



# *View from the Top*

An uncanny way with crystals led Tom Steitz to a clear view of the ribosome's structure—and to the Nobel Prize.

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*Tom Steitz likes to tell a story about the day that* launched him toward a Nobel Prize. It was spring 1963, and he was a graduate student at Harvard University. A buzz ran through the medical campus: Austrian-born chemist Max Perutz of the Cambridge Laboratory of Molecular Biology was lecturing about how he and John Kendrew had unraveled the shapes of the oxygen-toting blood protein hemoglobin and the muscle protein myoglobin. The two were the first to reveal the atomic structure of a protein, and they did it with the powerful yet fussy technique of x-ray crystallography. The work earned them the 1962 Nobel Prize in Chemistry.

In front of a capacity crowd, Perutz turned on a stereoscopic projector and told the audience to don their 3-D glasses. An assistant twiddled some projector knobs. “Out popped this gargantuan molecule over Max’s head,” Steitz recalls. “And the whole audience went, ‘Whoa!’ Everybody was stunned. None of us had seen the atomic structure of a protein—ever.”

As Perutz stood under the molecule pointing out features now familiar to any freshman biochemistry student, Steitz remembers thinking, “‘Wow. This is the way to understand biological molecules.’ And I wanted to do it.”

So he did. And 47 years later, Steitz, an HHMI investigator since 1986, joined Venkatraman Ramakrishnan of the MRC Laboratory of Molecular Biology in England and Ada Yonath of the Weizmann Institute of Science in Israel in winning the 2009 Nobel Prize in Chemistry.

The trio, working independently, used the same basic techniques as Perutz to scale the Mount Everest of biological molecules—the ribosome. Weighing in at more than 150,000 atoms, the ribosome is the engine of life, a delightfully intricate cellular gizmo that churns out countless billions of proteins that brick by biological brick build bacteria, birds, and biochemists. As Steitz’s map of the large subunit of the ribosome helped show, the structure reaches back to the very beginning of cellular life on Earth, some two billion years ago.

Decoding its structure afforded a glimpse into that almost unknowable past—and offered a roadmap to the future of antibiotics. “I’ve hiked up a lot of mountains,” says Steitz, speaking literally and metaphorically, “and when we got that first glimpse of the ribosome, well, that was the view from the top.”

### *Mapping the Machine*

It’s Thanksgiving week; the Yale University campus is half empty. But Steitz’s lab hums with a dozen workers mapping the molecules of life. Steitz arrives at 10:30 a.m., fresh from the gym and relaxed in a fleece pullover—a hale, white-topped, and bearded 69-year-old still feeling a “subdued glow,” as his wife Joan puts it, from the Nobel announcement six weeks prior.

As Steitz chats, laughing easily, he remembers things to do—come up with a title for his upcoming Nobel speech, send an artifact to the Nobel museum, revisit a manuscript with a postdoc. He grabs a colorful plastic model of a ribosome—a grapefruit-

*The deep structural understanding of the ribosome offered by Tom Steitz's team is enabling Rib-X, the company he cofounded, to invent new antibiotics.*

sized riot of blue, red, yellow, green, and purple whorls—and mutters, “Maybe I’ll send them this.”

Steitz returns the model to a low cabinet packed with a dozen more, all molecules he has mapped over four decades.

“A lot of scientists would consider their careers a success if they’d done just one of them,” says Peter Moore, Steitz’s long-time friend and Yale colleague who also played a key role in determining the structure of the large ribosomal subunit.

Later, Joan Steitz—herself a Yale professor and HHMI investigator—lists the structures her husband solved before the ribosome. “A lot of regulatory proteins, polymerases, transposases, all these different kinds of proteins. And the ultimate peak on the horizon was the ribosome. It was a very logical progression of his life’s work,” she says.

There’s a theme to all those molecules. Each is a cog in the central dogma put forth by Francis Crick in 1958 that explains how information flows in organisms: from DNA to RNA to proteins. Early in Steitz’s career, exposure to some of the great minds in biology helped trigger the notion of mapping every cog in the machine.

An audacious goal, but one Steitz has largely fulfilled, says Moore. “When you look at what he’s contributed to fundamental aspects of information transfer in organisms, it’s just enormous. The ribosome is the capstone, but it’s by no means his only big contribution.”

### *Crystal Wrangling*

Steitz was born in Milwaukee and through high school considered a career in music, earning gold medals playing his

saxophone. In the fleeting summers he bunched radishes at his grandfather’s truck farm outside of town, the dirt imbuing a love of green things that has carried to his ever-expanding garden on the Connecticut coast.

