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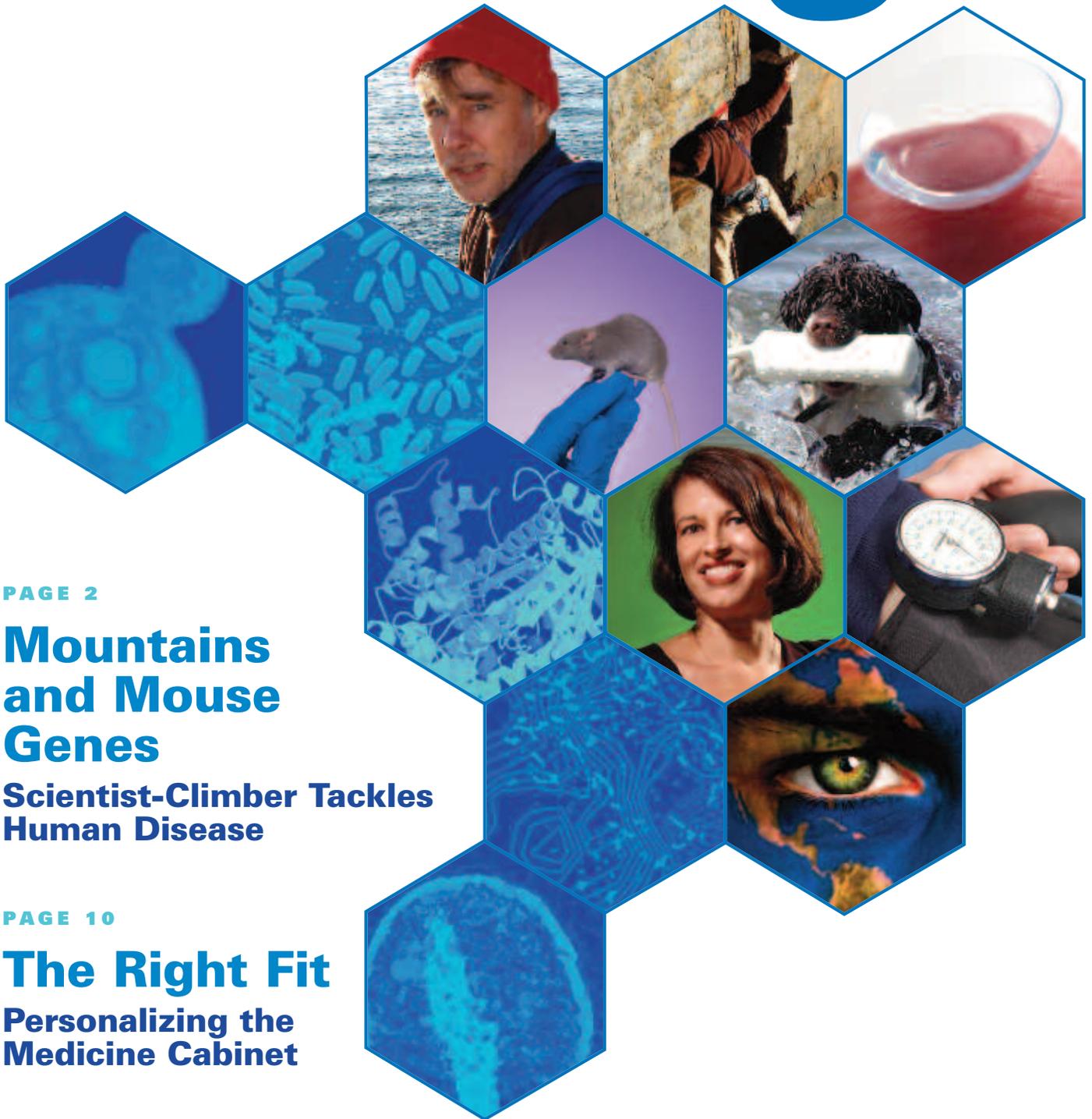
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Findings

MARCH 2010



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Scientist-Climber Tackles Human Disease

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The Right Fit

Personalizing the Medicine Cabinet



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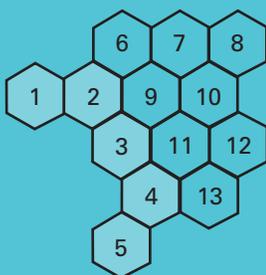
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Up Close With

Gary Churchill

BIostatistician

“Doing science is like bending the universe. It’s really magical.”

