

Ahead of the Curve

Jack Szostak is drawn to uncharted territory. His curiosity and big thinking have earned him a Nobel Prize.

by Dan Ferber

photography by Leah Fasten



It was not the first time Jack Szostak gambled on an experiment, nor would it be the last.

Risky, big-payoff experiments like these kept science exciting. Sure, bread-and-butter studies that would inform no matter how they turned out were always going to be necessary, he knew. But it was experiments like these that Szostak liked best—far-fetched, perhaps, but potentially groundbreaking.

What if he took chromosome tips from a single-celled pond creature called *Tetrahymena* and transplanted them into baker's yeast, an organism evolutionarily miles away. In *Tetrahymena*, those tips, called telomeres, functioned like the tips of shoelaces, protecting the DNA in chromosomes from damage. Would they protect yeast DNA in the same way?

“We thought it was a long shot because yeast and *Tetrahymena* are so distantly related,” recalls Szostak, now an HHMI investigator at Massachusetts General Hospital, whose early work on telomeres won him a share, with Elizabeth Blackburn and Carol Greider, of the 2009 Nobel Prize in Physiology or Medicine. “Yet it was a very easy experiment to do. If it worked it would tell us a lot, and it would open up the field.”

Mysterious Ends

It was the autumn of 1980 and Szostak, then 27 and a new faculty member at Harvard Medical School, had been excited about trying the experiment ever since he'd returned from a Gordon Research Conference on nucleic acids a few months earlier. At Harvard, he had focused the efforts of his small team on understanding the molecular nature of recombination—the process by which higher organisms shuffle the genetic deck, exchanging pieces of DNA between chromosomes before reproducing.

Szostak was particularly interested in what happens to the ends of DNA molecules. DNA exists as a double helix that can be extended like a long piece of rope. Just as the ends of a rope tend to fray, the ends of a DNA molecule are less stable than the rest of the molecule: enzymes inside the cell can chew them back, attach them to other DNA ends, or recombine them with other DNA molecules.

But the DNA at the tips of chromosomes is not degraded, and biologists had long wondered why.

At the Gordon Conference, Elizabeth Blackburn, of the University of California, Berkeley, presented her results on *Tetrahymena*'s curious chromosomes. The unicellular freshwater

organism contains thousands of very short chromosomes that are linear yet remain stable inside the cell. Blackburn had used these minichromosomes to get a large enough quantity of chromosome tips to study, and at the conference she described how the unusual, repetitive DNA sequence of those tips seemed to confer stability.

“It was a surprise, a shock almost,” Szostak recalls. “Here I was working on all these reactions that DNA ends engage in. Then here's Liz talking about some little piece of DNA that just makes a stable end. It was completely the opposite behavior.” He button-holed her, and the two had an intense conversation about chromosome tips. Szostak floated his wild idea about a telomere transplant experiment, and the two agreed to try it.

Blackburn sent Szostak some DNA from *Tetrahymena*'s chromosome tips. Szostak attached it to a piece of linear yeast DNA and then introduced the hybrid into yeast cells. Once the yeast had multiplied in culture, he ran their DNA on a gel, transferred it to a special paper, treated the paper with a radioactive probe that would bind to *Tetrahymena* DNA, and exposed it to a sheet of x-ray film. If the yeast maintained the hybrid DNA as a linear chromosome, Szostak would see a single band on the film.

In the darkroom, with gloved hands, he separated the x-ray film from the paper and inserted the film into an automated processor. In a matter of minutes, the machine would spit out the developed film outside the darkroom. Szostak walked to the hallway and waited.

An Early Passion

Szostak's headlong dive into science started early. As a precocious 14-year-old high school student, he got a summer job in a lab at a Montreal chemical company, where his mother also worked, testing the ability of fabric dyes to withstand light and detergent. Later, as a teenaged cell biology major at McGill University, he bounced around a few chemistry labs before launching his first true research project: he showed that a simple species of algae called *Eudorina* released hormones that triggered sexual development.

