

UC Berkeley

Berkeley Scientific Journal

Title

Unpacking Cellular Trafficking: Randy Schekman on Basic Science and Parkinson's Disease

Permalink

<https://escholarship.org/uc/item/7cp5q6fw>

Journal

Berkeley Scientific Journal, 30(1)

ISSN

1097-0967

Authors

Ensign, Jace

Bode, Siri

Kabakibi, Rami

Publication Date

2026-10-30

DOI

10.5070/BS3.69977

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Unpacking Cellular Trafficking:

Randy Schekman on Basic Science and Parkinson's Disease

Randy Schekman is a professor of Molecular and Cell Biology at the University of California, Berkeley, a Howard Hughes Medical Institute Investigator, and a recipient of the 2013 Nobel Prize in Physiology or Medicine. His pioneering research has transformed our understanding of how cells organize and transport proteins through vesicular trafficking—a fundamental process essential to all eukaryotic life. Schekman's early work using yeast as a model organism uncovered the genetic and molecular machinery that controls membrane assembly and vesicle formation. These discoveries have since shed light on key aspects of human cell biology and disease. His lab now applies these principles to mammalian systems, exploring how cells secrete complex molecules such as collagen, autophagosomes, and extracellular vesicles.

Schekman is also deeply interested in fundamental Parkinson's disease research, particularly in uncovering how the protein alpha-synuclein is secreted and spreads between neurons, a process thought to drive disease progression. He serves as the chair of the Scientific Advisory Board of the Aligning Science Across Parkinson's (ASAP) initiative, a global research effort that fosters collaboration among scientists who seek to deepen our understanding of Parkinson's disease mechanisms and identify novel therapeutic targets.

INTERVIEW WITH:
Dr. Randy Schekman

BY: Siri Bode, Jace Ensign,
and Rami Kabakibi

BSJ: Professor Schekman, in 2013, you received the Nobel Prize in Physiology or Medicine with James Rothman and Thomas Sudhof for your discovery of the machinery regulating vesicle transport, which is a major transport system in all of our cells. Your career has mostly centered around vesicle transport and membrane assembly. What hooked you on biochemistry research, and what made vesicles and membrane assembly the problems you wanted to focus your career on?

RS: It began in my undergraduate years at UCLA. I started out as a pre-medical student, but after doing well in freshman chemistry, I got put in an honors section taught by a Nobel laureate who had invented carbon-14 radiodating. That was inspirational, although he was not a terribly good teacher. The virtue of the class was that every student got to pick a chemistry professor's lab to work in for that term. That felt natural for me, because all I did in junior high and high school was science fair projects. When I got into the lab, the young faculty member said, 'Well, you don't really have much of a background, so I want you to read this book.' It was called *Molecular Biology of the Gene*, first edition, by James Watson. This was a very revolutionary book at the time, and I was just captivated

by it. It changed my plans altogether. I decided, 'No, I am not going to be a doctor. I am going to be a scientist.'

During my years at UCLA, I had the opportunity to work in a lab and study the mechanism of chromosome replication using isolated replicating DNA molecules and figure out how they made copies. I realized there was a higher level of precision that could be obtained by understanding the enzymes that are involved in replication. As a result, I aspired to do my PhD in the lab of the best person in the world in this field, who was a professor of biochemistry at Stanford. I did well as an undergraduate, so I got admitted to Stanford, and I convinced him to take me into his lab, and I learned from him the craft of biochemistry and the appeal of solving complicated problems by taking them apart piece by piece. I did well, but I did not like the competition. I really thought this was intrinsic to me. We had competitors, and I was always worried about someone beating us to the punch with publishing. I wanted to be in an area where I could, in a sense, create my own field and not have to worry about other people doing the same experiments. So many scientists are just in a race to do something more quickly than someone else. What is the point of everyone doing the same thing? I would rather do my own thing.



Figure 1. Schekman with his 2013 Nobel Prize in Physiology or Medicine for his contribution to the “discovery of machinery regulating vesicle traffic, a major transport system in our cells.”

