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Media release

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Coalition launches Global Scientific Strategy to Cure Hepatitis B

The ICE-HBV Global Scientific Strategy, published today in *The Lancet Gastroenterology and Hepatology*, lays the groundwork for the momentum behind hepatitis B (HBV) cure research and the long-term implementation of HBV cure preparedness worldwide.

HBV is a global public health challenge on the same scale as tuberculosis, HIV and malaria. More than 257 million people worldwide are chronically infected with HBV and nearly 900,000 people died from the disease in 2017.

Worldwide efforts to eliminate HBV have been boosted today by the launch of a Global Scientific Strategy to Cure Hepatitis B (the ICE -HBV Strategy) by the International Coalition to Eliminate HBV (ICE-HBV), a global group of researchers, patient representatives and health organisations.

The ICE-HBV Strategy, published simultaneously in *The Lancet Gastroenterology and Hepatology*, was released and webcast live on the opening day of the The International Liver Congress taking place in Vienna, and hosted by the European Association for the Study of the Liver (EASL).

HBV is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is transmitted through contact with the blood or other body fluids of an infected person. Today, more people die from chronic hepatitis B (CHB) virus infection than from malaria.

CHB causes almost 40 per cent of hepatocellular carcinoma, which is the second leading cause of cancer-related mortality worldwide.

"Some 900,000 people dying unnecessarily of hepatitis B every year is simply unacceptable," said Professor Peter Revill, ICE-HBV Chair and Royal Melbourne Hospital Senior Medical Scientist at the Doherty Institute.

"Inexplicably, despite the huge human and economic toll of chronic hepatitis B, HBV research remains largely underfunded, to the point of being compared to a neglected tropical disease. HBV cure research could make all the difference and prevent adverse outcomes in all people infected with the virus, allowing them to live treatment-free, fully productive lives and reduce the stigma associated with this chronic infection."

If we have a vaccine and drugs for treating hepatitis B why do we need to research a cure?

A safe and effective vaccine to prevent HBV infection exists and its universal delivery is essential for the elimination of HBV as a public health threat. Lifelong treatment is also needed for those already chronically infected but currently is only accessed by some eight per cent of the millions of people who need it, partly due to the complexity of disease monitoring. The ICE-HBV Strategy argues strongly for the need for appropriate cure research and preparedness to complement the World Health Organization's global elimination strategy, the HBV vaccine and the well-tolerated but poorly-accessed therapy.

The current treatment regime helps keep HBV under control, but it is not a cure because it cannot completely clear the virus from infected cells. cccDNA (covalently closed circular DNA) is a special DNA structure that arises during the propagation of HBV in the cell nucleus and may remain permanently there. Following HBV infections, cccDNA can remain in liver cells following clinical treatment and can even reactivate.

Even with ongoing treatment, people are still at a higher risk of developing liver cancer, particularly those with underlying cirrhosis due to CHB. It raises issues of medication adherence and requires considerable investment for ongoing monitoring, adding to the challenges of achieving elimination.

Twin-pronged approach

To achieve the goal of HBV cure, the ICE-HBV Strategy proposes and describes in detail two main approaches; curing of HBV infection without killing infected cells, and inducing immune control to safely eliminate infected cells. The ICE-HBV Strategy argues that each of these approaches will need to be underpinned by coordinated clinical studies to advance HBV cure.

The ICE-HBV Strategy also cites emerging evidence that the HBV disease 'time-clock' commences ticking earlier than previously appreciated and that HBV DNA integrations are associated with liver cancer – hence treatment might be advisable at a much earlier stage than currently recommended.

New collaborations are key

"Curing hepatitis B is not a pipe dream and should not be thought of as such," said Dr Su Wang**,** Hepatitis B Foundation Board Member and President-Elect of the World Hepatitis Alliance.

"The 257 million of us living with hepatitis B are desperate for this to be reality to stop the needless suffering and deaths. We applaud the ICE-HBV Strategy as a sign of the commitment to scale up the necessary research and collaboration to get us there.

"We believe if the same kind of fervour and investment is given to HBV that was poured into hepatitis C therapeutic development, we would dramatically expedite the timeline to a cure. The ICE-HBV Strategy is important in how it details a multi-pronged plan to attack and eliminate deadly HBV with virological and immunological approaches.

"But it is also landmark because it not only includes renowned scientists and clinicians, it values the contribution of the HBV patient community. People living with HBV have the central stake in a cure and should be included as a partner on this road to cure."

A more universal health coverage approach

Recent scientific progress and the momentum created by the discovery of a cure for the hepatitis C virus (HCV) has created a sense of hope to find a cure for HBV.

ICE-HBV is calling for increased investments in HBV cure research and cure preparedness to save the lives of the 257 million people living with CHB worldwide, most of whom are unaware of their infection.

