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Pamela Silver

Pam Silver was born in Palo Alto, California and grew up in the nearby suburb of Atherton. Her one sibling was ten years older and off to college when Silver was still just a child, so her impression of youth is as an only child. Both of her parents were psychotherapists, her father a Freudian psychiatrist and her mother a child psychologist: "inter-esting people, to say the least", remembers Silver with understatement. Silver recalls her mother earning her Ph.D. from Johns Hopkins University in the 1930's, an accomplishment that left Silver with the conviction that you can do anything when you try.

Silver's parents encouraged her to be a free thinker and to be driven in her choice of career by her own interests rather than her hope of pleasing them. From a very early age, Silver was interested in deductive reasoning, exhibiting a precocious mathematical ability. Her father fostered her predisposition by teaching her to play "Go". "I think I was the only six-year-old girl who knew how to play Go. It's funny in retrospect, but at the time I didn't realize this was unusual," Silver recalls.

As a child, Silver often accompanied her father to Stanford Hospital, where she waited in the doctor's lounge while he saw patients on the psychiatric ward. On those visits, her father also took her to visit the hospital labs. Scientific research appealed to Silver from the beginning. "This was the post-Sputnik era when there was a huge push to teach science in school," recalls Silver. With this combination of exposure to science at school, an interest in deductive reasoning, and encouragement from her parents, Silver reflects, "I never thought of doing anything else except science."

High school was spent at a local all girls' school. "I was not very pleased with this decision", says Silver. "My parents were strong proponents of the public school system, but in the late 1960's there was a lot of turmoil in the public schools that led them to send me to a private school." Despite her opposition, Silver credits the school with providing an excellent secondary education.

At her father's advice, Silver attended the University of California, Santa Cruz in 1969. It had only 2,000 students at the time. "After going to a conservative all girls' high school, I wanted to choose the most radical college I could." Silver started her undergraduate studies as a physics major, but switched to chemistry because she wanted to do hands-on experiments. Biology did not appeal to her because she wrongly perceived it as primarily observational.

After graduation, Silver considered immediately entering graduate school in Chemistry, even applying to and visiting the Chemistry departments at UC Berkeley and Harvard. But she delayed graduate school, instead spending several years working as a chemist in industry making polymeric food additives. "At that time in my life it just wasn't right to go to graduate school. I think I was a little intimidated." This period also coincided with her parents' illness and death, as well as the disappearance of her sister. Silver described this post-college job as a good experience, providing her not only with welcome stability, independence and money, but also some experience working as part of a scientific team.

"My company encouraged people to take courses at Stanford, and I was still pursuing this chemistry/physics idea in those years. So, I always tried to take the hardest classes." But by 1978, Silver had November 2000 7 left the Bay Area to live in Los Angeles and decided the time had come for graduate school. After meeting Bill Wickner at UCLA, she entered the Ph.D. program there. "I wanted to finish my Ph.D. as fast as possible so that I could get on with being a scientist. Bill agreed with my strategy and helped me a lot. It worked out really well."

Wickner was working on the assembly of proteins into membranes in a model system that used bacteria. At first Silver was hesitant to work on a prokaryotic system, but eventually she decided "this was a cool problem, and I dove into the study."

Silver finished her Ph.D. in 1982 and moved to Boston. "There was this whole question of how things get into the nucleus. At the time people were thinking it must just be diffusion and that they stick there. Having studied signal sequences, I thought the same rules could apply to the nucleus. I thought yeast would be a good model system to look for nuclear localization sequences." So she joined the lab of Mark Ptashne, who was making a transition to studying gene expression in eukaryotes. "I came to him with this idea about looking for nuclear localization sequences. I'm not sure he was excited about nuclear transport, but he liked the idea that I wanted to work on yeast," says Silver.

