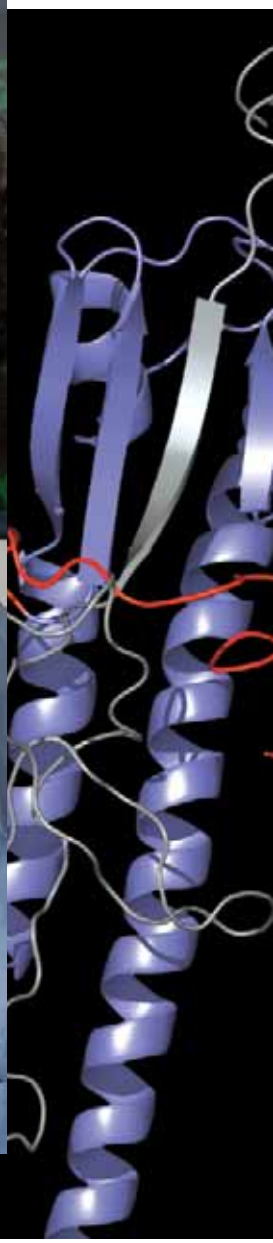
FINDINGS

September 2005



inside

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National Institutes of Health
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On the Cover

Photo of Dyann Wirth: *Rick Friedman*

Photo of David Baker: *Dan Lamont*

Editor's Note

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Look at the list on the left. What do these jobs have in common?

Over the past 4 years, *Findings* has featured scientists working in all these fields. Every one of these women and men, and many others like them, are making discoveries that grow our understanding of life and strengthen our ability to fight disease.

Want to see more examples of cutting-edge medical research? Check out *Biomedical Beat*, an electronic newsletter from the National Institute of General Medical Sciences that reports on scientific discoveries happening all across America.

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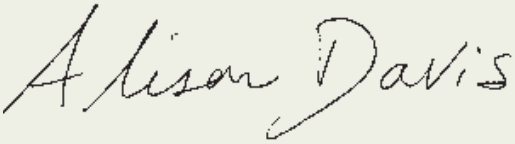

Alison Davis

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Science Withou

ut Borders

RICK FRIEDMAN

RICK FRIEDMAN

Dyann Wirth is a geneticist at the Harvard School of Public Health. Wirth works with researchers throughout the world to study malaria.

By Alison Davis

In the time it takes you to read this page, three African children will have died of malaria.

The devastation caused by this mosquito-transmitted disease in many areas of the developing world is almost too huge to imagine, stealing a child's life every 30 seconds.

"Among infectious diseases, malaria is one of the top three killers worldwide," says Dyann Wirth. "It's a huge public health problem."

Wirth, a geneticist at the Harvard School of Public Health in Boston, Massachusetts, studies malaria and how it spreads. Because of the global scope of the problem, Wirth teams up with scientists in countries faced with the harsh reality of the disease.

Ultimately, she wants to transfer what she learns through basic research into practical strategies for managing malaria, wherever it strikes.

New Tricks for an Old Disease

Malaria is one of the oldest diseases known to humankind, with early descriptions of it etched into ancient Egyptian scrolls. As recently as the 1700s, people believed malaria rose from stinky swamps and passed through the air. They gave it the name *mal aria*, for "bad air."

Not until just before the turn of the 20th century did researchers identify the true source of malaria. The British physician and entomologist Sir Ronald Ross found evidence of malaria infection inside the egg cells of female mosquitoes carrying certain types of parasites.

With more study, scientists eventually confirmed that female *Anopheles* mosquitoes, which feed on blood to nourish their eggs, spread malaria. Infected mosquitoes pass on the disease as they bite people in search of their next blood meal.

Malaria can be tricky to diagnose because its early symptoms resemble those of many other conditions. These include fever, chills, sweating, headaches, muscle pain, nausea, and vomiting—all symptoms that can appear with common viral infections that usually go away by themselves.

CDC/ JAMES GATHANY

During a blood meal taken from a person infected with malaria, *Anopheles* mosquitoes pick up parasites and spread them to the next person they bite.

Left untreated, though, malaria can quickly progress as the parasitic invasion travels to the liver and all over the body, leading to organ damage; severe swelling of the abdomen, eyes, feet, and hands; coma; and death.

If malaria is caught early, doctors can treat it with medication. One of the most widely used treatments is a drug called chloroquine, which destroys malaria-causing parasites in the bloodstream. Chloroquine is a synthetic derivative of quinine, a natural chemical isolated in the early 1800s from bark of the cinchona tree (early civilizations called it the "fever tree").

When researchers learned how to make chloroquine around the time of World War II, they heralded this discovery as a major victory for public health.

Today, though, public health officials face a substantially gloomier outlook. Parasites quickly develop ways to outwit drugs, allowing the disease to spread.

"When it comes to malaria, the single most important problem is the [lack of] effectiveness of drugs in the Third World," says Wirth.

Although malaria strikes mostly in developing countries, it is not just someone else's problem.

World travelers can play an unsuspecting role in spreading infectious diseases. If you take a trip overseas and come into contact with an infected mosquito, you're at risk for getting, and spreading, malaria.

The relative ease of global travel makes our world an ever smaller place, and mosquitoes don't care who they bite.

Seeds of Science

Wirth, 54, isn't a medical doctor. She is a basic researcher who earned her Ph.D. in cell biology and virology. She loves pursuing the fundamental mysteries of biology by asking questions and testing things.

She grew up in the midwestern town of Racine, Wisconsin. Neither of Wirth's parents were scientists, yet she remembers an early fascination with the natural world. The first toy Wirth ever specifically asked for was a microscope, when she was about 8 years old.

"It's true!" she admits.

Even though Wirth attended a relatively small grade school that didn't have a lot of resources or high-tech scientific gadgets, she clearly recalls a feeling of excitement about science. Every few months, shipments of new supplies for science class showed up, and she couldn't wait for her teacher to unpack them.

