Following nature's challenges

Michael P Sheetz

It is a great honor to be recognized by the Lasker Foundation for solving some problems that I have worked on in the past with outstanding collaborators. I emphasize the collaborators because it is a critical element of what I wish to convey in this essay.

Having grown up in the Midwest with parents who were children during the Great Depression and World War II, I was provided with a strong appreciation of delayed gratification and independence. My studies at Albion College in Michigan emphasized math and chemistry, with a strong dose of physics that grounded me in the basic sciences. But my father, who was a chemist for Dow Chemical, kept trying to convince me that the instant gratification of curing people would be better than waiting five to fifteen years as he did for his ideas to become products. To test this view, I worked as a hospital orderly on the night shift, where I came to realize that most treatments were based on the idea of "do no harm" and that the understanding of the underlying biology at the time was elementary at best. In the fall of 1967, while on a research program at Argonne National labs in Illinois, I decided to become a biochemist and study biomedical problems, because there was a lot that could be discovered. I chose to enter the chemistry program at Caltech because there were no boundaries between departments there, and I could move to biology or physics to follow my interests.

During my graduate work with Sunney Chan, I became interested in membranes. This was a new focus for the lab, which was largely involved in the nuclear magnetic resonance (NMR) of nucleic acids. However, NMR signals of membranes were disappointing because of the lack of detail, and only profound alterations of their structure, such as cleavage of the lipid head groups[1], sonication to form 15-nm vesicles[2] or thermal denaturation, could elicit substantial signals. Giving up NMR to focus on membranes, I moved to Jon Singer's lab at the University of California–San Diego. The pace of membrane biochemistry was slow, but Jon asked me to look into the effect of drugs on erythrocyte shape. His idea was that the anionic lipids on the inner surface were attracting cationic drugs and expanding that surface. Because the two halves of the lipid bilayer were joined, the cell was changing shape and bending, similar to bimetallic couples. This 'bilayer couple' idea seemed too simplistic to me at the time, and I was reluctant to devote much effort to it. Nevertheless, our report on the bilayer couple[3] is my most cited paper, second only to the paper that reported the discovery of kinesin.

I started my independent career further focusing on the erythrocyte-shape question. This involved the more challenging problem of determining how biochemical systems could sense the bilayer couple and keep the cell membrane physically balanced as a biconcave disc. Basically, a lipid flippase or lipid metabolism would be needed to adjust the bilayer couple to keep the red cell as a biconcave disc (a problem that has not been fully solved yet). Taking a more pragmatic approach, I collaborated with Dennis Koppel and Mel Schindler to understand why membrane proteins in erythrocytes diffused 100-fold more slowly than they would in lipid bilayers in other cell types. We found a mutant mouse that lacked the major membrane skeleton protein spectrin and found that, in that background, the proteins diffused as in lipid bilayers[4]. This was surprising because spectrin removal did not change rotational mobility, which led us to propose that spectrin formed 'corrals' on the membrane surface that enabled local diffusion but prevented long-range diffusion. At this point, I went on sabbatical and my research took a dramatic change of direction.

When I arrived in James Spudich's lab at Stanford in 1982, I had no direct experience with myosin motility and had only a vague idea of a myosin motility assay that I wanted to develop. Within a few short weeks, the *Nitella* motility assay was working. It was a bit crude, but it showed for the first time that myosin is capable of moving on actin in a unidirectional fashion (**Fig. 1**)[5]. As luck would have it, I obtained the one variety of *Nitella* that would work in the assay from a colleague (Lincoln Taiz at University of California–Santa Cruz), and Peter Sargent, a neurobiologist at Stanford, showed me how to open single *Nitella* cells and expose the actin cables with electolytically sharpened tungsten pins. The following summer, because it was an El Niño year and no squid were available in California, Ron Vale and I embarked on an adventurous trip to the Marine Biology Labs (MBL) in Massachusetts to determine how axonal transport was powered. That task took two-and-a-half years. It was part of a larger effort by multiple labs, and it was helped by major early contributions from the labs of Robert Allen, Ray Lasek and Scott Brady. Crucial for us was a long-term collaboration with Tom Reese and Bruce Schnapp at a US National Institutes of Health satellite within the MBL[6,7].

