

# FIFTY

KONRAD HOCHEDLINGER

MOLLY PRZEWORSKI

SINISA URBAN

MING

LEI

AMY WAGERS

TAMIR GONEN

JOAQUIN ESPINOSA

KARL DEISSEROTH

KEVIN EGGAN

BRENT

STOCKWELL

ERIC

GREENE

TIRIN MOORE

NEIL HUNTER

JAMES BEAR

CHRISTOPHER SASSETTI

JENNIFER

ZALLEN

RUSSELL DEBOSE-BOYD

BRADLEY

BERNSTEIN

HOWARD CHANG

HUI SUN  
HARMIT MALIK

REUBEN SHAW

ANITA SIL

MARTIN BURKE

AVIV

REGEV

# STORIES

LUIS AMARAL JOSHUA MENDELL  
RACHEL WILSON  
MARC FREEMAN  
MARCIA SPIES  
PETER BAUMANN  
ROB KNIGHT  
JOSEPH THORNTON  
KENNETH POSS  
IANNIS AIFANTIS  
JEREMY DASEN  
DANIEL BOLNICK  
KRISTIN SCOTT  
XINZHONG DONG  
MARTIN COHN

## TOP EARLY CAREER

RYOHEI YASUDA  
JOHN WALLINGFORD  
MICHAEL LAUB  
MICHAEL DYER  
SEAN BRADY  
TOSHIYASU TANIGUCHI  
JEFFREY KIEFT  
ACADEMIC SCIENTISTS GET  
SIX YEARS OF SUPPORT FROM HHMI  
TO PURSUE THEIR BEST IDEAS.  
BY JOHN FLEISCHMAN

# “SO”

is perhaps the most ubiquitous term in science. “So,” says the researcher about to explain why a virus overtakes its host or how proteins fold. And so begins the story that every scientist carries in his or her head, the up-to-the-minute mental narrative of what is really happening—in genes or proteins or phylogenetic trees.

Maria Spies tells “single molecule stories” in DNA biochemistry. She describes what happens when DNA helicases, molecular motors that drive DNA repair, find breaks and “hot spots” in DNA or encounter other proteins bound to the DNA molecule. Spies studies DNA helicases that are linked to breast and ovarian cancer and to rare genetic disorders involving premature aging, stunted growth, and a dangerous sensitivity to sunlight. DNA repair is vital to all cells. By one estimate, every cell in the body must undertake 190,000 DNA repair events every day to keep up with the damage inflicted by ultraviolet light, toxic chemicals, and the dangerous by-products of normal metabolism.

Spies’ most gripping single molecule story so far involves the bacterial helicase RecBCD running on a sort of home-built DNA drag strip, a long stretch of nucleic acids laid out so Spies could insert recombination hot spots. Using laser optical trapping and single-molecule fluorescent markers, Spies recorded RecBCD barreling down the DNA track, pausing at a hot spot and then changing speed. The helicase did this by switching the lead positions of its two driving molecule subunits, which run at different speeds. Spies described it as a “molecular throttle.” A colleague described this story as stunning.

But Spies has another story, her own, that is equally gripping. She entered Russian science in the mid-1990s, a time when research in the former Soviet Union was in freefall. Her first publication in a Russian journal was a mark of achievement, according to an outside observer familiar with post-Soviet Russian science who noted that any publication at this chaotic time was “an indication of a strong desire and determination to do science.”

That determination led Spies into scientific research in three languages: in her native Russian as a student at St. Petersburg State Polytechnic University, in Japanese for her doctorate at Osaka University, and in English, first as a postdoctoral fellow at the University of California, Davis, and since 2005 in her own laboratory at the University of Illinois, Urbana–Champaign. With this long prelude, Spies’ independent career is taking off at last.

## TIME FOR DARING

There is a third story here. It goes beyond the science or any one scientist. It is the story of what happens to newly launched researchers like Spies in their early careers. It’s a story that worries the scientific advisors of HHMI who see many promising investigators heading for a career-deadening crunch. Just as their independent research and their scientific imaginations are supposed to be taking off, they run into professional prudence.

