

Findings

FEBRUARY 2009



PAGE 2

African Adventures

Tracing Our Past

PAGE 10

Evolution Revolution

Finding Our Future

SPECIAL ISSUE

Evolution

February 2009—
The 200th Anniversary
of Charles Darwin's Birth



U.S. DEPARTMENT OF
National Institutes of Health
National Institute of General Medical Sciences

●●● **Inside Science:** Life in the Lab

- 1 *Up Close With:* **Sarah Tishkoff**
- 2 **Genetic Footprints**
- 6 The Big Family Tree

- 9 *Up Close With:* **Joe Thornton**
- 10 **Past to Present**
- 14 Joe the Scientist

●●● **Just Found:** Quick Takes on Hot Science

- 5 Chimp Changes
- 8 Mystery Malaria
- 13 Bugs On Us
- 16 Lifestyle Effects

Edited by Alison Davis under contract HHSN263200800496P

Contributing Writers

Emily Carlson
Alison Davis
Erin Fults

Production Manager

Susan Athey

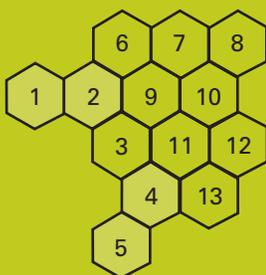
Online Editor

Jilliene Mitchell

Produced by the Office of Communications and Public Liaison
National Institute of General Medical Sciences
National Institutes of Health
U.S. Department of Health and Human Services

<http://www.nigms.nih.gov/findings>

On the Cover



- 1 **Kidney Ischemia**, *Hamid Rabb, Johns Hopkins Medicine*
- 2 **G Protein**, *Protein Data Bank*
- 3 **Charles Darwin**
- 4 **Mouse Fibroblast Cells**, *Torsten Wittmann, Scripps Research Institute*
- 5 **Fruit Fly Embryo**, *Hyung Don Ryoo and Hermann Steller, Rockefeller University*
- 6 **Sarah Tishkoff**, *Tommy Leonardi*
- 7 **Samburu Girls**, *Jibril Hirbo*
- 8 **Bacteria Under Toenail**, *Darlyne Murawski, National Geographic Society*
- 9 **Africa Variation Map**, *Noah Rosenberg, Martin Soave*
- 10 **Berber Village**, *Luc Viatour, Wikimedia Commons*
- 11 **Joe Thornton**, *Jack Liu*
- 12 **Octopus**, *Joe Thornton*
- 13 **Ancestral Receptor**, *Joe Thornton*

A portrait of Sarah Tishkoff, a woman with long, wavy brown hair, smiling slightly. She is wearing a dark grey, textured cardigan over a dark turtleneck. The background is a blurred green and blue pattern.

Up Close With

Sarah Tishkoff

EVOLUTIONARY GENETICIST

“In some contexts, I’m a geneticist. In others I’m an anthropologist. And other times I’m an evolutionary biologist. I wear many hats.”

FAVORITE AFRICAN ANIMAL

Warthogs ... or giraffes

INTERESTING FACT

Speaks Kiswahili

MUSICAL TALENT

Plays Beethoven on
the piano

MISSES MOST WHILE IN AFRICA

A hot shower

TOMMY LEONARDI





TOMMY LEONARDI

Genetic Footprints

BY ERIN FULTS

Where did I come from?

What makes me unique?

What makes a human... a human?

These simple questions are not so easy to answer. We still do not know what makes you “you,” your mother “her” and your brother “him.” Nor do we know, precisely, why we do not look or act just like chimps.

Evolutionary geneticist Sarah Tishkoff doesn’t know the answers either. But these are the questions she asks every day as part of her job running a lab at the University of Pennsylvania in Philadelphia.

You might say Tishkoff has a long commute—traveling more than 8,000 miles to do her fieldwork in Africa. There, she collects data to help her understand evolution and its role in shaping human history and human health.

Working alongside African researchers, Tishkoff looks at DNA to trace the paths of human evolution. Her training in anthropology—the broad study of humanity itself—gives Tishkoff a unique perspective on genetic research, the study of heredity.

Tishkoff says that in many ways, genetics can begin to answer the questions of where we came from and what makes us unique—as individuals and as a species.

“What drove me to this work was being able to ask the questions philosophers ask,” says Tishkoff.

Every new answer brings with it a new question. And that means a lot of changing and adapting. With each project she meets new people and finds new diseases. The work is not always easy, Tishkoff says.

