Richard Cheney: Life on the move

Cheney's work focuses on the molecular basis of cell movement.

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Richard Cheney

Richard Cheney grew up in a small town in the Cascade Mountains, spending many summers exploring the local creeks and forests. His parents encouraged his early interest in science, taking him to aquariums, letting him set up a chemistry lab in the bathroom, and even allowing some unwise experiments, like making rocket fuel on the stove. When his parents bought him a small microscope, Cheney was utterly fascinated by the beautiful spirogyra, diatoms, and copepods from the pond behind the house.

Today, Cheney studies the movements of microscopic life in his lab at the University of North Carolina School of Medicine. His work is centered on understanding the molecular players that mediate various forms of cellular movement. We contacted him to learn more.

Where did you study before starting your own lab?

I did my undergraduate work at Oregon State University, where I majored in biochemistry and biophysics. Although this was challenging, it provided a rigorous and useful foundation for my subsequent research. I spent my last two years doing undergraduate research with George Rohrmann, a pioneer with baculovirus, where I received great hands-on experience in protein biochemistry. I had also become fascinated by the idea of working out the molecular bases of synapse formation and axonal transport, so for graduate school I joined Mark Willard's lab at Washington University in St. Louis. Wash U was an exciting place for molecular neurobiology, and the Willard lab had done classic work with axonal transport and had recently identified nerve growth associated proteins such as GAP-43, so it was a very stimulating environment. My thesis research focused on a major brain protein that the lab had named fodrin, but that we now know as nonerythroid spectrin. This led me to a lot of protein purification and antibody work, with the eventual goal of understanding the structure of the spectrin cytoskeleton in nonerythroid cells. The one place where this worked well was in the stable and beautifully organized cytoskeleton of the intestinal brush border, where a stimulating collaboration with Nobutaka Hirokawa using quick-freeze deep-etch EM allowed us to show that spectrin linked microvillar actin bundles to one another and the membrane.

When I was considering possibilities for a postdoc, I wanted to get back to neurobiology but, as a backup, met with Mark Mooseker at Yale. Mark had done much of the classic work on the brush border cytoskeleton, including work on what was then the only unconventional myosin known in mammals, brush border myosin-I. The first thing Mark said to me was that there might be a myosin I in growth cones. He asked if I would be interested in identifying it, and I was instantly hooked. Unfortunately, after several months of chasing will-o-the-wisp bands in blots, I wasn't finding anything. I thus started to work with Enilza Espreafico, a student from Roy Larson's lab in Brazil, who was working to make monoclonal antibodies to p190, a protein her lab had identified in brain actomyosin. We decided to clone p190, leading to a wonderful long-term collaboration and to the cloning and localization (1), as well as the purification and characterization of myosin-V (2). The work with myosin-V also led us to define the IQ motif as a calmodulin/light chain binding site and to perform phylogenetic analyses showing that the myosins weren't just divided into myosin-I and myosin-II, but instead formed a large superfamily with many distinct classes. In addition, a PCR strategy I had designed to identify novel myosins was revealing that a typical mammalian cell expressed upwards of a dozen or more unconventional myosins. The Mooseker lab was filled with an incredibly stimulating group of students and postdocs, and at times we were discovering a new myosin every week. Since our main work with myosin-V was leading us to believe that it might be processive, a then novel activity for a myosin, Mark suggested that we collaborate with Jim Spudich's lab at Stanford, which had just developed the dual beam optical trap system to measure myosin step sizes. Going to the Spudich lab for the first myosin-V stepping experiments was incredibly exciting, and revealed that myosin-V was indeed a processive motor and that it took very large steps, consistent with its long neck with six IQ motifs (3). Processivity made myosin-V ideal for a host of single molecule studies and has allowed much progress in understanding the fundamental mechanisms of myosin stepping.

> "Imaging also allows one to appreciate the beauty of cell biology in a natural and intuitive way."

What is your lab actively working on?

