Structural biology bags chemistry prize

Chemistry Nobel for trio who described the ribosome.

Thomas Steitz, Venkatraman Ramakrishnan and Ada Yonath share this year's chemistry Nobel.

LEFT TO RIGHT: L. JACKSON/REUTERS; A. GRANT/AP PHOTO; XINHUA NEWS AGENCY/EYEVINE

Three structural biologists who mapped the structure and inner workings of the ribosome — the cell's machinery for churning out proteins from genetic code — have won this year's Nobel Prize in Chemistry.

Venkatraman Ramakrishnan, who works at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, UK; Ada Yonath of the Weizmann Institute of Science in Rehovot, Israel; and Thomas Steitz at Yale University in New Haven, Connecticut, share the prize equally.

"So many people contributed, and the ribosome is so important, that I am just pleased to be one of the three," says Ramakrishnan.

Explaining the ribosome's structure was a key step towards understanding how it translates DNA into proteins. "Until you see how atoms are arranged, it's hard to integrate biochemical knowledge into that framework," Ramakrishnan says. "High-resolution pictures change the nature of the field, directing biochemical experiments. They have a disproportionate impact."

Ramakrishnan and Steitz's groups used X-ray crystallography to solve increasingly high-resolution structures of different ribosomes, mostly from simple organisms such as bacteria. Yonath paved the way for these studies by creating the first ribosome crystals. From such structures, researchers have worked out how the ribosome grabs messenger RNA — transcribed from DNA — follows its amino-acid recipe, and binds these units together to produce proteins.

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Even in its smaller bacterial form, the ribosome is a large and complex structure, consisting of two subunits and more than 50 different proteins. In the late 1970s, this was orders of magnitude larger than other biological molecules that had been coaxed into forming crystals, such as haemoglobin and myoglobin. Yonath tried anyway.

"The idea of crystallizing the ribosome was completely outrageous, but Ada had a deep-rooted belief that she knew what she was doing," says Yehiam Prior, head of the Weizmann Institute's chemistry department.

By using resilient organisms with particularly stable ribosomes, including salt-loving creatures from the Dead Sea, Yonath succeeded in creating three-dimensional crystals of the molecule. By hitting these with X-rays, she produced the first blurry images of the ribosome.

At that point, other teams piled in to create structures of high enough resolution to determine atomic structure. Steitz's team focused on the molecule's larger 50S subunit, which joins amino acids together into proteins, and published the first atomic-resolution structure in 2000 (N. Ban *et al. Science* **289**, 905–920; 2000).

"These were very exciting times, with huge competition with other groups in the field. We had hourly discussions every day," recalls Nenad Ban, who worked in Steitz's laboratory as a postdoc and is now at the Swiss Federal Institute of Technology Zurich.

Ramakrishnan's group, meanwhile, attacked the smaller 30S subunit, which latches onto mRNA (B. T. Wimberley *et al. Nature* **407**, 327–339; 2000).

Unravelling the ribosome's structure may produce dividends in terms of the potential to develop novel antibiotics. "The ribosome is already starting to show its medical importance," Ramakrishnan notes. All three researchers have published analyses of how antibiotics attack bacteria by disrupting their ribosomes and so preventing them from creating proteins.

Chloramphenicol, for example, binds to the 50S subunit's active site, preventing it from joining amino acids together, whereas erythromycin 'constipates' the ribosome by blocking the channel through which a completed chain of amino acids is normally released into the cell's cytoplasm to fold up.

As bacteria have evolved resistance to these antibiotics, start-up companies such as Rib-X Pharmaceuticals — based in New Haven, Connecticut, and spun out of Steitz's team — are using knowledge of the ribosome's structure to create new antibiotics, which are currently in clinical trials.

It is the third time in seven years that the chemistry Nobel has been awarded to crystallographers who have determined the structure and function of a complex biological molecule. "It does seem to be a recurring theme," says Thomas Lane, president of the American Chemical Society in Washington DC.

But at its heart, this structural biology is "fundamentally chemistry", adds Jeremy Sanders, head of physical sciences at the University of Cambridge, UK. "Even if many chemists had never heard of any of the winners." ■

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