Laudatio

von

Dr. Rino Rappuoli

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-Preises 2011

an

Prof. Dr. Cesare Montecucco

Paulskirche, Frankfurt am Main

14. März 2011

Es gilt das gesprochene Wort.

Ladies and Gentlemen,

Federal and Regional authorities,

I am pleased to be here today to introduce you the 2011 winner of the Paul Ehrlich Award. Today we celebrate Cesare Montecucco for his discovery of the mechanism of action of tetanus toxin. This scientific discovery is unique because on one side it explains with a beautiful simplicity the mechanism by which an infectious disease such as tetanus has been killing millions of people for millennia, and therefore solves one of the oldest scientific problems, at the same time it allowed the most advanced biomedical research of the 1990s to make a quantum jump in the understanding of the molecular mechanisms that govern the traffic and export of molecules within our cells, providing the basis for development of new therapies against a variety of diseases.

During the next few minutes I will first describe the importance of this discovery for tetanus and then I will focus on the implications of this discovery for the research of the 21st century.

Tetanus is a very old, deadly disease. The first written record of the disease dates back to Hippocrates, 400 years before Christ. He described with remarkable accuracy the symptoms and the development of the disease: "the master of a large ship mashed the index finger of his right hand with the anchor. Seven days later a somewhat foul discharge appeared; then trouble with his tongue-he complained he could not speak properly. The presence of tetanus was diagnosed, his jaws became pressed together, his teeth were locked, then symptoms appeared in his neck; on the third day opisthonos appeared with sweating. Six days later after the diagnosis was made he died." In 1884, 2300 years after Hippocrates, A. Nicolaier showed that the disease was of infectious nature by reproducing the disease in animals injected with soil. Five years later, Shibasaburo Kitasato isolated the bacterium that caused the disease and reported that animals injected with small doses of tetanus toxin developed in their blood the power of neutralizing the toxin, and together with Emil Von Behring showed that their blood serum could protect other animals from the effects of the toxin. This discovery (antitoxic immunity) quickly led to the use of serum (made in horses) for treating tetanus. Passive protection by antiserum was a field very dear to Paul Ehrlich. Effective vaccines made by the tetanus toxin detoxified by formaldehyde treatment were described in 1924 and the vaccine was effectively introduced into routine vaccination during the World War II. Then we learned that tetanus toxin was so powerful because it is taken up into the nerve axon and transported to the central nervous system where it prevents inhibitory motor nerves from releasing the vesicles containing the inhibitory neurotransmitters. The consequence of this is dangerous over activity in the muscles because the smallest stimulus causes generalized contractions of the agonist and antagonist musculature, termed a tetanic spasm.

In spite of the great progress in understanding the mechanics of tetanus toxin, no advance had been made in understanding how such a small molecule could be so powerful since the times of Hippocrates and Kitasato until 1992 when Prof. Cesare Montecucco discovered that the toxin is an enzyme that cleaves a protein, called synaptobrevin, that is essential to anchor the secretory vesicles containing the neurotransmitters to the membrane. How did Prof Montecucco arrive to this discovery?

In science there are two fundamentally different ways to go and solve important problems: one is to have a lot of resources, an army of scientists and the most sophisticated technologies and equipment and approach fundamental questions; the other is to have a very small laboratory and to focus on molecules that for their nature target fundamental scientific mechanisms. Cesare Montecucco belongs to the latter category of scientists. He had and still has a small laboratory at the University of Padova in Italy, one or two brilliant students and decided to focus on toxins produced by bacteria, snakes and scorpions. Why toxins? Because these are the most efficient molecular nano-machines selected by evolution. In nanogram quantities they are able to kill large animals and humans. In order to be so efficient, during evolution these toxins have learned to attack the most essential molecules of our cells. Therefore, Cesare Montecucco thought that if he was able to understand the mechanism by which these toxins kill human cells he would very likely make a fundamental discovery about human cells. That is exactly what happened. In the early 1980s Cesare was very busy studying toxins from *Corynebacterium diphtheriae*, *Clostridium tetani* and *Clostridium botulinum*, the bacteria that cause diphtheria, tetanus and botulinum, respectively. He was also working on scorpion and snake toxins. In each of these fields Prof. Montecucco made fundamental discoveries, but in the early 1990s he succeeded to make one of the most important discoveries in biology. While he was looking at the recently published sequence of the gene of the tetanus toxin, he found that the sequence contained the amino acids HEXXH, typical of zinc-binding motif of metalloproteases. He immediately realized that the toxin was very likely an enzyme, acting as a scissor, cleaving a molecule essential for the release of the vesicles containing the neurotransmitters. He went back to the laboratory, isolated the secretory vesicles, treated them with tetanus toxin and looked for molecules that had been cleaved by the treatment of the toxin. As predicted, he found that one membrane protein, named VAMP/synapobrevin was cleaved into two fragments by treatment with tetanus toxin. Finally, he had solved a mystery of centuries! He had found that tetanus toxin is so powerful because it cleaves and inactivates one protein of our nerve cells that is essential for the release of vesicles containing neurotransmitters. This finding immediately showed that synaptobrevin, the newly discovered molecule, to be very important in human cells. In fact, two other laboratories one in California run by Randy Sheckman and the other run by Jim Rothman at Rockefeller University had been working for 20 years using genetic and biochemical methods to understand the traffic of vesicles within cells. The discovery that cleavage of synaptobrevin was enough to jam the vesicle traffic in a cell, was like the discovery of the Rosetta Stone. Immediately all the work of Jim Rothman and Randy Sheckman made sense, the puzzle of their work was assembled showing the beautiful picture of how organelles are organized within cells, how cells manufactured and secrete proteins like insulin and growth hormone that govern metabolism or how brain cells discharge the chemical transmitters that mediate thought, feeling and movement. Indeed today we cannot conceive a cell without thinking at the fundamental processes that were discovered by learning the mechanism of action of tetanus toxin. Jim Rothman and Randy Sheckman received the Lasker award in 2002, for their discoveries. Today we are very pleased to recognize Prof. Montecucco for making all this possible.