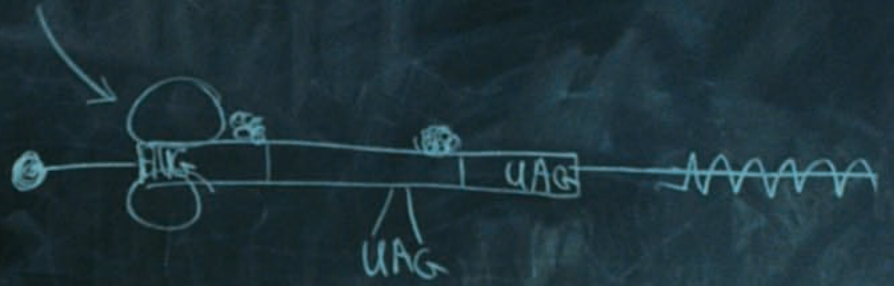
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# Trailblazer Turned Superstar

Joan Steitz
started up the scientific ranks when few women did. Today, Nobel laureates laud her research and scores of scientists praise her mentoring acumen.

BY MARGARET A. WOODBURY
*Photographs by* Ethan Hill

If anyone had told HHMI investigator Joan A. Steitz when she was an undergraduate chemistry major at Antioch College in Yellow Springs, Ohio, that she would someday run her own research lab, and that a Nobel laureate would call her a star scientist, she most likely would have exclaimed, "Come on!" It's a phrase she uses often, usually meaning: Get real! >> A Minnesota native who came of age in the 1960s, Steitz says she was always interested in science and got plenty of encouragement from her parents, even though a far different model was everywhere around her. "Women of my day," she recalls, "had six kids and a station wagon." >> "At that time, there were no women professors in the natural sciences at any major university," Steitz says. "Consequently, I never envisioned myself being where I am today: I never thought I would teach undergraduates. I never thought I would mentor graduate students. I never thought I would be on the faculty of a prominent university. I really thought I would be a research associate in someone's lab—a man's, of course."

But Steitz persevered, and now holds high ranks in the world of molecular biology. She is Sterling Professor of Molecular Biophysics and Biochemistry at Yale University and has served as chair of her department and as scientific director of the Jane Coffin Childs Fund for Medical Research. Moreover, Steitz has earned an international reputation for her research on RNA—the chemical that delivers DNA's genetic messages and performs an impressive repertoire of cellular functions. "Joan is looked up to as one who has contributed to a cohesive view of RNA science," says Thomas R. Cech, HHMI president and a Nobel laureate for his work on catalytic RNA. "When I became interested in RNA in the early 1980s, she was already a star. Her work continues to evolve and remains at the forefront."

## OPENING DOORS

In the early years, Steitz's decisions clearly reflected her doubts. Thinking her chances of autonomy in a laboratory setting were minimal, she set her sights on becoming an M.D. She was accepted to Harvard Medical School, but summer research in the laboratory of Joseph Gall at the University of Minnesota made her change her mind. Instead, in the fall of 1963 she became the only woman in a class of 10 incoming students in a new program in biochemistry and molecular biology at Harvard's Graduate School of Arts and Sciences. James D. Watson—fresh from winning his Nobel Prize for solving the structure of DNA—became her mentor, and the door to science opened a crack.

Steitz soon discovered, however, that the door could just as easily swing shut. During her first year at Harvard, she approached a male scientist she will only identify as "famous, well-respected, and now deceased." Steitz wanted to work with him for her graduate thesis. But Dr. Famous had other ideas, namely that men belonged in the lab and women at home with those six kids and the station wagon. Steitz recalls running from the room and then dissolving into tears, but she now looks back on the event as one of the best things that ever happened to her: She completed her thesis with Watson, and their professional relationship strengthened into a lifetime bond.

These days, it's hard to imagine Steitz running from anything. (She still counts herself as a bit of a shrinking violet, but only because she dislikes being in the spotlight; despite her status, she rarely grants media interviews and is an intensely private person.) "Joan is extremely competitive in her field, as are all good scientists," says molecular biologist Susan J. Baserga, who was a postdoc in Steitz's lab from 1988 to 1993 and is now a faculty colleague at Yale. "She is not afraid to offend, but her manner is such that she gets done what needs to get done in a way that usually *doesn't* offend."

