You’ve Got Some Gall

These green tendrils are not a natural part of the branch they’re sprouting from. A colony of tiny aphids has spurred the growth of this gall and lives inside it. Despite their small size, aphids—also called plant lice—are among the critters most destructive to plants. Feeding on sap through long mouthparts, aphids not only drain plants of their nutritional resources but also spread viruses from plant to plant. Gall-forming aphids, like the members of Tuberaphis taiwani that formed this gall in Taiwan, use their self-built home as a place to hide from predators and rain. HHMI investigator David Stern, an evolutionary biologist, studied aphids for his Ph.D. and still finds them fascinating (see page 5). Visit the Bulletin online to see more photos of galls and aphids.
Loved by bird-enthusiasts for their beautiful bright colors, intelligence, and affection, parrots are the quintessential pet bird. But a mysterious and contagious virus is threatening parrot aviaries around the world. One team of biochemists worked with some concerned veterinarians to solve the 30-year mystery and name the deadly virus.

This November marks the 150th anniversary of the publication of Charles Darwin’s magnum opus, best known by its shortened title The Origin of Species. In this Year of Darwin, celebrating the bicentennial of the English naturalist’s birth, it is fitting to revisit his poetic and passionate words, which, in light of a century and a half of scientific findings, sing with as much relevance today as ever.

It is interesting to contemplate an entangled bank, clothed with many plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other and dependent on each other in so complex a manner, have all been produced by laws acting around us. These laws, taken in the largest sense, being Growth with Reproduction; Inheritance, which is almost implied by reproduction; Variability, from the indirect and direct action of the external conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a Struggle for Life, and as a consequence to Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms. Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

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PAUL SAHRE (cover art) is a graphic designer, illustrator, artist, surfer, author, teacher, community organizer, and the world graphic design foosball champion. He’s also a new dad, the proud father of twins. He works from his office in New York City. (1)

A recent graduate of the Maryland Institute College of Art, NA KIM is a freelance illustrator in Baltimore. This issue’s story on teaching evolution (“The E Word,” page 8) inspired her to channel the surrealist painter René Magritte, whose work *Ceci n’est pas une pipe (This is not a pipe)* typifies his sometimes humorous representational use of objects. In her free time, she enjoys bike rides, 1990s romantic comedies, and pondering the cosmos with her cat, Aioli. (2)

When he’s not chasing parrots, BRIAN VASTAG (“A Curious Catastrophe in the Parrot World,” page 20) works as a freelance science journalist in Washington, D.C. He’s written for The Washington Post, U.S. News & World Report, and Science, among other publications, and is a former associate news editor for *JAMA: Journal of the American Medical Association*. (3)

From quarks to stem cells to health policy, writer CHRISTINE SUH (“Building Solid Bridges,” page 26) has covered a range of scientific research and science-related news for various newspapers and magazines. She worked as a reporter for eight years and has academic training in both biology and journalism. She lives in Arlington, Virginia. (4)
Through Evolution’s Prism

Our cells rely on complex molecular machinery to decode the genetic information we carry inside ourselves. Hundreds of molecular players must mobilize in a highly orchestrated manner so that the right piece of DNA can uncoil from its protective cocoon and the aptly named messenger RNA can be produced to deliver precise instructions for making the proteins needed to keep a cell running. And that’s only stage one.

Scientists have borrowed a simple word from everyday speech—transcription—to encompass the steps required to generate the instructions to activate specific genes. Except that the biochemical process of “transcribing” a gene is so ornate that it’s rather like having to whittle the pencil, make the paper, and assemble the components for a desk and chair before you can sit down to begin copying your roommate’s lecture notes—each and every time.

This isn’t a manufacturing process that an engineer would devise, if given the opportunity. Rather, this almost Rube Goldberg-like assembly could take hold only through a random trial-and-error process such as evolution. And that is one reason I have found transcription so fascinating for better than 30 years. What events initiate the process? How do the essential molecules assemble? Does the machinery vary? What cues enable RNA polymerase—the enzyme that makes messenger RNA—to latch onto the right snippet of DNA and begin assembling a transcript?

Nothing we study in biology and medicine would have a rational, predictable foundation without Charles Darwin’s insights into evolution. The process of ceaseless experimentation that drives an organism’s ability to adapt and survive over huge spans of time. Throughout this issue of the HHMI Bulletin, we consider different aspects of evolution: from how teachers introduce basic concepts to their students to the mathematical models used by HHMI investigator Jonathan Pritchard to gauge the impact of natural selection on human traits. We conclude with Darwin’s magisterial prose, honoring the 150th anniversary of the publication of The Origin of Species.

Many Americans struggle with the fundamentals of evolution and whether to accept its tenets. As teacher Suzanne Black has discovered, focusing on relevant concrete examples is often the best approach. After all, without a firm understanding of evolution, scientists would have been utterly stumped by the new strain of influenza that is sweeping the world. The H1N1 strain of influenza is a mixed pot of genes drawn from viruses that infect pigs in Eurasia and the Americas, birds, and humans. By looking at changes in the proteins that dot the surface of the virus—changes that help the virus survive and adapt—researchers can assess its evolutionary path and map a vaccine strategy for the upcoming flu season. Likewise, each time a forensic scientist uses a sample of DNA from a crime scene to screen potential suspects, knowledge of evolution comes into play because each person’s genetic signature is unique yet related and predictable in its relationship to other individuals. Such everyday examples have been compiled by colleagues at the National Academy of Sciences in the book Science, Evolution and Creationism, a survey of modern evolutionary biology written for the public. A free PDF is available at www.nap.edu/sec.

As a hard-core biochemist, I see the process of genetic inheritance through molecular eyes and, specifically, through the prism of transcription. My scientific journey has taken a path through evolution that began with trying to understand how genes got turned on (and off) in bacteria while I was a graduate student in the Harvard University laboratory of Richard Losick, now an HHMI professor. As a postdoc in Jim Watson’s lab at the Cold Spring Harbor Laboratory, I studied a monkey virus called SV40 that does its damage by taking control of the genetic machinery of an infected primate cell. These early studies provided a path for discovering the huge family of regulatory proteins called transcription factors that govern how a gene gets activated. Thousands of such factors have now been found, along with a host of related molecules—all required to control gene activity.

Today, my lab group is trying to pin down the extraordinarily elastic orchestration of gene regulation in stem cells: What mechanisms allow the flexible capacity of genetic programs that define stem cells? What regulates the expression of genes specific to a particular cell type, such as muscle, liver, or neuron? Pushed by a highly creative group of graduate students and postdocs, we are finding surprising answers. We have also learned a major lesson: The machinery that has evolved is more elaborate, diversified, and convoluted than anyone anticipated. And that is a continuing source of wonder.

“Nothing we study in biology and medicine would have a rational, predictable foundation without Charles Darwin’s insights into evolution.”

Robert Tjian

President’s Letter

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**Something to Say**

**Physicist Stephen Quake** has learned the power of the pen. But not from his 99 scientific papers describing his research in biophysics, microfluidics, and genomics. None of those writings stirred the kind of impassioned feedback he got as a guest blogger for *The New York Times*.

Online reviews of his accounts of life in the ivory tower ranged from enthusiastic (“Bravo!” and “marvelously insightful”) to cranky (“lopsided and unfair”).

Quake wrote four weekly guest columns for *The Wild Side*, a science blog on the *Times* website. Starting on February 10, he gave a taste of the daily realities of being a scientist at a modern research university—warts and all.

For instance, he described the brutal pressure to win enough research funding, especially for creative, high-risk projects. And he shot down “the snobbish idea” that “pure” basic science research is separate from and superior to applied research. “I had a lot to get off my chest,” says Quake, an HHMI investigator at Stanford University. “And it was fun to do a little venting in a public forum.”

The writing stint came about when *The Wild Side*’s longtime blogger, Olivia Judson, an evolutionary biologist at Imperial College London, took a six-month sabbatical. The *Times* wanted several guest columnists to fill in. Judson thought of Quake, who she met in 1987 when they both attended Stanford. “He was good at physics and I wasn’t,” says Judson, laughing. “Insofar as I made any progress in physics, it was because Steve talked me through it.” The two lost touch over the years, but Judson would occasionally happen upon one of his research papers. “I saw he was doing exciting and important work.”

When Judson e-mailed in November to ask if he’d be willing to dive into the blogosphere, Quake says he was “a little bit daunted” but open to the challenge. So Judson passed his name and a few others to her editors, who were considering a number of candidates. He was one of seven who made the cut.

Quake shoehorned time for writing into the crevices of an already crammed schedule. “I did it everywhere—at home, in the office, on the airplane, in a taxi, in hotel rooms,” he says. To his surprise, he found himself focusing mostly on policy and social issues.

In his hardest-hitting post, “The Crumbling Ivory Tower,” Quake argued that when academic researchers have a financial stake in commercializing their basic lab discoveries, peer review can protect against potential biases in results. Instead, he wrote, university bureaucracies try to manage conflicts of interest “often by meddling into faculty research in ways that create more heat than light.” He also criticized university licensing offices for impeding technology transfer.

That essay elicited some of the most heated reader responses. Although he wasn’t expected to answer comments, sometimes, Quake says with a laugh, “I had to hold myself back.”

He admits to catching the blogging bug. With those four essays under his belt, Quake is keeping a list of future topics. —*Ingfei Chen*

**FOR MORE INFORMATION:** To read Quake’s blogs, go to: judson.blogs.nytimes.com/author/Stephen-Quake.
Study Aphids, See the World

To gardeners, aphids are disease-carrying pests that can suck the life out of plants. The tiny, soft, green insects, known as “plant lice,” brought France’s legendary industry to near collapse in the Great French Wine Blight of the mid-1800s.

To evolutionary scientists, however, aphids are a fascinating oddity that have played an “outsized role” in the history of biology, says David Stern, an HHMI investigator at Princeton University. And they were his ticket to see the world.

Stern describes aphids’ unique characteristics: “With the same genome, they can make different phenotypes, depending on the environment.” For example, they can reproduce with or without the help of a mate and can spawn offspring with wings or without them. Certain aphids provoke trees into forming galls—bizarre, sometimes beautiful, hollow growths that serve as aphid hideaways. Some aphid species breed castes of “soldiers”—fierce (but sterile) warriors. Some variants poison their predators and some stab them with sharp horns, wrote Stern in an admiring essay, while others “squeeze their enemies into submission with their fat hind legs.”

To Stern, an avid gardener since age six, aphids were merely a nuisance until, during his graduate studies, he took a five-year sojourn in Japan, Malaysia, Indonesia, and Taiwan to study aphids in the field.

The discovery of the sterile caste of aphid soldiers in the 1970s by a Japanese taxonomist had raised interesting questions about the evolution of social behavior. Intrigued, Stern packed his bags for Japan in 1989 and spent several years collecting aphids and sequencing their DNA—a time-consuming process in those days. He then used DNA evidence to determine how many times the soldiers had emerged in aphids’ evolutionary history.

The fieldwork for his Ph.D. “was not as romantic as it sounds,” Stern admits. The sapsuckers were most abundant on roadside plants. “So I would walk along the road, flipping over leaves.” He also attached clippers to long poles to cut off branches where soldier-producing species had formed galls, so he could bag the aphids inside their domiciles.

The lone scientist based himself in rented apartments in cities like Kuala Lumpur, and sampled many indigenous foods. “I remember eating the most outstanding homemade noodles and chicken soup in a roadside stall,” Stern recalls, “and a vegetarian restaurant where everything was supposedly made from bean curd but looked identical to, and tasted strongly of, every imaginable body part. I remain skeptical to this day.”

After completing his doctorate, Stern continued to study evolution and development in aphids, but his interests shifted. He began to study the fruit fly and devised powerful methods for hunting genes that he plans to use in probing the control of quantitative traits, such as body size, life span, reproductive rate, and—Stern’s current enthusiasm—behavior. Aphids haven’t disappeared from his radar screen, however. Back in 2001, he pushed hard for funding to sequence the aphid genome, a project that is now nearing completion.

And the lifelong gardener says that on his mile-and-a-half walk to his Princeton lab, he checks daily progress on several trees that are forming galls. “I must admit I still harbor some crazy plans to attack the problem of gall development,” he confesses. “But I’m putting it off—at least for a couple of years.” —Richard Saltus

WEB EXTRA: Visit the Bulletin online to see photos from Stern’s aphid-collecting travels and more.

As a graduate student, David Stern traveled to far-flung lands to study the evolutionary history of a sterile caste of plant-sucking aphids.
Serious Softball

It’s a sunny April weekend and immunologist Richard Locksley is drilling a cluster of teenage girls: “Hard throws please, hard throws. Way to stay down. Throw it hard over the top, don’t sling it from the side.”

Locksley coaches a softball team that includes his twin 13-year-old daughters, Morgan and Sydney. In between jostling and laughing, the players respond to his near-constant chatter during an infield warm up. “Okay, everyone take an easy lap together,” says Locksley, an HHMI investigator at the University of California, San Francisco.

“If the girls are goofing around, throwing their mitts at each other, I know they’re ready for a game,” Locksley says. “It’s when they’re sitting too quietly or looking to me for what to do next, that I know that they’re too uptight about the game. Then it’s time to stop coaching, diffuse everything, and get them comfortable. Then they’ll do fine.”

Locksley hasn’t always been so clear about his coaching style. But after seven years, he’s come to realize that a well-coached team is one that knows the fundamentals of the game—and has fun.

“At the beginning I took it much more seriously if we won or lost. Now I’ve let that go a little bit.”

Maybe a little, but daughter Sydney says he still takes it seriously enough to review the game during the car ride home. And Morgan smiles: “Sometimes he gets mad when we forget his signs; he thinks they have to be all complicated so the other team can’t figure them out.”

When the twins started playing soccer and softball as young kids, Locksley, who played competitive baseball and soccer through college, was content to help the girls’ soccer coach and watch softball from the sidelines. But after one season, that changed. Their first softball coach pitched to the girls with a baseball-style overhand, instead of using the underhand style required in softball. “It bugged me that someone wouldn’t take the game seriously enough to even learn how to throw the ball right to the girls.”

So he took a couple of coaching clinics led by a former U.S. Olympic softball coach. And when he registered the girls for softball the next spring, he signed on as coach.

Before long, his team was learning the basics and doing pretty well. Many of the same girls come back each year—and they continue to win. In 2007, Locksley became the first softball coach to win the San Francisco Little League’s Best Coach of the Year Award.

Next spring, the girls will have to choose whether to switch to their high school team or keep playing with their dad as coach. When the inevitable happens and they move on, Locksley says he’ll miss his time with them. “It is so fun working with all these girls—not just my daughters—watching them develop, seeing how happy they are when they win, how collected they are when they lose.”