“Not easy” means setting up a lab in the middle of nowhere. It means using a car battery to power equipment, riding in a Land Rover® and colliding head-on with a bus, and sleeping in tents where zebras come to visit.

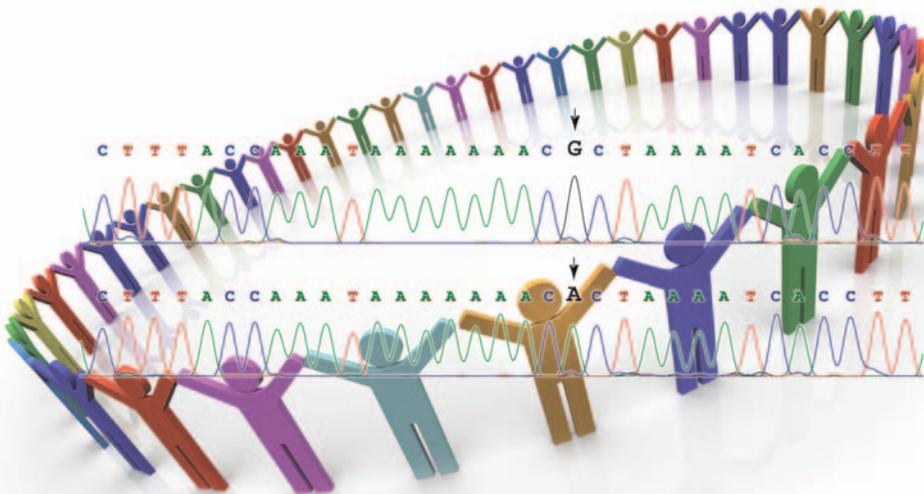
It also means: She’d hardly give it up.



JIBRIL HRIBO

Sarah Tishkoff’s research gives her the opportunity to learn about African culture.

What drove me to this work was being able to ask



These two DNA sequence readouts show genetic variation, with either a G or A nucleotide at the same position in the DNA of two different people.

Little Letters, Big Dig

A genome is all of the genetic information in an organism, stored in the form of DNA. This DNA is Tishkoff's archaeological "dig site."

Often called the code of life, DNA carries the genes you got from your parents.

To an extent, genes are what give you your mother's eyes or your grandfather's hair. Genes also affect your health—if heart disease runs in your family, you may be at risk for getting it yourself.

Of course, genes aren't the whole story. Where and how you live, what you eat and whether you exercise, drink alcohol or smoke are all hugely important in your health and your appearance.

DNA has four different nucleotide "letters" that string together into gene "words." Our bodies use genes as the templates to make RNA and proteins, which are the main workers in cells.

While the genome is mostly the same in all people, slight differences exist. This genetic variation makes up about one-tenth of a percent of each

person's DNA. These spelling differences, spread across many genes, are what make you unique.

This genetic variation is enough to distinguish you from your next-door neighbor, the president of the United States and millions of other people all over the world.

Genetic variation is inherited, so the more closely related two people are, the more similar their DNA is likely to be.

Individuals within a population have DNA that is more similar to each other's than it is to that of people in other populations, because they share an ancestry that is at least partly captured in DNA variation. So people whose ancestors have lived for generations in Sweden will have DNA more similar to other Swedish people than to modern-day Koreans

whose families settled long ago in Korea.

Medical researchers are interested in genetic variation because it helps them understand disease risk. For example, some people are naturally resistant to getting AIDS after becoming infected with HIV because they have a specific change, or variant, in their DNA. The variant is extremely rare, but examining the genetics of how it happens could lead to ways to prevent or treat this killer disease.

Scientists like Tishkoff who study genetic variation are actually studying evolution. Over time, changes occur in DNA, affecting the readout of the genetic message. If the changes are helpful to the organism, they have a greater chance of being passed on to future generations because they provide a survival advantage.

Of course, it takes many, many generations for these changes to catch on.

Into Africa

Tishkoff first got hooked on tracking evolution in the early 1990s while in graduate school at Yale University in New Haven, Conn. She had the chance to scan one of the largest collections of DNA samples from populations all over the globe.

One of Tishkoff's first observations was that Africa was represented by genetic information from only two ethnic groups. That's hardly enough to cover this vast continent, she thought.