"My very favorite elementary school memories were investigating the contents of those huge steamer trunks, which had tons of goodies for learning about biology, astronomy, geology, you name it," says Wirth.

Exploring the trunk contents gave her great satisfaction, nurturing what became a lifelong interest in many different areas of science. Later, Wirth was lucky to find summer research programs for high school and college students. She enjoyed the experiences so much, she knew science would be a permanent part of her life.

"I can't imagine not thinking about science," she says.

Wirth's inquisitive nature has not faded with time. But as she grew into adulthood, she felt a pressing need to connect science with society. The mindset stuck.

"I feel very strongly that scientists have an obligation to help get their discoveries translated into treatments," she says.

On her own time, Wirth works with international groups such as the World Health Organization and Doctors Without Borders. Through these alliances, Wirth hopes to advance the development of treatments for tropical diseases, in spite of the modest financial incentive they offer to drug companies.

Parasite Secrets

Moved by this compelling blend of scientific curiosity and social conscience, Wirth has dedicated nearly all her professional life to investigating the basic workings of *Plasmodia*, the parasites that cause malaria. These organisms' bizarre ability to infect creatures as different as humans and mosquitoes continues to amaze her.

As Wirth explains, *Plasmodia* and other parasitic protozoans (the word means single-celled animal) do something else very unusual: They live within other cells.

Think about it, says Wirth. That's an entire, eukaryotic (nucleus-containing) cell living *inside* another eukaryotic cell that's not a whole lot bigger than itself.

Despite this sizing challenge, parasitic protozoans can deftly maneuver inside different cell types and infect different parts of the body. As a class of organisms, parasitic protozoans harm humans and other forms of life in many ways.

For example, one such parasite, *Giardia lamblia*, can settle into the cells of your small intestine if you drink unfiltered stream water. Even crystal-clear, icy-cold water can be contaminated with small amounts of fecal matter that contains

CDC

This microscopic photo shows the malaria parasite *Plasmodium falciparum* (ring-shaped objects) growing inside human red blood cells (larger, reddish circles).

Giardia-infected intestinal cells. A *Giardia* infection can give you diarrhea and vomiting that lasts for days.

Toxoplasma gondii is another example of a single-celled parasite that can be harmful to people. This organism finds its way into the intestines of cats, which can pass on the disease to people through cat feces containing cells with *Toxoplasma* living inside. Many people who are infected have no symptoms or may feel like they have the flu. Unborn babies and people with weak immune systems, however, can develop serious eye or brain damage.

Of the four species of the *Plasmodium* parasite that cause malaria in humans, a variety called *Plasmodium falciparum* is the most widespread and dangerous, accounting for 80 percent of all human malarial infections and 90 percent of deaths.

Yet despite the impact of these tiny organisms on public health, scientists still don't know most of the details about how *Plasmodia* and other parasitic protozoans damage the body.

What happens to a *Plasmodium* parasite once it gets into a red blood cell, then the liver? What does it do inside the gut of a mosquito?

What about the mosquito? Is it changed by a parasitic interaction? Do red blood cells hold secrets of past encounters with *Plasmodia* or other parasites? Exactly how does the human immune system react to the parasite?

These and many other mysteries of parasite biology remain unsolved. But, according to Wirth, knowing the answers is absolutely critical for understanding and treating malaria and other diseases caused by parasites.

DNA Shows the Way

The trouble with parasites, Wirth explains, is that they are especially agile when it comes to developing counterattacks to the drugs we use to kill them. With their strange characteristics and uncanny talent for evading medical attack, *Plasmodia* are by all measures biological survivors.

The biological survival process works like this. When a constraint of any kind is put on an ecosystem, all species within the system feel pressure to find a way around it in order to survive. The ones that are best at adapting "win," and live. The others, unable to change, die off. This is evolution at work.

In the case of antimalarial drugs, only those parasites that have the molecular tools to fight off our medicines can survive and make more of themselves. Through evolutionary change, the molecular features that give a survival advantage are passed on to offspring. Over time, these features show up as DNA signatures: particular, recognizable genetic sequences.

Wirth's main focus is on DNA. As a geneticist, she studies inheritance, the process of transmitting genetic information from one generation to the next.

DNA carries genetic information in creatures as varied as earthworms, sunflowers, people—and of course, in parasites like *Plasmodium*. You might think of it this way: Each organism's genome, or its entire set of genes, is like a molecular scrapbook that chronicles events happening over time.

Millions of these events occur. A parasite's interactions with the human immune system…its encounters with the body chemistry of a mosquito…run-ins with antimalarial medicines…and so on. All these interactions leave traces in DNA. Evolution leaves its marks within genes, through slight changes, additions, and subtractions of DNA building blocks, or nucleotides.

But the tricky part is that the scrapbook comes without captions. There's nothing indicating what's what. No tags saying, "DNA changed by chloroquine, September 10, 2005," or, "*Anopheles*, Argentina, summer 2001."

Rather, scientists like Wirth compare DNA sequences of the resistant parasites with those that still respond to drugs. They focus on regions of sequences thought to be involved in drug resistance, as suggested by earlier lab work.

"We look across populations of parasite genomes and ask a very simple question: Where are the differences?" Wirth explains.

In genetic-speak, researchers call those differences polymorphisms. When a genetic change affects a single DNA nucleotide, the change is known as a single-nucleotide polymorphism (SNP, pronounced "snip").