While ICE-HBV supports both the World Health Organization global health sector strategy on viral hepatitis and the World Hepatitis Alliance's 'Find the Missing Millions' campaign, it urges a more universal health coverage approach to the HBV response.

"We strongly believe that public health and research agencies need go beyond the existing objectives and work together to discover and ensure access to curative treatment regimens for people living with HBV," said Professor Fabien Zoulim, ICE-HBV Deputy Chair, Vice-president of the scientific advisory board and head of the HBV cure programme at the French National Agency for Research on HIV and Viral Hepatitis (ANRS) in Paris, France.

Recommendations

The ICE-HBV Strategy sets out a series of research priority areas to tackle HBV, which include:

HBV Elimination

- Developing standardised methods to quantify cccDNA and study mechanisms of cccDNA homeostasis and processes affecting its biogenesis, homeostasis, structure, transcriptional control and decay.
- Define mechanisms determining HBV infection establishment: characterise all steps from cell entry to cccDNA mini-chromosome formation and maintenance.
- Improve methodologies for the study of cccDNA processing and virus-host interactions to reveal new targets for therapeutic approaches to clear cccDNA, by applying state of the art 'omics' approaches (e.g. genomics, transcriptomics, proteomics, metabolomics, kinomics) to increase understanding of HBV-host interactions at a genome-wide level.
- Develop and validate new serum markers (e.g. core-related antigens (HBcrAgs), HBV-RNA) as reliable biomarkers of cccDNA activity in the liver. Once markers are identified and characterised, ensure they are standardised.
- Develop methods to specifically degrade HBV cccDNA.
- Develop methods to prevent transcription of cccDNA and integrated HBV DNA. Continue to develop methods to inhibit the additional key steps of the viral replication cycle, that may be included in combination strategies to cure the infection.
- Develop efficient and convenient in vitro functional cccDNA systems.
- Develop convenient in vivo model systems, particularly immunocompetent non-human primate and mouse models susceptible to HBV infection.

HBV Immunity

- Clinical studies with existing immune interventions.
- The relative contribution of different components of the immune system to viral clearance versus viral persistence, immunopathology and treatment response among neonates, children, adolescents and adults.
- The mechanisms of T cell exhaustion and the extent to which T cell restoration is reversible, durable and needed for viral control.
- The role of B cells in the natural history of disease and how they can be effectively monitored for research and clinical trials.
- The impact of liver microenvironment on the composition and function of innate and adaptive cells and identification of biomarkers in the blood that best reflect the intrahepatic immune response.
- The number of infected hepatocytes in each category of patients and the degree of immune mediated destruction that is required for clearance but can still be tolerated before hepatic decompensation occurs.

Implementation

- Increase funding for individual and collaborative cure-related research projects by governmental and private funding agencies and philanthropic benefactors. Consideration should be given to establishing international

research consortia, similar to the Martin Delaney Collaboration for HIV research managed by the NIH in the USA. HBV cure research investment strategies should be prioritised in national HBV plans globally.

- The WHO Hepatitis Elimination Strategy should be funded in full, with particular focus on delivery of birth dose vaccines and substantially increased investments in HBV research and the improvement of point-of-care diagnostics for treatment and cure roll-out.
- Concentrate on the discovery of interventional strategies that will permanently reduce the number of productively infected cells or permanently silence the cccDNA in those cells and also stimulate HBV-specific T cells and the production of neutralising antibodies that will prevent viral spread to uninfected cells, mimicking spontaneous resolution of acute HBV infection.
- Establish repositories of standardised HBV reagents and protocols and facilitate access to all researchers across the world and support the development of in vivo models of HBV infection.

- ENDS

About the International Coalition to Eliminate Hepatitis B (ICE-HBV)

ICE-HBV is an international research-driven forum, which is coordinating, promoting and establishing public-private collaborative partnerships to accelerate the discovery of a chronic hepatitis B (CHB) cure. ICE-HBV aims to fast-track the discovery of a safe, effective, affordable and scalable cure to benefit all people living with CHB, including children and people living with hepatitis C, hepatitis D and HIV co-infection. ICE-HBV intends to contribute to the elimination of CHB as a global public health challenge. ICE-HBV is a non-profit initiative initially created in 2016 by academic researchers from the ANRS (France Recherche), the Peter Doherty Institute for Infection and Immunity and the International HBV Meeting. Its growing list of individual members and member organisations now spans the globe.

ICE-HBV.org @ICE-HBV #ICEHBV

About the Peter Doherty Institute for Infection and Immunity

Finding solutions to prevent, treat and cure infectious diseases and understanding the complexities of the immune system requires innovative approaches and concentrated effort. This is why The University of Melbourne – a world leader in education, teaching and research excellence – and The Royal Melbourne Hospital – an internationally renowned institution providing outstanding care, treatment and medical research – have partnered to create the Peter Doherty Institute for Infection and Immunity (Doherty Institute); a centre of excellence where leading scientists and clinicians collaborate to improve human health globally.

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