**As one Harvard faculty member points out on page 519, the percentage of women in professorial posts in science is much lower than it is for men. This unfavorable ratio of women-to-men in senior jobs is fairly ubiquitous across biomedical research and is all the more surprising given that roughly equal numbers of men and women undertake PhD courses. There are few exceptions to this rule, but the field of telomerase research is one. This area of investigation appears to be dominated by women generally and one woman in particular, Elizabeth Blackburn.**

# Elizabeth Blackburn

According to the 'grandmother' of telomerase, Elizabeth Blackburn, it is not the case that women dominate telomerase research, it is more that this line of investigation has not seen the drop-off in women at higher ranks that happens in other fields. "In the telomerase field there's been a critical mass of women to sustain other women." That mass includes several female professors who were at one time under Blackburn's tutelage, such as Carol Greider, Janis Shampay, Vicki Lundblad, Drena Larson, Dorothy Shippen and Marita Cohn. The line continues with Blackburn's 'academic granddaughters' such as Maria Blasco and Chantal Autexier who are former students of Greider.


Elizabeth Blackburn

Blackburn, who has run her own lab in the School of Medicine at the University of California, San Francisco since 1990, illustrates the gender disparity, "I was the only woman chair of a department in the School of Medicine here at UCSF. I've rotated off the chair and now there's another woman chair in another department but there's still only one woman chair."

When we talked she had just returned from a meeting on telomerase at Cold Spring Harbor—the first for two years and one at which, she enthuses, "there wasn't a single poster I wasn't interested in." Although she says that attendees didn't go home "thinking that the world had been turned on its head," the meeting was highly satisfying from the point of view that the different molecular aspects of the field were consolidated. She explains: "Some of the proteins associated with telomeres and telomerase had been found in a ciliate here, a yeast there, and it was unclear whether they were an oddity of their systems. What has become clear is that all these components are found universally. The situation where everyone was wondering if their system was the obscure one fell away at the meeting, just as it did at one time with the RNA splicing field, where there used to be impassioned debates about whether yeast do it differently."

Few are better placed than Blackburn to arrive at such a conclusion. After moving from Fred Sanger's lab in the UK to Yale in the early 1980s, she worked as a postdoc with Joe Gall who had discovered a class of small, high-copy mini-chromosomes in *Tetrahymena thermophila*. When she began sequencing the ends of these chromosomes she identified telomeres for the first time, which she remembers as "…very strange, heterogenous DNA sequences at the ends, quite different to anything that we had seen before."

A few years later, Blackburn moved to the University of California, Berkeley to set up her own lab where she made the discovery that adding *T. thermophila* telomeric DNA to yeast resulted in the yeast acquiring that DNA. "So we had to roll up our sleeves, break open the cells and try and find out what this potential new enzyme was that was adding DNA. That was in 1984 and we published telomerase in 1985. The transformation came when I had my own lab because I was more adventurous and thought, 'now I can do crazy experiments.' NIH grants don't like you to say that you're going to look for an enzyme that nobody thinks exists." In short, she had kick-started an entire field of research by isolating the reverse transcriptase telomerase enzyme in a single-cell pond organism.

Since then, telomeres and telomerase have been linked to two main aspects of human health: cancer and aging. "The cancer link is looking strong," says Blackburn. "If you look at fully blown metastatic cancer, the chances are 80–90% that telomerase is upregulated." The burning question of the moment, she says, is whether telomerase drives cancer progression, which involves increasing genetic instability, or if it drives cell proliferation. The evidence weighs in favor of proliferation, but as is often the case with science, the answer isn't straightforward. "In fact, telomerase stabilizes telomeres and protects against one form of genetic instability. So ironically, telomerase may even be protective against cancer early on but once the cells have become genetically unstable then proliferation—a hallmark of a cancerous cell—is helped by telomerase."

The role of telomerase in aging makes for a more fantastic media story but is less definite scientifically speaking. Although the loss of telomeric DNA causes events such as delayed wound healing, and although adding telomerase to cells in culture extends their lifespan, telomerase's aging function in human cells *in vivo* is not clear.

Another complicated aspect of the enzyme is its position with respect to DNA damage. The old school of thought was that a telomere had to be distinguished within the cell from a broken end of DNA in order to shield it from the DNA repair machinery. But it now appears that DNA damage machinery is actually required for telomere maintenance. "How telomeric DNA material deflects the repair machinery into telomerase action is the molecular Holy Grail question," says Blackburn.

She is examining this issue and addressing more clinically oriented questions in her own lab. "We have a range of interests from looking at human xenografts in animal models to looking at the molecular action of telomeres and telomerase. For example, what can we do to telomerase in cancerous cells to throw them into apoptosis? We're also looking at the fact that telomerase is a ribonuclear protein, which puts reverse transcriptases into the realms of essential cellular enzymes. And we're studying changes in the RNA that are required for telomerase to be active."

With only 12 people in her lab, this is a lot of work, but the intensity reflects her style. "My goal is to keep a creative front edge with a lab the right size to have a mental nimbleness to keep ahead of the crowd. We don't monolithically pursue one thing. And anyway, I'm the grandmother of an extended family. You know you could never do it all yourself and there are so many questions to be answered, it's a very exciting feeling. I'm kept young by telomerase but for completely different reasons."

**Karen Birmingham, London**