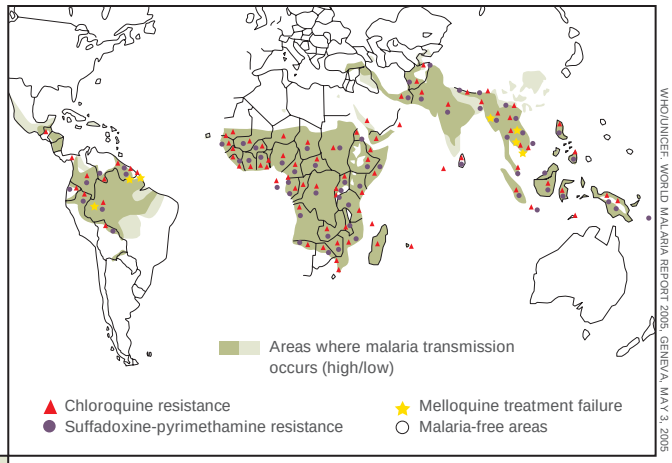
DYANN WIRTH

Wirth collaborates with Senegalese researchers working at a malaria clinic in Pikine, Senegal (top), and at a hospital lab in Dakar (bottom). The scientists also spend time gaining expertise in Wirth's Boston lab.

Wirth and her international research team are currently scanning the DNA of several *Plasmodium* chromosomes in search of SNPs, or patterns of SNPs called haplotypes, that spell drug resistance in the genetic language of parasites.

For these experiments, Wirth and her coworkers first draw small amounts of blood from patients at malaria clinics in Africa, South America, and Asia. Everyone has already agreed to participate in these research studies. After retrieving parasite DNA from the blood samples, the scientists used standard chemical techniques for reading and comparing DNA sequences.

Since the scientists must compare millions of DNA nucleotides from hundreds of samples, they let a computer equipped with specialized software do the grunt work. Certain recurring SNPs that the computer identifies become promising targets for designing vaccines or creating new drugs.



WHO/UNICEF. WORLD MALARIA REPORT 2005. GENEVA. MAY 3, 2005

Resistance to antimalarial drugs such as chloroquine (red triangles) is widespread throughout much of Africa and other parts of the developing world where malaria transmission is high (dark green).

Team Science

For about 7 years, Wirth has been collaborating with researchers in Dakar, Senegal, to use genetic approaches like these to track and fight malaria. Part of the effort involves working closely with local scientists in this West African region, teaching them how to use and apply modern genetic technologies. This partnership helps to inform their decisionmaking about implementing public health measures.

One interesting observation that Wirth and her team have made is that human activity, such as commerce, can help spread mosquito populations and drug resistance. For example, standing water in irrigation ditches or old construction sites can create breeding sites for mosquito larvae.

In other words, the things people do can propagate malaria and the drug resistance that goes along with it. Through her studies, Wirth and her coworkers have been surprised and alarmed to observe the spread of resistance across extremely wide geographic areas.

An overarching goal of Wirth's research is to use genetic testing to develop an early warning system to detect when malaria drugs aren't working, allowing time to try different approaches. For example, a mixture of different drugs can minimize the development of resistance, says Wirth.

The global significance of Wirth's efforts may seem obvious. Yet she's quick to note that progress wouldn't have been possible without somebody digging around asking basic questions.

Among other things, her experiments have helped guide the search for genetic signatures of antimalarial drug resistance

among the 24 million nucleotides that make up the *Plasmodium* genome.

Without the fundamental groundwork, Wirth emphasizes, "We wouldn't even know where to look."

A Magical Time

While Wirth's research helps lead the effort to develop new methods for malaria surveillance and treatment, it also creates new understanding about genetics. This information helps build on knowledge of the role heredity plays in disease.

In a similar vein to the approach Wirth is pursuing, other scientists scan the genomes of people to find small differences that may foretell our health. The scientific methods Wirth and her coworkers use are the very same techniques used by researchers looking for hereditary links to breast cancer, heart disease, depression, and many other disorders.

This scientific pursuit helps us paint a picture of the past and plan for the future. Learning how an organism's biology and behavior change over time is even helping scientists create predictive models for responding to disease outbreaks (see sidebar below).

Now that researchers have access to the sequences of many parasite genomes, it is fairly easy for scientists like Wirth to look broadly at parasite DNA and compare it with that of other organisms. Vast scientific horizons, like the uncharted galaxies once facing early astronomers, lie ahead.

As with planet hunters, today's biologists explore genome space, searching for yet-undiscovered patterns—biological constellations, perhaps—hiding in an organism's genome. The information will most surely have ripple effects, extending our understanding of the larger universe of human health and disease.

Wirth predicts that as technology races forward, new tools will fuel rapid growth in fundamental knowledge. This, she says, is the raw material needed to stop infectious diseases in their tracks and improve global health.

"I think this is a magical time for discovery, for really making a difference," Wirth says. ■

The MIDAS Touch

RICK FRIEDMAN

Admit it, you need a computer to get through the day. Doing homework, instant-messaging your friends, buying stuff online, finding directions—computers make it easier for you to get these and many other things done.

Believe it or not, computers may also make your world a safer, healthier place.

Biology is changing into an information science, with computers taking on new roles in the discovery process and even playing the part of a community health investigator. For example, as part of a National Institutes of Health-funded experiment, scientists use computers to play out various scenarios and develop action plans to respond quickly to a sudden infectious disease outbreak or a deadly act of bioterrorism.

The project, named MIDAS, for Models of Infectious Disease Agent Study, hinges on an international network of scientists with a wide range of expertise: mathematicians, computer scientists, epidemiologists, geneticists, and public health experts.

As one of its first projects, the MIDAS team created mathematical models to simulate an outbreak of a particularly deadly strain of avian influenza virus, or "bird flu." The researchers created a hypothetical Southeast Asian community of people living close together in neighboring towns or cities.

