Berkeley School of Public Health

Forum for Collaborative HIV Research

HBV Forum 1
November 15th 2016
Hyatt Regency Hotel
Boston

www.hivforum.org

Berkeley School of Public Health

Forum for Collaborative HIV Research

Opportunities for Collaboration: ICE-HBV

Peter Revill

International Coalition to Eliminate Hepatitis B

ICE-HBV

International HBV Meeting Steering Committee

The Molecular Biology of Hepatitis B Viruses

Expectations for cure of chronic hepatitis B

- A number of factors have raised expectations of HBV cure, including:
- The discovery ot the NTCP entry receptor (*Yan et al, eLife, November 2012)*
- *New in vitro and in vivo models to interrogate the complete HBV life cycle.*
- Curative regimens for hepatitis C virus

HBV cure initiatives

A number of HBV Cure research initiatives have commenced:

- ANRS HBV cure initiative (France)
- French-German ANRS-DZIF collaboration (HIV and HBV)
- HBV Cure Program (Singapore, Prof. Seng Gee Lim)
- HBV Therapeutics and Curative Interventions, The HBV Project, Berkley School of Public Health, Washington DC.

But to date there has been no global co-ordinated approach to HBV cure research.

ICE-HBV

Advance HBV Cure Science

The HIV Cure initiative was established to facilitate scientific discussion, exchange and collaboration to promote and accelerate research towards an HIV cure, provide leadership in advocating for increased investments and resource optimisation in HIV cure research as well as disseminate knowledge to the scientific and broader community.

Formation of Multidisciplinary International Working Groups

- Virology,
- Immunology,
- Innovative Tools,
- Clinical Trials.

- Such a coordinated approach did not exist for HBV on a global scale.

- We believed there was a strong need for such an organisation, bringing the best minds in HBV research together, across the globe.

We have established an International Coalition dedicated to the Elimination of HBV

- **ICE- HBV (International Coalition to Eliminate HBV)**
  - ICE-HBV will coordinate the Multidisciplinary Working Groups.
  - Facilitating the establishment of subgroups for **research** on **Virology, Immunology, Innovative Tools, and Clinical Studies.**
  - These four pillars of HBV **research** will drive HBV cure **research** in a coordinated approach across the world.

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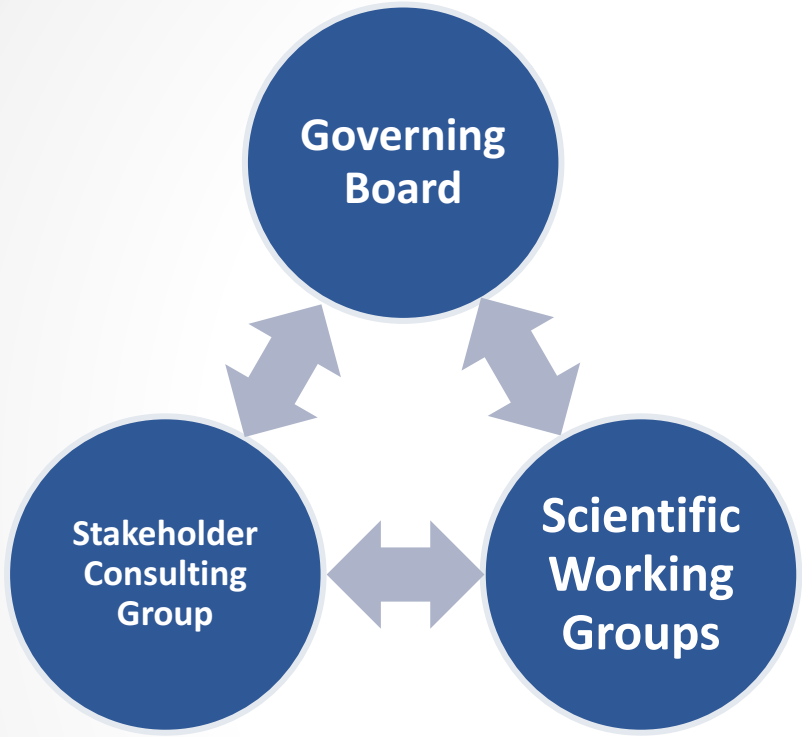

