A *chemist* building paths to cell biology

Douglas B. Weibel
Departments of Biochemistry, Chemistry, and Biomedical Engineering, University of Wisconsin–Madison, Madison, WI 53706

ABSTRACT **Galileo is reported to have stated, "Measure what is measurable and make measurable what is not so." My group's trajectory in cell biology has closely followed this philosophy, although it took some searching to find this path.**

BUILDING A PATH *TO* CELL BIOLOGY

I am honored to receive the 2013 ASCB Early Career Life Scientist Award. Readers will remember a similarly titled essay written by Gia Voeltz and Iain Cheeseman, previous winners of this award—"Building a Path in Cell Biology" (Voeltz and Cheeseman, 2012). I likewise reflect on my journey into cell biology research: my divergence from my formal training as a chemist and informal education as an engineer. My entry into cell biology was rapid and disruptive; I was a chemistry postdoc with George Whitesides in 2004 when a collaborator encouraged me to apply to attend the physiology course at the Marine Biological Laboratory (MBL) at Woods Hole. I hadn't heard of the course, and my only familiarity with Woods Hole came from the deep-sea submersible *Alvin* (which was from the Woods Hole Oceanographic Institution, not the MBL). Whitesides graciously encouraged me to apply to the 2005 course. I did so and, to my surprise, was accepted. My participation in this course proved to be one of the most important events in my career, and I wish to share my experience with emerging (and emerged) cell biologists.

The 2005 physiology course was a seven-week experience in experimental cell biology under the direction of course directors Tim Mitchison and Ron Vale. The course, now more accurately named Physiology: Modern Cell Biology Using Microscopic, Biochemical, and Computational Approaches, consisted of one week of rotations in core experimental cell biology techniques in cell biology and biochemistry, followed by three, two-week-long research projects in small teams consisting of students, course faculty, and their research assistants.

DOI:10.1091/mbc.E13-07-0401

Douglas B. Weibel is the recipient of the 2013 Early Career Life Scientist Award from the American Society for Cell Biology.

Address correspondence to: Douglas B. Weibel (weibel@biochem.wisc.edu).

Abbreviation used: MBL, Marine Biological Laboratory.

People

Daily interactions with outstanding cell biologists were certainly the highlight of the course; they played a major role in shaping my long-term interests in cell biology. The student body consisted of 25 scientists from diverse scientific, cultural, and professional backgrounds, hailing from graduate programs, postdoctoral positions, and faculty posts at top research institutions around the world (Figure 1). Leaders in cell biology and related fields also visited the course on a weekly basis to lecture and interact with students. My discovery of cell biology was largely a product of input from classmates and course faculty. The course format and time frame made it natural for me to form meaningful relationships and lifelong friendships with brilliant young scientists and faculty.

Science

The 2005 course provided a broad and diverse introduction to cell biology. It covered topics spanning prokaryotic and eukaryotic cell biology and placed a strong emphasis on applying quantitative approaches to experimental biology. In fact, the first week of the course included a weeklong primer in MATLAB and an opportunity to discover how to apply it to analyze, interpret, and quantify experimental data. We wasted no time conducting imaging experiments using marine organisms, and I recall the awe (and, to be honest, some embarrassment at my naiveté) I felt when, for the first time, I watched the process of fertilization and early development of a sea urchin unfold. Those feelings of wonder surfaced repeatedly throughout the course, and I soon learned to see each experience as a cool new opportunity. These experiences included (but were by no means limited to) 1) collecting sea urchins and isolating sperm; 2) performing small interfering RNA studies in *Caenorhabditis elegans*; 3) learning how to *really* use a microscope: calculate the limitations of a particular electron-multiplying charge-coupled device and fit the point-spread function back onto the data to increase the resolution of the image; and 4) learning how to take a microscope apart and put it back together. I worked on a range of projects, each with different course faculty. With classmate Ian Schneider and faculty

FIGURE 1: Students and faculty in the 2005 physiology course.

Shahid Khan and Ron Vale, I studied the blue-light response of *Escherichia coli* cells. With course faculty Clare Waterman and classmate Andrea Stewart, I studied the dynamics of proteins in mouse fibroblast focal adhesions. With course faculty Tony Hyman and classmates Chi Pak and Léa Trichet, I studied proteins that alter *C. elegans* embryo dynamics during the early stages of development.

