

Peter Walter



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“Since all of our new knowledge is built on existing knowledge, we need to have full access to the scientific literature to do our jobs as scientists,” says Peter Walter. “The knowledge base of mankind is a global resource that belongs to the citizens of the world. It shouldn’t be locked up in the archives of some private publishers who are basically driven by the need to make greater profits.” Walter’s passionate views on access to the scientific literature have made him, along with UCSF colleague Keith Yamamoto, a national advocate. Their efforts led in 2003 to the organization of a boycott of six prestigious scientific journals published by Elsevier.

Walter’s advocacy has made him a momentary media darling. “At times, I felt like one of those little pop-up generals on CNN,” Walter says. “Whenever there’s a war somewhere, they pop up to talk about it, because suddenly they are experts.”

Walter, who is an HHMI Investigator and Professor of Biochemistry and Biophysics at UCSF, is even better known for his groundbreaking research in cell signaling, protein localization, and the regulation of organelle abundance. He is particularly noted in recent years for his work on the “unfolded protein response” or UPR, a novel, cyto-protective signaling pathway that controls ER abundance in cells according to need, and seems to stand a number of cell signaling “rules” on their heads.

“The UPR is what happens when you overload the system with too much protein or with proteins that don’t fold correctly. This triggers a response that has an effect on the transcription gene expression profile,” says Vivian Siegel, Peter Walter’s first graduate student at UCSF. Of Walter’s recent work, Siegel says, “Peter first studied the UPR in yeast. There are all sorts of puzzles so it isn’t just a simple kinase activation. It has mechanistic twists and turns. But it’s a brand new secretory-regulatory mechanism, a feedback loop that regulates transcription without being a genetically programmed response.”

Peter Walter has been attracting notice in cell biology since his early days as a graduate student in the Rockefeller University laboratory of Günter Blobel. Walter joined the lab in 1977 as Blobel was gaining hard-fought acceptance for the signal hypothesis which he had published two years before and for which he was eventually

awarded the Nobel Prize in Chemistry in 1999. Blobel’s signal hypothesis postulated a protein-conducting channel that is made up of protein subunits that attached polypeptide “addresses” to target proteins to the ER. “This was a large bone of contention for the next 20 years,” says Blobel, who served as President of the ASCB in 1990. “But when Peter came, we had the hypothesis. We had a cell-free system. The question was how we get the components of the system.”

Walter had unique skills at the bench and as an experimental thinker, says Blobel. “He was among the best graduate students I’ve ever had in my lab. He is a very good thinker, supremely well organized logistically, but also willing to take risks. He thinks very carefully about experiments, not only when they go right, but especially when they go wrong.” This, says Blobel, is how Walter made his key contribution to the search for the SRP, the “signal recognition particle” that was at the center of Blobel’s hypothesis.

Walter was instrumental in finding the six polypeptides that the lab published as the SRP, but they had not detected the real RNA particle. “Two years later, by accident, we found it,” says Blobel. Walter was running samples of super gradients on a spectrometer that had been accidentally left at 260 nm instead of 280 nm. The response was double what was expected. “I say, ‘by accident,’ but Peter knew exactly how much to expect so when he got a much higher peak, it caused him to stop and ask himself, ‘Why did I get twice as much signal?’ When he discovered the mix-up in the settings, he immediately realized that there must be a nucleic acid in there. He looked and quickly identified it as a small RNA that had already been published by Harris Bush but nobody knew what it did. Peter recognized that this was our SRP, only it wasn’t a protein. We changed the name from ‘signal recognition protein’ to ‘signal recognition particle’ so we could keep the initials,” says Blobel.

“His subsequent career has just been brilliant and this latest thing, the unfolded protein response, it’s a departure into a completely new area of cell biology. Peter all but created the field with his work,” affirms Blobel.

Peter Walter was born and educated in West Berlin at the height of the Cold War. His father owned a “chemist’s shop,” a drugstore

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which included a compounding lab bench. The chemicals fascinated Peter. "I love chemistry from when I was very little. In part, I got into it from being in my father's shop. From the age of 12, I was determined to become a chemist, and I admit there was a certain pyrotechnic interest in it as well." His parents were not college-educated themselves, but totally supportive. "Both my parents were incredibly encouraging of me, especially my mother. Her childhood was in the war so at the age when she should have been learning in school, she was sent out onto the streets to collect scrap metal, essentially to feed the German war machine. She wanted me to have the education she'd lost."

In school, Peter Walter was a wizard in science but a dud in languages. "I was always a 'C' student in English. Chemistry was my passion, that and recycling all kinds of electronic junk. In high school, I built a chromatography cell out of junk that was fully automated." He was unimpressed, though, with biology. "The biology I was taught in school was basically taxonomy. I thought it was like stamp collecting, and it didn't appeal to me at all."