Research → Education → Collaboration → Innovation

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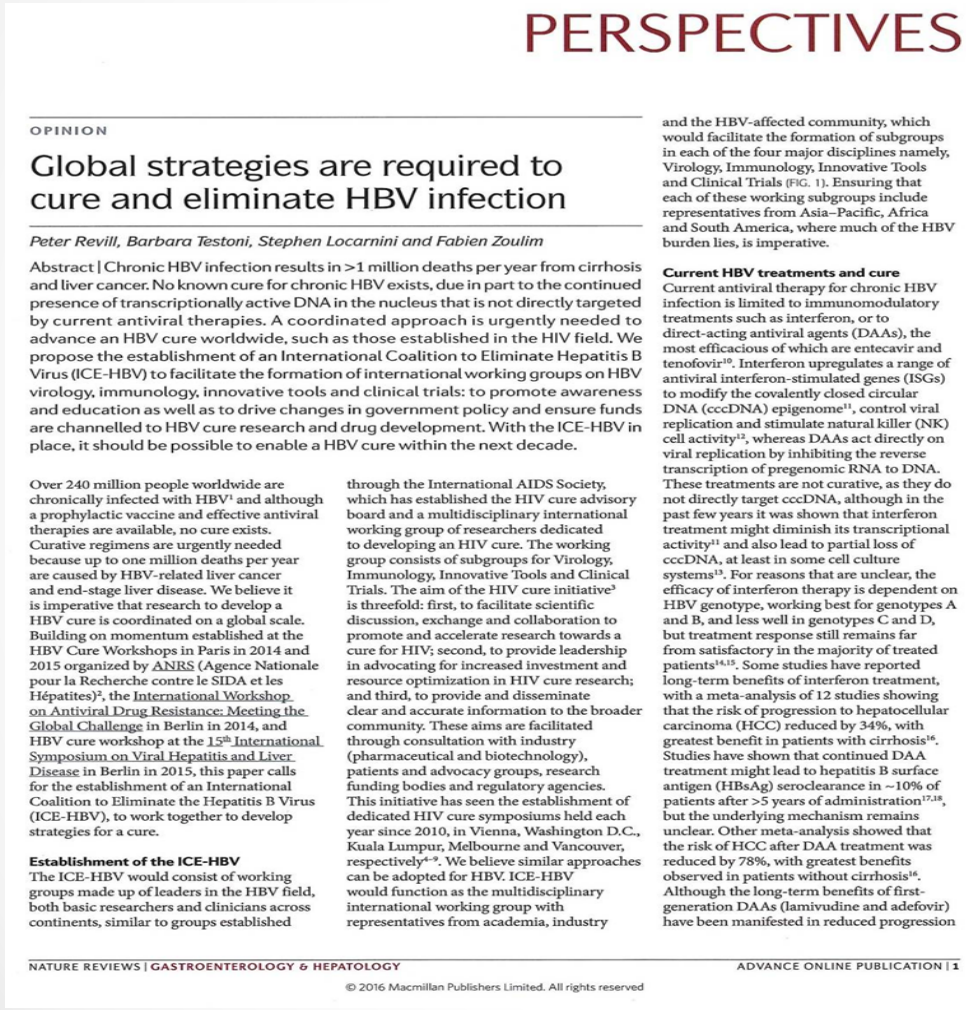
Building An International Scientific Coalition Dedicated to Curing HBV



PERSPECTIVES

OPINION

Global strategies are required to cure and eliminate HBV infection

Peter Revill, Barbara Testoni, Stephen Locarnini and Fabien Zoulim

Abstract | Chronic HBV infection results in >1 million deaths per year from cirrhosis and liver cancer. No known cure for chronic HBV exists, due in part to the continued presence of transcriptionally active DNA in the nucleus that is not directly targeted by current antiviral therapies. A coordinated approach is urgently needed to advance an HBV cure worldwide, such as those established in the HIV field. We propose the establishment of an International Coalition to Eliminate Hepatitis B Virus (ICE-HBV) to facilitate the formation of international working groups on HBV virology, immunology, innovative tools and clinical trials: to promote awareness and education as well as to drive changes in government policy and ensure funds are channelled to HBV cure research and drug development. With the ICE-HBV in place, it should be possible to enable a HBV cure within the next decade.