I started looking around and was influenced by my best friend, who was a postdoctoral researcher in the same lab, who had previously worked on membranes. I thought, this is an area that is just emerging as a topic in cell biology, for which there was only descriptive analysis at the time. This was the mid-1970s. We knew of eukaryotic cells and their organelles, and we knew that things moved from station to station, but there was nothing known about the mechanism of this process. As I thought about it, and then did a postdoctorate in that general area, I realized there was an opportunity to choose a simple organism that cell biologists had not really studied in that aspect of membranes, but for which strong genetic tools already existed. Before cloning, we relied on classical genetics, isolating mutations and eventually discovering the genes involved in an essential process. I was not the first person to do this for a process, but I was the first person to do this for that aspect of cell biology. I decided when I got to Berkeley in 1976 to embark on this search for the mechanism of protein secretion in yeast.

BSJ: Your career has been shaped by using yeast genetics and biochemistry to dissect the secretory pathway in cells. Could you walk us through the story of how you first used yeast as a model organism, and how that work evolved into uncovering membrane trafficking processes conserved in human cells?

RS: When I arrived at Berkeley, I had no relevant experience. I had not worked on this process before. I had not done genetics. I had no preliminary results because my postdoc was on a different topic. But I had ideas, and I thought that would be good enough. So I wrote an NIH grant, which was trash. That was demoralizing, but the National Science Foundation gave me a few dollars, enough to get started, and I had the particularly good fortune

to attract a fantastic graduate student in my first year. Together, we set out to search for mutations that block protein secretion, assuming this would reveal a central cellular process through the discovery of essential genes. To study essential genes in model organisms, you look for conditionally lethal mutations. Yeast had already been used for similar genetic searches in cell division, so it seemed like the right system.

Things worked out really well. By chance, I reconnected with the grandfather of this field, George Palade, whom I had met as a graduate student when he gave a version of his Nobel lecture where I was a postdoc. He really is the founding father of eukaryotic membrane cell biology. He came to Berkeley when I was two years into my assistant professor position to give two honorific seminars, and I was his host. I told him about that first yeast mutant that blocked protein secretion. We had not looked at it, other than to show that it blocked secretion and caused secretory proteins to accumulate inside the cell. He had dinner with the graduate students that evening, and Peter Novick, a cell biologist who has gone on to become a Professor at the University of California, San Diego, told him about these results. Palade said, ‘Well, now you must, of course, cut thin sections and look at the cells.’ I have that very image here in my office that I hold dear in my heart. These are the original pictures that Novick took, after Palade’s encouragement.



Figure 2: Schekman holding photos showing the original sections of wild type and mutant yeast cells, which sparked his decades-long investigation into the molecular mechanisms of cellular transport and vesicular traffic.

This is a wild-type yeast cell 2, mostly just ribosomes, and you can see a few remnants of organelles. This is the mutant that we isolated. It was temperature-sensitive and lethal, but when grown at the permissive temperature, it behaved normally. Once shifted to the restrictive temperature for an hour or two, however, the cells filled their entire cytoplasmic volume with vesicles. These vesicles, which should have fused with the bud to discharge their contents, instead piled up inside the cell until it literally choked. This was my eureka moment! I knew when I went to the basement of Barker Hall to see those images that I would have 20 years of work pursuing this — not just this mutation, but hundreds more to subsequently isolate, and all their corresponding genes to identify.

For me, genetics was just a tool. After all, I am not a geneticist, although I recognize the importance of that as a tool. For me, the value was to use these mutants as a window into a mechanism to break into the cell and discover what these gene products do. By the late 1970s, it became possible to clone genes. We cloned several of our genes, though at first, their sequences did not tell us much. They were just long strings of predicted amino acids, with few clues since genome databases were still small. But within a few years, when the human genome was sequenced, we found that these yeast genes were conserved in the human genome. That was reassuring, though it still did not tell us what the proteins did.

