"Every discovery raises new questions" Nobel Laureates discuss the prospects of genome research

Newspapers throughout the world rejoiced about it on their front pages, US President Bill Clinton held a press conference and scientists heralded the dawn of a new era: when the decoding of human heredity information was announced in the year 2000, expectations were high – diseases previously believed to be incurable would soon be treatable and the secret of ageing would possibly also be revealed. Eleven years later, this euphoria has given way to a sober optimism as the mapping of the human genome has raised many more questions than it answered. It has shown that the complexity of biological processes is less dependent on the genetic blueprints than was believed to be the case and only really takes shape through the flexible interaction of proteins. Nobel Laureates who have been making invaluable contributions to this research field for decades will exchange views about current questions and assessments during the 61st Nobel Laureate Meeting in Lindau with 570 junior scientists from 80 countries.

The eleventh anniversary of an historical milestone in the history of genome research falls on 26 June 2011. Then US President Bill Clinton invited researchers Francis Collins and Craig Venter to the White House to announce the decoding of the human genome to the international media: the Human Genome Project (HUGO) under the leadership of Collins and entrepreneur Venter had reached its goal. Hamilton O. Smith, who had been working for Venter since 1994, was in the audience of the press conference at the White House: together with Werner Arber and Daniel Nathans, Smith had been awarded the Nobel Prize in Physiology or Medicine in 1978 for the discovery and application of restriction enzymes.

The restriction enzymes were a crucial precondition for the project of recording the approximately three billion letters in our genetic code as they provide the molecular scissors with whose help the DNA can be deliberately cut into pieces. As far back as 1965, Werner Arber had speculated with visionary foresight, that



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"restriction enzymes might provide a tool for the sequence-specific cleavage of DNA. Application of enzymes of different specificity should then be useful in attempts to determine base sequences of DNA molecules."

Data flood as an obstacle to the big breakthrough

Following the decoding of the genome, numerous projects were initiated to make its information suitable for use in cell biology and to improve our understanding of diseases. However, we are still waiting for the big breakthroughs. This comes as no surprise to Hamilton O. Smith, who explains: "We need to sequence thousands of individuals and correlate the genetic information with the phenotype of those individuals. Individualized medicine based on genome information will follow, but this is at least 20 years away."

Thomas Steitz sees the explosion of gene, protein and structural data volumes as a further reason for the slow progress made in reaching new scientific insights: " ... without experiments designed to explore what the macromolecules do and answer questions concerning their functions and mechanisms of action, the accumulation of data may not be enlightening." Together with Ada E. Yonath and Venkatraman Ramakrishnan, Steitz was awarded the Nobel Prize in Chemistry in 2009 for the structural representation of the ribosome, the cell's largest and most complex component, using x-ray crystallography. Here too, however, it is important to note that structure does not answer all of the questions. "Every discovery raises new questions. This is the real meaning of scientific research," comments Yonath in advance of the Lindau Meeting.

One way of revealing the functions of genes is knockout technology, with which certain genes can be specifically switched off. This makes it possible to establish the role that the genes in question play, for example, in cardiovascular diseases, diabetes or cancer. Sir Martin John Evans and Oliver Smithies, who, together with Mario Capecchi, were awarded the Nobel Prize in Medicine in 2007 for their research on knockout mice, will be participating in the Lindau Meeting this year.

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Smithies will provide insights into the biomedical processes that paved the way for their groundbreaking achievements in a paper entitled 'A Toolmaker's Story'.

The epigenetic code

It is gradually emerging that individual genetic information is not carved in stone, but that its activity can be changed through the influence of external factors. The dogma of biology, according to which DNA is first translated into RNA and then into proteins in the ribosome on a kind of one-way conveyor belt, comes nowhere near describing the complexity of these processes. "There are indeed many factors, mostly proteins involved in DNA replication, transcription and its regulation, as well as in protein synthesis," stresses Thomas Steitz.

Such insights come from the still relatively young field of epigenetics. This discipline researches the factors that regulate the reading of genetic information. A corresponding international research project, the International Human Epigenome Consortium (IHEC), has been established. One of the first epigenetic processes to be described in detail is methylation, the addition of methyl groups (CH₃) to certain components of the DNA which causes genes to be switched off permanently. When stem cells become body cells, this process plays a particularly crucial role in the specialisation of the cells, a process known as differentiation. It was long thought that these differentiations were very stable. Sir Martin John Evans, a pioneer in the field of stem cell research, will explain during the Nobel Laureate Meeting just how unstable cell differentiations can be: 'The Lability of the Differentiated State'. Research carried out in recent years has shown, for example, how brain cells can be produced from skin cells with the help of certain proteins (transcription factors).

DNA from the laboratory

The famous physicist Richard Feynman once said: "What I cannot create, I do not understand". Hamilton O. Smith has since adopted this motto: "We still do not fully understand the genetic information in even the simplest bacteria." However, last year, together with Venter, he presented a bacterium (*Mycoplasma*)



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mycoides), whose DNA had been produced completely synthetically and inserted into the cell envelope of a bacterial cadaver. The researchers had previously availed of the knockout method to establish which genes this simple bacterium needed to survive under laboratory conditions and then used these genes exclusively in their synthesised bacterium. The aim is to one day facilitate the fulfilment of biological tasks, such as fuel production, by such reduced organisms. Smith believes that it will be possible in the future to construct cells that are controlled by a synthetic genome and which, thanks to their design, can produce a variety of useful products.

Of the aforementioned Nobel Laureates, Ada E. Yonath, Werner Arber, Sir Martin John Evans Hamilton O. Smith, Oliver Smithies and Thomas Steitz will take part in the 61st Lindau Nobel Laureate Meeting.

Abstracts zu den Vorträgen von im Text erwähnten Nobelpreisträgern:

Oliver Smithies: "A Toolmaker's Story" http://tinyurl.com/3utwlex

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Hamilton O. Smith: "Synthetic Genomics: Working with Whole Bacterial Genomes" <u>http://tinyurl.com/3rbcvdw</u>

Werner Arber: "Updated Notions on Darwinian Evolution" <u>http://tinyurl.com/3awccl7</u>

Sir Martin J. Evans: "The Lability of the Differentiated State" <u>http://tinyurl.com/3sjkcmp</u>

Thomas A. Steitz: "From the Structure of the Ribosome to the Design of New Antibiotics" <u>http://tinyurl.com/3tlslcc</u>

Ada E. Yonath: "Climbing the Everest Beyond the Everest" <u>http://tinyurl.com/3qpqr5e</u>

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