

**Rede**  
**von**  
**Prof. Dr. Ruth Arnon**

**anlässlich der Verleihung**  
**des Paul Ehrlich- und Ludwig Darmstaedter-Preises**  
**2007**

**an**

**Prof. Dr. Harry F. Noller**  
**Prof. Dr. Ada Yonath**

**Paulskirche Frankfurt/Main**  
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**Es gilt das gesprochene Wort!**



Dr. Kopper, Chairman of the Scientific Council of the Paul Ehrlich Foundation, members of the Scientific Council, your Excellencies, and dignitaries, Ladies and Gentlemen:

It is a great pleasure and honor for me to present to you this morning the winners of the Paul Ehrlich and Ludwig Darmstaedter Prize 2007, Professor Ada Yonath and Professor Harry Noller. The prize is awarded to them for their contribution to the elucidation, by x-ray crystallography, of the detailed 3-D structure of the ribosome, and its decisive role in protein synthesis. They will of course tell us themselves about their own unique contributions.

What I would like to do is to relate to their discoveries in perspective to other milestones in biology – since science is a continuum and the various crucial discoveries are like steps of a ladder on which we climb to reach new levels of knowledge.

Both our prize winners today have reached their breakthroughs and scientific achievements using crystallography. It is therefore, of interest to note that till recently almost our entire knowledge base in biological structure and molecular biology was achieved by X-ray crystallography.

One of the most crucial milestones in molecular biology was the discovery of the DNA double helix, in the early 1950's, by Crick and Watson, that was based on the x-ray diffraction measurements of Rosalind Franklin. It led to the understanding of the function of DNA and its ability to replicate in our chromosomes, before cell division, so that each daughter cell has an identical set of chromosomes. Furthermore, the DNA carries all the genetic information in the cell and is responsible for coding for all the proteins, which consist of long chains of amino acids and serve as the building blocks of our body that carry out all its vital functions.

What is less known is that a few years after that discovery of the DNA double helix, in 1956 Rich and Davis discovered, again by X-ray crystallography, that the "other type of nucleic acid" namely RNA also has a double-stranded helix structure. For many years this was demonstrated only for one type of RNA – the transfer RNA, but, more recently, the double helix structure has been demonstrated for other types for RNA, including ribosomal RNA. This initial discovery, followed by the demonstration of spontaneous RNA hybridization, laid the foundation for many other important discoveries and inventions, including the Polymerase Chain Recombination technology that led to a revolution in molecular biology, and is the foundation of an entire biotechnology industry. It also led to the development of DNA microassay technology for gene identification. In addition, it led, though indirectly, to the discovery by Craig Mello and Andrew Fire of the small interfering RNA for which they were awarded the Paul Ehrlich and Ludwig Darmstaedter Prize in 2006.

Several years ago we celebrated another important milestone - the deciphering of the human genome, namely the complete sequence of the entire human DNA that codes for all the proteins that play a role in our life. The Paul Ehrlich and Ludwig Darmstaedter Prize in 2002 was awarded to Craig Venter for his crucial contribution to this achievement. The scientific world was in euphoria – it was believed that the sequence of the human genome, comprising 25,000-35,000 genes was going to provide all the information necessary to understand the blueprint of man. However, it was soon realized that DNA is not the only player, and that RNA, in its various forms – messenger RNA,

transfer RNA and ribosomal RNA – plays a crucial role in the actual synthesis of the proteins.

The genetic information in the DNA is first transcribed to the mRNA, and the actual synthesis is done in the ribosomes, a large number of which act simultaneously on the same mRNA synthesizing different proteins. These ribosomes, which are the focus of the Prize today, are giant cellular assemblies, each composed of two subunits comprising mainly RNA, in which more than 50 proteins are embedded. Assembled together, they provide the structural site in which the proteins are synthesized and the entire process can occur. During this extremely complex process, at each protein elongation step the correct amino acid has to be brought in, one after another in the right sequence, the bond between them has to be formed, and then the complete molecular chain of the protein has to exit the ribosome. This has to be done extremely fast with high accuracy to ensure the correct sequence of the synthesized protein with no mistakes. All this is made possible by the precise structure of the ribosome.

Like most other biological structures, the determination of the structure of the ribosomes was carried out by X-ray crystallography, which as already mentioned, is the major tool in structural biology, not only for nucleic acids but for proteins as well. Ever since the pioneering studies of Max Perutz and John Kendrew who were awarded the Nobel Prize in 1962 for solving the structure of myoglobin, the structure of numerous proteins has been determined. Today, almost every soluble protein can be purified and crystallized, even though crystallization itself is a special expertise. Once crystallized, the three dimensional structure of the protein can then be determined from its x-ray diffraction measurements. In many cases, this structure by itself can tell us about the function of the protein, its active site and mode of action.

Crystallization of the ribosomes was a much more complex objective, mainly due to their huge size, enormous flexibility, significant functional heterogeneity and remarkable tendency to deteriorate. For many years this was considered an impossible mission. It has been achieved only thanks to the pioneering studies of Prof. Yonath and the sophisticated techniques and procedures that she developed. Once available, the crystallized ribosomes and their two subunits lent themselves to structure determination. The pioneering studies of Noller that started already in the 1980's, using biochemical analysis, led to the correct prediction of the ribosomal RNA secondary structure. By analysis the 3-D ribosome structure, Yonath discovered the element of the spectacular ribosomal architecture that guides and ensures peptide bond formation. This stunning and originally unexpected architectural element is made of ribosomal RNA, thus corroborating Noller's previous biochemical findings, obtained over 2 decades ago.

Furthermore, since the ribosomes are molecular machines, whose moving parts enable the dynamic process of molecular translation, from RNA to proteins, the structural data contribute to the understanding of their mode of action. Moreover, taking the discoveries of Professors Yonath and Noller one step further – it is now possible to devise procedures for specific selective inhibition of protein synthesis in the ribosomes of pathogenic bacteria – which may lead to the development of novel drugs.

I would like to end my remarks with a few general words, particularly on the quantitative aspect of protein synthesis: The body of an adult human being is composed of

approximately  $10^{14}$  or 100 trillion cells and each cell contains about a billion protein molecules fulfilling its different functions.

Furthermore, the body is a dynamic machine: At all times programmed death of cells occurs, by a process called apoptosis (for the discovery of which the Paul Ehrlich and Ludwig Darmstaedter Prize 2000 was awarded to Drs. Kerr and Horvitz) and simultaneously there is a constant production of new cells according to demand – just for example the immune response to infection or vaccination, or muscle build-up as a result of exercise. In each cell there is a programmed degradation of proteins initiated by Ubiquitin (for which the Nobel Prize 2005 was awarded to Rose, Hershko and Chichanover) and simultaneously there is a non-stop synthesis of new proteins according to demand and function. In each human cell there are hundreds of thousands of ribosomes acting on a continuous basis. Each ribosome synthesizes a whole protein molecule in approximately one second! I made a rough calculation: During the few minutes in which it took me to deliver these words, in each of us the ribosomes have synthesized about  $10^{19}$  or 10 million trillion protein molecules. Isn't it incredible!

The two prize winners are honoured today for their contribution to determining the 3-D structure of this huge cellular organelle on an atomic level, a discovery that led to the understanding of the detailed mechanism of the complex process that it performs. We are talking about the synthesis of proteins, which is the essence of life in every organism.

Their discoveries are not only an additional milestone in molecular and structural biology, but may also serve as a basis for practical applications and novel class of therapeutic agents.