I knew that we had to somehow break the cells open so that we could reconstitute some aspect of traffic with membranes and soluble proteins in a test tube. Around that time, my now friend, but then competitor, James Rothman, devised biochemical assays with lysates of mammalian cells that recapitulate traffic within the Golgi. We struggled to get a similar system to work with lysates of yeast until I had another brilliant graduate student named David Baker, who has gone on to his own fame. He came in and probably thought we were incompetent. Within a few weeks, though, he found a way to gently break open yeast cells and reconstitute the first half of the pathway in vitro.

We confirmed, through the efforts of the students in the lab, that the cell-free reaction was a faithful replica of what happened in the cell. If you used lysates from mutant cells, the same defect appeared in vitro. That was critical because in Rothman's system, it was more a matter of faith that his reconstructed reactions were physiologically meaningful. We could prove it. This became the tool that allowed us to purify the key proteins.

I spent various years pursuing this, isolating molecules. That was very gratifying, and at a certain point, it turned out that both Rothman and I were working on the same protein. We had not known this. We had two proteins that had been purified by biochemical assay. He cloned human genes, while we had cloned their yeast counterpart. When we compared notes, it turned out the two were homologous. At that point, we became more cooperative and slightly less competitive.

BSJ: In your recent review, 'Extracellular Vesicles and Cellular Homeostasis,' you argue that extracellular vesicles are often the cell's housekeeping system, supporting homeostasis more than broad, long-range communication. Extracellular vesicles show up across medicine; neurodegeneration, cancer, and even cardiovascular and metabolic disease. If extracellular vesicles are more about homeostasis than communication, what does that mean for their role in disease or as tools for diagnostics?

RS: You mentioned one area where I think these vesicles are going to be very useful, and that is as a diagnostic. In a way, vesicles are sentinels that are shed by all the tissues in your body. They spill out into the bloodstream, and if you found a way to make them detect rare species, they could reflect the development of a tumor at a very early stage. I consulted for a biotech company that has a really cool way of doing this to detect stage I ovarian cancer. Usually, by the time ovarian cancer is detected, it is too late. It has metastasized, and there is a very high mortality rate. Stage I can currently be detected only sort of by chance, and if it is detected early, then there is some possibility of therapeutic intervention.

What the biotech company did was survey the literature on ovarian tumor antigens — membrane proteins that are expressed more highly in ovarian tumors. They found a bunch of them, and they made individual antibodies against each one. They then took just a small volume of blood plasma samples or an additional medium, and they immobilized antibody number one on a bead. That way, when you mix it with blood plasma, the vesicles that have antigen number one will bind to antibody number one and just fall out of solution. You then wash and probe those vesicles with the two other antibodies to which you have covalently attached an overlapping oligonucleotide sequence. What you are looking for are the other two antibodies to bind in proximity to the first antibody on the vesicle that has been pulled down. That will only happen if they are on the same vesicle. Since you have overlapping oligonucleotides, you just do a single PCR reaction across the junction, and that is a readout of the simultaneous presence of three different tumor antigens. You get clear discrimination, even at stage I ovarian cancer, in a way that has not been possible previously.

This is precisely the kind of test that could be used for all kinds of progressive diseases. You just need to identify the antigens characteristic of the disease progression and apply the same technique. With a panel of such tests, you might be able to evaluate multiple diseases in an annual blood sample, including lung cancer, liver disease, and many others. So, as a diagnostic tool, it is very exciting. I am a basic scientist, and I am happy to let companies focus on that.

However, I still believe, in the years that I have remaining, that there are some unanswered questions. I am particularly interested in the possibility that some dedicated set of these vesicles is serving as ligands to stimulate other cells. There is no question, even with the crude work that is typically done, that preparations of these vesicles do things to other cells. They change the behavior of other cells, so they are doing something to them. And how is that done? Well, I think it is likely through signaling methods. So stay tuned.

BSJ: Much of your interest in basic Parkinson's Disease research focuses on alpha-synuclein, a protein essential for nerve cell health, but which in Parkinson's accumulates and forms clumps in the brain. In your recent review, "Intracellular transmission of alpha-synuclein," you discuss many current hypotheses regarding how alpha-synuclein spreads between neurons in Parkinson's. How far are we in understanding the true mechanisms of its spread in Parkinson's?