At the time, Tishkoff explains, researchers hadn't yet realized what

FIND MORE

Hear a native Xhosa click-speaker at

<http://www.youtube.com/watch?v=gytCi5a7AJg&feature=related>

The Big Family Tree

Where was your grandmother from? Your great-grandmother? Now how about your great-great-great-great-grandmother?

No doubt your family tree gets fuzzy the further back you go. But as humans, we can all trace our roots back to a common ancestor. Evolution and the migration of ancient peoples made humans a large and diverse population today.

But how do we find our ancestors? How do we learn where we came from and how we got here? The answer is molecular anthropology.



This field of science uses a blend of methods to determine evolutionary links between ancient and modern people. It can also be used to reveal our connections to closely related species, like chimps and gorillas.

To connect the dots using molecular anthropology, scientists look at DNA. They look for differences and similarities in the sequences of nucleotides—the “letters” that make up the genetic material.

As different as people look, our DNA is actually amazingly alike. And, get ready for this: Your DNA is about 96 percent the same as a chimp and 85 percent the same as a mouse!

Molecular anthropology is important for understanding human origins and human evolution. Knowing our DNA roots can also help us learn more about diseases and genetic changes that our ancestors developed and passed on to us. This knowledge may be the key to finding new treatments and vaccines. —*E.F.*

continued from page 5

disease spread by parasite-infested mosquitoes. Despite the fact that effective prevention methods exist—including bed nets and medicines like chloroquine—malaria is an enormous worldwide health menace. In Africa, where access to prevention and treatment is scarce in many regions, the disease kills a child every 30 seconds.

Yet some people inherit protection against malaria. Variations in a gene called G6PD are common in people who live in areas of Africa with widespread malaria. But although this variant of a particular gene guards against malaria, it also has a dark side, causing anemia and sometimes death.

Another example of a double-edged genetic variation is sickle cell disease, a lifelong problem in which the body makes misshapen red blood cells that don’t move easily through blood vessels. They’re stiff, gummy and tend to form clumps that get stuck, causing intense pain, serious infections and organ damage.

By any standard, sickle cell disease is not a good thing to have, except for the fact that people who have a sickle cell gene variant—along with one normal gene—have protection against malaria. As with the G6PD genetic variant, evolution tolerates the sickle cell gene variant and it gets passed on to future generations of people because it gives them a survival advantage.

But the story gets even more complicated. Just as the human genome adapts, so too does that of the parasite living inside the mosquito that transmits malaria. For this reason, Tishkoff laments, we will probably never be fully protected from the disease.

“We’re in an arms race with the parasite that causes malaria,” Tishkoff says.

what makes everybody unique.



However, all is not lost. Tishkoff thinks that by finding the genetic variants that contribute to parasites' resistance to our drugs, scientists may be able to develop more durable malaria treatments and vaccines.

Got Milk?®

Tishkoff explains that the evolutionary race between the malaria parasite and human defense mechanisms is an example of co-evolution, where two species adapt and evolve in response to one another.

Other interactions occur, such as genetic adaptation to a cultural change. Take the case of humans who can drink milk and eat dairy products without getting sick.

Believe it or not, the inability to drink milk, called lactose intolerance, is very common in adults around the world. Most have a burned-out version of the enzyme lactase that digests milk and dairy products.

That's in contrast to baby mammals, who need milk to survive and can easily digest it because their lactase enzyme is working fine.

Most adults who trace their ancestry to Asia or Africa cannot digest milk. However, some people from these African tribes are pastoralists, meaning that they keep domesticated cows. These people can drink milk long into adulthood.

Tishkoff wondered: Could there be a connection between raising cows and being able to drink milk as an adult?

She collected blood samples from different tribes in Africa and analyzed



SARAH TISHKOFF

African populations that domesticated cattle acquired a genetic variation enabling them to digest milk, an advantage passed on to future generations.

their DNA. Her hunch was correct: African populations with recent ancestors who were pastoralists had a genetic change in the gene that produces lactase, allowing them to digest milk.

Tishkoff also found a link between genetic and archaeological evidence. The genetic variant for lactose tolerance became common in East Africa between 3,000 and 7,000 years ago. Archaeological data suggest that cattle were domesticated in parts of Eastern Africa at the same time.

"To me, this was the ultimate find," says Tishkoff. "It was everything I had been trying to do since college—tying together history, anthropology and genetics."

So, a genetic change—the lactase gene variation—and a cultural

change—the domestication of cattle—occurred at the same time and created a selective advantage. People with the genetic change could drink milk, become stronger and have more children, thus passing on the beneficial trait to more individuals and extending the benefit to future generations.

