Pamela Silver: Synthesizing a new biology

Silver's lab uses systems biology to inform the design of novel synthetic functions in cells.

It's no wonder there's such a buzz about synthetic biology these days. Researchers are already innovating new forms of life by inserting novel genetic and biosynthetic pathways of their own design into cells. They are poised to convert the vast informational troves of modern biology into concrete applications.

Pamela Silver is a strong believer in the potential of synthetic biology and is a leader in this young and rapidly developing field (1, 2). Although she's now interested in designing novel biological systems, she began as a more conventional scientist, coming to the discipline after forging a successful career studying nuclear (3, 4) and RNA (5) biology. We called her at her office at Harvard's Department of Systems Biology to discuss how she arrived at this new frontier and what she sees coming up on her horizon.

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Pamela Silver

NO ROAD MAP

What are your strongest memories from your childhood?

One thing that stands out to me is that I had precocious math ability, which at the time—don't ask me why—was considered unusual for girls. So I was a girl nerd, and I remember being very conscious of the dichotomy between trying to be popular but also being a nerd. Nerds weren't as trendy then.

Another thing I remember is that there was a huge music scene in Northern California, where I grew up. Members of the Grateful Dead lived in my neighborhood, so, when we were little kids, we used to go listen to them. I went to a lot of their concerts and was a huge fan.

Are you still a "Dead Head"?

As much as one can be these days. They were always a live performance band, but they don't do many concerts anymore, especially since Jerry Garcia died. I spend more of my time in other hobbies now. I recently started doing hot yoga, and my other big passion is sailing.

I first took up sailing while I was growing up because my father had a boat, and I competed in races during college. I've stuck with sailing over the years, and recently my racing partner and I got together to buy our own boat. It's not a pleasure boat; we wanted something inexpensive but fast, and it's worked out well for us. We placed second in the Marblehead series last summer, and that was when we were still warming up. Look out for next year, because we're going to be on top! [Laughs]

Did you have any career in mind when you were a child?

One thing that's characterized my life is that I've never really had a plan. When it came time for college, I went to UC Santa Cruz because it was a new campus and I thought that would be exciting. At first I studied physics, and I quickly realized that I wanted to do research. But neither theoretical physics nor high-energy physics appealed to me, so I switched to chemistry because it was more experimentally oriented. Interestingly, I took almost no biology classes in college. My main exposure to biology was through my best friend, who became a marine biologist. We used to go out and collect algae at five in the morning.

> "The [graduate] program I designed is really focused on student empowerment."

CHANGE IN PLANS

What led you to study biochemistry as a graduate student?

For graduate school, at first I only applied to Berkeley and Harvard, which had the best chemistry departments in the country at the time. But when I went out to visit Harvard, I found the atmosphere very intimidating. There were lots of hard-core, famous chemists. I felt overwhelmed by the whole thing, so I took a job as a polymer chemist in a startup company in Palo Alto instead. There, I met and married my first husband, and, when his internship took us to Los Angeles, I enrolled in graduate school at the University of California, L.A. By that time, I'd gotten interested in molecular biology, and there were several faculty at UCLA who were doing interesting work in that field.

But you did eventually end up at Harvard…

I had followed my husband to Boston and arranged to do a postdoc in a lab there, but, before I started, I enrolled in the Cold Spring Harbor yeast course. That was a transformative experience for me. I was immersed in this amazing intellectual culture, and for me it was a summer of intense science and intense play. I guess I grew up there, in a way, because when I came back to Boston I made a lot of changes in my life—both personal and scientific. Most importantly, I switched to Mark Ptashne's lab for my postdoc.

Mark was starting a yeast group, and I had an idea for something I wanted to

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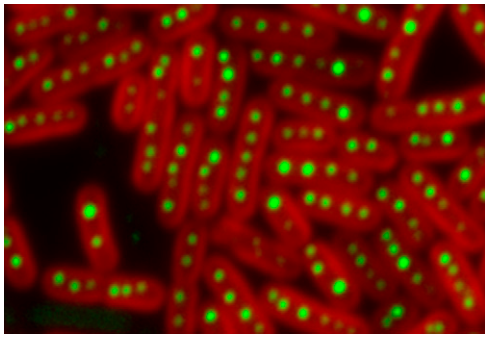

IMAGE COURTESY OF DAVID SAVAGE

Silver's lab is engineering cyanobacteria like these to crank out useful commodities.

work on, using yeast as a model system. I wanted to test the hypothesis that there were sequences in proteins that target them into the nucleus, which was a new idea at the time. I have a feeling that Mark thought I would fail and then I would help him set up his yeast group and study yeast transcription. [Laughs] Instead, I discovered one of the first nuclear localization signals.

Was that also what you worked on when you first started your lab at Princeton?

Yes, and that then evolved into studying RNA transport and both nuclear export and import. I worked on that for a number of years, with decent success, at Princeton. But, to be honest, I came to a point where I decided that (at least for me) the problem was sufficiently solved that I wasn't very excited about it anymore. I started to question whether it was a good idea to continue training new students in those fields. Would it be better to start something new?

In the meantime, I had remarried and moved to the Dana-Farber Cancer Institute at Harvard. I worked there for several years, and then I was invited to be one of the initial members of the Department of Systems Biology. I became the first director of a new Harvard-wide graduate program in systems biology. That was really important to me because I had several ideas about how I wanted to reform graduate education.

What sort of things did you want changed?

I wanted graduate programs to be more focused on research. I was getting really frustrated by seeing students come up for their oral exams with these boring, cookie-cutter presentations. In my perfect world, courses would be optional; I wanted students to get out of that and to challenge themselves more. Ultimately, of course, I had to compromise. Students still take a few courses, but the program I designed is really focused on student empowerment and on getting them into basic research as soon as possible.

NEW TERRITORY

How did you get into synthetic biology?

At some point I realized that my future was probably not going to be in curing cancer, although I still work in this area and can't seem to let it go. But through a young colleague at MIT, I met a number of computer scientists and bioengineers, who formed what we called the Synthetic Biology Working Group. I participated in some inter-session courses at MIT where students could design their own synthetic systems, and some of my Harvard students also became interested in this. Eventually, I found that I was no longer attracting people to my lab who wanted to work on the old stuff, so now almost my whole lab works on synthetic biology.

> "Systems biology... gives us a parts list of useful biological components and modules."

What pitfalls have you encountered when trying to build a synthetic biological system?

I think it probably helps that we have a good intuition about the underlying biology. My lab also has a strong background in systems biology, which we can use to reveal the different kinds of circuit logics that nature uses. Systems biology also gives us a parts list of useful biological components and modules to choose from.

But to be honest, we've been remarkably lucky in our efforts. We've faced issues around optimization, but mostly, whenever we set out to build something, we've succeeded. For example, we have one grant that involves engineering CO_2 fixation into non-photosynthetic bacteria and redirecting sunlight into the production of useful commodities such as sugar. Our preliminary data on that look quite promising. We also have a group of people designing tools and circuits that record changes to cell states. So for example, we've designed yeast cells that can remember and report past exposure to DNA damage, and now we're replicating that in mammalian cells. Another project involves designing microbes that can report on the situation in the gut or that could report on whether they've ever been used in the laboratory. These are all exciting projects that offer real-world applications.

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4. Hieronymus, H., M.C. Yu, and P.A. Silver. 2004. *Genes Dev.* 18:2652–2662.
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Silver helps crew a racing sloop off the coast of Newport, Rhode Island.