Steitz headed to Harvard for graduate school, where he hung around the laboratory of James Watson who was poking into ribosomes. While Steitz developed an interest in cellular structures, he also grew interested in one of Watson’s students, a Minnesotan named Joan Argetsinger. Joan and Tom soon married, and, in 1969, Joan became the first in the family to publish key discoveries about the ribosome, figuring out how the molecular machine initiates its protein-making cycle. (Joan Steitz was profiled in the February 2006 *HHMI Bulletin*.)

The new couple moved to the other Cambridge, in England, in 1967 and began work in the same institution where Watson and Crick had puzzled out the structure of DNA. Steitz thrived in the all-science-all-the-time environment, where the lunchtime conversation rarely strayed from the laboratory business of the day. Here an idea seeded at Harvard germinated: Steitz wanted to take apart the central dogma, piece by piece, like a clock.

He set to the task soon after the couple both landed faculty slots at Yale in 1970. In 1980, he tackled one of the enzymes that copies DNA, a polymerase, and solved it, the first polymerase structure published. Then “he marched through,” as he puts it. Over the next 25 years, he published a staggering number of structures.

Revealing these hidden shapes has always been a means to understanding how the machines work, what they do. So Steitz dogs after a target for years, decades, capturing snapshots in the

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life of a protein. Frame by hard-earned frame, a movie appears. Molecular behaviors emerge. Actions make sense.

Early on, Steitz discovered he had a knack for making crystals—the fickle first step in the process of figuring out a molecule’s shape. “Crystallography is a little bit of witchcraft—or maybe it’s a lot of witchcraft,” says François Franceschi, a crystallographer at Rib-X Pharmaceuticals, the New Haven, Connecticut, company Steitz cofounded in 2001. When starting with an unmapped protein, a scientist doesn’t know the conditions under which the particles will line up and solidify. The scientist doesn’t even know if any given protein *can* make a crystal. The protein might be too floppy, too fragile, too this, too that. Superstitions abound: Maybe this lucky lab jacket will do it; maybe if I hop on one foot while stirring; maybe if I turn around three times and say a Hail Mary while tossing salt over my shoulder.

Though Steitz stopped his direct crystal wrangling in the late 1980s, he still takes pride in the skill. He recalls a Christmas break—he often works during breaks—late in his hands-on career, when a lab member was stymied. Steitz crystallized the stubborn protein and at the end of the week had “one and two millimeter monsters.” He left them in the lab with a note saying, “There it is.”

### *RNA at the Core*

Around that time Steitz began eyeing the looming peak, the last in the line, the reason all those other shapes existed. There was a problem, though: Someone else, his Nobel co-laureate, Yonath, had staked out the turf. In 1980, she made the first ribosome crystals. Among crystallographers, says Moore, there is a “courtesy convention that says you don’t jump in on top of somebody who had crystallized something. You give them the opportunity” to use the pretty, hard-won specks to solve the structure themselves.

But the years ticked by, and Steitz grew antsy. He began planning to use Yonath’s recipe as a jumping off point. “I’ve gotten some heat about that,” says Steitz. “In the crystallography field, they say, ‘Oh, those are Yonath’s, right?’ But after 10 years, good grief.” There was no reason for Steitz to start from nothing—Yonath had published her work.

Franceschi, who collaborated with Yonath’s lab for 12 years, says, “It was clear that at some point other people were going to jump on the train. But, I think at the end of the day, competition is what fuels progress.”

The Yale ribosome project launched in 1995 when an incoming postdoc named Nenad Ban agreed to take on the challenge. After a lot of noggin-scratching, Steitz, Ban, and Moore found a couple of possible reasons why Yonath was not succeeding: First, the crystals were hypersensitive to salt. A drop in salinity caused them to “twin.” The ribosome particles aligned in two distinct patterns instead of one. That slowed progress for a year or so until it was solved. The more challenging problem, however, was how to make a heavy atom derivative of these crystals and correctly locate the positions of the bound heavy atoms in the crystal. It required new approaches.

At 10 times the size of the biggest molecule anyone had ever solved, the ribosome crystals demanded a stronger heavy atom signal than is provided by simple heavy atoms. As the team worked through the twinning problem, they made a derivative using a super heavy atom cluster containing 18 tungsten atoms bound very tightly to each other. “At low resolution they scatter essentially as one atom containing 2,000 electrons,” explains Steitz. “That gave a strong signal, which got us started.” Ban did much of the heavy lifting, with Steitz offering a stream of ideas. Two more postdocs signed on, Poul Nissen and Jeff Hansen, and

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the quintet decided to inch their way up the mountain instead of racing to the top. That is, they collected low-resolution data producing fuzzy, low-resolution images, double-checked against all available data, and then gradually sharpened the picture. They developed new techniques at low resolution without investing the huge resources needed to obtain high-resolution data.