Right now, however, all three Locksleys are focused on what’s happening on Ketcham field. In the bottom of the third, Morgan hits a long fly ball to right field for a grand slam. As she rounds second base, Locksley hollers from his third-base coaching position “Morgan, get on your horse!” The SF Angels, as Locksley’s team is called, won the game, and they finished the season undefeated. —Rabiya Tuma
While researchers explore the imprint of evolution on individuals, species, and populations, teachers must find innovative ways to present the subject in the classroom. Evolution and religion coexist uneasily in some minds, and students often arrive in biology classes with reservations or even a set notion about evolution’s improbability. Many teachers have thoughtfully devised ways to reach their students in the face of such resistance. And they’ve got some great resources to help them.
TWENTY-SIX WEEKS INTO SUZANNE BLACK’S 10TH-GRADE BIOLOGY class in a Seattle suburb, she drops the bomb. *Evolution.* Black didn’t purposely avoid the word before then, but in 25 years of teaching she’s learned to minimize conflict by presenting information about evolution gradually. *Though the principles of evolution underlie biology from genetics to ecology, the religious beliefs of some students can make teaching the topic difficult. Experienced high school educators have learned to get past the controversy by working up to the important concepts and keeping lessons relevant to the students’ lives.*

Black also trains teachers as part of the HHMI-supported Science Education Partnership, a professional development program for high school teachers based at the Fred Hutchinson Cancer Research Center. She and others like her build their case with each day’s lesson until the bigger picture forms. Then they let on that they’ve been teaching evolution. It’s like adding shredded zucchini to a homemade chocolate cake. No one knows it’s there, and once it’s pointed out, people realize it’s not at all what they thought.

“We start with evidence that’s based in molecular biology and genetics and slide in the ‘evolution’ word later on,” agrees Ann Findley, professor of biology at the University of Louisiana at Monroe. She teaches college students as well as high school seniors and high school biology teachers in an HHMI-supported summer course. “[Some students] have been misled to think it’s something else, and they don’t see what all the fuss is about.”

The same day Black formally introduced the “E” word, a student asked a question about intelligent design.

“I explained that intelligent design is a religious viewpoint that says that some things are so complex that you can’t explain them, and that it’s not scientifically supported,” she says. “The kids wanted to know what I meant, and I asked how we could design experiments to test the ideas behind intelligent design. And that was it.”

She adds, “It was great that he asked, because you know 10 other kids were thinking the same thing and just not asking.” Years ago, Black remembers taking a different tack, with dreadful results. She inaugurated a student teacher with a unit on evolution. “That was a mistake,” she says. “The kids ganged up on her and were literally firing questions at her like, ‘Were you married in a church? How could you do that and believe in evolution?’”

Black’s own early attempts were “too textbook,” she adds. “I came across as too confrontational. With high-school students, it has been more successful to present learning experiences that let them construct their knowledge from evidence they can see, hear, touch, and analyze.”

Taking that approach, teachers say, can be the tipping point between keeping high school biology teachers and students from falling further into controversy.


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school students interested in science and turning them off for good.

**Make it Relevant**

Deb Whittington, a teacher in Lake City, South Carolina, encourages science teachers in her district and state to pair evolutionary evidence and interesting, relevant examples embedded throughout instruction and not just during a "unit" on evolution. Teachers might, for example, discuss antibiotic resistance, sickle cell anemia, bird evolution, or family trees. "It helps them see where evolution affects life every day," she says.

In 2005, she helped organize South Carolinians for Science Education after realizing that some fellow teachers were apprehensive about presenting evolution in the classroom. Whittington has also participated in, and helped run, HHMI-supported summer courses on the topic for biology teachers at Clemson University.

“We take the teachers into the labs, show them evolution in action, try to present it as something that’s happening every day, not some abstract concept,” says Barbara J. Speziale, associate dean of summer programs and undergraduate studies at Clemson.

Providing information and dispelling myths can open doors to students and to their families and friends, as well.

“A few years ago in our precollege program, we had a young woman whose father and grandfather were Baptist ministers,” Findley says. “At the end of the program, she said she was excited to go home and talk to her father about evolution. I thought that was great—she can at least start a dialogue in her community. That’s what I’d like to achieve.”

Black agrees. “For a student to see the power and beauty of evolutionary theory … that’s worth any of the barbs you might get along the way.” —Nancy Volkers

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**For More Information:** Visit [http://ncseweb.org](http://ncseweb.org) to find information and advice for teachers. To learn more about Na Kim’s illustration, see Contributors on page 2.
The Pay-Off of Persistence

What began as a side project has become a primary focus for this physician researcher.

A college project studying how elephant seals’ fat cells change after the seals are weaned triggered Vivien Cheung’s long-time interest in how different human traits appear.
The children came to the clinic usually before the age of two. They had difficulty walking or even sitting upright. In some, angry red veins bulged in the corners of their eyes. Vivian Cheung, then a pediatric neurologist at Children’s Hospital of Philadelphia, recognized the signs of ataxia telangiectasia (AT), an inherited disorder. The good news was that it was rare; the bad news was that there was no cure.

The AT gene defect normally rendered its victims wheelchair bound by the age of 10 and plagued them with respiratory ailments and cancers until they succumbed, often before turning 30.

Cheung had been on track for a medical career. “My dad was a surgeon,” the HHMI investigator says now, with a dutiful daughter’s smile. But while working as a clinical fellow at Children’s, a teaching hospital affiliated with the University of Pennsylvania School of Medicine, she began doing research in her spare time to unravel the mysteries of this heartbreaking disease.

It was a journey that would eventually make her one of the world’s foremost experts on the genetics of DNA repair. In AT patients, a defect in an important repair-related gene leaves them vulnerable to a bewildering variety of bodily dysfunctions: balance and motor-control problems, spider veins in the eyes, diabetes and infertility, immune system defects, and—perhaps strangest of all—an extraordinary sensitivity to ionizing radiation.

“I had long been interested in how different traits appear,” Cheung says. As an undergraduate at the University of California, Los Angeles, majoring in microbiology, she had studied how fat-cell metabolism changes radically in young elephant seals to enable them, after weaning, to hunt fish at half-mile depths. Later, in medical school at Tufts University, she took part in a multiyear epidemiological project in Turkey to study the genetics of lipoprotein levels.

At Penn, Cheung set up a small laboratory to study the genetic havoc of AT, and she quickly focused on the radiosensitivity problem. Patients with the disorder have inherited two mutant copies of a gene known as ATM (ataxia telangiectasia mutated). The gene normally codes for an enzyme whose most evident role is to act as the foreman of a special repair crew—called into action after the gravest of cellular events, a double-stranded DNA break. The “ATM crew,” which includes several powerful tumor-suppressing molecules, must either attempt DNA repairs or trigger a cellular self-destruction process known as apoptosis, lest the damaged DNA lead to runaway cancerous growth. Cells that lack this repair capacity are much more susceptible to damage from radiation and are more likely to turn cancerous.

That told me that ATM wasn’t the only gene responsible for radiosensitivity,” she remembers.

Cheung still does some clinical consultation at Children’s Hospital. But for the past several years, and with support from HHMI since early 2008, she and her colleagues have been trying to understand the genetic underpinnings of radiosensitivity in AT patients as well as in the wider population. In a study published in Nature in April, Cheung and her lab members looked at gene expression responses to irradiation in a large sample of human cells. They were able to link individual differences in these responses to DNA-sequence variations in more than a dozen master regulators of the radiation response, which were found throughout the genome.

“One goal of this is to develop a DNA-based test to determine how radiosensitive a person is likely to be,” she says, adding that such information is becoming more important, given the rapid increase in the use of radiation for CT scans and cancer therapies over the past two decades. Detailed knowledge about the molecular first responders to radiation damage could help, too, in the development of drugs to make tumors more sensitive to radiotherapy.

Cheung also has a deeper goal in mind, which broadly relates to the popular concept of personalized medicine: “We can apply the same tools developed for this study to see how people differ in their responses to drugs or environmental toxins that they are exposed to in their ordinary lives,” she says.

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VIVIAN CHEUNG

“Even ordinary background radiation, from cosmic rays and radon gas, can contribute to cancers in AT patients,” says Cheung.

AT occurs in fewer than 1 in 40,000 children, yet Cheung soon realized, as her lab grew, that radiosensitivity was a trait not confined to these rare patients. Gene-expression studies in her lab suggested that AT carriers, who have one nonworking copy of ATM (and represent fully 1 percent of the population), are also more sensitive to radiation. In fact, Cheung noted from the literature that more than 10 percent of all patients receiving radiation therapy for cancer showed signs of excessive damage or secondary cancers.

“One goal of this is to develop a DNA-based test to determine how radiosensitive a person is likely to be.”
The Foldit team has been analyzing the skills and strategies of prodigies like Pletsch—so-called folding savants—for guidance on how to teach computers better ways to predict protein structure. And through a new version of the game, these virtuosos and other Foldit fans now have a chance to take on a bigger task: designing proteins that might become the next generation of treatments against diseases such as influenza, cancer, and HIV/AIDS.

Every protein folds into a characteristic shape that dictates what job it can perform. Like the seating arrangement at a dinner party, the conformation reflects attractions and repulsions. Water-shy amino acids, for example, huddle in the interior of the molecule. Some pairs of amino acids make good neighbors, whereas others don’t mesh because of their bulky side chains. Scientists often nail down a protein’s shape experimentally through x-ray crystallography and nuclear magnetic resonance spectroscopy, but these laborious techniques can’t keep up with all the new proteins being discovered, says Baker.

As an alternative, researchers often hand the job over to a computer, which can make folding predictions based on the amino acid sequences of proteins. Over the past decade, Baker’s team has devised some of the best algorithms for making these forecasts, consistently topping a biennial fold-off called CASP (Critical Assessment of Techniques for Protein Structure Prediction). But predicting the shape of a protein that comprises hundreds, or maybe thousands, of amino acids can overwhelm even a supercomputer.

To speed up the work, Baker and colleagues parceled out the analysis in 2005 through Rosetta@home, a project in which some 200,000 people have allowed their computers, during downtime, to perform a portion of the folding calculations. Baker says that the inspiration for Foldit came from Rosetta users who watched the program’s progress on their screen savers and reported that it wasted time testing obviously incorrect configurations. The researchers wondered whether humans could do better. Computers are stuck with a big limitation, says Baker—they select the
next step at random. “People won’t be moving around randomly. They will use insight to find the best step.”

Pletsch says he started playing Foldit shortly after its Internet release in May 2008. Folding solo, he has set the top score on more than 30 of the challenges posted on the website, and he’s one of the star performers on the “Another Hour Another Point” team.

Over the last year, Baker and colleagues have invited a handful of Foldit savants, including several Another Hour members, to Seattle for debriefings. In two 20- to 30-minute computer sessions last October, Pletsch showed off his best moves. He says he doesn’t stick to a script when he folds, but he does follow a rough plan. For example, he usually starts by giving the protein a few good shakes, which can jostle the molecule into a more efficient configuration.

What impressed Baker about Pletsch’s play was his facility for breaking up the molecule onscreen and piecing it back together in a more efficient shape. According to Baker, that requires “phenomenal visual ability.”

Baker won’t say that humans are better than computers at folding proteins. But he and his colleagues are poring over the savants’ play to reveal steps that a computer could emulate. Some attributes of these master players are already clear, though, such as having really good three-dimensional visualization skills. “Being a scientist doesn’t help at all,” says Baker, who admits his own performance on the game is middling—his 13-year-old son trounces him.

The team recently provided the savants and other Foldit aficionados with a new way to tickle their brains: designing compounds that could possibly furnish treatments for AIDS, malaria, and other diseases. The first challenge, which the team plans to release soon, will ask players to craft a molecule that can jam the flu virus and prevent it from entering cells to start an infection. Pletsch says he’s eager to give the design feature a try. “It allows someone with a casual interest to take a crack at some usable solutions.”

--MITCH LESLIE
Jonathan Pritchard has been an arbiter in one of the most contentious debates in biology: How much has natural selection influenced human traits?

WRESTLING WITH DARWIN

by Steve Olson | photography by Kevin J. Miyazaki
The discovery of natural selection was both a triumph and a burden for Charles Darwin.

Through careful observations of the living world, he concluded that most organisms have many more offspring than can survive. Those offspring with advantageous characteristics tend to live while others succumb to disease, are eaten by predators, or otherwise fail to reproduce. This "struggle for life" tends to perpetuate favorable traits, enabling populations of organisms to adapt to their environments. Yet the struggle reveals an amoral ruthlessness at the heart of nature. When Darwin reflected, late in life, on his loss of faith, one consideration he cited was "the sufferings of the millions of lower animals throughout almost endless time."

Humans are not exempt from this competition for reproductive success. The miscarriage of a fetus, the death of a child from disease, a young couple's inability to have children—all are more than human tragedies; they also prevent particular versions of genes from passing into future generations. As Darwin said of his theory, "the vigorous, the healthy, and the happy survive and multiply."

Jonathan Pritchard, an HHMI investigator at the University of Chicago, has been fascinated by evolution and natural selection ever since he began collecting insects and watching birds near his childhood home outside London. "Understanding the role of selection in any species is one of the fundamental questions in biology," he says.

It's also a problem with many practical applications. Selection modifies genes that influence our phenotypes—our biological forms and functions—including susceptibility to disease and responses to environmental toxins. If geneticists like Pritchard can identify places in our genomes shaped by selection, they might shine a spotlight on genetic regions implicated in some of the major scourges of humanity. "Selection could influence common diseases—like diabetes, hypertension, and stroke—that fill up hospital beds," says his University of Chicago colleague Anna Di Rienzo.

More controversial issues are at stake. Some biologists claim that the biological differences between human populations are largely the product of selection. They say that skin color, body shape, and even certain dispositions such as aggressiveness and intelligence are the product of people with particular heritable traits having more successful offspring.

Other biologists scoff at these claims. They insist that complex characteristics like intelligence depend much more on a person's experiences than on the genetic differences between individuals or groups of people. And they claim that, for most traits, factors like the movement and growth of human populations are more likely than selection to determine genetic inheritance.

Pritchard, a lanky ex-athlete who exudes the calm of a serious runner, has been at the forefront of these controversies throughout his research career. But he has served more in the role of mediator than combatant. Pritchard is an expert at the mathematical techniques needed to determine how natural selection has influenced our genomes. While others argue in the abstract about how genes might affect human traits, Pritchard focuses on facts: what historical processes could have produced the sequences of genetic letters in our DNA?

AN EXTRA YEAR

Pritchard's proficiency in both mathematics and biology can be traced in part to a bum knee. He and his father, William G. Pritchard, an applied mathematician who moved the family from England to the United States to take a faculty position at Pennsylvania State University, shared a love of running. Pritchard's first scientific paper, which he wrote as an undergraduate with his father as coauthor, analyzed the effects of wind on sprinters and concluded that the women's world record in the 100 meters, set by Florence Griffith-Joyner at the Olympic Trials in 1988, should have been disallowed because of a strong tailwind. However, the anemometer, which recorded a wind speed of zero, appears to have malfunctioned. ("Running officials have occasionally asked us about our results," says Pritchard, "but they don't want to change the record.")

Pritchard planned to run the 1500- and 5000-meter track events for Penn State when he entered as a freshman. But a knee injury forced him to redshirt for a year, which meant he was in college for five years. That gave him plenty of time to double-major in biology and mathematics while still competing on the track and cross-country teams. A freshman class taught by Andrew Clark on population genetics—the study of changes in DNA sequences in populations of organisms...
Jonathan Pritchard, fascinated by evolution since childhood and gifted in math, combines computation and population genetics to learn how natural selection has influenced our genomes.

team of researchers who used structure to analyze genetic data from more than a thousand people drawn from 52 worldwide populations. At the time, geneticists thought the extensive genetic overlaps among all humans would make it difficult to divide people into categories. But structure clearly sorted the people into groups centered on continents or parts of continents, including sub-Saharan Africa, western Eurasia, eastern Asia, and the Americas. The resulting paper, published in Science in 2002, was named “Paper of the Year” by The Lancet.

