



## {Wit & Wisdom}

*One researcher's approach to science and service  
has a lasting impact on many.*

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In 9<sup>th</sup> grade, Randy Schekman was socking away his lawn-mowing money. He had his eye on a used Bausch & Lomb microscope at the local pawnshop, and he needed \$100 to buy it. 📁 But his earnings envelope was a convenient source of grocery cash for his parents, who borrowed from it regularly. 📁 Fed up one day after mowing yet another lawn, Schekman biked to the police station and told officers he was running away because his parents were stealing his money and wouldn't let him get a microscope. After a chat with the law, Schekman's dad topped off his son's savings and took him to make the purchase. 📁

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BY EVELYN STRAUSS  
*photography by Mark Richards*

# Schekman's passion for science has prompted bold action at other points as well

—and his audaciousness has paid off. His initial research proposal was so daring, experts trounced it, yet the strategy produced results that have earned him some of the most prestigious awards in biomedical science. Now an HHMI investigator at the University of California, Berkeley, Schekman has illuminated the mechanism by which membrane-bound sacs shuttle proteins within and out of cells. The system provides a way to organize enzymes into unique work stations and avoid cellular chaos. A host of normal activities—for example, insulin release, nerve-cell communication, and growth-factor export during embryonic development—depend on this trafficking process. Defects in it underlie many human diseases, some of which Schekman is studying.

His dedication to science extends beyond his lab and outside his field. He has spearheaded change in professional societies, at major journals, and on his university campus. “Randy has repeatedly taken on huge social responsibilities for science,” says Bruce Alberts, former president of the National Academy of Sciences. “He takes on positions because he thinks he can make a difference. But that requires a lot of work and a lot of personal sacrifice.”

Schekman can't pinpoint the origins of this drive to serve, but he thrives on it. “I've had the benefit of the scientific enterprise and I feel that those who are capable have to stand up so that young people can have the same benefits. I'm well organized and

am capable of doing it, so I do it. But I wouldn't do it if I didn't enjoy it.”

## { *Catching the Bug* }

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Schekman's predilections surfaced early. Wandering around science fairs during junior high school “really turned me on,” he says. “I liked the feel of it—people doing their own things, competing for awards.” In 8th grade, he set up metal-capped honey jars in his bedroom, each containing a different type of dirty water. In this makeshift lab, Schekman grew protozoa and then used a toy microscope to see which creatures flourished best in which types of scum.

After winning several county science fairs, he took fifth place in the California State Science Fair, an achievement for which Vin Scully, announcer for the L.A. Dodgers, interviewed him on television. Schekman was thrilled. “I had hit the big leagues,” he says. “I was a Dodgers fan and he was It, Mr. Dodger.”

Schekman first figured he would be a doctor, he says, “because I didn't know any better.” When he was an undergraduate at the University of California, Los Angeles, *The Atlantic Monthly* serialized James Watson's new book, *The Double Helix*, and Schekman found himself diving into each installment. “Then I knew,” he says. “None of this medicine for me. Working in a lab ... really resonated with me.” Realizing that he needed biochemistry “to get to the depth of what I was interested in,” he apprenticed with master biochemist Arthur Kornberg while a graduate student at Stanford University. Kornberg knew how to “relentlessly dissect a problem,” Schekman says.

He got more out of the Kornberg lab than lessons in how to tease apart a biological process and reconstitute it from its parts. There he met a postdoc named Bill

Wickner, who introduced him to two central figures in his life: Nancy Walls, whom Schekman later married, and the process of membrane assembly. Late at night, Schekman and Wickner ran experiments, played Scrabble, and plotted how to probe this emerging field of research. Schekman became intrigued by the notion that he might study membranes with the techniques Kornberg used to untangle the intricacies of bacterial DNA replication.

Later, as a postdoc with Jon Singer at the University of California, San Diego, Schekman studied membrane biology but felt squeezed by the experimental limitations of mammalian cells. When he set up his own lab, he decided he would exploit the power of yeast genetics to unearth the molecular players in membrane assembly.

## { *Debate and Results in the Lab* }

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By 1976, when Schekman joined Berkeley, scientists knew that membrane-bound containers called vesicles ferry proteins among cellular compartments. They had seen vesicles bubble from the surface of one compartment, detach, and float off to fuse with another—and they had established that different types of vesicles shuttle distinct protein cargo to specific sites. For example, secreted proteins—those the cell exports to its surroundings—travel from a compartment called the endoplasmic reticulum (ER) to the cell surface by way of a structure called the Golgi apparatus. Schekman wanted to know how transport

vesicles form, choose their protein cargo, and home in on their destinations.

Reviewers trashed Schekman's first proposal. "He was not a geneticist, he had never worked with yeast in his life, and he had no preliminary data," says David Sabatini of New York University School of Medicine, who served on the National Institutes of Health study section that evaluated Schekman's request.