By plugging in data related to the infectiousness of the virus, population density, and the locations of schools, hospitals, and other community structures, the scientists programmed the computer to figure out the consequences of vaccinating specific groups, giving antiviral drugs, limiting travel, and other interventions … all in preparation for the real thing, should it happen.—*A.D.*

The Family Bu

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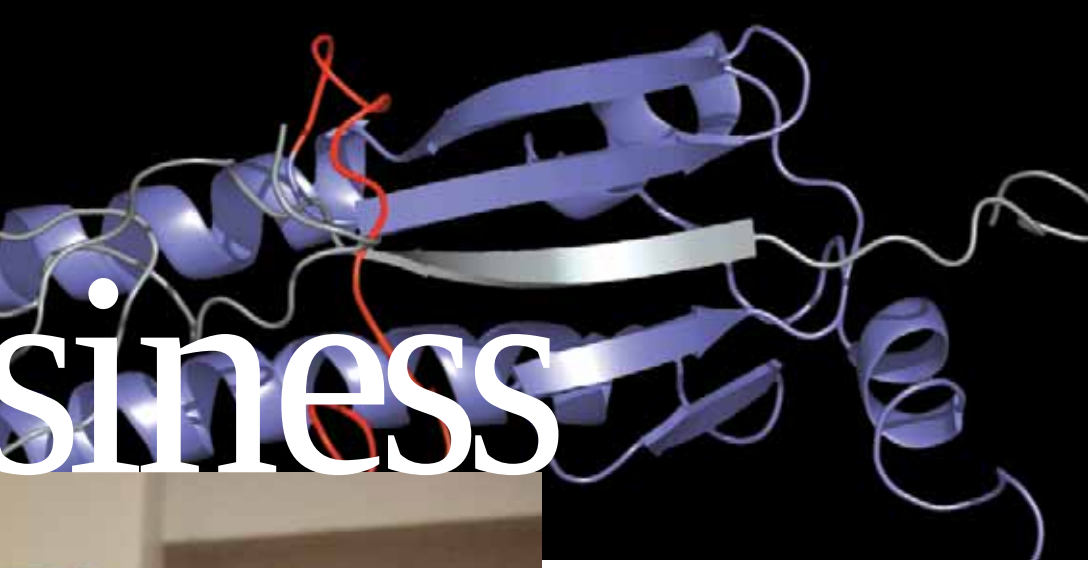


RYAN HARRISON/PROTEIN DATA BANK

DAN LAMONT

David Baker is a computational biologist at the University of Washington in Seattle. Baker custom designs computer software to predict the three-dimensional shapes of proteins.

By Emily Carlson

Although he's only 42, David Baker is already a grandfather. Well…sort of. Baker is raising a second generation of scientists in his lab at the University of Washington in Seattle. The Baker scientific family tree now includes scientists all across the country linked by a common goal: a driving curiosity to predict the shapes of proteins, the basic building blocks of our bodies.

Would you believe that all this happened in just 10 years?

Baker's remarkable enthusiasm for science and endless energy to solve hard problems keeps the family growing. This combination easily attracts new students to Baker's lab, and his captivating way with people keeps them there.

As with any good parent, Baker instills a sense of independence in his scientific children. After they leave the nest, most continue the journey in their own labs, where they raise their own research families.

Like glue, good communication holds everything together. Baker, a computational biologist, believes conversation gives birth to great ideas. Starting open discussions in the lab, he says, is one of his most important jobs.

"I remember a very lively energy in [David's] lab," says Jeffrey Gray, who started working with Baker 5 years ago. "David was the catalyst that increased the flow of ideas."

Gray, now a biomolecular engineer at Johns Hopkins University in Baltimore, Maryland, carries on the family tradition. Modeling his own career after Baker, Gray mentors many young scientists. Among them is a student who, as a high school senior under Gray's mentorship, placed fifth in the 2005 national Intel Science Talent Search competition (see sidebar, page 13).

Birth of an Idea

Baker has spent much of his life tucked between two mountain ranges. A Seattle native, he hikes the local trails in the summertime and skis the slopes when the snow starts to fall.

"This is the greatest place on Earth!" Baker says. "The mountains are one of the great advantages of living here."

But for Baker, the mountains offer more than just pretty scenery and recreational opportunities. They symbolize an inner passion to achieve.

"David approaches science like he does a mountain," says Gray. "He finds the highest peak and heads toward it."

But what Baker now heads toward isn't what he originally set out to find. At first, he thought modeling the shapes of proteins was, well, boring.

"I remember writing a report for a college biochemistry course and thinking, 'Protein folding seems like a neat problem, but not much is happening in the field,'" Baker says.

He admits that his opinion changed during graduate school when he began studying how cells organize their many parts, which of course include proteins.

Our bodies consist of billions of proteins, large molecules made of smaller components called amino acids. Anywhere from a few to tens of thousands of amino acids link up in a particular sequence, and then each amino acid sequence folds into a unique three-dimensional structure.

It's this shape that really determines a protein's job. When a protein attaches to other molecules, it triggers a host of chemical reactions that run all of our biological machinery.

LUKASZ JOACHIMIAK, BRIAN KUHLMAN

One of Baker's passions is exploring the mountain ranges near Seattle, Washington.

"Proteins are incredibly organized and do amazing things," says Baker.

But sometimes the things go wrong. Altering just one amino acid in the chain can change the entire shape of the protein. This switch can lead to life-threatening disorders like sickle cell disease or cystic fibrosis.

If we want to treat and prevent diseases, Baker says, we need to know what proteins look like. Having this information will help scientists custom-design medicines to target proteins and fix health problems.

The Shape of Things

At first glance, determining the structure of a protein from its amino acid sequence seems like it would be easy. But things have not turned out to be so simple. Score one for Mother Nature.

If a protein is really big, scientists can spend months or even years trying to determine its structure. Sometimes, knowing the shape of a similar protein and using that as a guide can speed up the process. But part of the problem is that researchers only know the structures of a small fraction of the proteins in the human body.

So where does that leave scientists who want to find out a protein's shape? They either do physics-based experiments with X rays or huge magnets, or they use computer models to make good guesses.