But which came first?

Did African farmers gradually gain the ability to digest milk after domesticating cattle, or did they seek cattle as a source of milk for protein?

Tishkoff is quick to point out that it's not so clear. Right now, no one knows for sure.

Out of Africa

Tishkoff has recently turned her evolutionary focus toward height, weight, taste perception and metabolism. She has lots to do, since very basic traits like these are often the most complex at the genetic level. Height alone, she says, is thought to be controlled by around 100 genes.

story continues on page 8

FIND MORE @

Watch an interview with Sarah Tishkoff at

<http://publications.nigms.nih.gov/multimedia/captions/tishkoff-captions.html>



Up Close With

Joe Thornton

EVOLUTIONARY BIOLOGIST

“To understand ourselves, we need to understand where we came from.”

JOB TITLES

Evolutionary biologist,
political activist, writer

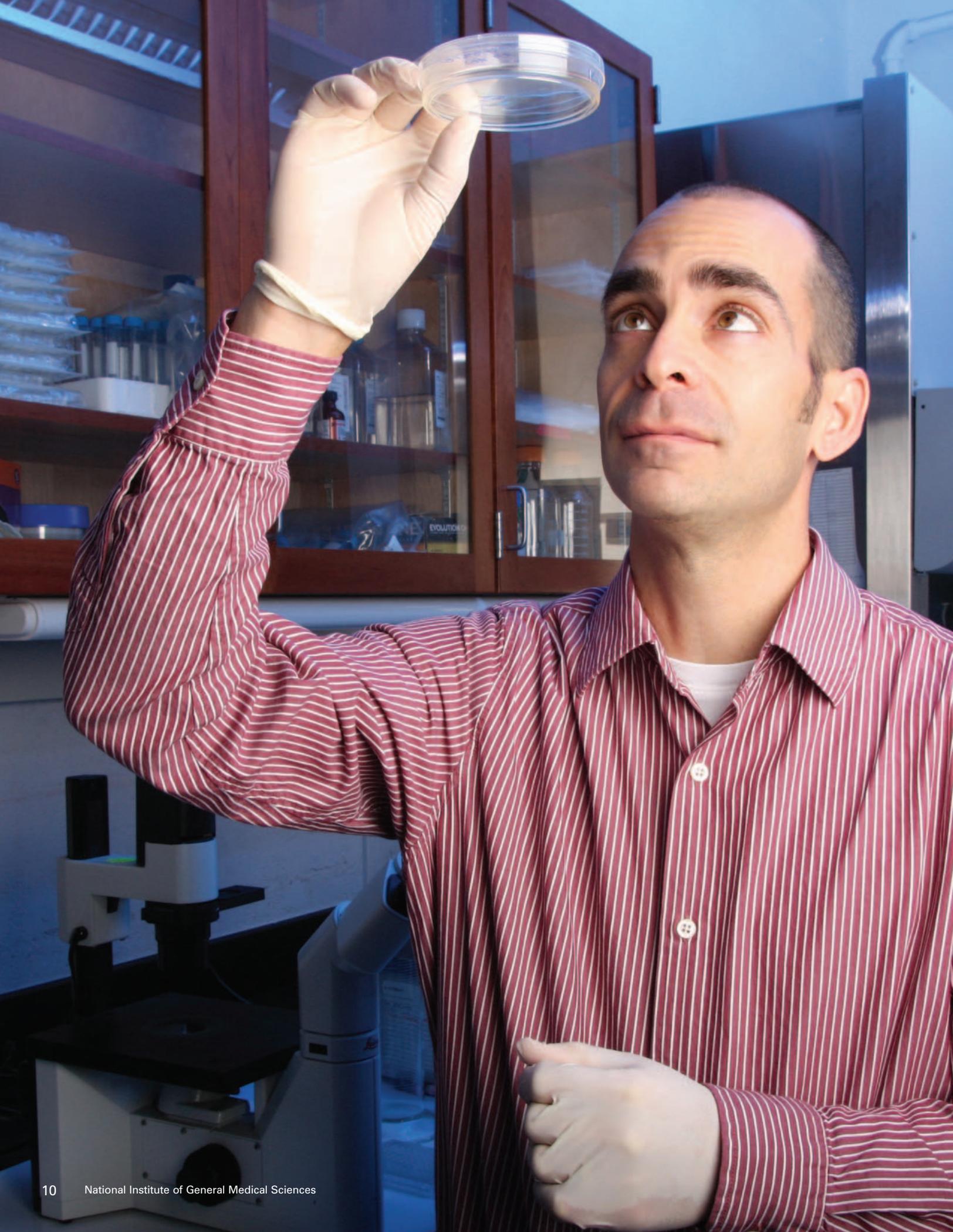
PAST CAREER OPTIONS

Rock bassist, English
professor

HOW HE SPENDS HIS SPARE TIME

Hiking and skiing Oregon’s
mountains, playing music
with his family, shooting
ice-hockey pucks

