

# Global Strategies to Eliminate Hepatitis B (ICE-HBV)

A/Prof Peter Revill

Doherty Institute & ICE-HBV

3 December 2017

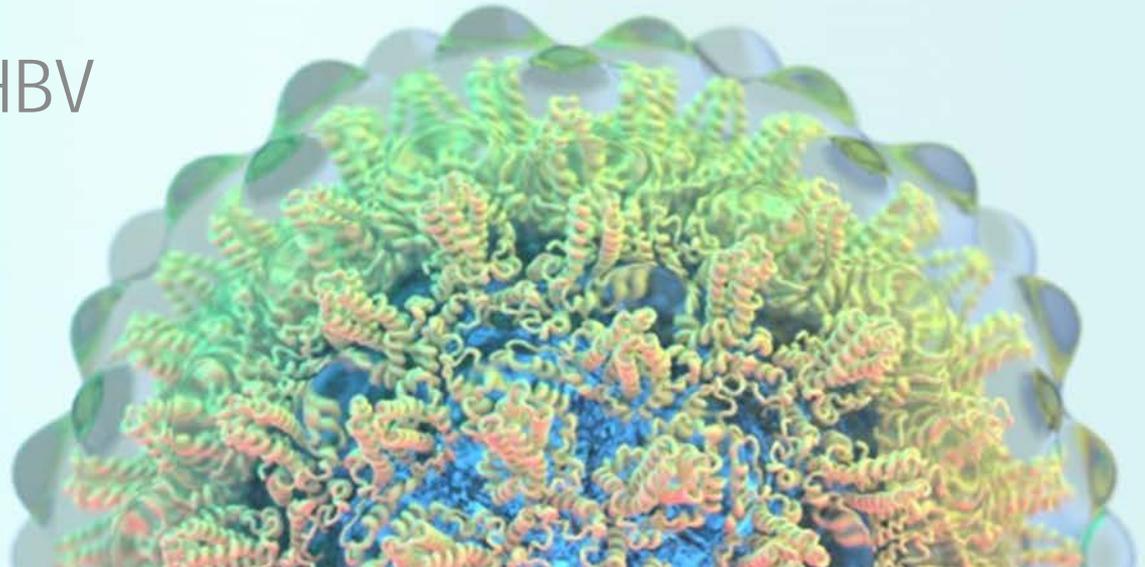


Photo Credit Jason Roberts, VIDRL - Doherty Institute

September 2016

## ANRS + Doherty + International HBV Meeting created ICE-HBV

- **Facilitated the establishment of subgroups for Virology, Immunology, Innovative Tools to define global HBV cure research priorities.**
- **Working with representatives from academia (basic and clinical sciences), industry (through the HBV Forum), research agencies and people affected by CHB.**
- **Defined governance terms of reference and mission statement.**
- **Established a secretariat.**

## ICE-HBV AIM

- **Safe, affordable, scalable and effective cure, available to all persons living with CHB.**