Newspaper stories heralded the results as providing a biological basis for traditional racial classifications, but Pritchard interprets the results somewhat differently. For him, the patterns in our genomes reflect the earth’s geography and the history of populations as much as they do the classifications societies use to divide individuals into groups. Anatomically modern humans evolved in Africa sometime before 150,000 years ago. They spread into the rest of the world and gradually replaced the more archaic forms of humans living in other parts of Africa and in Eurasia, including the Neanderthals in Europe, Homo erectus in Asia, and the most recently discovered Homo floresiensis in Indonesia.

As modern humans colonized the world, groups developed genetic differences that make it possible to distinguish Africans, Asians, and Europeans today—both visually and by using computer programs like structure. People, however, have continued to move within and among continents throughout history, blurring the genetic differences among populations. In some cases, the movements were extensive, as between Europe and Asia. In others, they were small but continuous, as between Asia and the Americas across the Bering Strait. Today,
all human groups appear to be the product of complex mixings and movements of previous groups, not isolated populations that have remained separate and immobile for long periods.

**SIGNS OF SELECTION?**

Pritchard moved from Oxford to the University of Chicago in 2001, the same year the full sequence of the human genome was published. Completion of the Human Genome Project marked a milestone in the history of science, but it was just one genome and population geneticists wanted more. They wanted to know how DNA sequences differ from person to person, both to gauge the effects of those differences on health and to learn more about human history.

They did not have to wait long. In the 1990s, Cavalli-Sforza at Stanford had initiated an effort known as the Human Genome Diversity Project to gather hundreds of human DNA samples from around the world; the data Pritchard analyzed with *structure* were some of the first results from the project. In 2002, the National Institutes of Health launched a more intensive effort that identified millions of common DNA differences in several hundred people with African, European, and Asian ancestry.

As data on human genetic differences flooded into databases, population geneticists scoured the data for signs of selection. For example, a group led by Pardis Sabeti at Harvard University developed a mathematical technique to look for large blocks of DNA suggested that the sections contained a genetic variant that had conferred an advantage on individuals with that variant, causing the representation of the variant to increase in the population. For example, Sabeti’s research team found two genetic variants involved in resistance to malaria that appeared to have increased dramatically in frequency over the past few thousand years—about the same time frame when the development of agriculture caused populations of malaria-carrying mosquitoes to explode.

Soon other signs of selection popped up in DNA data. For example, the strongest signal of selection in the entire human genome emerged from the gene that encodes the enzyme lactase, which breaks down the sugar in milk, lactose, into more easily digested sugars. Most people in the world make lactase when they are children so they can digest their mother’s milk, but the gene shuts off when they become adults. Many people with European, Middle Eastern, or African ancestry have a variant of the lactase gene that remains active in adulthood, so that they’re able to digest milk their whole lives. These versions of the gene are most common in populations that domesticated animals for milk, which would have created a selective pressure for a lifelong ability to digest lactose. The genetic variants in these populations began to increase in frequency at about the same time that dairy animals were domesticated.

Another strong selective signal turned up in genes that affect skin color. As modern humans expanded out of Africa into more northern latitudes, their dark skin became a distinct disadvantage, probably because in high latitudes it blocks too much of the sunlight that humans need to synthesize vitamin D. Genetic variants that produced lighter skin therefore gained a significant advantage. In early Europeans, variants in several genes that lighten skin color began to increase in frequency. Meanwhile, the same process was occurring on the other side of Eurasia as dark-skinned people from southeastern Asia moved north, but there, different sets of variants became responsible for lighter skin.

Pritchard and other geneticists also began to find signs of selection in parts of the genome with unknown functions. In a 2006 paper, for example, he and a group of colleagues found selective signals scattered throughout the genome. Some signals were associated with genes of known function, but others appeared in genes of unknown function or even in areas that had no genes.

Meanwhile, other studies suggested that the rate of selection markedly increased in recent human history. A research team led by anthropologist John Hawks at the University of Wisconsin concluded that selection was more than 100-fold faster in recent human history than before the movement of modern humans out of Africa. Two members of that team, anthropologist Henry Harpending and physicist Gregory Cochran, have used the data to speculate that many features of modern populations—such as the higher average scores of Ashkenazi Jews on IQ tests—reflect the influence of selection.

At this point, arguments about selection often acquire political overtones. But Pritchard has avoided those arguments. He wants to know whether selection actually produced the signals he and others have detected. Recently, he’s come up with some surprising answers.

**AMBIGUITY**

Last year, a group of researchers at Stanford used a new technology to measure differences in DNA sequences from the Human Genome Diversity Panel at many more genetic locations than in the past. With postdoctoral fellow Graham Coop, graduate student Joseph Pickrell, and several collaborators at Stanford, Pritchard
began searching the data for signals of selection.

Previously known signals jumped out right away, including the lactase and skin pigmentation genes. Pritchard and his colleagues also found several interesting signs of selection where they hadn’t been seen before, such as in a set of genes involved in the development of heart, neural, and mammary tissue. Geneticists have few clues about how these genes operate and why they might have been selected, but “we’re keen to learn what these genes are and how they work,” says Coop, now an assistant professor at the University of California, Davis.

In a paper published in *PLoS Genetics* on June 5, 2009, Pritchard, Coop, Pickrell, and a group of colleagues, including Feldman and Cavalli-Sforza, describe an unexpected result of their analysis. Beyond the clearest signs of selection—like lactase persistence, skin color, and resistance to several infectious diseases—there appear to be few unambiguous cases of strong selection in the human genome. “Natural selection may shape the human genome much more slowly than previously thought,” says Pritchard. In fact, some of the DNA sequences identified earlier as possible signs of selection look like something else to Pritchard. They look like the patterns generated by the migration of modern humans out of Africa and by the continued movements of people since then.

Pritchard’s team has concluded that selection in the human genome is often overwhelmed by the movement and expansion of populations. “Selection is a weaker force than people thought,” says Pickrell. Populations that are closely related genetically, because they split recently or exchange many migrants, have very few genetic variants that are markedly different. With more distantly related populations, demographic processes have usually had a greater influence than selective pressures. Selection may be driving groups of genes that all influence a trait in particular directions, but “simple models of strong selection pushing single variants to high frequencies appear not to be the case,” Pickrell says.

As a result, it may be difficult to determine which human genes have genuinely been affected by recent natural selection. “It’s hard to be confident about individual signals beyond the top 10 or so,” says Pritchard.

Some dispute these conclusions. “It depends on the model of population history that you use,” says Hawks. “We believe that populations were larger in the past, which means that there was more selection.”

Sabeti, however, finds Pritchard’s conclusions convincing. “There has to be a false-positive threshold,” she says. “We don’t really understand the demography of these populations, and there are lots of question marks.”

New data will help answer some questions. The 1000 Genomes Project will soon begin delivering full DNA sequences—not just the most common DNA differences—of more than a thousand people from around the world. Geneticists also will learn more about the genes that have been selected, which will help them separate true examples of selection from misleading signals. “As functional studies go forward, people will start figuring out the phenotypes that are associated with selective signals,” Coop says. “That will be very important, because then we can figure out what the selection pressures were on these phenotypes.”

Pritchard remains cautious about whether new results will answer every question. “For lots of these historical questions, some things are fundamentally unknowable,” he says. But he acknowledges that geneticists may be on the verge of answering a historic question: To what extent has selection shaped both our bodies and our minds? If Darwin were alive today, he would be eagerly awaiting the answer.

“I was fascinated by the idea that you could use the mathematics of population genetics to learn about human history.”

—Jonathan Pritchard
A CURIOUS CATASTROPHE IN THE PARROT WORLD

AN HHMI TEAM ENTERS THE MYSTERIOUS DOMAIN OF PARROT BREEDING TO DECIPHER THE VIRUS THAT’S KILLING EXOTIC BIRDS.

BY BRIAN VASTAG
ILLUSTRATION BY RICCARDOVECCHIO
was feathered and failing. The prognosis: grim. On a hot Friday before Labor Day 2008, Amy Kistler fought holiday traffic to make a house call. She was greeted by a high cyclone fence and snapping rottweilers. When the owner opened the gate and dismissed the guard dogs, Kistler stepped into the world of a parrot breeder.

Behind the house, dozens of cages—some as big as 6 feet square and 8 feet tall, with wooden nesting boxes inside—littered the yard. Each held a pair of parrots. Majestic macaws, big cream-colored crested cockatoos, African grays with blood-red tails.

As the owner showed Kistler around, the birds screamed and shrieked—a cawing cacophony. “There were more than 100 birds, and they absolutely flipped out,” Kistler says. “I had never seen anything like it before.”

Ignoring the riot, the owner explained the situation: A young macaw was sick. It had stopped eating and was losing weight. During the past six weeks, other parrots in his collection, mostly chicks that lived inside the house, had wasted to the bone and died. Kistler collected the red bird, put its carrier in the backseat of her car, and drove to a local bird veterinarian, Jeanne Smith.

At Smith’s office, the pair euthanized the sick bird and opened it up. Smith pointed to one of the digestive organs, the proventriculus. Situated in the upper gastrointestinal tract of birds, the proventriculus normally passes partially digested food farther down the line. In this macaw, though, the organ was grotesquely swollen and clogged with food. This young bird had PDD, proventricular dilatation disease. This and the other dead birds meant an outbreak was spreading.

PDD is the AIDS of the parrot world, devastating captive flocks and stigmatizing breeders whose birds carry it. How Kistler, a virology postdoctoral fellow at the University of California, San Francisco (UCSF), got involved is a story of DNA chips, perseverance, and good timing.

THE VIRUS HUNTERS
When she arrived at UCSF in 2003, Kistler had never heard of PDD, let alone touched a bird. She had signed on for a postdoctoral position with two HHMI investigators, Joseph DeRisi and Don Ganem, attracted to the operation they had built to link viruses to human diseases. (See “Modern Day Virus Hunters,” HHMI Bulletin, August 2006.) Ganem, the physician of the operation, had found in the late 1990s that human herpesvirus 8 causes Kaposi’s sarcoma, a tumor found in many AIDS patients. DeRisi, the lab polymath, is a pioneer in DNA microarrays—glass slides spotted with thousands of genetic fragments.

In 2002, DeRisi and David Wang, a postdoctoral fellow in his lab at the time, invented the Virochip, a DNA array for detecting every virus found in plants, animals, insects, and humans. The Virochip can also identify unknown viruses if they share a smattering of genetic code with a known virus.

In 2003, the Virochip pinned severe acute respiratory syndrome (SARS) on a previously unknown coronavirus, proving the worth of the chip in a pressure-cooker international outbreak that killed hundreds of people.

Since then, Ganem and DeRisi had received stacks of entreaties from researchers wanting to tap their technology. In 2006, two unusual requests arrived. Both asked the researchers to help unravel the mystery of a parrot disease, PDD.

“Parrots seemed kind of off the subject, so at first we just filed the letters,” Ganem recalls.

ELUSIVE BIRD KILLER
At the time, Kistler was studying upper respiratory illnesses with the Virochip, but she had a growing interest in animal viruses. When she got wind of the letters, she read up on PDD and discovered the disease first appeared in macaws imported to the United States from Bolivia in the 1970s. Since then, veterinarians had recorded it in more than 50 species of Psittaciformes, the avian order that includes many pet species, such as parrots, macaws, cockatoos, cockatiels, lorikeets, parakeets, budgerigars, conures, parrotlets, and lovebirds. The disease jumps between birds in close contact, suggesting an infectious agent.

Under the microscope, veterinarians see tiny round specks in tissue from sick birds, specks that resemble virus particles. Veterinarian Susan Clubb had written one of the letters pleading for a viral investigation of PDD. “For a very long time, researchers all over the world have been trying to find the agent that causes the disease,” says Clubb, who has a bird clinic in Loxahatchee, Florida. “It’s been very elusive.”

Clubb calls PDD an obsession. Over her 30-year career, she’s treated hundreds of birds with it. She’s watched PDD wipe out whole indoor aviaries in Canada and the northern United States. “It’s devastating,” says Clubb, who counts 280 parrots in her own breeding flock.

Like AIDS, PDD is a wasting disease. Inflammation attacks the nerves at the base of the proventriculus, paralyzing the organ. As the organ swells, birds stop eating, regurgitate, and pass undigested food in their feces. Affected parrots often become clumsy and fall off their perches. Seizures sometimes strike. But
symptoms can wax and wane, and birds might rally for a time after treatment for secondary bacterial and yeast infections.

Most cases are diagnosed symptomatically. Owners sometimes spring for an arduous and costly crop biopsy, in which veterinarians search for tell-tale inflammation of the gastrointestinal nerves. Even then, biopsies miss about half of positive cases, says Clubb. A definitive diagnosis—as confirmed by the inflamed nerves—can be made only via necropsy.

There are cultural parallels to AIDS, too. PDD is freighted with stigma. No breeder wants a reputation for keeping birds with the disease. Organizations of parrot lovers have sprung up to raise awareness, some launching a campaign called Stop PDD, which made a PDD quilt, each square hand-sewn to recall a parrot that had passed.

As Kistler discovered, parrot breeding is a big backyard business, exploding after a 1992 law banned the importation of most wild parrots. Now, virtually all the estimated 12 million pet parrots in the United States are captive bred, providing income for several thousand breeders, according to the American Federation of Aviculture. Rare, hard-to-breed, “super-exotics,” such as the magnificent hyacinth macaw, can fetch $10,000 to $15,000. African grays, known for their intelligence and longevity, typically cost $1,200 retail.

NEW TERRITORY
Ganem delved into the pathology of the parrot disease to determine whether it resembled any human ailment. He made a connection with a condition called achalasia. In this disease, the esophagus—alogous in form and function to the proventriculus of birds—is affected, impairing the peristalsis that normally propels food along the digestive tract. The cause is unknown, but esophageal biopsies of achalasia patients show “active inflammation of the nerves and ganglia,” Ganem says, “which in fact is the exact pathology of PDD. I realized this wasn’t just important for parrot owners, it actually had relevance to human disease.”

Buttressed by Ganem’s findings and the enthusiasm of Kistler and Alexander Greninger, an M.D./Ph.D. student who joined the project, the team decided to make PDD the first veterinary disease they would study with the Virochip. Clubb sent tissue from birds that died of PDD and birds that died of natural causes. The writer of the second letter, an Israeli veterinarian named Ady Gancz, sent his own samples.

In January 2007, Kistler selected one of the samples Clubb had sent from Florida, extracted the genetic material, added fluorescent tags, and then washed the mixture over the Virochip. She slipped the chip into a scanner, which reads each of its 20,000 spots, and watched bright dots scroll up the screen: green spots are hits, white spots are strong hits.