Science classes of all sorts engaged the talented student; in one memorable lecture, a professor named John Southin described how scientists had deduced the mechanism of DNA replication from test tube observations. “It was so amazing—this

long chain of logical deduction between the actual experimental observations,” Szostak recalls. Far ahead of his classmates, Szostak graduated from McGill at the age of 19 in 1972 and headed to Cornell University for graduate school.

He worked with molecular biologist Ray Wu at Cornell, developing a way to make a small snippet of DNA and use it to detect the messenger RNA encoding a specific protein—routine now, but pioneering in the mid-1970s.

As an advisor, Wu was relatively hands off. He let Szostak pursue experiments that interested him. But, “he was always there to talk about things when I needed someone to talk to,” Szostak recalls. After a postdoctoral fellowship in Wu’s lab, Szostak landed a faculty job at Harvard Medical School in 1979, at the relatively young age of 26.

There, Szostak adopted a management style similar to Wu’s. He assigned each graduate student and postdoc a project in a distinct area of biology. “He had people spread out so they really enjoyed their creativity,” says Terry Orr-Weaver, Szostak’s first graduate student at Harvard, now at the Massachusetts Institute of Technology (MIT). But that also meant they were solely responsible for whether a project succeeded or failed. “It’s really tough training, but it’s the best kind,” she says.

Orr-Weaver remembers a crowded laboratory, with graduate students and postdocs sharing lab benches and squeezed into just two bays. Szostak would often head to the same lab benches to do his experiments. The lab “smelled great, like a bakery” from the yeast they all worked on, and there was tremendous intellectual ferment as well. “He had all these great ideas. There was this kind of buzz about the place,” Orr-Weaver recalls.

Szostak’s telomere transplant experiment contributed to that buzz. As he stood waiting in the hallway outside the darkroom that day, the x-ray film emerged, dropping from the developer into his hands. “All the DNA was in a single band, which meant that it had to be replicating as a linear piece of DNA,” Szostak recalls. He showed the film to everyone in the lab, including Orr-Weaver. In those days, Szostak was very slender, with a long ponytail and a scraggly beard, and quiet, Orr-Weaver recalls. “I can’t imagine him ever raising his voice. But when something worked, his face beamed with excitement.”

Once Szostak knew that *Tetrahymena* telomeres functioned in yeast, there were loads of experiments to do. He excised one of the two *Tetrahymena* tips from the linear DNA, for example, and then fished for pieces of yeast DNA that stabilized it—and isolated yeast telomeres. Janis Shampay, a graduate student in Blackburn’s



Today, Jack Szostak is focused on creating a cell from scratch. His lab team is working to build a self-replicating nucleic acid genome and put it into a fatty acid vesicle, something he calls a “protocell.”

lab compared the sequences of *Tetrahymena* and yeast telomeres that had been maintained in yeast and learned that yeast cells were adding a characteristic DNA sequence of their own to the transplanted *Tetrahymena* telomeres. This finding suggested an enzyme existed in the cell that built up telomeres—an enzyme that Carol Greider, as a graduate student in Blackburn’s laboratory, would later isolate and name telomerase. Greider is now at the Johns Hopkins University School of Medicine.

A graduate student in Szostak’s lab, Andrew Murray, now a professor at Harvard University, combined yeast telomeres with several other essential pieces of chromosomes, thereby creating yeast artificial chromosomes, which would be used to map and clone human genes for the human genome project.

Vicki Lundblad, then a postdoc in Szostak’s lab and now a professor at the Salk Institute, identified a yeast mutant in which telomeres grew shorter with each generation. After more than 50 generations, the cells sickened, lost chromosomes, and died. “That made us think that perhaps what happened in aging was that the telomeres were getting too short,” Szostak says. This turned out to be true in cultured human cells, though the jury’s still out about the role telomere shortening plays in human aging.