Both approaches have their drawbacks. X-ray crystallography and NMR spectroscopy, the methods from physics, are labor-intensive and can be expensive. The computer modeling approach can be inaccurate and unreliable.

For Baker, the Holy Grail is developing software programs that generate high-resolution models of proteins. Ideally, these models would reveal every feature of a protein's landscape, including its atoms, hydrogen and other bonds, and all the places where important chemical reactions occur.

With refined pictures, researchers can examine single proteins and track their interactions with other molecules. Accurate models could ultimately let researchers make entirely new proteins with custom functions, motions, and chemical reactions.

Scientists have been trying to develop accurate computer models for years. But the models rarely capture all the details, instead creating mostly "rough sketches" of how protein parts fold together into complex structures.

"Simplifying the model of a protein is like smoothing out a mountain until you have rolling hills instead of sharp peaks and deep valleys," explains Baker, adding that a lot of extra work goes into finessing the computer's output.

Quality Time

With an intense interest in trying to solve what others find unsolvable, Baker splits his time between his two families—his wife and two children and his lab personnel. During the week, he spends regular work hours with about a dozen postdoctoral fellows, 10 graduate students, and a handful of other researchers. Many come from different

countries and different scientific fields, like chemistry, engineering, and medicine.

"It's a privilege to walk out of my office and talk to really smart people interested in the same problem I am," he says. "I feel very lucky to be here."

Together, the group focuses on a computer software program that Baker developed called Rosetta. Just like the famous stone of the same name once helped linguists decipher ancient languages, Baker and his group hope their Rosetta will decode the mysterious shapes of proteins and even help them build new and better versions.

Basically, Rosetta uses information about a protein's amino acid sequence to predict its possible shape. It breaks the protein into small chunks of amino acid sequences, searches for all the different shapes each chunk could assume, and then mixes and matches them until it finds a perfect fit. Rosetta may create up to 10,000 simulations and run for 100 days before honing in on the structure of even the simplest protein.

Baker and his team have created many Rosetta flavors, each of which can answer a different question, such as how a protein interacts with another protein or with a DNA sequence. Some varieties incorporate experimental data or the structural information of other, similar proteins.

One version of Rosetta being developed could run on the computers in University of Washington dorm rooms when students aren't using them. This could add up to 10,000 processors to the team's protein structure prediction effort and make the work go faster.

Because Baker wants as many minds as possible working on the problem, he gives Rosetta to other scientists for free.

Baker and his students take the Rosetta models and go to work refining them. Sometimes, they run into problems, but that doesn't stop progress. When this happens, Baker says he knows it's time to talk, and he brings the lab together to troubleshoot.

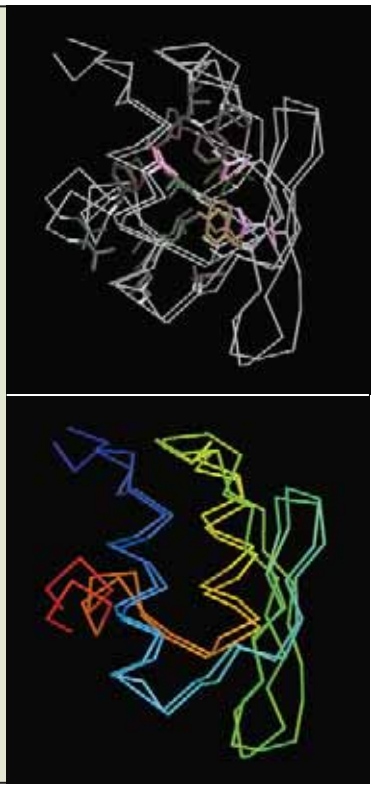
"I think the human factor is one of the most important elements [of science]," Baker says.

Baker is developing a version of Rosetta that can run on University of Washington dorm room computers, adding processing power to his protein prediction experiments.

Outward Bound

Whether the lab takes the day off to go hiking or sits around the lunch table trying to solve a problem, Gray says, "David has the energy to push people beyond their boundaries to explore new ideas."

Baker's ultimate goal is predicting a detailed structure at a level of resolution, or clarity, of 2 angstroms, or 200 billionths of a millimeter.



PHILIP BRADLEY, DAVID BAKER

During the 2004 Critical Assessment of Techniques for Protein Structure Prediction (CASP) community-wide experiment, Baker's team successfully modeled the structure of a protein they had never seen before. Their computer model (top) was strikingly similar to this protein's actual X-ray crystallographic structure (bottom). The model highlighted even more protein detail (pink, brown, and dark gray, top) than did the X-ray experimental data.

"If we can successfully model protein structures with a level of accuracy so that biologists are confident the models are right, we could compute all the protein structures that already exist without [doing] experiments," Baker says.

This, he notes, would save researchers a lot of time and money.

Some people may find it ironic that Baker, who never took a computer course in his life, not only developed a tremendously useful software program but also spends his days (and sometimes nights) thinking about computers.

But he doesn't see it that way.

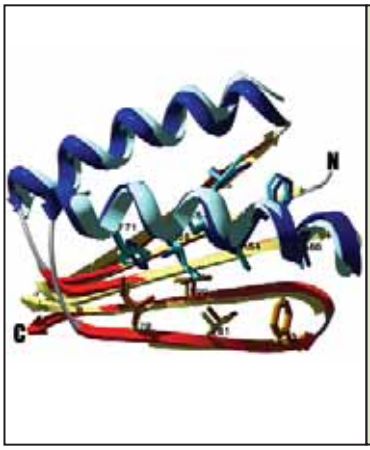
Baker says he finds a problem he wants to solve, meets up with a great group of people, and then learns whatever he needs to know along the way.

Every year, Baker recruits more adventurers to join him on his climb to model proteins. Only together, he says, can they reach the top—better models of protein structures that may lead to new drugs and vaccines for keeping us healthy.