Kistler noticed a white spot on the right edge, one she’d never seen in the hundreds of human disease Virochips she had processed. The computer identified it as “bornavirus.” She’d never heard of it. An Internet search revealed that “Borna disease virus,” named for the town in Germany where a peculiar outbreak
The virus latches onto nerves and can cause encephalitis. The association to PDD was striking. Five of the 8 samples, but none of the controls, lit up with bornavirus. “That was it,” says DeRisi, recalling when he and Kistler watched the first data roll in. “That was a thrilling moment. It gave us an answer that was pretty clear cut.” In two days, the team and their Virochip had solved a 30-year mystery.

Next, Kistler fished out segments of the virus’s genetic code. The segments confirmed that they had found a bornavirus unlike any seen before. The viruses recovered from horses and sheep all closely resembled each other at the genetic level, but the parrot viruses looked much different from those viruses and from each other. The team called them avian bornaviruses (ABVs). After analyzing samples from more dead birds, the team discovered five ABV subtypes across a range of parrot species. Kistler, Ganem, and DeRisi eventually spelled out the entire genome—all six genes—of one strain of the new virus. They had found their quarry.

**THE OUTBREAK**
The team published the discoveries in *Virology Journal* in July 2008. “We became rock stars of the parrot world,” Ganem says. Soon the calls began. Veterinarians asked if a diagnostic test was available. (“Nothing commercially available.”) Breeders hoped the discovery somehow meant a cure was at hand. (“Not yet.”)

That’s when bird doctor Jeanne Smith called. She suspected an active PDD outbreak. Did the researchers want to play disease detective? At this point, Kistler had worked only with tissue samples from dead parrots. She jumped at a chance to investigate live cases, and on that scorching Friday in August 2008, she drove three hours and met Smith at the breeder’s compound.

The facts of the case: Several months earlier, a female African gray named Kiwi had fallen ill, lost weight, and developed a nasty fungal skin infection. The breeder isolated Kiwi outside, but brought her inside to the kitchen to medicate her. Too close, it turned out, to where he kept the hatchlings, 50 chicks, stacked in cages in the erstwhile living room and dining room and in the pantry, next to the kitchen. In July, some of the chicks started showing symptoms; a few quickly died.

Kiwi also died, and the necropsy tissue was positive for PDD. “He introduced a sick bird with PDD into the nursery. He wasn’t washing his hands, washing the counters, taking precautions,” Smith says. “So it just spread like wildfire.”

The breeder was worried. He agreed to let Kistler take samples, but only if he could remain anonymous.

On Kistler’s first visit, she collected the young red macaw, and she and Smith sampled nearly every organ. At the UCSF lab, Kistler ran the tissue through a polymerase chain reaction (PCR) test she had developed with the ABV genome data. The test can quickly fish out bits of ABV. The brain and digestive tract were marinating in virus. Kistler returned to the compound for another dying bird. Same results.
The breeder panicked. He wanted all the indoor chicks tested. In mid-September, Kistler and Smith arrived armed with vials for blood and a batch of large Q-tips for swabbing the birds’ cloaca, or backsides. They started with the African grays and spent three hours wrangling screeching parrots. When Kistler ran the samples at the lab, she found virus in 12 of 46 chicks. She e-mailed the results to the breeder. He never wrote back. The breeder also cut off contact with Smith, his veterinarian for 10 years. “He went into denial,” Smith says.

There were still more casualties. Another client of Smith’s, a second breeder, had boarded three hatchlings at the first breeder’s house earlier that summer. After the second breeder brought the chicks home, one of them displayed symptoms and died. Kistler and Smith found ABV in 8 of 10 other birds exposed to the dead chick, even though some were asymptomatic. It was the same strain found in the first breeder’s birds. The case was a slam dunk. “We linked the strains,” says Ganem. “We proved the birds in the second aviary caught the strain we saw at the first place.”

The second breeder wanted the virus gone, the birds out; she needed to protect her flock. She asked Smith to quarantine the exposed birds. Kistler and Smith watched the birds for a few months, but Smith eventually euthanized all of them to search for virus in their tissues.

Though they were long-time friends, the two breeders no longer talk. The second breeder, who eliminated the virus from her flock, also doesn’t want to be identified. “It’s one of those things that can severely damage my reputation,” she says. “I’d never sell another bird again.”

ANSWERS BREED QUESTIONS
DeRisi acknowledges that it is a complex situation. It’s a small world and breeders are a close-knit community. “Maybe someday when birds have certificates of health, and you get a test result from an independent testing service before you buy a bird, it will help clear that up.”

DeRisi, Ganem, and Kistler are convinced that ABV causes PDD. In late 2008, Gancz, the Israeli veterinarian collaborating with the HHMI team, injected three cockatiels with an extract from ground-up ABV-infected parrot brain. One rapidly died from severe PDD, and the other two got sick. The group expects to publish its findings in an upcoming issue of the journal Virology.

A host of other questions now come into play. DeRisi wonders where the parrot outbreaks originate. Do wild ducks or geese carry it? “Maybe parrots are just the dead end,” he says. “What about poultry?”

Kistler discovered that some asymptomatic birds test positive for the virus. Does that mean they’re carriers, spreading the infection? And is ABV like HIV, infecting the host for a long period before causing symptoms? How accurate is the PCR test Kistler produced? Can a vaccine be developed?

Already, the veterinary research community is jumping in, with teams in Canada and Germany also finding ABV in dead parrots. Any company can now license the technology that UCSF patented and commercialize a PCR diagnostic test. An accurate test could help eradicate PDD by identifying birds that need to be quarantined.

Ganem and DeRisi plan to back off PDD to focus on their work on achalasia and other human diseases. Ganem wants to know if a virus like ABV triggers achalasia, the human disease eerily similar to PDD. To that end, he has obtained esophagus biopsies from 10 patients, which he has begun scanning for viruses.

Kistler, though, might just make a career of it. She’s looking for a faculty position at a university with a strong veterinary research program. “I’m going to work on it for a while,” she says. “There are a lot of interesting questions left unanswered.”

SAVING THE RAREST OF BIRDS
With the cause of a deadly viral disease in hand, HHMI researchers at UCSF and colleagues have a chance to save a bird that exists only in captivity. On a lush island of vegetation in Qatar’s desert lies an ark of sorts, Al Wabra Wildlife Preservation. Owned by a member of Qatar’s royal family, the park shelters 2,000 animals from 100 rare species—including 50 Spix’s macaws, the rarest bird in the world. The last wild Spix’s, spotted in Brazil in 2000, is presumed dead. Veterinarians at Al Wabra breed the powder blue birds, and in 2008 the compound’s owner bought a tract of land in Brazil with plans to reintroduce the Spix’s there. But proventricular dilatation disease (PDD) is stalling his plans. Veterinarian Susan Clubb, a PDD expert, flew to Qatar and found the disease in several birds (she won’t say how many).

Ganem and DeRisi’s research into the viral cause of PDD might just save the species. After months of red tape wrangling, DeRisi won approval to import samples from the Spix’s. He plans to run them through a battery of tests to search for signs of avian bornavirus. If the tests identify birds carrying the disease, the animals can be quarantined, reducing the risk to their flock-mates. “This is a case where finding PDD could make a difference in whether a species survives,” Clubb says.
BUILDING
SOLID
BRIDGES

COMMUNITY
COLLEGE
STUDENTS
INTERESTED IN
PURSUING
SCIENCE ARE ON SURER
FOOTING, THANKS TO WELCOMED SUPPORT.

BY CHRISTINE SUH
ILLUSTRATION BY PADDY MOLLOY
RYAN

DOSUMU-JOHNSON

had a big decision to make the spring after his 18th birthday: apply for a promotion with RadioShack or enroll in classes at a community college. Though he came from a well-educated family—his father is a doctor and his sister a medical anthropologist—in high school he barely eked out a C average. But, craving an intellectual challenge, he decided to give school another try, and in the fall of 2003 he enrolled in classes at southern California’s Orange Coast College.

This spring, Dosumu-Johnson faced an altogether different kind of choice: enroll in the joint M.D./Ph.D. program at Harvard University and the Massachusetts Institute of Technology (MIT), or accept admission to the tri-institutional program at Weill Cornell Medical College, Rockefeller University, and Memorial Sloan-Kettering Cancer Center.

Clearly, school suited him just fine. Dosumu-Johnson’s story offers a lesson to educators as they search for the next generation of scientists: don’t forget community colleges.

A handful of educators have built “bridge programs” between community colleges and four-year institutions. The Bridges to the Baccalaureate program that steered Dosumu-Johnson toward a Ph.D. is based at the University of California, Irvine, and includes an undergraduate summer research program at the university. It’s one of dozens of similar initiatives administered by four-year colleges and universities to help community college science students successfully transition to four-year institutions.

The funding for such programs comes from organizations, including HHMI, the Virginia-based Jack Kent Cooke Foundation, the National Science Foundation (NSF), and the National Institutes of Health (NIH). These institutional programs are experimenting with different formulas to see what it takes—in addition to financial aid—to find and nurture future scientists among the ranks of community college students.

“Teasing apart the winning components of these endeavors is no simple task. The strategies and goals are as diverse as the students, who often are from groups underrepresented in the sciences. But lots of close attention and advising for the students, plus a hands-on research experience, appear to be essential. And for students like Dosumu-Johnson, these efforts are well worth the investment.”

“The range of student talent at community colleges is extraordinary,” says Chris Craney, director of undergraduate and sponsored research at Occidental College, a four-year private college in Los Angeles. In the mid-1980s, Craney, a chemistry professor, started a summer research program at Occidental for community college students interested in science. Over the years, he drew from a variety of funding sources, including HHMI. He says some of his best students transferred to Occidental via the research program.

“It tapped a talent pool that’s often overlooked,” he says.

Two-year colleges have long been undervalued in two significant ways. First, they lack federal support. Although community colleges serve nearly half the undergraduates in the country, the federal government provides them with less than one-third of the funding that it gives public four-year colleges, according to a report released in May by the Brookings Institution.

Second, their students are not always accepted at four-year institutions with open arms. Harvard and Princeton currently do not accept any transfer students, says Emily Froimson, director of higher education programs at the Jack Kent Cooke Foundation, a private organization that provides assistance to low-income students. At highly selective schools that do accept transfers, a shrinking handful come from community colleges. A national study partially funded by JKCF and published in 2006 found that, between 1984 and 2002, the number of transfer students accepted at elite institutions dropped from 10.5 percent of entering students to 5.7 percent.

Those schools that do accept transfer students generally do so simply to make up for attrition rates, and once accepted, students often receive inadequate financial aid, according to Froimson.

“That’s not a very proactive approach,” she says.

At the same time, Froimson notes, research has demonstrated that high-achieving, low-income students are more likely to graduate if they attend selective schools.

Chances are, many more will attempt this route as families turn to community colleges to cut education costs for their baccalaureate-bound kids. Indeed, enrollment in community colleges has swelled during the economic downturn, making bridge programs increasingly important.
for giving students a rich and inclusive educational experience.

**A CHANCE TO DO RESEARCH**

One of the most common components of bridge programs is undergraduate research. Program directors say it’s an effective way to engage students in science and to help them figure out whether research is for them.

For Dosumu-Johnson, it dramatically altered his goals.

At Orange Coast College, he loved his science classes but hadn’t really been introduced to research.

“The teachers were amazing,” he says. They knew the subject matter, they were passionate, and they engaged and challenged students to understand science, not just memorize facts, he says.

Though he developed a deep appreciation for science, Dosumu-Johnson didn’t realize that a career in scientific research was even a possibility from where he stood. His community college professors had Ph.D.s, but they weren’t active research scientists.

“Most students don’t have a perception of what’s out there, of what’s available in science and math,” says Melanie Gill-Shaw, a coordinator at Eastfield College in Dallas County, Texas.

Community colleges emphasize teaching more than scholarly output. Professors carry heavy teaching loads compared with their four-year counterparts, leaving little time or incentive to do research (see sidebar, page 31). Often, their campuses can’t afford maintenance or expansion of lab space, according to an article last fall in the Council on Undergraduate Research journal.

Dosumu-Johnson was considering taking a job as an emergency medical technician the summer before he transferred from Orange Coast to the University of California, Los Angeles (UCLA), when he received an invitation to apply for the NIH-funded bridge program at UC Irvine.

If accepted to Irvine’s program, he would receive a stipend, neutralizing the money issue. Curious to learn more about research, he applied, landed a spot in the program, and found a laboratory at Irvine to host him.

Dosumu-Johnson says that hands-on experience sparked his interest in research as a career. In the lab, he was encouraged to troubleshoot problems that arose during experiments instead of just doing what he was instructed in “cookbook”-style experiments with predetermined results.

“It was an amazing experience on multiple levels,” he says. He presented his summer research project in San Francisco at a conference of the American Association for the Advancement of Science. He’d never been to the Bay Area or to a scientific meeting bustling with people who thrived on research. Despite his inexperience in the conference environment, the chance to network led him to meet the UCLA professor who became his mentor when he later transferred to the four-year school.

Gill-Shaw at Eastfield College agrees that research experience is a big plus. She received an NSF grant to increase the number of students majoring in science, technology, engineering, and math (called STEM fields). The program places students in research settings at the Big Thicket National Preserve in Saratoga, Texas, and at the University of Texas Southwestern Medical Center at Dallas.
The results have been promising. During the three academic years before the program was implemented, Eastfield's STEM enrollment hovered at about 2,100 students. After the program's kickoff, enrollment jumped to 2,401. In 2007–08, the number of STEM students topped 3,500.

**Support and Advice**

Intensive peer and administrative support make a difference as well, according to bridge program students and program directors.

Students who participate in peer groups develop strong bonds and help each other meet the demands of the rigorous curricula. The peer group can relieve the family and life pressures that weigh on the students.

Former bridge scholar Alejandra Mendoza says she became very close to her support group of Miami–Dade College students, all enrolled in the University of Miami program.

“We really did become a family,” she says.

Advice from faculty, staff, and administrators can be just as potent. When the program novelty has worn off, doubts bubble to the surface, says Paul E. Hertz, professor of biological sciences at Barnard College and head of a bridge program that partners with LaGuardia Community College. Barnard’s summer program, which has been fully funded by HHMI since 1992, brings LaGuardia students to live on campus. Every year about a week into the session, they start telling themselves they don’t belong there, he says.

“We usually work through the issues,” he says, adding that more than 70 percent of the scholars who go through Barnard’s program transfer to four-year institutions including Barnard and Columbia University. Most pursue science or science-related degrees, says Hertz.

That’s substantially better than national averages. Among community college students who intend to obtain a bachelor’s degree, on average only about one-third ultimately transfer to four-year institutions, according to a 2001 report from the National Center for Education Statistics.

“Part of the problem is that advising comes late,” says Becky Wai-Ling Packard, associate professor of psychology and education at Mount Holyoke College in Massachusetts. Packard’s research focuses on first-generation college students in STEM fields. Many are community college students, who, she says, think they don’t have time to seek out advisers for information. More than 75 percent of full-time community college students have jobs, according to the American Association of Community Colleges, and 83 percent of part-time students are employed.

Even the most determined student is often uninformed when it comes to transferring, for example, says Packard. A large portion of community college students who plan to transfer do not talk to anyone at a four-year school about prerequisites and transfer credits, she says.

