Profile of Randy Schekman: Reflections on his first year as PNAS Editor-in-Chief

While the pace, tools, and culture of science have evolved over Randy Schekman's distinguished career, he has continued to hold on to some core principles of research. Inspired in part by his mentor, Nobel laureate Arthur Kornberg, Schekman takes a "reductionist" slant to science—identifying, separating, and purifying the individual components of a system so that each can be intently studied until its nuances are understood. Schekman also believes that although new technologies certainly have their place, classical techniques, such as biochemical assays, remain powerful approaches to tackling fundamental questions. As editor-in-chief, Schekman holds these same values in his vision for PNAS.

Although he expresses a desire to continue to expand and modernize the journal by bolstering online content and fine-tuning the rules governing member submissions, his main goal is to turn back the clock. "This journal was considered one of the best back in the 1960s and 70s," he says. "When I was in Kornberg's lab, we were all dying to have our papers in the *Proceedings*; anything less was almost an embarrassment. Today, things have changed, and other journals have risen to prominence, and we need to make scientists 'want' to put their best stuff in our journal again." As proof, Schekman recalls that his first PNAS paper from Kornberg's lab was just the type of major discovery that people wanted to publish in PNAS (1).

Schekman took the reins of PNAS in November 2006, following in the footsteps of Nicholas R. Cozzarelli just as he had many times before. Schekman acknowledges that his own path closely mirrored Cozzarelli's: studying under Arthur Kornberg; becoming a professor of molecular and cell biology at the University of California, Berkeley (Berkeley, CA); and assuming the chair of the National Academy's biochemistry section. Just as Cozzarelli was able to talk to a variety of scientists, Schekman's academic background—from his early training focused on biochemistry and his longstanding work on the mechanics of the secretory pathway—has enabled him to intelligently cross a multitude of scientific disciplines.

Schekman also brings two decades of editorial experience to PNAS, including turns as editor of the *Journal of Cell Biology*, the *Annual Review of Cell Biology*, and *Molecular Biology of the Cell*, in addition to stints on the editorial board of several other journals. And although his PNAS editorship is another similarity to Cozzarelli, Schekman is clearly his own man. "Nick set the bar very high, and I at least want to match it, but I'm not his clone; I'm going to try things my way."

Randy Schekman

Swimming in Science

"I remember the exact moment," says Schekman. "Seventh grade. I walked into the school science fair, and the whole world was revealed to me." All around him fellow students, some only a year older, were putting their exhibits on display, and Schekman felt the tingle of competition. "Athletics weren't for me," he notes, "but this was an immediate turn-on." The following year he began exhibiting his own science projects, a pursuit that he would continue over the course of his high school years, winning awards and accolades along the way. On three occasions, the precocious Schekman advanced from his local high school competition in Anaheim to the California State Science Fair. "Every year was a new adventure," he says of the time.

His adventures began with pond scum, of all things. "I was fascinated with all the tiny things that lived in the water," he says, "so I got a little toy projecting microscope, and I spent hours in my room following all the swimming protozoa." Schekman's excitement with his first scientific instrument was tempered when his father pointed out that it was just a "toy" microscope. "I remember being very upset that he was being so disparaging, so at that point I decided to buy a professional microscope." He began mowing lawns and babysitting to save up money, but his savings never accumulated because his parents kept borrowing from him.

"One day, I just had enough," he says. "I rode my bike to the police station and told the police that I was running away from home because my parents were keeping me from getting a good microscope." Schekman's father had a stern look on his face when he arrived at the station to pick up his runaway son, but that was the afternoon Schekman got his Bausch and Lomb microscope, which enabled him to study his swimming microorganisms in a more professional manner.

An Assorted Training

Schekman entered the University of California, Los Angeles (UCLA; Los Angeles, CA) in 1966, initially choosing pre-med as his major because that seemed like a natural outlet for his interests in biology. "Then I realized there was a whole other world at the university that I hadn't really known about." After doing well in freshman chemistry during his first semester, Schekman was placed in an honors section taught by Willard Libby, the inventor of carbon-14 dating. One of the course requirements was to work in a chemistry laboratory, and Schekman ended up in the laboratory of Michael Conrad, a molecular biologist in the chemistry department.

"The first thing he had me do was read the then-first edition of a book by James Watson called *Molecular Biology of the Gene*, which really opened my eyes. I remember reading it in my leisure time like it was the Bible." The combination of that book and his laboratory experience quickly scuttled Schekman's medical aspirations and sent him on the path toward academic science.

