A Global Approach to Curing Chronic Hepatitis B – the International Coalition to Eliminate Hepatitis B Virus (ICE-HBV).

Dr. T Jake Liang
ICE-HBV Governing Board Member

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International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Structure of Presentation

- ICE-HBV Global Strategy
- Current ICE-HBV projects and future directions

A Coordinated Approach for HBV Cure

- Prior to 2016, global HBV cure efforts were not coordinated.

- Given that chronic HBV infection is a global problem, we believed there was an urgent need for global collaboration for HBV cure – similar to the HIV field.

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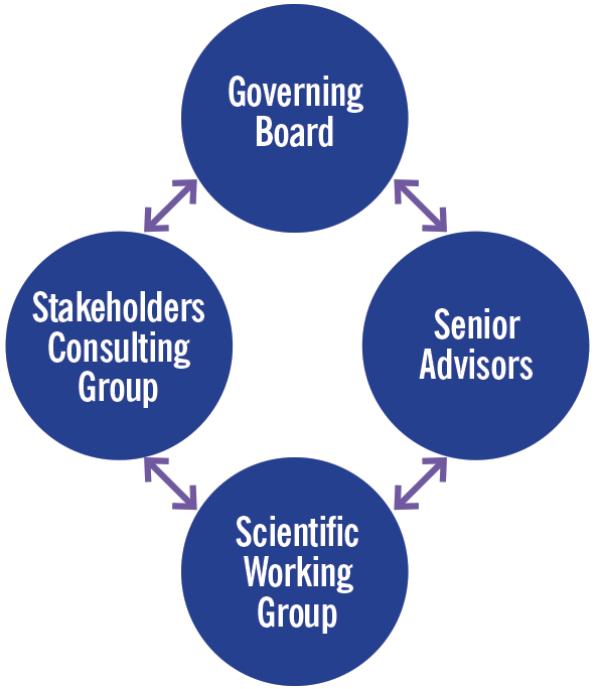
ICE-HBV was formed in 2016 and aims to fast-track the discovery of a safe, effective, affordable and scalable cure to benefit all people living with CHB, including children and people living with HCV, HDV and HIV co-infection. ICE-HBV intends to contribute to the elimination of CHB as a global public health challenge.

ICE HBV Model

- Governance structure established
- Developed resources to fund the initiative



Virology

Immunology

Clinical Sciences

Innovative Tools

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Stakeholders Group with Advisory Role

- **Chairs: Veronica Miller, Ulla Protzer, Tim Block.**
- **Stakeholders**

ANRS; ASHM; Asian Liver Centre; Bill and Melinda Gates Foundation (Beijing); Biomed Central/WHO CC; CEVHAP; NCHHSTP, CDC; DZIF; Hepatitis Australia; Hepatitis B Foundation; Hepatitis Education Project; Inno Community Development; MRC Unit – The Gambia; NIAID; Pasteur Institute/International Network of Pasteur Institutes; The Forum for Collaborative Research; The World Hepatitis Alliance; World Indigenous Peoples' Conference on Viral Hepatitis; WHO; WHO Collaborating Centre for Viral Hepatitis; Yellow Warriors.

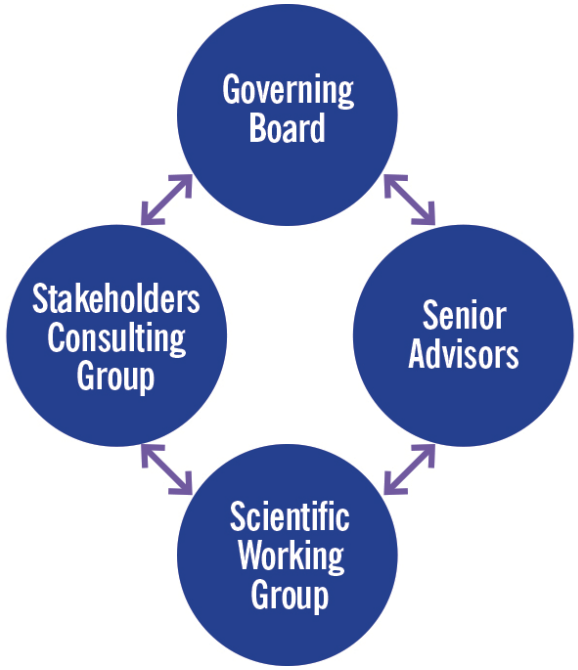
Current Projects

- cccDNA Harmonization project
- Reagents and protocols repository
- Population modelling for HBV cure and elimination (Mehlika Toy, Stanford University and Ben Cowie, RMH/Doherty Institute).
- HBV Cure policy paper - (Jeffery Lazarus, Barcelona Institute for Global Health, in Nat. Rev. Gastro. Hep)
- **Scientific Strategy Position paper**

ICE-HBV Position Paper

A Global Scientific Strategy towards Cure of Chronic Hepatitis B Virus Infection.

