How lucky can one be? A perspective from a young scientist at the right place at the right time

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How amazing to receive a call that I, along with my friends and colleagues James Spudich and Michael Sheetz, won the Lasker Award for Basic Medical Research. An important part of the research cited for the Lasker Award stems from a time when I was a graduate student. I was 21 years old when I first met Jim Spudich while applying to MD-PhD programs, 23 when Mike Sheetz, Tom Reese, Bruce Schnapp and I began work on axonal transport, 25 when our papers on microtubule-based transport and kinesin were published and 27 when I started my first job at UCSF. It was an extraordinary period of time. I was at the right place at the right time, hanging on tight, and enjoying the scientific ride of my life. This essay is aimed at young scientists who are starting their own journeys. I will provide a perspective and ten lessons learned from my own experiences in graduate school and travels to the discovery of kinesin.

An abbreviated history of my journey to Woods Hole and kinesin

In 1980, I interviewed with Jim Spudich for the MD-PhD program at Stanford University. We had a great discussion, and his recommendation was crucial for my admission. Who would have thought at that time that we would enjoy sharing the Lasker Award together? With my thesis advisor Eric Shooter, an eminent biochemist and neuroscientist, I began studying the ligand binding and biochemical properties of the nerve growth factor (NGF) receptor.

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I was also intrigued by the problem of how a signal initiated by NGF binding to its receptor at the nerve terminal might travel back to the nucleus, a question that brought me in touch with the literature of axonal transport. In 1982, I learned about the beautiful experiments that Jim and Mike Sheetz were doing on reconstituting the motion of myosin-coated beads along actin cables[1]. I wondered, might a similar actomyosin mechanism account for axonal transport of membrane vesicles? Mike and I decided to test this idea using the squid giant axon. The attraction of the squid was a consequence of a landmark paper by Robert Allen, Scott Brady, Ray Lasek and their co-workers where they used Allen's recently developed video-enhanced microscopy technique to image axonal transport in the giant axon[2,3]. Never before had the fine details of the interior of a living cell been visualized so clearly. Axonal transport could now be studied in a ten-minute experiment under a microscope rather than in a laborious week-long experiment with radioactivity, the traditional measurement at the time.

A meteorological disturbance then changed the course of the project and my life. We arranged to get squid from the Hopkins Marine Station, a satellite of Stanford in Monterey, California. But no squid were caught that year. It was 1983, the year that an El Niño warmed the ocean waters and chased the squid away from the Monterey coast[4]. What to do? If the squid would not come to us, we had to go to the squid. Mike and I decided at the last minute to go to the Marine Biology Laboratory (MBL) in Woods Hole. Within three weeks, airplane tickets were bought, an MBL lab was rented, an old, rusty Volkswagen Beetle was purchased, the essential supplies from Mike's University of Connecticut lab were packed in the car, and off we went on a scientific camping trip to Woods Hole. Mike and I teamed up with Bruce Schnapp and Tom Reese from the US National Institutes of Health (NIH), outstanding microscopists who had a year-round laboratory at the MBL. It was a perfect team (**Fig. 1**), as we all brought different skills and thinking and enjoyed the camaraderie of working together on the problem.

The goal of the project was focused on identifying the machinery powering axonal transport. Bruce and Tom performed a *tour de force* experiment combining light and electron microscopy to show that single microtubules served as tracks for long-distance axonal transport[5,6]. Our initial ideas of axonal transport being primarily driven by actomyosin were not right. Next, we sought to reconstitute transport from isolated components, a strategy that worked well for many biological processes including DNA replication, transcription, vesicle transport, ubiquitination and others. In the summer of 1984, reconstitution of vesicle transport worked, but unexpected results led to even simpler and more powerful assays. Molecular motors, without membrane vesicles, could be attached to glass cover slips and could translocate microtubules across the surface; motors also could be attached to beads and propel them along stationary microtubules[7]. I asked Stanford whether I could postpone my medical clerkships, which were coming up in a few weeks. That winter, the biochemical hunt for the molecular motor was on; with these powerful assays in hand, the dominant motor was not hard to find. It was a previously uncharacterized protein, which we called kinesin[8]. That same winter we also found evidence for another motor that moved in the opposite direction to kinesin[9], which was later found by Richard Vallee's group to be a cytoplasmic dynein[10]. The work was published in five

Figure 1 Mike Sheetz, Tom Reese, Bruce Schnapp and Ron Vale (left to right) at the Marine Biological Laboratories in Woods Hole circa 1984.

papers in 1985, and I was lucky enough to get a job offer at UCSF in 1986. I am still on leave of absence from completing my MD degree.