JACK LIU



Past to Present

BY EMILY CARLSON

Evolutionary biologist Joe Thornton rolls up his sleeve and reaches into a blue and white plastic cooler, just like the one you might take to a soccer game or the beach.

But you won't find cold sodas or turkey sandwiches in this one, and its contents might be among the grossest things you've ever seen.

Inside, sand-colored, snakelike hagfish writhe like hoses bursting with water. They lunge against the side of the cooler and squirm under Thornton's grip as he reaches in with his arm. When he pulls out his hand, it drips with wads of clear, snotty goo.

"A few of these hagfish can fill a 5-gallon bucket with slime in a few minutes," Thornton says. "It's amazing."

Hagfish are slimy, slithery creatures that offer a clue to our deep past. By studying the DNA of hagfish and other unusual animals, Thornton has been able to resurrect 450-million-year-old genes and use them to make equally ancient proteins. This archaic biology, he says, can help us better understand who we are today.

"Science isn't just about shining a bright light on nature and seeing the truth," says Thornton. "It's a way to reflect on the human condition and to see our place in the world."

Thornton's research focuses on our endocrine system, a complex network of glands and hormones found in most animals with well-developed nervous and circulatory systems. Glands like the thyroid, adrenal and ovary make hormones, which travel through the bloodstream as chemical signals that trigger our bodies to do all the things we need to survive.

Thornton studies a specific group of hormones called steroids. Examples include estrogen and testosterone. While known mostly for their role in reproduction, these hormones are also key players in bone and cardiovascular health, our stress response and diseases like cancer.

To do their jobs, all hormones must latch onto specific proteins called receptors on or inside cells. Think of them as part of a lock-and-key system. When you have a match,



Steroid hormone receptors are ancient molecules that are widespread throughout the animal kingdom, including this octopus.



One of the most important aspects of doing science well is

the door opens—triggering a cascade of biochemical changes within the cell.

“Virtually everything a living cell does is controlled by specific interactions between molecules, like hormones and their receptors,” explains Thornton. “But despite their importance, we know very little about how these kinds of specific interactions evolved.”

Origin of a Scientist

Thornton wasn’t always interested in studying steroid hormones. Before graduating from college with a degree in English, Thornton says he wanted to “connect with reality” and began working for Greenpeace, an international organization that educates the public on global environmental problems and solutions for a greener future.

For about 10 years, Thornton traveled to communities with major sources of chemical pollution. Part of his job involved reading about scientific studies and translating the results for local residents.



JOE THORNTON

Evolutionary biologists can learn a lot from jawless, slime-producing hagfish.

Thornton wrote dozens of reports and articles describing the health hazards posed by chemical pollution and arguing for specific solutions. He explained these ideas to the press and testified before Congress.

“I became a specialist in helping communities understand the scientific literature to protect themselves and the environment,” says Thornton.

The experience sparked his interest in endocrine disruptors, synthetic chemicals that mimic our natural hormones. They enter the air, water or food supply as byproducts of many chemical, manufacturing and agricultural practices.

Because they are so widespread, everyone is exposed to them. Endocrine disruptors have been linked to reproductive problems, impaired immune function and various cancers.

Endocrine disruptors affect animals, too. Scientists suspect they’re responsible for a decline in Florida’s alligator population, the feminization of male marine organisms, and damage to fish and bird populations.

Alarmed by these potential threats to our environment and our bodies, Thornton started asking questions of his own.

Why do these chemicals have such a big effect on biology? How did hormones and their receptors evolve? Can we predict which chemicals are likely to cause endocrine disruption if we have a better basic understanding of receptors?

“When it came time for me to move on [from Greenpeace], I was so fascinated with the science that I wanted to pursue it directly,” says Thornton.

