JOANNE STUBBE PROFILE - 2017 RECIPIENT

When a topic grabs JoAnne Stubbe, she grabs back. The illustrious chemist has earned a reputation for drilling into enzyme mechanisms, but numerous other activities might have consumed her instead. During a college art history course, she fixated on Rembrandt. She read everything she could find about him and pored over reproductions of his paintings, weeping because "he made me feel what the people were feeling," she says. At a different time, tennis captivated her. Earlier this year, she read The Stranger in the Woods, a book about a hermit who exiled himself for 27 years. She briefly toyed with the idea of holing up too. In many ways, the notion of Stubbe as hermit feels natural. For most of her adult life, she has created a sanctuary for herself in her passionate pursuit of discovery.

Over the last four decades, Stubbe has applied her ferocious curiosity to enzymology. Her digging has excavated an unanticipated mechanism for ribonucleotide reductase, the enzyme that manufactures DNA's building blocks. She has shown how this protein exploits powerful but potentially hazardous chemistry and guides it to perform complex feats with acute specificity. Stubbe has illuminated a constructive side of long vilified molecules called free radicals, known mostly for promoting aging and disease, and her insights have influenced the development of cancer treatments. She is fearless about devising new techniques and seeking collaborators who possess complementary expertise that unlock the next problem. Her fresh and inventive approaches have yielded many successes, and she has earned numerous awards, including the National Medal of Science and the James R. Killian, Jr. Faculty Achievement Award, conferred by her Massachusetts Institute of Technology colleagues as recognition of her extraordinary professional achievement.

A high school chemistry class in Stubbe's hometown of Worcester, Massachusetts, seeded her interest in the subject. Every day, she'd check a beaker where salt crystals grew bigger and bigger. During summers, when she worked in an organic chemistry lab at Clark University, and in college at the University of Pennsylvania, her enthusiasm intensified. For instance, she learned how particular structures translate into visible light, and was bewitched by the basis of color changes during chemical reactions. Although experimental life was enchanting her, frequent explosions in lab class rattled her burgeoning ardor. Students dumped volatile solvents in a trough that ran the length of the bench to the sink, and when Bunsen burner flames caught the vapors, the entire trench would ignite. It "almost scared me off of science," she says.

Having absorbed from her parents the idea that she could take whatever career path she wanted, Stubbe was surprised when she arrived for graduate school at the University of California, Berkeley, in 1968 and discovered that not everyone shared that view. The professor of the first lab she wanted to join told her that he did not accept female students. The professor of the second lab she wanted to join told her they would choose a project that was appropriate for her future as a technician.

She wound up working in one of Berkeley's first chemistry labs that was branching toward biology. At the time, many chemists thought the field lacked rigor. "I didn't like biology in high school either," says Stubbe. "There was no understanding at the molecular level." The degree of disdain might be

difficult to imagine in the current age of chemical–biological embrace, but her home department did not even give her credit for a biochemistry course that she took from two of the world's preeminent enzymologists.

Undeterred, she chose to discuss a paper that describes how the antibiotic penicillin inhibits its target enzyme when she gave a required seminar. That study "profoundly affected" her scientific trajectory, she says. To Stubbe, "it was a revolution that you could take your understanding of chemical structure to understand how an essential bacterial enzyme was inactivated," she says. The allure of unraveling an enzyme mechanism at the atomic level propelled much of her subsequent inquiry.

A brief stint at Williams College, where she taught several subjects that were outside her area of expertise, boosted Stubbe's confidence and made her realize that she yearned to move to a research institution. She took a leave of absence to study at Brandeis University with mechanistic enzymologist Robert Abeles, "one of the most creative people in the world," she says. That experience allowed her to pivot professionally, and she found her way to Yale University School of Medicine in a department that was exploring rational drug design. About 50 faculty members competed for four graduate students every year and she shared an office with another new hire. It was so small, they couldn't simultaneously get in or out of their back-to-back chairs. Still, she was pursuing her own project. "We had a good time," she says. "We talked science."