While mapping their first low-resolution images, the team double-checked their data against ribosome images made by HHMI investigator Joachim Frank of Columbia University College of Physicians and Surgeons. Though fuzzy by crystallography standards, Frank's electron microscopy images offered proof that the new techniques developed by the Yale team were, in fact, working. They drove on.

In 1998, the Yale team published their first paper on the ribosome, a low-resolution map of the large subunit—the factory component of the machine, the part that actually builds proteins. (The other part, the small subunit, is the foreman—it receives messenger RNA and tells the large subunit what to do. Co-laureate Ramakrishnan mapped it.) The team revealed their methods, and the race was on. “Everybody changed course,” says Steitz, adopting the new methods his team had developed.

Within a year, the Yale team sharpened the image threefold. It was time for the push to the summit—a trip to the powerful beam at Argonne National Laboratory in Illinois. Data poured in. Moore remembers seeing it and thinking, “Oh my god. We went out and caught the whale. Now what are we going to do with it? How are we ever going to figure out what all that stuff means?”

Raw crystallography data resemble blobs on a gray field. “There’s nothing that says, ‘I am a carbon, I am a nitrogen,’” says Moore. The team spent months interpreting the blobs, nearly hand-placing each atom—all 100,000 of them. In early 2000, the team completed a finely wrought 2.4-angstrom-resolution structure. “It was extraordinary,” says Steitz. “We had no idea what the ribosome was going to look like.”

Some 31 proteins glued together the outer shell and helped with housekeeping. But deep inside, where the protein-making magic happened, there was nothing but coiled RNA, 3,000 bases of it. Here, laid bare, was the secret of life, or at least one of them: Proteins were not built by other proteins, as biologists had once assumed. RNA did the job. For several decades, starting with Francis Crick in 1968, some ribosome researchers had theorized that to be the case, but the Yale structure proved it.

The implications were profound: The ribosome structure provided deep support for the theory that the first organisms on Earth were built from RNA. “The ribosome is a prime basis for the ‘RNA world’ hypothesis” of how life began, says former HHMI president Thomas Cech.

And while the shell differs from organism to organism, the business end, the RNA center, is nearly identical across every species on the planet. For some two billion years of cellular evolution, the same heart of machine has been there churning out

proteins, building life. Fortunately, there exist minute differences between bacterial and human ribosomes. That’s good news for Rib-X, and bad news for bacteria.

### *Approach to Antibiotics*

On a computer screen, Rib-X scientist Brian Wimberly rotates a bacterial ribosome, a tangled, multihued mass. He zooms in, flying through the green and yellow outer shell, deep into the red and purple heart. He points to a hexagon jutting into a vast black hole. The hexagon is a single base of RNA, an adenine labeled A2058. Wimberly clicks his mouse and a blue filament appears next to it, an antibiotic of the macrolide class. This drug binds to A2058 deep inside the ribosome, blocking protein production. No protein means no life for the bacteria.

Human ribosomes, in contrast, display a different base at that location, a guanine. The substitution subtly alters the shape of the protein-making center of the ribosome, rendering our cells impervious to macrolides. In the never-ending evolutionary arms race, though, bacteria exposed to macrolides learn this trick, too. They change adenine to guanine, and bingo: antibiotic resistance.

Such miniscule alterations, along with other types of antibiotic resistance, account for some 99,000 deaths in the United States each year. About half of antibiotics work by interfering with bacterial ribosomes, and the scientists at Rib-X exploit the deep structural knowledge Steitz’s team provided to invent better ones. The 40-person company has two new antibiotics poised for pivotal phase three studies, with two more ready for human safety tests.

Rib-X CEO Susan Froshauer says there’s been but a trickle of new antibiotics from big pharma, hampering efforts to treat, for example, drug-resistant tuberculosis and nasty hospital-borne bacteria like *Staphylococcus aureus*. “These are serious, serious infections,” says Froshauer.

Steitz didn’t tackle the ribosome to make new drugs, but once he did, he understood the opportunity. In eight years, Rib-X scientists have determined the structures of some 400 ribosome–antibiotic complexes. It took the Yale team five tough years to solve just one of them.

Steitz talks about the company as a parent might talk about a child. “I’ve been so pleased,” he beams. During the Yale press conference announcing his prize, Steitz repeatedly bent questions about himself into praise for Rib-X.

Maybe his Midwestern roots are responsible for that self-effacing manner. In any case, Steitz is right at home in Connecticut now, with a house on the coast, the sailboat he enjoys with Joan and their son Jon, the roses, the 600-bottle wine cellar, the gourmet-chemist meals, a warm coterie of life-long friends and colleagues, a view from the top. Taking a rare moment to survey his career and the ever-expanding knowledge of the ribosome pouring in—his original publication has been cited 1,500 times—Steitz knows his work isn’t done, saying, “There’s always just one more step.” ■