FAVORITE BOOK

The Mouse and the Motorcycle by Beverly Cleary. Good bedtime reading with my youngest son

PERSONAL HERO

My wife, Katie

HIDDEN TALENT

Carpentry. I built the most awesome tree house

CAREER ALTERNATIVE

Rock star

FRANÇOISE GENAIS



Mountains and Mouse Genes

BY STEPHANIE DUTCHEN

The massive boulder looms 12 feet tall, an imposing hulk of flecked, gray granite.

Gary Churchill, 6'0", stands at its base, thinking. Equipped with lightweight climbing shoes and chalk to sketch out a path, he studies the rock's pitted surfaces and jutting angles.

He's looking for the best way up.

Sometimes the path is obvious: Step here, grab there, and you're at the top. Other times, boulders yield fewer clues. Those are the ones Churchill loves most. Patience and focused attention help him figure them out.

Calmly turning the problem over in his head, he seeks an answer that is simple and elegant.

"If you solve it in the right way, you don't muscle your way to the top," Churchill says. "You float."

That steady determination comes into play even when Churchill isn't facing off against boulders and cliffs. It has also helped him forge an innovative and successful path in science.

Gene Guru

On Mount Desert Island just off the coast of Maine, in the soft shadow of Acadia National Park's tree-blanketed mountains, lies a cluster of brick buildings. Inside scamper thousands of specially bred research mice.

This is the Jackson Laboratory, a world-class scientific facility where researchers study mouse genetics to advance human medicine. Because our DNA is remarkably similar to that of these small, furry mammals, mice are an effective and efficient stand-in for our own bodies (see "Medical Mice," page 6).

When he isn't clambering up Acadia's cliffs and boulders, Churchill works here at the Jackson Lab. He's a biostatistician: a scientist who uses the precision of math to examine biology. His focus is on genes and disease.

Genes, in part, give us our mom's hair or our grandfather's nose. They make some of us tall and others petite. They also play a role in determining how healthy we are and what diseases we may be prone to.

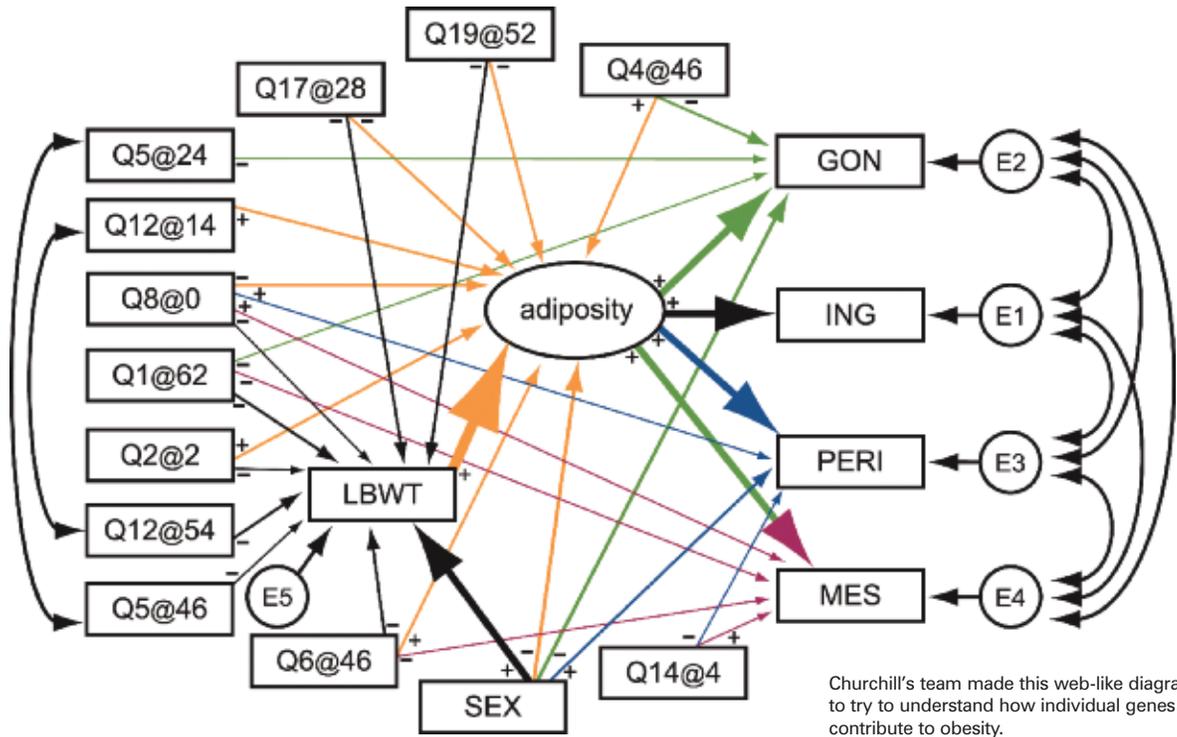


THE JACKSON LABORATORY

The Jackson Laboratory houses mice and scientists near Maine's Acadia National Park.