Over 240 million people worldwide are chronically infected with HBV[1] and although a prophylactic vaccine and effective antiviral therapies are available, no cure exists. Curative regimens are urgently needed because up to one million deaths per year are caused by HBV-related liver cancer and end-stage liver disease. We believe it is imperative that research to develop a HBV cure is coordinated on a global scale. Building on momentum established at the HBV Cure Workshops in Paris in 2014 and 2015 organized by ANRS (Agence Nationale pour la Recherche contre le SIDA et les Hépatites)[2], the International Workshop on Antiviral Drug Resistance: Meeting the Global Challenge in Berlin in 2014, and HBV cure workshop at the 15th International Symposium on Viral Hepatitis and Liver Disease in Berlin in 2015, this paper calls for the establishment of an International Coalition to Eliminate the Hepatitis B Virus (ICE-HBV), to work together to develop strategies for a cure.

Establishment of the ICE-HBV

The ICE-HBV would consist of working groups made up of leaders in the HBV field, both basic researchers and clinicians across continents, similar to groups established through the International AIDS Society, which has established the HIV cure advisory board and a multidisciplinary international working group of researchers dedicated to developing an HIV cure. The working group consists of subgroups for Virology, Immunology, Innovative Tools and Clinical Trials. The aim of the HIV cure initiative[3] is threefold: first, to facilitate scientific discussion, exchange and collaboration to promote and accelerate research towards a cure for HIV; second, to provide leadership in advocating for increased investment and resource optimization in HIV cure research; and third, to provide and disseminate clear and accurate information to the broader community. These aims are facilitated through consultation with industry (pharmaceutical and biotechnology), patients and advocacy groups, research funding bodies and regulatory agencies. This initiative has seen the establishment of dedicated HIV cure symposiums held each year since 2010, in Vienna, Washington D.C., Kuala Lumpur, Melbourne and Vancouver, respectively[4–9]. We believe similar approaches can be adopted for HBV. ICE-HBV would function as the multidisciplinary international working group with representatives from academia, industry and the HBV-affected community, which would facilitate the formation of subgroups in each of the four major disciplines namely, Virology, Immunology, Innovative Tools and Clinical Trials (FIG. 1). Ensuring that each of these working subgroups include representatives from Asia–Pacific, Africa and South America, where much of the HBV burden lies, is imperative.

Current HBV treatments and cure

Current antiviral therapy for chronic HBV infection is limited to immunomodulatory treatments such as interferon, or to direct-acting antiviral agents (DAAs), the most efficacious of which are entecavir and tenofovir[10]. Interferon upregulates a range of antiviral interferon-stimulated genes (ISGs) to modify the covalently closed circular DNA (cccDNA) epigenome[11], control viral replication and stimulate natural killer (NK) cell activity[12], whereas DAAs act directly on viral replication by inhibiting the reverse transcription of pregenomic RNA to DNA. These treatments are not curative, as they do not directly target cccDNA, although in the past few years it was shown that interferon treatment might diminish its transcriptional activity[11] and also lead to partial loss of cccDNA, at least in some cell culture systems[13]. For reasons that are unclear, the efficacy of interferon therapy is dependent on HBV genotype, working best for genotypes A and B, and less well in genotypes C and D, but treatment response still remains far from satisfactory in the majority of treated patients[14,15]. Some studies have reported long-term benefits of interferon treatment, with a meta-analysis of 12 studies showing that the risk of progression to hepatocellular carcinoma (HCC) reduced by 34%, with greatest benefit in patients with cirrhosis[16]. Studies have shown that continued DAA treatment might lead to hepatitis B surface antigen (HBsAg) seroclearance in ~10% of patients after >5 years of administration[17,18], but the underlying mechanism remains unclear. Other meta-analysis showed that the risk of HCC after DAA treatment was reduced by 78%, with greatest benefits observed in patients without cirrhosis[16]. Although the long-term benefits of first-generation DAAs (lamivudine and adefovir) have been manifested in reduced progression

