Robert-Koch-Stiftung

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The 2017 Robert Koch Award goes to Rafi Ahmed and Antonio Lanzavecchia / Christopher T. Walsh receives the Robert Koch Gold Medal

Milestones on the way to new vaccines and immunotherapies

The award winners deciphered central mechanisms of the human immune system, pointing the way forward to the future of medicine

Berlin – The Robert Koch Foundation is jointly awarding the 2017 Robert Koch Award, with prize money of 120,000 euros, to Professors Rafi Ahmed, Emory University and Emory Vaccine Center, Atlanta, USA, and Antonio Lanzavecchia, Institute for Research in Biomedicine, Università della Svizzera italiana, Bellinzona, and ETH Zurich, Switzerland. The award recognizes the two immunologists' pioneering research on regulation of immune system and their ground-breaking contributions on the development of new vaccines and immunotherapies.

Christopher T. Walsh, emeritus professor of Harvard Medical School in Boston, USA, receives the Robert Koch Gold Medal for his life's work as a pioneer in chemical biology and catalyst in the search for pharmacologically active substances, especially for new antibiotics.

The awards and the honorary medal will be presented at an official ceremony on November 3, 2017 at the Berlin-Brandenburg Academy of Sciences and Humanities in Berlin.

Rafi Ahmed will receive the Robert Koch Award for his pioneering studies on immunological memory and T cell exhaustion, which have also proven highly fruitful for clinical research and treatment. His research centered on how memory cells can store an immune response for a practically unlimited time, once learned. Several of his papers were real game-changers, with Ahmed marking a radical departure from dogmas previously presumed to be reliable. For example, this is true of his proof that virus-specific memory CD8 T cells do not require a permanent stimulus with low quantities of corresponding antigens, as was believed until the mid-1990s. On the contrary, it is a property inherent in these cells themselves, which permits them to respond faster and more effectively on re-infection. Ahmed's studies also defined long-lived plasma cells in the bone marrow that are responsible for maintaining antibody responses after infection or vaccination.

A milestone in Ahmed's research was the discovery of T cell exhaustion during chronic viral infections and showing that the PD-1 inhibitory receptor is the major brake on these chronically stimulated T cells. It had long been known that chronic

infections are associated with decreased T cell immunity and it was assumed that either the virus specific T cell responses were not generated or these T cells had been deleted. Ahmed's studies showed that virus specific CD8 T cells were indeed present during chronic infection but their function was compromised. This finding suddenly presented the opportunity of breathing new life into these exhausted T cells and reviving their function. Ahmed then showed that exhausted CD8 T cells expressed high levels of the PD-1 inhibitory receptor and that in vivo blockade of this inhibitory pathway restores function in exhausted cells and results in viral control. This linking of T cell exhaustion with PD-1 has had a significant impact on the development of PD-1 directed immunotherapy for chronic infections and cancer.

PD-1 inhibitors have been clinically tested and are already approved for the treatment of several different cancers including lung, melanoma, bladder, etc. Rafi Ahmed believes that these new treatment strategies hold a lot of as yet untapped potential. His laboratory is currently seeking other factors that impede the immune system and is using a rational approach for combination therapy with PD-1 blockade including the use of therapeutic vaccines. While making his fundamental discoveries, Ahmed established one of the world's largest vaccine research center at Emory University in Atlanta, which strives to find vaccines for HIV, hepatitis, tuberculosis, malaria and a universal flu vaccine, among others.

Antonio Lanzavecchia is considered one of the most influential modern immunologists. Besides its immense range, the scientist's comprehensive oeuvre is characterized by the great vision with which he investigated the molecular details of human immune response. For Lanzavecchia, this was always associated with the hope of better vaccines and more effective immunotherapies. Fundamental studies of the highly efficient division of labor between antigen-specific T- and B-cells in adaptive immune response were followed by in-depth cell biology research into the maturation process of dendritic cells in the mid-90s. They are the sentries of our immune system, and as such are responsible for stopping intruding pathogens and antigens, and presenting them to the cells of the immune system.