When transfer time comes, they might find they have to retake a class or two because they took the wrong class at the community college.

“Students don’t have time or money to retake a class,” Packard says. Having the right credits is more problematic for would-be science students. Some of their required classes have to be taken in a certain order, Packard explains. And often,
Though bridge programs focus on student development and assistance, the University of Miami and Occidental College offer something for community college teachers as well. Miami hosts one faculty member each semester in a research lab to keep the hands-on and inquiry aspects of science fresh. Occidental, a private four-year college in Los Angeles, has taken this idea a step further and recently made research by community college faculty a top priority.

“There is good evidence in the literature that says if faculty stay active scholars, they are more effective teachers than those who rely on what they learned ‘X’ number of years ago,” says Chris Craney, head of Occidental’s bridge program. Chemistry professor Dennis Mitchell from Los Angeles City College says it worked for him. Last year, he became the first of two community college faculty members to receive support from Occidental’s HHMI grant. Becoming a teacher, he says, didn’t mean he was done learning.

“I talked to Chris and came up with my own project,” says Mitchell, who studied the use of porphyrins for solar energy storage. “The amount of insight you get [from research] is incredible. Chemistry is more than just what’s in the book.” This summer, Asmik Oganesyan, a chemistry instructor at Glendale Community College, became the second teacher to take advantage of the experience offered by Occidental’s program. Her students are seeing the benefits. —C.S.

FOR THE PROFS

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For each man with prostate cancer, which treatment gets the green light?

By Sarah C.P. Williams

Illustration by The Heads of State
2001, Jim Foley learned he had prostate cancer. Suddenly, the 56-year-old engineer from a New York City suburb faced a daunting dilemma: What next? Though he can explain the ins and outs of compressors and steam turbines effortlessly, Foley was clueless about prostate cancer. He knew no one with the disease, he says, and was unprepared for the lack of clarity his diagnosis—and prognosis—offered.

Of the roughly 190,000 men diagnosed with prostate cancer in the United States every year, many have slow-growing tumors that are unlikely to spread. Without treatment, men with nonaggressive tumors will likely live for decades and eventually die of something unrelated. But others will have cancers that spread to lymph nodes and bones. Predicting, on initial diagnosis, which tumors are deadly is a matter of guesswork for physicians.

With Chinnaiyan’s recent discovery of a gene that drives more than half of prostate cancers, however, and work by other HHMI investigators, physicians may soon have new tools to predict the course of prostate cancer and identify the most aggressive tumors. They’re developing new treatments, too, and Foley can attest to their success: In 2008, during a recurrence of his cancer, he was one of the first patients to enroll in a clinical trial for a novel prostate cancer drug developed in part by HHMI investigator Charles Sawyers at Memorial Sloan-Kettering Cancer Center (MSKCC). Today, Foley’s cancer is in remission. When he thinks “What next?” he’s planning his retirement or his next trip to Virginia or Iowa to visit his daughters and grandkids, not deciding how to treat his cancer.

LOTS OF OPINIONS

Foley’s diagnosis came after an annual PSA test, which men are encouraged to undergo beginning at age 50. A PSA of up to 4 (measured in nanograms per milliliter) is generally considered normal. Higher levels can be okay too, though—it varies from person to person. The rate at which PSA changes is often more indicative than its level. The red flag for Foley came when his PSA rose from 4 one year to 10 the next.

In December 2008, the New England Journal of Medicine presented the case of a 63-year-old man with rising PSA scores and polled more than 3,000 doctors on how they would treat him. They were split three ways: about 39 percent said they would remove the patient’s prostate; about 33 percent would treat the tumor with radiation; and about 29 percent would wait and monitor the patient’s PSA levels.

With this lack of consensus, the decision often comes down to a gut reaction by an informed patient. Foley and his doctors—including oncologist Michael Morris at MSKCC, who became his primary prostate cancer doctor—weighed the options after considering his PSA levels, his age, general health, and MRI scans.

For Foley, an MRI technique considered experimental at the time revealed that his cancer had already spread to his
seminal vesicles, so a course of radiation and hormone therapy seemed the best option. In his case, PSA was a valid warning sign that caught his cancer before it spread even further. PSA and scans leave others in the dark as to whether their cancer is growing and how aggressive treatment should be. There is a lack of useful diagnostic tests to classify a prostate cancer. In the near future, though, genetic analysis of tumors may fill this void.

Chinnaiyan’s team studies genes that, when rearranged incorrectly, cause prostate cancer. His research relies on a large bank of prostate cancer tissue samples at the University of Michigan. Using microarrays—a technology that can quickly analyze the activity of massive numbers of genes in a sample—Chinnaiyan has looked at the molecular signatures of hundreds of prostate cancers. Traditionally, researchers sort through such data by looking for genes expressed in all the cancers. But Chinnaiyan didn’t think that was the best approach. Instead, he looked for genes that were expressed at high levels in some, but not necessarily all, of the cancers. He calls these genes “outliers” and reasons that typical averaging techniques would cause scientists to miss them.

His analysis paid off—it found parts of two normal genes that had been combined into one single cancer-causing “fusion gene” in about half the tumors he analyzed. One of the normal genes was in a family of transcription factors; the proteins produced by these genes bind directly to DNA and can activate cancer-causing genes that are turned off in a healthy prostate. This “ETS transcription factor” was fused with the on-off switch from an unrelated prostate gene—one regulated by male hormones. So whenever this fusion gene came into contact with testosterone, a constant presence in the prostate, the ETS transcription factor was switched on and went into action turning on other cancer-causing genes.

Chinnaiyan’s work was published in 2005; his fusion gene was the first to be linked to prostate cancer, and the discovery drew wide acclaim from the prostate cancer community. Chinnaiyan believes the fusion gene could lead to treatments and, even sooner, to new ways

PROSTATE PIRATES

Like the liver and just a few other organs, the prostate gland has the ability to regenerate itself. In castrated mice, the prostate shrinks to a tenth of its original size. But giving the mice testosterone restores the prostate. HHMI investigator Owen Witte, at the University of California, Los Angeles, thinks some prostate cancers may be co-opting the gland’s regenerative properties. ¶ “The majority of cells in the gland require testosterone for their maintenance but there is a group of cells that can survive in the absence of testosterone and re-grow the whole organ,” explains Witte. He has created numerous prostate cancer cell lines and mouse models that can report what genes and proteins are activated when prostate cancers grow. With the help of these tools, he is studying what role stem cell–related proteins in the prostate might play in cancers. He has found one protein—dubbed prostate stem cell antigen—in higher levels in prostate cancers, a hint that cancers could be pirating the prostate regeneration system. By understanding how different molecules interact at different points during prostate cancer growth, Witte hopes his research will lead to treatments to stop the tumors at their earliest stages. —S.W.
to detect and track prostate cancer if the gene can be monitored in blood or urine.

He has already found a related indicator in urine, a metabolite called sarcosine that’s elevated when prostate cancer exists. According to Chinnaiyan, one ETS fusion gene boosts sarcosine production. Screening men’s urine for sarcosine levels, he says, could be one way to monitor disease, alongside or instead of blood tests for PSA.

Screening men’s blood for genetic markers of prostate cancer—which could potentially differentiate cancer types, unlike PSA—is also on the horizon. HHMI investigator Daniel Haber, of Massachusetts General Hospital, thinks blood holds clues not only for prostate cancer but also for most other cancers. Haber wanted to study genetic mutations in various cancers and, because repeated biopsies of tumors are often invasive and costly, he turned to an emerging technology to detect rare cancer cells—called circulating tumor cells, or CTCs—that break off tumors and enter the bloodstream.

“The initial literature [on CTCs] goes back to the 1800s, when a woman with advanced breast cancer was found to have tumor cells in her blood,” Haber says. “Really, we’ve always known that cancer spreads through the bloodstream, but we haven’t been able to see the CTCs.”

Unsatisfied with the sensitivity of commercial CTC detection kits, Haber collaborated with Mehmet Toner, a biomedical engineer at Massachusetts General Hospital, to develop and test a new kind of detection device. While the commercial technology can detect only one or a few cells per teaspoon of blood, Haber and Toner’s technology can force that same teaspoon of blood through a centimeter-wide silicon chamber that has 80,000 microscopic pillars in it, each coated with antibodies that can bind to cells. The pillars can sort through billions of blood cells per teaspoon of blood: the antibodies grab the rare cells that originate from tumors while blood cells flow right on by.

Once he’s gathered these circulating cells, Haber can analyze them to identify which, if any, possess particular pieces of genetic information. For example, he can track whether circulating prostate cancer cells have Chinnaiyan’s fusion gene.

“This could really add to PSA in terms of being able to identify which cases of cancer may be more likely to spread,” says Haber. The technology is still in early days, though Haber says it’s raising as many questions as it’s answering. Do only certain types of cancer cells enter the bloodstream? When during early cancer development are these cells first detectable? What makes circulating cells more likely to lodge in a new place and cause a metastatic cancer?

OVERCOMING RESISTANCE

In 2001, Foley went through the first course of treatment for his prostate cancer: radiation, which kills cancerous cells wherever it’s directed, and two common anti-hormone drugs—Lupron and Casodex. Both aim to block testosterone in the prostate. Physicians had known since the late 19th century that thwarting male hormones from acting on cells was one way to treat prostate cancer. The ETS fusion gene discovered by Chinnaiyan now explains why this works (in the cancers that it causes)—testosterone turns on the cancer-causing fusion gene; blocking testosterone turns off the rogue fusion gene.

Lupron directly decreases the amount of circulating testosterone, while Casodex works by binding to testosterone receptors, so that the hormone itself cannot. Used in conjunction, the drugs lowered Foley’s PSA to less than 1.

The problem with Lupron and Casodex is that enterprising cancer cells eventually evolve resistance to them. In 2006, almost five years to the day after Foley finished radiation treatment and hormone therapy, his PSA started rising. By July 2006, it was 13, higher than when...
he’d first been diagnosed. His doctor put him back on the anti-hormone drugs, but the PSA dropped only slightly and then started rising again.

“Essentially 100 percent of men who go on these drugs eventually develop resistance to them,” says Sawyers, who turned his attention from drug-resistant leukemias to drug-resistant prostate cancers after developing a drug that overcame resistance to the successful drug Gleevec in leukemia patients. What happens in prostate cancers, Sawyers found in mouse models, is that cancer cells start overproducing testosterone receptors. There are still trace amounts of testosterone in the prostate, even when patients are being treated with Lupron. If the number of receptors begins to increase, those tiny amounts of testosterone eventually find free receptors and once again turn on cancer-causing genes.

Sawyers’ drug-hunting mind went to work. “What we needed was a new drug that’s not perturbed by higher levels of the receptor.” So Sawyers’ lab made a cell line overexpressing the receptor and screened it for compounds that would still block the receptor. One compound emerged: MDV3100, a drug that blocks testosterone receptors, like Casodex, but blocks them earlier in their activity cycle—before they transition from being free in the watery interior of a cell to being inside a cell’s nucleus and able to bind DNA.

By February 2008, Foley’s PSA had risen drastically—hitting 22—and his cancer spread to half a dozen lymph nodes. He had just returned from a conference in California, where more than 700 prostate cancer patients met to share stories, learn about how to live with their disease, and hear about new treatment options. “It was so encouraging to hear that the fact that I had slipped into advanced prostate cancer wasn’t a death sentence,” says Foley. “There were still treatments that would allow me to keep going.”

When Foley returned to New York, Morris presented him with an alternative to chemotherapy: Sawyers’ MDV3100 was in clinical trials, and Foley qualified to be one of the first patients to try it. He joined the trial—a dose escalation trial in which patients are put on increasing doses of the drug and checked for side effects.

Between February 8 and 15, 2008, thanks to MDV3100, Foley’s PSA dropped from 22 to 12. In the next month it dropped to 2 and then a month later to less than 1. It’s been undetectable since, and his lymph node tumors have all but disappeared. He’ll continue on the drug until it stops working, Foley says, which he hopes is many years away.

“When you first get those high numbers, you never think you’ll see low numbers again,” says Foley. “But it just dropped like a rock. I was blown away.”

MAKING PREDICTIONS

Not all prostate cancers are the same. In the clinical trial that Foley attributes with giving him a second life, some patients didn’t see such dramatic improvements. Sawyers is collaborating with Haber to determine whether there are different markers in the CTCs of patients helped by the drug versus those who saw less improvement. They want to develop a rapid screening test to show who the drug might benefit.

To complicate matters, there may be variety within a single patient’s cancer. “One individual might have multiple distinct cancers within the prostate gland that are independently arising,” says Todd Golub, an HHMI investigator at the Dana-Farber Cancer Institute. Instead of one tumor that spreads, he hypothesizes, a cancer-ridden prostate could often have separate tumors, each genetically distinct.

“So if you sample one of these tumors,” Golub says, “it’s not necessarily going to be predictive of how the other ones are going to behave. The tumor you die of may not be the tumor that was biopsied and genetically analyzed.”

It’s a vexing problem—to analyze all these potentially different tumors in the prostate, the whole gland would need to be removed, and then there would be no measure of which tumors grew. This situation is, in part, leading to dead ends in prostate cancer research, Golub believes. He’s collaborating with a group of (continued on page 56)

NOW RESEARCHERS MUST TURN [CHINNAIYAN’S DISCOVERY OF THE FUSION GENE] INTO DETECTION METHODS, WAYS TO MONITOR THE DISEASE, AND NEW TREATMENTS FOR PROSTATE CANCER.
Robert J. Alpern

A PRESCRIPTION FOR FUTURE PHYSICIANS

RETHINKING THE COLLEGE CURRICULUM.
A revolution in biomedical science has transformed medicine, yet premed course requirements have not changed in decades. Robert J. Alpern, dean of Yale University School of Medicine, served as co-chair with Sharon R. Long, former dean of Humanities and Sciences at Stanford University, of the 22-member Committee to Establish the Scientific Foundation for Future Physicians. Organized by the Association of American Medical Colleges and HHMI, the committee was charged with making recommendations to bring standard premedical and medical school curricula in line with the practice of modern medicine.

Why change medical school preparation for undergraduates now? The same premedical requirements have been in place for 40 years or more, and while many students have made it through the curriculum and gone on to become good physicians, others who could have become outstanding physicians have been held back. The courses are often too difficult or not interesting enough. They’re seen as barriers rather than opportunities to teach material in exciting ways. Organic chemistry in particular is perceived as the course that determines who should go into medicine, but we don’t want course requirements to be the gate that keeps students out.

And the issue is larger than medicine. When premed students are unhappy with required courses, all too often other undergraduates thinking about research careers become dejected along with them. That’s driven many aspiring scientists away.

The committee called for replacing premed course requirements with what it terms “scientific competencies.” What do you mean by that? Physicians today need to be scholars of science whether they pursue research or not. So we started out by defining specific competencies all physicians should attain in medical school. We then worked back from there to define the broader competencies an undergraduate will ideally acquire before entering medical school, like applying quantitative reasoning and mathematics to describe phenomena in the natural world or explaining how biomolecules contribute to the structure and function of cells.

