated them along the way,” says Tang, who acted as a scientific consultant to Zapaq in the company’s early stages. “It’s trial and error, and you’re constantly examining which direction you can move to build inhibitor structures that could create a more effective drug. The process is extremely complicated, because there are 10,000 different ways you can change an inhibitor.” The ideal candidate would have to be extremely small, allowing it to move from the bloodstream to the brain. It would also have to possess the proper shape to bind to its target. And it would have to disable only memapsin 2—not any of the many other proteases (like stomach enzymes) that perform vital functions in the human body.

Drawing on their experience in the realms of HIV and hypertension, the researchers developed scores of new inhibitors. Over time, the candidates they designed became more selective and potent. In other words, they zeroed in

The Drug Development Process



on the memapsin 2 protease, and they were growing more effective at disabling the cutting action of the enzyme. When Zapaq scientists tested them in test tubes and cell culture dishes, the newly synthesized compounds appeared much more “drug-like” than the basic inhibitor first engineered by Tang and Ghosh.

Still, Tang felt Zapaq could continue to refine its work and develop compounds that were even better. Then it would need to move to the next stage: studying those compounds in living organisms. That meant administering the inhibitors to laboratory rats and mice and assessing the animals’ reactions.

Those next steps carried a price tag that totaled millions of dollars. And Zapaq was running out of money.

S

Start-up companies are like zombies in horror movies. Just when you think they’re dead, they spring to life again.

In 2004, on the strength of the progress it had made designing its inhibitor, Zapaq received \$6 million in financing from a pair of leading venture capital firms. With this infusion of capital, the company spent the next two years developing hundreds of new inhibitors. From those, it identified the most promising candidates and began testing them in mice genetically engineered to develop a condition resembling Alzheimer’s. By 2006, results from several of the compounds pointed to the next step: testing in humans. But clinical testing is expensive, especially for a small company with limited resources. So if Zapaq was going to move forward, it would have to put all its eggs in one basket; it would have to choose a single inhibitor to undergo human clinical trials.

To provide the company with the capital necessary to continue, the venture capitalists gave Zapaq another infusion of cash. This funding, known in finance circles as a “series B round,” once again shrunk OMRF’s ownership stake in the company, to the point that the foundation held only a tiny fraction of Zapaq’s stock. That, says Prescott, was exactly what OMRF had anticipated from the get-go.

“When we start a company, we never do it with the goal of making money. In fact, we know that for OMRF, there’s no pot of gold at the end of the rainbow. But to translate our discoveries into treatments for human disease, this is the only path available.” If those investments yield any proceeds, he says, “We pour them right back into disease research.”

With this new round of funding, the venture capitalists decided to merge Zapaq with another biopharmaceutical company they owned. The new, combined company would have a new name, CoMentis. It would also have a new management team and move its corporate headquarters to California. “The merger,” says Tang, “effectively weaned the company from OMRF.”

Although Tang did not have an active hand in CoMentis’ scientific operations, his legacy loomed large. When it came time to choose an initial lead compound, the company’s scientists selected one known as CTS 21166, an inhibitor

based on Tang and Ghosh’s work. Then CoMentis filed an investigational new drug application with the US Food and Drug Administration and prepared to begin human clinical testing.

The initial round of testing, known as Phase I, would involve administering the drug to healthy volunteers and assessing its safety. In 2007, CoMentis began this phase with an intravenous form of the drug. The following year, when it developed a pill version of the drug, it initiated a second clinical trial.

This was no small feat. At the time, says Tang, many big pharmaceutical companies were working on similar drugs, known technically as beta secretase inhibitors. “But here was a company with less than 20 people initiating the first—and second—Phase I trials on its beta secretase inhibitor. The little guy had beaten a group of 800-pound gorillas!”

The trials proved a success. “As far as Phase I testing goes, we could not have expected better results,” says Tang. Both formulations of the drug showed no side effects in human subjects. Data also suggested that the drug would prove effective in keeping Alzheimer’s at bay when administered to patients suffering from the disease.

In 2008, Japanese pharmaceutical giant Astellas entered into an agreement with CoMentis. In exchange for an investment that could amount to as much as \$760 million, Astellas would become partners with CoMentis in developing an Alzheimer’s drug. The funds would give this once-tiny company all the capital it would need to take an experimental drug all the way through clinical trials and, if successful, to market.

Since that time, CoMentis has not initiated any additional trials of CTS 21166. Tang is no longer involved in the company’s operations, so he is not privy to its inner workings or decision-making. Of course, he’d like nothing more than to see CTS 21166 or one of its sister compounds reach the market. “This is a terrible disease, and there’s so much need.”

