People & Ideas

Irina Conboy: Making the old feel young again

Conboy has found her niche in chasing down what ails aged, decrepit muscle stem cells.

Originally from Russia, Irina Conboy joined Susan McConnell's laboratory at Stanford University in the early 1990s, where she later pursued her PhD, studying autoimmunity in the laboratory of Patricia Jones. Around the same time she married Michael Conboy, and the two have been scientific partners ever since—making a splash in the highly competitive pond of Bay Area stem cell science.

Starting with her postdoctoral fellowship with Tom Rando at Stanford, Conboy has dissected what causes muscle stem cells, or satellite cells, to age and lose their capacity for repair and regeneration of muscle tissue. In 2002, she showed that satellite cells use Notch signaling, the same pathway that guides embryonic organogenesis, for activating adult tissue repair (1).

She and her husband, also working with Rando as a postdoc, developed novel techniques to tease apart skeletal muscle into single cells called myofibers in a process which activates satellite cells by mimicking muscle damage in the laboratory dish. This allowed them to study satellite cells and compare the regenerative capacity of old and young tissue (2). They discovered that old stem cells never actually die out, they just stop responding to injury. If they gave old stem cells an artificial boost of Notch activation, they behaved like young stem cells again.

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From there, Conboy set out to find the root of satellite cell aging. In collaboration with Irv Weissman, she and Michael took a pioneering approach that hooked up the circulation of young mice to old mice. They found that circulating factors from young mice rejuvenated aged stem cells (3). More importantly, in Conboy's mind, they found that old factors negatively influenced repair in young tissues (4). In 2008, as an assistant professor at University of California, Berkeley, Conboy identified at least one of the culprits emanating from aged muscle tissue—an excess of TGF-β that shuts down cell cycle progression in satellite cells (5).

These findings confirmed Conboy's unorthodox view of aging. Rather than a lack of the positive influences of youth, she sees aging as an excess of negative outputs from aged tissues and the stem cells' microenvironment. In an interview, she explained why old niches should concern anyone designing stem cell–based therapies and what parrots and samurai philosophy have taught her about research.

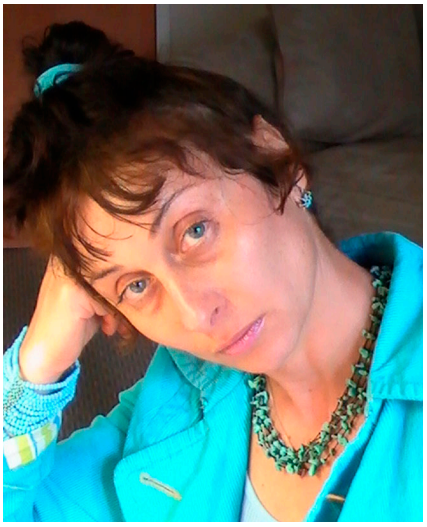
NEW APPROACHES TO OLD AGE

Why did you choose to work with muscle stem cells?

I had the idea that perhaps when we grow old, our stem cells remain relatively young. Therefore if we could boost the regenerative capacity of organ stem cells, we would maybe delay, or even reverse, the onset of aging. I started to look around for a good experimental system to test this hypothesis. I thought skeletal muscle would be good because the existence of satellite cells had been known since the 1960s. These stem cells reside in a well-defined niche, and it was known that a muscle's regenerative capacity declines with age. Tom Rando's laboratory worked on skeletal muscle; he generously allowed me to spearhead this new stem cell direction.

How did you come up with the parabiosis experiment—an old and young mouse sharing circulation?

For some time, I'd thought that the "aging environment" might be contained in the blood circulation. Earlier reports in the 1980s on muscle transplantation took



Irina Conboy

pieces of young muscle and transplanted it to old animals and vice versa. In every situation, it was the age of the host that determined how successful or unsuccessful regeneration was. That implied to me that perhaps the responses of muscle stem cells are regulated by their niche much more than by the age of the cell itself.

But, I didn't know how I would explore this hypothesis until my husband had this idea at journal club. We were discussing a paper from Weissman's laboratory where they did parabiosis of animals the same age. My husband said, "What if we connect young and old mice together?" I immediately met with Irv—he was one of my thesis committee members and he always at least pretended that he was glad to talk to me. And before I even finished my first sentence, he had already started nodding and said, "The people in my lab will help you."

ENGINEERING THE NICHE

Your work has shown that it's the age of the stem cell's environment that is key. Isn't that going to put a damper on using cell-based therapies to treat aging-related disorders?

