Joan Argetsinger Steitz

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Attention for attention's sake is not the Joan Steitz style. Her Yale career, her publications, and, most of all, the generations of students who've trained in her lab are honors enough, says Steitz. Yet the announcement from Toronto this spring that Steitz was a winner of the Gairdner International Prize set off a wave of rejoicing among Steitz's colleagues, collaborators, and students. The Gairdner, which comes with $30,000 (Canadian) and a reputation as a Nobel "short list," recognized Steitz for her 1980 landmark "discovery of the reactivity of autoimmune sera with nuclear riboprotein particles and elucidation of the rules of small nuclear RNAs in gene expression."

A "Snurp" in Time

Although Steitz now calls this work "ancient history," it was a true breakthrough. Her observation that antibodies from lupus patients react with small nuclear ribonucleoproteins or snRNPs (that is, small particles containing RNA and proteins) gave Steitz a way to test her hypothesis about what snRNPs do in cells. Namely, that they are adaptors involved in recognizing splice sites in newly transcribed messenger RNA. Using the antibodies as probes, Steitz and graduate student Michael Lerner characterized the U1, U2, U4, U5, and U6 snRNPs, ("snurps," as the name has been pronounced ever since). Moreover, they hypothesized that the U1 snRNP defines a splice site through complementary base pairing with the 5′ end of an intron sequence. Intron sequences need to be spliced out of gene transcripts, leaving exons, a preliminary step in making proteins. The U1 snRNP was the first element of the long-sought mechanism that edited out introns. The remaining exons are the part of transcribed mRNA that carries genetic instructions from the nucleus to the ribosome, where proteins are made. The excised introns are degraded in the nucleus.

"Her insight was a true inspiration," according to Susan Berget of the Baylor College of Medicine. "Her hypothesis set the field ahead by light years and heralded the avalanche of small RNAs that have since been discovered to play a role in multiple steps in RNA biosynthesis."

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Opening the Door

"This is fabulous news," says Kim Mowry, a former Steitz graduate student now at Brown University. "Joan deserves every honor that comes her way, but this work, in particular, really opened the door to understanding splicing."

For those in the field, the Gairdner prize only underscores what has long been recognized about Joan Steitz, according to Christine Guthrie of the University of California, San Francisco. "Indisputably, Joan is the most famous contributor to the world of small RNA and RNP particles," says Guthrie, "and one of the greatest scientists of our generation."

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For women in biology, Steitz has been a sterling role model and "a tireless promoter of women in science," Guthrie continues. For women in the Steitz lab, Joan led by example, Mowry adds. "It was clear that anything was possible (for women) because Joan had already done it all."

Big Shy Country

Such praise usually sends her heading for cover, Steitz admits. A Minnesota native, Steitz was raised to be attention-shy. Besides, Steitz would rather talk about her more recent work on other "snurp" families, including the role of U7 snRNP in the synthesis of histone mRNA and her discovery of a secondary, highly specialized spliceosome built around the U12 snRNP family.

Yet the Gairdner must bring some quiet satisfaction to a woman who entered science at a time when women researchers were merely tolerated and certainly not expected to win international science prizes. Steitz recalls that when she graduated from Antioch College in 1963, she decided to go to medical school because she knew some women doctors, but she didn't know any women scientists. "There weren't any women professors in science at any of the major research universities," she adds.

An Embarrassment of Honors

Nevertheless, Steitz went on to become a professor at a major research university— Yale— where she now holds a prestigious Sterling Professorship in Molecular Biophysics and Biochemistry (MB&B). She is an HHMI Investigator at Yale's Boyer Center for Molecular Medicine, a former chair of her department, and a member of the National Academy of Sciences since 1983. The Gairdner prize joins an honors list that includes the National Medal of Science (1986), the Weizmann Women and Science Award (1994), the FASEB Excellence in Science Award (2003), and the National Cancer Institute's Rosalind E. Franklin Award for Women in Science (2006). At the 2005 Annual Meeting, the ASCB awarded Steitz its highest scientific honor, the E. B. Wilson Medal. All this talk of honors is slightly embarrassing to Steitz. Ask how many honorary doctorates she has to date and she groans. (It's 11.)

Joan Argetsinger Steitz is the daughter of schoolteachers and a graduate of an all-girls high school, which, she says, probably accounts for her solid grounding in science and math. At Antioch College in Yellow Springs, OH, Steitz's chemistry classmates included Stephen Jay Gould, the future Harvard evolutionary biologist and essayist, and Judith Greenwald Voet, the future Swarthmore biochemist and textbook author. Science textbooks weren't as advanced, however, in the late 1950s; they hadn't caught up with such discoveries as that of the double-stranded nature of DNA in 1953, Steitz recalls. She didn't encounter the emerging science of molecular biology until she took an Antioch "coop" job placement in the Massachusetts Institute of Technology laboratory of Alex Rich. There she was excited by the science, but the career prospects for a woman in research science seemed nonexistent.

