

SEPTEMBER 17, 2006

Jack Szostak Receives Lasker Award for Basic Medical Research

The Albert and Mary Lasker Foundation announced today that Howard Hughes Medical Institute investigator Jack W. Szostak at Massachusetts General Hospital, Carol W. Greider of Johns Hopkins University and Elizabeth H. Blackburn of the University of California, San Francisco, have been awarded the 2006 Albert Lasker Award for Basic Medical Research.

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.

Including Szostak, nine current HHMI investigators have won the Lasker Award, the nation's most distinguished honor for outstanding contributions to basic and clinical medical research. Since 1962, more than half of the recipients of the Lasker Award for Basic Medical Research have gone on to receive a Nobel Prize.

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.

The Lasker is a fitting reward for these three terrific scientists and their trail-blazing discoveries of the mechanism of replication of chromosome ends, said Thomas R. Cech, president of HHMI and 1988 Lasker awardee. Telomeres provide chromosome caps that safeguard our genetic heritage, and as such they are essential for human life.

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 as 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.