Healthcare industry BW

Against chronic liver inflammation and liver cancer

Chronic hepatitis B and C are the major causes of liver cancer. In contrast to hepatitis B viruses, there is no hepatitis C virus vaccination available. New research carried out by Professor Bartenschlager and his colleagues from Heidelberg might give rise to new strategies for the development of vaccines and medications for the prevention and treatment of chronic hepatitis C virus infections.

Hepatitis is a treacherous disease; it is virtually painless and the symptoms are often so unspecific that those affected are not aware that they have the disease. However, when left undiagnosed and untreated, liver inflammation can lead to chronic hepatitis, and eventually also to liver cirrhoses and hepatocellular carcinoma (HCC). Liver diseases and their consequences are among the most common causes of death in the world.

Why liver tests?

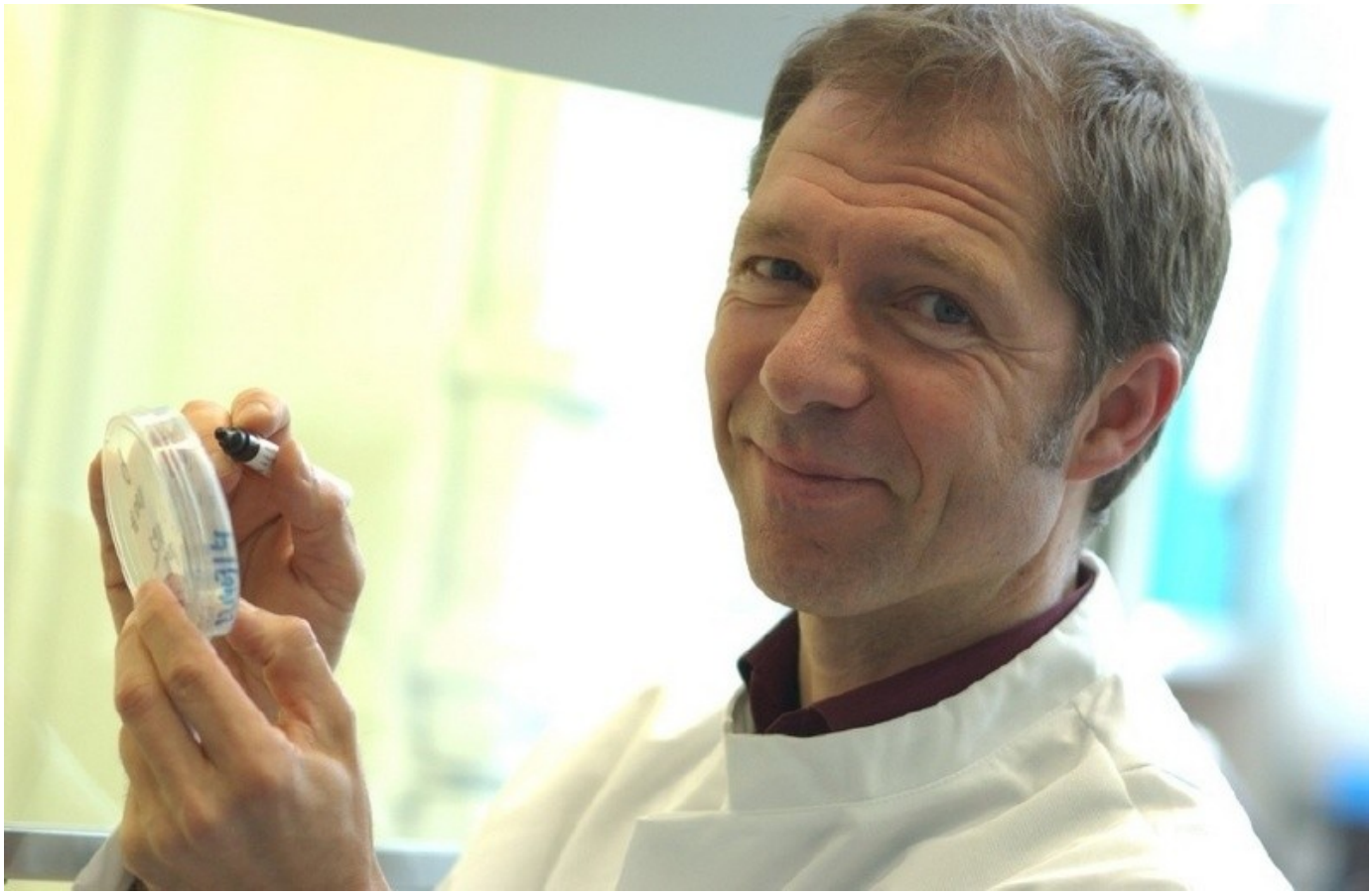
Human liver with hepatocellular carcinoma.