So he went back to school and took his first biology class at age 30. Now 43 and running his own lab at the University of Oregon in Eugene, Thornton is finding the answers to the questions that drove him to science and environmental activism.

Molecular Time Machine

Like a historian studying the past to make sense of current events or an anthropologist examining ancient cultures to understand today’s customs, Thornton goes back in time to piece together the evolution of hormones and their receptors. His main objective: to unravel the history of our endocrine system. The findings could help other researchers understand the origins of hundreds of diseases related to the endocrine system and identify new ways to treat or prevent them.

Thornton starts by studying hormone receptors in living animals. On any given day, Thornton’s lab might have a cooler full of undulating octopi, jawless lampreys, predatory worms, sea slugs or the slimy hagfish. These organisms, he says, occupy critical spots on the evolutionary tree of animal life for understanding the evolution of the endocrine system. Each species shares an ancient common ancestor with humans and split off the evolutionary tree around the time that certain receptors first evolved.

“My kids like coming in and seeing us dissect these fantastic creatures,” says Thornton, whose children are 8 and 11.

FIND MORE



Watch hagfish dance and make slime!

<http://www.uoregon.edu/~joet/hagfish.html>

continued from page 13

the sea a more hospitable environment. That was a good thing, because the ocean offered just about the only real estate.

It might seem nearly impossible to imagine we'd share anything in common with the ocean dwellers that lived hundreds of millions of years ago. But Thornton has a fridge of tiny test tubes and incubators with petri dishes to prove that we do.

Each tube contains millions of copies of resurrected receptor genes. Cells living on the plastic plates in the incubator produce the receptor proteins encoded by these ancient genes. Thornton and others can use these proteins to see how they respond to different hormones. By changing the ancient DNA, they can retrace the process by which evolution tweaked the receptors' sensitivity to various hormones.

With the help of a technique called structural biology, they can also see how the receptor proteins' shapes changed over time. Under certain conditions, proteins form crystals that can be bombarded with high-energy X-rays to determine their shape. By using these methods, Thornton has determined the precise atomic structure of several ancient receptors and has shown how that structure changed as the receptors evolved to bind new hormones in a lock-and-key fashion (see image, page 13).

Evolution Explained

Often called the father of evolution, biologist Charles Darwin thought of evolution as a tree where all species branched from a common ancestor. As nature selected for certain advantageous traits, he reasoned, organisms with helpful genetic changes survived to pass those genes to offspring.

Joe the Scientist

I became a scientist for two reasons. I wanted to use knowledge to help protect the environment and human health. And I wanted to contribute to culture—our shared understanding of ourselves and our world—the same way writers and artists do.

Think of an interesting or controversial issue, and science probably has something important to offer on it. For some issues, like global warming or high breast cancer rates, science's role is obvious. But science has a lot to say about less technical questions, too, including some that go right to the core of our self-understanding.

Consider the biggest one of all: What does it mean to be human? Writers and philosophers have been wrestling with this one for centuries. But scientific discoveries have radically reshaped the answers we can give today.

We have learned that we share many behaviors—and even more aspects of the nervous and endocrine systems that produce them—with chimpanzees, zebrafish and even sea slugs. In my lab, we are discovering precisely when and how some of these features first evolved.

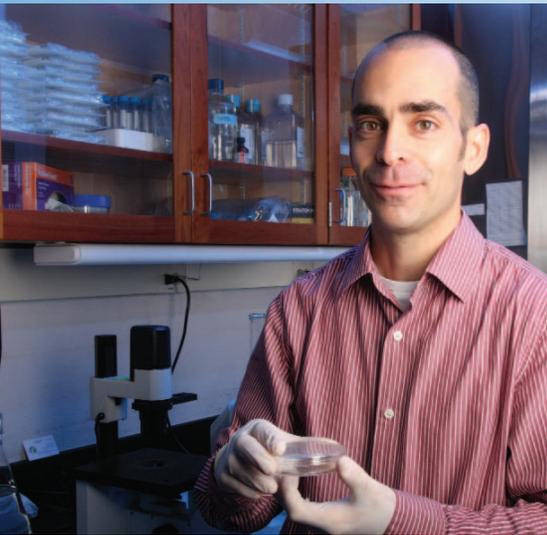
Big cultural issues will never be answered by science alone, because they also involve values, ethics and spirituality. But our biology is a significant part of

who we are, and science is the best way to generate knowledge about nature.