New Direction

One of the latest Baker family franchises involves designing new proteins not found in nature. Unlike the usual approach of starting with an amino acid sequence and then building a structure, Baker and his team are working backwards. They're designing proteins from scratch.

Like architects who design a house before drawing up blueprints, Baker and his trainees began with a sketch of a made-up protein structure. Using Rosetta, they pieced together a string of amino acids that most likely would link up to create the new protein, and then made the actual protein in the lab. In an early experiment, the researchers found that the real protein was virtually identical to the one Baker had imagined.



BRIAN KUHLMAN, GAUTAM DANTAS, DAVID BAKER

Baker used his computer program, Rosetta, to design a small protein not found in nature. His computer model of the protein's structure (dark blue, red) is virtually identical to its lab-determined structure (light blue, yellow).

The scientific community recognized this work as monumental and Baker and his research group received a prestigious prize for the best paper published in a 2003 issue of the journal *Science*.

Next, Baker wants to design proteins that cause particular chemical reactions on demand.

"This would open up a whole new world of functional proteins," says Baker.

The ability to create proteins made to order offers a promising route for developing custom proteins that could interrupt or enhance a particular reaction inside a cell.

Community Center

When it comes to modeling protein structures, Baker and his group have proven that they can climb with the best. Every other year, the group enters a friendly competition

BRIAN KUHLMAN

Baker's annual scientific family reunions always include a mountain trek, like this one to Dragontail Peak in Washington's Wenatchee National Forest.

called CASP (Critical Assessment of Techniques for Protein Structure Prediction). They go head to head with hundreds of labs worldwide to see who can make the best predictions.

In December 2004, scientists from more than 200 labs gathered in Italy, submitting a total of 15,000 predictions for selected protein structures. The only people who knew what the proteins actually looked like were the judges.

Baker's group used Rosetta to develop their models, and as in previous years, Baker's team did very well. One of the post-doctoral researchers in Baker's lab modeled a protein structure with a very small average error of 1.59 angstroms.

"I like working on the methods and seeing them pay off," says Baker. "CASP is very collegial and a great experience for the people making the predictions."

Although there are some competitive aspects, everyone walks away from CASP with a prize—the opportunity to work together, learn about current challenges, set future goals, and assess the methods and technology used to predict protein structures. For this reason, scientists prefer to call CASP a "community-wide experiment" instead of a contest.

Despite this progress, and even with Baker's many successes, a lot still needs to be done. When it comes to accuracy, many current, low-resolution models are in the ballpark, Baker says, but they have a way to go.

As Baker and his team continue to work on the problem, one thing stands in their way: insufficient computing power.

"For a long time, the problem was not having accurate descriptions of proteins and their interactions," explains Baker. "But now the problem is that we don't have enough computer power to run the simulations."

For example, Rosetta can run for months before it finally spits out a model that closely resembles the real thing. Not only does this take computer time, it also takes a lot of computing power, Baker says.

Making really accurate predictions, and lots of them, means having a herd of computers that can quickly process data. Currently, Baker is talking to large computer companies to try

to get his hands on more machines, especially ones with faster processors.

Family Reunion

Every summer, Baker invites his extended scientific family to join him in Seattle for what he calls "Rosetta Commons." For 2 days, they talk about prediction projects, challenges they're encountering, and potential ways to improve the software behind it all.

"We've all started labs that are working on different problems," says Gray, who attended the reunion last summer. "But we're still related by the Rosetta code."

On the third day, the group usually heads for the hills, something the former students fondly remember from their days in Baker's lab.

"If you're walking next to David, you're going to be talking about science," jokes Gray. "David focuses so much on science. It's what he does naturally."

Last summer, the group hiked up Dragontail Peak, which looms about 9,000 feet above sea level. The trail, recalls Gray, was quite ambitious.

Minus the time for picnicking and swimming in a crystal-blue lake, the group spent nearly the entire day climbing to the top. They were only halfway down when the sun started to set.

"It was 8:00 p.m., and we still had several hours of hiking," says Gray.

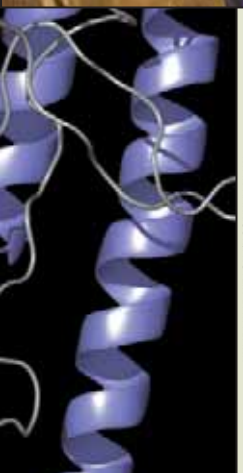
Without enough flashlights to guide their way down, Baker and former postdoctoral researcher Brian Kuhlman—by far the most experienced hikers in the group—volunteered to run back to the cars, drive into town, and bring back extra supplies. The two met up with the other hikers, still creeping their way down, with flashlights and chocolate.

Everyone finished, still in good spirits, remembers Gray.

"It was definitely a bonding experience!" he says. ■

The Next Generation

STEPHEN SPARTANA



RYAN HARRISON/PROTEIN DATA BANK

Every year, more than 1,500 U.S. high school seniors enter the ultimate science fair: the Intel Science Talent Search, dubbed the "Junior Nobel Prize."

"If you're doing high-level research in high school, it's expected that you'll apply to Intel," says Ryan Harrison, a recent graduate of Baltimore Polytechnic Institute in Maryland who ranked fifth in the 2005 national competition.

Harrison got his prize, a $25,000 scholarship, for work that follows in the footsteps of two generations of scientists who predict the shapes of proteins, molecules vital to our everyday health.

With the help of his mentor, Johns Hopkins University professor Jeffrey Gray, Harrison spent more than 2 years developing a version of Rosetta software that models protein structure in a particular pH environment.

Just 17 years old, Harrison already has won the respect and admiration of many scientists. Among them is David Baker, a computational biologist at the University of Washington in Seattle, who mentored Gray (see main story).

