Published February 7, 2011

People & Ideas

María Blasco: Keeping a cap on cancer and aging

Blasco is at the forefront of research on the function of telomeres in cancer and aging.

Telomeres, found at eukaryotic chromosome ends, are made up of tandem DNA repeats. In most cells, the number of telomeric repeats is reduced with each cell division. If telomeres are ever completely lost, the exposed chromosome ends are recognized as damaged DNA, activating a DNA damage response that can eventually lead to senescence or apoptosis. The rare cell that escapes these fates risks developing chromosomal aberrations or genomic instability and becoming cancerous (1).

The contribution that telomeres and telomerase—the enzyme that maintains telomere length in cells—make to preventing cancer (2) and aging (3–5) is the research passion of Dr. María Blasco at the Spanish National Cancer Research Center (CNIO) in Madrid. She entered the telomerase field just as it was taking off, as a postdoc in Carol Greider's laboratory at the Cold Spring Harbor Laboratory in New York (1). Her career took off as well, and her work has been at the leading edge of the field ever since. We caught up with her at her office to learn more about her work on the cell's internal countdown clock.

PRE-LAUNCH HOLD

What attracted you to studying telomere biology?

I think I always had a love for science generally, even as a child. I had a chemistry set growing up, and I loved to play with it. When I was in University, the topics that interested me most were cancer and aging. But I didn't get to work on these subjects right away because when I was looking for a laboratory for my PhD I felt the best laboratory at my institution was Margarita Salas' laboratory. She worked on the bacteriophage DNA polymerase Phi29 and on the end-replication problem, which concerns how you copy DNA at the very end of a linear strand. While I wasn't initially interested in that topic, I knew I would learn a lot of useful techniques in her laboratory, like molecular biology. And I was right—those skills were very helpful when I got to Carol Greider's laboratory for my postdoc.

Carol was just starting a junior group at Cold Spring Harbor, and I was happy to have the opportunity to work with her because a link between telomeres, cancer, and aging was hypothesized, but it had not yet been proven. The genes that make up the mammalian telomerase had not yet been identified, so there was a lot of room for discovery in the field. My project was to try to isolate one of the telomerase genes and then make a knockout mouse lacking telomerase activity. That part of the project was a big change for me because I'd never worked with mice before. I had to take a course on mouse embryology.

Was being in Cold Spring Harbor—in a different country—a big change for you, as well?

Professionally, yes it was. Most of the people there were postdocs, and it was a competitive environment—everyone wanted to succeed, to get a job as an independent researcher somewhere. You had the feeling that you were in a place that was making a big impact, where you could learn many things, and that, if you were successful, it would help you in the rest of your career.

> "Increasing telomerase expression extends the lifespan of mice."

What things did you learn there that you think have served you best?

I think an important thing I learned is that European scientists lack a little bit of the self-confidence that American scientists have. Americans have a different attitude toward science and toward their careers; they set their goals much higher. And I think that's important. You need to have the confidence to ask vital questions.

IMAGE COURTESY OF CNIO

María Blasco

COUNTDOWN

Did you consider staying in the United States after your postdoctoral studies?

I had always planned on coming back to Spain. I had some job offers in the US, but in the end I got a very good position in Madrid, so I decided to start my independent career there.

I got a civil service position at the Spanish National Biotechnology Center. For a position like that, you take an exam, and if you pass then you can be hired by the government as a civil servant. The good thing about that is that you have a permanent, indefinite contract—you don't have to worry about anybody firing you. My department had plenty of money, so I had a lot of space, the ability to hire people, and so on. It was very easy to get a lot done in a short time.

I did enjoy my time in the States, and of course I go back every few years for meetings and so on, and I hope I will someday get to go back for a sabbatical. But I think it was a good decision to return to Spain. I have done the research I

Published February 7, 2011

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

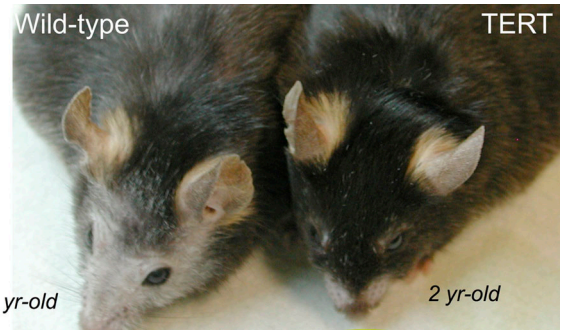

IMAGE COURTESY OF THE BLASCO LABORATORY

Mice overexpressing telomerase (TERT) age more slowly than normal mice.

wanted to do, and I also wanted to give back to my country. Spain isn't a very well-known country for research, so I think it's good when Spanish scientists who go abroad come back and help bring science in Spain to a higher level.