When the disease is diagnosed very early, sufferers have an excellent chance of cure if they are given the right medication. Results from simple tests carried out by general practitioners that show elevated liver values provide information about potential liver disorders. It was no coincidence that the German Liver Foundation named the "11th German Liver Day" held on 20th November 2010 "Liver values are worth knowing". The objective of this day was to inform people about the importance of early diagnosis of liver inflammation. The World Hepatitis Day on 19th May 2010 organised by the WorldHepatitisAlliance had the same objective.

Viral infections are a major cause of liver inflammation (hepatitis). Among the five known hepatitis virus types (A, B, C, D, E), the hepatitis B virus (HBV) and the hepatitis C virus (HCV) in particular are

the major causes of chronic hepatitis and hepatocellular carcinoma. According to information provided by the World Health Organisation (WHO), around 400 million people worldwide are infected with HBV (and 170 million with HCV) of whom around 60 million will develop liver cancer within the next ten years if effective therapy is not initiated. In many regions of the world, HCC is the most common of all cancers. Professor Harald zur Hausen, who was awarded the Nobel Prize in Physiology and Medicine for discovering cancer-causing viruses, concluded that of the 500,930 registered cases of liver cancer worldwide in 2006, 80 per cent (i.e. 400,000) are due to HBV infection and to a lesser degree to HCV infection (Harald zur Hausen: Infections Causing Human Cancer, Wiley-VCH, Weinheim, 2006). For this reason, the WHO has classified HBV as "the most important natural human carcinogen". In Germany, around one million people suffer from a virus-associated liver inflammation, and more than 5,000 are diagnosed with hepatocellular carcinoma every year. "Despite the improvements made in hepatitis therapy, the number of incidences of liver cancer are constantly increasing," said the chairman of the German Liver Foundation, Prof. Dr. Michael Manns, going on to explain that "this is because far too few liver diseases are detected at an early enough stage for effective treatment to be put in place. This is why the liver tests are so important."

The Hep-Net competence network



Professor Dr. Ralf Bartenschlager

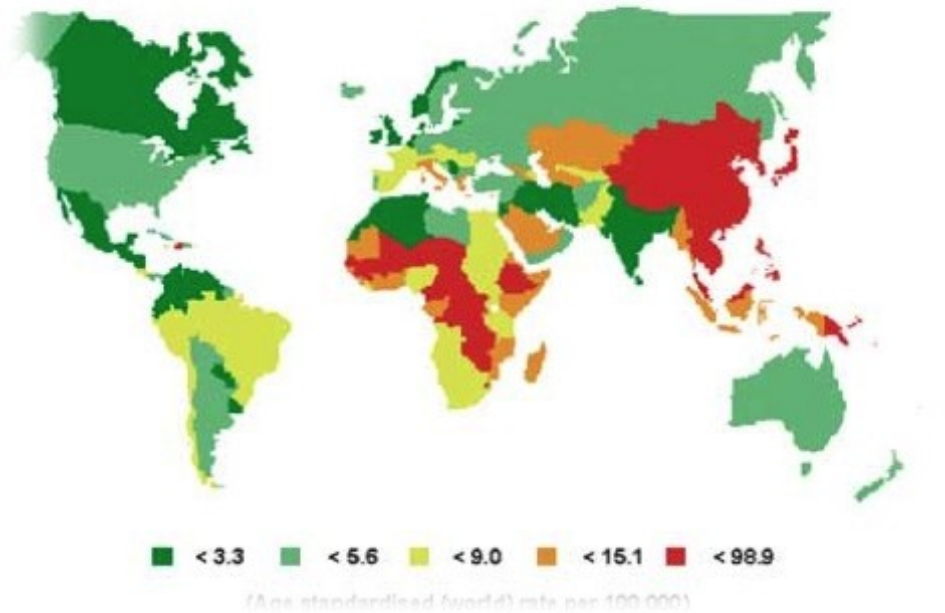
In 2002, the German Ministry of Education and Research founded the "Hepatitis Competence Network", Hep-Net for short, whose goal is to bring together research on virus-associated hepatitis in Germany and improve the treatment for those suffering from chronic hepatitis. The German Cancer Foundation is in charge of Hep-Net since 2007 and will continue to support the work of the consortium when public funding comes to an end in 2010. Hep-Net also deals with liver diseases that are not caused by viruses, for example autoimmune hepatitis, genetic iron storage disease and non-alcoholic fatty liver disease (non-alcoholic steatohepatitis; NASH) and develops new treatment

strategies.