Revill et al.
Lancet Gastro Hep
April 2019



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Two Key Strategies for Cure of Chronic Hepatitis B

1. **Cure HBV infection without killing HBV infected cells**

2. **Induce Immune Control to safely eliminate HBV infected cells.**

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Research Priorities - Strategy 1

1. Develop standardized methods for cccDNA quantification and to study mechanisms of cccDNA biogenesis, homeostasis, structure, transcriptional control and decay.

2. Define mechanisms determining HBV infection establishment: characterise all steps from cell entry to cccDNA mini-chromosome formation and maintenance.

3. Improve methodologies for the study of cccDNA processing and virus-host interactions to reveal new targets for therapeutic approaches to clear cccDNA
   - apply state of the art “omics” approaches (e.g., genomics, transcriptomics, proteomics, metabolomics, kinomics)

Research Priorities - Strategy 1

4. Develop and determine new serum markers (e.g., core related antigens, serum HBV RNA) as reliable, standardized, biomarkers of cccDNA activity in the liver.

5. Develop methods to specifically degrade HBV cccDNA.

6. Develop methods to prevent transcription of cccDNA and integrated DNA.
   -Understand the role of HBV DNA integrations in carcinogenesis and in HBsAg production

7. Continue to develop methods to inhibit the additional key steps of the viral life cycle, that may be included in combination strategies to cure the infection.

Tool Kit

1. Develop efficient and convenient ***in vitro*** functional cccDNA systems

2. Develop convenient ***in vivo*** model systems, particularly immunocompetent non- human primate and mouse models susceptible to HBV infection.

Strategy 2: Inducing Immune Control to Safely Eliminate HBV Infected Cells

Priority Research Areas.

1. Clinical studies with existing interventions
2. The relative contribution of different components of the immune system to viral clearance vs viral persistence, immunopathology and treatment response among neonates, children, adolescents and adults.
3. The mechanisms of T cell exhaustion and the extent to which T cell restoration is reversible, durable and needed for viral control.
4. The role of B cells in the natural history of disease and how they can effectively be monitored for research and clinical trials.
5. The impact of liver environment on the composition and function of innate and adaptive cells and identification of biomarkers in the blood that best reflect the intrahepatic immune response.
6. 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.

Immediate and Future Actions Required to Achieve HBV Cure – the ICE-HBV Strategy

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.
- We support recent calls from the Hepatitis B Foundation for increased HBV cure research funding.

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Immediate and Future Actions Required to Achieve HBV Cure – the ICE-HBV Strategy

CONCENTRATE on the discovery of interventional strategies that will permanently reduce the number of productively infected cells and/or permanently silence the cccDNA in those cells, AND that will stimulate HBV-specific T cells and the production of antibodies that will prevent viral replication and spread to uninfected cells, mimicking spontaneous resolution of HBV infection

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Immediate and Future Actions Required to Achieve HBV Cure – the ICE-HBV Strategy

ESTABLISH repositories of standardised HBV reagents and protocols and facilitate access to all researchers across the world and support the development of a new animal model.

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HBV Specific Reagent Repositories

- There is an urgent need for centralised repositories of HBV-related materials that are readily accessible to HBV researchers globally.
- Similar resources are available to colleagues in the HIV field (NIH).
- Critical to this will be quality assurance of the samples, and the availability of matching clinical data.
- This repository would be accessed by basic researchers, clinicians, biotechnology and pharmaceutical companies, to facilitate studies and development of new drugs.

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Repository for Advancing HBV Cure Research is underway (NIAID, NIH, USA)

- Peptide libraries for clinical immunology studies
- Monoclonal antibodies against HBV proteins
- Viral DNA, RNA and protein standards
- Replication competent HBV clones of various genotypes
- Compounds for studies in experimental models
- Cell lines susceptible to HBV replication and cell to cell spread
- Collection of serum and liver biopsy samples from cohort study for research purposes

In parallel, ICE HBV is establishing and Open Access Protocols Database

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NIH Funding Call

Research to Advance HBV Cure: HIV/HBV Co-Infection and HBV Mono-infection (R01)

Virology

- Explore basic mechanisms of HBV replication or HBV protein expression.
- **Elucidate the mechanisms responsible for cccDNA biogenesis, homeostasis, and decay.**
- Study epigenetic regulation of cccDNA transcription.
- Explore the influence of the host on the HBV life cycle.
- Identify new viral targets and strategies, including drugs to prevent resistance.

ICE-HBV Research Priority - Strategy 1

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ICE-HBV 2019 Activities

- NIAID HBV resources repository
- ICE-HBV Open Access Protocols Database
- ***In vivo* models working group and workshop, October 1, Melbourne**
- cccDNA standardization, serum biomarkers, POC diagnostics
- EASL-ICE Think Tank on HBV Cure- Vienna, April
- HBV cure workshop – ANRS, Paris, May 13
- HBV & HIV Cure Forum at IAS, Mexico, July 20-21
- **HBV Public Forum, Melbourne, October 4**
- **HBV Cure Symposium, Melbourne, October 5,**
- HepFree Asia Conference, Hong Kong, November
- HBV elimination messaging & media engagement & scientific workshops

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