Walter entered the Free University in West Berlin and also took some advanced classes in protein chemistry at the Max-Planck-Institute in West Berlin. But the need to learn better English was becoming apparent, and an exchange year in the US seemed the best way to immerse himself. "My intent was to stay in the States for nine months," Walter recalls. Decades later, "my mother keeps reminding me and asking when these nine months will be over." He was assigned, through a government program, to Vanderbilt. "I had to look Nashville up on the map because I had no idea where it was." Luckily, the movie "Nashville" had just come out, so at least he had heard of it.

The culture shock was striking, but scientifically it was to Walter's liking. "Students were treated so differently," he recalls. "In Germany, it is very much practical courses and historical experiments. By contrast at Vanderbilt, even as young students we were being trained to work as independent researchers." Walter says he was lucky to be taken into the lab of Thomas Harris. "I did hardcore organic chemistry, working on the synthesis of an alkaloid, slaframine, that is

produced by a fungus that grows on red clover in Tennessee. When cows eat that clover, they slobber. I never quite felt a long-term commitment to that project."

By squeezing in required courses and writing a thesis, he was able to earn a Master's degree at Vanderbilt in nine months. In Nashville, Walter also met Stanford Moore, a Rockefeller University biochemist who'd won the Chemistry Nobel in 1972 for his work on protein chemistry. Moore ("an impeccably dressed Southern gentleman," recalls Walter) was also a Vanderbilt graduate and trustee. Moore suggested Walter should look at Rockefeller. Walter looked, applied, and was rejected. Then he got in off the waiting list. "Many years later, I gave one of the Harvey Lectures at Rockefeller,"

Walter recalls. "It's a big deal, a black tie lecture. My first slide was my initial rejection letter from Rockefeller."

Walter loved everything about Rockefeller, the Blobel lab and New York City, calling this period, "the best six years of my life - so far."

Among his contemporaries in the lab were David Anderson (now at Caltech), Larry Gerace (now at Scripps), and Keith Mostov (now at UCSF).

It was also at this time that he met his wife, Patricia Caldera, a Mexican studying for her doctorate in chemistry at NYU. Today they live in San Francisco's Inner Sunset District in a house that they bought from a departing Bay Area scientist and Walter renovated himself. Caldera works for the UCSF Science & Health Education Partnership with the San Francisco Public Schools. Their eldest daughter, Gabriela "Gabi" Walter-Caldera, 18, is an architecture student at USC. Their youngest, Sylvia Walter-Caldera, 16, is a high school junior, interested in musical theatre. Both parents are naturalized Americans, both children are tri-nationals. As Walter puts it, "We are four people with three last names, three nationalities and 10 passports." The family celebrates its international diversity, says Walter, but finds San Francisco the ideal home. "I wouldn't make a good Mexican. Patricia wouldn't make a good German. So we live on neutral territory."

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Walter also finds UCSF ideal scientific territory, with fascinating colleagues but limited expansion room that discourages empire building. Walter was a key player in the development of the new UCSF facility at Mission Bay. The move is what triggered the Elsevier boycott, says Walter. Without the old Parnassus campus’ library at hand, it was assumed that Mission Bay could easily arrange electronic access to journals for those who moved to the new facility. At first, Elsevier offered those at Mission Bay full access. But just as students were arriving on campus and starting their assignments, Elsevier cut off access. Walter said, “You must be joking to cut us off now.” Elsevier wasn’t joking, nor was Walter, who launched the UC system-wide boycott drive a few days later. The boycott and the UC-Elsevier dispute are over for now, says Walter, but

the battle has moved to other universities. “The scientific community needs to wake up and save itself,” he says.

Walter has just finished a three-year term on the ASCB Council, and has served the Society

in other critical capacities, including as 1991 Program Chair and as an Associate Editor of *Molecular Biology of the Cell*. He was recently appointed Chair of the International Affairs Committee. Almost 3,000 of the ASCB’s 11,000 members are outside the U.S. “We have to figure out what’s important to the international members,” says Walter. The first step in that direction will be a survey of visa problems being encountered by international members.

Walter is also deeply involved with textbook writing since joining Bruce Alberts et al. as a co-author for the 4th edition of *Molecular Biology of the Cell*. Walter realizes now that being a member of “et al.” is much more time consuming—but also much more rewarding—than he had ever imagined.

Walter’s greatest non-scientific recreation is woodworking, he says. Besides renovating his house, he converted half the garage into a woodshop, where he makes furniture. “I need to do something with my hands. With furniture building, you see right away if it’s going to be a perfect fit, or a perfectly machined piece of firewood.” ■



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