Other intriguing results followed. In cells from normal adult tissues, telomerase is repressed. A therapeutic door opened when Bill Hahn’s team at the Dana-Farber Cancer Institute showed that expressing telomerase can help make normal adult cells cancerous, and drug companies have pursued telomerase inhibitors for use in cancer chemotherapy. “Jack didn’t work on telomeres all that long,” says Hahn. But his ideas about telomeres “were the seminal ideas, at the beginning of the field.”

Life’s Murky Beginning

Although important questions remained about telomeres in the late 1980s, Szostak was ready to move on. He knew that scientists streaming into the telomere field would follow up. Says Szostak: “My approach is to find something off the beaten path.”

In the mid-1980s, that meant RNA. Tom Cech, who later became president of HHMI, and Sidney Altman had just discovered that RNA could catalyze chemical reactions inside cells, just like today’s protein-based enzymes. Biologists proposed that the earth’s earliest life forms lived in a so-called “RNA world,” in which RNA was both a carrier of hereditary information—a role played today by DNA—and a ribozyme, or catalyst of chemical reactions. “What made the whole ribozyme field so exciting is that it provided a new model of the origin of life,” Szostak recalls.

Over the next decade, Szostak’s team worked out methods to evolve new and useful RNAs, and later DNAs, from scratch. Jon Lorsch, then a grad student in the lab and now a professor of biophysics and biophysical chemistry at the Johns Hopkins School of Medicine, recalls “an interestingly laid-back and fun

place,” with Szostak “spending a lot of time sitting on the couch in his office reading papers and thinking great thoughts.”

Lorsch himself took lab-evolved RNAs that bound ATP (the cell’s energy-supplying molecule) and evolved them further in test tube experiments into RNAs that actually catalyzed chemical reactions on ATP. “Even though everyone else said it was crazy, Jack knew it was going to work.” Szostak’s decade of work on RNA evolution shed light on how RNA molecules might have evolved and how early cells could have evolved increasing metabolic complexity.

Shortly after being named an HHMI investigator in 1998, however, Szostak began contemplating an even more fundamental problem. How did the earth’s first cells form from a brew of organic chemicals? For about a year, beginning in 2000, Szostak, David Bartel, a former student of Szostak’s and an HHMI investigator at MIT, and Pier Luigi Luisi of the Swiss Federal Institute of Technology in Zurich brainstormed, discussed, and debated this question. In an important theoretical paper published in *Nature* in 2001, the three argued that membrane biophysics and test tube evolution of RNA and DNA had advanced enough to envision creating cells from scratch in the laboratory. The title of the paper was “Synthesizing Life.”

“Having put all those ideas down on paper, I thought that it was incumbent on us to actually explore them experimentally and see where it led,” Szostak says.

Building the Protocell

Today, Szostak’s 18-member team operates from an airy, sunlit laboratory at Massachusetts General Hospital, a far cry from the cramped space of his first years at Harvard Medical School. At his lab bench, Itay Budin, an easy-going graduate student, uses a syringe to draw a volume of cloudy lime-green solution from a flask, inserts its needle into a small, stainless steel contraption containing a paper filter, and inserts a second glass syringe into its other side. Then, he pushes hard on the plunger of the full syringe with the heel of his right hand, forcing the liquid through the filter. The plunger on the other side slowly fills with liquid, which is now clear. Budin is preparing microscopic sacs of lipids called vesicles—as small as one-thousandth the width of a human hair—that can serve as membranes for the simple model cells that Szostak hopes to synthesize.

After contemplating the basic properties of life, Szostak, Bartel, and Luisi had realized that the simplest possible living cells—which they dubbed “protocells”—required just two components: a nucleic acid genome to transmit genetic information encapsulated by a lipid sac that could itself grow and divide. Szostak set out to build a protocell in the laboratory.

Budin is part of a contingent of Szostak’s team that is building the protocell’s lipid sac. Modern cell membranes are relatively impermeable and require an array of protein pumps and channels

“I can’t imagine him ever raising his voice. But when something worked, his face beamed with excitement.”

