# The weapons of modern medicine

# The development of new antibiotics and drugs is a topic on the agenda of the Lindau Nobel Laureate Meeting (June 26 – July 1, 2011)

The human race urgently needs new antibiotics. "The world is on the brink of losing these miracle cures", warned Margaret Chan, Director General of the World Health Organisation, in April 2011. An increasing number of bacteria strains are proving resistant to treatment with these drugs, which were once the most powerful weapon at the disposal of modern medicine. The Nobel Laureates in Chemistry of the past two years have discovered very promising synthesis processes and starting points for the development of new antibiotics. Three of them (**Ei-ichi Negishi**, **Thomas Steitz**, **Ada Yonath**) will participate in the 61<sup>st</sup> Nobel Laureate Meeting, which is dedicated to the theme of medicine, and will bring together 570 young scientists, 24 Nobel Laureates in Lindau, and Unni Karunakara, International President of "Doctors without Borders" which was awarded the Nobel Peace Prize.

Half of all of the available antibiotics attack the ribosomes of bacteria, which differ in structure to those found in human cells. The ribosomes are molecular machines consisting of hundreds of thousands of atoms that translate the genetic blueprint of an organism into proteins. Many antibiotics kill bacteria by preventing them from producing vital proteins - a fact that was already known when **Ada Yonath**, Venki Ramakrishnan and **Thomas Steitz** succeeded in decoding the structure of bacterial ribosomes at atomic resolution, for which they received the 2009 Nobel Prize in Chemistry. However, their x-ray-crystallographic view of the interior of the ribosome provided information for the first time about the exact locations where different antibiotics bind to the ribosome, and how they take effect there.



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### Lead structures from the ribosome

The macrolide class of antibiotics, for example, blocks the tunnel through which the newly formed protein chains leave the ribosome, and thus prevent the extension of the chains. The bacteria try to defend themselves against this "molecular constipation", as **Thomas Steitz** describes this phenomenon, by developing mutations that alter parts of the tunnel in such a way that the macrolides are no longer able to gain a hold there. Other antibiotics act before the proteins enter the tunnel: they falsify the translation of the genetic information or prevent individual amino acids from binding with the emerging protein. The bacteria have also responded to these approaches by developing mutations that render them resistant to the antibiotics in question. The "atomby-atom" analysis of the binding sites between the antibiotics and the bacterial molecules enables the deduction of lead structures for the synthesis of antibiotics that bind more precisely to the bacteria and are, therefore, less vulnerable to mutations.

Although all three chemistry Nobel Laureates of 2009 studied the binding behaviour of numerous antibiotics in the ribosome, **Steitz** focuses, in particular, on the development of new antibiotics in his work. He will report on his journey from basic research to applied science in his lecture "From the Structure of the Ribosome to the Design of New Antibiotics" at the 61<sup>st</sup> Meeting of Nobel Laureates. A company, which he co-founded, specialises in the structure-based computer-aided design of new active substances that attack at ribosomal level. Two of these active agents are already undergoing clinical trials.

### Palladium facilitates accurate synthesis

Antibiotics are originally the metabolic products of fungi and bacteria. Like all organic molecules, they mainly consist of a carbon skeleton. In order to synthesise these single bonds between carbons, for example, in structure-based design, chemical tricks are required that incite the carbon atoms to react with each other. They prefer to saturate their external electron shell in stable bonds Datum | Date 10 June 2011

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with hydrogen, and rarely have any reason to detach themselves from such bonds unless they are given a helping hand by a catalyst, which triggers a reaction without undergoing a change itself. Richard F. Heck, **Ei-ichi Negishi** and Akira Suzuki have developed specific synthesis processes for complex organic molecules, in which the platinum-like metal palladium acts as a catalyst. This work earned them the 2010 Nobel Prize in Chemistry.

**Ei-ichi Negishi** will report on the possibilities offered by the catalyst palladium in his lecture "Magical Power of Transition Metals: Past, Present and Future". For example, the antibiotic vancomycin was isolated from soil samples collected in the Borneo jungle in the 1950s. It was long viewed as the last possible resort ("reserve antibiotic") for the treatment of serious infections with multi-resistant *staphylococcus aureus* bacteria (MRSA), which, as hospital pathogens, can have life-threatening consequences, particularly in post-operative patients. However, MRSA strains increasingly arose that were also resistant to vancomycin. With the help of the catalyst palladium, pharmaceutical researchers have succeeded in synthesising new antibiotics that can also keep vancomycin-resistant pathogens in check.

The synthesis processes developed by **Ei-ichi Negishi** and his co-laureates also enable the precise replication of natural substances that have a therapeutic effect. This replication is often required to facilitate the examination of the potential of these substances because, as is the case with the anti-cancer agent discodermolide, for example, which was discovered in a deep-sea sponge, they only arise in small quantities in nature.

### Regulatory interventions in cell recycling

As opposed to this, the cells of living organisms have an abundance of barrelshaped recycling machines which dismantle proteins that are incorrectly formed or no longer required, making their components available for re-use. Every cell in the human body contains around 30,000 of these proteasomes, without which



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they would not be able to maintain a healthy equilibrium. Incorrectly folded proteins must be removed immediately after their formation so that they cannot cause any damage. Growth factors, which play an important role during cell division, must also be dismantled quickly to prevent the cell from growing uncontrollably. On the other hand, growth-inhibiting molecules, i.e. tumour suppressors, must not be destroyed too hastily.

The cell marks the proteins that are intended for dismantling and recycling using special labels, the omnipresent ubiquitins. **Aaron Ciechanover**, **Avram Hershko** and Irwin Rose were awarded the Nobel Prize in Chemistry in 2004 for the discovery of this central component of the cellular quality control system. In keeping with its fundamental significance in the cell, the ubiquitin-proteasome system offers important starting points for the development of new drugs. The first proteasome inhibitor for the treatment of certain types of cancer has already been licensed for a few years now. In his lecture "The Ubiquitin Proteolytic System as a Novel Drug Development Platform", **Aaron Ciechanover** will present the indications for which the ubiquitins and proteasome are potentially suited as target sites for new drugs.

**Aaron Ciechanover** provided an informative overview of the main milestones in pharmaceutical research, from the discovery of pain medication to the perspective of personalised medicine, at the 2009 Nobel Laureate Meeting – his lecture "Drug Discovery and Biomedical Research in the 21st century – The third revolution" can be viewed at the Lindau Nobel Laureate Meetings website:

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