When it comes to studying genes, mice offer a lot



Almost a decade ago, the Human Genome Project recorded the precise order of the billions of DNA “letters,” or nucleotides, that string together to make the complete human genome.

Researchers have done the same for nearly 200 other organisms, including mice.

But even though these genomes have been “decoded,” knowing the nucleotide sequence is only the beginning. Researchers still need to figure out what it all means.

That’s where Churchill comes in.

Armed with an enduring curiosity and quick wit (friends and coworkers describe him as being “scary smart” and having a mind “like a sponge”), he brings together computational biologists, molecular biologists, geneticists, statisticians and other scientists to try to understand how different genes work together to influence human health.

Churchill calls this holistic approach systems genetics.

A Tangled Web

Today, doctors diagnose diseases based on measurable symptoms and lab tests. For instance, diabetes can be measured by a person’s blunted response to the hormone insulin, and heart disease can be measured by things like high cholesterol, high blood pressure and abnormal electrocardiogram readings.

But it’s not as simple as saying that gene X raises blood cholesterol, gene Y causes high blood pressure or gene Z creates insulin resistance.

That’s because our most common diseases—including heart disease, cancer, diabetes and obesity—have been linked to many, many genes. Like complicated machines, human bodies can break in myriad ways.

What’s more, our behavior has a big impact, too. What we eat, how we live and how much we exercise all affect whether we’ll get sick.

Trying to comprehend the genetic information alone overloads our

brains. So Churchill designs and runs computer programs to untangle these genetic webs and try to understand their role in sickness and in health.

His specialty is finding meaningful patterns within the billions of nucleotides that make up the mouse genome. He and his team are trying to link gene combinations to traits, including disease susceptibility.

This work could help make it possible to one day diagnose diseases using genetic signatures. Then doctors would have much more precise tests, enabling early detection and prevention that currently isn’t possible.

Of Mice and Maine

When it comes to studying genes, mice offer a lot of benefits over people.

For one thing, can you imagine conducting breeding experiments on people to narrow down genetic links to diabetes or depression?



Medical Mice

Mice don't walk on two legs, they don't watch

TV and they don't tweet (or squeak) moment-to-moment updates to their rodent friends online.

But they actually have a lot in common with us.

About 98 percent of human genes have a counterpart in mice, and mice get diseases that are similar or identical to ours.

For instance, mice are prone to getting cancers like we are. Their cancers grow in the same places ours grow, and their cancer cells look and function like ours look and function.

So it's not surprising that studying mice has taught us about how certain human diseases develop, how they make us sick and how they might be treated.

Because of such research, most children with acute lymphoblastic leukemia—who were once expected to live less than 3 months after diagnosis—can now lead long, healthy lives.



Lab mice have also helped us understand:

- Autoimmune diseases
- Obesity
- Diabetes
- Organ transplantation
- Memory and learning
- Stem cells

Mice, which are warm-blooded mammals, like us, help researchers explore questions that wouldn't be ethical or practical in people. In part, that's because mice breed fast and have short lifespans, so experimenters can study generations in months.

It's also because researchers can inbreed mice until their genomes are virtually identical. Such control helps researchers find "culprit" genes involved in disease.

Because mice aren't people, and because humans have much greater genetic variety than the inbred mice, the results don't necessarily translate right away to human health.

Nevertheless, projects like Gary Churchill's Collaborative Cross (see main story) give scientists a trail map that helps them design studies to investigate human diseases.

In 2007, three scientists won the Nobel Prize in physiology or medicine for their discovery of how to "cut and paste" genes into lab mice to help define genes' specific functions. Their technique has revolutionized medical research by allowing scientists to create so-called "mouse models" of human disease.

Not bad for a 1-ounce, twitchy-nosed rodent. —S.D.

continued from page 5

"I imagined myself in a lab full of bubbling test tubes and dinosaur bones," he remembers.

In high school, Churchill's love of science found its focus. Paleontology took a back seat when, in sophomore biology, Churchill learned about how mice can inherit different coat colors from their parents. Thinking that was "really cool," he decided to try some experiments at home.

"But my mom wasn't happy with that idea," he recalls with a rueful laugh. They compromised on fruit flies instead.

Churchill ordered his specimens from a science supply catalog, and soon his bedroom filled with containers stuffed with the tiny, short-lived insects. Some had red eyes and some had white ones.

Curious about how eye color is inherited, Churchill mated the flies, mated their offspring and mated the offspring's offspring. He took careful notes on the ratio of eye colors in each successive generation.

"Even then, I was counting things," he says.