Yet he persevered, with funding from the National Science Foundation. He had "incredible optimism and a can-do spirit," says Peter Novick, one of Schekman's first graduate students, now at Yale University School of Medicine. Novick and Schekman triumphed, identifying 23 so-called *SEC* genes involved in protein secretion.

Even then, intellectual sparks flew in the lab, recalls Susan Ferro-Novick, another former Schekman student, now an HHMI investigator at Yale University School of Medicine (and married to Peter Novick). "Randy would build these models and we thought 'Oh no, it can't be that way.' And then we'd have debates. Or he'd encourage us to do experiments that seemed crazy. But they got us started."

With Schekman's projects, "you weren't just filling in facts," says Ferro-Novick. "You had to make leaps. He made it clear that science was not easy and you had to rise to the challenge. I learned how to be a scientist in his lab." Ferro-Novick is one of three former graduate students from the Schekman lab who are now HHMI investigators.

Schekman's discoveries about yeast secretion dovetailed with findings that James Rothman of Columbia University was making in mammalian cells. The two researchers leapfrogged over each other



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*While others played football or a musical instrument in high school, says Randy Schekman, "I watched rotifers crawl around."*

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to establish key features of many protein-trafficking steps.

### *{Terrific Role Model}*

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During this period, Schekman also honed his mentoring style. He would choose a problem and then spur people to solve it

together. "Every person was working to purify a single protein but no protein worked by itself, so everyone had to mix their proteins together," says David Feldheim, who earned his Ph.D. in Schekman's lab and is now at the University of California, Santa Cruz.

While encouraging collaboration, Schekman nurtured his trainees' individuality as well. "In group meetings, Randy would come up with an idea and people would say, 'That's nuts!'" recalls Ray Deshaies, a former student who is now an HHMI investigator at the

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California Institute of Technology. “Other [principal investigators] might have pummeled the opposition into oblivion, but Randy didn’t need to do that. He let people have their own intellectual presence and ideas.”

These traits, as well as an impressive ability to juggle the different parts of his life, made Schekman a terrific role model, says Nina Salama, another former Ph.D. student who is now at the Fred Hutchinson Cancer Research Institute. “He was equally dedicated to science and his family, working from 8:30 until 6:00 or 6:30 and only very occasionally coming in on weekends,” she says. “Randy really showed by example that you can do both, but you have to be organized and have confidence in your decisions.”

Schekman says, “I do work hard and take on too many responsibilities, but I really thrive on keeping busy and

managing to juggle things reasonably effectively.... No doubt I am overextended and some things don’t get as much attention as they deserve.”

Despite the demands of his packed life, Schekman takes time to make people smile. He spends hours planning comic ways to introduce speakers and can make fun of himself, says Salama. “Randy’s wit ... always teeters on the verge of inappropriateness and the joke is often on him.” For example, Salama recalls that when his son was in Indian Guides, a father-son program at the YMCA, Schekman named himself Flying Arrow—until a vasectomy, when he changed the moniker to Broken Arrow.

He periodically poses challenges that focus lab members on the next “big picture” issue. The prize? A gourmet restaurant meal on Schekman’s dime. On one such occasion, the group dressed up

and dined at Domaine Chandon, a winery in California’s Napa Valley.

### { *Nonstop Service* }

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In discussing his favorite movie, *It’s a Wonderful Life*, Schekman reveals part of what propels him toward work that supports the scientific society. “I start crying before the opening credits are finished,” he says. The film is “about loyalty and commitment and the public good. In this small way, in an out-of-the-way place, one person can have an impact on many lives.”

Berkeley qualifies as an out-of-the-way place only if you’re from Manhattan, but Schekman is certainly having an impact on many lives there. “If things get a little tense, you can count on Randy to cut through the haze with some joke,” says Robert Tjian, an HHMI investigator also at Berkeley. Another Berkeley colleague,

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## { *Moving Toward Human Disease* }

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**Although Schekman is still studying** membrane trafficking in yeast, about half of his lab has turned to mammalian cells. His students and postdocs are probing possible trafficking defects in familial forms of Alzheimer’s disease and exploring illnesses known to stem from malfunctioning secretory genes. ➔ **For example, the molecular defect** underlying craniolenticulosutural dysplasia (CLSD), a disease that affects the facial skeleton, was a mystery until recently. In 2006, researchers established that the condition arises from a marred version of Sec23, a protein that Schekman discovered in yeast. Now his lab has discerned how this miscreant molecule is causing trouble: the ER cannot export proteins properly because flawed Sec23 cannot bind and recruit two other Sec proteins that normally shape new vesicles and help them pinch off. ➔ **In the same issue** of *Developmental Cell* where Schekman reported these findings, in November 2007, Jonathan Goldberg, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, published the crystal structure of those two Sec proteins, showing that they snuggle up next to the amino acid in Sec23 that is altered in CLSD. ➔ **The observation that these proteins** embrace this specific amino acid suggests that changing it would disrupt the interaction, just as Schekman revealed through his experiments. “It’s just too good to be true,” he says of the

