Knowing when to change: reprogramming (my) life

Pamela A. Silver

I begin every year by asking the new graduate students to recall why they became excited about science. What led them to a fascination with nature? What do they dream about? At the same time, I ask myself these questions. Growing up in California's Silicon Valley was more special than I realized at the time. On the one hand, spending time outdoors cultivated my respect for what nature has on offer. On the other, the atmosphere of experimentation was everywhere from the nascent personal computer industry to drugs, music and politics. This combined with my own precociousness and rebellious nature made mathematics and science particularly attractive — although being a female nerd was not an easy social path. Fortunately, I had supportive teachers and friends and the confidence to explore outside my social niche leading to my own experimentation with early 'computers' (I was an early adopter of programmable calculators). College brought the opportunity for total freedom and immersion in mathematics and science. In retrospect, I was fortunate to not have the distractions that many undergraduates face today as they try to be 'well-rounded'.

Graduate school was a further opportunity to immerse myself in science and gain more independence. My dilemma at the time was whether to work on a simple organism such as *Escherichia coli* or more complex eukaryotic cells. My decision was made following my conception of an experiment that was warmly received by my future thesis advisor. So, I ended up working on the lowly M13 phage and studying how proteins assemble into bacterial membranes.

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With my inclination toward scientific independence, I sought a postdoctoral experience that would allow me to pursue my own ideas. I chose to work on the nucleus, and to question how proteins cross the nuclear membrane. I speculated that amino acid sequences might exist within proteins that specifically target them to the nucleus. In doing so, I employed hybrid protein approaches (modern technology at the time) to tackle this old problem, and discovered signals that target proteins to the nucleus. Although this work was well outside the themes of my postdoctoral laboratory, it allowed me to develop my own identity as an independent researcher, prepared me well for starting my own lab and is a formula that I believe works to this day for new investigators starting their own research groups. Many years later, continuing on with this philosophy and experience of independence, I was fortunate to be part of the new Systems Biology Department at Harvard Medical School and was made head of the Harvard University graduate program in systems biology, which has allowed me to exercise the principle of student empowerment to shape graduate education. We strive to create an environment where students are stimulated to come up with their own ideas, and faculty members are encouraged to be receptive and provide critical but constructive input.

The nucleus was good to me for many years. It took me from basic biology all the way to development of potential cancer therapeutics. However, there came a time when I was ready to move on. But how do you do this when you have achieved success in a given field and have, for example, numerous students and grants and receive invitations for seminars and meetings? One colleague pointed out that if you change fields you run the risk of 'being unknown'. Nonetheless, I learnt from this experience the importance of realizing when it feels to you as though your scientific problem has been solved. For some, this might not be until every atom is in place but for others, like myself, it might be when the mystery of the phenomenon is no longer present and others are pursuing the details.

A key turning point came about ten years ago. I had the good fortune to meet a group of computer scientists and bioengineers who were interested in understanding how one could make biology easier to engineer. This led to my immersion in the field now termed synthetic biology. This opened a new world of exploration and created a group of colleagues who tolerated me as the token biologist. Together we taught classes and initiated a summer competition where undergraduates build 'genetic machines.' I began to launch some projects in my own lab and, thanks to a fearless group of students and postdocs, our own work now includes designing genetic circuits that affect disease states and engineering organisms for global sustainability. It's hard to say what the impact will be, but it feels good to think that we might be changing the world.

In summary, the things that I wished I had learned sooner are as follows. Risk taking is good. Change what you are doing — make sure you are not bored. Success is not guaranteed — it's us versus nature, and nature has a head-start. If you are working at the cutting edge of research topics, then failure is an option. This is especially true given the current funding system. But playing it safe does not always guarantee success. I never had a well-defined career plan — my motto is that every day is interesting and something new can happen. As I say to my students, being a scientist is great — you can create your own schedule, travel, meet different types of people, mess around with nature and maybe do something that changes the world. Not many other careers can offer that.

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