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HHMI Researcher Jack Szostak Wins 2009 Nobel Prize in Physiology or Medicine

The Nobel Assembly at the Karolinska Institutet announced this morning that the 2009 Nobel Prize in Physiology or Medicine was awarded to Jack W. Szostak, a Howard Hughes Medical Institute investigator at Massachusetts General Hospital and Harvard Medical School, Elizabeth Blackburn of the University of California, San Francisco, and Carol Greider of the Johns Hopkins University School of Medicine. The three were honored for “for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.”

According to the Royal Swedish Academy, this year's Nobel Prize in Physiology or Medicine was awarded to three scientists for solving a major problem in biology: how chromosomes can be copied in a complete way during cell divisions and how they are protected against degradation. The three scientists are being recognized for the discovery of the specialized process by which the ends of chromosomes are synthesized, and the discovery of the enzyme telomerase. Their work has revealed how organisms rely on the enzyme to protect their genome from degradation, and laid the groundwork for later studies linking telomerase to cancer and aging-related ailments in humans.

The long, thread-like DNA molecules that carry our genes are packed into chromosomes, the telomeres being the caps on their ends. Telomeres provide chromosome caps that safeguard our genetic heritage, and as such they are essential for human life. Elizabeth Blackburn and Jack Szostak discovered that a unique DNA sequence in the telomeres protects the chromosomes from degradation. Carol Greider and Elizabeth Blackburn identified telomerase, the enzyme that makes telomere DNA. These discoveries explained how the ends of the chromosomes are protected by the telomeres and that they are built by telomerase.

In the 1970s and 1980s, Szostak, Blackburn, and Greider's work solved a longstanding puzzle of how cells prevent the loss of crucial genetic information in the face of the shortening of their chromosomes that occurs each time they divide.

In preparation for cell division, cells must produce new copies of their chromosomes. Each time the enzyme that copies DNA performs this task, it leaves a few of the DNA building blocks, or nucleotides, off each end of the new molecule. Scientists knew that cells must have a way to protect their genes from this gradual erosion to ensure survival through repeated cell divisions.

Working in single-celled organisms, Szostak and Blackburn demonstrated that the ends of linear DNA molecules had some unusual characteristics. In her studies of a pond-dwelling organism called *Tetrahymena*, Blackburn had found that the same six-nucleotide sequence was repeated 20 to 70 times at the tips of each chromosome—in regions known as telomeres. Szostak, a yeast geneticist, and Blackburn decided to see if these sequences would work as telomeres in yeast. Ordinarily, when scientists added linear pieces of DNA to yeast cells, the cells would destroy the DNA or turn the linear fragments into circular molecules. But when Szostak and Blackburn tacked on the repetitive *Tetrahymena* end-sequences to these linear DNAs, they remained intact and replicated as linear DNAs. This experiment showed that the biochemical machinery involved in telomere replication had to be very broadly conserved, and opened the door to studies of telomere biochemistry and genetics in yeast and other organisms.

The two researchers found that yeast, too, had a characteristic repetitive sequence capping the ends of its chromosomes. And when they discovered that yeast cells added their own telomere sequence to the *Tetrahymena* telomeres that they had introduced, they knew that the telomeres were not being maintained through the usual mechanism of DNA copying. They speculated that instead of the DNA polymerase, which produces most of a cell's DNA by copying it directly from another DNA molecule, a separate enzyme must add telomeric sequences to chromosome ends. Subsequent work by Blackburn and Greider identified that enzyme, which is now known as telomerase, and showed that it was composed of both a protein and a molecule of RNA that serves a template for telomere synthesis.

In Szostak's lab, further work with yeast demonstrated just how vital telomerase activity is for cells. Szostak and postdoctoral fellow Victoria Lundblad identified genetic mutants of yeast that were unable to elongate their telomeres. They called one such mutant EST1, for “ever-shorter telomeres”—the first of many genes found to be essential for maintaining telomeres. Without this ability, telomeres shrank with each cell division. Eventually, after many cell divisions, the cells started to lose essential genetic material, and stopped being able to divide. This was the first link between the molecular biology of telomeres and cellular senescence, the aging and death of cells.

Since Szostak's, Blackburn's, and Greider's early work on telomerase, researchers have found that the enzyme is closely tied to human cancers and aging. While the enzyme actively elongates telomeres in rapidly dividing cells, such as those in an embryo, in most healthy adult cells, telomerase is

shut off. Thus, telomeres slowly shrink during cell division. This normal process is thought to be associated with some age-related ailments, but is important to help limit cells' lifespan. Cancer cells, however, usually find a way to turn telomerase back on, achieving a dangerous immortality. In fact, the enzyme is overactive in as many as 90 percent of human tumors. Researchers are actively pursuing drugs that target telomerase as a way to treat a wide variety of cancers.