Terry Orr-Weaver

to transport molecules from one side to the other. But Szostak’s team has developed sacs for their protocells that are composed of fatty acids—simple precursors of today’s membrane components that are far more permeable and would have allowed primitive cells to “feed” on simple molecules.

Fatty acid vesicles can also divide into daughter cells, as any cell must. In March 2009, Szostak and graduate student Ting Zhu reported in the *Journal of the American Chemical Society* that adding fatty acids to vesicles caused them to morph into long filaments. But, remarkably, gentle shaking severs these filaments, and the pieces become daughter vesicles. Szostak calls the work a “breakthrough” because it provides a plausible mechanism by which a small force—say, the force of wind moving water in a pond—would cause the membranes of primitive cells to reproduce.

A second contingent of Szostak’s lab is working on the protocell genome. For a protocell to evolve in a Darwinian fashion its genome must replicate accurately, yet occasionally make mistakes. Bartel’s team at MIT has evolved a replicase—an RNA molecule that begins to catalyze its own replication in test tubes—though better replicases are needed. In contrast, postdoc Alonso Ricardo and other Szostak lab members are devising protocells that need no replicases. They’re fine-tuning chemical cousins of RNA and DNA that assemble spontaneously when provided with their respective building blocks, called nucleotides.

In 2008, Szostak’s team reported in *Nature* that they created protocells that combine two of the essential properties of life. Fatty acid vesicles containing DNA could “feed” on nucleotides outside them, and then the ingested nucleotides could chemically replicate the DNA fragment inside. The findings are crucial, Szostak says, because researchers had thought that nucleotides were too bulky to make it through a cell membrane unaided.

To be truly alive, according to the accepted scientific definition, protocells would also need to evolve via Darwinian natural selection. To do that, they’d need at least one trait specified by their genome that would let one protocell outcompete another. In 2004, Szostak and graduate student Irene Chen provided a proof of principle that such test tube evolution was possible. Physical and chemical forces alone, they found, make vesicles with more

RNA grow bigger faster—and steal lipids from adjacent vesicles with less RNA. The results suggested that early cells that reproduced their RNA faster would have had a competitive advantage, and early cells with just a single gene—perhaps an RNA gene that could copy itself—could have undergone Darwinian evolution.

They also suggest that if Szostak can succeed in building a self-replicating nucleic acid and put it into a fatty acid vesicle, he’ll have a living, self-replicating protocell.

Life with Nobel

At 4:45 in the morning on October 5, the phone rang at Jack Szostak’s house, waking Szostak and his wife, Tel McCormick. It was Göran Hansson of Sweden’s Karolinska Institute, who told Szostak that he, Carol Greider, and Elizabeth Blackburn had won the Nobel Prize for their groundbreaking early work on telomeres.

Szostak had little time to react. At 5 a.m., there was an interview with someone from the Nobel Foundation’s website. By 6 a.m., a photographer from Harvard arrived, who shot photos of Szostak as he fielded call after call. When he finally made it to the lab, he saw balloons, streamers, and high-spirited lab members. There was a 10 a.m. party in the conference room with champagne, cheese, and crackers; lunch with the hospital’s president; a visit to the statehouse to meet the governor, and nonstop interviews with newspaper and television reporters. It was enough to make anyone’s head spin.

But not Szostak’s. The next morning, Szostak rushed into his group’s weekly lab meeting, where graduate student Ting Zhu would present his recent findings on lipid vesicles. An animated discussion followed, in which young chemists, biophysicists, and Szostak himself interrupted with questions and made theoretical and technical suggestions. It was a typical lab meeting.

Still, for weeks reporters and dignitaries remained in hot pursuit. There was a documentary for the BBC, a thick stack of requests for autographs, even a congratulatory note from President Obama, followed by an invitation to the White House. Nearly a month after the event, a reporter asked Szostak about his post-Nobel life. Was he eager to get back to science after the Nobel hullabaloo? Replied Szostak: “I definitely am.” ■