Ten lessons

Here is my top-ten list of what I learned from this experience, most which only became obvious in retrospect. I was immersed in the science, making and sometimes learning from mistakes and having very little idea of where it would all lead and how or where I would emerge at the end.

1. Find good mentors, learn from them and then develop your own style. Soak up your surroundings. Science is as much about philosophies of approaching problems, personal styles of research and working with others as the process of experimentation itself. As a young scientist, you need to be exposed to different ways of doing science, absorbing the ideas and attitudes of more senior scientists. The net result is a maturation of a hybrid style that best suits you and is a composite of the characteristics that you admire in different individuals. Neither idolize nor ignore anyone. I was fortunate to have many great mentors, which included the core group of Bruce Schnapp, Tom Reese, Mike Sheetz and Jim Spudich. I gained tremendously from their unique personalities and scientific approaches. But they all shared one thing in common—they were incredibly kind and supportive of me as a young scientist. I had additional heroes in graduate school. First was my wonderful advisor, Eric Shooter. How many thesis advisors would let their graduate student wander off quite a distance to work on a project unrelated to his or her own lab's work and without any thought of gaining credit for something that might emerge? I did not completely appreciate at the time how different Eric's unselfish attitude about his lab 'family' is from that of many scientists. I also met lively older scientists at the MBL—Shinya Inoue and Andrew Szent-Gyorgyi who 'adopted' this kid from the West Coast during the Woods Hole winter. They had small and focused labs (unlike the generally larger labs at Stanford) and merged a love of life and a love of science without compromising either.

2. Pick an important problem. Everyone would rather solve a fascinating problem than a boring one. However, it is not easy to identify a project that is both important and ripe for solving. Furthermore, pragmatics dictate getting results in a defined time period in order to obtain a degree, job or grant. As a result, most of us are not always working on grand issues in biology all of the time. However, you should be vigilant and thoughtful, looking for a wedge or an opening to tackle an important problem, even if it is not in your area of research or expertise. If the opportunity comes along (see next point), seize it. In most cases, you cannot make an important discovery if you are not asking an important question from the start.

3. Get ahead but then take a chance: seek adventure. In my first two to three years in Eric Shooter's lab, I published a couple of papers that were solid but not outstanding, but I knew that they were sufficient to get a PhD. With that safety net, I had the freedom to look for and take on an important but risky project. That opportunity came along with the chance to build upon the Sheetz/Spudich experiment. The whole axonal transport project was an adventure, beginning with a relatively last-minute decision to go to Woods Hole. Thinking of science as a grand adventure makes it fun and allows unexpected things to happen, in terms of both scientific outcomes and your personal career.

4. Read the literature but don't be crippled by it. It can be daunting to enter a new field because of its considerable history and literature. You have to be knowledgeable about prior work, but it is also good to avoid getting caught in the trap of doing variations of prior experiments and thinking along the lines of existing models. Fresh eyes and some naïveté can be a good thing. Fast axonal transport at the time had a long literature but relatively little clarity on the mechanism. The Allen, Brady and Lasek video microscopy studies, however, were a turning point because they provided a new way to image small moving vesicles[2,3]. Going forward, it made sense to build upon that method by doing biochemistry and not sticking to pharmacology, which had dominated work in the past.

5. You don't need a fancy lab to do good science. I came from a pristine, well-organized laboratory in a relatively new building at Stanford. Tom Reese's lab at the Marine Biology Laboratory, in contrast, was a chaotic rabbit warren of small rooms in the basement of the Loeb building, with a monolayer of chemical reagents and small equipment covering most of the available bench space. We dissected squid giant axons in a wet and dank seawater room in the basement, which we called 'Neptune's cave'. But none of this mattered, and it was a refreshing change from the well-organized rows of monotonous lab benches that popu-

late most modern research buildings. Tom's lab had state-of-the-art equipment that proved essential for the work—video light and electron microscopy. But at the start of the kinesin purification, there was no centrifuge in the building (we had to go to a building across the street) and no chromatography equipment (we initially used syringes with glass wool). One can adapt to any surroundings and make things work. This also adds to the scientific adventure.