The Department of Molecular Virology, which is part of the Department of Infectious Diseases at the University of Heidelberg, is one of the Hep-Net centres with a major focus on research into hepatitis-causing viruses. The department is closely connected with the figure of Heinz Schaller, a renowned virologist and pioneer of hepatitis B virus research who worked for many years at the Centre for Molecular Biology Heidelberg (ZMH) before his death in April 2010. Financial support provided by the Chica and Heinz Schaller Foundation, founded by Schaller and his wife, made it possible to establish the Department of Molecular Virology under Prof. Dr. Ralf Bartenschlager.

The hepatitis B virus

The genome of the hepatitis B virus (HBV) is made of circular DNA, but the DNA is not fully double-stranded. The DNA is contained in a capsid consisting of many copies of the HBV core antigen (HBVcAg), which is surrounded by a lipid envelope. The virus is transmitted through body fluids and is highly infectious, so that the tiniest wounds can lead to infection. Since blood preservations are checked for virus contaminations, HBV infections in Germany mainly occur as a result of sexual contact or drug addicts using contaminated syringes. HBV infection can also be transmitted by tattoos and piercing. HBV vaccination provides an effective means of prevention. Heinz Schaller made a huge contribution to the development of this vaccine.



Incidence of liver cancer worldwide
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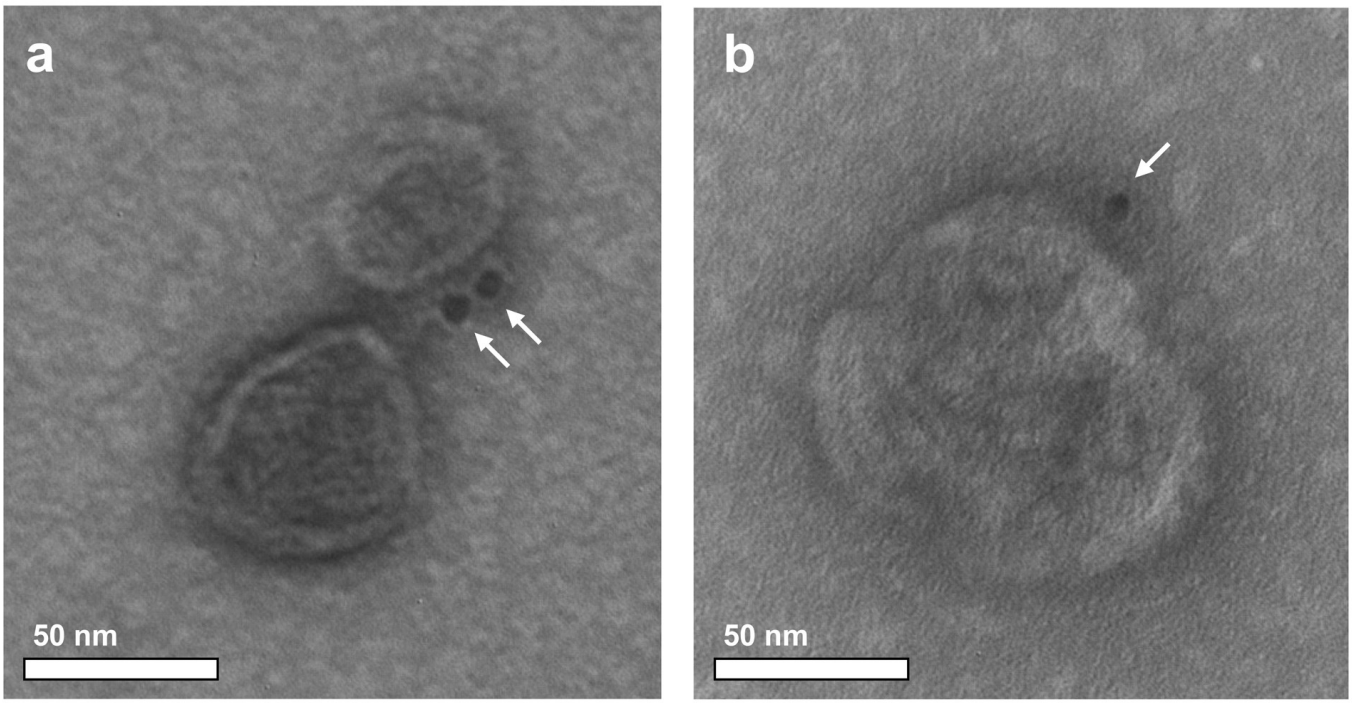
Around five to 10 per cent of all HBV infections are chronic. Herein lies the major medical problem due to the risk of developing liver cirrhoses and liver cancer. The global extent of this risk is clearly shown through the huge frequency of HBV infections and hepatocellular carcinoma, in particular in East, Southeast and Central Asia as well as in tropical Africa. The treatment of chronic hepatitis B has recently progressed enormously due to the use of interferons and particularly the development of new drugs which directly target the viral polymerase. These drugs enable the effective inhibition of viral proliferation as long as the medication is taken. The Hepatitis B Research Group of the Molecular Virology Heidelberg, led by Dr. Stephan Urban has also developed a specific inhibitor for

