Healthcare industry BW

Treating cancer by activating the immune system

Vaccines that prevent infection with cancer-causing viruses are already available. Moreover, the development of therapeutic vaccines for the treatment of a number of other cancers is well under way. These vaccines not only prevent the development of cancer, but also treat early stages of cancer. Antigen-armed antibodies have long been used in vaccines against infectious diseases, and can now also be used for treating cancer.

The first ever cancer vaccine was placed on the market in 2006. This particular vaccine effectively protects against primary infection with carcinogenic human papillomavirus (HPV) and therefore protects women against cervical cancer. Back in 2008, Harald zur Hausen, former chairman of the German Cancer Research Center (DKFZ) in Heidelberg and recipient of the 2008 Nobel Prize in Physiology or Medicine for his achievements in developing a prophylactic HPV vaccine, set the next research goal, namely the development of therapeutic vaccines for both prevention and therapy of precanceroses and early stages of cancer.

The junior research group "Immunotherapy and Prevention" was then established with support from the Manfred Lautenschläger Foundation. Since 2010 the group has been headed up by PD Dr. Dr. Angelika Riemer, previously of the Cancer Vaccine Center at Harvard Medical School in Boston.

Towards a therapeutic HPV vaccine

PD Dr. Dr. Angelika Riemer
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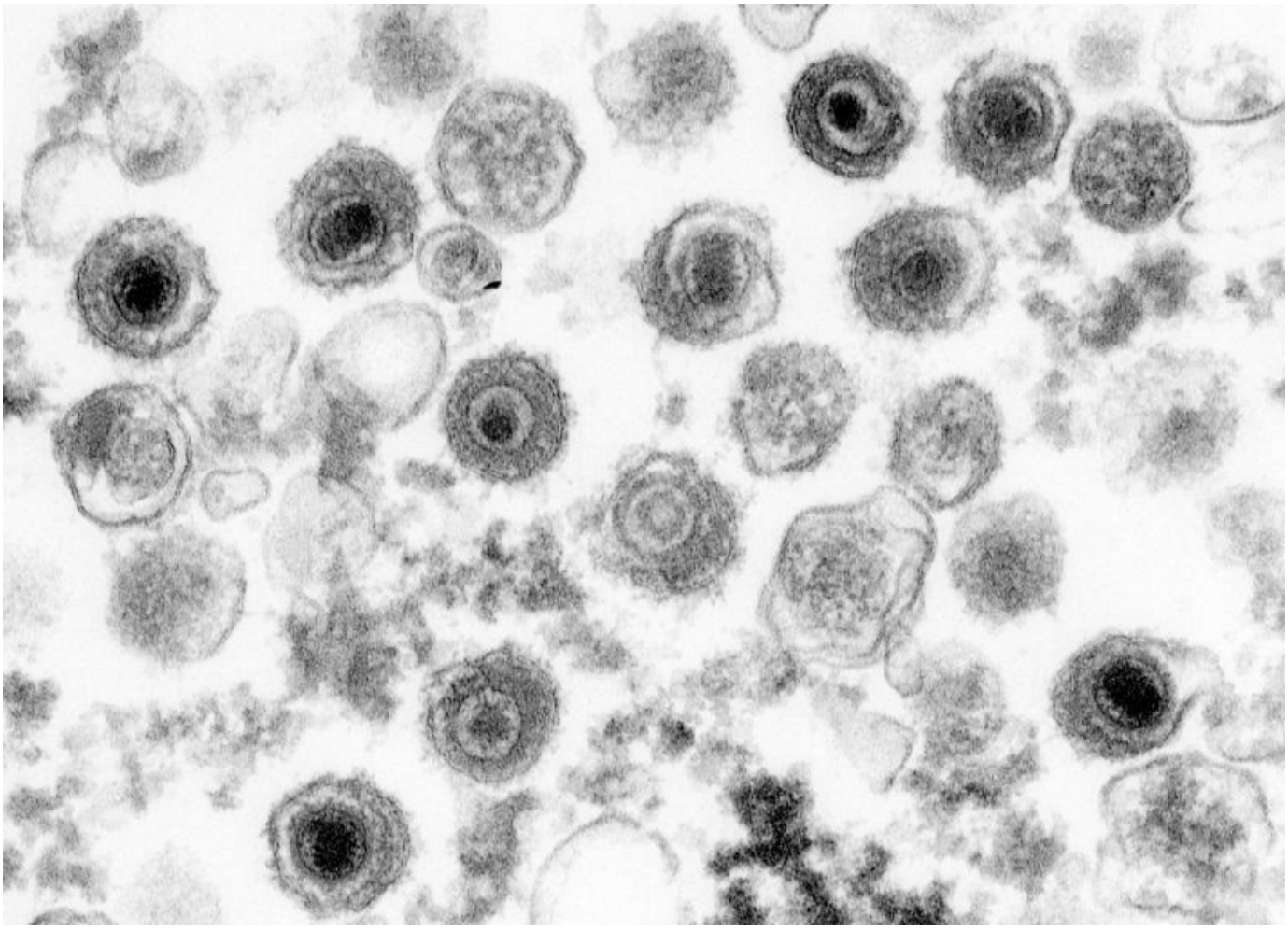
While prophylactic HPV vaccines are designed to induce the body's immune system to produce