It wasn't the scene he'd once imagined with skeletons and frothing beakers, but the fruit fly experiments gave Churchill his first taste of genetics, and he liked it. A lot.

Like many scientists, though, Churchill didn't follow a straight path to his research area. In college at the Massachusetts Institute of Technology in Cambridge, he tried physics, then electrical engineering, and dabbled in cognitive psychology. He eventually ended up in the math department (partly because it had the fewest required courses, he jokes).

Things finally clicked into place when he took a class in genetics taught by David Baltimore, who had recently won the 1975 Nobel Prize in physiology or medicine for his work on the genetics of cancer-causing viruses.

important in life than inspiring other people.

Looking at the endless combinations of the four nucleotides—A, T, C, G—that make up the genes of all living things, Churchill was mesmerized by unexpected patterns. He saw palindromes, symmetries, strings looping and folding back in on themselves.

The mathematician in him delighted in the play of numbers and structures.

"I was hooked," he says. "There was nothing I was going to do but this."

It's About the People

Large, mysterious creatures haven't quite gone extinct in Churchill's life, though.

Working with Randy Von Smith, then a program manager at the National Science Foundation, Churchill developed an educational program called GeniQuest. The 3-week module encourages high school students to think like geneticists as they use real analytical software and actual mouse data from the Jackson Lab to study how traits are inherited.

The students use virtual animals for their experiments, but the animals aren't mice. They're fictional creatures called dragons and drakes. Weighing less than 2 ounces and reproducing every 3 months, the little drakes are to hefty dragons as mice are to humans.

GeniQuest is a distillation of a bigger effort that Churchill helped develop, called Independent Studies in Computational Biology. This two-semester, distance-learning course teaches students at magnet high schools how to do what Churchill loves: combine mathematics and biology.



Churchill teaches Jackson Lab summer students how to be geneticists.

He guides students in both programs via Webcam and e-mail, and hosts students during special summer programs at the Jackson Lab.

Over time, Churchill's everyday job has evolved from delving into genetic patterns himself to more supervising and teaching. While he sometimes misses the intellectual rush of solving a math problem, he has found deep satisfaction in these new, inter-personal roles.

In fact, Churchill now concludes, "There is nothing more important in life than inspiring other people."

One lesson he delivers to all his students is to find a healthy balance between work and personal pursuits.

Saunak Sen, now a biostatistician at the University of California, San Francisco, trained under Churchill at Jackson. Sen remembers being "shocked and thrilled" when

Churchill said he expected him to work about 40 hours a week, "but not too much more."

"I had always focused on how much I worked and not thought about the quality of those hours, or the quality of the hours outside of work," says Sen.

As Sen and others testify, Churchill is intent on following his own advice. He forces himself to keep to-do lists and make neat stacks of prioritized tasks on his desk so he can stay productive enough to have time for what matters to him outside the lab.

"I need to have some time for my family and for myself," Churchill says. "Otherwise work would eat up my life."

Finding His Balance

One of Churchill's favorite things about working at the Jackson Lab is that he can walk out the back door and hike, climb, watch the ocean crash and spray or ice skate on a frozen beaver pond.

story continues on page 8

FIND MORE



Meet GeniQuest's dragons and drakes at
<http://cgd.jax.org/education/geniquest.shtml>





Drug-filled contact lenses may deliver medicines more efficiently than eye drops.

Contact Medicine

Ever had itchy, swollen and painful pink eye?

Then you know the hassle of treating it: Tilt your head back, gently pull your eyelid down and plunk a few antibiotic or steroid drops into your eye.

Repeat twice a day for a few days to a week.

What if, instead, you could simply insert a disposable contact lens into your affected eye and have the medicine slowly drip out by itself?

That day may come sooner than later, thanks to clever new technology invented by pediatrician Daniel Kohane of Children's Hospital Boston. The inside layer of his prototype lens is made of a biodegradable substance that slowly releases a medicine into the eye for weeks to months.

Although other researchers have tried to make drug-filled lenses, none has been able to deliver a specific dose in a predictable way over very long periods of time.

Also, previous studies say that as little as 1 to 7 percent of an eye drop-administered dose actually makes it into the eye. If proven to work better than that in humans, Kohane's lens would be a big step forward. —A.D.

...it's about focusing your attention.



continued from page 7

Whether in the fresh summer air or snowy winter chill—"There's something about being cold that makes you feel you're alive," Churchill says—he loves to relax in the wilderness or contemplate his work from a different perspective.

Sen recalls that it wasn't unusual for Churchill to disappear from the lab in the afternoon and then reappear, "slightly sweaty," after climbing some huge rock face.