Szostak has since shifted the focus of his lab to study fundamental questions of how life began. Szostak and other scientists suspect that RNA may have existed long before DNA or proteins, because it not only carries genetic information, but might also be able to catalyze its own reproduction. To understand how such an RNA world might have evolved, Szostak recreates the forces of evolution in the laboratory, screening vast number of RNA molecules for those that can catalyze chemical reactions in a test tube. Building on these studies, his lab is now working toward the construction of a simple artificial cell that can grow and divide as well as adapt to its changing environment.

How Did Life Begin? Scientists may never know exactly how a swirl of chemicals came together to form the first living organisms some 4 billion years ago, but Jack Szostak is working to recreate a hypothetical model of this process in the laboratory. By building simple cell-like structures in a test tube, he and his colleagues are attempting to establish a plausible path that led primitive cells to emerge from simple chemicals. Ultimately, Szostak hopes to answer fundamental questions about evolution's earliest steps.

At the outset of his career, Szostak made pioneering contributions to the field of genetics. His discoveries helped clarify the events that lead to chromosomal recombination—the reshuffling of genes that occurs during meiosis—and the function of telomeres, the specialized DNA sequences at the tips of chromosomes. He is also credited with the construction of the world's first yeast artificial chromosome. That feat helped scientists to map the location of genes in mammals and to develop techniques for manipulating genes.

But a Nobel Prize–winning discovery in the 1980s by former HHMI President Tom Cech and Sidney Altman propelled Szostak down a new research path. The pair independently demonstrated that RNA, the sister molecule of DNA, can catalyze certain chemical reactions inside cells, a job previously thought to be the exclusive domain of proteins. Until then, RNA was thought to have just one function: storing the genetic information cells need to build proteins. This new revelation about RNA's dual role suggested to some scientists, including Szostak, that RNA likely existed long before DNA or proteins because it might be able to catalyze its own reproduction. Their discovery made it easier to think about the origin of life, Szostak says. "They inspired me to try to think of ways to make RNAs in the lab that could catalyze their own replication."

By 1991, Szostak had shifted the entire focus of his lab to evolving new functional RNAs and other molecules in a test tube. As the basis for his work, Szostak developed a technique called *in vitro* selection to study the evolution of biological molecules. This method screens vast numbers of molecules for a predetermined function, such as the ability to catalyze a specific chemical reaction or bind a target molecule. Those that don't fit the desired profile are filtered out and the process is repeated over and over again until researchers find the molecule that does a particular job.

Using *in vitro* selection as a way to apply the forces of natural selection in a laboratory setting, Szostak and his colleagues evolved RNAs that bind to ATP, a common biological substrate, from a massive library of 1,000 trillion random RNA sequences. Such artificially evolved RNAs that bind to target molecules are now known as aptamers, and they have many potential applications in the diagnosis and treatment of diseases and as biosensors. Szostak's team has also used *in vitro* selection to evolve catalytic RNAs, called ribozymes, from trillions of random-sequence RNA molecules. "Many new ribozymes have now been evolved by *in vitro* selection," Szostak says. "The range of chemistries these artificially produced ribozymes can catalyze is much greater than that carried out by ribozymes found in living cells. It raises the interesting possibility that in an earlier era, ribozymes might have played a wider role than they do today." Szostak is also investigating *in vitro* selection for its ability to identify small molecules that bind specific target proteins. If successful, the technique may provide a streamlined way to pinpoint potentially useful drugs to fight disease.

Today, Szostak's main focus is the construction of a simple, artificial cell that can grow and divide as well as evolve in a Darwinian sense to adapt to its changing environment. To do this, he is attempting to make and then combine two self-replicating systems: a nucleic acid (such as RNA or DNA) that can transmit genetic information and a simple membrane-bound vesicle that keeps the nucleic acid chains from drifting apart. A major challenge is coordinating the growth and division of the membrane-bound vesicle with the replication of its contents. Szostak has found that the nucleic acids themselves can drive the growth of the fatty acid membrane; as they replicate, the internal osmotic pressure increases, swelling the vesicle and stretching the membrane so that it absorbs fatty acids from other vesicles that are under less internal pressure. Cells with faster nucleic acid replication should therefore grow faster than cells with slower nucleic acid replication. In this way, simple physical principles coordinate the replication of the nucleic acid genome and the replication of the rest of the cell structure, leading to the emergence of natural selection and Darwinian evolution based on competition between cells.

Dr. Szostak is also Professor of Genetics at Harvard Medical School and Alexander Rich Distinguished Investigator at Massachusetts General Hospital, Boston.