antibodies against human papillomaviruses, therapeutic cancer vaccines are designed to stimulate the cellular defense line. This involves cytotoxic T cells (cytotoxic lymphocytes, CTL) that recognise and eliminate cancer cells without attacking healthy cells.

Angelika Riemer explains how a therapeutic HPV vaccine works. CTLs eliminate cells that have been infected by cancer-causing papillomaviruses (e.g. of the HPV16 type) after viral epitopes presented by so-called HLA (human leukocyte antigens) molecules found on the T-cell surface have been recognised by the CTLs as foreign. HLA genes are the human version of the major histocompatibility complex (MHC) genes found in mammals. There are many thousand HLA molecules, all of which present different epitopes. Moreover, they also differ from person to person. Riemer's group of researchers uses highly sensitive mass spectrometry to identify HPV epitopes that are presented by virus-transformed tumour cells. For the planned vaccine, the researchers selected epitopes that were found on different tumour samples.



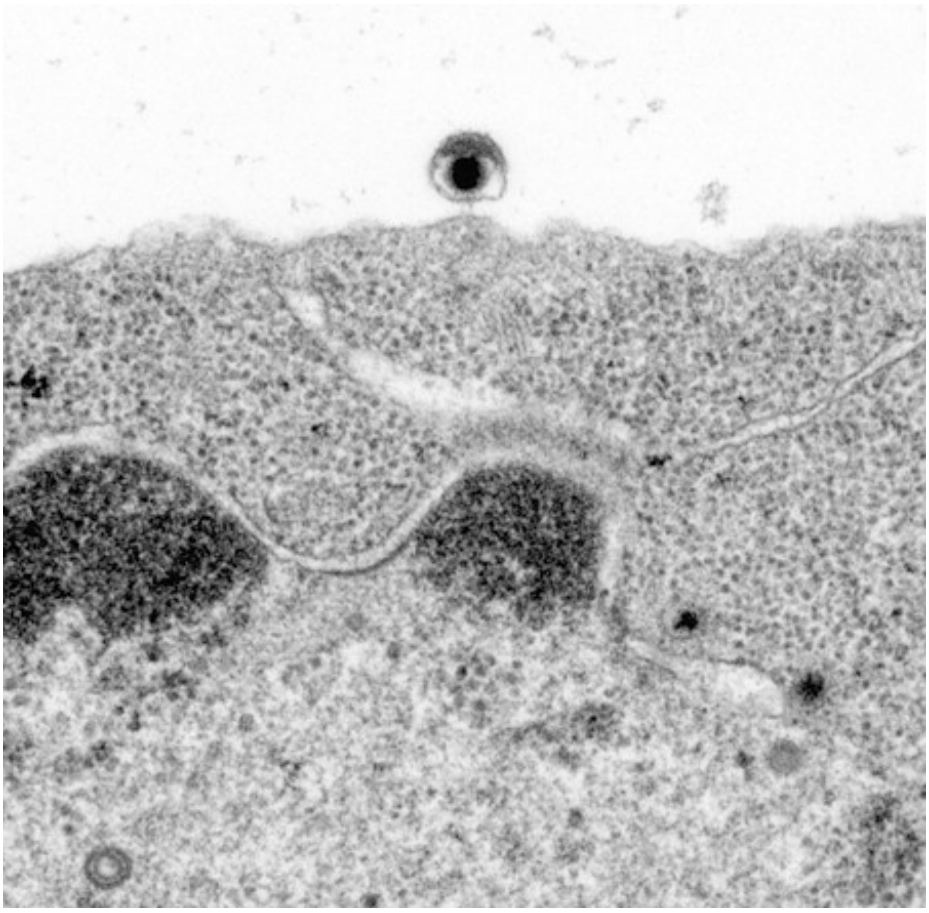
Electron microscope of Epstein-Barr viruses.