At UCLA, Schekman quickly found himself in the minority among his fellow biology majors, who were taking only the courses for their pre-med re-

quirements and were not especially interested in science. During his sophomore year, he thought about transferring to another school, until he discovered a program for education abroad. One of Schekman's professors mentioned a potential destination, noting that the eminent bacterial geneticist William Hayes had just started a Medical Research Council (MRC) unit at the University of Edinburgh (Edinburgh, U.K.). Schekman was accepted to spend his junior year there.

"After I was accepted to this program," recalls Schekman, "I wrote to Hayes to express my interest in working for him. However, he mistakenly thought I was a sabbatical visitor, so when I arrived they already had set me up with my own office, complete with my name on the wall, and even had me listed in their program as a visiting scientist from UCLA." The confusion was quickly cleared up, and Schekman proceeded to have a wonderful time, even though he didn't get to keep his office.

After returning to UCLA for his senior year, Schekman continued to be consumed by laboratory work, to the point that he eventually stopped going to classes and his grades began to suffer. "I had become so determined to work in a lab that I found course work to be too artificial," he says, adding that his academics didn't drop too badly, noting that he still managed to get accepted to Stanford University (Stanford, CA) for graduate school, which had one of the premiere biochemistry departments at the time.

Schekman had developed an interest in DNA replication while working in the laboratory of Dan Ray at UCLA and had chosen Stanford specifically for the chance to work in that field under Arthur Kornberg. "Maybe I was a little too narrow-minded," Schekman says, "but I knew exactly that I wanted to learn how to dissect a problem biochemically, and I knew [Kornberg] was going to teach me what I wanted to learn."

At Stanford, Schekman befriended postdoc Bill Wickner, who proved to be a bit of a muse on two different fronts. First, he introduced Schekman to the woman who later became his wife, Nancy; second, he helped persuade Schekman to consider studying biological membranes.

At that time, Jonathan Singer at the University of California at San Diego (La Jolla, CA) had just published his fluid mosaic model of membrane structure. "Since he clearly was doing the most creative work on the subject, I went to postdoc with him, not necessarily to pick up a project, but so I could learn the field. I felt it was important to head off and do something new."

That attitude proved fortunate, because Schekman ended up working on a relatively obscure phenomenon: the difference in endocytosis that was observed between neonatal and adult red blood cells (2). "Having worked with microorganisms in the past, I felt that when I was ready to start my own career, I would return to microorganisms." He eventually settled on yeast, which was easy to grow and genetically manipulable. Beyond that, research in yeast membrane assembly lagged behind that of animal cells and seemed to be an area "ripe for investigation." Soon after, in 1976, Schekman was appointed as an assistant professor at Berkeley.

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Entering a Budding Discipline

Schekman's eagerness and admitted naivety about yeast—his only experience was a crash course on yeast genetics he took at Cold Spring Harbor Laboratory (Cold Spring Harbor, NY) after completing his postdoc—contributed to a somewhat rocky start to his career as a principal investigator. His first grant attempt was rejected for a lack of necessary details, and his first experiments likewise met with failure. "I was thinking too much like a biochemist," he says. "I initially thought that we could grow up large quantities of yeast and then inhibit secretion by some chemical means, allowing us to accumulate intermediates in the process. That didn't work." Fortunately, that short-term failure would lead to long-term success.

"Even though I consciously chose yeast as my model because it was manipulable, I didn't think I would ever use much genetics," he says. "But after my first attempts failed, I thought, 'All right, I guess we'll just have to isolate mutants.'" With the aid of a pair of highly skilled laboratory members, graduate student Peter Novick and technician Charles Field, Schekman soon had dozens of mutants ready. Of course, he didn't know whether any of them would pan out, but one day Novick called him over to look in the microscope. "The moment I saw that mutant was accumulating vesicles, I knew that we were going to have 20 or 25 years of work based on continuing that path." Schekman had just found his first secretion mutant, *sec1* (3).

