

Q & A

Jonathan Scholey

Jon Scholey is Professor of Cell Biology at the University of California, Davis, where he studies molecular motors, microtubule-based motility and protein machines. His current research focuses on intraflagellar transport and cilium biogenesis, the assembly and function of the mitotic spindle, and (with mathematician Alex Mogilner) the quantitative modeling of mitosis and motility. He teaches an undergraduate class in cell biophysics and a graduate class in cell biochemistry.

What is interesting about cell biology? Understanding the principles by which molecules form living, moving, reproducing cells is a fundamentally fascinating scientific problem. I also enjoy its interdisciplinary nature — cell biologists currently use biochemistry, microscopy, genetics, physical sciences and, increasingly, mathematical modeling to probe the molecular basis of cell structure and function.

How did you become interested in biology in the first place? I was lucky enough to become interested in science early on, as a kid in Yorkshire. By the time I started grammar school I was already interested in science and throughout school I loved chemistry and also biology, especially the parts that had to do with genes, enzymes, metabolism and cells.

How did you decide on a career in science? As I recall, I focused on pursuing my scientific interests and, by good fortune, a rewarding career evolved over time! As an undergraduate at King's College, London, I studied for a B.Sc. in cell and molecular biology, and this turned out to be a superb degree course organized by the MRC Cell Biophysics Unit in Drury Lane — a research unit set up by J.T. Randall to apply

physical principles, such as X-ray diffraction, hydrodynamics, and light and electron microscopy to cell and molecular biology. This interdisciplinary approach to cell biology was reflected in our degree curriculum which, in addition to typical classes in biochemistry, molecular biology and genetics, included advanced classes on the physical chemistry of macromolecules, microscopy (including optical theory), enzyme systems and macromolecular assemblies. The latter class, with lectures by Gerald Offer, Dennis Bray and Maurice Wilkins, covered allosteric enzymes, the assembly and symmetry of protein assemblies such as virus shells, and muscle contraction and cell motility; this class was a major influence in my decision to pursue research on the molecular biology of cells. I loved my undergraduate experience and managed to emerge with a first class degree and a studentship to do a PhD in molecular biology at the MRC Laboratory of Molecular Biology in Cambridge.

How did you choose your research topics? I pursued my interest in the general problem of how molecules form cells and I fell on my feet — I had two fantastic mentors with different, equally powerful approaches to science. My thesis advisor, Jake Kendrick-Jones, was a brilliant and innovative 'hands on' protein biochemist who studied myosin-based motility and took time to teach me laboratory techniques as we researched the regulation of myosin assembly and activity. While reading papers on motility for my thesis, I decided the next problem I wanted to study was the molecular mechanism of mitosis, mainly because, during this process, the motility machinery performs such a fundamental biological process as the segregation of replicated genes. I was fortunate to get an opportunity to come over to the US to study this problem as a post-doc with Dick McIntosh. I found Dick to be an insightful thinker who sacrificed doing experiments full time in order to direct a sizeable laboratory

that was performing pioneering studies of mitosis at the University of Colorado in Boulder, a beautiful town at the base of the Rockies. Dick's lab was an exciting intellectual and technical environment to work in, and there I was fortunate to also work with Ted Salmon, Mary Porter, Bill Saxton and others as I learned to use microscopy and biochemistry to study microtubule-based motors and mitosis. Overall this postgraduate/postdoctoral training was a great experience and, by the end of my post-doc, I was even starting to discuss science verbally, something that wasn't always easy for me.

How do you run your lab? Well I think of it as being equivalent to a sports team, with myself as the coach who coordinates the overall game-plan and lab members being the players whose individual skill, creativity and ideas determine whether we win or lose in our efforts to solve the problems we work on. I believe science is a cooperative venture and accordingly I try to emphasize the value of contributing to a team, while at the same time pursuing one's individual scientific and career goals. I've been incredibly fortunate in having some terrific students, post-docs and technicians work in the lab and take us into fascinating new areas. For example, we are excited about our current studies of the mechanisms of mitosis in *Drosophila* embryos and the motors that drive the assembly of sensory cilia on *Caenorhabditis elegans* neurons.

Are there any aspects of your job you wish you didn't have to deal with? The thing I find most stressful is funding, especially around the time when my NIH grants are up for competing renewals, as maintaining our laboratory infrastructure, not to mention the salaries of some hard-working, dedicated lab members, is dependent on success. So like other cell biologists that I know, I work hard at writing proposals and by juggling grants we've managed to stay funded for two decades

now — touch wood. It is hard when a grant gets a non-fundable score, even though we all know its pretty much par for the course for most labs these days, but at the end of the day I feel very grateful to have precious NIH funds to do what we find so interesting!