6. Work hard, play hard and squeeze in time to do your laundry. Science is not a 9-to-5 job. I worked very hard on the projects at Woods Hole; during the winter of 1984, I pretty much only worked (there was not a lot to do during the winter at Woods Hole, so I was not missing much). Special times require special effort, and I was incredibly happy spending as much time as I could in the lab and seeing the science come together. But later in the following spring, I needed time off and went on a long bike trip in Europe. I also spent four months in Nepal and Japan before starting my job at UCSF. It is crucial to push a project hard at some points, but you also must make time to balance your life.

7. Persistence is more important than brilliance. If you are not naturally brilliant (my case), you can still do well in experimental science if you are persistent. The converse is harder. As an example, for much of the summer of 1984, I failed to reconstitute axonal transport *in vitro*, mostly owing to a series of experimental mistakes. The summer was drawing to a close and I was soon off to start my medical clerkships. With no success up until that point, it might have been a juncture at which to relax and spend time at the beach. Perhaps the only point to my credit in the kinesin story is that I did not take this path. I was dogmatic about giving this experiment my best shot before returning to Stanford. Then, one magical night followed by one magical week, everything came together. I cancelled my return flight.

8. No project or career is immune from mistakes. As successful as the 1983–1985 period was, it was not as scientifically perfect as it may appear. We took some conceptual wrong turns and made technical mistakes. We were fortunate that they did not derail us too far off the track. Perhaps this will be comforting to students whose projects may not be going forward in a straight line; moments of confusion and doubt are typical for any project. There were also plenty of missed opportunities. We noted that "microtubules in solution also moved relative to one another to form a contracted aggregate of microtubule"[8] (in modern terms, an 'aster') but did not pursue it. Self-organization of microtubules by motor proteins later became an important area of research. I also thought to 'save' the purification of the retrograde axonal motor (most likely the ATPase called HMW_1)[8,9] for an aim in my first NIH grant, which turned out not to be a sensible decision, as I was scooped before I had the chance to do it. Every career is marked by poor and by good decisions; you just have to try to keep the scorecard favoring the latter category.

9. Don't be afraid to change your life plans. My twenties and early thirties could have been on autopilot—an MD-PhD program most likely followed by an internship and residency and a later return to science. However, the *in vitro* motility assays from Woods Hole threw a wrench into that plan. Return to medical school? Certainly not now from my point of view, but what would others say? My mentors encouraged me to stick with the project and defer my clerkships; Stanford Medical School was incredibly supportive, as well. I never returned to medicine; it became abundantly apparent that my heart was in science and that a scientific career would keep me happy. Many years later, it is gratifying to me that molecular motors are having an impact on medicine and that drugs are being developed that target these proteins.

10. Science is moving fast: hold on and enjoy the ride. It is nice to make your own discovery. But there is also great pleasure in having a seat in the big scientific arena and watching the amazing progress that is taking place overall. As an illustration, I was captivated by watching kinesin move vesicles or plastic beads, but it seemed hard to imagine in 1984 how one would be able to understand the detailed inner workings of a motor so small. At that time, I could not envision the many new tools that would come along (single-molecule techniques, better structural methods, genomic studies of a multitude of kinesins) and the ideas contributed by the many people who would enter the field. In the subsequent two decades, we know of many kinesins and the many roles they play and have reasonable ideas of how they produce motion. This incredible progress is being played out in all areas of the life sciences, and we scientists are fortunate to have a front-row seat and witness the tremendous advances that are taking place.

Perspective

I began this essay by saying how lucky I was—lucky to be a young person in the right place at the right time. Now that a few decades have gone by, I have come to appreciate that my job as a senior scientist is to offer students the taste of independence and discovery that I had when I was young. And for the young scientists reading this essay, you don't need to discover kinesin to be excited about science. Discoveries come in all flavors and sizes. Scientific adventures come in many forms. Embrace the wonderful small discoveries and adventures that can happen any day in the lab, and then a big one may eventually come along.

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COMPETING FINANCIAL INTERESTS

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