For medical school applicants, competencies might be achieved through a variety of courses or educational experiences. We want to give colleges freedom to teach in the most interesting ways they can. This will make the courses more relevant for undergraduates interested in medicine and biomedical science in general and bring students to medical school better prepared to learn the science they’ll need throughout their careers.

For instance, undergraduates need much more preparation in statistics and the handling of large databases, yet the bulk of students take calculus, which is much less important. Similarly, biochemistry is so much more important for medicine today than organic chemistry, yet it is not universally required in undergraduate programs.

Ultimately, won’t this come down to a specific set of courses or some other well-defined requirements a student will need to prepare for the MCAT [Medical College Admission Test]? The appearance of this report couldn’t have been better timed because another committee is reviewing the MCAT. To be frank, the MCAT will define specifics of the competencies to be tested. Changes to the test will drive changes in the curriculum—they need to change together to bring about reform. The critical element will be changing the MCAT and giving colleges enough lead time to rewrite courses to prepare students for the changed test.

Changing undergraduate and medical school curricula won’t be easy, will it? We thought there’d be enormous resistance to the proposed changes, but every medical school dean we surveyed was wildly enthusiastic. The same is true for most undergraduate faculty. The students I have spoken with have all said, ‘Can’t you do it faster?’ Resource-rich schools are not waiting; they’re making changes already. With the help of HHMI and other organizations, we want to make sure less wealthy colleges have the resources they need to make the changes.

Underrepresented minorities come disproportionately from those schools, and we don’t want to cut off that pipeline of future doctors and researchers.

Realistically, it will take at least five years and some say ten to have every student arrive at medical school with the competencies we’d like. It’s not going to happen overnight, but when it does, I think it will represent a major transformation in medical education.

Mark Davis

CENTER STAGE:
THE IMMUNE SYSTEM
The field of immunology is stuck in the lab and needs a major overhaul to become more relevant to human health, says Mark Davis, an HHMI investigator and immunologist at Stanford University. He argues that now is the time for large-scale human studies of the immune system—a human immunology project.

The immune system is one of our major health systems and is just as important as our cardiovascular system or nervous system. If your immune system goes haywire, you’re in deep trouble. But for many years, the immune system has been a black box. That situation has now changed dramatically over the past few decades in that enormous progress has been made in basic immunology. But unfortunately, very little of this knowledge is being applied medically. After decades of study, immunologists still can’t define what constitutes a healthy human immune system.

We know a lot about what the immune system can do and should do, but no one has put together a test that can identify whether a patient’s immune system is working correctly. Such a test would be more complicated than, say, a cholesterol test, but it would have a similar vital function: providing clinicians with an easy-to-understand readout of the health of the patient. That way, trouble could be spotted early and interventions taken when necessary. Cholesterol tests are a good model because they’re proactive. We need a similar, proactive test for immune function that lets physicians and patients know when a big problem lies ahead.

If such a test were developed, it might help reduce the burden of the almost 90 known autoimmune diseases and the 120 known immune deficiency diseases. More recently, immune dysfunction has been found to play a role in big killers such as Alzheimer’s disease and atherosclerosis, the inflammation and hardening of the arteries that causes heart disease. These diseases could be handled better if we had a deeper understanding of how the human immune system works and what goes wrong with it.

Much of the lack of progress in human immunology is due to the tremendous success of inbred mice as a scientific model. As a result, the whole field is severely tilted toward studying mice, with some 80 percent of articles published in immunology journals involving rodents, not people. Yet the mouse is a poor clinical model.

Sure, the thousands of immunology studies conducted on mice have provided, and continue to provide, major insights into how the mammalian immune system functions. Yet mice aren’t people, and the mouse immune system does not accurately mimic the human immune system. Sixty-five million years of evolution separate mice and men, a vast divide. Researchers can regularly cure cancer and autoimmunity in mice, but almost none of those cures work in people.

Here’s one example: Recently, an antibody developed as an antitumor therapy showed outstanding results in laboratory mice, leading to human trials. But after hundreds of millions of dollars and two large human studies, only 14 percent of patients showed any benefit. Everyone involved with this therapy had great hopes for it. But it’s been very disappointing, and it’s unclear if the Food and Drug Administration will ever approve the drug. Dozens of similar examples litter the drug development landscape.

Part of the solution is that some of the money spent on mouse research should be funneled into explicating the differences between human and mouse immunity. Defining this gap would be incredibly valuable. Another part is to begin a human immunology project focused on defining immunological health, taking some important cues from the human genome project. In the 1970s, human genetics was a very limited field with almost no ability to inform medical care. But after a huge investment in sequencing and cataloguing the human genome, genetics is now at the center of the search for cures.

A large-scale human immunology project could work similar wonders. Such a project would focus the field on human, instead of mouse, immunology. The project would create or ease access to large banks of blood samples from clinical trials. And it would encourage researchers to mine these large samples for critical information on immune function in healthy and ill people.

As a step toward that goal, I’ve helped organize the Human Immune Monitoring Core at Stanford. Clinicians running human trials are encouraged to send patient samples to the facility, where we can collect data across patient populations. We also aim to combine data from dozens of such studies to learn a lot in a hurry and to uncover previously unrecognized similarities between diseases.

More projects like this are needed. Immunology has always held the potential to be clinically useful across a broad spectrum of devastating diseases. But it’s going to take a serious rethinking of the whole field to achieve that potential.

Interview by Brian Vastag. Mark Davis is director of the Stanford Institute for Immunity, Transplantation and Infection.
Q&A

What is an example of evolution at its finest, when an elegant efficiency is selected over time, that you’ve come across in your research?

There are countless examples of how natural selection explains not only how entire organisms evolve but also how the organs, behaviors, and intricate molecular parts within an organism have been perfected over time.

—EDITED BY SARAH C. P. WILLIAMS

Tanya T. Paull
HHMI INVESTIGATOR
UNIVERSITY OF TEXAS
AT AUSTIN

“I think the perfect micro-cosm of efficient evolution is the virus. A virus uses every nucleotide of its nucleic acid, sometimes many times over, to store all the information it needs in the smallest space. A virus can change over the course of many years to reproduce successfully in its host but also has the ability to change during the course of a single infection to suppress a host’s defenses. The random changes that are constantly introduced into the virus genome show us that the virus has evolved to evolve—one of the best examples of the power of natural selection that exists in nature.”

Erich D. Jarvis
HHMI INVESTIGATOR
DUKE UNIVERSITY MEDICAL CENTER

“A remarkable example of evolution at its finest is that of song and spoken language in birds and humans. Human language is often considered a pinnacle of evolution, a source of our civilization, and a final frontier of science. But humbling to me, we find that the required brain pathways and associated genes in distantly related song-learning birds and in humans have undergone a remarkable parallel evolution. In both, the pathways appear to have evolved similarly multiple times using an old trick similar to gene evolution: the duplication and then modification of existing brain pathways involved in learning.”

Catherine L. Drennan
HHMI INVESTIGATOR
AND PROFESSOR
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

“The class II ribonucleotide reductase (RNR) from Lactobacillus leichmannii is a perfect example of evolution. RNRs are proteins essential to all organisms—they help make DNA. In higher organisms and many micro-organisms, RNRs work together in complexes, with two or more proteins attaching to one another to do their job. But for some micro-organisms, simplicity is the key to life. L. leichmannii has an RNR that has neatly evolved to do its job with only a single molecule of protein present. We recently showed that this single RNR chain works because it contains a helix-shaped structure that typical RNR proteins can form only when joined together. This simple RNR in L. leichmannii is a perfect example of evolution.”

Carlos D. Brody
HHMI INVESTIGATOR
PRINCETON UNIVERSITY

“The brain is clearly a marvel of evolution: using only some 20 watts, it seems to effortlessly accomplish myriad tasks that we cannot yet imitate using our fastest, biggest, and most energy-hungry computers. But is it an elegant, perfect example of evolution? Most experiments reveal an extremely noisy, bewilderingly complex thicket of interacting components. It is easy to imagine the brain as a Rube Goldberg device, chock-full of irrelevant peculiarities picked up through a long evolutionary history. But I don’t think so. I prefer to believe that the brain holds hidden elegance that we are working to reveal.”
This millimeter-long Strongyloides worm can tunnel from soil through a human’s bare foot, eventually burrowing in the small intestines, reproducing, and causing disease. Getting rid of the parasites is tricky, but a new drug aims to kill them before they mature into adults and reproduce (see page 49).
Next-Generation Scientists

EXPERIENCING THE REALITIES OF A RESEARCH LAB CAN BE LIFE-ALTERING FOR SOME STUDENTS.

WHEN SHEARMAN JABARI MILLER LOOKED AROUND THE BIOLOGY department during his undergraduate years at Georgia State University, he saw mostly white and Asian faces among the graduate students, postdocs, and professors.

But this summer the graduating senior and biology major, who is African American, took a step toward changing that picture, through HHMI’s Exceptional Research Opportunities Program (EXROP).

EXROP gives undergraduate students from groups underrepresented in the sciences or from disadvantaged backgrounds a chance to work in some of the world’s top research labs run by HHMI investigators and HHMI professors. Miller was one of 62 students selected this year to participate in EXROP, the largest group in the program’s seven years.

“Jabari has enormous potential as a scientist, and yet he has never been exposed to the kinds of opportunities that are available,” says Barbara Baumstark, a biochemist at Georgia State and the HHMI program director who nominated Miller for EXROP. “Now he will be.”

Since 2003, EXROP has placed 359 students from 97 colleges and universities in the labs of 130 HHMI investigators and HHMI professors. The hope is that students who experience the excitement and intensity of a top research lab and see other students like them doing the same thing will be inspired to one day become academic scientists—and serve as examples for others.

“I’ve experienced the positive impact that highly talented faculty from diverse backgrounds can have on students in science departments,” says Peter J. Bruns, HHMI’s vice president for grants and special programs. “We desperately need more professors like that, and EXROP is part of that effort.”

So far, 189 EXROP students have completed their undergraduate degrees. Of those, 93 percent are still in science: 38 percent are pursuing a Ph.D. or M.D./Ph.D., and 29 percent an M.D. The remaining students are working as research technicians or science teachers, or are studying for a master’s degree.

EXROP’s talent scouts, as Bruns calls them, are the directors of HHMI’s undergraduate grants at colleges and universities across the country. They identify top students who could someday become academic leaders and who are ready for the challenge of working in an intense research environment, both academically and emotionally.

The program is popular among the HHMI lab hosts. Every year, more of these high-profile scientists volunteer to host students than are needed.
HHMI President Robert Tjian has hosted three EXROP students at his University of California, Berkeley, laboratory. “Working in a lab as a college sophomore really is the thing that got me into science, so I can’t imagine a more interesting pathway for students to understand what real research is about,” he says. “And EXROP is special … You could be anywhere, and if you show some promise you could end up in one of the best labs in the world.”

Miller, 22, is just one of those students. Inspired by Bill Nye the Science Guy, Miller grew up loving science, but his high school in Atlanta didn’t provide many opportunities. “We didn’t really have any labs, just bookwork,” he explains.

Despite that, Miller decided to major in biology at Georgia State. Though he struggled through required physics and chemistry courses, his professors recognized his talents and recruited him into an HHMI-sponsored biotechnology program. He worked in a research lab studying how bacteria change their genes in response to the environment. That experience lit his fire.

In June, Miller joined the lab of HHMI investigator David G. Schatz at the Yale School of Medicine, who studies how the immune system makes antibodies that fight invading pathogens. Schatz has hosted three previous EXROP students, all of whom have gone on to graduate school in some field of science. “These are serious kids who want to learn and want to make a difference, so they come in ready to work,” Schatz says. “They have been fun to work with and they have been productive.”

The EXROP program has almost doubled in size since its beginning, and the Institute continues to consider ways to grow the program while maintaining the factors that make it successful.

Miller says he was excited to have the opportunity this summer to learn a new subject and new techniques, and to meet people who have the same interests and background. “I used to hate school,” says Miller, who is beginning a master’s degree program in biotechnology at Georgia State this fall. “Now I can’t get enough of learning about biology.”

HHMI Gives Research Training Awards

In 1985, The Howard Hughes Medical Institute first gave medical students the chance to spend a year working in a research lab on the Bethesda campus of the National Institutes of Health (NIH).

Twenty-five years and more than 2,000 students later, HHMI remains committed to encouraging medical students, including dental and veterinary students, to hone their scientific skills and prepare for possible careers in research. This year, 112 students from 44 institutions will spend a year in the laboratory, either at the NIH through the HHMI–NIH Research Scholars Program or at a research center anywhere else in the United States through the HHMI Research Training Fellowships Program. This year, HHMI has joined in a partnership with the Ben and Catherine Ivy Foundation to support four HHMI–Ivy research training fellows who are studying glioma, a deadly and incurable brain cancer.

“These programs give the students a chance to immerse themselves in research,” says Peter J. Bruns, HHMI’s vice president for grants and special programs. “For many, this will be a pivotal experience that helps them decide whether to pursue a career in research.” And many do: nearly 45 percent of alumni are still doing research 15 years or more after participating in the scholars or fellows program.

Scholars and fellows who pursue an academic research career have a chance for more HHMI support. Since 2006, former fellows and scholars have been eligible for Early Career Physician-Scientist awards, grants totaling $375,000 over five years. The funds help these researchers set up their labs and commit to science at a vulnerable time in their careers, when many are pushed to abandon research so they can spend more time seeing patients.

More than 50 physician-scientists have received HHMI support through the program. And it appears to be working—among the 2006 award recipients half of them later successfully competed for an RO1 award, the NIH’s main research funding vehicle. This year, 11 new early career physician-scientists from seven institutions were chosen, with research interests ranging from cancer to obesity to autoimmune diseases.

For more information: To learn more about the new HHMI–NIH research scholars, visit www.hhmi.org/news/20090507scholarsfellows.html. For more on the new early career physician-scientist awardees, go to www.hhmi.org/news/ecps20090707.html.
Janelia Farm to Expand Campus Housing

HHMI has announced plans to develop additional housing at the Janelia Farm Research Campus in Ashburn, Virginia. The 60 one-bedroom apartments will support the recruitment of graduate students, postdoctoral researchers, and other early career scientists. Ground breaking for the project is planned for late August or early September.

“Graduate students and postdocs are with us for a relatively short period of time and they place a high value on living close to their laboratories. As a result, expansion of on-campus housing is an important element in recruiting the most talented candidates from around the world and building a vibrant research community,” says Gerry Rubin, Janelia Farm’s director.

The apartments will be located in an 80,000-square-foot building on a portion of the campus that lies just southeast of the research building, near the main entrance to Janelia Farm. The four-story building will have a slightly curved design that echoes the shape of the nearby research building; it will include one floor of covered parking and three floors of apartments.

“Attraction the best and brightest graduate scientists to HHMI and Loudoun County requires making them feel welcome and at home in our community. Expanding housing for scientists will help us in that goal,” says Loudoun County Supervisor Lori L. Waters, whose Broad Run District encompasses the Janelia Farm campus.

Ashburn-based Dietze Construction Group and WDG Architecture of Washington, D.C., were selected to design and build the project.

Each of the three residential floors will contain 20 apartments—eight one-bedroom units and 12 larger ones with an added den. The complex will include 61 covered parking spaces dedicated to residents, plus common areas. Visitor and handicap parking spaces will be located nearby.