Do you have a favorite paper?

No. I enjoy reading good papers and I cannot identify a favorite as there are so many excellent ones! How does one choose between classics such as Watson and Crick's paper proposing a structure for DNA, Jacob and Monod's on the operon theory for gene regulation, Casper and Klug on the structure of spherical viruses or Huxley and Hanson's on the sliding filament mechanism of muscle contraction? Focusing only on microtubule-based motility, there are so many outstanding papers its impossible to pick one. But restricting myself to papers from the last decade, one that stands out is from Joel Rosenbaum's lab (Cole *et al.* 1998, *J. Cell Biol.* 141, 993) on the purification of intraflagellar transport particles — a beautiful combination of biochemistry and genetics that exploits conditional motor mutants to purify a new macromolecular assembly required for cilium biogenesis.

Do you have a scientific hero?

Yes, Francis Crick, for two reasons. First, he epitomized clear thinking and seemed able to reduce even the most complex biological process to sets of simple principles — thus he was able to identify important scientific problems and to attack them with unprecedented insight. Second, he took an interdisciplinary approach and applied whatever expertise was needed to solve the problem he was working on, from helical diffraction theory and chemical bonding when working on DNA structure and coiled-coils, to phage genetics when working on the triplet nature of the code. Indeed, when reflecting on the latter project, he emphasized the limitations of taking a single,

albeit clever, genetic approach, as solving the code, codon for amino acid, required scientists who were prepared to dig in, get their hands dirty and do biochemistry.

You work on an undergraduate campus, rather than a research institute: is that by choice?

Yes. I believe that teaching is an important part of science. I know I owe a lot to my own education and I feel that, by teaching, I am paying back a debt by educating potential future scientists. More generally I feel that the basic principles of biology embodied in the central dogma of molecular biology, the cell theory, Mendelian genetics and evolution by natural selection are key to understanding our existence, and they are not all that difficult to understand, at least in outline. So it is reasonable to expect every educated American to be just as familiar with these ideas as they are with the US constitution, yet this is seldom the case. It is scary to hear our President say that 'intelligent design' should be taught in science classes alongside Darwinian evolution; the public might be less tolerant of such nonsense with improved science teaching at all levels and I feel that undergraduate teaching contributes to this effort. I sometimes find lecture preparation tedious, but overall I enjoy teaching cell biochemistry and biophysics classes, especially at a fine public university such as the University of California.

What are the important problems in cell biology?

It is broadly recognized that one wants to understand the physical, chemical and engineering principles by which macromolecules organize themselves and function as components of 'protein machines' — macromolecular assemblies whose moving parts are motor proteins that generate nanometre scale displacements and pico-Newton scale forces to coordinate virtually every aspect of cell function. These include, for example, the machinery involved in gene expression, the cell division machinery, the motility

machinery in the leading edge of a moving cell or in a muscle sarcomere, the rotary machines of ATP synthesis and the signal transduction machinery. A major challenge for cell biologists is to obtain a quantitative and molecular understanding of the general principles by which such machines function as whole entities and to understand how different protein machines are integrated to produce a living cell.

Can mathematical modeling help solve such problems?

Yes. Ultimately one would like to formulate a set of simplifying principles that can describe the dynamic output of a protein machine in terms of the properties of all its parts. Explanations based on purely qualitative descriptions, equivalent to, say, the periodic table or genetic code, are unlikely to prove satisfactory in this case, but I think mathematical modeling, combined with molecular and biophysical studies, may provide general rules. At the University of California in Davis, Alex Mogilner and I pool resources to co-direct a small group of modelers and cell biologists in trying to analyze the mitotic spindle machinery this way.

Any ambitions beyond research and teaching?

If someone ever gives me *carte blanche* to build a cell biology department, I'd like to recruit an interdisciplinary group of faculty who use biochemistry, genetics, microscopy, physical science and mathematical modeling to dissect the assembly, mechanisms and functions of protein machines, from single molecules to the system level. Actually, together with my friend and colleague, Steve Kowalczykowski, I proposed the formation of such a group here at the University of California in Davis, but in their wisdom, our leaders in the administration did not bite.....oh well, back to the lab!

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