"Gary probably gets more math done hanging off the side of a mountain than some other scientists get done sitting at their desks," adds Smith.

For Churchill, climbing is "about focusing your attention. Being 300 feet above the ground, you're totally in the moment," he says.

The ability to zero in on a problem and devote all his energy to conquering it comes in handy at the cutting edge of systems genetics as much as when dangling over the Atlantic.

Still, it's not a lifestyle suited to everyone.

"Waves are pounding against these cliffs," says de Villena. "It's not only

that you can fall, it's that if you fall, there is no way you can get out of there. And the guy is fine with that."

"It's slightly insane to me," he continues. "I play golf."

For 15 years, Churchill has also been practicing yoga. While it lacks climbing's "imminent death" factor, as he puts it, yoga still requires him to quiet his mind, be aware of his body and concentrate on breathing.

Not that he needs the meditation to chill out. Colleagues note that he maintains a steady, Zen calm, always keeping a level head and speaking reasonably.

"He has the climbing personality. He's always cool and equanimous," says de Villena. "If you didn't know him, you might think he doesn't care that strongly about things because he's very moderate in the way he talks with everybody."

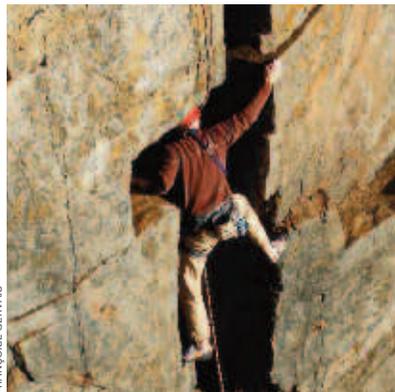
On the other hand, he points out, "It's great [for Churchill's students] to have a mentor who doesn't lose his cool."

Everything doesn't always go smoothly. Five years ago, Churchill fell on a climb, hitting a tree on the way down and breaking his collarbone. He taught a class for researchers that summer with his right arm immobilized in a sling.

But even the fall didn't shatter Churchill's calm—or deter him from climbing again.

Outside on this crisp afternoon, Churchill takes another look at the boulder in front of him. Soon, his lunch break will end and he'll head back to work.

For now, he takes his first hold of the rock and pushes up. ● ● ●



FRANÇOISE GERVAIS

Churchill applies his skill and determination to rock climbing as well as math and science.

FIND MORE



See the eight types of mice that launched Collaborative Cross at http://compgen.unc.edu/wp/?page_id=99



Up Close With

Julie Johnson

CLINICAL PHARMACIST

"I kept dabbling at things, trying out different career options until I found a really good fit."

FAMILY VACATIONS

Scuba diving in the Caribbean

CHILDHOOD HOBBY

Raising beef cattle

PETS

One dog, two cats, a bunny, three fish

FAVORITE AUTHORS

Richard Russo,
Jhumpa Lahiri,
Edith Wharton

SARAH KEWELUP HEALTH SCIENCE CENTER NEWS



The Right Fit

BY ALISA ZAPP MACHALEK

“All things are poison
and nothing is without poison.
Only the dosage distinguishes
the killer from the cure.”

(loose translation from the original German)

—Paracelsus, Swiss scientist (1493–1541)

If that sounds crazy to you, consider

the case of the blood thinner warfarin. Now one of the most widely prescribed drugs in the world, warfarin was originally marketed—and is still commonly used—as a rat poison.

Killer or cure? The difference is in the dose.

But it gets more complicated: A safe dose for one person might be dangerous—even lethal—for another.

So how do doctors know how much of a medicine to prescribe? Essentially, they make an educated guess. Then, depending on how well the patient responds, they might adjust the dose.

Unfortunately, for very sick patients—or for very strong drugs—the delay caused by this trial-and-error process can be harmful or even life-threatening.

Julie Johnson, a clinical pharmacist at the University of Florida in Gainesville, hopes to speed things up, getting the right prescription to each patient right away. To do this, she focuses on genes.

“The hope is that through a person’s genetics, we can minimize the trial-and-error process and quickly identify the drug therapy that will work best for that person,” Johnson says.

The ultimate goal is to enable doctors to tailor prescriptions for each patient.

This area of research is called pharmacogenetics or pharmacogenomics. Johnson’s team is one of a dozen groups that are part of a nationwide pharmacogenetics research network (see “Genes, Disease and Drugs,” page 14).

Steering in the Right Direction

Before she landed in her current career, Johnson went through her own trial-and-error process. She was raised in rural Ohio, where her parents had a small farm.



The same substance that kills rodents protects the lives of millions of people.



Your genes influence how your body responds to medicines.