In fact, I experienced pretty immediate satisfaction in those three years rather than the frustration that those who work on problems for many years typically experience, and my Midwestern ethic made me feel a little guilty for getting results without the requisite pain and suffering. Part of that ethic involved a desire to give back to the community, and I became Department Chair at Duke Medical School, but I would never give up scientific research, which, like any narcotic, had me hooked.

Our lab has continued to experience considerable good fortune in following the basic formula of pursuing interesting leads even when they take us in totally new directions. Thus, my research portfolio is not a consistent

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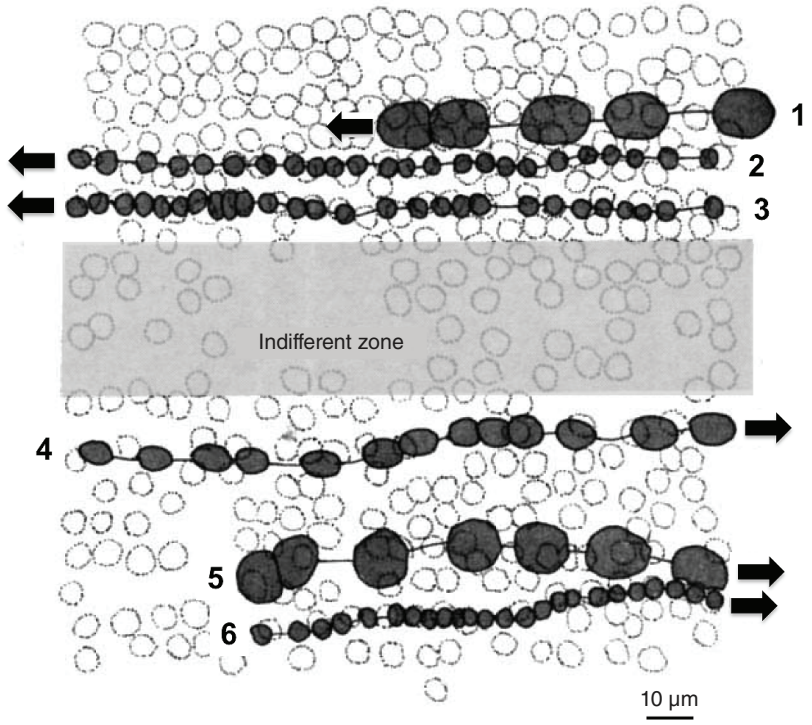

Figure 1 Opposite direction of movement of HMM beads on either side of the indifferent zone. The positions of the chloroplasts (dotted circles) and the six HMM beads (that is, distinct bead aggregates) were determined directly from a video monitor equipped with digital time readout by tracing the particles onto Saran Wrap. The positions of the chloroplasts remained fixed while the HMM beads moved in the directions shown by the heavy arrows. The long thin arrows indicate the direction of cytoplasmic streaming observed *in vivo* before dissection. The positions of the HMM beads are shown every 5 s for beads 2, 3 and 6, every 10 s for bead 4 and every 20 s for beads 1 and 5 (taken from ref. 1).

body of literature in a single field but rather is an eclectic mixture of papers and ideas. Currently, we have several new areas of interest: membrane tension as a master regulator of endocytosis, motility and membrane resealing[8], mechanosensing by protein stretching at integrin sites[9] and rigidity sensing by local contraction units like sarcomeres[10]. There are common threads to these projects, and the formula has worked well for me throughout my career.

Like the *in vitro* motility assays and the discovery of kinesin, all these studies were made possible by the melding of multiple technologies with good biological systems. They were all unfunded before the first publication. Thus, it was most important to demonstrate a concept by the simplest method possible. Our illustration of the initial myosin movement on *Nitella* was drawn by an artist based on tracings of bead positions on Saran Wrap adhered to a TV screen (**Fig. 1**). It took many other elements to complete the papers, and I am deeply indebted to colleagues (students, postdocs, technicians and collaborators) who stayed focused until the papers were published. Still, the challenge of facing a surprising result has been a major driving force and keeps me excited to this day.

