First drug for hepatitis D has been approved by european commission

August 5 2020

Over the course of 25 years of research, Stephan Urban and his team developed Hepcludex, the first drug for Hepatitis D. Credit: Universitätsklinikum Heidelberg

What started off as basic research 25 years ago has now lead to a successfully approved drug: The entry blocker bulevirtide (brand name Hepcludex, formerly known as Myrcludex B), jointly developed by researchers from Heidelberg University Hospital (UKHD) and the Medical Faculty of Heidelberg, the DZIF and other partners, has now been approved by the European Commission. Hepcludex is a first-in-class entry inhibitor for the treatment of hepatitis D and prevents hepatitis D and B viruses (HDV/HBV) from entering liver cells. The development of this new drug brings new hope to approximately 25 million people in the world suffering from hepatitis D infection, as no other approved drug has been available to treat this infectious disease up to now. Hepatitis D virus infections are a particularly severe form of viral hepatitis as they only occur as co-infections with HBV and lead to an accelerated progression of liver cirrhosis and liver cancer. To date, liver transplants have been the only chance of survival for many patients.

"We are very pleased about this success which is based on decades of virology research in Heidelberg," notes Prof. Hans-Georg Kräusslich, spokesman of the Center of Infectious Disease Research at the UKHD and Chairman of the German Center for Infection Research (DZIF). "This drug was developed in close collaboration between partners in science, public funders and a biotech company and is therefore an epitome of successful translation of laboratory results into clinical application."

How a "broken key" protects liver cells

Hepcludex's mechanism of action is based on a lock-and-key principle: Hepatitis B and D viruses exclusively replicate in the liver as they require the bile acid transporter NTCP to do so, which is only found on liver cells. They use this transporter like the 'lock' (virus receptor) through which they enter the cell. Hepcludex blocks this lock, acting like a broken key that is stuck in the lock. However, Hepcludex also works

after an infection has occurred and the virus has already entered the cell, why is this so? "The virus continually needs to infect healthy liver cells in order to persist, as the infected ones either die or are eliminated by the immune system," says Prof. Stephan Urban. Over the course of 25 years of research, Urban and his team developed Hepcludex and, since his appointment as a DZIF professor in 2014, have focussed on developing the drug. "Liver cells evidently divide very rapidly when the liver is infected. The drug then protects the new, regenerated liver cells from infection whilst the infected cells are eliminated," explains Stephan Urban. Several phase I and II clinical trials showed that humans tolerate the agent well and that it efficiently prevents the replication of hepatitis B and D viruses. A phase III trial is currently being conducted, investigating Hepcludex's long-term effects, amongst other things.

The research was initially funded by the German Federal Ministry of Education and Research (BMBF), which provided 2.4 million euros for the preclinical development through the funding program "Innovative Therapies". As of 2014, the German Center for Infection Research (DZIF), which was founded in 2012, joined in and has been financing Stephan Urban's professorship at the Medical Faculty of Heidelberg, amongst other projects.

They searched for a receptor and found a drug!

When molecular biologist Stephan Urban started his research in a small laboratory, he did not have the development of a drug for hepatitis D in mind—he was initially interested in a different virus and was looking for the site used by hepatitis B viruses to enter liver cells. Many researchers across the globe where involved in this mission, which Urban called the 'Holy Grail of hepatitis research' because hepatitis B is so widespread. This formed the starting point of their meticulous work: They first had to find a way of propagating the virus in cell cultures so that its replication process could be studied. The second step involved

determining the correct receptor from a large number of candidates. "We used parts of the viral envelope sequence to generate protein fragments that mimick a part of the natural viral envelope, which we added to non-infected liver cells to see if we could inhibit viral entry," says Urban. They finally made a discovery:

The virus used a bile salt transporter, the NTCP receptor (NTCP: sodium taurocholate co-transporting polypeptide), to enter the cell like a stowaway. Virions, i.e. infectious virus particles outside of the host cell, are unable to enter the cell when this transporter is blocked by these synthetically produced protein fragments. Blocking just some of the receptors is enough to prevent virions from entering. "Our clinical studies show that Hepcludex is effective in very low concentrations, so that bile salt transporters can continue to operate for the cell," Urban summarizes.

