

Captivated by Chromosomes

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Scientists have a reputation for being driven, and Johns Hopkins University's Carol Greider is indeed driven—by curiosity. She pursues and champions what she calls “curiosity-driven science.” It led her to the 2009 Nobel Prize in Medicine for critical work characterizing the ends of chromosomes and discovering telomerase, the enzyme that attaches a repetitive sequence of the bases thymine and guanine on the ends of chromosomes, essentially buffering the gene-containing areas from damage. Curiosity has also driven her to a long list of discoveries in basic cell biology that shed light on cancer, degenerative diseases, and aging.

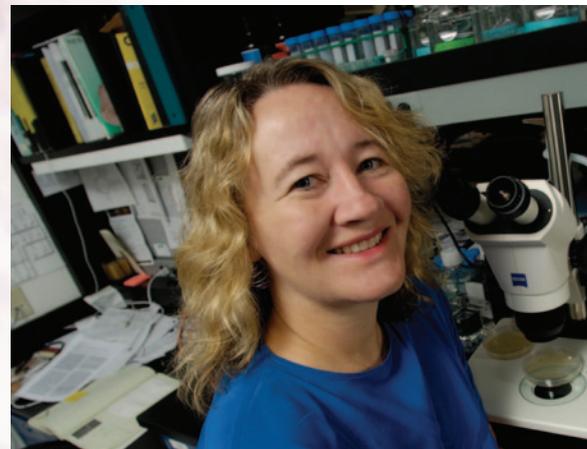
How I got hooked

As an undergraduate at the University of California in Santa Barbara, I started as a marine ecology major. But there's nothing like the experience of being in a lab and doing experiments to let you know whether you're actually interested in that field. It was through working in a number of different labs in my first two years that I found that I didn't like to think as a marine ecologist—I preferred more mechanistic, biochemical ways of thinking, such as treating proteins in different ways to see how they behaved.

So when I studied in Germany for my junior year in college and wanted some lab experience, I found a place in a lab at the Max Planck Institute for Biophysical Chemistry. There, I studied giant chromosomes from the larvae of a type of fly related to the fruit fly *Drosophila*, which is often used as a model system in biology. Giant chromosomes are 10,000 times bigger than most chromosomes, so we could actually dissect them out under a simple light microscope and stain them with various things to see what proteins were there. It was a lot of fun to have this hands-on experience, and I was captivated by the beauty of chromosomes.

Finding my niche

I was having so much fun doing molecular biology and biochemistry in the lab as an undergraduate that I decided I would also pursue it in graduate school. It was while I was interviewing for various graduate positions that I met with Dr. Elizabeth Blackburn, a faculty member at the University of California at Berkeley. She



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was studying how chromosome ends—which scientists predicted should get shorter and shorter and lose genetic material as a cell replicates, because the copying machinery of the cell can't work all the way to the end of the chromosome—somehow stay elongated. Dr. Blackburn and her collaborator Dr. Jack Szostak (both also joint winners of the 2009 Nobel) had found that in both *Tetrahymena* (related to paramecium) and baker's yeast, the ends were very simple repeats of the bases thymine and guanine—specifically, TTGGGG. These repeating, protective ends are called telomeres.

Drs. Blackburn and Szostak had made a very bold proposal—with only indirect evidence supporting it—that perhaps telomeres are maintained when this simple sequence is actively added onto the chromosome end, rather than being copied from another chromosome location. So that's what I set out to do for my PhD research in Dr. Blackburn's lab: see if we could find an enzyme that would add these simple telomere sequences onto chromosome ends.

We did. Our discovery of the enzyme telomerase, which ended up winning us the Nobel Prize, really started off as what we call curiosity-driven science. We wanted to understand the puzzle of how chromosomes stay long and keep their genes intact even though they “should” get shorter with each replication. Telomerase was the missing piece to the puzzle.

Following my curiosity

I've continued to follow my curiosity in my research, first by asking basic questions like “What if cells can't maintain chromosome ends?” We did experiments

in both yeast and mice to get rid of the telomerase so we could see what would happen. It turns out that telomerase is essential for all cells that have to divide many times: when telomeres are too short, cells die. We developed a mouse that lacks telomerase and began to study the diseases that the mouse was then susceptible to. This led us to understand that there are age-related degenerative diseases that appear in part because cells that divide many times over a lifetime need telomerase to maintain chromosome ends.

By starting off trying to understand the fundamental problems at the level of cells, we ended up finding mechanisms of major human degenerative diseases. For instance, we were very interested in the structure of the RNA component in telomerase. Shape is important because telomerase RNA has to interact with proteins to do its job. Over a period of five or six years, we did extensive biochemical experiments to clearly define its structure. Then we analyzed a whole lot of regions in the RNA by making a number of small changes in the RNA and observing the consequences.

Separately, the genetic research community discovered that dyskeratosis congenita—a disease in which affected people can develop bone marrow failure, cancer, or scar tissue build-up in the lungs—is caused by defects in telomerase RNA. By the time it became apparent to the human genetics community studying the disease that telomerase RNA was critical, we had a whole series of functional studies characterizing all the different components of telomerase. We had just been following our interest in trying to figure out how telomerase worked. But suddenly there was a large body of studies that were directly relevant to human disease.

Life after a Nobel

Winning the Nobel has not really changed my research. My job is to train the next generation of scientists and hopefully discover things along the way. So I run a research group that includes six to eight graduate students or postdoc researchers at any given time, as well as two technicians who help me run the lab. Everyone has a particular project they're working on, and the weekly data meetings I have with each of

my lab members are the most fun part of my week. Then, of course, I have to spend a fair amount of time designing and writing grants. I am also chair of the Department of Molecular Biology and Genetics at the Johns Hopkins School of Medicine, so I represent the 14 faculty members in my department to the university as a whole and to the medical school.

The Nobel has had a bigger influence in terms of my life. It certainly has given me an opportunity to meet people I wouldn't normally have and allowed me to have a soapbox to point out why it's important to fund the curiosity-driven research that will fuel innovation in the future.

Future of biology research

The biggest technology jump in molecular biology and genetics in the recent past has been the huge boom in sequencing. Although we don't do a lot of heavy-duty sequence analysis in my lab, we and all our colleagues in molecular biology are beneficiaries of that technology. What used to be a four-year project to identify and clone a single gene is now reduced to about two weeks.

Because of advances in sequencing technology, I often encourage developing scientists to go into genomics and bioinformatics. There has been a lag in graduate training of computationally minded people, and we don't have that many students entering our biology labs with training in computational areas. So I encourage people to keep up their math skills and think about areas where biology intersects with computer science and mathematics. That's what I would do if I were going to go back and do it again.

Your future

Getting hands-on experience early in my education was critical to my finding a field I loved. I was fortunate to have mentors before "mentoring" was a common idea, and they encouraged me to jump in to the lab. You may think you don't know how to get started, but all you need is one person to get some advice from, to ask who might be interested in having a student in the lab, and who can point you in the right direction. **i**

To see a short documentary about the work for which Drs. Greider, Blackburn, and Szostak won the Nobel Prize, visit www.nobelprize.org/nobel_prizes/medicine/laureates/2009/greider-docu.html.