"[I heard] Ryan give this great talk, and I thought he must be a graduate student," says Baker. "It turned out he was a high school senior!"

To that end, when Harrison talks about his science, he purposely omits details about his schooling. "I've learned that you have to fool people, otherwise they won't take you seriously," he explains. "You need to prove yourself first."

With a laid-back attitude and energy that keeps him bouncing in his chair, this scientific prodigy doesn't sacrifice fun for success. A self-described "goofball," Harrison says his main objective is to have a good time.

When he headed to Washington, DC, for the final round of the Intel competition, he says, "I just wanted to hang out with cool people. I never expected to take home a prize."—*E.C.*

A World Without Pain

You glide across an icy canyon where you meet smiling snowmen, waddling penguins, and a glistening river that winds forever. You toss snowballs, hear them smash against igloos, then watch them explode in vibrant colors.

Back in the real world a dentist digs around your mouth to remove an impacted tooth, a procedure that really, really hurts. Could experiencing a pretend world distract you from the pain? NIGMS grantee **David Patterson** shows it can.

Patterson, a psychologist at the University of Washington in Seattle, helped create the virtual reality program "Snow World" in an effort to reduce excessive pain in burn patients. To find out if life in Snow World really is painless, Patterson and his coworkers strapped healthy undergraduate student volunteers into immersive virtual reality headgear that completely shut out physical reality by offering wintry sights and sounds. The researchers fitted a second group of students with gear that only partially blocked out the real world.

HUNTER HOFFMAN, UNIVERSITY OF WASHINGTON

Patterson and his team exposed all the students to brief periods of heat both before and during their virtual reality experiences, and then measured their perception of pain. Students fully immersed in a virtual reality experience reported 60 percent less pain, whereas the partial virtual reality gear offered only limited relief.

The researchers say that an interactive digital experience may distract us from the real world because our minds can focus on just a few things at once.

While virtual environments can have drawbacks—like motion sickness, for one—they offer a promising new way to manage pain during medical or dental procedures. And, as recent research shows, reducing pain can speed recovery. Now that's a relief!—*Emily Carlson*

Making Sense of It ALL

About 2,400 U.S. children, most of them toddlers, are diagnosed each year with acute lymphoblastic leukemia (abbreviated ALL). This disease, the most common childhood cancer, starts in bone marrow cells and can spread to other parts of the body.

Fortunately, doctors can cure about 80 percent of patients with ALL using chemotherapy medicines. Some of the remaining 20 percent don't completely respond to treatment because cancer cells become resistant to the chemotherapy's effects. In such patients, the cancer can come back a few years later.

To get a handle on why some patients are cured and others aren't, NIGMS grantee **Mary Relling** of St. Jude Children's Research Hospital in Memphis, Tennessee, looked at the cancer cells' DNA. Relling, a research clinical pharmacist, found 124 genes associated with resistance to chemotherapy drugs. To her surprise, the genes that turned up are known to carry out processes that seem unrelated to cancer, such as building or breaking down proteins and sugars.

Relling and her coworkers also identified genes that reveal which patients might not be able to tolerate the chemotherapy drugs used to treat patients with ALL. For these young patients, the side effects of the medicine can be as deadly as the cancer itself.

The findings of this study could help doctors customize and improve treatments for leukemia, taking into account the genes of each patient. The information may also help drug developers, who could use certain genes as guides for designing completely new anticancer therapies.
—*Alisa Zapp Machalek*

Ginseng's Many Moods

Traditional Chinese medicine holds that different varieties of the herbal product ginseng have opposite effects on mood. New research shows that ginseng can also have variable effects on other body processes.

NIGMS grantee **Ram Sasisekharan** of the Massachusetts Institute of Technology in Cambridge identified several active ingredients from different kinds of ginseng and figured out how they impact the growth of blood vessels.

Past studies of ginseng's effects on blood vessels have provided puzzling results. Some scientists have reported that ginseng may help combat cancer by stunting the growth of blood vessels that feed tumors. Others have shown that ginseng can help heal wounds by stimulating blood vessel growth.

THOMAS G. BARNES, USDA-NRCS PLANTS DATABASE

So who's right?

Sasisekharan's findings show that both are correct. Using a combination of lab techniques, the biological engineer and his coworkers studied the chemical properties of four different varieties of ginseng. They discovered that the

molecule Rb1, found predominantly in American ginseng, starves blood vessel growth. Conversely, they found that a different molecule, Rg1—which is abundant in Asian ginseng—does just the opposite, nourishing blood vessels and helping them grow.

Molecular studies such as these may eventually lead to a better understanding of the many different biological effects of ginseng and other herbs, which are now widely used across the globe.

Sasisekharan offers a note of caution to those taking ginseng, or any herbal product for that matter. Herbal supplements are not subject to review and approval by the U.S. Food and Drug Administration, so specific contents of grocery-shelf bottles can vary dramatically. —*Kirstie Saltsman*

Genes Help Treat Trauma

Each year, millions of trauma victims end up in emergency rooms, where doctors must decide immediately how to treat them. Yet the choices aren't easy, since the extent of internal damage and a patient's general health before his or her injury are often not known.

Due in part to this lack of information, predicting an individual patient's outcome can be agonizingly difficult. Among people with nearly identical injuries, some respond to treatment and steadily improve, while others struggle for days and die.

Now, thanks to a national team science effort involving clinicians and basic researchers, doctors are one step closer to knowing exactly what to do for each patient.

Trauma surgeon **J. Perren Cobb** of the Washington University School of Medicine in St. Louis, Missouri, led a team that scanned genetic material from trauma patients and healthy volunteers, looking for differences in gene activity that might be associated with the most deadly effects of severe trauma. Knowing these genetic signatures in advance may enable doctors to act early to prevent life-threatening complications such as multiple organ failure or body-wide inflammation.