When a scientific discovery changes the lens through which we see ourselves and the world, we can appreciate it the same way we do a van Gogh painting or a Shakespeare play.

My job is to go to the lab each day and try to continue that tradition.

How cool is that?—*Joe Thornton*



PHOTOGRAPH BY JACOB

we're contributing to culture.



Repeated over long periods of time, populations would adapt to their environments. Isolated populations that evolve independently would diverge, eventually forming new species.

Can this explanation of such gradual adaptation apply to the evolution of systems in which the function of the whole requires all the parts to be present? If a hormone needs a receptor and a receptor needs a hormone, then how do you explain the evolution of one without the other?

Or, for that matter, how do you explain the evolution of any complex system with many parts?

The explanation is beautifully simple, Thornton says.

"These systems were assembled by evolution in a piece-by-piece fashion from molecules that once did other jobs." And his research tells the whole story, from beginning to end.

Here's what Thornton has learned. In distant times, there was a single ancient hormone receptor that worked in partnership with a single ancient hormone. That receptor was only as specific as it needed to be at that time. Other hormones with slightly different shapes could have activated it, but only one of these was actually available.

Then, about 450 million years ago, the gene for the ancient receptor got duplicated. Over millions of years, the two copies gradually amassed different sets of genetic changes, leading to two different receptors present in most vertebrates living today.

One of these duplicate receptors retained the ancestral shape and continued to partner with the ancient hormone and other similarly



Over time, genetic changes create new species on the evolutionary "tree of life."

shaped hormones that emerged later in evolution. Today, this receptor interacts with aldosterone, the hormone that regulates salt and water balance in humans and four-legged animals.

As for the other duplicated copy, Thornton has tracked the changes in its DNA over time. He showed that two mutations altered the receptor's shape in a way that changed its lock-and-key fit. As a result, the receptor lost its ability to interact with the ancestral hormone but gained an ability to partner with cortisol, a hormone that today controls our response to long-term stress.

Thornton explains that the specific hormone-receptor pairs we have in our bodies today came about by subtle modifications of hormones and receptors that already existed for different purposes. He calls this idea "molecular exploitation."

"It's taking old parts and reusing them for new purposes by bringing them into newly built systems," he says.

Because of modern scientific tools and technologies like ancestral gene

resurrection, Thornton says evolutionary biologists can now study evolutionary changes and the processes driving them in a much more detailed and decisive way than has ever been possible.

Citizen Scientist

But understanding evolution can also help us to understand the present and future, Thornton says. The concept of molecular exploitation, for example, helps him explore endocrine disruption and try to make sense of it.

The discovery that hormone receptors are only as specific as they need to be at any one time in evolution, he says, explains why they are susceptible to disruption by pollutants.

"The chemical industry has produced tens of thousands of chemicals in the last 60 years, but our receptors evolved hundreds of millions of years ago and have not had a chance to evolve resistance against them," he says.

Could our bodies evolve to shut out endocrine disruptors? That process could take thousands of generations, "and I'm not willing to wait for evolution to solve the problem for us," Thornton says.

So Thornton does what he can for the environment. After his time with Greenpeace, Thornton wrote a 600-page book, *Pandora's Poison*, outlining the health dangers of chemical pollution. It was printed on chlorine-free paper.

On a more personal level, Thornton and his family try to leave a small environmental footprint. When he and his wife built their house, they avoided using materials containing

story continues on page 16

EXPLORE IT PUZZLE IT FIND IT

?

What is the process by which advantageous traits are passed to offspring?

What are the building blocks of DNA?

How many genes are thought to control height?

What do hormones latch onto to do their jobs?

Who are our closest living animal relatives?

Who is called the father of evolution?

What field of science is the broad study of humanity itself?

**Think you know the answers?
...Then It's Game On!**

**Check out our new games today
FIND MORE @ <http://www.nigms.nih.gov/findings>**

Discrimination Prohibited

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the programs of the National Institute of General Medical Sciences must be operated in compliance with these laws and Executive Orders.

Accessibility

This publication can be made available in formats that are more accessible to people with disabilities. To request this material in a different format or to order additional copies, contact the NIGMS Office of Communications and Public Liaison at 301-496-7301; send e-mail to info@nigms.nih.gov; or write to the office at the following address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200. If you have questions about this publication, you can use the same contact information to reach the editor, Alison Davis.

Free Publications

Browse and order NIGMS publications at <http://publications.nigms.nih.gov/order>.