## VISION

- **International, independent, research-based and patient-centred forum**

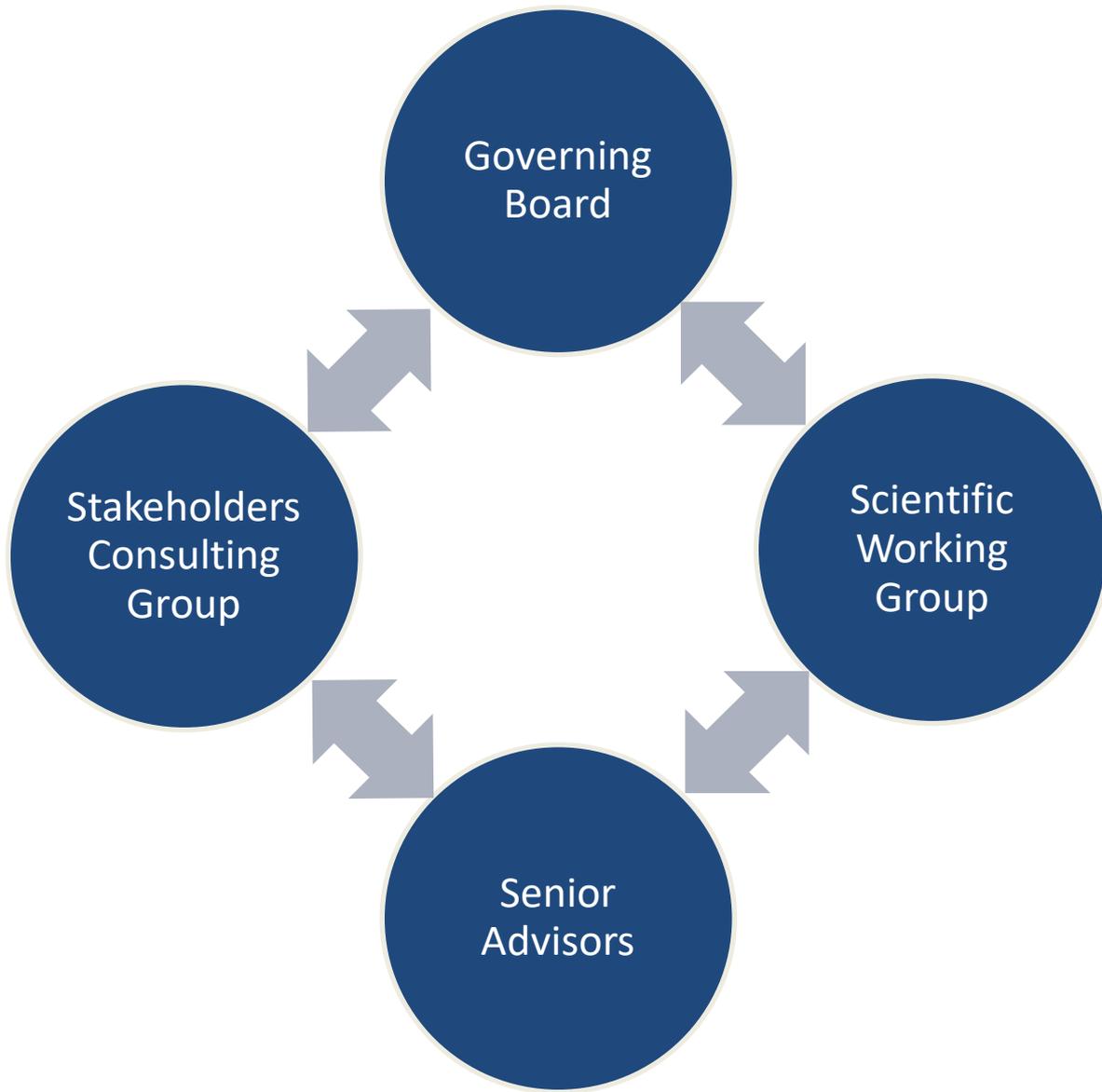
Our 2016 Nat. Med. Gastro. Hep. position paper was highlighted by Nature editors this year

Change the World - One article at a time

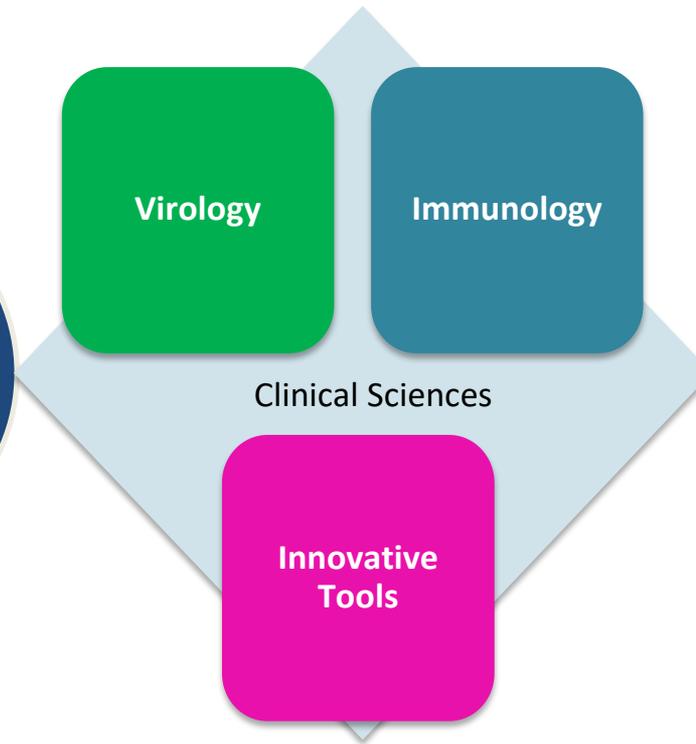
“Browse the following groundbreaking articles nominated by our Editors-in-Chief and read why they believe they could help change the world”.

Global strategies are required to cure and eliminate HBV infection

“This must-read article is a call to action for international efforts to advance scientific research towards a cure for hepatitis B virus infection worldwide.” Nature editors



# STRUCTURE



# Governing Board

- Honorary President Frank Chisari
- Chair Peter Revill (Doherty)
- Co-Chair Fabien Zoulim (ANRS)
- Other Members
  - (New) Joan Block (Hepatitis B Foundation)
  - Massimo Levrero (ANRS)
  - Stephen Locarnini (Doherty)
  - Jake Liang (International HBV meeting)
  - John Tavis (International HBV meeting)
  - Ex-Officio: Capucine Penicaud, Program Manager.

New governance systems designed. Membership to be expanded to representatives from Asia, Africa and Latin America. Gender balance targeted.

