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2003

Charles Sherr

When Chuck Sherr arrived in 1983 at the St. Jude Children's Research Hospital in Memphis to set up a basic cancer biology lab, Tennessee was the last place he expected to be in 20 years. Yet he and his wife and collaborator, Martine Roussel, with son Jonathan, 17, are still in Memphis, where their roots have grown deeper than they could have imagined.

A Howard Hughes Investigator since 1988, National Academy of Sciences member since 1995, and ASCB member since 1995, Sherr was awarded the Landon-AACR Prize this year for his role in the discovery of two mammalian cell control pathways which have major implications in cancer. The Prize carries a $200,000 unrestricted cash award.

The Sherr-Roussel lab identified the first D cyclin involved in the G1 "gap" phase and traced its influence on the critical "stop cycle" protein, RB (retinoblastoma). Without functional RB, a master switch called E2F will allow even defective cells to cycle into S phase. Exploring RB mutations further, the Sherr-Roussel lab homed in on the INK4a gene, finding within it an overlooked "alternative reading frame," a gene encoding for what the lab quickly dubbed the ARF protein. ARF controls an-other protein, Mdm2, which controls the renowned tumor suppressor gene, p53. "Half of all human cancers have mutations in p53 itself," says Sherr. "So the question is what about the other half? They likely have mutations in other regulators that affect p53 activity, rather than in p53 itself. ARF and Mdm2 are two of those regulators, and there are others, but the argument is that if you knew what all of these regulators were and added up their frequency of involvement in human cancers, eventually you would come close to 100 percent." Tumors that have wild-type p53 preserve some p53 function, but the protein may be handicapped, says Sherr. "Our ARF-null mice get spontaneous tumors although they retain wild-type p53, and the reason is that we've disconnected abnormal mitogenic signaling from p53 activation. And, there are mutations affecting other regulators that disconnect DNA damage responses from p53. So it's the p53 neighborhood that's probably corrupted in many, if not all, tumors. Similarly, the neighborhood around RB is probably corrupted in most cancers, either through cyclin D overexpression or CDK4 amplification or INK4a protein mutation. So the simplistic paradigm is that the loss of RB and p53 checkpoint functions is necessary to become a cancer cell," says Sherr.

Tennessee is a long way from the Bronx where Charles J. Sherr was born in 1944. When he was ten, his family moved to Long Island's North Shore where he graduated from Oyster Bay High in 1962 (thus allow- ing the Cold Spring Harbor Laboratory to claim him as a "local boy" and as a member of their Board). That was also the year Sherr remembers first hearing about DNA and how the genetic code worked.

Yet when Sherr went off to Oberlin College in Ohio, he was the classic "undecided" liberal arts student. He was good in science, interested in medicine but also a natural musician (guitar and piano). Medicine had become the logical choice by his senior year but Sherr was so caught up in a research project on newt limb regeneration that he had little interest in practicing medicine and none in being drafted for Vietnam. Sherr jumped at the chance to join the "Yellow Berets" of the US Public Health Service by taking an NIH post-doctoral fellowship. took his "crazy experiment" with him when he enrolled at the NYU School of Medicine and begged for some free lab space to finish. Down the hall was the lab of Lewis Thomas who as NYU's Chairman of Medicine was running the University's new MD/PhD program. A few months into the first term, Thomas appeared at Sherr's bench. Someone had just withdrawn. Would Sherr be interested in the MD/PhD?

To catch up on missing prerequisites, Sherr spent the next year as a regular medical student by day and a catch-up grad student by night. In between, he was in the immunology lab of Jonathan Uhr. Everything was under control, Sherr thought, until he took biophysical chemistry. "I wasn't getting a lot of sleep at this time and after a while I couldn't see how I was ever going to get the minimum B. Fortunately my instructor didn't want to be the reason I didn't get my PhD. He said that if I promised never to do an experiment in biophysical chemistry during the rest of my career, he promised he'd give me a B."

Sherr finished both degrees by 1972 but after a year's residency in pathology at Bellevue Hospital, he had little interest in practicing medicine and none in being drafted for Vietnam. Sherr jumped at the chance to join the "Yellow Berets" of the US Public Health Service by taking an NIH post-doctoral fellowship. He landed with George Todaro at the NCI who was working on retroviruses. It was the subject of the hour. President Nixon had declared "war on cancer" in 1971 and Sherr found himself in the front lines. With Robert Huebner, Todaro was a leading ad- vocate for a viral connection to human cancer. Harking back 60 years to Peyton Rous's controversial discovery of a sarcoma-caus- ing virus in chickens, they hypothesized that tumor formation in humans resulted from the activation of silent retroviruses that carried what Todaro dubbed "oncogenes."