That still may come. But, he says with a shrug of resignation, it’s something he’s learned to accept that he cannot control. “The job of scientists is to make discoveries and publish those findings. We’ve done that. We’ve done our job.” Now, he says, “It’s in the company’s hands.”

That might be the end of the story, at least as far as Tang and OMRF are concerned. The narrative arc would go something like this: Scientist makes groundbreaking discovery, hands it off to corporate partner, hopes for the best.

But Jordan Tang is no ordinary scientist.

For a half-century, he’d picked apart proteases. If they were at the heart of Alzheimer’s, there was no one better suited to solve this mystery than he. Besides, sitting still and leaving the work to others just isn’t a part of Jordan Tang’s DNA.

As CoMentis continued to evolve its inhibitors, Tang and his lab branched off to explore other facets of Alzheimer’s. In 2007, they uncovered a molecular mechanism that helped explain why individuals with a certain gene are at a higher risk for the disease. Later that year they showed that vaccinating mice bred to develop symptoms of Alzheimer’s with memapsin 2 could slow or even prevent the onset of disease. This work, says Tang, was “extremely exciting.” “What we saw is that the mice immunized with memapsin

2 developed fewer plaques than mice who didn't receive the vaccine. Those immunized mice also performed better than control mice in tests that assessed their cognitive function."

Tang saw the work as a complement to his work on inhibitors. "Like cancer and heart disease, Alzheimer's is a complicated, multi-faceted disease. It demands that we develop many different approaches to combat it, because what works in one patient will not necessarily work in another." Despite promising early results, though, the vaccination project stalled following the mouse studies. "The next step"—progressing the research to the point that vaccines could be tested in humans—"required a lot of money. And no one wanted to pay for it."

But Tang refused to be discouraged. Instead, he kept pushing ahead on other fronts. In particular, he focused his efforts on developing new inhibitors.

"Alzheimer's is untested territory, and the odds for any single drug are not good," he says. "So instead of sitting there and hoping one will be perfect, you have to have multiple tracks of attack." In other words, you have to keep churning out new, more promising candidate compounds. And that's exactly what he's done.

Last year, in the scientific publication *FASEB Journal*, Tang published a study showing the effects of administering a new experimental compound to Alzheimer's mice. Using mice genetically altered to exhibit Alzheimer's-like symptoms, Tang's lab treated some of the animals with another new inhibitor he and Ghosh had developed. The animals that received the compound developed 75 percent fewer disease-

causing plaques than untreated Alzheimer's mice. The treated mice also performed significantly better on memory tests. In those tests, where the animals had to remember the location of a platform in a pool full of opaque liquid, the mice who received the experimental compound performed nearly as well as healthy mice without the Alzheimer's gene.