Mixing complementary views helps discovery

As I consider what was most productive in terms of new insights or concepts, it is clear that it was the early phase of collaborations where the parties were learning from each other and asking critical questions over an experiment. If your collaborator views things differently from you and you both try to understand the other's viewpoint, a new insight can often occur. Such a discovery phase is very subject to chance, and a lot of experiments fail. Still, an experiment, even a flawed one, can reveal the solution to an important problem. The goal is to find a problem that can be solved now with the tools and people available, preferably an important problem for the field where the lack of a solution is limiting further advancement and understanding. I encourage young scientists to perform speculative experiments whenever they have such an idea, even if most of them fail. When these speculative experiments work, they often lead to major papers or breakthroughs. Taking a page from the Taleb book *The Black Swan: The Impact of the Highly Improbable*, it is very important to spend some of your resources on risky ventures that can pay off dramatically.

Can we encourage the discovery process?

The three of us, Jim Spudich, Ron Vale and I, have worked to improve our professional environments to encourage further discoveries and to enable others to experience the joy that we have shared. This ranges from service to societies and journals and granting agencies to administrative duties. We all understand the importance of an open culture for scientific exchange. From his early days in the Stanford biochemistry department, Jim was a firm believer in an open laboratory concept where students from different labs shared benches and often ideas that would speed the rate of discovery. He and Ron came up with an idea for an institute with major central facilities support and an open lab to enable scientists to move as rapidly as possible from an idea to an experiment. Later and independently, I evolved a similar idea that was then generously funded by the Singapore government and is now the Mechanobiology Institute. Taking advantage of the revolutions in nanotechnology and single-molecule biophysics, the institute provides an open lab environment with the opportunity for engineers, physicists, chemists and biologists to share ideas and expertise as each works toward his or her individual goal. After three years, it seems to be working in the sense that our researchers are productive, excited and serving as ambassadors for the institute. An important element for the community is that the labs are funded from a common source, which harkens back to Arthur Kornberg's original plan for biochemistry at Stanford University. Singapore's structured environment has provided some order that enables facilities to function for the scientists and makes it possible for the day-to-day aspects of research to work while freeing the researchers to focus on science. Because there are many important technologies and tools that are impossible for a single lab to provide, the pace of discovery can be increased by easing the energy barrier to access the needed tools. Many institutions, such as Stanford's Bio-X, the Howard Hughes Medical Institute's Janelia Farms and others, are providing similar support for their researchers because it can increase the pace of discovery.

Conclusion

My career in research has been a wonderful journey through a range of scientific problems,

with the one common theme that our most interesting scientific insights result from collaborative, interdisciplinary adventures. In the particular cases of the discovery of an *in vitro* motility assay, followed by the discovery of kinesin, there was a remarkable string of successful but very speculative experiments (requiring a fair amount of luck) that were converted into a string of major publications. This required a focus on the scientific problem at hand while avoiding the many pitfalls that can prevent a collaborative project from being published, most of which relate to the egos of the investigators. The papers that resulted were rewarding and fueled further collaborations that resulted in my following other scientific avenues. My greatest excitement comes from considering the puzzle provided by an unexpected result when new technology is applied to an old problem.

I consider myself very fortunate in having had a series of wonderful colleagues and collaborators, who contributed in many ways large and small to our ability to solve important puzzles. The pace of discovery is greatest when people set aside their egos and focus on the problem at hand, becoming a complementary team. With the proper tools and the willingness to see tough problems through to publication, collaborative teams can solve them. They can best do so in an environment that encourages open exchange of questions and ideas without disciplinary boundaries. The new model of open laboratory environments in interdisciplinary institutes provides an excellent way to encourage this type of discovery process in the future.

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