Silver attended the Cold Spring Harbor yeast course that summer in preparation for starting in Ptashne's lab. "I figured my research had a 50-50 chance of working," remarks Silver. "I was going around getting help from different labs. I wanted to learn more about isolating nuclei from yeast, and also about doing different kinds of cell biologic methods." So in 1985 Silver contacted John Kilmartin at the Laboratory of Molecular Biology and visited Cambridge to work with him for several months. "It was exciting being at

MRC at that time. Kilmartin was a different kind of scientist, working by himself in his lab. I learned a lot while there.”

She returned to the U.S. following her time in Cambridge and took a job as Assistant Professor of Molecular Biology at Princeton University. She remained at Princeton through 1992, moving back to Harvard in 1993 to become an Associate Professor in the Department of Biological Chemistry and Molecular Pharmacology. Since 1997 she has served as Professor in the same department at Harvard with a joint appointment at the Dana-Farber Cancer Institute.

Unlike many people, tenure has provided Silver with the opportunity to indulge her passion for teaching. “I love teaching, and by medical school standards I do a lot of teaching. But I really miss teaching undergrads. I’m trying to find a way to do more undergraduate teaching. I also like to have undergraduates in my lab.” Silver’s research today is focused on transport into and out of the nucleus. “I was one of the first people to work on how proteins get into the nucleus. I’ve watched the whole field grow up. A big part of our work for many years was finding the factors that mediate transport in and out of the nucleus. Now we know many of the factors and our work is headed in the direction of how they work. It’s taken on a more biophysical approach. We’re also doing a lot of RNA now.

The problem of how RNAs get transported out of the nucleus is less well understood than protein import. We’re also working a lot on the nuclear pore itself, trying to understand how the proteins interact with one another and what they do.”

Of her lab, Silver remarks proudly that, “the unique thing about my lab is that we are not technique-limited. We sort of do everything. We do yeast genetics, we do biochemistry, we do a lot of microscopy, and we’re doing some crystallography in collaboration. We’re trying to move what we know into mammalian cells and into the disease arena. That’s pretty daunting for me. So we’re trying to find small molecules that affect the transport proteins relevant for cancer. Dana-Farber has a drug discovery program with Novartis and I’ve been involved with that – trying to find targets for anti-tumor compounds. It’s opened my eyes to whole new areas of science.”

ASCB member Anita Corbett, an Assistant Professor of Biochemistry at the Emory University School of Medicine, recalls her post-doctoral work with Silver: “during my final year in graduate school I saw Pam talk at a meeting. After that I decided that I wanted to do my postdoc with her. I didn’t apply to any other labs.”

“I had never worked with yeast or done anything molecular or cell biological so I was excited but scared,” continues Corbett. “In retrospect I could not have made a better choice for my post-doctoral training. The most important thing that I learned from Pam was not to be afraid of anything. I’ve encountered many scientists (and others outside the scientific world) who do things one way and are afraid to branch out. This I think is one of Pam’s great strengths that she really instills in people in her lab—if there is a better or different way to do an experiment, why not try it? I credit Pam with making me the scientist I am today. I only hope that I can live up to the legacy and instill some of Pam’s excitement about science, drive to succeed, and willingness to try anything to the students I train.”

As with many scientific researchers, Silver loves what she does. “The fact that I get paid to do something I love this much is a miracle,” she remarks appreciatively. She is also a committed distance runner, participating in the Dana-Farber Marathon Challenge and running in the Boston Marathon. Silver helps fund raise for the Dana-Farber charity event. “One thing I’ve always liked is to meet lots of different kinds of people. As a scientist you can get too narrow in the kinds of people you get to know. The Marathon gives you a chance to meet the most fantastic people, in this case people whose lives have been touched by cancer in some way, and they want to do something about it.”

Any spare time is spent fixing up her new house in Cambridge, with her partner, Jeff Way, who works for a biotech company, or traveling. Silver’s contributions to the ASCB are broad and long-standing: she has served on the Program and Nominating Committees, is an Associate Editor of *Molecular Biology of the Cell*, and just recently concluded a three-year term of service on the ASCB’s Council, an elected position. That service deepened Silver’s awareness of the political process at the federal level and awakened in her a desire to participate more politically in her local area.