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Finding Herself at the Bench

Accepted by Harvard Medical School for the fall of 1963, Steitz went home to Minneapolis after graduation in search of a summer job. She found one in the University of Minnesota lab of Joe Gall. Gall put her to work, not as a technician, but as a bench researcher. "Joe gave me my own independent project. This was the first time I wasn't helping somebody else with a project," she noted. "Having to do it all myself made me realize that is what I wanted to do." At Gall's urging, Steitz decided to transfer from the medical school to Harvard University's new "committee" graduate program in biochemistry and molecular biology (BMB).

Gall says he did little more than recognize a first-rate scientific talent and call his friend, Jim Watson, to see what could be done about a transfer. "I've always claimed Joan as my student, although she really wasn't," admits Gall. "She just had that summer in my lab. But as she's become more and more famous, it's been gratifying to think that I had a small part in influencing her. Still, my guess is that she would have gone into research, no matter what."

Watson and the Important Question

At Harvard, Steitz was the only woman in her BMB class of 10 and the first female graduate student in Watson's lab. Watson, who won the Nobel Prize in 1962, only the year before Steitz's arrival at Harvard, was a one-of-a-kind mentor, according to Steitz. For one, Watson "capitalized on his grad students," Steitz recalls. "Jim always said that postdocs came to him with 'malformed ideas' that he had to re-engineer. He also taught me the Watson philosophy: Study the important problems. I like to think I've done that." It was Watson who first introduced Steitz to RNAs in bacteriophages and the important question of how a ribosome recognizes the beginning of a gene for translation.

At Harvard, Steitz also met classmate X-ray crystallographer Thomas Steitz. The couple married in 1966 and, after finishing their doctorates, moved in 1967 from Cambridge, MA, to Cambridge, UK, for postdoctoral work. Watson contacted friend and co-Nobel recipient Francis Crick, who said Joan Steitz would be welcome at the Medical Research Council Laboratory of Molecular Biology. Unfortunately, Crick failed to arrange lab space for her. When Steitz arrived in England, Crick could only suggest a dry lab library project instead. Fortunately, Steitz found her way around Crick's suggestion and was given three feet of bench space by staff scientist Mark

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Bretscher. There, she made her first mark as an independent investigator by locating three translation "start points" on bacteriophage mRNA.

The mRNA Black Box

In 1970, both Steitzes were offered positions at Yale. In New Haven, Joan Steitz continued her work on bacteriophage RNA binding sites before moving into eukaryotic cells and the black box mystery of mRNA splicing. Working with antibodies from lupus patients, Steitz made her key discovery about the role of snRNPs in splicing. It was a basic science breakthrough, but one that used tools from clinical medicine, autoantibodies from patients with immune disorders. Today, experts believe that mRNA splicing defects are involved in 10–15% of all human genetic diseases.

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Yale remains a family affair for the Steitzes. Their son, Jon, majored in their department, MB&B, because "it was easy for him," according to his mother. "He really majored in baseball." Bitten by the baseball bug at age six, Jon Steitz pitched for the Yale varsity team. He was drafted after his junior year in 2001 by the Milwaukee Brewers organization. He played in the minors for three seasons before shoulder trouble ended his pro-baseball dreams. Jon Steitz is now back in New Haven … at Yale Law School.

From Bench to Bullpen

Although Jon Steitz didn't follow his parents' footsteps into biomedicine, his two best friends in the Yale bullpen, Matt McCarthy and Craig Breslow, were admitted to medical school by way of the Steitz lab. After majoring in MB&B, McCarthy and Breslow were both drafted into professional baseball, but not before they'd been drafted to the bench. "Part of the reason Yale is so great is that it has such fabulous undergraduates," Steitz says. "Getting them into your lab is such a joy, so I made sure I got those baseball guys in here."

Add McCarthy to the long list of Steitz mentees: After one year in the minors, McCarthy is now at Harvard Medical School. Meanwhile Breslow has deferred, yet again, his place at New York University Medical School. In the summer of 2005, Breslow made it to the majors with the Padres; for the 2006 season, he is with the Red Sox. Steitz loves to be in the stands, whether it is Yale, the Brewers, or the Red Sox on the field. "I'm a fan of the kids. I'm not a fan of the team," she says. Baseball or research science, Joan Steitz always roots for the players. ■