HHMI investigator Jennifer A. Doudna, who was a junior faculty member in Steitz's department at Yale and is now at the University of California, Berkeley, recalls numerous times when Steitz "called a spade a spade"—times when it might have been easier to let things pass. "If a faculty member wasn't being treated fairly, Joan spoke up in a way that I really respected," says Doudna.

Both Baserga and Doudna are vigorous in their praise of Steitz as a scientist, but it is with particular gratitude that they cite her mentorship in teaching them how to navigate the system and the ins and outs of starting one's own lab. For her part, Steitz recalls what it was like not to have other women around in her early days as a scientist—lonely. So she has made it a priority to give the Basergas and Doudnas of the next generation something she didn't have: a female network within the system.

## GIANT STEPS

Steitz characterizes her relationship with RNA as a "personal romance" that dates back to her time in Watson's lab and her initial work on bacteriophage RNA. But her first major leap forward in RNA science came during her postdoctoral years overseas. After finishing at Harvard, the newly married Steitz traveled with her husband, Tom Steitz (also an HHMI investigator at Yale), to Cambridge, England. There, in the division run by two more renowned scientists, Francis Crick and Sydney Brenner, she focused her research on determining the exact point on a strand of messenger RNA (mRNA) that binds a bacterial ribosome to begin the manufacture of a protein. (A ribosome is the machine that does protein synthesis in the cell.) Success came in 1969 when she published a paper in *Nature* showing the

nucleotide sequences in bacteriophage mRNA that act as such start points.

She continued her work on bacterial and bacteriophage RNA upon her return to the United States in 1970, when she joined the Yale faculty as an assistant professor of molecular biophysics and biochemisty (her husband also took a position at Yale). By 1975, her efforts were further rewarded when she published how ribosomes identify the start site on a strand of mRNA: by complementary base pairing.

That discovery remains a highlight of her career—in fact, it tops the list, she says. But she rebuffs a request to rank past accomplishments, preferring to talk about what's currently underway. It's clear this energetic woman would rather get on with her research than rehash "such ancient history." Her cramped office—piled with papers and stacks of books everywhere—is a bit mazelike. She apologizes for the mess, but in pro forma fashion that says, come back next year and it'll look the same.

Dozens of empty champagne bottles line a top office shelf, remnants of an honored lab ritual. Each is savored and signed by a student who has successfully completed a thesis. Steitz has a particular smile that flickers beneath her rosy, yet elegant cheekbones when talking about or with her students. It's something her students notice and appreciate. The smile plays there as a message of encouragement, endorsing their right to think aloud even as they sometimes fumble with their biological formulations.

LEFT *Joan Steitz gives high priority to teaching undergraduates and mentoring graduate students.* BELOW *SnRNAs are part of the spliceosome, which splices introns from mRNA. They are the fourth class of RNAs, essential for gene expression.*

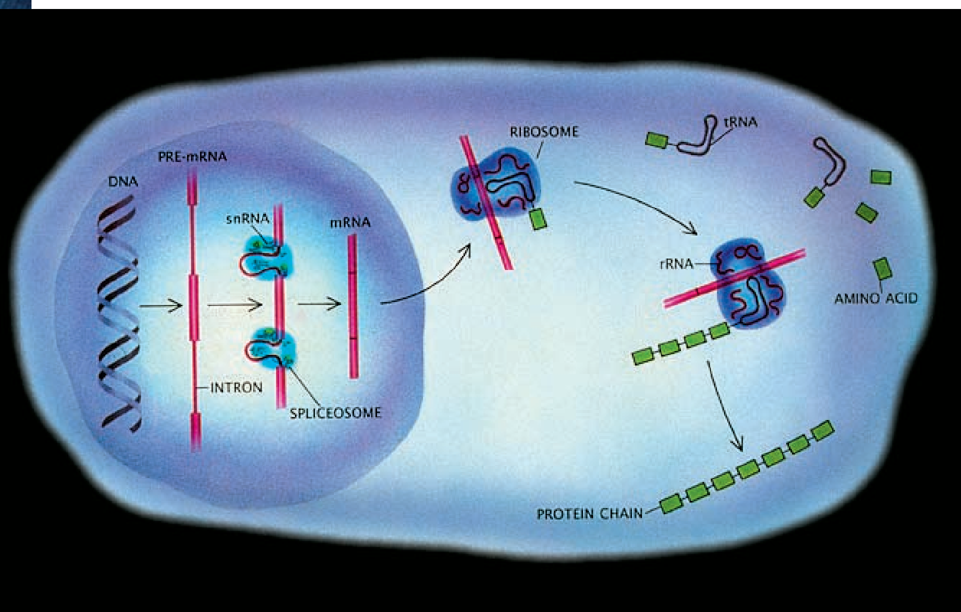


Image by Ian Worpole; reprinted with permission from *Scientific American*, June 1998.