The apartments will augment the housing village developed as part of the original campus plan. Those units—a mix of 21 studios and 32 multibedroom apartments—are intended for visiting scientists who typically come to Janelia Farm for short-term collaborations.

HHMI has submitted an application with the Loudoun County Industrial Development Authority for up to $21 million in tax-exempt bonds to finance the apartment building project and related costs.

Opened in 2006 as HHMI’s first freestanding campus, Janelia Farm provides an interdisciplinary research environment for scientists studying how networks of brain cells work together to enable complex behaviors and the development of new technologies for imaging and data analysis. The campus is home to approximately 240 scientists—including 33 laboratory heads who anchor the research program and 100 visiting scientists from 15 countries as well as postdoctoral researchers and graduate students.
HHMI Doubles Postdoctoral Fellowships

HHMI announced in June that it is increasing support for outstanding postdoctoral researchers through expanded collaborations with four foundations. Since 2007, HHMI has supported four postdoctoral fellows a year through the Jane Coffin Childs Memorial Fund, the Helen Hay Whitney Foundation, the Damon Runyon Cancer Research Foundation, and the Life Sciences Research Foundation. The new initiative doubles the number of fellows to eight per organization each year.

As is already the case, each group will competitively select candidates—who come from universities across the country—based on its own criteria. The foundations focus on basic biomedicine, general life sciences, and cancer research.

“These organizations consistently select outstanding scientists for their prestigious fellowship programs, and this support comes at a critical moment in the young scientists’ careers,” says HHMI President Robert Tjian. “We are pleased to expand our partnership as well as the funding needed to develop and nurture some of the most talented among a new generation of scientists.”

Each fellowship will have a three-year term. Start dates will vary, but most of the new funding will take effect in 2010. When the initiative is at full capacity, HHMI will be supporting 96 postdoctoral fellows through this program at an anticipated annual cost of about $5 million. HHMI separately funds postdoctoral associates at the Janelia Farm Research Campus.

“By expanding its funding for this program, HHMI will enable these organizations to offer 32 additional fellowships each year,” says Jack E. Dixon, HHMI vice president and chief scientific officer.

In Memoriam

Alexander G. Bearn
1923–2009

Former HHMI Trustee, Alexander G. Bearn, a distinguished physician, scientist, and author, died May 15, 2009. He was 86.

Bearn served as a Trustee of HHMI for 18 years, from 1987 to 2005, providing wise counsel and thoughtful guidance during a period of sustained growth and transformation for the Institute.

Born in England, Bearn received his M.B., B.S., and M.D., degrees from the University of London. He came to The Rockefeller University in 1951 and in 1966 moved next door to The New York Hospital, where he served for 11 years as physician-in-chief and as chairman of the Department of Medicine for the Cornell University Medical College. He founded the first human genetics laboratory at the Medical College and, with colleagues at Rockefeller, initiated the joint M.D./Ph.D. program at the institutions.

An expert on the genetics of rare metabolic diseases, Bearn defined the genetic nature of Wilson’s disease—an inherited disorder that causes copper to accumulate in the liver and brain. He also demonstrated that the disease was associated with decreased function of a blood protein that binds copper.

After nearly 30 years in academic medicine, Bearn joined Merck & Co. as senior vice president for medical and scientific affairs of its international division from 1979 to 1988.

In addition to serving as a Trustee of HHMI, Bearn was a Trustee of The Rockefeller University, the Helen Hay Whitney Foundation, and the Josiah Macy Jr. Foundation and was an overseer of The Jackson Laboratory. In recent years, Bearn wrote biographies of three scientists: Archibald Garrod, Sir Clifford Allbutt, and Sir Francis Fraser.

Bearn was a member of the National Academy of Sciences, the Institute of Medicine, the Harvey Society, and the American Society of Human Genetics. He was also a member of the American Philosophical Society and served as the organization’s vice president from 1988 to 1996 and then as executive officer from 1997 until his retirement in 2002.
The Power of One

ALTERING A SINGLE NEURON CAUSES A SURPRISINGLY SWEEPING CHANGE IN THE RAT BRAIN.

Maybe the flapping of a butterfly’s wings in Brazil can’t really cause a tornado in Texas, but this whimsical idea may be an apt analogy for how the brain works. Perturbing one single neuron, HHMI researchers have discovered, can change the electrical landscape of the whole brain.

Yang Dan, an HHMI investigator at the University of California, Berkeley, didn’t set out to show this. She wanted to probe how the strength of connections between neurons changes over time. So she and her colleagues set up an experiment: they would activate single neurons one at a time in a rat brain and then measure local connections from nearby neurons.

They found that instead of just tweaking how it interacted with other nearby neurons, activating any one neuron flipped the anesthetized rat’s entire brain between two states. In one state, which resembles deep sleep, brain waves are slow and synchronized throughout the brain. In the other state, which resembled rapid eye movement (REM) sleep—a less deep state of sleep—neurons were less synchronized and fired faster and more often. The flip worked in both directions.

“This is surprising,” says Dan, “because it shows that the weight of a single neuron is so much greater than we thought. It’s the power of the individual.” There are 100 billion neurons in the human brain, she points out, with only weak connections between them. But with each neuron connected—albeit weakly—to thousands of other neurons, a signal can spread like wildfire.

Why activating a single neuron would cause such a drastic change throughout the entire brain, Dan can’t fully explain. “So far what we have is a fascinating observation,” she says, “but in terms of explanations we only have speculation.”

Dan’s research, published in the May 1, 2009, issue of Science, suggests that the cortex—the part of the brain where her team was perturbing neurons—plays an important role in controlling the state of the brain. Previously, scientists had focused mostly on other areas—the hypothalamus and brain stem. To further flesh out the issue, Dan hopes to study rats that are awake, rather than anesthetized.

—Sarah C. P. Williams

IN BRIEF

HEARTBEAT TO HEARTBEAT

The first beats of an embryo’s heart do more than pump blood. HHMI investigators George Q. Daley and Leonard I. Zon, both of Children's Hospital Boston, have shown. The force of the beating heart triggers production of blood stem cells, which give rise to new red and white blood cells. The effect can be mimicked with drugs, the researchers also discovered.

Daley first noticed in 2001 that streaming a fluid across embryonic stem cells compels them to develop into blood cells. A later collaboration—with a scientist who invented a system to expose cells to different degrees of fluid flow—helped Daley take a closer look. They put embryonic stem cells into the setup and showed that when fluid flowed over the cells with the same force as blood in a developing heart, blood stem cells formed.

Meanwhile, Zon was looking for compounds that boost the production of blood stem cells within bone marrow, to treat patients with weak immune systems or blood diseases. To test thousands of drugs for whether they increase blood cell production, Zon used a technique that stains new blood stem cells purple. In 2007, his team found a class of compounds that did just that. The compounds, it turned out, also increased blood flow, corroborating Daley’s observation. Since then, Zon has discovered drugs that allow developing zebrafish embryos that lack a beating heart to produce blood cells. Daley’s results appear in the June 25, 2009, issue of Nature and Zon’s results are in the May 15, 2009, issue of Cell.

LISTERIA’S TWO SIDES

With the flick of a few genes—some on, others off—the bacterium Listeria monocytophages can turn from a harmless soil dweller into a dangerous human pathogen. HHMI international research scholar Pascale F. Cossart has made headway into understanding this transformation by investigating what parts of its genome Listeria expresses in different environments.

Cossart, at the Pasteur Institute in Paris, compared Listeria grown in the lab with bacteria from the intestine of Listeria-inoculated mice as well as bacteria from inoculated samples of human blood. Her team also compared normal bacteria with bacteria genetically altered to be less virulent.

The analysis turned up many surprises, says Cossart. First, they revealed that different groups of genes are expressed in the soil-dwelling and in the human pathogen versions of the bacteria. They identified one protein—SigB—that controls genes Listeria uses to adapt to the intestines and another protein—PrfA—that helps the bacteria survive in the blood. The bacteria switch between expressing SigB and PrfA, depending on which surroundings they sense.

More surprisingly, the scientists found that some of the genes important to the switch don’t code for proteins—they are small noncoding RNAs. They also discovered long antisense RNAs and other RNA elements that highlight new regulatory mechanisms in bacteria. The findings appear in the June 18, 2009, issue of Nature.

ULTRAVIOLET’S CELLULAR KILLER

When a cell is exposed to ultraviolet radiation from the sun, two things can happen: the cell can stay alive but accumulate DNA mutations that may lead to cancer, or the cell can sacrifice itself, preventing the spread of the possibly cancer-causing mutations. An HHMI researcher has unraveled the molecular pathway that leads a cell to head down the self-sacrificing path. Alberto R. Kornbluh, an HHMI international research scholar at the University of...
The trick to killing roundworms—such as hookworms and threadworms, which infect humans—may be to force the parasites to grow up too quickly. HHMI investigator David J. Mangelsdorf discovered that the molecular pathway governing how the harmless roundworm Caenorhabditis elegans exits a hibernation state controls the transition between life stages in many parasitic worms. He’s figured out a way to intervene in that pathway and kill larvae—something existing drugs can’t do.

In 2006, Mangelsdorf’s team at the University of Texas Southwestern Medical Center at Dallas identified molecules—dafachronic acids—that bind to DAF-12, a receptor involved in longevity. They found that the receptor is a checkpoint for worms exiting dauer diapause—a dormant state that C. elegans larvae enter when they perceive low temperature, crowding, or a lack of food. When the worms sense more favorable times, they produce dafachronic acids, which activate DAF-12, ending dauer diapause by turning on genes involved in reproduction and food metabolism.

Mangelsdorf’s group has now shown that the parasitic worm Strongyloides stercoralis, among others, also has DAF-12. While these parasites don’t enter dauer diapause, they do go through a similar dormant stage. So-called stage 3 infective larvae (iL3) keep their metabolism low until they sense a friendly environment inside a host. Taking hints from the C. elegans pathway, Mangelsdorf and his collaborators treated the iL3 parasites with dafachronic acid. It forced the worms out of their infectious state but not fully into the next life cycle stage—the worms died before they could reproduce, the team reported in a Proceedings of the National Academy of Sciences article that appeared online on June 2, 2009.

The current drug of choice to kill S. stercoralis targets adult parasites—eggs and larvae inside the host remain viable. Using dafachronic acid to force larvae out of their infectious state and kill them could end the hard-to-stop cycle, says Mangelsdorf. His lab is screening synthetic compounds for drugs that could mimic dafachronic acid’s effects and is looking more closely at the biochemical pathways that DAF-12 controls.

—Sarah C.F. Williams

**IN BRIEF**

Buenos Aires and the National Research Council of Argentina, zapped cells with a strong form of radiation, called UV-C, which is normally blocked by the ozone layer. He and his collaborators looked inside the cells to determine how the radiation affected gene expression.

The UV radiation affected many genes, among which were two genes involved in apoptosis—cell suicide. The messenger RNAs from the genes, Bcl-X and caspase-9, can be spliced into two forms—one that promotes cell suicide and one that blocks it. The UV-C caused the switch from the form that keeps cells alive to the form that kills cells. Even in cells missing a protein that normally triggers the switch in Bcl-X and in caspase-9, the UV-C was enough to make the change. The team further explained how the switch was made, and their results appear in the May 15, 2009, issue of Cell.

Kornblihtt plans to repeat the experiments with UV-A and UV-B, the lower energy forms of UV radiation, which are the reasons we slather on sunscreen.

**THE BREAST-BRAIN BARRIER**

It takes a special set of skills for breast cancer to spread to the brain and grow into a new tumor. The spread is slow, but deadly—cancers that have spread, or metastasized, from one area to another account for 90 percent of cancer deaths. HHMI investigator Joan Massagué, of Memorial Sloan-Kettering Cancer Center, has published the first account of just what it takes for breast cancer to invade the brain.

Massagué implanted tumor cells from an advanced breast cancer patient into mice. His team then isolated cells that spread to the animals’ brains. They found 243 genes expressed at abnormal levels and narrowed them down to 17 by looking at their activity in clinical tumor samples.

Knowing which genes allow a cancer to spread may help doctors predict how likely an individual patient’s tumor is to metastasize and could lead to targeted drugs. Already, Massagué’s group has discovered that patients with breast cancer expressing some of the 17 genes are more likely to experience brain metastases. The research appeared in Nature on June 18, 2009. The researchers hope to further characterize the roles of the genes within the cancer cells.

**FROM SIDE TO SIDE**

To the untrained eye, the mass of cells that make up an embryo may look like a jumbled mess, but each cell must be in the right spot at the right time for an organism to develop correctly. Faulty cellular orientation can lead to problems such as spina bifida, polycystic kidney disease, and metabolic cancer. Two genes that help cells determine their orientation have now been identified by HHMI international research scholar Jeffrey L. Wrana. The genes—Smad ubiquitin regulatory factors, or Smurfs—help cells move and distinguish front from back as well as top from bottom.

Wrana and his colleagues at the University of Toronto genetically engineered mouse embryos that lack the two Smurfs genes and observed what happened. The embryos failed to develop correctly—appearing short and wide when they should have been long and thin and improperly forming the tube that becomes the spinal cord. The anomalies didn’t stop there: hair cells in the inner ear, normally organized neatly, were scattered in all directions.

To explain how Smurf genes control a cell’s sense of space, or polarity, the researchers looked for other proteins that interact with Smurf gene-encoded proteins. They found two, the team reports...
Finding the Off-Switch

BLOCKING A COMMON GENETIC VARIATION IN HUNTINGTON’S PATIENTS MIGHT DIMINISH THE DISEASE’S EFFECTS.

Although the gene mutation that causes Huntington’s disease—a neurodegenerative disorder that causes jerky, random movements—was discovered in 1993, a genetic cure has been elusive. Huntington’s patients have one abnormal version of the Huntingtin gene and one healthy version that allows for limited motor function. Researchers have been unable to find a drug target that exists only on the diseased copy of the gene. Now, HHMI investigator Phillip Zamore has spotted a key difference.

Huntingtin contains a region with a repetitive sequence of DNA—it reads “C-A-G” between 6 and 28 times in the normal gene. The abnormal gene contains this repetition many more times—over a hundred in some cases. More repeats means more severe disease and an earlier age of onset.

Zamore, at the University of Massachusetts Medical School, studies small molecules called small interfering RNA (siRNA) that can bind to a given mRNA sequence and prevent it from functioning. It was hard to imagine how an siRNA could bind just the abnormal Huntingtin if the only difference from the healthy copy was a greater number of repeats.

“The problem is that even the normal gene has too many C-A-G repeats for an siRNA to tell the difference between it and the disease version,” says Zamore. But it occurred to him that if he looked more closely at the disease version, there might be small, but common, variations—called polymorphisms—that don’t affect the way a gene works but could be exploited to block it.

Zamore and his collaborators sequenced the genes of more than a hundred patients. They uncovered a polymorphism that, in 48 percent of the patients, appeared only in the disease-causing version of Huntingtin. It was far rarer in healthy copies of the gene—either in patients or in control subjects. The results appear in the May 12, 2009, issue of Current Biology.