RS: Not very far, unfortunately. We study alpha-synuclein in cell culture, including in differentiated dopaminergic neurons, and we find that it gets unconventionally secreted. It is a

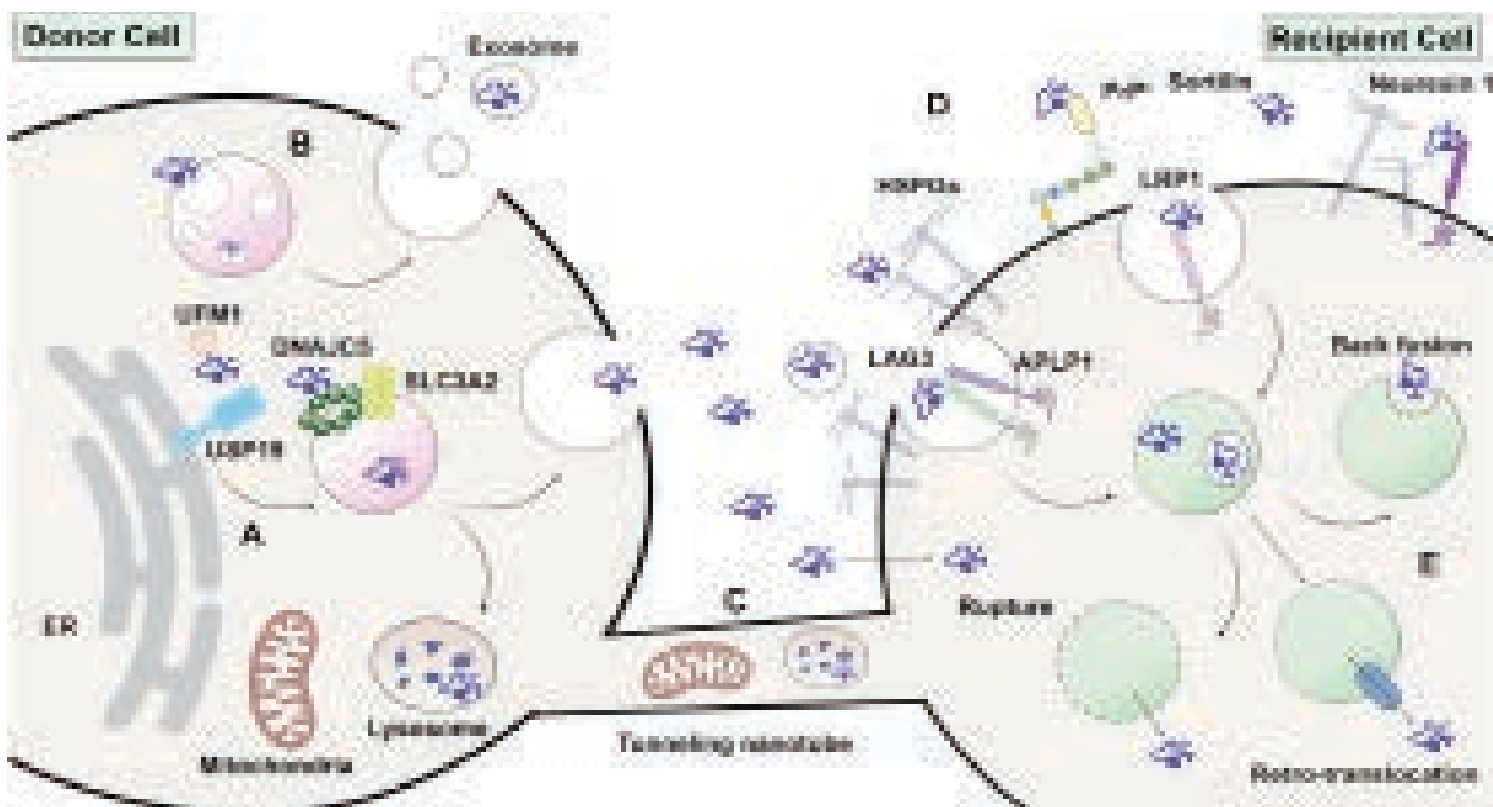


Figure 3. Various proposed mechanisms of alpha-synuclein spread between neurons in the brain. (A) Unconventional secretion as a free protein via UFM1/USP19-dependent export and DNAJC5/SLC3A2-mediated translocation into secretory compartments (B) Packaged into the intraluminal vesicles (ILVs) of endosomes and secreted in exosomes (C) Direct intercellular transfer through tunneling nanotubes (D) Extracellular entry into recipient cells via membrane penetration or receptor-mediated endocytosis involving candidates such as HSPGs, LAG3, APLP1, LRP1, PrP^C, Sortilin, and Neurexin-1 (E) Following endocytic uptake, escape into the cytosol through endosomal rupture, back-fusion, or retro-translocation.

small, relatively unstructured protein. Alpha-synuclein does not have a signal peptide, yet it somehow crosses the membrane and exits the cell. This mechanism may be a means by which alpha-synuclein spreads in the brain, for instance, although that has not been definitively established. There are two alternative views. One proposes that alpha-synuclein is packaged into exosomes and subsequently taken up into target cells. However, we see no evidence of that. The alternative, which we are particularly interested in, is that adjacent cells, especially in dense tissues such as the brain, form intercellular membrane tubules that enable direct cytoplasmic continuity. You can easily imagine that there is a cell spread that is not extracellular, but intracellular. We are currently developing and testing approaches to evaluate this possibility.

We have something in the works that we have not yet published, showing that there is a family of endosomal membrane proteins required for the propagation of alpha-synuclein within the cell and possibly between cells. One of the questions we think we should be able to answer is whether there is a channel somewhere through which the alpha-synuclein passes to exit the cell. We think what happens is that the alpha-synuclein enters an endosome through some kind of channel, and then when the endosome fuses at the cell surface, it gets secreted out. This is a working model that we are pursuing.

BSJ: You are chair of the Scientific Advisory Board for the Aligning Science Across Parkinson's (ASAP) organization, a global research initiative devoted to better understanding Parkinson's and targeting its root cause. ASAP puts a significant

