ELEMENTS

Randy Schekman

As a pioneer in the field of membrane traffic, Randy Schekman shares a compelling historical perspective on the roles of various disciplines in forming a field and defining a scientist.

Membrane traffic is no different from many other fields in which advances in technology pave the way for advances in our thinking about biological processes. The study of membrane traffic has a history that dates back to the introduction of electron microscopy to the field in the 1960s and 70s and to cell and fractionation techniques before that (*Nat. Cell Biol.* **6**, 483–486, 2004). Since then, the functional approaches of genetics and biochemistry have led to a rich understanding of the machinery involved in sorting membrane and protein components as they make their way through the cellular maze, fusing and budding with one organelle or another. This could not be more evident than when one looks at the course of Randy Schekman's 30-year career at the University of California, Berkeley.

Schekman's group began with a search for chemical agents that block yeast secretion. He notes that it was fortunate that they were unsuccessful because it led to a different course that would occupy them for decades to come. Schekman explains that his "key moment came early on with the isolation of the first *sec* mutant." Once Peter Novick, then a graduate student, called him down to the electron microscope room to look at the mutants, "it was immediately evident that I was going to be busy for some years sorting this out—so that was a career-defining moment." The first of these budding yeast mutants, *sec1*, is featured on this month's cover. The collection of *sec* mutants described in Schekman's early studies with Novick has provided insight into every aspect of membrane traffic, including signal-mediated transit between the endoplasmic reticulum and the Golgi complex as well as endocytosis from the plasma membrane through endosomes and lysosomes.

It is impossible to place Schekman squarely into one scientific discipline. He was formally trained as a biochemist and enzymologist, but cell biologists are quick to claim him as one of their own. Indeed, he served as president of the American Society for Cell Biology (ASCB) in 1999. Says Schekman, "I'm a cell biologist in the sense that the topics that I study are the traditional topics of cell biology, but the principal means at my ready disposal are the techniques of the biochemist. There are a few of us like that in cell biology."

In keeping with his biochemical roots, his group has recently established an *in vitro* vesicle-budding reaction to explore membrane protein traffic from the endoplasmic reticulum. The assay was most recently used to show that defects in a multimeric protein complex that coats transport vesicles (COPII coat) are responsible for at least two rare diseases. Though superficially there is no connection between the diseases, they highlight a general principle that his group established in budding yeast: the process of sorting and transport, at least early in the pathway, is highly selective. Schekman says, "in the history of this subject, the dominant feeling 15 to 20 years ago was that secretory proteins were not actually sorted," but rather they were secreted "by default." But the above results support the model developed in his lab, which maintains that a default pathway "can't be true for secretory proteins and membrane proteins;" instead there is a sorting signal that can be decoded by the COPII coat.

Schekman firmly believes in the power of biochemistry to elucidate cellular pathways and to reveal the mechanistic details of protein function. He says, "I'm amazed when people who use genetics and traditional tools of cell biology and then once they've recombinantly expressed an interesting protein they go right to trying to solve its crystal structure without necessarily knowing functionally what the molecule does except in a very general sense." He points out that this is "a common path that people use to just skip right over the functional biochemical analysis. There are a few of us left that feel very strongly that that is a powerful approach to solving problems."

While acknowledging that "the new technologies are really quite remarkable," Schekman maintains that "classical genetics and classical biochemistry still have a role." With the widespread use of proteomics and genomics strategies, it is perhaps even more important to reintroduce the classical techniques, as these 'omics' strategies "are not sufficient to solve problems." Schekman believes that "divorced from functional analysis where you understand things one molecule at a time, it's not the full picture." Given the legacy that was created by the generation of the *sec* mutants, Schekman occupies a middle ground among numerous disciplines. And although he wouldn't have minded having the ability to follow dynamic processes in real time 30 years ago, he is perplexed by the unwillingness of some scientists to embrace the techniques that will lead to functional understanding. He notes, "the traditional tools of the enzymologist in studying complex pathways still are as powerful as they always were, and yet less frequently used by people to solve problems."

"The traditional tools of the enzymologist in studying complex pathways still are as powerful as they always were."

When he is not fueling his passion for membrane-traffic research, or fielding the "new and interesting naïve questions" from freshman students in one of the seminars that he leads, he advocates on behalf of public institutions like UC Berkeley that struggle to compete with private universities like Stanford in light of the systematic decline in investment in public education. In the public speaking he does on behalf of the university, he is pleased to find numerous alumni who are "genuinely grateful that they had this opportunity, many of them at a time in their life when they couldn't have gone to a place like Stanford." It is not common anymore to find an accomplished researcher and professor who has stayed at one institution for as many "defining moments" as Schekman has. It is just as rare to find one who speaks openly about his opinions, all the while demonstrating the idea of maximizing what you already have, be they tools or training, to succeed in science. There must be something to his dedication and his embrace of traditional tools, though, given that he was able to turn a random collection of yeast mutants into an entirely new scientific discipline.

Mirella Bucci, Berkeley, California