People & Ideas

Jonathon Howard: Motor proteins go walkabout

Howard studies motor proteins and how they shape cell behaviors.

Kinesins are a large family of plus-end–directed microtubule motor proteins. They are involved in many cellular processes, including organellar trafficking to cell division and regulation of the microtubule cytoskeleton.

Jonathon Howard began studying kinesins shortly after kinesin-1 was discovered (1). Thanks to his efforts, the motor protein field has made major strides toward understanding the mechanical properties of several kinesin motors (2–4) and the impact of motor proteins on microtubule dynamics (5), flagellar motility (6), and more. But there's yet more territory to cover in this long trek, as we heard when we called him at his new lab at Yale University.

PHOTO COURTESY OF JONATHON HOWARD

Jonathon Howard

WELL TRAVELED, WELL READ

I understand that you're originally from Australia…

Yes, I grew up in Sydney. Probably the most memorable thing to me about growing up there was the Australian bush. We lived right near Ku-ring-gai National Park, and I always loved spending time in the bush. I think I imprinted on the eucalyptus trees and the subtle beauty of the flowers, valleys, and creeks. I miss it, having been away from Australia now for 25 years or so.

> "That was how we discovered the processivity of single kinesin molecules."

If you want to see eucalyptus trees, you can always visit California…

But the trees in California haven't got all the parasites that the southern Australian ones have, so they grow much taller in California. They just look bizarre to Australians. [Laughs]

How did you end up coming to the States then? Clearly not for the trees…

I had completed my PhD in Australia on vision and then spent a year in Bristol, England, working with Jonathan Ashmore on hearing. But things weren't going very well for me there, so I took a position instead with Jim Hudspeth in San Francisco. And that worked out much better. For the next three or four years, we did a lot of exciting science together on the mechanobiology of hair cells in the inner ear.

What got you interested in that topic?

Actually, I first became interested in hearing—and biology in general—when I was an undergraduate. I was a math major with a minor in applied mathematics, so I studied very little besides mathematics until one day I came across Hermann von Helmholtz's work. He discovered the conservation of energy, but he also did incredibly interesting work on musical instruments, using Fourier analysis to describe the richness of notes and harmonics. I read his book "On the Sensation of Tone," and in the back of the book was an appendix containing his theories on how hearing worked. I was fascinated by this even though I knew nothing about neurobiology at the time.

When I found out that there was a Department of Neurobiology in Canberra at the Australian National University, I went for a visit and was excited to learn that there were plenty of things for theoreticians to do there. For my PhD I worked with Simon Laughlin, who is an experimentalist, and Allan Snyder, who's a theoretician, on the optics and electrophysiological properties of the fly compound eye.

KINESIN'S LONG WALK

And then as a postdoc you finally got to work on hearing…

Jim was working on the hair bundle, which is the mechanically sensitive structure in the sensory hair cells of the inner ear. Force acting on this structure causes ion channels to open. I reasoned that, when the hair bundle experiences a force and when the ion channel opens, there should be a little bit of give as the ion channel opens. The hair bundle should be a little bit softer in the region where it's sensitive to displacement. But if you push on it in a direction that doesn't cause the ion channels to open, then it should be stiffer. I worked out a theoretical model for this—what we called the "gating compliance"—and then tested the model to show that gating compliance is real.

But soon you were publishing papers on kinesin. How did that happen?

Jim and a former graduate student, David Corey, had theorized that there is a spring-like element connecting the hair bundle to an ion channel. We suspected that a motor protein, probably myosin, set the tension on this spring-like element, and I thought that it would be extremely interesting to work on these motors. The apparatus I developed for measuring the gating compliance was very, very sensitive, and I thought we should be able to measure the forces from single motor proteins.

Then Ron Vale moved into the lab next door to Jim's. He was working on a protein called kinesin that had just been discovered at Woods Hole. We decided to try making measurements on kinesin instead of myosin.

Text and Interview by Caitlin Sedwick
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You discovered kinesin's processivity: that a single motor can run for a long distance along a microtubule before falling off…
Ron had a microtubule gliding assay where you first put the motors on a surface. Then you put microtubules down, and the microtubules glide along the surface. One of the first things that I found was that the microtubules moved very smoothly along the surface. There was no hint of the step sizes of individual motors because all of their discrete movements were averaged out over probably hundreds of motors. But if we diluted the kinesin density so that only a few motors could interact with a microtubule at any time, then at low dilutions you suddenly wouldn't get any motility at all.