Compared to healthy people, the trauma patients' white blood cells showed dramatic differences in the activity of certain genes. The team is now working to harness this information into quick genetic tests that would help identify the most vulnerable trauma patients.

The researchers plan to further develop their approach into a nationwide program that uses genetic information to treat trauma. If things go as planned, emergency-room physicians will someday be making split-second, life-and-death decisions with a powerful new set of predictive tools.—*K.S.*

Stressed Out DNA

"In the last month, how often have you felt nervous and stressed?"

That was one of the questions posed to 58 women in a study to determine how psychological stress affects cells. Chronic stress has long been known to influence immune function and raise heart disease risk, but scientists aren't exactly sure how.

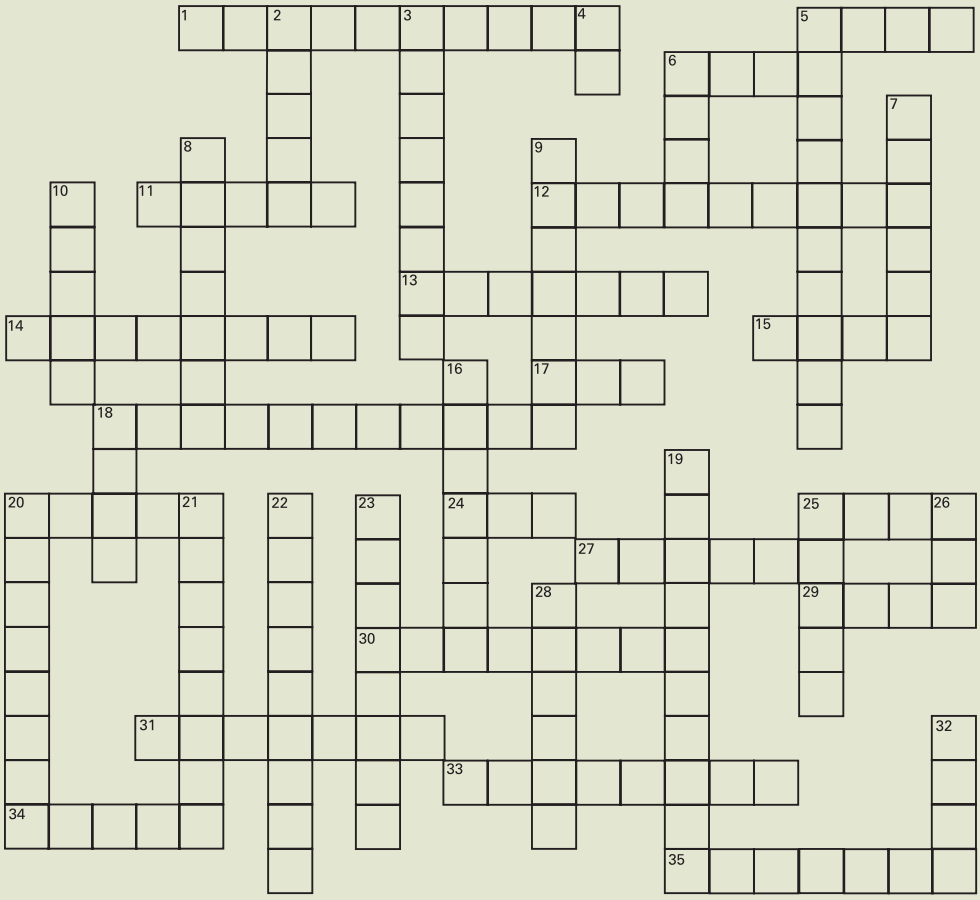
Now, NIGMS grantee **Elizabeth Blackburn** of the University of California, San Francisco, has found that psychological stress causes damage by boosting levels of harmful chemicals inside cells. She also found that stress quickens the loss of telomeres, the protective caps on chromosome tips that are fastened on by the enzyme telomerase. Telomere length approximates a cell's biological age; each time a cell divides, its telomeres shrink.

Blackburn, a molecular biologist, teamed up with clinical researchers to test two groups of women: 39 mothers of chronically ill children (caregivers) and 19 mothers of healthy children (controls). The scientists expected that the caregivers would be more stressed out than the controls. They discovered that telomere length wasn't much different between the two groups. However, the researchers found that the length of time spent caring for a sick child did make a difference. Within the caregivers group, cells of the women spending more time had less telomerase, and thus shorter telomeres.

The team then used a set of standard questions to rate the women's perceived stress levels. Those reporting the most stress (including some of the women with healthy children) had markedly less telomerase, and shorter telomeres, than their more relaxed counterparts. Compared to the low-stress group, the high-stress group's cells appeared to have aged an extra 9 to 17 years! The findings provide the first cellular evidence that chronic stress really can take years off your life.—*K.S.*

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport and it is important to realize that many researchers work together to carry out these studies.

The Last Word



ACROSS

1. stops medicine's effects
5. it hurts
6. always
11. geneticist Dyann
12. parasites' effect on the body
13. protein modeling software
14. runs Rosetta
15. Baker lab activity
17. look
18. first malaria drug
20. big cat that lives in 32 DOWN
24. single-letter DNA change
25. computer "word"
27. severe physical injury
29. windy day toy
30. hundred billionth of a millimeter
31. amino acid chain
33. blood-sucking insect
34. trench
35. parasitic disease

DOWN

2. yell
3. chromosome tip
4. where trauma patients go
5. educated guess
6. rim
7. an organism's entire set of genes
8. unreal
9. malaria is an old one
10. mosquito meal
16. two-faced herb
18. wire enclosure
19. malaria parasite
20. ten hundred
21. scientific investigation
22. change, in biology
23. organism living on another
25. Rosetta inventor David
26. night before
28. anxiety
32. home of 20 ACROSS

Puzzle answers can be found at
http://www.nigms.nih.gov/findings/

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