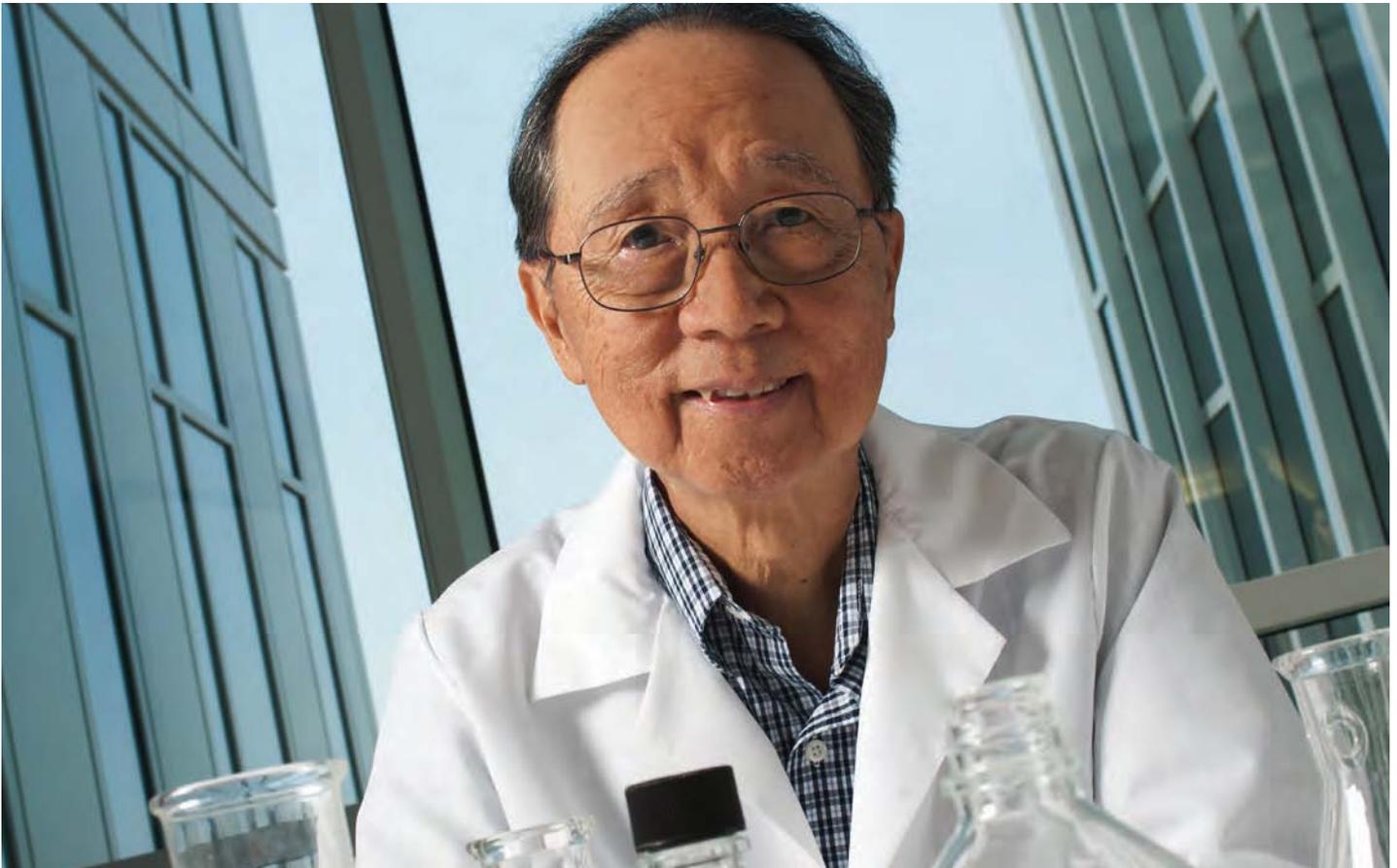
"Once again, these are remarkable results," says Prescott. "Every time Dr. Tang makes a new insight, I think, 'Fantastic, but surely he can't take this any further.' And then he does."

At the moment, Tang is working with this compound and 30 or so other inhibitor candidates that he and Ghosh have developed. By continually improving, testing and refining these compounds, he believes they can develop a lead candidate for a next generation of inhibitors. That candidate would eventually become a new experimental Alzheimer's drug that would go to human clinical trials. Which would require—cue the theme from *Groundhog Day*—lots of money.

