# "Long Live" the Winners of the 2009 Nobel Prize in Physiology or Medicine

Guoliang Yu

In early morning on October 5, 2009, telephone ring woke me up. It was Professor Weijun Pan, my longtime friend and a colleague in the Blackburn lab. "Liz wins Nobel Prize! She will be sharing the Nobel Prize with Carol Greider and Jack Szostak. I waited several hours to call you because the announcement came at 2 AM in the morning west coast time." Pan exclaimed. "Really?! I was dreaming about it just a few days earlier! I am getting up now to call Liz." I was widely awake and excited. After several unsuccessful tries to call Liz to send my congratulations, Liz called me back in the afternoon. She thanked me for my work in her lab that led to the honor. Later, watching her Nobel Lecture, I noticed that my article published in Nature was referenced in 9 of the 72 slides. What else can make me feel more proud? Not surprisingly, when interviewed by The Scientist in March 2003, our 1990 Nature paper was cited as the paper of which she was proudest.

*Elizabeth H. Blackburn receiving her Nobel Prize*

I spent my first 6 years in the US in Blackburn's lab as a graduate student. There are so many details to refresh and so many stories to tell. But now I do not know where to start. So I decided to pick up some pieces from the interviews and from the news, and use my best judgment to filter the information and present a true Liz in this article. What I benefited the most from being her graduate student was Liz's daily mentorship to guide me to become a critical thinking scientist and to become someone who contributes to society.

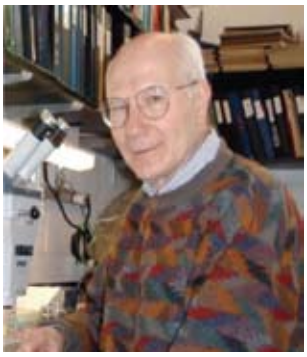
## The Significance of Teleomere and Telomerase

*Add a caption.*

The 2009 Nobel Prize in Physiology or Medicine, awarded to UCSF's Elizabeth Blackburn, PhD, along with Carol Greider, PhD, of Johns Hopkins University School of Medicine and Jack Szostak, PhD, of Massachusetts General Hospital, recognizes the importance of the most fundamental kind of basic biological science. The three scientists were recognized for key discoveries that help explain how our genes remain intact through repeated cell divisions. They study the DNA end caps – called telomeres – within gene-bearing chromosomes inside living cells, and also study the enzyme telomerase, which makes telomeres and keeps them from being whittled away through repeated cell divisions. Telomeres protect DNA from fraying, like plastic shoelace tips protecting a shoelace. The gradual progress of science has revealed that they also do much more. Growing evidence continues to point to a role for telomere length in aging and major diseases such as cancer.

### A Science Traveler

*Fred Sanger*



*Joe Gall*

*Carol Greider*

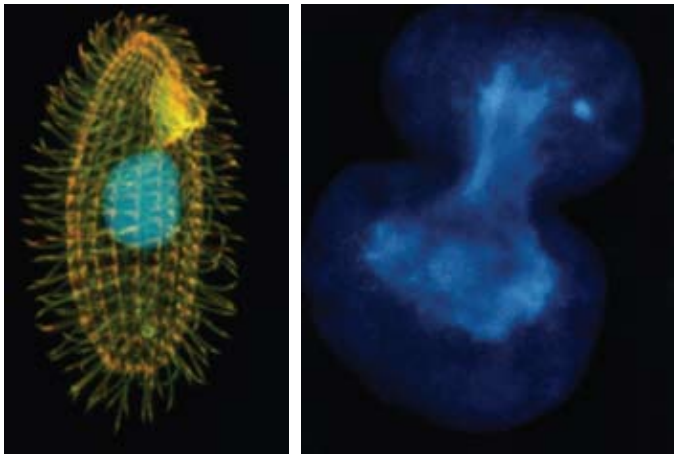
I always believe that in order to seek the wisdom and be successful either in science or art, one has to travel far away. The journey that has brought Liz to Stockholm was long. Liz told me that all her parents and siblings were medical doctors and she was an outlier. She travelled from Tasmania, Australia, to study in the UK for her PhD and then in the USA for postdoctoral training. She was a graduate student with Fred Sanger, a two-time Nobel Prize recipient in Cambridge University in UK. She met John Sedat, her husband, there. Liz said she first really became interested in science in high school, when she started reading textbooks describing "ideas of how the molecules of life work." That got her thinking about the huge implications of understanding basic cellular biology, the field to which she would devote the next four decades of her life, she said. Plus, she joked, she wasn't skilled enough to make a career out of her other passion, playing the piano, thus a career in science seemed like the most logical path. Liz began her study of Tetrahymena, a single-celled protozoan, as a postdoctoral fellow in the lab of Joseph G. Gall, at Yale University. She brought to the lab a thorough understanding of the latest techniques for spelling out sequences of DNA code. Liz started up her own lab at UC Berkeley in the early 1980s. Weijun was a visiting professor from Peking University who published the first two papers in Cell. Liz moved to UCSF in 1990, the same year I left her lab to pursue my postdoctoral training at Harvard University in Fed Ausubel's lab. After I left her lab we continued working on an experiment that was eventually published in Cell. Liz has expanded her studies to explore the roles of telomeres and telomerase in cancer, aging, as well as stress and stress-related illnesses.

