Award speech for Prof. Dr. Michel C. Nussenzweig

By Prof. Dr. Andreas Radbruch

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The Robert Koch Award for 2016 goes to Professor Michel C. Nussenzweig from the Rockefeller University, New York, for his groundbreaking research work on the development of B lymphocytes, and the discovery of effective antibodies against HIV viruses.

Michel Nussenzweig, doctor and researcher, began his scientific career at the Rockefeller University in the laboratory under Ralph Steinman, the Robert Koch award winner of 1999, who also won the Nobel prize for medicine 2011 for his discovery of “dendritic cells”. In his early work, Michel Nussenzweig made an important contribution from 1981 onwards to the characterisation of these dendritic cells. He demonstrated that they adopt antigens, dismember them and present them to T lymphocytes, either activating them if they are pathogens or inducing tolerance when they are safe antigens such as those belonging to the body.

In 1986, after completing his doctoral thesis, Michel Nussenzweig joined the working group headed by Philip Leder, who won the Robert Koch Medal in 2008. At Harvard University, with the decipherer of the genetic code, he became a microbiologist and studied the fascinating question of how in early B cell development the genes for the antibodies are formed through the aggregation of gene segments, so that each B cell can compile precisely only one gene for the heavy chain and one gene for the light chain, in other words, it can produce only one antibody. Michel Nussenzweig was able to demonstrate how the B cell prevents the genes from also being successfully compiled on the chromosome of the other parent, a phenomenon known as allelic exclusion. This was achieved through a signal of the first successfully compiled antibody itself, communicated by the lg-ß molecule. When gene segments are aggregated for antibodies, imprecisions in the connection points create antibodies with random specificities, and Michel Nussenzweig was able to show that a very large number of these, more than half, even detect structures inherent in the body, making them potentially very dangerous. However, the cells which make these autoreactive antibodies, are clearly already being eliminated in the bone marrow or are given a second chance and can change their antibody genes one more time in a process known as “receptor editing”. These studies, which attracted attention, were only made possible due to the fact that Michel Nussenzweig had developed a method of isolating the antibody genes from individual B lymphocytes and producing the antibodies using genetic technology, and in so

doing, enabling a sufficient quantity of an individual antibody to be created in order to precisely study its properties.

In 1990, Michel Nussenzweig returned as a professor to Rockefeller University and the Howard Hughes Medical Institute, where he still works today. The key question: How is the formation of antibodies regulated? First, a series of impressive publications, in which he shows that in the development of B lymphocytes, there are certain “checkpoints” on which autoreactive B lymphocytes are eliminated, thus directly following the formation of the antibody genes in the young B lymphocytes in the bone marrow. They then travel through the body via the blood and in the case of an infection are activated in the lymph nodes or the spleen, when they recognise this antigen. This activation occurs in the so-called “germinal centres”, in which antigen-presenting cells, T lymphocytes and B lymphocytes interact and mutually activate each other. Michel Nussenzweig and his colleagues were able to demonstrate in highly elegant studies using intravital microscopy that during this process, the B lymphocytes travel to and from between two zones, a zone where their antibody genes go through a series of mutations, resulting in a change in specificity, and a zone where the B lymphocytes are selected, the antibodies of which best match the antigen. Through this “affinity maturation”, antibodies are created which match to an increasingly accurate degree. The B lymphocytes which they carry on the cell surface are then transformed into plasma cells, which secrete large quantities of these antibodies. The antibodies can neutralise the infectious agents, encourage their elimination by phagocytes, or kill infected cells.

The immune reaction in the germinal centres also entails certain risks, however. Thus, Michel Nussenzweig’s working group was able to show that when antibody genes are mutated in the B lymphocytes, it is unfortunately also the case, albeit rarely, that other genes are mutated, including genes which cause lymphomas. And in almost all cases, the mutations also lead to the creation of autoreactive B lymphocytes, which are normally eliminated again, a second tolerance checkpoint for the development of B lymphocytes, which the group under Nussenzweig succeeded in defining. If the autoreactive B lymphocytes are not eliminated, severe auto-immune diseases result, such as lupus erythematosus or rheumatoid arthritis.

Michel Nussenzweig put his fundamental knowledge on the development and activation of B lymphocytes and the maturation of their antibodies to practical use. From 2009 onwards, with his method for cloning the antibody genes from individual B lymphocytes, he studied the human immune response to the human immune deficiency virus, or HIV. HIV: one of the major infection biology challenges of the present day, leads to AIDS (Acquired Immunodeficiency Syndrome). An estimated 35 million people are infected worldwide. Every year, 1 to 2 million people who are infected die, while a further 1-2 million new cases of infection occur. Effective medication keeps the progress of the disease in check, but is

expensive and not available to most of those infected. There is no effective preventive or therapeutic vaccination. One of the reasons is that the virus eliminates T lymphocytes, which induce the maturation of antibodies. Another is that the virus can quickly change through mutation – faster than the B lymphocytes are able to mutate their antibodies. The immune system can't keep up. For 30 years, immunologists tried in vain to develop vaccination methods in which effective antibody responses against HIV are induced, but success eluded them. The antibodies still only provide protection against a small number of HIV variants and these, too escaped detection by the antibodies through rapid mutation. Indeed, it seemed clear that antibodies would not be able to provide protection against HIV.

Michel Nussenzweig's achievement is that he demonstrated that protection against HIV can in fact be provided through antibodies. The starting point was the clinical observation in 2009 that in very rare cases, the immune system of AIDS patients successfully defended itself against the virus. The patients developed antibodies which were able to neutralise a very large number of HIV types. From these patients, the working group under Michel Nussenzweig isolated individual HIV-specific B lymphocytes and cloned their antibody genes. That was the key to the discovery of broadly neutralising antibodies. Against the background of his fundamental work on B lymphocytes and their antibodies, it then also quickly became clear which HIV target structures are recognised by the broadly neutralising antibodies, and why they are so rare. They bear an unusually large number of mutations and are clearly the result of an intensive, long and repeated selection process. However, the individual broad neutralising antibodies then detect up to 95% of all HIV variants, and if several are combined, almost all variants are detected and neutralised. Antibodies of this type are not present in healthy humans, for reasons that are not entirely clear. It will also take some time to develop vaccination methods in order to induce such antibodies as a preventive measure. However, now, we are already in a position to make therapeutic use of the cloned, broadly neutralising antibodies. Michel Nussenzweig and his colleagues have demonstrated in pre-clinical model systems, on humanised mice and apes, but also already in the first clinical trials on humans, that even small quantities of the therapeutic broadly neutralising antibodies dramatically and sustainably reduce the viral load. His studies have enabled the use of passive immunisation as a therapy for AIDS, provided a decisive impulse, and pointed AIDS research in a new direction, in the development of vaccination methods in order to induce protective antibodies against HIV.

With Michel Nussenzweig, the Robert Koch Foundation honours an outstanding researcher who from his fundamental knowledge of the formation of antibodies, to which he contributed essential aspects, demonstrated new, original ways of treating AIDS.

I warmly congratulate Michel Nussenzweig on being presented with the Robert Koch Award, 2016.