Unfortunately, this approach did not initially lead to the expected clinical success. Riemer and her team then extended their epitope search to T helper cells (Th) which play an important role in CTL activation. The researchers were successful with an approach aimed at identifying promiscuous HPV16 Th epitopes which are capable of inducing T-cell immunity in a large proportion of the population. They were able to show that a Th epitope mixture derived from several HPV16 proteins effectively induced a specific immune response in the blood of HPV16-positive patients with cervical cancer. The researchers' findings, which were recently published in the International Journal of Cancer, could be the breakthrough in the development of the therapeutic vaccine against cancer-

causing human papillomaviruses that Harald zur Hausen was calling for back in 2008.

Angelika Riemer is also involved in research into a therapeutic vaccine for the treatment of gliomas, tumours that occur mainly in the brain and that make up a large percentage of malignant brain tumours. BiOPRO has previously published an article ("Therapeutic vaccines against brain tumours") about this vaccine, which is already undergoing clinical phase I testing.

Fighting lymph gland cancer with EBV-derived proteins



Epstein-Barr virus as it leaves a cell (electron microscope image).

The Epstein-Barr virus (EBV) was the first human virus to be identified as a direct cause of cancer. EBV belongs to the herpes family and is one of the most common viruses in humans; around 90 percent of adults carry the virus, but only a small number actually develop the disease. In Central Africa, EBV is associated with Burkitt's lymphoma, in Eastern Asia with nasopharyngeal carcinoma and in Western Europe and North America with infectious mononucleosis (the latter is not a cancer). Prof. Dr. Henri-Jacques Delecluse and his team at the DKFZ have shown that genetic differences in the EBV strains are the reason why the virus leads to different diseases in different human populations. The DKFZ scientists have used surface proteins of these viruses to activate the body's own immune system against B-cell lymphomas, cancers that are characterised by abnormal antibody-producing B lymphocytes.

Delecluse and his team produced antibodies that are able to bind to specific receptors on the surface of lymphoma cells and that also carry EBV protein fragments at their C-terminal tail. The antigen-armed antibodies are internalised and broken down into peptides that are subsequently

Prof. Dr. Henri-Jacques Delecluse, head of the Division of Pathogenesis of Virus Associated Tumours and director of the research unit "Unité Inserm 1074" of the Institut National de la Santé et de la Recherche (Inserm) at the DKFZ.

presented by MHCII molecules on the cell surface. This includes peptides that stem from viral proteins and which mimic an EBV infection, thereby mounting an immune response.

A viral infection is such a strong signal that the T helper cells in the lymph glands, which are

responsible for activating B cells, are unable to ignore it. The researchers have been able to show in vitro that T cells kill the infected lymphoma cells. Moreover, it was possible to successfully activate memory T cells with antigen-armed antibodies in the blood of people who had previously suffered an EBV infection. “This is a reliable indication that an immune defence is also mounted against lymphoma cells in vivo,” says Delecluse. He pointed out that their findings showed that antigen-armed antibodies were suitable for treating cancer, whether it is B-cell lymphomas or other types of cancer. Prior to Delecluse’s work, genetically engineered antigen-antibody complexes were only used as preventive vaccines for immunising people against infectious agents.

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Boosting the immune system can improve cancer prevention and treatment