Zamore is working to develop an siRNA that targets the polymorphism; it would block only the diseased Huntingtin gene, allowing the normal version to keep doing its job. —SARAH C.P. WILLIAMS

IN BRIEF

in the April 17, 2009, issue of Cell. In healthy cells, the two proteins accumulate on opposite sides of a cell. Smurf genes create this necessary imbalance, they found, by destroying one of the proteins on one side of the cell.

PLUG AND PLAY SYNTHETIC BIOLOGY

Creating novel biological systems in the laboratory, for study purposes, is a time-consuming, difficult task. But it’s one that gets easier as scientists understand more about how parts of cells—genes, proteins, and signaling pathways—work together. To save some time in the process of putting parts together into new systems, HHMI investigator James J. Collins, at Boston University, has developed a strategy to generate “plug and play” parts.

The difficult part of putting together a new biological network is predicting how different parts will interact. Collins and his colleagues set out to create and test one set of parts—gene promoters, which tell genes when to turn on and off—to create guidelines for how to use these parts together. They created libraries of two types of promoters, with 20 in each set. They then matched up promoters from each set with one another to see which would win out. The genes, Collins explains, play tug-of-war, with each wanting to turn others off. By developing a quantitative model of the constructed network, Collins can predict how future combinations of the promoters will work. The results were published in the May 2009 issue of Nature Biotechnology.

To test whether the components could be assembled into a useful network, Collins’ team used the promoters, and a predictive mathematical model, to create a cellular network that successfully controlled the timing of steps within yeast sedimentation, a precise chain of events used in industrial beer, wine, and bioethanol fermentation.

Sperm Instruction Manual

Some paternal genes aren’t needed until an embryo is well into development; others are important soon after a sperm and egg fuse to form a zygote. New research by HHMI investigator Bradley R. Cairns has revealed that the genes needed early on are packaged in a distinctive manner for easy access.

Cairns, of the University of Utah, found that a sperm passes along information to the zygote in the form of histones—proteins that form spools for DNA. DNA that’s more loosely wound around the histones is easier for a cell to access.

Previously, researchers had noticed that in mature sperm, rather than wrapping around histones, DNA primarily winds around a different protein, protamine, which compacts the DNA even tighter. This finding hinted that mature sperm don’t pass along much information about when to express various genes.

To test whether histones still played a role in passing along developmental information, Cairns used sperm from human donors and analyzed which DNA was bound to histone proteins and which was bound to protamine proteins. He found that a number of genes needed in embryonic development are bound to histones in sperm. Depending on when the genes are needed in development, the histones carry different tags, likely telling the cell when to unwrap them. These tags ensure that genes are expressed only when needed. The results were published online, on June 14, 2009, in Nature.
Laughing, speaking, and coughing all originate at our larynx, or “voice box,” which serves as our primary sound producer. It contains paired vocal cords that vibrate when air passes over them. When we’re quietly breathing, our vocal cords are completely open. Completely closed vocal cords stop airflow. Slightly open vocal cords cause exhaled air to pass through very quickly, which makes a vibration that we shape with our mouth and tongue to create speech. By adjusting the tension on the vocal cords, we can adjust our pitch. Stretching out vocal cords creates a higher pitch—like tightening the string of a violin.

Speaking is a voluntary act. We choose what we say (although we are capable of making “involuntary” sounds, such as when we are startled). Coughing and laughing can also be voluntary, if we choose to clear our throat or want to fake laughter, but are more typically involuntary.

Coughing occurs in response to stimulation of the airway and is designed to clear out something unwanted, like mucous or a piece of popcorn. This action protects the airway from getting clogged. Of course, this reflex is not perfect—sometimes we cough when our larynx is stimulated by spicy foods or irritated by a virus.

When we cough, the vocal cords first close completely. The diaphragm and other respiratory muscles build up air pressure below them. Then the vocal cords release, allowing air to suddenly rush outward. This rush of air is a cough.

Another, less-well-understood reflex is the hiccup; the respiratory muscles pull in air, but the vocal cords slam closed, resulting in the “hic” sound.

Laughter is probably the least understood airway-related reflex. The mechanics are simple, but why we laugh is more mysterious. The sound of laughter happens when we are exhaling and the vocal cords periodically close. As they get close together, laughing occurs. Periodic activation of the respiratory muscles produces the rhythmic airflow that helps make the sound.

Everybody has a unique laugh, and there is evidence for a laughter “pace-maker” that controls how fast or slow the beats of our natural laugh occur. This action is similar to hiccups, which also occur at a frequency that tends to be constant within individuals.

In the brain, laughter involves many regions—those needed to understand and process the humorous stimuli (a joke or situation) and those that tell the larynx and respiratory muscles what to do. This system is distinct from that used to control voluntary speech. In fact, some patients with speech production disorders related to the larynx can still produce involuntary sounds like laughter.
**Sticky DNA** Problem-solving chemists begin to build three-dimensional tissue.

Developing organisms know just where to position various cells so they can communicate and cooperate with their neighbors to establish three-dimensional structures. For biologists, emulating the body’s architectural dexterity, even for simple tissues, has been a frustrating pursuit.

“The spatially encoded information in tissues is very difficult to replicate outside the body, but also really important for function,” says HHMI investigator Carolyn Bertozzi at the University of California, Berkeley.

“In the lab, we typically culture cells on flat substrates like tissue culture plastic. But we don’t live in a flat world,” adds Zev Gartner, who began to study cell-to-cell interactions as a postdoctoral fellow in Bertozzi’s lab. “Cells in our bodies are surrounded on all sides by their neighbors and by an extracellular matrix, and the behavior of cells in 3-D is very different from when they are grown on these rigid, inert surfaces.”

If they could control tissue assembly, researchers could design biomaterials to replace or repair injured tissue and would have more true-to-life models of tissues, both healthy and diseased, for study in the lab. To Bertozzi and Gartner, the challenge of organizing cells into more complicated structures looked like the kind of problem they solve best: a chemistry problem. Chemists synthesize complex molecules by performing a series of reactions with simpler building blocks. The team’s building blocks were short single-stranded sequences of DNA linked to the outer surface of cells to make the cells selectively “sticky.”

The approach relies on DNA’s discriminating nature: because each building block or nucleotide that makes up a DNA sequence has a preferred partner, a strand of DNA will bind only to another strand whose sequence is complementary to its own. For years, Bertozzi’s lab and colleagues in the chemistry department have been exploiting this property of DNA to create simpler, two-dimensional patterns of cells. By linking a strand of DNA to a cell, and a complementary DNA strand to a spot on a flat surface, the researchers can direct the cell to bind there—a useful strategy for tasks such as designing cell-based biosensors or drug-screening technologies. When Gartner joined the lab in 2006, he realized the approach could be taken, literally, to another dimension.

To jump from two to three dimensions, Gartner linked complementary strands of DNA to the outer membranes of different types of cells. Then he allowed those cells to interact so they could bind to one another. By varying the length of the DNA strand, the complexity of its sequence, and its abundance on a cell’s surface, he could control how quickly the cells came together and how stable the resulting complexes would be. He incorporated fluorescent markers so that, after the cells had mingled, the sought-after multicellular assemblies could be sorted from cells that remained solo.

Gartner used the approach to create a tiny sphere in which two onion-like layers of cells encase one another. The innermost cells secrete a protein growth factor that the outer layer of cells needs to survive. This intercellular signaling depends on the close proximity of the cells to one another due to their DNA “glue.” The team calls the structure a “microtissue”—simpler than most of the tissues the body builds but a useful model for studying specific cell-to-cell interactions in the lab. The contact-dependent exchange of survival factors in their system mimics signaling that spurs the growth of tumors and immune cells, according to their paper, published March 24, 2009, in the *Proceedings of the National Academy of Sciences.*
This first microtissue demonstrates that Bertozzi and Gartner’s technique works. The method should be readily accessible to researchers in other labs who want to design their own microtissues, and because the DNA “glue” on the surface of each cellular building block “really has nothing to do with the individual cell type,” the possibilities for directing different assemblies are virtually limitless, Gartner says.

Gartner, now a faculty member at the University of California, San Francisco, is experimenting with building larger microtissues that include more cell types, and encoding more structural information into the cells so researchers can direct their orientation and construct asymmetric assemblies, such as the layers of cells in the skin. “We’re trying to see how much further we can push the basic idea,” he says. —Jennifer Michalowski
Ten Elected to National Academy of Sciences

FREDERICK W. ALT, an HHMI investigator at Children’s Hospital Boston, received the 2009 William B. Coley Award for Distinguished Research in Basic Immunology given by the Cancer Research Institute. Alt shared this annual award with Klaus Rajewsky of Harvard University.

DAN ARNSTEIN and ANGELINA GOMES, both interdisciplinary scholars in an HHMI-funded program at Haverford College, received 2009 Fulbright Scholarships to study abroad.

Seven HHMI investigators, one Janelia Farm Research Campus group leader, and one member of HHMI’s scientific review board were elected to the American Academy of Arts and Sciences in April 2009. The investigators are Ralph R. Isberg, Tufts University School of Medicine; Tyler Jacks, Massachusetts Institute of Technology; Shirleen Roeder, Yale University; Kevan M. Shokat, University of California, San Francisco; Paul W. Sternberg, California Institute of Technology; Jonathan S. Weissman, University of California, San Francisco; and S. Lawrence Zipursky, University of California, Los Angeles. The senior scientific officer is Marian B. Carlson, whose lab is at Columbia University. The HHMI professor is Baldomero M. Olivera, University of Utah. The international research scholar is Pascale Cossart, Institut Pasteur, Paris, France.

HHMI investigator JAMES J. COLLINS of Boston University received the inaugural Anthony J. Drexel Exceptional Achievement Award from Drexel University for his development of novel medical devices that address complications resulting from diabetic neuropathy.

LISA G. DODSON, an HHMI precollege program director at Oregon Health & Science University, was named the 2009 Oregon Family Doctor of the Year by the Oregon Academy of Family Physicians for her HHMI-funded work with children in rural areas of the state.

HHMI investigator BRIAN J. DRUKER of the Oregon Health & Science University was named a European Inventor of the Year 2009 in the area of industry. He shares the award with Jürg Zimmermann of the Novartis Institutes for Biomedical Research for their development of Gleevec to treat chronic myelogenous leukemia.
EDWARD E. EVANS, a teacher at the Health Sciences and Technology Academy—a West Virginia University program funded by an HHMI precollege grant—was named America’s Top Science Teacher by Discovery Education and 3M.

KATHERINE A. HIGH, an HHMI investigator at The Children’s Hospital of Philadelphia, received a 2009 Board of Directors’ Award from the Foundation for Fighting Blindness. She also is recipient of an International Society on Thrombosis and Haemostasis Investigator Recognition Award.

HHMI investigator FRIEDHELM HILDEBRANDT of the University of Michigan Medical School received the 2009 Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease. Hildebrandt shares the prize with Lisa Guay-Woodford of the University of Alabama at Birmingham and Corinne Antignac of the Necker Hospital in France.

HHMI investigator RICHARD O. HYNES of the Massachusetts Institute of Technology received the 2009 Robert J. and Claire Pasarow Award for Cardiovascular Research.

HHMI-funded undergraduate BRIAN GOH of Louisiana State University was named to the 2009 USA Today All-USA College Academic First Team.

STEVEN E. JACOBSEN, an HHMI investigator at the University of California, Los Angeles, received the 2009 Charles Albert Shull Award from the American Society of Plant Biologists.

HHMI investigator CHRISTINE JACOBS-WAGNER of Yale University was recognized by the New York Academy of Sciences as one of six finalists, in the faculty category, for a 2008 Blavatnik Award for Young Scientists.

HHMI President ROBERT TJIAN; HHMI Trustee ALISON F. RICHARD, vice-chancellor of the University of Cambridge; HHMI investigator CRAIG C. MELLO of the University of Massachusetts Medical School; and HHMI medical advisory board member ROWENA G. MATTHEWS of the University of Michigan were elected to the American Philosophical Society.

The 2009 Freeman Award from the National Alliance for Research on Schizophrenia and Depression was awarded to HHMI investigator KERRY RESSLER of the Emory University School of Medicine.

HHMI investigator CHARLES L. SAWYERS of Memorial Sloan-Kettering Cancer Center received the 2009 Dorothy P. Landon-AACR Prize for Translational Cancer Research from the American Association for Cancer Research.

LESLIE B. VOSSHAL, an HHMI investigator at The Rockefeller University, won the Lawrence Katz Prize for Innovative Research in Neuroscience.

The 2010 Priestly Medal, the highest honor bestowed by the American Chemical Society, was awarded to HHMI professor RICHARD N. ZARE of Stanford University. The honor recognizes Zare’s scientific contributions to chemistry as well as his teaching, mentoring, and public service.

SHAW PRIZE GOES TO FRIEDMAN

The 2009 Shaw Prize in Life Science and Medicine was awarded to HHMI investigator Jeffrey M. Friedman of The Rockefeller University and Douglas L. Coleman of The Jackson Laboratory for their work leading to the discovery of leptin, a hormone that regulates food intake and body weight. Studying morbidly obese, diabetic mice, Coleman was the first to hypothesize that a hormone was linked to appetite and weight gain. More recently, Friedman used genetic mapping to pinpoint the gene encoding leptin, which was mutated in the mice Coleman studied.

CAMPBELL AND KUNKEL SHARE MARCH OF DIMES AWARD

Kevin P. Campbell, an HHMI investigator at the University of Iowa Roy J. and Lucille A. Carver College of Medicine, and Louis M. Kunkel, an HHMI investigator at Children’s Hospital Boston, received the 2009 March of Dimes Prize in Developmental Biology. They were chosen to share the prize for their research on muscular dystrophy. More than 20 years ago, Kunkel identified dystrophin, the protein mutated in some forms of muscular dystrophy. Since that discovery, Kunkel and Campbell have further unraveled the molecular mechanisms of muscular dystrophies, leading to the development of several drugs now in clinical trials.
researchers in Sweden, where the wait-and-see approach is used much more often than in the United States. Golub’s Swedish collaborators have followed a large cohort of prostate cancer patients from early diagnosis to see whether their tumors worsen—this approach is more difficult in U.S. cohorts as the prostate is more often removed. To identify differences between prostate cancers, Golub is using DNA chips to quantify the genetics of bits of biopsied tumors.

He’s also working—as many researchers are—to create drugs to target the fusion gene identified by Chinnaiyan.

As for Foley, he’s become an outspoken advocate for prostate cancer patients learning about their disease and staying informed of the latest drugs and clinical trials. “Do the research, read the data, talk to doctors. If my cancer rears its head again, I’ll look to other trials.” In January, on inauguration day, he and one of his prostate cancer groups sent a petition to President Obama requesting more federal funding for prostate cancer research. He’s also started a prostate cancer support group in his hometown and is active in online message boards, touting his success with MDV3100.

Though Chinnaiyan’s discovery of the fusion gene is heralded as the greatest leap in understanding prostate cancer in the past decade, it’s only half the battle toward changing the way prostate cancer is dealt with clinically. Now researchers must turn that discovery into detection methods, ways to monitor the disease, and new treatments for prostate cancer, so that the disease can be managed in a more personalized way. PSA needs a helping hand.