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dult stem cells are essential for tissue maintenance and repair. If the biology of these cells can be fully understood, their therapeutic possibilities may be limitless.

To Fernando Camargo, who first worked on adult stem cells as a graduate student under Peggy Goodell (1), the possibilities of a research career also seemed endless. This enthusiastic outlook buoyed him as he skipped doing a traditional postdoc in favor of a position as a Whitehead Fellow at the Whitehead Institute for Biomedical Research of the Massachusetts Institute of Technology, where he explored the regulation of hematopoietic stem cell lineages (2, 3) and how organ size is regulated during development (4, 5).

We reached Camargo at his lab at Harvard’s Department of Stem Cell and Regenerative Biology to learn about the many possibilities he sees ahead.

**LIMITLESS POSSIBILITIES**

**I understand you’re from South America…**

Right. I was born and grew up in Arequipa, in the Andes of Peru. My father is an onion farmer, and I think he wanted me to become a farmer, too, but my mother, who was a principal in an all-girls school, always pushed my brothers and me to study hard in school. I think I first became interested in medicine when I was 11, when a cousin of mine died of pancreatic cancer. That marked me—I always knew I wanted to do something medicine related, such as become a physician like some of my uncles.

In Peru, you go straight to professional school after high school, so I started medical school directly. But I was only there for about six months when I realized that a career in research would be more exciting to me. Everyone I spoke to said that, if I wanted to do biomedical research, I should try to go abroad. So I applied to 30 or 40 schools, but only one of them, the University of Arizona, gave me a full scholarship, so that was where I went.

**What did you study in Arizona?**

I was a biochemistry major, and the first thing I did was to look at the catalog of faculty members to see which ones had labs. Within my first two months I joined Bob Erickson’s lab. They were doing gene therapy, which seemed very exciting to me. So I joined the lab and learned all the basic stuff: how to pipette, how to handle mice, and how to run a PCR. I fell in love with it and stayed in that lab until I graduated.

**You first started working on stem cells as a graduate student at Baylor…**

I did my PhD with Peggy Goodell. She’s one of the leading stem cell experts in the country. At the time that I got there, there was this big controversy about whether adult stem cells might be equivalent to embryonic stem cells. Peggy and I addressed the issue with some experiments that showed adult hematopoietic stem cells do not have any unexpected plasticity, but, remarkably, their progeny can fuse with cells in a particular tissue and take on the characteristics of that type of cell. Later, Peggy nominated me for a position in a special program at the Whitehead Institute, which basically let me start my own lab right away without doing a postdoc first.

**Was it hard to start your own lab fresh out of grad school?**

As a graduate student, you’re like a teenager; you have the support of your parents, and they do lots of stuff for you. But at the Whitehead I had to basically start from scratch. It was just me in an empty lab, and I had to not only come up with an entirely novel research program but also buy equipment and instrumentation for the lab and hire one or two people. It suddenly felt like I was supporting a small family. With all of those things happening at once, it was stressful and very challenging, especially initially. But it was remarkable and exhilarating, too.

**ORGANIC CONSTRAINTS**

**What did you decide to work on?**

Because I came from the hematopoietic stem cell field, my idea was to develop a system in which you could genetically label individual stem cells in situ, in a mouse, without doing transplants or any sort of manipulation. With our model, basically every stem cell carries a unique genetic tag, and that tag is then transmitted to each cell’s progeny so we can track them. But at first, we had a hard time making transgenic mice and getting the right strains, so we’re just now getting these data in my lab—seven years after we started—and it’s looking really, really exciting.

In the meantime, I was working on a couple of other projects. One of these came about because of my interactions...
with Rudolf Jaenisch and David Bartel, with whom I started doing some work on microRNAs. At the time, microRNAs had just emerged as a class of gene regulators, and we were one of the first to generate a knockout mouse for a microRNA. We knocked out a microRNA that negatively regulates the myeloid lineage.

I also started another project, on the Hippo signaling pathway, in collaboration with another Whitehead fellow there at the time, Thijn Brummelkamp, who is now at the Netherlands Cancer Institute.

Your lab is doing a lot of work on the Hippo pathway these days…

With Thijn, I started reading about this signaling pathway in the fly. Drosophila geneticists had identified a group of genes that they suggested could be important in limiting the size of organs. Thijn and I realized that there was really nothing known about this pathway in higher organisms, so we decided to start trying to characterize the pathway in mammals.

The question of how organ size is set is one of the least-understood questions in developmental biology. Hippo signaling might provide important insight into this process. What was known at the time, at least from the fly, is that there is a core set of kinases that controls organ growth by phosphorylating a transcriptional coactivator and preventing it from reaching its targets in the nucleus. We showed that the mammalian orthologue of this crucial coactivator, Yap1, also controls organ size and that it is a potent regulator of stem and progenitor cells. These data provide a potential conceptual and functional link between tissue size and stem cell activity. One of the questions we’ve been working on most recently is what activates this pathway—what’s upstream of it?

Recent work, for instance, suggests that a cell-crowding signal might activate and control the pathway. For example, we showed that, in epidermal cells, α-catenin, a component of intercellular adherens junctions, helps negatively regulate Yap1 by promoting Yap1 binding to 14-3-3 proteins. That was exciting because it dovetailed with other peoples’ observations that loss of α-catenin causes massive overgrowth in some tissues. Other lines of work suggest that cell polarity or mechanotransduction inputs can impinge upon activity of the pathway. My take on this is that there may not be a single ligand or receptor that ultimately regulates Yap1 activity. There are going to be a lot of microenvironmental and “neighborhood” inputs.

SEVEN KILOMETERS UP TO THE TOP,

It’s prominent in several tissues that show an overgrowth phenotype mediated by α-catenin, such as the brain and the skin, but for other tissues it’s a bit unclear. For instance, we’re working now with α-catenin mutants in the intestine and the liver, and we don’t see the same drastic overgrowth phenotypes that people have seen in the other tissues. So it might be that there’s a different set of adhesion or polarity complexes that is more relevant in sensing cell crowding in those tissues. I think the next frontier in understanding Hippo signaling is going to involve elucidating more physiological signals that can modulate Yap1 activity.

Another key question is: What are the targets of Yap1? There’s a core set of genes that people have described, but, if you look at those genes carefully, only a few of them can explain the really massive and striking phenotypes that you see when you manipulate this pathway in vivo. And finally, my lab is also putting a lot of effort into trying to identify small molecules that could inhibit or manipulate the pathway.

With all these things going on, do you ever miss living in Peru?

I think about that a little bit more now because my wife and I had our first child last year and all my family is still in Peru. But my career’s just getting started, so any change like that would be far in the future. Anyway, I would have to convince my wife, who’s an American from Texas, to agree to it. But she speaks Spanish, and she loves the food there, so maybe it wouldn’t be too hard! [Laughs] The food in Peru is amazing—it’s actually what I miss the most from my country.

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DEVELOPMENTAL PATH

How universal is α-catenin-mediated regulation of Yap1?

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