importance on having open scientific communication. What can you tell us about the importance of open science communication in solving major research questions?

RS: Open access to publications has been a goal for many people for a long period of time. I was relatively late to the game in adopting and embracing that view, but I embraced it, particularly when I started this journal, *eLife*. It is so obvious that the public has paid for this, and they should have access to it. If they can understand it, they should have access to it. Yet, these large commercial publishers have guarded this jealously. Fortunately, they have been forced against their will. At first, they considered it a threat. The bottom line is they like to have control of the copyright and access to publications, so that they can charge an arm and a leg for people to have access. Fortunately, government agencies, now starting with private agencies, are increasingly insisting that their investment should be made available publicly through open access. I think that is a good thing. However, the program I helped initiate, ASAP, extends beyond open access.

My philosophy has evolved over the years. When I started my own lab, I had my own team, and we were happy to independently pen and publish our findings. But in the middle of my career, I realized that there is a big advantage to collaborating with others who have different perspectives but want to answer the same questions. I had a wonderful relationship with an Italian scientist in Geneva. For fifteen years, we spoke every day. It was amazing because he was a really gifted morphologist, and I am not, but together we examined countless samples and published many papers. You realize that when

you really have a meaningful collaboration with somebody, you can make progress that you could not have made by yourself. It is obvious. In the real world, that is the way it works. In biotech, it is all about the team, not about the individual. The problem in academic science, though I have benefited from it, is that the reward structure favors the individual. It does not really favor the team effort. For example, if an assistant professor comes to our department with a fantastic new technique, everybody wants to collaborate with this person, and this person ends up as a middle author on many papers. When it comes time for tenure, and I have seen this happen, the question is, 'Well, what did he or she actually do themselves?' Which is a stupid question, but that is the problem. We need a new way to evaluate collaborative contributions.