Right now most of our research is focused on myosin-X (Myo10) and filopodia. The mechanisms by which Myo10 induces huge numbers of filopodia are still not very clear, and I'd like to figure this out. I'd also like to understand the functions and composition of the filopodial tip complex, although at this point it isn't clear if the tip is a relatively stable structure

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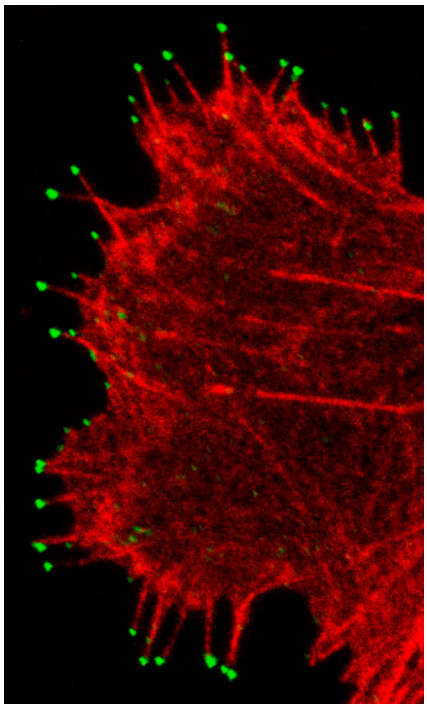

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PE1 cell showing localization of endogenous Myo10 (green) at the tips of filopodia labeled with phalloidin (red).

or a set of proteins that independently localize there. I am particularly intrigued by the long range movements of Myo10 within filopodia that we term intrafilopodial motility. We were able to detect extremely faint particles of Myo10, probably corresponding to individual dimers, moving rapidly up the shafts of filopodia at rates of over 800 nm/s (4). This represents a novel form of motility, and raises questions about what Myo10 might be transporting and if this kind of movement in filopodia is analogous to the intraflagellar transport of cilia and flagella. The small size of filopodia and their relatively simple and polarized organization also makes them attractive targets for modeling to develop a rigorous understanding of processes such as filopodial growth and transport. To me, filopodia provide an interesting middle ground between the simplicity of an in vitro motility assay and the daunting complexity of a living cell. Since there is growing evidence showing that Myo10 is up-regulated in major forms of cancer and is important for invasion, it will also be important to investigate the functions of Myo10 and filopodia in cancer. In this regard, we have become very interested in the filopodia on the basal surface of epithelial cells since the components of basal filopodia may be hijacked by cancer cells to form invadopodia. It will also be important to investigate the organismal functions of Myo10.

What kind of approach do you bring to your work?

I am a reductionist at heart and like to focus on situations where a given molecule or simple biophysical principle has a large effect. I particularly enjoy new areas of research where little is known. Although I was trained as a biochemist, I consider myself a cell biologist and, over the years, my lab has shifted to live cell imaging to determine what molecules are doing in cells. Live cell imaging is also ideal for discovery driven science and for suggesting hypotheses. My favorite way to spend Friday afternoon is in the microscope room going over the latest imaging data with a student or postdoc who has discovered something new or unexpected. Imaging also allows one to appreciate the beauty of cell biology in a natural and intuitive way.

> "It is hard to beat the intellectual excitement of science [and] the thrill of discovery."

What did you learn (or not) during your PhD and postdoc that helped prepare you for being a group leader?

My thesis advisor Mark Willard was very supportive and also gave me independence, which provided good training for running projects on my own. By letting me oversee the myosin-V project and work with a series of students, my postdoctoral advisor Mark Mooseker gave me invaluable experience in running a small group. Although I thought I knew how to do science when I started my own lab, I was unprepared for the huge amount of work and intellectual energy it took to deal with things like animal care protocols, hiring guidelines, and NIH accounting rules. Working with the students and postdocs in lab was a great antidote to this.

What hobbies do you have?

I enjoy outdoor activities such as hiking, backpacking, cross-country skiing, and caving. One of the advantages of life in Chapel Hill is that I can start my day with a walk along the creek behind our house and get into lab a few minutes later. The mountains and beaches here in North Carolina are also very beautiful, and I try to get out to them a couple of times a year. I especially enjoy taking my family back to the Northwest for a week or two each summer to go backpacking and mountaineering.

What do you think you would be if you were not a scientist?

I spent three summers in college fighting wildfires with the forest service, including a summer on the volcano fire crew about a month after Mt. St. Helen's blew up. I loved the physical work, excitement, and camaraderie of firefighting and was tempted to stay with it. That being said, it is hard to beat the intellectual excitement of science, the thrill of discovery, and the opportunity to work one-on-one with students and postdocs.

1. Espreafico, E.M., et al. 1992. *J. Cell Biol.* 119:1541–1557.
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3. Mehta, A.D., et al. 1999. *Nature*. 400:590–593.
4. Kerber, M.L., et al. 2009. *Curr. Biol.* 19:967–973.

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Cheney and family on the summit of Mt. Adams.