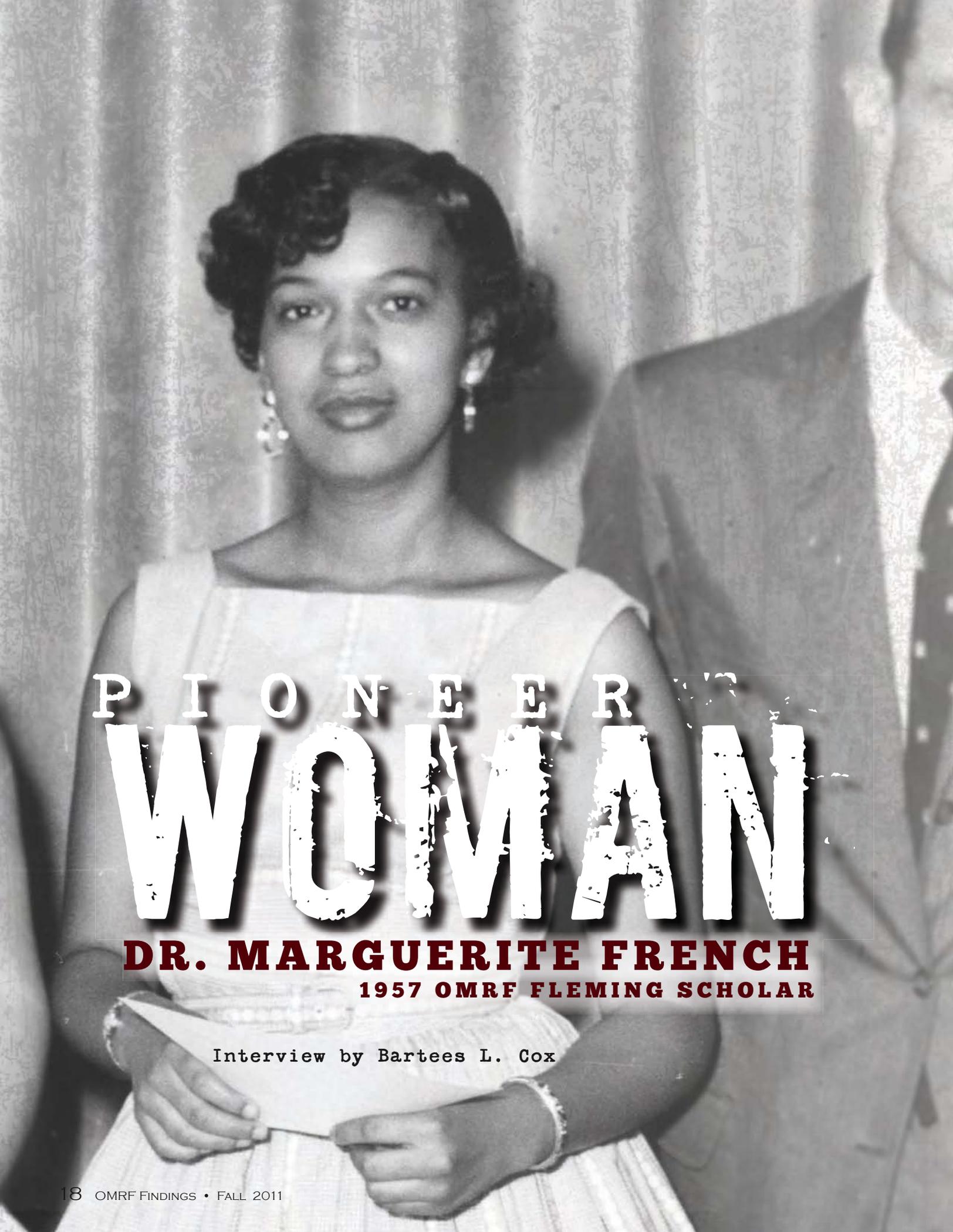
So that means drug companies and commercial partners, right?

Tang lets out a deep breath and shifts in his chair. It's almost palpable, the weight he feels in carrying the hopes and expectations of so many. "We won't worry about those things until we get there."

Then the edges of his mouth turn up, and with them the corners of his eyes. "But wouldn't that be a nice problem to have?" He grins. Broadly. It's the kind of smile that comes when you imagine what it's like to reach the summit at last.



"If all of what we have learned about Alzheimer's is correct, **there will be a drug**," says Tang. "But I can't tell you when."



PIONEER
WOMAN

DR. MARGUERITE FRENCH
1957 OMRF FLEMING SCHOLAR

Interview by Barteas L. Cox



I thought of myself as a typical teenager.
Just an **Okie from Muskogee**.

Back then, the **TOWN** was still
divided, with a railroad track
separating the black and white sides of
town.

When I was 17, I scored well on the Iowa
Test of Basic Skills. My high school science
teacher nominated me for OMRF's Sir
Alexander **Fleming Scholar
Program**.

It was only three years after Brown vs.
Board of Education, two years after
Rosa Parks sat at the front
of the bus.

I was the **first African-
American** selected as a
Fleming Scholar.

When I got to OMRF, I can't recall any
SEGREGATION. We scholars
did everything together.

The highlight of my summer came when I
met **President Dwight Eisenhower**.

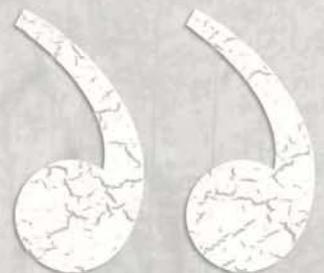
I was **nervous**, but he was kind and
soft-spoken.

He asked what I wanted to be when I grew
up. Without hesitating, I said, 'I want to be
a **doctor**, just **like my father**.'

After **medical school**, I
worked as a pediatrician for a few years,
then I went into **psychiatry**.

One ear infection looks just like another,
but the **joy** of psychiatry is seeing each
person's life unfurl differently.

OMRF was an **absolute miracle** for me. I
learned that there was a whole, big world
out there just waiting to be explored.





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Meet our scientists

WORK



AT OMRF, DR. LIJUN XIA STUDIES SUGARS CALLED O-GLYCANS, WHICH HELP THE BODY PROCESS FAT AND FATTY ACIDS.



PLAY

OUTSIDE THE LAB, LIJUN HAS BEEN CAPTAIN OF THE EDMOND CHINESE THUNDER BASKETBALL TEAM FOR NEARLY 10 YEARS.