Hepatitis D infection only occurs as an HBV co-infection because the D virus is unable to produce its own viral envelope. Instead, like a parasite of a parasite, it uses parts of the B virus to enter the liver cell. Effective but non-curative treatments for hepatitis B exist and with this small protein fragment, Urban and his team had now created the first effective hepatitis D drug in the world. Subsequently, Hepcludex was granted PRIME scheme eligibility by the European Medicines Agency (EMA). PRIME is short for "Priority Medicines" and was launched by the EMA to enhance support for the development of medicines that target an unmet medical need. On 28 May 2020, EMA recommended Hepcludex for approval and the European Commission has now approved it for prescription in Europe.

Hepatitis research—a core focus in Heidelberg

Heidelberg's success story continues beyond the approval of Hepcludex for the treatment of hepatitis D. A few years ago, at the same institute, a

pivotal contribution was made towards the development of hepatitis C drugs. Using information discovered about hepatitis C's molecular characteristics and replication cycle, Prof. Ralf Bartenschlager, Director of the UKHD Department of Infectious Diseases, Molecular Virology, elicited sites that could be targeted for developing antivirals. He has been accompanying and supporting Stephan Urban's research for many years: "Viral hepatitis in its different forms poses an immense global public health problem," says Bartenschlager. He congratulates Stephan Urban's team for their success and also adds some food for thought with regard to research funding in Germany. "I would wish for more consistent and long-term government funding for projects that are transitioning from basic research to the development of clinical applications, so that in future, promising projects no longer fail at the stage of finding funders." In his view, a positive example is the Trans regional Research Centre (TRR) 179 "Determinants and Dynamics of Elimination versus Persistence of Hepatitis Virus Infection" at the Medical Faulty of Heidelberg, which he heads. It is being funded by the German Research Foundation (DFG) and is currently in a second period of funding with approximately 13 million euro. This strengthens Heidelberg as a hepatitis research site. The DZIF was also founded with the specific aim of translating anti-infective agents into clinical applications.

From bench to bedside

There are comparatively few people suffering from hepatitis D infection in Germany. A part of the reason for this is that many people are vaccinated against hepatitis B through which they are also protected against hepatitis D. "The Robert Koch Institute estimates that approximately 240,000 people in Germany suffer from chronic HBV infection. We expect that approximately 2.5 percent of these people are co-infected with HDV, which corresponds to approximately 6,000 people," says Stephan Urban. "However, we do not have precise figures as many people with HBV infection have not been additionally tested for

hepatitis D." Prof. Uta Merle, Acting Medical Director of the Clinic for Gastroenterology, Infectious Diseases and Poisoning at the UKHD, treated several hepatitis D patients within clinical trials and underlines the implications of having a new agent: "Chronic infections with hepatitis D are particularly aggressive and difficult to treat. Patients with chronic hepatitis D often develop hepatic restructuring through to liver cirrhosis within five to ten years of infection. This severe course is observed in 70 to 90 percent of HDV infections including those in young people. At the stage of liver cirrhosis and its complications, a liver transplant is the only treatment option," she summarizes. This most severe form of hepatitis is particularly widespread in Africa, South America, Mongolia, Russia and Eastern Europe and many are unaware of their infection because of a lack of testing methods. For this reason the drug was approved in Russia and the former Soviet Union under the brand name Myrcludex at the end of 2019.

The Medical Faculty of Heidelberg and the French state research institution INSERM (Institut national de la santé et de la recherche médicale) granted the license for Hepcludex to the independent biotech company MYR Pharmaceuticals GmbH. The French involvement resulted from previous collaborations between Urban and INSERM researchers, based upon which the basic patent for the further development of Hepcludex at the Heidelberg Campus was created. Potential gains from the license go to the institutions in charge (Heidelberg University, INSERM, DZIF), the developer Stephan Urban, other researchers at the hospital involved in the development, as well as the Department of Molecular Virology.

As hepatitis B viruses also use the bile salt transporter NTCP to enter cells, Hepcludex is also an effective treatment for hepatitis B. Meanwhile, the agent has also been tested in combination with the immune modulator interferon alpha (IFNalpha), which is approved for hepatitis B, with very successful results. "After 48 weeks of treatment,

the viral loads significantly decreased and all viral markers consistently disappeared in some of the patients," says Stephan Urban. However, as established treatment for hepatitis B already exist, the prerequisites for fast track approval for HBV monoinfection were not met, which is why Hepcludex can initially only be used for patients who are particularly severely affected by dual infections. "In future, it will be very interesting to examine whether a combination of Hepcludex and an immune modulator can also cure HBV patients who are not co-infected with HDV," says Stephan Urban.

Provided by German Center for Infection Research