While growing up, she was very active in 4-H and showed beef cattle every summer at the county and state agricultural fairs. She even won the Grand Champion award for her steer when she was a senior in high school.

Although raising cattle may seem far afield from medical research, it actually taught Johnson skills that help her excel in the laboratory, says Deanna Kroetz, a fellow scientist (and pharmacogenetics network member) with whom Johnson has been close friends for more than 30 years.

"Julie has been doing long-term projects and setting goals since she was a kid. It contributes to how she works on things, how she thinks," says Kroetz.

As a girl, when Johnson thought about what she wanted to be when she grew up, she looked to the careers of her family and neighbors. She considered being a kindergarten teacher, veterinarian, hospital pharmacist or drugstore owner. For one reason or another, none of these was a good fit. Eventually, she considered being a faculty member in a college of pharmacy.

While studying pharmacy in college, she took an elective class in research.

"Much to my surprise, I really, really liked it," she says. "It fit. It was intellectually stimulating and allowed me to address clinically important questions."

What's Genetics Got to Do With It?

Johnson's continued interest in medical issues led her to focus on the pharmacogenetics of cardiovascular drugs.

In addition to determining whether you will be tall or short, black-haired or blond, your genes influence how your body responds to medicines.

But genes aren't the only factor. Your age, weight, lifestyle and other characteristics also play a role.

Here's how it works. When you swallow a pill, it lands in your stomach and soon moves to the small intestine. From there, it is absorbed into nearby blood vessels, then carried to your liver.

Among its many functions, the liver is your body's main toxic waste-processing plant. It is chock-full of enzymes that metabolize drugs, alcohol and toxins, changing these substances into new chemical forms.

Within the liver is a large family of enzymes known as cytochrome P450s, or CYPs (pronounced "sips"), which together are responsible for metabolizing about 75 percent of all medications.

Some CYP enzymes change toxic compounds into harmless ones. Others chemically alter substances to prepare them for elimination in urine or feces. Still others convert drugs into their active form.

There are five main CYP enzymes involved in drug metabolism, each of which comes in many variations.

Every person has a unique combination of CYP enzymes, genetically

selected from countless possibilities. Whether your combination is advantageous, pharmacologically speaking, depends on which medications you take.

Take a CYP

Take for example CYP2D6, an enzyme that is responsible for processing about one-fourth of all prescription drugs. This enzyme has more than 100 versions, based on tiny differences in the genes that code for it. Depending on which versions you inherit, your CYP2D6 enzyme activity could be normal, superfast or nonexistent.

Why should you care what kind of CYP2D6 activity you have? Because it could make a big difference in how well medicines work for you.

Say you broke a bone or had surgery. A doctor might prescribe codeine for your pain. In order to work, codeine needs CYP2D6 to transform it into the potent painkiller morphine.

If you have nonexistent CYP2D6 activity (along with about 5 percent of Americans), codeine will do nothing for you because your body can't convert it into morphine. Your pain will just keep throbbing.

But having too much CYP2D6 activity could have even worse consequences.



A single liver enzyme, CYP2D6, is responsible for processing about one-fourth of all medicines, including these.

ALISA Z. MACHALEK

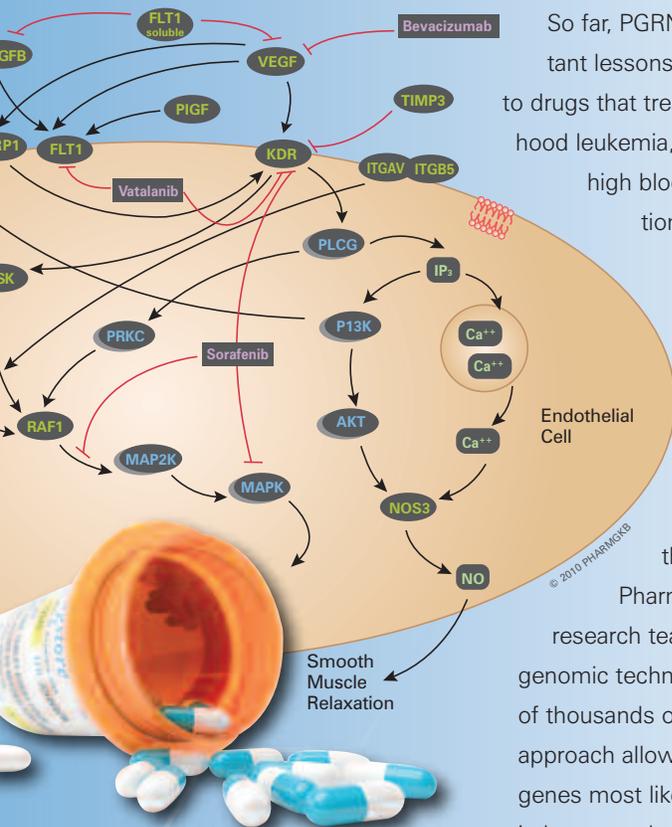
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Genes, Disease and Drugs

Have you ever taken a medicine that didn't work or that caused bad side effects? If so, you know that not everyone responds the same way to medications.