What I thought must be happening was that, at high densities, kinesin motors would be propped up by all the neighboring motors. However, at low densities the motors would just fall over, bind to the surface they were plated on, and start to denature. So, I opened up the Sigma catalog and started ordering proteins that I thought could block the surface. When I put some cytochrome *c* down I started seeing motility at very low densities. That was how we discovered the processivity of single kinesin molecules.

SCALING UP

Kinesin-1 captured your attention for several years…
After San Francisco I went to Seattle because I felt it would be a fantastic place to work on the problem of how motor proteins generate force. Kinesin was very good for that work because single kinesin molecules are sufficient to generate force, which meant we could study the behavior of single molecules. But after several years I felt that we had a good idea about force generation at the single molecule level, and I thought it would be a great time to go back into the cell and start to investigate complex motile behaviors. That was why I decided to go to the Max Planck Institute in Dresden. It's a great environment in which to study cell biology.

PHOTO COURTESY OF JONATHON HOWARD

Howard and family just moved to New Haven.

What got you interested in other kinesins?
I became a postdoc at UCSF in 1985, just after Tim Mitchison and Marc Kirschner discovered microtubule dynamic instability. This was a big discovery that generated a lot of excitement. Later, Tim's group was the first to show that MCAK, or kinesin-13, is a microtubule depolymerizing protein.

My lab used the single molecule assays we developed for working on motility to study MCAK's depolymerase activity. We also worked on kinesin-8, which is extremely interesting because it is a microtubule length-dependent depolymerase. We were studying the effects of these motors on stabilized microtubules as models of the GTP cap, which was thought to be at the end of growing microtubules and whose loss was thought to cause microtubule catastrophe. We thought these motors might cause catastrophe by eating up the microtubule GTP cap.

We've devoted a lot of effort into studying how kinesin-8 and kinesin-13 regulate microtubule dynamics, and today we're still very interested in the regulation of microtubule dynamics. In fact, in collaboration with Tony Hyman's lab, we recently had a breakthrough on purifying tubulin from yeast. Now we can get enough tubulin to study microtubule dynamics and microtubule-associated proteins in yeast, which has very few posttranslational modifications to tubulin.

The other major project here is one that we began working on in Dresden and that is something that's really always fascinated me: flagellar motility. *Chlamydomonas* use a beautiful sinusoidal beat for cell locomotion. It's orchestrated by axonemal dynein motors through a very interesting collective behavior that we're quite interested in understanding.

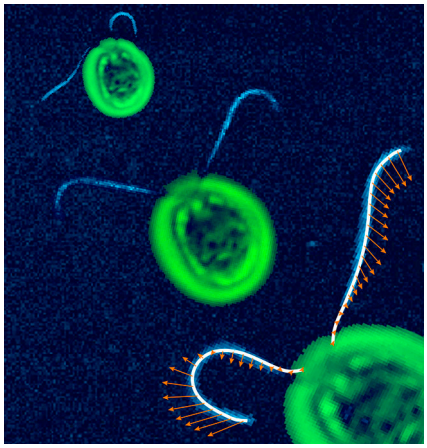

IMAGE COURTESY OF VEIKKO GEYER AND BENJAMIN FRIEDRICH

Force vectors (orange arrows) during *Chlamydomonas* flagellar motility.

> "I'm excited to be back in an academic environment and to start working on a new book."

Why did you recently return to the US?
There were many reasons. One of them is that my wife is a scientist also but she did not have a great situation in Germany. For her to come to Yale was really fantastic because she works on RNA biology and Yale is a mecca for RNA research. And when I looked at my life and career, I felt I really wanted to write another book. The first one I wrote, *The Mechanics of Motor Proteins in the Cytoskeleton*, was published in 2001. It was a very rewarding experience.

I wouldn't be able to write another book as a Director at a Max Planck Institute because, to write, I really need to be able to teach. I'm excited to be back in an academic environment and to start working on a new book.

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