corroborating evidence. ➔ **But Schekman is not turning** ice buckets into footrests yet. He’s moving on to another cellular mystery: how peroxisomes are formed. These membrane-bound organelles house enzymes that detoxify and break down various molecules within cells. Defects in them can lead to serious diseases (see “Parsing Peroxisomes,” page 20). Scientists had assumed that peroxisomes arise by duplicating themselves rather than by budding off from other membrane-bound structures: no one had detected peroxisomal proteins in other membranes and peroxisomes form in the absence of *SEC* genes. ➔ **In 2005, however, researchers discovered** that one of the two proteins known to be essential for peroxisome formation clusters in the ER and pinches off in a vesicle that becomes a brand new peroxisome. Because *SEC* genes do not contribute to this process, the observation implies the existence of a membrane-trafficking pathway that depends on mostly unidentified genes. Schekman is devising ways to uncloak members of this possible transport network. ➔ **The challenge poses** “another opportunity to discover the rules that govern protein segregation,” says Schekman. If *SEC*-related vesicles are not involved, “what the hell is? We’re going to go back and think more clearly, I hope, about how to find the right genes.” —E.S.

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Michael Botchan, says this gift is especially handy during personnel discussions. “You can disarm people with a good joke or a comment that is at once funny and caustic. Randy has sharp elbows sometimes, and he can use his humor to his advantage. That’s a great talent.”

Schekman acknowledges that “certain people ... get under my skin. Usually this is because of dishonesty or arrogance.... I must admit that I am not a patient person.”

Because he aims to benefit the community rather than himself, “people trust him,” says Botchan. In 1997, Schekman was offered a “very big job.” Most faculty members use such situations to get raises or resources for their own research, but not Schekman. “He negotiated for more junior faculty positions in cell biology,” says Botchan. “That’s atypical.”

Schekman’s influence has rippled across the campus. He chairs the Chancellor’s Advisory Council on Biology, which provides input on the direction of the life sciences, focusing particularly on hiring. When Schekman took this position, he angled for control of a pot of money that previously had been distributed by “scattering shots,” he says. “I saw that as a waste.” The funds now seed faculty-driven, cross-disciplinary projects.

The larger science community has benefited as well. In November 2006, Schekman took the reins of the *Proceedings of the National Academy of Sciences*, where his mission, he says, is to improve quality. “When I became a grad student at Stanford, PNAS was *the* journal,” he says. “It was the place where you wanted to put all your best stuff. Up until the end of the 1970s, it was still the preeminent journal in the molecular biological sciences.”

Schekman is picking up where the journal’s last editor-in-chief, the late Nicholas Cozzarelli, left off in his efforts to revive PNAS’s standing. Schekman is continuing the quest to bolster its peer-review process and funnel more papers

into a rigorous path toward publication. The journal’s editorial board supports Schekman’s philosophy, as does the membership at large. “Every Academy member would agree that the papers should be high quality,” says Alberts. But “when their paper gets questioned, they get upset. [Schekman and the editorial board must] get members used to the idea that their papers will undergo some scrutiny.”

In addition to raising the journal’s caliber, Schekman is expanding the types of material it will run. For example, he’s introduced

for dinner with the family: Lauren, wife Nancy, and their son Joel. And for years, Lauren says, he “schlepped me all over the [San Francisco] Bay area, multiple times a week, to choir rehearsals.”

Lauren recalls that she “didn’t have a concept of where he fit into the scientific community” until she was in middle or high school. But she did know he was a scientist. In third grade, every student in her class had to come up with a question about the world. She wondered how electricity was made, for example, and one classmate

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long feature articles “that would otherwise go to *Cell*, *Nature*, and *Science*,” he says.

Given his track record, his success at PNAS is a good bet. Elizabeth Marincola, who was executive director of the American Society for Cell Biology when Schekman was its president, says he “threw himself into” improving that organization’s journal, *Molecular Biology of the Cell*. “You would have thought his full-time job was being president of ASCB,” she says. “I can’t imagine what it’s cost his family [for him] to be so responsive.”

### {Home for Dinner}

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At home, Schekman’s daughter, Lauren, has always felt his presence, even though he spent a lot of time on the road. “I do remember him traveling, but I mostly remember him coming home,” she says. When he was in town, he always appeared

asked about earthquakes. “At first the idea was that we’d get different people to come to answer the questions,” she says. But in one visit, “he explained them all. I remember feeling really proud.”

Father and daughter enjoy laughing together too, she says. “He’s always the first person who I tell my new jokes to.” And laughter seems to form a thread that connects all aspects of Schekman’s life. In October, comedian Jon Stewart derided Schekman and Rothman on his late-night TV show during an extended joke about a pool on the 2007 Nobel Prizes. Upon seeing the excerpt, Schekman wrote in an e-mail, “Who needs a Nobel prize? I’ve made it to *The Daily Show*.”

It’s a wonderful life. ■