Stubbe was trying to understand how the enzyme ribonucleotide reductase converts RNA building blocks to DNA building blocks. Because these components are required to make and repair DNA, they are indispensable for life. On paper, the reaction looks simple: The enzyme replaces an oxygen–hydrogen duo—a hydroxyl—with a hydrogen. But "nothing could be further from the truth," Stubbe says. Despite great effort, researchers couldn't discern how ribonucleotide reductase renders the hydroxyl more eager to leave the carbon to which it is attached. "Everyone told me it was suicide to work on because no one could figure it out," she says.

Stubbe triumphed by establishing that a quirky feature of the enzyme was crucial for its activity. Years earlier, investigators had shown that ribonucleotide reductase contains a chemical group with an unpaired electron. Although such free radicals were well-known entities and some participated in enzymatic reactions as helpers, no one had implicated them as integral, functional parts of an enzyme. Furthermore, free radicals were most famous as physiological miscreants. They wreak havoc because their lone electrons are so impatient to pair up, they react willy-nilly with proteins, DNA, lipids, and other vital biological molecules.

With an open mind, Stubbe approached ribonucleotide reductase. From reading the scientific literature about the effects of ionizing radiation, she knew that one way to break a carbon–hydroxyl bond is to cleave a carbon–hydrogen bond next to it by utilizing an unpaired electron. To explore this idea, she set the enzyme loose on a modified version of its normal substrate and analyzed the chemicals that formed. One particular product made "a lightbulb go on," she says. "Immediately I knew what the mechanism was" because "there are very few ways" to generate that compound from the starting material.

The observation, which she published in 1980, suggested the involvement of free radicals. These results and others established that ribonucleotide reductase's unpaired electron performs a central role, and also that the important chemistry occurs not at the carbon that trades a hydrogen for a hydroxyl, but at the adjacent one. These achievements "put me on the map," Stubbe says, and got her a job at the University of Wisconsin, Madison, home of the most chemically oriented biochemistry department in the country, where she was able to recruit graduate students**.** She pursued her work on ribonucleotide reductase there and after she went to MIT in 1987.

During the past several decades, Stubbe and her collaborators have shown how free radicals can perform challenging chemistry in biological systems, where nature has supplied an appropriate molecular environment. If the chemical group in human ribonucleotide reductase that sparks catalysis were loose in solution, it would steal an electron from surrounding atoms in a millisecond. In the protein, the electron can remain unpaired for minutes to days. Scaling up, that's like lengthening the lifetime of something that normally lasts for a second into something that survives for between a year and a millennium. Evolutionary forces have surrounded the electron with exceptionally inert chemical groups and thus provided a setting that subdues its propensity to react.

As Stubbe dug deeper into the intricacies of ribonucleotide reductase, she addressed many of its remarkable riddles. For example, other researchers suggested that the instigating electron forms in the enzyme 35 Angstroms from where it needs to act. Stubbe "didn't believe it at first," she says, "because it was ridiculous. Why would you do that when you could make it sit right next to the substrate?" Nevertheless, she decided to investigate and found strong experimental support for the idea. Furthermore, she and her collaborators discovered that the free electron hops from one atom to another through a precisely controlled path as it journeys through the enzyme. So not only does ribonucleotide reductase deploy a type of chemical that has the capacity to incite biological catastrophe, but it moves the potentially destructive electron a tremendous distance through the protein—past numerous atoms where it could cause trouble—before delivering it to the catalytic site.

A relentless drive to understand basic biology has fueled Stubbe's accomplishments, yet numerous practical applications have arisen from her discoveries. She and her collaborators elucidated the detailed mechanism by which free radicals enable the drug bleomycin, used mostly to fight cancer, to cleave DNA. These findings promise to guide improvements in bleomycin-based treatments by enhancing potency and minimizing harmful side effects. Stubbe has also shown how chemotherapeutic medications such as gemcitabine and clofarabine thwart ribonucleotide reductase and thus impede rampant growth of cancer cells. These observations have opened up new strategies for foiling the enzyme.

Throughout her career, Stubbe has peered into nature's corners and brushed off cobwebs to reveal surprising features and new mysteries. "I'm a details person," she says. "I have worked on the same problems for my whole life, but what I study keeps changing."

(Authored by Evelyn Strauss, Ph.D.)