Although Steitz gives top ranking to her work on ribosomes, it was her seminal 1980 paper in *Nature*, "Are snRNPs involved in splicing?", that clinched her scientific reputation. Steitz, like many others in the early 1970s, had turned her attention to eukaryotic cells (a eukaryote is an organism whose genetic material is located within a membrane-bound nucleus). Of particular interest to Steitz was the mystery of why so much RNA was made in the nucleus, but so little—about 10 percent—ever made it out to the cytoplasm to be translated into proteins. As she tried to figure out the answer, experiments by Philip Sharp at the Massachusetts Institute of Technology (MIT), Richard Roberts at Cold Spring Harbor Laboratory, and many others coalesced into the realization in 1977 that the DNA in eukaryotic cells alternates between exons, which contain gene sequences, and introns, which do not code for any protein ("junk DNA").

Yet the discovery of introns did not explain the machinery or how all the noncoding introns were removed from a newly transcribed length of RNA. Steitz kept at the problem, and by analyzing blood samples from patients with an autoimmune disease, she and her student Michael Lerner discovered a novel entity—the snRNP. A snRNP (pronounced snurp) comprises a small length of RNA (about 150 nucleotides long) that is complexed with several proteins. "It turned out," says Steitz, "that the blood samples we analyzed contained antibodies against snRNPs.

"After we discovered snRNPs, we proposed they were involved in splicing [removing the introns from newly transcribed RNA, or pre-mRNAs, as they're now called] and we did the first experiments that showed they were, in fact, involved in splicing," says Steitz. Her lab also determined that it is a particular small nuclear RNA (snRNA), U1, in a snRNP that defines one of the splice sites of an intron via base pairing with complementary pre-mRNA.

Later, other labs coined the term spliceosome for a large assembly made up of several different snRNPs as well as additional proteins. The big mystery—why so little transcribed RNA becomes mRNA—was no longer so baffling.

Shortly after Steitz published her celebrated snRNP paper in *Nature*, ribozymes were discovered by Thomas Cech and by Sidney Altman of Yale and Norman Pace of Indiana University. As the name implies, these large molecules of RNA actually have the ability to catalyze a reaction—namely, they can splice or cut strands of RNA. And while it's yet to be proved, Steitz thinks that RNA catalysis is responsible for the cutting and rejoining actions of the spliceosome. "Like a standard enzyme, snRNPs come together and form a spliceosome, do their business, fall apart, and do the whole thing over

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(JOAN STEITZ)
somewhere else," says Steitz. If this turns out to be the case, the RNA portion of a snRNP would be considered a ribozyme.

By this time, Steitz had already advanced up the Yale ladder to become a full professor. Her lab subsequently discovered a second spliceosome that eliminates a rare class of "black sheep" introns that have atypical sequences at their splice sites.

And with her discovery of another kind of snRNP particle, small nucleolar RNPs (snoRNPs), she proved that the term junk DNA was a misnomer. Introns, the so-called noncoding regions of DNA, sometimes code for the small nucleolar RNA found in a snoRNP. These molecules (pronounced snow-RNPs by Steitz) chemically modify ribosomal RNA and are essential to its function.

Currently, Steitz is exploring viral snRNPs as well as the welter of effects splicing has on the downstream life of an RNA message. "For instance," she says, "we know that in the process of splicing proteins are put on RNA that are important for getting the RNA out of the nucleus to the cytoplasm."

While her work is on the bench side of science, others are translating her findings in the clinic in ways Steitz finds "absolutely amazing." A recent paper in *Science* details a way to use aberrant splicing to prevent the ravages of muscular dystrophy in dog models. "Basically, they designed a snRNP to undo the drastic consequences of a mutation," Steitz marvels. "I think that is just extremely cool!"