This is very important for any stem cell scientist because, until we understand

Text and Interview by Kendall Powell
kendall2@nasw.org

why organ stem cells do not work efficiently when people grow old, we cannot hope to solve the problem by transplanting more cells. What is going to happen once you have these healthy, young cells exposed to an aged environment? Will they remain young and healthy, or will something bad happen to them? In 2007, we discovered that if you have an aged organ niche or tissue, those tissues will block regenerative responses not only of old stem cells, but even of young stem cells. Those young cells stop working immediately, like in the next 24 to 48 hours.

So you need to provide transplanted cells with a microenvironment that will allow them to work in an aged body. You might also need to identify inhibitory culprits and neutralize them. And since I'm faculty in the bioengineering department, we are developing youthful, healthy micro-niches for cell and tissue transplantation.

What would those engineered micro-niches look like?

A niche would be basically made out of components of the extracellular matrix [basement membrane] that typically surround cells in normal skeletal muscle. It would orchestrate signal transduction necessary for tissue maintenance and repair. Right now, we have this exciting study—it's not published yet—where we biochemically and structurally recapitulated the muscle stem cell niche. This biosynthetic niche maintains productive stem cell responses and guides self-assembly of 3D muscle fibers.

Are you trying to "cure" aging?

I do not want to speculate on whether we can achieve immortality or a fountain of youth, but I would certainly be willing to speculate that the onset of age-related degenerative disorders, including muscle wasting, could be delayed significantly. I believe that the productive time in our lives could be extended if we remained healthier for decades.

My idealistic impression is that if people lived healthily for many more decades, they might start caring about their environment more. It's not just, "I'm going down the hill and I don't care." They'd say, "Oh, this is the place I will enjoy for the next 50 years."

> "We cannot hope to solve the problem of old age by transplanting more cells."

PARROTS AND PARTNERSHIPS

Your e-mail signature has a quotation from the Japanese swordsman Miyamoto: "Do not think of possible outcomes until you've finished with your battle." Does that sum up your approach to science?

Yes, exactly. My husband is an avid martial artist, so we have several translations of Miyamoto's *Book of Five Rings*. It originally told how to win physical samurai battles, but these days, it could be the battle of how to get your manuscript accepted.

I also have a typical Berkeley bumper sticker on the door to my office, that says, "Don't believe everything you think."

One of the downfalls of a scientist can be to have such a strong hypothesis before starting an experiment that it overpowers the data interpretation. You always want to believe that you were right to begin with. But if you conduct science like that, then at some point you're going to be in trouble. If you conduct science as if it's just an interesting path you are taking then, whether the answer is yes or no, you accept it and move forward.

How has collaborating so closely with your husband been?

It has been a blast, to tell you the truth, because we like the complementary sides of science. My husband loves doing experiments more than writing grants, for example. I actually enjoy writing grants, going to conferences to present my work, and providing new ideas for experiments. We analyze the data together. I think that between us, we kind of comprise this perfect scientist. For now, we run one big group and that allows me to be 100 times more productive—I can go to conferences and know that my laboratory is still running.

The only time we had potential friction was when I already had my position at Berkeley and Mike was still in Rando's laboratory, which had become my competition. All of a sudden, I could not discuss science with my husband as openly anymore. This was a really awkward half a year. But outside of that, it has been—knock on wood—excellent.

Conboy with her husband, Michael, and parrots, Charlie and Shishka.

In a two-scientist household, is there ever time for nonscience activities?

We don't have children because our projects are our children, and we go on "vacation" to conferences. But we do have exotic parrots at home. Charlie is a big Blue-and-gold Macaw and Shishka is a little green Amazon. When we go to work, we turn on "Sesame Street" for them so they can learn the songs. And we teach them to use words intelligently and say what they want, like "cookie," "juice," and "fly."

Parrots live until they're about 75 years old, which completely boggles my mind because most of them are just tiny compared with people and have a high metabolism. And rats, which are a similar size, live only until they're three years old. It just tells us that we understand very little about aging and what truly controls how long animals live. If we don't discover a fountain of youth, I might have to find new owners for our parrots one day!

1. Conboy, I.M., and T.A. Rando. 2002. *Dev. Cell.* 3:397–409.
2. Conboy, I.M., et al. 2003. *Science.* 302:1575–1577.
3. Conboy, I.M., et al. 2005. *Nature.* 433:760–764.
4. Carlson, M.E., and I.M. Conboy. 2007. *Aging Cell.* 6:371–382.
5. Carlson, M.E., et al. 2008. *Nature.* 454:528–532.