And now you're the director of the molecular oncology program at CNIO?

Yes. I was recruited here by the director of CNIO, when they were just building the center. In the context of Spanish science, CNIO is really a center of excellence. It runs on a different model than the civil servant system; it's more similar to the American model of a research institute.

Have telomeres and telomerase remained the major focus of your laboratory?

My laboratory has always focused on trying to understand the role of telomeres and telomerase in cancer and aging. Our main tools in our work have been various mouse models. First we studied a telomerase-deficient mouse, which showed us both that telomere loss can cause aging and also that telomeres act primarily as a tumor-suppressing mechanism. In other studies we showed that short telomeres could interfere with the normal repair of lesions in the genome. We also generated telomerase-overexpressing mice, through which we demonstrated one of the most significant contributions my laboratory has made: that increasing telomerase expression extends the lifespan of mice. That was really the first time it was shown that telomerase has anti-aging activity in a mammal. And, of course, we have also been using mice to try to understand the role of telomerase in cancer.

TAKE-OFF

Why does telomere loss cause aging?

It's well known now that, as cells age, their telomeres become shorter and shorter. If you delay this telomere shortening, you can delay aging. On the other hand, if you accelerate telomere shortening, you can accelerate aging. This is particularly relevant at the level of the stem cell because stem cells with dysfunctional telomeres are not able to mobilize into tissues. It's because of this impact on stem cells that we think telomeres affect aging, and this is something we're studying quite a lot in the laboratory.

> "Stem cells with dysfunctional telomeres are not able to mobilize into tissues."

More recently we have also been studying telomeres in induced pluripotent stem cells. Induced pluripotency is a technology that allows you to convert a differentiated cell back into an embryonic stem cell–like state. It's very interesting for us because we found out that, during this conversion process, telomeres are rejuvenated. It would be interesting to find out which factors are important for this rejuvenation of the telomeres because they could be important targets in cancer and aging.

Have you also been working on other components of the telomere maintenance machinery?

Yes. We started by being interested in DNA repair proteins that are also bound to telomeres—Ku and DNA-Pk, for example—and later we became interested in activities that are important for the epigenetic regulation of telomere length. More recently we have been interested in understanding the role of telomere-binding proteins called shelterins. There are six shelterins, and we've developed both loss-of-function and gain-of-function mouse models to explore the role of shelterins in cancer and aging.

What's the project you're most excited about at the moment?

I think one of the things that we are most excited about right now is the anti-aging activity of telomerase. We're still exploring that and trying to come closer to a real therapy where you could use telomerase activation as a way to rejuvenate tissues. We're also very excited about using induced pluripotency to identify factors that are important for regulating telomere length.

I'm excited about the directions we're taking now. Ours is a competitive field, so it's important to think about trying things that others are not doing. Your work has to be both original and relevant to the field.

1. Blasco, M.A., et al. 1997. *Cell.* 91:25–34.
2. Gonzalez-Suarez, E., et al. 2000. *Nat. Genet.* 26:114–117.
3. Flores, I., et al. 2005. *Science.* 309:1253–1256.
4. Tomas-Loba, A., et al. 2008. *Cell.* 135:609–622.
5. Marion, R.M., et al. 2009. *Cell Stem Cell.* 4:141–154.

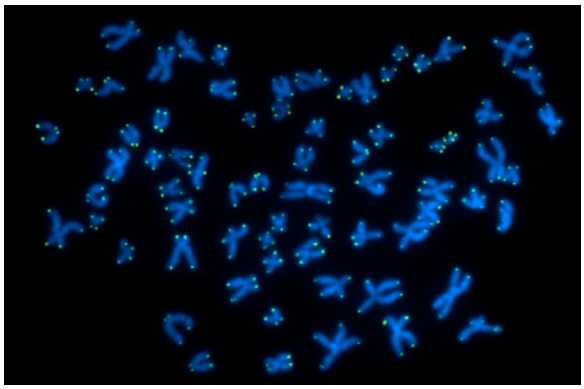

IMAGE COURTESY OF THE BLASCO LABORATORY

Telomeres (green) cap the ends of chromosomes (blue).