## THE PLEASURE OF HER COMPANY

Apart from the official kudos Steitz has received, including the National Medal of Science, postdocs and graduate students in her lab say it's a genuine pleasure to be there. They rave, for example, about her "really great parties." At their most recent Halloween bash, Joan was the Statue of Liberty and Tom was Uncle Sam. And Doudna recalls delightful afternoons spent sailing with Steitz and her husband, drinking wine, discussing science—or the wind. "Working as a postdoc under Joan was such a fantastic experience," says Baserga, "that I spent the first several years on my own wishing I were still there."

While science itself is clearly Steitz's first priority, education is her second. "I adore teaching undergraduates and consider it a privilege to interact with the fabulous students at Yale," she says. Her recent participation in a committee that wrote the National Academy of Sciences report titled "Bio 2010" inspired her to completely revamp a course for advanced undergraduates that teaches them, by group participation, how to read the literature. "Almost every time I lecture at another university, someone comes up to me and says, 'I took your biochemistry course back in 19xx, and it was terrific.' What more can one wish for?"

Another passion is a desire for women scientists to be appreciated as men's equals. Steitz stands firmly by her 2001 comment in *The New York Times* that a woman scientist needs to be twice as good for half the pay, although, Thomas Cech points out, she doesn't picket for change but rather leads by example. Steitz spends time on oversight issues to remedy remaining inequality problems—time she would far rather devote to her science.

She bristles when asked about Harvard President Larry Summers' recent suggestion that women have less innate scientific ability. But she's certainly circumspect in her reply: "What he said, and the sequelae at Harvard and throughout the nation, is the best thing to happen for women in science since the MIT report." She is referring to the report out of MIT in the late 1990s that found women scientists at that institution suffered significant discrimination in terms of pay and stature. After that report was made public, remedial changes were initiated at many universities. Steitz says she is optimistic that Summers' comments will again prompt positive change for women in science. Regarding his continuation as Harvard's president, post-gaffe: "That's something I find very interesting," replies Steitz without expression.

It's not hard to imagine how she would respond to Dr. Famous today if he questioned her place in and dedication to science. She might show him her weighty CV and invite him sailing with her beloved son and husband to remind him that a career in science does not exclude a happy family life—even without the station wagon. ■

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(ERIC BETZIG)

*Do you have thoughts on how to speed up progress?*

EB: Well, that gets into the wider philosophical issues of how research is done, which Janelia will try to address in some ways. In particular, I'm hopeful that the innovative engineering group within Janelia will help, at least for stuff we start to develop internally.

The problem with the near-field microscope—a device I was using fairly successfully—was that there was no mechanism for turning it into a good turnkey instrument. And it's still too embryonic for most biologists to consider using. There are hundreds, if not thousands, of examples in science and technology of good ideas that just languish because of the gulf that exists between the conception/demonstration of an idea and something that's economically viable.

My hope is that Janelia will be a step in the right direction, because mechanisms will be in place there to take ideas that have been shown to work from a proof-of-principle standpoint to the point where they might be broadly applied. Right now, that's pretty damn rare. **–Interview by Jennifer Michalowski** ■

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(NEVER TOO YOUNG FOR SCIENCE)
tools, observing, drawing conclusions, and making predictions.

Evaluations show that the children's vocabulary for the names and functions of science tools increased significantly over a 5-month period during the 2005 program and that most were able to select the appropriate tool to solve a new problem. The results "tell us that children not only know how to use the tools but are also more likely to transfer that knowledge into a new situation," says Garner.

"When we looked at outcomes," adds CLS president Keith Verner, a former HHMI grantee at the Penn State College of Medicine, "we saw increases that were not dependent on a particular teacher or a particular class. We believe it was the program itself that made the difference."

Loudoun County's Scovel agrees, and notes, "We don't want to repeat what children will learn in kindergarten, but we want to build skills they can use in kindergarten and beyond."**–Judith B. Saks** ■

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(EVOLUTION/RELIGION DEBATE)
nonbeliever like myself or a believer like Father Wiseman. It seems to me that [science and religion] are two separate things." He added, "The Bible is not a work of science."

"I find it beyond ironic that society depends on DNA evidence for questions of life and death," Carroll remarked, "yet we're not willing to contemplate the DNA record of natural history and evolution."**–Jennifer Boeth Donovan** ■