



PROFILE: PARDIS SABETI

## Picking Up Evolution's Beat

Pardis Sabeti mixes geek cool with hot science as she studies how human populations have evolved to resist malaria and Lassa fever

**CAMBRIDGE, MASSACHUSETTS**—Over the past 72 hours, Pardis Sabeti has managed only 2 hours of sleep each night, most of them inside a crumpled blue sleeping bag she keeps under a desk at the Broad Institute Center for Genome Research in Cambridge, Massachusetts. Sabeti, who burst on the scientific scene in 2002 with a novel test for natural selection in the human genome, has been racing to meet the submission deadline for a National Institutes of Health (NIH) grant to support her research on the evolution of resistance to malaria and Lassa fever. Also in her schedule this year: serving as a panelist at the World Economic Forum in Davos, Switzerland; a research trip to Africa; speaking to young women about careers in science; and writing songs and recording for her pop/rock band.

To manage all this, Sabeti, 32, has been sleeping under desks for much of her relatively short career. The petite Iranian-American with a toothy smile has cut a wide swath through the research world, racking up awards and honors at a dizzying pace: a Rhodes scholarship at Oxford University, a L'Oreal Women in Science award, and summa cum laude honors at Harvard Medical School, to name a few. She's also made a name in the wider world: The London *Daily Telegraph* recently called her one of the "top 100 living geniuses" (she tied for 49th place with Henry Kissinger, Richard Branson,

Stevie Wonder, and Meryl Streep), and CNN named her one of eight "geniuses who will change your life."

Sabeti also seems to have a genius for raising money. While still a postdoc, her own grants totaled more than \$600,000, and she is currently a co-investigator on a \$2 million Bill and Melinda Gates Foundation grant. She was recently hired as a Harvard assistant professor, turning down offers from several other leading universities.

And then there's the band: She's the lead singer in the Boston-based alternative group Thousand Days, which plays gigs up and down the East Coast and has released three albums. Sabeti's singing voice is "sweet and sexy," wrote one music reviewer, adding wryly that "it's nice to know she has a successful back-up career in case her attempts at winning the Nobel Prize don't pan out."

The band may boost Sabeti's visibility, but it's her scientific drive that elicits enthusiasm from her colleagues. Broad Institute geneticist David Reich, who has worked closely with Sabeti, sums her up this way: "She is a very cool person but also sort of a nerd."

Sabeti was born in Tehran, Iran, where her father was a high-ranking official in the Shah's government. He sought asylum in the United States shortly before the 1979 revolution, and Sabeti grew up in Orlando,

Florida, with a large extended family.

She traces her academic success to her early life in this close-knit clan. "My mother created a summer camp in our house, where she would teach the children and make us do book reports. And my sister, who is 2 years older than me, would teach me and my cousin what she had learned in school." Sabeti says mathematics was her first love. Her high-energy personality, she adds, appeared in those early years. "I'm a hyper person," she says. "My parents always told me to relax."

Reich, who met Sabeti when they were both grad students at Oxford, says she has always been "very driven." Her habit of pulling all-nighters was well-established by then, recalls Hans Ackerman, a fellow Rhodes scholar who is now a medical fellow at NIH in Bethesda, Maryland. "I would come into the lab and find her asleep under her desk after a full night of doing PCRs."

Why does she work so hard? "I guess I just want to make my parents proud of me," she says.

Although Sabeti's workaholic ways have brought her scientific success, Broad Institute Director Eric Lander and others also note her charisma and her efforts to reach out to the community. For example, as an undergrad at the Massachusetts Institute of Technology, Sabeti founded a still-thriving program to help incoming freshmen develop leadership skills. She also worked with RNA pioneer David Bartel, who recalls only one glitch in their association: "She gave out the lab phone number as the contact" for the leadership program. So many students called, "we had to change the



number,” says Bartel.

Sabeti also took the lead at Harvard Medical School, producing a lighthearted orientation video for first-year students, featuring prancing, juggling, balloon-wielding students and faculty. She now presents this video in person to each entering class. In fact, she’s still making videos. One will be shown during a *NOVA* profile of her to be aired in July, featuring appearances by researchers including Lander, as well as Sabeti’s music.