### A Pedigree of Nobel Family

I knew Liz would win the Nobel Prize sooner or later. Liz had been nominated for Nobel Prize several times in the past and had received all possible scientific awards on the earth. Besides, she was always associated with Nobel Laureates. Her PhD advisor Fred Sanger won Nobel Prize twice for discovering DNA and protein sequencing methods. Her postdoctoral advisor Joe Gall won the Larsker Award, which is also known as the American Nobel Award. Her good friends Tom Cech and Jack Szostak also won Nobel Prize. Now her graduate student Carol Greider shared the Nobel Prize with her.

### A Small Single Cell Organism Led to the Prize

A tiny pond organism called Tetrahymena thermophila became the key to the understanding of telomeres and to the discovery of telomerase. The findings in this organism have led to medical implications that reach into the realms of human diseases and aging. In the lab we used to call it "hairy potato." As a ciliated protozoan, Tetrahymena thermophila exhibits striking nuclear dimorphism: two types of cell nuclei, a large, somatic macronucleus and a small, germline micronucleus, exist in a single cell at the same time and carry out different functions with distinct cytological and biochemical properties. This unique versatility allows scientists to use Tetrahymena to identify several key factors regarding gene expression and genome integrity. In addition, Tetrahymena possesses hundreds of cilia and has complicated microtubule structures, making it also an ideal model to elucidate the diversity and functions of microtubule systems. Because Tetrahymena can be easily cultured in a large quantity in the laboratory, for years it has been a great source for biochemical analysis of important enzymatic activities and for purification of sub-cellular components.



*Altered telemeres make it difficult for cells to divide*

### Following Her Heart

Though her family was supportive of her choice, Liz said she didn't always receive the full support of her friends, and some even tried to talk her out of becoming a scientist. However, Liz followed her heart and continued to pursue her love for science, which took her from the University of Melbourne, Australia, to the University of Cambridge, England, where she received her PhD. She then accepted a postdoctoral fellowship at Yale University and later a faculty position at UC Berkeley before joining the UCSF Department of Biochemistry and Biophysics in 1990. Along the way, Liz often said she benefitted tremendously from good mentors, particularly Joseph Gall, PhD, her principle investigator at Yale, who has made major contributions to the field of chromosome structure and function. Liz said she had modeled her own lab leadership after Gall's and others'.

"I just try to copy what they did in various settings," she said, emphasizing the importance of treating lab members with respect and remembering that "every graduate student is an individual and everybody has a different way of doing science, approaching science." In addition to her successes and career highs, Liz described periods of self-doubt and fear, such as her search for a job after leaving Gall's lab. "That was the most discouraging time for me," she said. "I was very much daunted and overcome by the challenges of finding jobs." Liz said she still kept a file filled with all of her rejection letters from various universities. "You have to kind of be tough," she said of weathering those disappointments.

### Balancing Work and Family

In reflecting on her career, Liz also tried to dispel some of the myths behind the idea of work-life balance, saying it was a worthy long-term goal, but not something that can be accomplished and maintained all the time.

"I understand family and career balance…and I think it can be over the years that the balance can be achieved, but not every single day necessarily," she said.

In her own life, she and her husband John Sedat, PhD, a professor of biochemistry and biophysics at UCSF, have prioritized different things at different times. When their son Benjamin was growing up, for example, the couple "just focused on science and family" and gave up going to the movies and restaurants, Liz said. Now that Benjamin is 22 and out of the house, there is more time to spend on such activities, she said. Right after Benjamin was born, I went to Liz's office carefully asked her if it was the right time for my wife and me to have an elder child. Her support was very strong. One year later, my old son David was born in the hospital of UCSF. Among many gifts she gave to David, one of the baby clothes was passed from Tom Cech (another Nobel Laureate) to Benjamin to David.

"Having intense relaxation is very important, such as traveling or something where you turn your mind off," she said, adding that such periods of escape can actually lead to greater creativity and productivity.

I think it's good to say, "Hey, I have my right to have a family. I'm not a failure as a scientist because I want a child." It's a very important message to send. Of course, it's always difficult, and it always requires very hard work. But it's always going to be that way, regardless of when you have your child. It'll just be a different set of factors that are being juggled. It's not easy, but it's rewarding. The family is very rewarding, and science is very rewarding.