Over the next few years, Schekman and Novick would characterize numerous other *sec* mutants, which affect all exits of the membrane traffic highway, from the endoplasmic reticulum (ER) to the cell surface (4). If there were any drawbacks to their plethora of findings, it was that people started thinking of Schekman as a geneticist. "When this work was first getting published, I kept getting all these inquiries from postdocs and students who wanted to do yeast genetics. And I kept trying to convince them to use the mutants to establish biochemical assays." Schekman hoped all along to use the mutants to study the mechanisms of transport in yeast, in a way similar to Stanford's Jim Rothman (who would later share the 2002 Lasker Award for Basic Medical Research with Schekman), who had developed an *in vitro* system of measuring Golgi transport by using mammalian cell lysates.

For a while, Schekman's group struggled with trying to mimic this system in yeast cells, which have less membrane transport activity than animal cells. Then, in 1985, David Baker, another gifted graduate student—"a true dynamo," says Schekman—joined the laboratory and began developing a functional cell-free system. "He essentially managed to reproduce the first half of the secretory pathway *in vitro*, and these reactions recapitulated the normal process, because mutant lysates were defective compared to non-mutant cell lysates" (5).

The first protein to be uncovered by this system was the product of the *sec23* gene, which is critical for transport between the ER and the Golgi apparatus (5). *sec23* didn't act alone in this process, and soon Schekman found that six proteins (Sec23, Sec24, Sec12, Sec13, Sec31, and Sar1) were required to bud vesicles from the ER; Schekman named this com-

plex COP-II (to distinguish it from another protein assembly necessary for intra-Golgi transport named COP-I). This complex has been a major focus of his research in the dozen years since its discovery (7).

Further probing revealed that COP-II not only pinches the buds from the membrane but also recruits the correct protein cargo. Schekman's findings helped establish that the secretion pathway mediates the highly complex sorting and transport of proteins.

Bringing Back the Golden Age

When he thinks about his tenure as PNAS editor-in-chief, Schekman says that the fast progress and interdisciplinary nature of current scientific research calls for the journal to keep pace. In particular, he notes that the word count limits imposed by many journals, including PNAS, may cause researchers to gloss over some of their data or even discourage them from submitting their work. Last year the journal launched a Feature Article category to encourage submissions of exceptional breadth and importance (8). Other ideas Schekman has for improving the journal can be found in his recent editorial, "Charting the course for PNAS" (9).

This is not Schekman's first time sprucing up a journal. In 1992 he became one of the founding editors of *Molecular Biology of the Cell*, a revamped version of the formerly staid journal *Cell Regulation*. He acknowledges the daunting challenge of achieving his lofty aspirations among all the competition in modern publishing but believes that, in time, this classic can be restored. "When I was in college and getting into science, I'll never forget those first moments surveying dusty old journals in the library, and there was the *Proceedings*. I vividly remember looking through it, and just the feel of it was alluring to me. And for people in college today who are making their career choices, I would like to project—obviously not in the stacks of the library, but on the screen of a home PC—that same allure of science. That's what the *Proceedings* can do."

Nick Zagorski, *Science Writer*

1. Brutlag D, Schekman R, Kornberg A (1971) A possible role for RNA polymerase in the initiation of M13 DNA synthesis. *Proc Natl Acad Sci USA* 68:2826–2829.
2. Schekman R, Singer SJ (1976) Clustering and endocytosis of membrane receptors can be induced in mature erythrocytes of neonatal but not adult humans. *Proc Natl Acad Sci USA* 73:4075–4079.
3. Novick P, Schekman R (1979) Secretion and cell-surface growth are blocked in a temperature-sensitive mutant of *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 76:1858–1862.
4. Novick P, Field C, Schekman R (1980) Identification of 23 complementation groups required for post-translational events in the yeast secretory pathway.*Cell* 21:205–215.
5. Baker D, Schekman R (1989) Reconstitution of protein transport using broken yeast spheroplasts. *Methods Cell Biol* 31:127–141.
6. Hicke L, Schekman R (1989) Yeast Sec23p acts in the cytoplasm to promote protein transport from the endo-plasmic reticulum to the Golgi complex *in vivo* and *in vitro*. *EMBO J* 8:1677–1684.
7. Barlowe C, *et al.* (1994) COPII: A membrane coat formed by Sec proteins that drive vesicle budding from the endoplasmic reticulum. *Cell* 77:895–907.
8. Schekman R (2007) Introducing feature articles in PNAS. *Proc Natl Acad Sci USA* 104:6495.
9. Schekman R (2008) Charting the course for PNAS. *Proc Natl Acad Sci USA* 105:2754–2755.