Recognizing the importance of understanding these differences, the National Institute of General Medical Sciences, together with other components of the National Institutes of Health, created the Pharmacogenetics Research Network (PGRN) in 2000.

Scientists in this nationwide collaboration study genes and medicines relevant to a wide range of diseases. The researchers expect that the knowledge they uncover will help doctors use genetic information to tailor treatments for each patient, in essence making drugs safer and more effective for everyone.



So far, PGRN scientists have learned important lessons about gene-based responses to drugs that treat asthma, breast cancer, childhood leukemia, depression, heart disease, high blood pressure and other conditions. Discoveries made by the network have already led to changes in the prescribing instructions for some medications.

In 2008, members of the PGRN joined forces with scientists in Japan to form the Global Alliance for Pharmacogenomics. The new research teams use state-of-the-art genomic technology to examine the sequences of thousands of genes simultaneously. This approach allows scientists to get a fix on the genes most likely to play an important role in how people respond to drugs.

You can find more information about the Pharmacogenetics Research Network at <http://www.nigms.nih.gov/Initiatives/PGRN>. —A.Z.M.

And here's the kicker: the ideal dose varies widely—one person may require 10 times more than another—so it's nigh impossible to get every prescription right the first time.

How do doctors even know where to start?

Typically, they begin with a generic dosage adjusted for factors like the patient's weight, age and gender. Then they wait up to a week, check the patient's blood for its clotting ability, and tweak the dosage as needed.

They repeat these steps for a few weeks until they've found the optimum dosage. The patient then remains on the final, stable dosage (with regular tests to check that it's still the right fit).

Fortunately, doctors have been doing this for decades and have carefully worked out the technique. But Johnson and her colleagues think there's a better way—through pharmacogenetics.

Johnson discussed this idea with other scientists from the pharmacogenetics research network and from the online knowledge base PharmGKB. They all knew that to fully investigate whether pharmacogenetics could improve warfarin dosing, they would need a worldwide effort.

So they created the International Warfarin Pharmacogenetics Consortium. The consortium is made up of about a hundred researchers on four continents.

The scientists already knew that variations in two genes, CYP2C9 and VKORC1 (an enzyme that activates vitamin K), could influence warfarin's effectiveness. But no one was really sure whether knowledge of a patient's CYP2C9 and VKORC1 variations could help doctors arrive at the optimal dose of warfarin more quickly. That's what the consortium set out to determine.

up when doctors repeatedly change the medicine.



By combining their data, consortium members had access to anonymized information from about 5,700 patients on stable dosages of warfarin. The patients came from around the globe: Taiwan, Japan, Korea, Singapore, Sweden, Israel, Brazil, Britain and the United States.

This kind of study—one that includes people of different races, ethnicities and lifestyles—is essential to draw conclusions that are applicable to a wide range of people.

From this vast pool of data, the consortium members created a computer program to predict the ideal warfarin dosage for each patient based on his or her genetic variations and clinical information like age and body size.

Then the scientists checked their predictions against the actual dosage for each patient. (These stable dosages had been established the traditional way—they were initially based on standard clinical factors, then adjusted until they were optimal.)

Voila! The genetically based computational predictions were closer to the stable dosages than were the starting dosages obtained using the standard, best-guess method.

The computer program performed especially well for patients at the low or high ends of the dosing range. This got the scientists' attention, because nearly half of the people on warfarin are at the extremes of the range, and they are the ones most susceptible to dangerous bleeding or clotting.

The consortium published these discoveries last year in a major medical journal.



To make the broadest discoveries in pharmacogenetics, scientists have to include patients from around the globe.

As the consortium's research continues, its strategy is being tested in a large clinical trial to determine whether a gene-based approach to prescribing warfarin will improve the effectiveness and safety of the drug for new patients. The trial is called Clarification of Optimal Anticoagulation through Genetics (COAG).

Lowering the Pressure

Most of Johnson's work focuses on drugs that treat high blood pressure, or hypertension.

In the case of warfarin, genes influence *how much* of the drug a patient needs. For drugs that treat hypertension, genes influence *which* drug—there are dozens—would be best for each patient.

"If doctors randomly pick one of those medicines, there's only a 50 percent chance that it will work," Johnson says.