The pace of the course was ferocious, and the intensity level was set high to accomplish meaningful science in a short time frame. We pulled sofas into the lab for recovery between 24-hour experiments; rediscovered that, when tired enough, napping on a cement floor is comfortable; and embraced a work-hard, play-hard attitude (Figure 2). It was common for students to dash outside for a swim or to go sailing between experiments, to play pranks on coworkers, or to spontaneously break out into a late-night dance party in the lab. One unfortunate classmate developed stress-induced shingles from his intense work ethic. I was physically and mentally drained and simultaneously euphoric when the course ended. In addition to learning the ins and outs of cell biology, I learned to identify important questions and to use modern cell biology approaches to study them.

Environment

The environment for the MBL—rustic Woods Hole, Massachusetts—is a grand part of the physiology course. It can be difficult to imagine a cutting-edge biological research station located in this part of the state. Beautiful beaches, harbors, and woods surround the MBL, and the town has the slow pace of a coastal New England town. In

FIGURE 2: The author taking a break from an all-night research session in the MBL lab.

the summer, however, the campus percolates with energy and ideas as scientists from all over the world converge on the MBL to populate nearly a dozen courses and many research labs. During any week, a broadly inclined scientist can find multiple talks by world experts in areas of science ranging from microbes to neuroscience. The level of camaraderie at the MBL is high, and students and scientists from different courses and labs meet each other (through sports, eating together, partying) and become fast friends. Local families join MBL scientists for weekly science colloquia on a range of biological topics. Importantly, the MBL has a rich tradition of biological discovery both past and present, and participating in the physiology course enables one to be part of that tradition.

BUILDING A PATH *IN* CELL BIOLOGY

The physiology course changed my scientific trajectory and shifted my equilibrium slightly away from chemistry and engineering and toward cell biology. We currently use chemical and engineering techniques to study cell biological phenomena in bacteria, with a particular interest in how bacteria control protein localization in space and time. As we pursue questions in this area, we benefit from collaborations with outstanding cell biologists (too many to name here—you know who you are!). As outsiders in the field of cell biology, we have a pragmatic view of our capabilities and have learned that collaborations enable us to penetrate deeper into the field and make sure we are asking broad and meaningful questions.

As our lab has grown, my own graduate students have attended the physiology course (under course directors Dyche Mullins and Clare Waterman), and I anticipate that future students will continue the tradition (under current course directors Jennifer Lippincott-Schwartz, Wallace Marshall, and Rob Phillips). It is safe to say that graduate students from our lab who have attended the MBL have—like myself—experienced a scientific and professional transformation. They returned to the lab with a noticeable scientific confidence, a new perspective, new skill sets, insight into how to identify and address challenging cell biological questions, and refreshed enthusiasm. They brought new ideas to the group and injected them into ongoing projects, and pushed projects in new directions. It is possible that I am imposing my enthusiasm for the course on their experiences, so I suggest you ask them yourself; I would be happy to put you in touch at the ASCB annual meeting.

Galileo is reported to have stated, "Measure what is measurable and make measurable what is not so." Our path in cell biology has closely followed this philosophy, and, as described above, the process of navigating this field was largely facilitated by the physiology course. At the MBL, my eyes were opened to the field of cell biology, my imagination sparked, and a foundation was created for key methods our lab has developed (and is actively developing) for manipulating bacterial cells, cell walls, and membranes to study protein and lipid localization and regulation in bacterial cells. For example, using these techniques, we have demonstrated that negative curvature causes the accumulation of anionic phospholipids in membranes, which bind to and regulate a broad family of bacterial proteins. To complement these studies, we are developing a toolbox of small-molecule inhibitors of key bacterial proteins involved in division, cell wall assembly, and chromosome segregation, and are applying these tools to study these processes. As the targets of these compounds are essential, modifications to their chemical structures enable us to introduce new families of chemotherapeutic agents for antibiotic development. Confident on our path, we strive to "measure what is measurable and make measurable what is not so."

More information on the course can be found here: http://hermes.mbl.edu/education/courses/summer/course_physio.html.

REFERENCE

Voeltz G, Cheeseman I (2012). Building a path in cell biology. Mol Biol Cell 23, 4145–4147.