The 2009 Nobel Prize in Chemistry

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On October 9th, 2009 three scientists were awarded the Nobel Prize in Chemistry "for studies of the structure and function of the ribosome". The awardees were Venkatraman Ramakrishnan of the MRC Laboratory of Molecular Biology, Thomas Steitz of Yale University and Ada Yonath of the Weizmann Institute of Science. The first Nobel Prize in Physics was awarded to Wilhelm Conrad Röntgen for the discovery of X-rays. Since then many Nobel Prizes have been awarded to X-ray crystallographers. The first Nobel in Chemistry that was awarded to an X-ray crystallographer was to Linus Pauling, "for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances" in 1954. The penultimate Chemistry prize was awarded to Roger Kornberg "for his studies of the molecular basis of eukaryotic transcription" in 2006.

This work begins with the statement of the central dogma of molecular biology that DNA begets RNA which begets protein and the process is irreversible, as proposed by Francis Crick in 1958. In 2006, the Nobel Prize in Chemistry was awarded to Kornberg for determining the structure of RNA polymerase and the mechanism of transcription, the DNA to RNA step in the central dogma. Ramakrishnan, Steitz and Yonath have helped confirm the second step of the central dogma, translation, of the RNA into protein. It was known the ribosome produced protein but how it worked explicitly was not known. The ribosome is a large complex of RNA and protein molecules nearly 250 Å in one dimension.

The first step in this decades long study was the selection of a species that would provide ribosomal material that did not degrade too rapidly. Yonath first generated crystals of the large subunit of the ribosome from a thermophile, *G. stearothermophilus* in 1980. Yonath packed these 1 μm crystals into a capillary and subjected the crystals to X-rays from a rotating anode and observed powder rings. Over the next decade Yonath found another species of bacteria, *H. marismortui*, that would provide the material for the high resolution X-ray crystallographic studies as well aid in the development of the cryocrystallographic techniques needed allow whole data sets to be collected.

In the early 1990s, Steitz began the effort to solve the phase problem of the ribosomal diffraction data. About the same time 3rd generation synchrotron X-ray radiation sources with advanced detectors came online and Wayne Hendrickson's multiple-wavelength anomalous diffraction (MAD) phasing method became *de rigueur*. In 1998, using cryoelectron microscopy (cryo-EM) data from Joachim Frank, and several new heavy derivatives Steitz and his colleagues published the structure of the large subunit (50S, 1500 kDalton) of the ribosome at 9 Å resolution. At 9 Å, one sees gross features of the structure, but not atomic details. In 2000, that resolution was increased to 2.4 Å and the question of whether or not the ribosome was a ribozyme was answered. The ribosome is a ribozyme, that is a catalytic enzyme with a mechanism based on RNA.

In the meantime, Ramakrishnan had been working on the small subunit (30S, about 800 kDalton) of the ribosome from *H. marismortui* and, using similar crystallographic methods as Steitz, published a 3.3 Å resolution structure in 2000.

The 30S subunit is responsible for accurate reading of the messenger RNA, derived from the DNA by RNA polymerase, and the 50S subunit is responsible for initiation, creation of the peptide bonds, elongation and termination of the protein chain. Both subunits must be combined into what is called the 70S unit to perform the operation of translation.

The significance of the work by Ramakrishnan, Steitz,

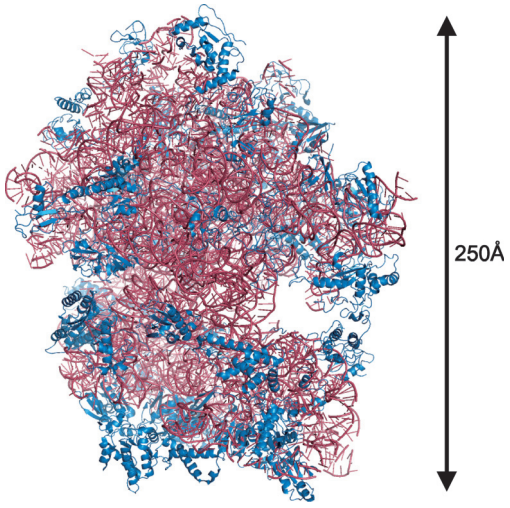

Fig. 1. PDB code 2J00 and 2J01. Picture by Angela Criswell.

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Yonath and all their collaborators is many fold. From a philosophical point of view, the knowledge the ribosome is a ribozyme suggests an evolutionary path from primitive life to today, in other words life started with RNA. Indeed, Yonath has identified a dimeric core of RNA found in all ribosomes that could well have been the prototype of the ribosome we know today. Of course, confirming the central dogma of molecular biology has its reward as well.

There is a very practical reason to study the ribosome. About half of all current antibiotics target the bacterial ribosome. About 90,000 people die every year in the US alone from methicillin-resistant *S. aureus* (MRSA). The structural work on the ribosome has already yielded a potential antibiotic developed by using the features of two known antibiotics to provide an even more powerful drug. Twenty times as many people die from tuberculosis every year worldwide. The structure of the ribosome is being used to develop a new drug against TB. It should be obvious that while basic science was served by this grand effort, humanity will also benefit directly in the near future.