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Thomas A. Steitz (1940–2018)

Biochemistry giant who illuminated ribosome structure

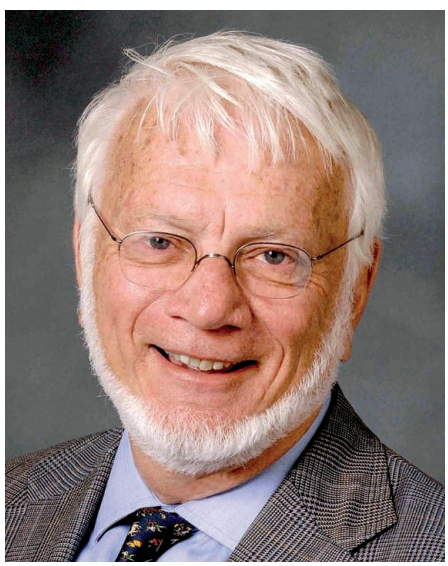
By **Venki Ramakrishnan** *and* **Richard Henderson**

Thomas A. Steitz, distinguished molecular and structural biologist, died on 9 October at the age of 78. Tom was known for his unerring judgment in picking fundamentally important problems, and persisting, sometimes for over a decade, until he solved them. His work on the information flow from DNA to RNA to protein culminated in work on the structure of the 50*S* subunit of the ribosome, for which he shared the 2009 Nobel Prize in Chemistry.

Born on 23 August 1940 in Milwaukee, Wisconsin, Tom attended Lawrence College in Wisconsin on a scholarship and earned his degree in chemistry in 1962. He then began his graduate work at Harvard University. Although Tom initially planned to work on biophysical studies of nucleic acids, he was thrilled by lectures given by Max Perutz, the pioneer of protein crystallography, in which Max presented the first atomic-resolution structure of the protein myoglobin. Inspired to become a protein crystallographer, Tom joined the group of chemist and crystallographer W. N. (Bill) Lipscomb to work on the structure and mechanism of carboxypeptidase A. During this time, he met and married Joan Argetsinger Steitz, who became an equally distinguished molecular biologist.

In 1966, Tom earned his Ph.D. in biochemistry and molecular biology at Harvard. The next year, he and Joan moved to the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) in Cambridge, United Kingdom, as postdocs, where Tom worked with crystallographer and biophysicist David Blow on the mechanism of protein hydrolysis by the serine protease chymotrypsin. The work led to an understanding of how all serine proteases cleave peptide bonds, as well as how the homologous trypsin recognizes positively charged side chains using a negatively charged aspartic acid at the bottom of its specificity pocket. Tom enjoyed discussions about research strategies with Brian Hartley and other pioneers of molecular and structural biology at LMB. He described his time at LMB as "the most important time in the development of my future research direction and my perspective on how creative science should best be done."

Next, Tom and Joan moved briefly to the University of California, Berkeley, where Tom had been offered a faculty job. As Tom described it, "I asked if there was any possibility of a job for Joan. The department chairman… said, 'She's a woman. Women do not run their own lab; they work in the lab of their husband.'" So they departed for Yale University, where Fred Richards offered both Tom and Joan faculty positions as part of his visionary



transformation of the Molecular Biophysics and Biochemistry Department into a powerhouse of structural and molecular biology. Joan said recently, "I was very, very lucky to have married Tom. He really believed that I should have as equal an opportunity to succeed as he." They were a star couple at Yale, both becoming hugely influential leaders in their respective and sometimes overlapping fields. They even published an important paper together on the role of metal ions in catalysis by DNA and RNA polymerases.

At Yale, Tom began by determining the structure of hexokinase, an enzyme that phosphorylates glucose. The enzyme was one of the early examples of induced fit, whereby the substrate induces a change in enzyme conformation to bring catalytic residues into their active positions. His lab then focused on the structural mechanisms underlying the central dogma of molecular biology: how information flows from DNA to RNA to protein. His group worked out the structures of a series of important enzymes and cofactors that form the central core of structural molecular biology. This work culminated in his collaboration with Peter Moore, whose lifetime of work on the ribosome complemented Tom's crystallographic expertise. Together, they and their colleagues worked out the structure of the 50*S* ribosomal subunit, which definitively established that the ribosome is a ribozyme, and obtained the structures of complexes of the ribosome with many different antibiotics.

In his steadfast determination to get to the heart of a problem, Tom was not afraid to make bold guesses about how a molecule works. This occasionally led to dramatically incorrect proposals. When he solved one of the first structures of a DNA-binding protein, the CAP repressor, he suggested that it bound to left-handed DNA. He joked that this was such an egregious mistake that he would have to solve five more structures before he would be invited to speak at a conference again. Later, he suggested a mechanism of peptidyl transfer in the 50*S* ribosomal subunit. Both of these ideas proved incorrect. In each case, Tom exemplified how science should progress from mistakes by admitting the error and correcting it. His lab went on to show that CAP bound to a sharply bent form of DNA, a tour de force at the time. His lab also obtained a series of structures of substrate and transition-state analogs bound to the 50*S* subunit that helped to establish the correct mechanism and was described by the Nobel Committee as the "jewel in the crown" of studies on the mechanism of peptidyl transfer. Rather than be overly wedded to his own ideas, Tom received corrections from others with interest as well. His ultimate goal was always to help establish the truth.

Tom was known for his direct manner, which, along with his enviable track record, could intimidate anyone who was insecure. However, this was simply another aspect of his eagerness to get to the crux of the matter without wasting time. It also meant that he could be bluntly critical, often with an amusing pun, when encountering sloppy science, but generous with praise when he came across beautiful work. His students and colleagues never doubted where they stood with him. Even so, he was a supportive and egalitarian mentor who believed that talent and drive should determine success. These traits, along with his commitment to working only on problems he thought were truly important, helped him to train many generations of outstanding protégés, who along with achievements from his own lab form part of the huge legacy he has left behind. ■

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