What needs to be done

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Unanswered virological questions

What are the other possible additional receptors/co-receptors required for viral entry?
What are the host and virological factors which regulate HBV replication?
Does cccDNA need to be eliminated, or will rendering it transcriptionally inactive be sufficient for effective cure?
Would the elimination of virus be sufficient to result in the resolution / reversal of established liver disease?
Standardization of assays for analysis of cccDNA is urgently required.

What we do

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Virology Working Group

Perform standardization of assays for analysis of cccDNA

Building on existing French-German Cooperation
First results expected by April 2017

Convener
Maura Dandri, Hamburg University, Germany

Co-Convener
Haitao Guo, Indiana University, USA

What needs to be done

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Unanswered immunological questions:

Is HBV a stealth virus that sneaks under the immune response or is it actively suppressing immune responses to establish infection and maintain persistence?

What are the mechanisms for virus-induced T-cell exhaustion in persons with CHB?

Can this T-cell exhaustion be reversed, or are T-cell responses "hard wired" in most individuals?

Are there better immunological biomarkers of HBV natural history than ALT?

What we do

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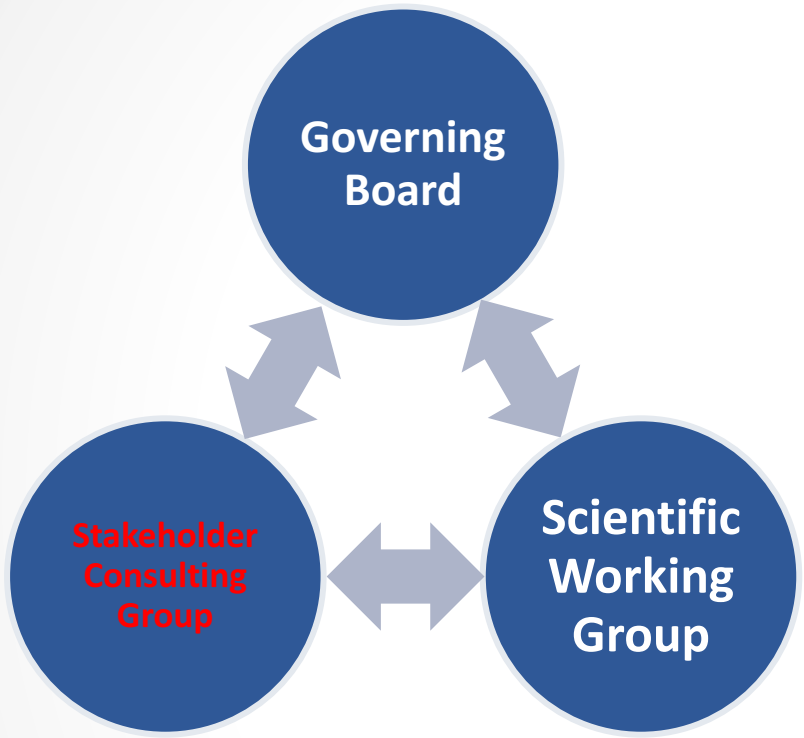
Immunology Working Group

Review immunological biomarkers of HBV natural history, treatment response and disease progression.