Sabeti’s band, Thousand Days—which describes itself on MySpace as a “love child” between the rock group U2 and the pop band Mazzy Star—has been a regular presence on the New England music scene for several years. Sabeti writes her own songs, including one called “Coming Up” that seems a metaphor for her career. She says she “loves the creative spirit” in both music and science but is “more at home” in science. Given her scientific schedule, she hasn’t found time to perform in recent months.

She continues to focus on the research she began at Oxford: teasing out signs of selection in the human genome. At Oxford, Sabeti focused on genetic susceptibility to malaria, zeroing in on two alleles that conferred resistance to the parasite. Most researchers assumed that these genetic variants had been favored by selection, but there was little evidence to prove it.

Over the previous 20 years, researchers

**Hyperactive.** Pardis Sabeti—malaria researcher, role model for young scientists, and rock performer—keeps on the move.

had developed dozens of tests for detecting “signatures” of natural selection in the genome (*Science*, 16 June 2006, p. 1614), but they had very low power to detect more recent evolutionary changes, particularly during the last 10,000 years, when many of the diseases that afflict humankind, including malaria, arose.

Working with Reich and with her doctoral adviser, Dominic Kwiatkowski of Oxford University in the U.K., Sabeti hit on a novel way of combining two types of genetic information to create a more powerful test: the frequency of a particular variation and the structure of the genome surrounding it. Normally, variants are shuffled in a random fashion across the genome. But if a particular variant is the target of recent natural selection, its rapid increase in frequency can create so-called haplotype blocks, groups of genes that have “hitchhiked” along for the Darwinian ride (see graphic, below). Some earlier selection tests looked at both variant frequencies and haplotypes in humans, but they weren’t very sensitive. Sabeti used her math skills to devise a genetic “clock,” based on haplotype structure, that could reveal whether recent,

was made. “This test is one of the most exciting developments in the field in the past few years,” says Chris Tyler-Smith, a genome researcher at the Wellcome Trust Sanger Institute in Hinxton, U.K. Evolutionary biologist Martin Kreitman of the University of Chicago, who had developed a similar test but was beaten into print by a few months, says he has “nothing but praise for her contributions.” He adds that Sabeti’s most recent contribution, a genome-wide search for selected genes in collaboration with Lander, the International HapMap Project, and others, “is a beautiful piece of work.”

Lander says Sabeti’s test anticipated the detailed information that the HapMap would later make available. “Pardis has a very energetic imagination,” he says. “Not many people think about what they would do if they had data they don’t yet have.”

The genome-wide study, published in *Nature* last October, identified two genes called *LARGE* and *DMD* that are involved in Lassa fever infection and show strong signals of natural selection in West Africans. Despite striking about 300,000 people each year and killing 20,000 of them, Lassa fever has been neglected by public health experts. Sabeti hopes to use her test to identify variants protective against the disease, which could eventually help in the search for new therapies and a vaccine. Looking at Lassa’s

evolutionary history is “a very innovative approach” that “might breathe some new life into field research” into the disease, says Lassa fever expert Joseph McCormick of the University of Texas School of Public Health in Brownsville, who is a consultant to Sabeti on the project.

At the moment, Sabeti seems to be flying high. But some colleagues are concerned that her fame could set her up for a big fall if her hyper pace slackens. “I worry that too many expectations are being put on Pardis,” says one researcher. But Nancy

Oriol, Harvard Medical School’s dean of students, isn’t worried. “If you are motivated by serving others and doing good work, as is Pardis, you won’t get burned out,” she says.

Indeed, despite all the attention she attracts, Sabeti says she feels more at home with her inner nerd: “Even though I am gregarious, I interact more with [scientific] papers than with people. Deep down, I am just a math geek.”

—MICHAEL BALTER



**Hitchhikers.** When a genetic variant favored by selection (pink bar) spreads rapidly in a population, other variants linked to it come along for the ride.

high-frequency variants were due to selection or just chance—greatly strengthening the power to detect evolution’s hand.

In collaboration with Kwiatkowski, Lander, Reich, and others, Sabeti then applied the new approach to the protective malaria variants. “We saw a whopping signal” of positive selection, Sabeti says. When these results were published in *Nature* in 2002, her scientific reputation