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Fighting hepatitis viruses with their own weapons

Virologist Prof. Dr. Stephan Urban from the University of Heidelberg has been awarded the DZIF Prize for Translational Infection Research for the discovery and development of a promising peptide drug for the treatment of hepatitis B virus infections. The peptide prevents viruses from entering the liver cells, and is also effective against hepatitis D infection. Hepatitis D is the deadliest of all viral liver diseases and no specific antiviral drugs are available to treat it.

Although an effective vaccine against the hepatitis B virus (HBV) has been available since 1986, HBV infections are still a major global health problem. Approximately 350 million people worldwide have chronic HBV infection, about 25 million people are coinfected with hepatitis D, and around 500,000 people die from HBV/HDV-related liver damage (e.g. liver cirrhosis and liver cancer) every year. Although the antiviral drugs and interferons used to treat chronic hepatitis B help delay the onset of potential complications, they are largely unable to completely eliminate the viruses and cure the disease. Treatment with existing antiviral drugs can lead to the virus resisting the drug and so drugs fail in many patients. New therapeutic strategies with higher cure rates are urgently needed.

Animal models for human hepatitis B infections

Prof. Dr. Stephan Urban worked on HBV when he did his doctorate in Peter Hans Hofschneider's laboratory at the Max Planck Institute of Biochemistry. He spent his post-doctoral research period at the University of Heidelberg Centre for Molecular Biology (ZMBH) in the laboratory of Prof. em. Dr. Heinz Schaller, who was instrumental in developing the hepatitis B vaccine. During this time, Urban discovered and characterised protein sequences on the viral protein envelope that enable the HBV virus to specifically bind to the surface of liver cells (hepatocytes) and enter them. He used Pekin ducks and duck hepatitis B viruses (DHBV) for his investigations, which were the animal model of choice for HBV research at that time. There were no other immunocompetent animal models available apart from chimpanzees, which were no longer used in research for ethical reasons. This meant that there were no test systems that could be used to develop drugs for humans. Nowadays, human viruses can be studied in cell cultures and immunodefective mice are useful animal models. HBV-infected human hepatocytes can for example be integrated into mice lungs.

Urban was thus able to continue his research with a human HBV-liver system and discovered a peptide that he could use to prevent the viruses from entering human hepatocytes. This peptide

Prof. Dr. Stephan Urban, professor for translational virology at the German Centre for Infection Research (DZIF) at Heidelberg University Hospital.
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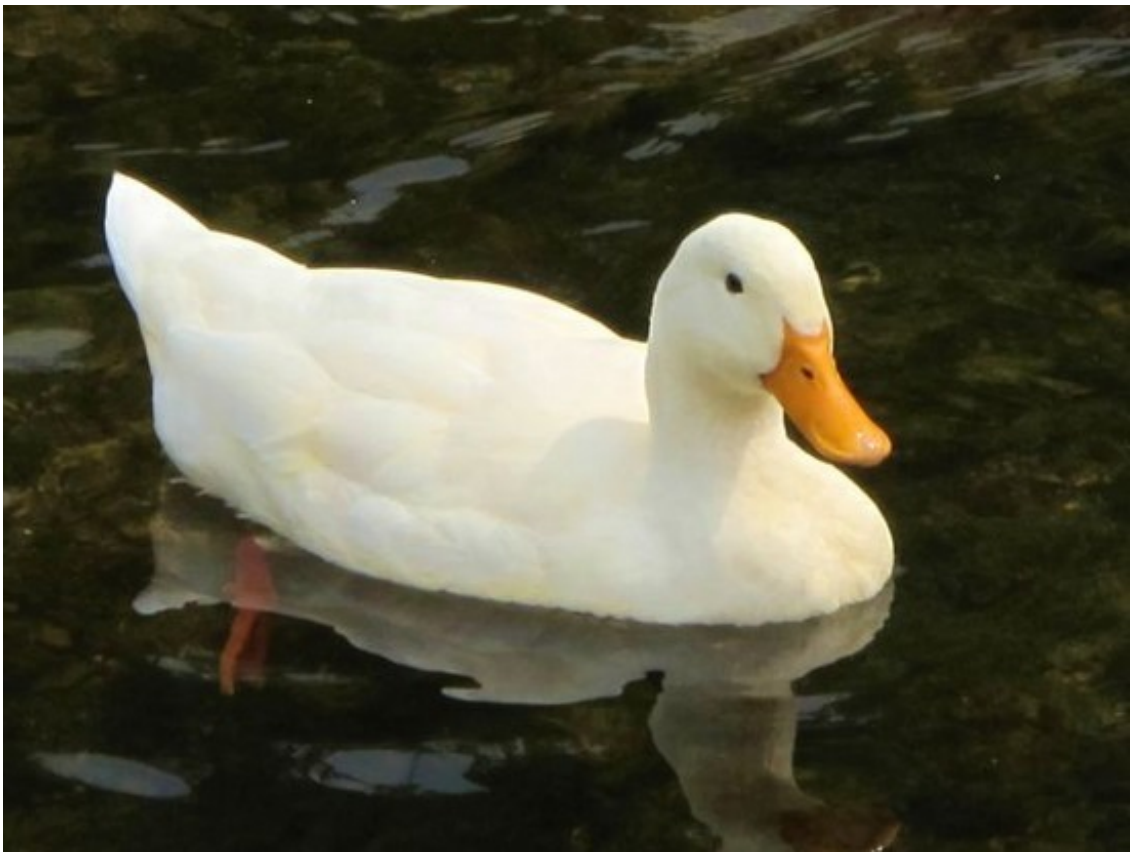