Convener
Adam Gehring, Toronto University, Canada

Co-Convener
TBA



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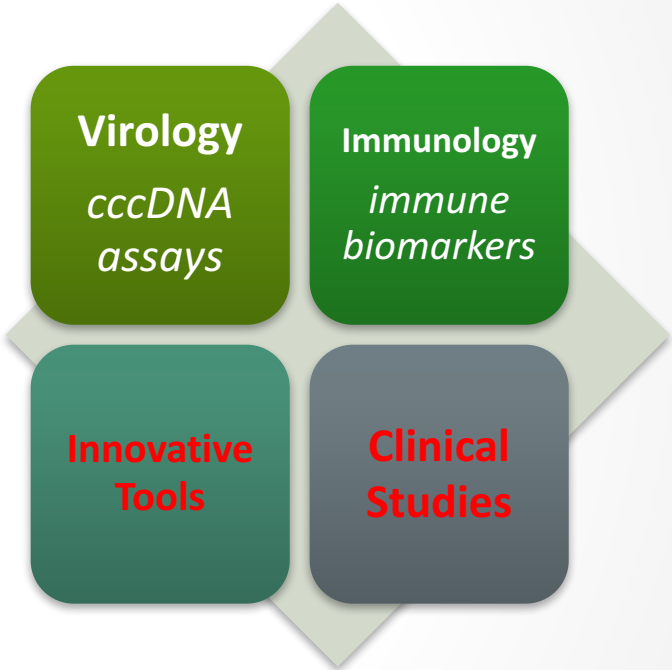

Opportunities for Collaboration =>

What we will do

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Innovative Tools Working Group

ToRs In Development

Convener

Jianming Hu, University of Pennsylvania, USA

Co-Convener

Fengmin Lu, Wuhan University, China

Clinical Studies Working Group

TBC

Next Steps

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✓*Develop proposals for each working group, secure resources, perform research & present results/publish them.*

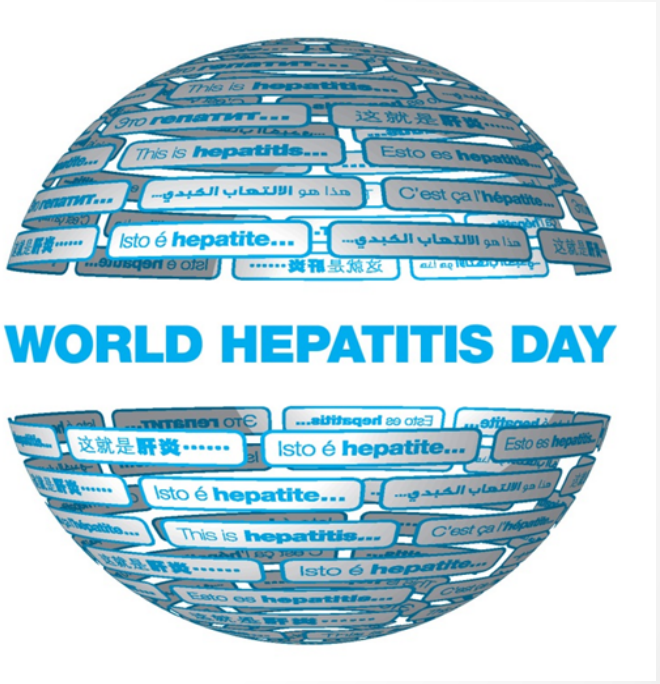
✓*Gather stakeholders to provide input on priorities (April 2017, EASL).*

✓*Support dedicated ICE-HBV Cure Symposia at existing conferences:*

✓*Singapore, Washington, Paris*

✓*Create an HBV Cure research prize & foster travel scholarship programmes*

✓***Publish ICE-HBV progress report in September 2018.***



2015 was the 50th anniversary of the discovery of the Australia Antigen

- **A "NEW" ANTIGEN IN LEUKEMIA SERA.**

Blumberg, Alter and Visnich. Journal of the American Medical Association (JAMA) 1965; 191:541-6.

- It cannot be another 50 years before we find a cure.

- There are 240 million reasons why we need to work together to succeed!!

Acknowledgements

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Fabien Zoulim
Jean-Francois Delfraissy
Anna-Laura Ross
Ani Abdi Halane,
Ventzislava Petrov-Sanchez

Stephen Locarnini
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