### Mentorship to the Young

Many of her postdoctoral fellows and students would agree with me that working in Liz's lab was such a pleasure. We had fun almost every day. Aside from exciting experiments that led to many publications of some high profile papers, I enjoyed daily stimulation of "the theory of the day". Several times a week, a group of us walked cross Berkeley campus to visit Café Roma on Bancroft Ave. I learned how to appreciate café laute, café aulate and café moca. More importantly I learned how to think like a scientist and how to challenge someone in science. Liz was like a mother to me, and she cared about my wellbeing and growth.

### Citizen's Responsibility

Liz taught me to take responsibilities to society by sharing scientific knowledge and coaching young people to do the same. One time, responding to my

*My Graduation Ceremony*

request about starting a company using her discovery in telomere and telomerase, Liz surprised me by saying that her knowledge had come from the people, tax payers' money, and she could not use it for personal financial gains. Although I could not fully appreciate her comments, at the time they were very genuine to me and had put a deep imprint in my mind. I know that Liz has debated with herself over how to translate basic research to applied sciences and that she has given up many opportunities to be funded by industry or benefit financially from her discovery. I always wonder if her mind has altered in this regard. In 2004, the world was shocked when George W. Bush dismissed Liz from the President's council on bioethics after she objected the council's suppressing stem cell research and protested the suppression of relevant scientific evidence in the council's report.

**Comments from Scientific Leaders**

Princeton University President Shirley Tilghman: "Today's announcement of the Nobel Prize in Physiology or Medicine to Liz Blackburn, Carol Greider and John Szostak recognizes their path-breaking work to uncover the mechanism by which chromosomes maintain their ends," Tilghman said. "I have taught their seminal papers for years to illustrate to students the importance of asking a fundamental question, choosing the right organism to study the question at hand – 'pond scum,' as Liz sometimes refers to Tetrahymena – and then inventing, if need be, new biochemical approaches. "

"Their work was beautiful on all three fronts," Tilghman added, "and would have deserved this prize even if the discovery of telomerase had not had such profound implications for understanding stem cells, cancer and aging. This is science at its very best."

Margaret Foti, PhD, MD (hc), who is chief executive officer of the American Association for Cancer Research (AACR), commented on the work of Blackburn, who is president-elect of that organization.

"Dr. Blackburn is a scientific pioneer who, along with AACR member Dr. Greider and Dr. Szostak, is revolutionizing the way we look at biology and translational science," Foti said. "Not only did the discovery of telomeres and telomerase propel cancer science forward on a grand scale, it is also changing the way we explore how to treat other types of disease and how to potentially prolong cell life."

Jeremy M. Berg, PhD, is director of the National Institute of General Medical Sciences, part of the NIH and a leading supporter of Blackburn's research. He said: "Dr. Blackburn's research, driven by curiosity, answered fundamental questions about a basic biological process now known to be involved in cancer and cellular aging. Her work has had a profound impact on many fields, and offers a classic example of how basic research can illuminate our understanding of health and disease in unforeseen ways."

Harold E. Varmus, MD, along with former UCSF Chancellor J. Michael Bishop, MD, won the Nobel Prize in 1989 for research at UCSF. He became NIH director during the Clinton Administration, and is now president of Memorial Sloan-Kettering Cancer Center. At UCSF, the Blackburn lab was next door to the Varmus lab, and for a time Blackburn was Varmus' department chair in the Department of Microbiology and Immunology.

"She's a totally wonderful person and a great scientist, and a great person to be doing science with," Varmus said. "She is enthusiastic about the work of others as well as her own work, and she is an inspiration to everybody, male and female."

"It's beyond dispute that her work on telomeres has revolutionized the way we look at chromosomes," Varmus added. "Those of us who are basic scientists, but who also are interested in disease and the amelioration of disease, find when we look at her work the importance of identifying significant and fabulously interesting problems in biology and working them out, regardless of whether the organism in question is of practical importance."

Elissa Epel, PhD, in the UCSF Department of Psychiatry has collaborated on research with Blackburn for several years. "She is at the same time a visionary, but practical thinker," Epel said. "This is paired with her generous mentoring and her devotion to discovery and to women in science. She has mentored a generation of researchers in the field of telomerase and telomere biology, which has grown exponentially."

"She's brilliant," said research collaborator Owen Wolkowitz, MD, of the UCSF Department of Psychiatry. "She knows telomeres and telomerase inside and out. She's meticulous in her science; she has an extremely high degree of integrity with her data. Working with her, and with Elissa Epel as well, has opened my eyes to an entirely new level of analysis – the ways in which subcellular functioning can affect the brain and behavior."

Peter Walter, PhD, a professor of biochemistry and biophysics and an investigator in the Howard Hughes Medical Institute, is a longtime UCSF colleague of Blackburn who headed the Department of Biochemistry and Biophysics until recently. "She has been a great role model," Walter said. "She has shown that women can have both a family and a great scientific career."