"We're trying to find out if there are genetic markers to use to pick the

right drug from the outset," she continues. "Right now, it's a trial-and-error process. It can be very frustrating for patients, especially for young people."

Too often, people get fed up when doctors repeatedly change the medicines, she says. The patients feel fine—hypertension has no obvious symptoms—and they may not understand the importance of finding an effective medicine.

"So they go untreated for an extended period. And that's bad," Johnson says.

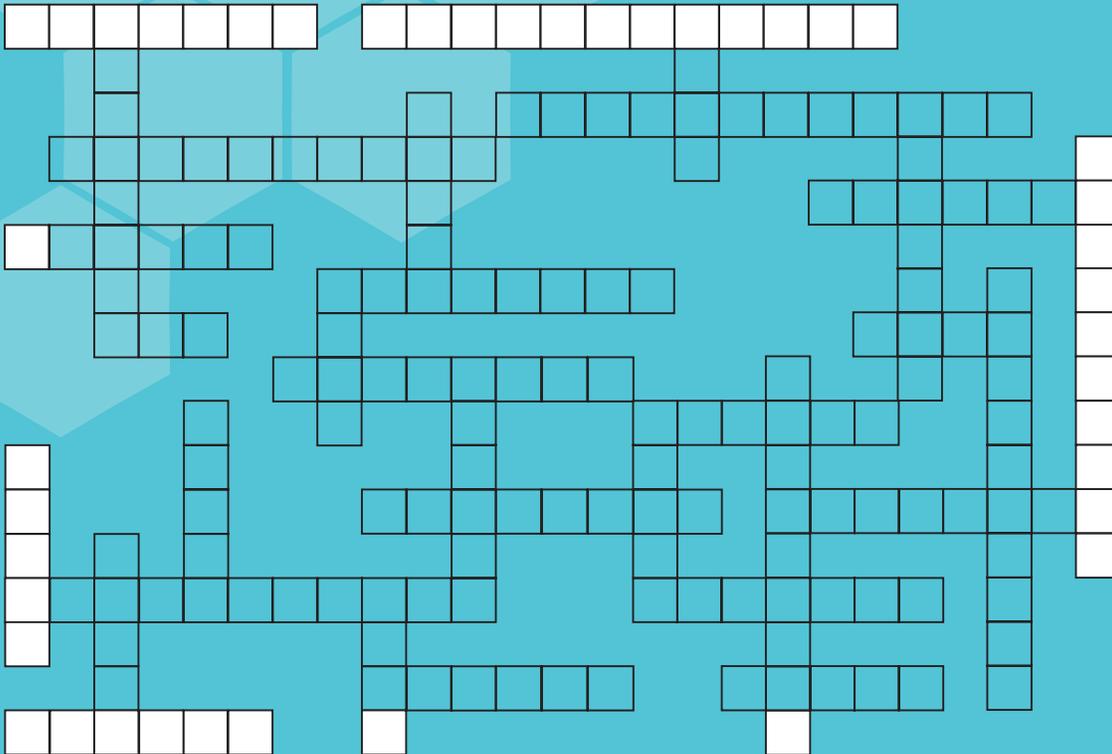
Even though they can't feel it, the extra force of blood smashing against artery walls can seriously damage internal organs. Long-term consequences include kidney failure, strokes, heart attacks, heart failure and death. Because of this, hypertension is sometimes called the "silent killer."

story continues on page 16

FIND MORE @

Check out an online tool for estimating warfarin doses at <http://www.warfarindosing.org>

EXPLORE IT PUZZLE IT FIND IT



ACROSS

1. Converted to morphine
3. Doctor's orders
6. High blood pressure
8. Juice that messes up some medicines
10. Often, many genes must come together to cause
11. As a kid, Johnson raised these
12. Rat-poison blood thinner
14. Family of drug-metabolizing enzymes
15. Drug taken orally
16. Laboratory insect
20. The Human _____ Project
22. Churchill's hobby
23. Biostatisticians look for _____ in information
25. DNA "letters"
27. Holistic, or _____, genetics
28. Goals of pharmacogenetics: better efficacy and _____
29. Mouse-breeding project: Collaborative _____
30. GeniQuest creature

DOWN

2. Lowers blood pressure
4. NIH Pharmacogenetics Research Network
5. Cleans up toxins
7. Diabetes-related hormone
9. Someone who studies DNA
12. Find a healthy balance between _____ and life, advises Churchill
13. Tamoxifen-taker cheers because she's a CYP2D6 _____ metabolizer
17. Genetically determined characteristics
18. These help scientists understand complex data
19. Common model organism
20. These partly determine our looks and health
21. Jackson Laboratory location
24. Johnson's hobby
26. Amount of drug delivered

SOLVE IT ONLINE

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