When I had the opportunity, together with the executive director of ASAP, who had already been appointed, we decided that what we really wanted to do was fund teams rather than individuals. We did not want to fund "cowboys". There are great people out there, and if they want to work alone, they are welcome to get their money somewhere else. We are looking for people who have already demonstrated that they can collaborate with other people without putting their ego up front. It is not that common, actually. Most of my colleagues have collaborated, but usually it is a one-off thing.

The thought with ASAP was, 'Parkinson's has been diagnosed for 200 years with nothing to show other than palliative treatments. Maybe we need a serious team effort on basic science, waves of pre-clinical stuff, stuff that biotech cannot afford.' This was all made possible because Sergey Brin, who has a family genetic history of Parkinson's, decided to fund basic science. I was asked not by him, but by the chief financial officer of his family foundation, to consider doing this. My wife had just died of Parkinson's, and I thought, 'This is what I want to do for the rest of my life.' So I dropped my position as editor of eLife to take up this work. It has been amazing because Brin is completely hands-off. He knows what we are doing and stays informed, but he is remarkably trusting. Essentially, he said, "Here's a billion dollars. Do something meaningful with it." Well, okay.

We have now been funding people for five years. At our peak, we had 35 teams of 163 investigators, with lab heads in 80 different institutions in 14 countries around the world. All are interlocked in an online space in which they are expected to communicate, with only one annual in-person meeting. There is great work being done. Just this month, we are going to make decisions about the next round of funding for the next five years. We have more great teams, some renewals, some new, and I am pretty confident that by the time we close shop, we will have solid leads that the biotech industry will be able to exploit to find new targets or develop drugs for new targets. Our policy is very clear. Everything has to be published openly within the network, and everybody has to share unpublished results. They have to share reagents. They have to share protocols. We ask that they collaborate with each other, within and between teams. From our end, we measure that behavior. We are not just measuring papers in so-called high-profile journals; we are measuring real teamwork, and those teams that really demonstrate that capacity are renewed.

BSJ: People often hear of success stories in science, but a large part of scientific discovery is about having failed hypotheses, experiments, and ideas, and finding the tenacity to work through them. What are some failures you have experienced in your scientific journey that were important in shaping you and

your career, and what did you learn from them?

RS: Well, my first NIH grant was a complete failure. That was a crushing blow. However, I was really fortunate in my PhD work, where I did some important work, and I developed confidence. It is hard to tell a student that you just "need to develop confidence." But in experimental science, if you have the patience to persist and you finally taste success, that can be kind of like a narcotic. I developed the confidence that I could make it work. Despite the rather harsh criticism my grant received, I knew the science was sound. Even without extensive prior experience in that specific area, I was confident we could make it work, and we did.

BSJ: For those just starting their scientific journey, what qualities do you think matter most for making a real impact in research, and what advice would you give to them?

RS: Here is what I always advise people who want to start their career: if you really want to be a successful scientist, you have to be willing to gamble. Most people are very conservative. Most postdoctoral researchers who are successful and publish lots of Cell, Nature, and Science papers go to their next position, and they just keep turning the crank. However, I do not think such people make big discoveries. They just peel another layer off the onion.

When I am looking at a junior faculty colleague, I am looking for somebody who is willing to take risks and do something different than what they have done. I tell people who are in such positions: spend a lot of time thinking about what areas of biology or the brain we know very little about. Then, pick a particular issue that you have an idea could be solved in a certain way, for which you have the skill set, or develop the skills. Then, devote yourself to it with blinders. The problem with smart people is that they can think of many other things to do, and then they divert their attention. It is really important to focus, and I learned this as a graduate student from my mentor:



Figure 4: Schekman standing in front of his 9th-grade science fair project.

focus. There are very few Einsteins. Most of us have one really good idea, and then just milk it for what it is worth. That worked for me. Once you have that idea and a clear vision of how to pursue it, just keep pressing.