treatment of acute and chronic hepatitis B and hepatitis D infections. This inhibitor, a lipid peptide, is derived from the HBV envelope protein and effectively blocks the virus entry into liver cells as shown in preclinical studies. In 2011 it will be tested in clinical phase 1 studies. In countries such as Germany, patients with advanced hepatitis who had no chance of survival around ten years ago, can now be treated successfully. In the long term, it is also expected that the number of patients suffering from liver cirrhosis and HCC will decrease. The complete curative treatment of hepatitis however, is only very rarely achieved with currently available drugs that need to be taken over long periods of time. Therefore, a solution for the global problem of the broad distribution of chronic hepatitis B and liver cancer is not likely to occur in the short term.

Hepatitis C virus

Researchers from the Department of Molecular Virology at Heidelberg University are primarily focusing on investigations of the molecular mechanisms that enable hepatitis viruses to permanently and chronically infect liver cells. A new DFG-funded research unit (FOR 1202) entitled "Persistence mechanisms of hepatotrophic viruses" was established in October 2009 which also includes research groups from the Department of Medicine II of the Freiburg University Medical Centre led by Prof. Dr. Robert Thimme. Professor Bartenschlager is the FOR 1202 spokesman and focuses mainly on hepatitis C viruses.



Immuno-electron microscopy of HCV particles from cell cultures. Immuno staining by an E2-specific antibody. It was detected by secondary antibodies conjugated to 10 nm gold particles (arrows).

HCV belongs to a completely different group of viruses than HBV. It is a single-stranded RNA virus (not retrovirus) with an envelope that is closely related to the virus that causes Dengue fever, which recently has become relatively common in Germany. The group of researchers under Prof. Bartenschlager are also investigating the Dengue virus. Liver inflammations caused by HCV were referred to as non-A non-B hepatitis prior to the discovery of the virus in 1989. The infection is almost always parenteral (i.e. through blood, blood products and contaminated injection needles) and asymptomatic, which means that it is not recognised in the acute stage. In the majority of cases (50

to 80 per cent) the infection becomes chronic and often leads to liver cirrhosis and eventually hepatocellular carcinoma. Around 400,000 to 500,000 people in Germany suffer from chronic HCV infections.

Mechanisms for an immune reaction against hepatitis C virus

In contrast to HBV and despite all efforts, no vaccination is yet available for HCV. The research groups led by Dr. Lohmann and Prof. Bartenschlager (both Molecular Virology in Heidelberg) and Prof. Thimme (Freiburg) have now discovered important mechanisms that are crucial for a successful immune response against HCV infection. The results have been published in the journal Gastroenterology.

The small number of HCV-infected patients that are able to destroy the virus immediately, display a strong immunological reaction against HCV in which specialised killer cells that express the CD8 receptor on their surface play a decisive role. It has previously not been known how these killer cells destroy the virus. In a newly developed cell culture model, the researchers from Heidelberg and Freiburg have now been able to show that CD8+ killer cells prevent the proliferation of the viruses using two mechanisms. The CD8+ killer cells can directly destroy HCV-infected liver cells. In addition, they release cytokines such as interferon gamma that lead to the inhibition of virus proliferation at the same time as keeping the liver cells alive. The researchers hope that the new cell culture model will help them to clarify the question as to why the killer cells of the majority of patients are unable to effectively destroy HCV. These findings might contribute to the development of new vaccines or medication that make it possible to prevent or treat hepatitis C.

Further information:

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Advances in the study and treatment of liver diseases