But in 1976, J. Michael Bishop, Harold Varmus and Dominique Stehelin knocked a hole in the Huebner-

Todaro hypothesis, showing that retrovirus oncogenes were homologues of mutated endogenous cellular chicken genes. Human cells had their own oncogenes, many of which would eventually be implicated in cancer.

Despite this revelation, retroviruses were still the best models to study in hopes of identifying oncogenes in action. Todaro offered Sherr his own intramural NCI lab in 1977 to sort through a class of RNA tumor viruses for the elusive oncogenes. The work was fascinating but, given the limited genetic technology of the time, very slow. The lifting of the cloning ban in the late 1970's finally opened the way for Sherr's investigations, and by 1983, he had worked out the genome structure of several feline retroviruses and cloned two oncogenes, fes and fms. Later, at St. Jude, he would trace c-fms in blood cell systems to its receptor for a phagocyte colony stimulating factor, CSF1.

Yet even as his first fms papers were attracting notice, Sherr knew he was "miserable" at the NIH, tired of its Byzantine power struggles and at odds with almost all camps in the cancer wars. In 1983, St. Jude was well known as a regional children's cancer center, less well known for flu virology research, and best known for its founder, the comedian Danny Thomas. But St. Jude's newly appointed CEO, Joseph V. Simone, was determined to remake St. Jude into a major center for basic cancer research.

"Sometimes it's better to be lucky than smart," says Simone, who went on to major posts at Memorial Sloan-Kettering in New York and the Huntsman Center in Utah after transforming St. Jude. Sherr, wanting to leave the NIH, was his first recruit. Simone's beginner's luck was phenomenal, because within a few short years, he recruited not only Sherr but James Ihle, a biochemist who would become St. Jude's second HHMI Investigator, and Peter Doherty, the Australian immunologist who would win the Nobel Prize in 1996.

Roussel's separate appointment at St. Jude allowed her to build her own career identity and still work so closely with Sherr that today he says, "I don't know where I end and she begins. Martine and I have done everything together for the last 20 years. It's fine that I got this honor [the Landon Prize] but really, we do everything together from raising kids to planning experiments as we dress in the morning."

Their son Jonathan is showing no interest in joining the family business, says Sherr. His father says Jonathan has a passion for political science and a flair for business, recently placing first in a state-wide student marketing competition and in the top ten nationally. Sherr's daughter by his first marriage, Sarah, 29, is a medical resident at Johns Hopkins, looking towards pediatric oncology. She recently decided to take her fellowship at St. Jude. Sherr's older son, Simon, 27, is a computer animator, now designing video games in Vancouver after heading the animation team for the character "Mystique" in the "X-Men 2" movie.

Sherr says he has stayed at St. Jude largely because his institutional bosses gave him the freedom to pursue the oncogenesis problem, in whatever direction the scientific data led him. Over 20 years, the Sherr-Roussel lab has changed fields repeatedly as the work moved from retroviral genetics to receptor mapping to signal transduction to cell cycles and now to tumor suppressors. HHMI has been similarly supportive, Sherr says. He remembers calling HHMI's formidable Scientific Director, the late Max Cowan, to nervously explain why he wanted to move into cell cycling. "Max said, 'We hired you. We didn't hire the project. The money is for you to do what you want'."

What Sherr wanted was to pursue a problem, not a protocol. "It's amazing how Chuck can assimilate an enormous amount of data that crosses several different mechanisms and end up putting them together in a single story," says Jason Weber, a former post-doc and Pew Foundation Scholar now on the medical school faculty at Washington University in St. Louis. "The story starts with fms, moves into cyclin D and now culminates in ARF. As more people begin to appreciate the role that ARF plays in human cancer, his reputation will skyrocket even more."

Sherr's polymath intelligence also made him a colorful person to work for, says Weber. "Chuck knows everything about everything in the literature. He can tell you the year, the journal, and maybe not the volume but he can definitely tell you first and last author of all the hallmark papers. In the lab, you never had to look anything up." Sherr is also, says Weber, "an unbelievable musician. He's a wonderful pianist. He mostly does jazz improvisation but at meetings or the annual St. Jude parties, he'd be up there adlibbing whatever people wanted to hear. I think it's part of the reason he likes Memphis, because it's such a great music town."