Most Berkeley undergraduates in the Molecular and Cell Biology (MCB) department do not want to be experimental scientists. Once you get into a lab, you experience the daily frustration of things not working, and most people do not want to live with that. However, if you can live for those moments where you have a really tangible success, then you realize it is worth the struggle. That is why I said, for undergraduates, if they want to do science, they have to be in a lab. Taking classes, reading textbooks, and even taking lab classes have no bearing on science. It's not "actually" science. I have had many undergraduates in my lab, and most of them want to go to medical school, and that is good. If it were not for all the pre-medical students in MCB, we would have a much smaller faculty. However, a few of them have a real taste for discovery, and that is how you know they belong in science.

BSJ: Next year marks your 50th year as a UC Berkeley faculty member. What is so special about the Berkeley students and community?

RS: My very first undergraduate, who worked in my lab, came in while I was still unpacking boxes in Barker Hall. This young woman was a transfer from Foothill College down on the peninsula, and she had a rough background. She got pregnant in high school, had two daughters, and an unsupportive husband — she eventually left him, went back to earn her GED, and then attended junior college, where she discovered she had a real talent for science. Then she came to my lab, and she worked incredibly hard. She used to use welfare money to pay for babysitters so she could come to the lab. She did extraordinarily well; she went on to earn her PhD at UCSF, built a very successful academic career, and is now a member of the National Academy of Sciences. I feel that is why Berkeley is so special, and why the University of California, in general, is so special.

BSJ: How has your research translated to your personal life? Have you changed any practices or developed new outlooks or perspectives because of the things you've learned?

RS: I think my life has informed my research, and vice versa. When I started out, even before I got married, I was one hundred percent working in the lab. I used to work 24/7, and I was completely obsessive. My wife was a nurse; she would work the night shift, and I would kiss her good night at three in the morning and go home. That worked for a while, but then we had children. I didn't want children, necessarily, because there were five kids in my family, but my wife wanted to be a mom. I am so grateful to her for that. Having children is the greatest uncontrolled experiment you will ever do. Despite the effort and occasional trauma, my family is what has informed my life, not so much the science.

People say, 'I do not want to be a professor, look at how you work. I want a work-life balance.' Well, I had a work-life balance, but I had kids. I was home for dinners and on weekends, and we took family vacations. Yes, I worked hard, but I had to be organized about it. I think being in a demanding career like this is not incompatible

with having a family, and I cherish that part of my life. Now I have two little granddaughters, and it is just a joy. There has been a wonderful connection between family life and science in my life.

REFERENCES

1. W. Ngo, J. Peukes, A. Baldwin, Z.W. Xue, S. Hwang, R.R. Stickels, Z. Lin, A.T. Satpathy, J.A. Wells, R. Schekman, E. Nogales, & J.A. Doudna, Mechanism-guided engineering of a minimal biological particle for genome editing, *Proc. Natl. Acad. Sci. U.S.A.* 122 (1) e2413519121, <https://doi.org/10.1073/pnas.2413519121> (2025).
2. Wu, S., & Schekman, R. W. (2024). Intercellular transmission of alpha-synuclein. *Frontiers in Molecular Neuroscience*, 17, 1470171. <https://doi.org/10.3389/fnmol.2024.1470171>

IMAGE REFERENCES

1. *Berkeley Talks: Nobel laureate Randy Schekman on new Parkinson's research.* UC Berkeley Research News. <https://vcresearch.berkeley.edu/news/berkeley-talks-nobel-laureate-randy-schekman-new-parkinsons-research>
2. *Nobel prize in physiology or medicine 2013.* NobelPrize.org. <https://www.nobelprize.org/prizes/medicine/2013/schekman/photo-gallery/>
3. Image courtesy of Dr. Randy Schekman
4. Wu, S., & Schekman, R. W. (2024). Intercellular transmission of alpha-synuclein. *Frontiers in Molecular Neuroscience*, 17, 1470171. <https://doi.org/10.3389/fnmol.2024.1470171>
5. *Nobel prize in physiology or medicine 2013.* NobelPrize.org. <https://www.nobelprize.org/prizes/medicine/2013/schekman/biographical/>