Researchers serve a long apprenticeship, laboring for years in other people’s labs, first as graduate students and then as postdoctoral fellows, before the opportunity to strike out on their own as principal investigators, or PIs. Hired for their first tenure track

faculty positions, new PIs are usually greeted with generous institutional start-up funds, protected research time, and “free” lab space. But within a few years, the grim reality of funding sets in. To keep it all going—labs, students, equipment, materials, overhead, and their own salaries—researchers must bring home the bacon, generally in the form of big, multiyear federal grants. With so much on the line, the tendency is to play it safe to win those grants. Mentors advise young colleagues to leave their grand, outside-the-mainstream projects for another day and to write up measured, incremental proposals that approach worthy scientific goals in precise steps.

That’s the story HHMI wants to rewrite. In 2008, HHMI issued a call for applications from early-stage, tenure-track researchers in biological and related fields (for example, bioinformatics) for six-year, nonrenewable, all-expenses-covered appointments as HHMI Early Career Scientists (ECS). Beyond salaries and staff, HHMI would underwrite the purchase of critical equipment and the leaseback of their lab space from their home institutions. In all, HHMI would earmark \$200 million over six years to support the ECS investigators. More than 2,000 applications flooded in. This March, HHMI unveiled the first 50 ECS investigators: 9 women and 41 men from 33 institutions. Maria Spies is 1 of the 50.

“These scientists are at the early stage of their careers, when they are full of energy and not afraid to try something new,” says Jack Dixon, HHMI vice president and chief scientific officer. “They have already demonstrated that they are not apt to play it safe—and we hope they will continue to do something really original.”

Given HHMI’s long-time preference for choosing “people over projects,” it’s not hard to see why certain ECS candidates jumped out of the pack. But even being among the best and the brightest was not enough. The selection committee was looking for something beyond sterling credentials, impressive publications, and glowing recommendations. Call it style, originality, grit, or fearlessness. Or call it a compelling story.

## CLEARING TECHNICAL HURDLES

Karl Deisseroth tells a dazzling story about controlling neural activity, neuron by neuron, in freely moving mice with a pulse of light. Deisseroth, a physician-scientist at Stanford University, calls his technique “optogenetics.” He gave it a grand demonstration of principle in 2007 by waking up mice, not by shaking or startling them but by switching on light-sensitive proteins deep within their brains. Deisseroth’s experiment was also an *in vivo* test of recent genetic findings linking human narcolepsy, a chronic sleeping disorder, to a defective set of cells in the lateral hypothalamus that produce proteins called hypocretins.

To rouse the sleeping mice, Deisseroth borrowed a light-sensitive switch from a microbe (in this case, a single-celled alga) and used a virus to deliver it into the cell membrane of neurons deep in the hypothalamus on the underside of the mouse brain. Then he and colleagues fired laser bursts down an optical fiber, bathing the switch in blue light and opening the microbial ion channel. Sodium ions flooded into the neurons, exciting them and causing them to release hypocretins.

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Deisseroth's mice were a wake-up call to a new day in neuroscience when targeted neurons in living animals can be flipped on or off by light.

This is just the tip of the iceberg, says Deisseroth, who has distributed optogenetic technology, free of charge, to more than 350 labs around the world. He is pressing ahead to refine new bio-optical switches that can inhibit as well as excite neurons and to apply the technology to better understand neural circuits in health and disease. Meanwhile, Deisseroth is board-certified by the American Board of Psychiatry and Neurology and continues to care for patients.

Russell DeBose-Boyd's story is about finding a way around the statin stalemate. Twenty million Americans take a statin every day to reduce their levels of “bad” cholesterol—low density lipoproteins, or LDLs. Statins dramatically cut LDL levels in some patients, says DeBose-Boyd, who is at the University of Texas (UT) Southwestern Medical Center, in Dallas. But the body responds to the plummeting cholesterol levels with a feedback system that tells the cells to compensate by making more cholesterol.

To understand the statin impasse, DeBose-Boyd studies HMG-CoA reductase, an enzyme that sets the rate of cholesterol synthesis. Statins block the enzyme but, paradoxically, also seem to drive up reductase levels, he says, by slowing their natural degradation. Blocked by statins, the accumulating enzyme convinces the cell's sensing system that cholesterol levels are crashing, and the cells respond by attempting to rev

up synthesis. DeBose-Boyd hopes to make statins work better, or find entirely new drugs that control reductases better and make statins obsolete.

