

# Biologists probe the machinery of cellular protein factories

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Proteins of all sizes and shapes do most of the work in living cells, and the DNA sequences in genes spell out the instructions for making those proteins. The crucial job of reading the genetic instructions and synthesizing the specified proteins is carried out by ribosomes, tiny protein factories humming away inside the cells of all living things.

Harry Noller, the Sinsheimer Professor of Molecular Biology at the University of California, Santa Cruz, has been studying the ribosome for more than 30 years. His main goal is to understand how the ribosome works and how it evolved, but there are also practical reasons to pursue this research. Many of the most effective antibiotics work by targeting bacterial ribosomes, and findings by Noller and others have led to the development of novel antibiotics that hold promise for use against germs that have developed resistance to current drugs. Drug-resistant staph infections, for example, are a serious problem in hospitals.

Noller's laboratory achieved breakthroughs in 1999 and 2001, producing the first high-resolution images of the molecular structure of a complete ribosome. Now, his team has made another major advance with an even higher-resolution image that enables them to construct an atom-by-atom model of the ribosome.

The new picture shows details never seen before and suggests how certain parts of the ribosome move during protein synthesis. A paper describing the new findings will be published in the September 22 issue of the journal *Cell* and is currently available online.

"We can now explain a lot of the results from biochemical and genetic studies carried out over the past several decades," Noller said. "This structure gives us another frame in the movie that will eventually show us the whole process of the ribosome in action."

The ribosome is a complex molecular machine made up of proteins and RNA molecules. The bacterial ribosomes studied in Noller's lab (obtained from the bacterium *Thermus thermophilus*) are made up of three different RNA molecules and more than 50 different proteins.

Noller proposed in the early 1970s that the RNA component was responsible for carrying out the ribosome's key functions. At the time it was considered a "crackpot idea," but subsequent findings by Noller and others proved he was right.

"It was a completely heterodox view when we first proposed it, but it is now the accepted paradigm," said Noller, who directs the Center for Molecular Biology of RNA at UCSC. "Our latest results confirm that the ribosomal RNA is really the key to ribosome function. The proteins are also involved, but more peripherally," he said.

To make a new protein, the genetic instructions are first copied from the DNA sequence of the gene into a messenger RNA molecule. The ribosome then reads the genetic code from the messenger RNA and translates it into the structure of a protein.

Proteins are linear molecules that fold into complex three-dimensional shapes to carry out their functions. They are made from amino acid building blocks, and the sequence of amino acids determines the protein's structure. Amino acids are carried to the ribosome by transfer RNA molecules. On the ribosome, the transfer RNAs recognize specific sequences of genetic code on the messenger RNA, and the amino acids are then joined together in the proper order.

The images from Noller's group not only show the complete ribosome, they show it with a messenger RNA and two full-length transfer RNAs bound to it. "We can now see the details of most of the interactions between the ribosome, the messenger

RNA, and the transfer RNAs," Noller said.

The results provide a snapshot of the molecular machine in action. By comparing his images with those obtained by other groups that have caught the ribosome or its subunits in different positions, Noller is finding clues to the molecular motions with which the ribosome does its work.

"Our next goal is to trap the ribosome in other functional states to get more frames of the movie," he said.

The authors of the paper, in addition to Noller, are postdoctoral researcher Andrei Korostelev, senior scientist Sergei Trakhanov, and postdoctoral researcher Martin Laurberg. The researchers used a technique called x-ray crystallography, which involves growing crystals of purified ribosomes, shining a focused beam of x-rays through the crystals, and analyzing the resulting diffraction pattern. Trakhanov prepared the crystals and Korostelev and Laurberg performed the crystallography and solved the structure, Noller said.

Source: University of California - Santa Cruz

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