Pekin ducks have long been the animals of choice for research into hepatitis B.
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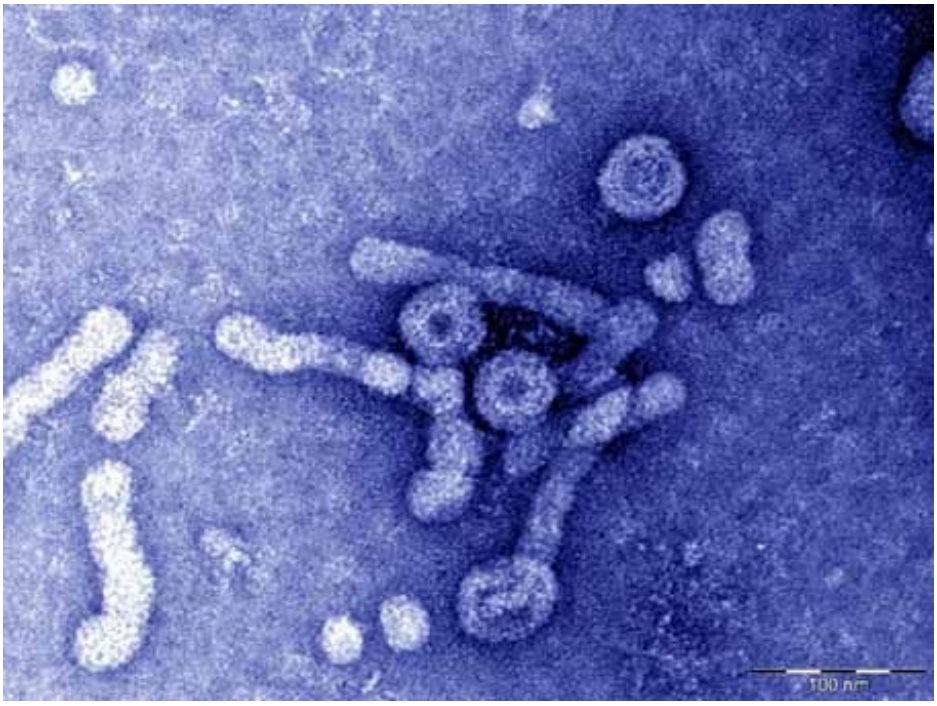
contained an evolutionarily highly conserved sequence in the L protein of the viral envelope. HBV uses this sequence to bind to a bile salt transporter (i.e. sodium taurocholate cotransporting polypeptide (NTCP)) on the hepatocytes through which the virus tends to enter the human host cell. The peptide binds specifically to this receptor, thereby inhibiting the docking of the virus by blocking the site. The peptide (Myrcludex B) was subsequently tested in preclinical studies and turned out to be stable and effective at low doses. The peptide enters the liver where it binds to the NTCP receptors on the cell surface, therefore effectively inhibiting virus entry and the infection of new cells. "Our aim is to rebuild the features that the virus has evolved over millions of years," says Urban explaining the research strategy, which, from the virus' point of view, is highly subversive.

Also effective against hepatitis D



Hepatitis B viruses under the electron microscope

Clinical phase I safety trials with healthy volunteers were positive and the preliminary results of phase IIa trials currently being carried out by licensee and DZIF contract partner MYR GmbH have been successful. These trials prove that the substance is safe and effective. They also demonstrate the substance's antiviral effects in patients with chronic hepatitis B. A particularly exciting finding was that Myrcludex B was also effective against hepatitis D virus (HDV) in patients coinfected with HBV. HDV can only propagate in the presence of the hepatitis B virus, which is why HDV infections only occur simultaneously with HBV infections. Worldwide, around 25 million people are coinfected with hepatitis D, which results in more severe complications than HBV alone. Coinfection with HDV increases the likelihood of liver cirrhosis and liver cancer, and also has a relatively high mortality rate. "At present, no direct antiviral treatment is available for patients with hepatitis D; interferon is the first-line therapy for hepatitis sufferers, but only has a limited effect," said Urban. Myrcludex B could be a major breakthrough in the treatment of HDV infections.

Urban believes that, unlike other antiviral drugs, it is highly unlikely that the virus will become

resistant to Myrcludex B due to the drug's similarity with an evolutionarily highly conserved protein fragment in the viral envelope that is crucial for the entry of the virus into the host cell. Any change in the protein sequence will most likely lead to the loss of the virus's infectious power.

Stephan Urban, who has headed up a group of researchers in the Department of Molecular Virology at the Centre for Infectious Diseases at Heidelberg University Hospital since 2001, was appointed to the first ever DZIF professorship for translational virology on 1st April 2014. The DZIF (German Centre for Infection Research) is a partnership of leading German universities, hospitals and non-university research institutes that focus on research and the development of methods for treating infectious diseases. The DZIF is specifically focused on developing new diagnostic, preventive and therapeutic methods for the treatment of hepatitis, and aims at translating basic research results quickly and systematically into the development of drugs and therapies. The development of Myrcludex B shows clearly how translational processes can lead to successful outcomes. At the DZIF's Annual Meeting on 26th November 2014, Stephan Urban was awarded the first ever DZIF Prize for Translational Infection Research.

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Advances in the study and treatment of liver diseases