DeBose-Boyd's other story is how he found his way into science. He comes from a tiny farming community in rural Oklahoma and began his studies at Southeastern Oklahoma State University, in Durant, an institution not noted for producing protein biochemists. He followed his interests in biology to the University of Oklahoma Health Sciences Center, in Oklahoma City, where his Ph.D. mentor, glycoprotein biochemist Richard Cummings, recognized his talent. Cummings enthusiastically promoted DeBose-Boyd as a postdoctoral fellow candidate to the UT Southwestern Medical Center research duo of Michael Brown and Joseph Goldstein, who won the 1985 Nobel Prize in Physiology or Medicine for their discovery of the regulation of cholesterol levels by statins. That discovery set off the statin revolution but the exact mechanism and the paradoxical self-limit of statin efficacy stymied their lab for a decade.

Then DeBose-Boyd arrived and turned his attention to the interplay between statins and reductase. He worked his way around a major technical hurdle by discovering a regulated binding partner of reductase that allowed overexpression of the enzyme in sufficient quantities while preserving its natural degradation. This discovery permitted him to map out interactions between reductase and its binding partner and focus on reactions that lead to the enzyme's degradation. It soon became clear to Brown and Goldstein that DeBose-Boyd was someone



**CLOCKWISE: MARIA SPIES, KARL DEISSEROTH, HARMIT MALIK, RUSSELL DEBOSE-BOYD**

to keep around UT Southwestern and they engineered his move to independent faculty status.

### **OF CONFLICT, VULNERABILITY, AND DOMINANCE**

Harmit Malik's story sounds like a viral fairy tale. In it, Malik and his collaborator Michael Emerman awaken a 4-million-year-old retrovirus to discover how our hominid ancestors evolved a stout genetic defense against it while our chimp cousins did not. What Malik and his colleagues were after was not a microscopic version of Retroviral Park but an evolutionary insight into HIV, another retrovirus that made the long evolutionary trip to modern times where it found human antiviral defenses unprepared for it.

Malik's scientific story is much wider than retroviral measures and countermeasures. He is interested in genetic conflict both within our own cells and between our DNA and that of outsiders like HIV. He has used the conflict paradigm to gain insights into long-standing problems such as the ability of viruses to mimic our proteins and also the evolution of centromeres, structural DNA elements that are critical for proper cell division.

The Harmit Malik story begins with a degree in chemical engineering from the Indian Institute of Technology in Mumbai and takes a turn toward evolutionary biology in a doctoral program at the University of Rochester. His engineering background made him comfortable with the flood of genomic data pouring out of mass sequencing and the ease with which living things could be sorted into evolutionary families, or phylogenetic trees, by new bioinformatics programs.

As a grad student, Malik helped usher the biology department into the bioinformatics age. It earned him a tribute from Barry Hall, the noted Rochester geneticist and author of *Phylogenetic Trees Made Easy*, who wrote in the foreword, "I am grateful to Dr. Harmit Malik, who patiently overcame my antipathy to phylogenetic analysis by teaching me how to use phylogenetic software. Much of the book comes directly from his help." Hall continued, "This book began as an effort to record and organize his advice when we realized we could not keep him on hand forever."

Malik left Rochester for Seattle and a postdoc with HHMI investigator Steven Henikoff at the Fred Hutchinson Cancer Research Center. It was in Henikoff's lab that Malik branched out into genetic conflict at centromeres, which occurs when chromosomes compete for survival during female meiosis. Henikoff soon realized the advantage of keeping Malik on hand for the Basic Sciences Division. In 2003, Malik became the first "in-house hire" of a postdoc for a faculty position at the center in nearly 20 years.

So, careers and stories follow an arc. The aim of HHMI's ECS program is to advance the career trajectory of these 50 talented researchers, and with them the prospects for research bioscience, far into the 21st century. This makes the 50 Early Career Scientists sound like human cannonballs, and they do share a certain scientific derring-do. Their instructions from HHMI are simple: Land somewhere unexpected. Discover something transformative. ■

**FOR MORE INFORMATION:** To learn about the 50 new HHMI Early Career Scientists, visit [www.hhmi.org/news/20090326ecs-ad.html](http://www.hhmi.org/news/20090326ecs-ad.html).