Lanzavecchia's distinction of two functionally different main groups of memory T-cells – which he termed "central memory T-cells" in the lymphatic organs and the "effector memory T-cells" in the peripheral tissue – is now an essential part of modern immunology. This is particularly relevant for development of T-cell-based vaccines. For Lanzavecchia, fundamental immunology research is therefore always a means to an end. That is also true of immunotherapies with monoclonal antibodies, which increasingly attracted his attention. Using revolutionary technologies, the researcher succeeded in cloning human memory T-cells and then also virus-specific memory B-cells, which produce high quantities of tailored antibodies. Lanzavecchia has repeatedly succeeded in isolating pathogen-neutralizing antibodies from the blood of infected patients, testing them and then producing them in large quantities in an astonishingly short time – for example for SARS, Ebola, avian flu or human cytomegalovirus (HCMV). He made headlines worldwide by discovering a natural "super-antibody", which detects all 16 sub-types of influenza A-viruses by binding to a conserved fragment of the viral membrane protein hemagglutinin – justifying the hope that a universal flu vaccine is possible. Lanzavecchia is certainly convinced that vaccination strategies like this are the future.

Gold medal for an impressive life's work

Christopher T. Walsh is one of the fathers of chemical biology, a new discipline at the intersection of chemistry, biology and medicine. With over 800 publications, Walsh, who specialized in enzymatic responses at an early stage, made a key contribution to deciphering the chemistry of life. His studies on how antibiotics work and the mo-

lecular mechanisms of antibiotics resistance were ground-breaking. Even in the early 90s, Walsh succeeded in proving the enterococci only need to change one enzyme from their cell wall (D-Ala-D-Ala ligase) slightly to decrease the effectiveness of the antibiotic Vancomycin thousandfold.

In a personal retrospective of his eventful research career, Walsh recently admitted that the results of his work also had medical consequences, for example when finding new antibiotics or immune modulators, always gave him great satisfaction.* His studies on blocking enzymatic reactions via inhibitors (suicide substrates) or on the production of selective iron-ion binding "siderophores" by enterobacteria were pioneering. Finally, Walsh focused intensively on the general rules of biosynthesis of natural substances, including a wide range of pharmacologically effective substances. In this way, Walsh gave colleagues from a wide range of disciplines the tools they needed for their own work. Even decades later, this outstanding researcher can still marvel at the "breathtakingly simple logic" with which hundreds of thousands of structurally and functionally different molecules are combined from simple chemical basic building blocks. Following Nobel Physics Laureate Frank Wilczek, Walsh calls this the "beauty in the heart of nature".

Photos of the laureates may be downloaded for editorial use at:
www.robert-koch-stiftung.de/Laureates2017

About the Robert Koch Foundation

The Robert Koch Foundation is a non-profit foundation dedicated to the promotion of medical progress. It was founded in 1907 and is based in Berlin. The Foundation promotes basic scientific research in the field of infectious diseases, as well as exemplary projects that address medical and hygienic issues.

The Foundation confers a number of distinguished scientific awards each year: the Robert Koch Award – one of Germany's most distinguished scientific awards, the Robert Koch Gold Medal, three awards for young scientists and, since 2013, the Hospital Hygiene and Infection Prevention Award.

Robert Koch (1843 – 1910), after whom the award is named, was the founder of modern-day bacteriology, for which he was awarded the 1905 Nobel Prize for Medicine and Physiology. From 1891 until his retirement in 1904, Koch was Head of the Institute for Infectious Diseases in Berlin.

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* Christopher T. Walsh: „At the Intersection of Chemistry, Biology and Medicine", Annual Review of Biochemistry, Vol. 86 (2017):

www.annualreviews.org/doi/abs/10.1146/annurev-biochem-110716-121241