

## NESACS Member Interviews

### Dr. Jack Szostak



#### Dr. Jack Szostak: An Interview

When Jack Szostak was on vacation with his family in Iceland in 2006, he received a call from Dr. Joseph Goldstein, Chairman of the Lasker Awards Jury. The prestigious Lasker Prizes are awarded annually in two categories: Basic Medical Research and Clinical Medical Research. Dr. Szostak assumed that Dr. Goldstein was calling him to write a recommendation for someone who was being considered for a Lasker Prize, and “I was on vacation, so I didn’t want to deal with it,” said Dr. Szostak.

As Dr. Szostak later found out, he had been awarded the 2006 Lasker Prize in Basic Medical Research, together with Dr. Elizabeth Blackburn and Dr. Carol Greider. The three scientists were awarded this prize, “for the prediction and discovery of telomerase, a remarkable RNA-containing enzyme that...maintains the integrity of the genome,” according to the text of the Lasker Prize. The discovery of telomerase sheds important light on how chromosome ends are maintained. In addition, the initial telomerase studies performed by these researchers have sparked discoveries that telomerase has a role in cancer and age-related degeneration.

Once the 2006 Lasker Prize was conferred, the announcement that the same three researchers won the 2009 Nobel Prize in Physiology or Medicine was not a complete surprise to Szostak. Nonetheless, one of the interesting aspects of the Nobel Prize was that it was conferred for work that Szostak performed 20 years ago, for research that has little relationship to his current research interests. “It was extremely nice to

have that work recognized,” Szostak said, “but I had to go read all of those papers again.”

Dr. Szostak currently runs a research group at Massachusetts General Hospital comprising 10 graduate students and post-doctoral researchers who are studying questions that relate to the origin of life. Specifically, the Szostak lab is researching the design and synthesis of an artificial “protocell,” that will be capable both of dividing into “daughter vesicles” and of replicating its genetic material. Researchers in the lab have already developed a reasonably good vesicle replication system.

Szostak hopes that in the next 5-10 years they will develop a good nucleic acid replication system and a functioning “artificial cell.” “I think that is a feasible goal in the time I have left,” Szostak said. Even if he does not reach this goal, though, Szostak is not concerned, because “there are still lots of interesting things to learn along the way.”

Most of the funding for Szostak’s research comes from the Howard Hughes Medical Institute (HHMI), a non-profit medical research organization that funds scientists across the USA and internationally. The Institute provides direct funding to researchers, including Szostak, allowing them the freedom to set their own research directions. Even before becoming an HHMI Investigator, Szostak decided to move to MGH from the Dana-Farber Cancer Institute in 1984 to take a position in which all his research was completely funded as part of an industry-academia collaboration over a ten year period. Szostak also receives some funding from the NASA exobiology program and from the National Science Foundation.

The freedom from grant applications is particularly useful in a field like Szostak’s, where other scientists may have difficulty understanding the importance of origin-of-life research. “Initially people are puzzled,” Szostak said, because they want to know how Szostak’s group can reach any definitive conclusions about life on prehistoric earth.

However, “all we are trying to do is think about what is possible.”

There has been a tremendous resurgent public interest in the study of the origin of life over the last few years, sparked in part by the discovery of extremophiles. “There is life everywhere,” said Szostak, “in the deep seas, under rocks, everywhere you can imagine.” At the same time, “every day there are new planets being discovered around stars. Of course you will wonder if there might be life somewhere else.”

The general state of science funding in this country is “terrible,” according to Szostak, in that it really “discourages innovation and doing risky things.” The constant cycle of grant writing and revising is also a tremendous waste of time. One

potential way to change the funding mechanism would be to “fund people and not projects,” said Szostak. “Take someone who has been productive, and let’s give them money to do what they think is important.”

The idea of funding people and not projects is the primary mechanism by which HHMI works, in that funding is provided for researchers to pursue any project of interest. “It [funding people] would be just as competitive,” said Szostak, “and we would actually get something interesting done.”

Dr. Szostak is particularly frustrated by people who are interested in science only for the potential “useful” applications. Szostak’s Nobel Prize winning telomerase research had virtually no applications at the time that it was discovered. “It was just a puzzle that we wanted to solve,” said Szostak. “It was pure curiosity about how something works.” Now, twenty years after this discovery, researchers have found a whole host of applications for telomerase research that substantially impact disease research and treatment. “You never know where there might be applications,” said Szostak

Szostak’s perspective on chemistry may be unique because his background and training is not in synthetic chemistry. In fact, Szostak was originally trained in yeast genetics, which is when he made the Nobel-Prize winning discovery that yeast without telomerase eventually stopped reproducing. However, after Szostak had spent some years studying yeast genetics, he felt that the field was getting more crowded. “Anything we did was going to be done by someone else sooner or later,” said Szostak.

Szostak sat in on a variety of courses at Harvard in an attempt to find a new research focus. In one of those classes, taught by Dr. Jeremy Knowles, Szostak learned about the interesting mechanistic aspects of enzymology. The recently discovered ribozymes seemed like a particularly interesting target for study. “I was surprised more people weren’t going into this field,” Szostak said. “It was the perfect mix of a not-crowded field with interesting questions that were technically approachable.” As a result, Szostak decided to pursue this field and ultimately switched his laboratory over to RNA biochemistry, which eventually led him to study the chemistry of the origin of life.

For somebody like Szostak who has a non-chemistry background, what strikes him about synthetic chemistry is really “how primitive it really is,” said Szostak. “We can draw a nucleic acid with one minor structural change...and it might take two years to learn how to make that compound efficiently.” If compounds were easier to synthesize, it would have a huge impact on biology, materials science, and a variety of other applications.

Szostak, who describes himself as “not the most organized person in the world,” nonetheless gave time-management advice to new chemistry researchers. “Avoid getting in a situation where you are constantly going from crisis to crisis or demand to demand,” said Szostak. “Spend some time with a blank piece of paper and think about the next experiment or the next problem you should be investigating.”

The intense demands of academic life are compounded for those who also want to spend time with their families, but one advantage to academia is that the daily schedule is fairly flexible. Szostak indicated that his schedule sometimes allows him to take off in the afternoon to watch his sons’ sports games. “I don’t want to give the impression that it’s easy,” Szostak said, “but it is definitely doable.”

In the aftermath of winning the Nobel Prize, Szostak’s schedule has become even more demanding in some respects. “I have a lot of opportunities to talk to students and help the institution with fundraising,” said Szostak, which he described as “very rewarding.” Nonetheless, Szostak declines a fair number of speaker requests in the interest of spending time with his family and maintaining an active research lab. “I wasn’t about to retire and spend my life traveling around the world,” Szostak said. “It would be too easy to do that.”

Interview by Mindy Levine Ph.D.