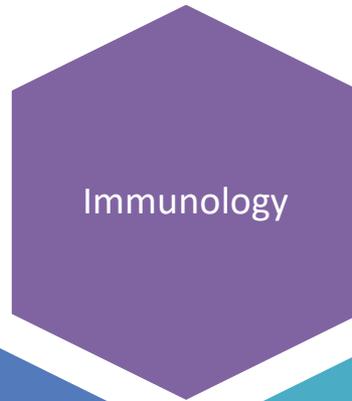
# Senior Strategic Advisors

Chair Professor Emeritus Francis Chisari

- Professor Raymond Schinazi
- Professor Marion Peters
- Professor Christian Brechot
- Membership will be expanded to include Asia, Africa and Latin America.

# Working Groups

**Maura Dandri &  
Haitao Guo**



**Adam Gehring &  
Robert Thimme**

**Jianming Hu &  
Fengmin Lu**



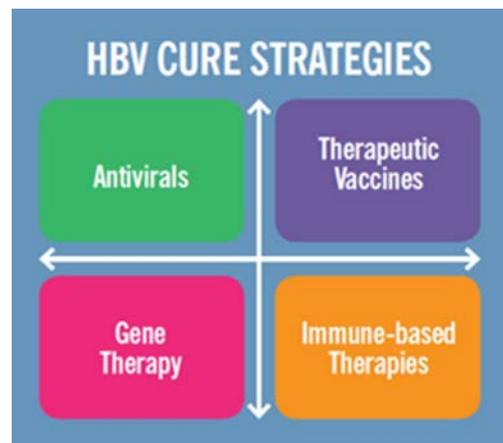
**Harry Janssen, Pietro  
Lampertico & Seng  
Gee Lim**

# Activities - Overview

1. HBV cure scientific strategy development
2. Targeted HBV cure international collaborative research projects:
  - Existing: cccDNA assay standardization + mathematical modelling (new!)
  - TBC: POC diagnostics/assays, new standardization projects and standardized assays networks
  - Implementation science & policy: health policy gaps analysis and cure funding mapping
3. HBV cure research promotion to increase resources for elimination and foster collaborations worldwide.

# HBV cure scientific strategy development

- Producing a joint position paper – a strategic plan for what will be needed to achieve HBV cure, similar to papers published in the HIV field (Deeks *et. al.* Nat. Med. 2016).
- Extensive brainstorming & prioritization process among Working Group members in 2017
- Prioritized the main areas for HBV cure research for immune control and cure



# HBV Cure Research Priorities - Virology

1. Define mechanisms determining HBV infection establishment: from cell entry to cccDNA minichromosome formation, chromatisation and metabolism.
2. Develop standardized methods to study mechanisms of cccDNA minichromosome homeostasis and processes affecting its stability and activity.
3. Understand the relevance and role of circulating viral markers to predict HBV functional cure.
4. Understand the role of HBV DNA integrations in carcinogenesis and in HBsAg production.
5. Improve methodologies for the study of cccDNA metabolism and virus-host interactions.

# HBV Cure Research Priorities - Immunology

1. New methods for *ex vivo* analysis of HBV specific immunity in peripheral blood and liver to better correlate HBV specific immunity with stage of disease and response to antiviral therapy.
2. Determine the relative contribution of different mechanisms to T cell exhaustion, the extent to which HBV-specific immunity can be safely restored and how much restoration is required for HBV cure.
3. Characterise the role of B cells in HBV specific immunity and mechanisms by which HBV escapes the innate immune system.
4. A clearer understanding of the number of infected hepatocytes. Also the relative contribution of cytolytic and non-cytolytic clearance of HBV infected cells induced by the immune response and immunotherapies in the liver.
5. Standardize immune monitoring in clinical trials that needs to be tailored to drug's mechanism of action with appropriate timing and intrahepatic sampling.

# HBV Cure Research Priorities - Tools

- **1. Develop efficient and convenient *in vitro* infection systems**
  - Human hepatocyte-like cells differentiated *in vitro* from embryonic stem (ES) or induced pluripotent stem (iPS) cells:
  - Transplant PHHs and human HLCs into the liver of immuno-deficient mice for expansion, so that progeny human hepatocytes isolated from chimeric mice can then be cultured *in vitro* for HBV infection.
  - organoids
- **2. Develop efficient and convenient *in vivo* model systems,**
  - Immunocompetent mouse models susceptible to HBV infection
  - Non-human “primate” HBV infection animal model:
    - eg Tupaia; hNTCP-Macaques.

# HBV Cure Research Priorities - Tools

- 3. Develop new research assays
  - *In situ*, single-cell, single-molecule, live-cell assays to elucidate the biogenesis, and stability of the cccDNA minichromosome.
  - visualize the localization and trafficking of cccDNA
  - **Omics.** Application of the various state of the art omics approaches (genomics transcriptomics, proteomics, metabolomics, kinomics.) to understand HBV-host interactions that may reveal new targets to clear cccDNA or infected cells.
- 4. Develop convenient and reliable methods to detect cccDNA minichromosome markers.
  - Empty virions (HBcAg), HBcrAg, Serum HBV RNA
- Point-of-care diagnostic tools for hepatitis B, particularly for LMIC.

# HBV Cure Research Priorities - Tools

- 5. Develop new methodologies for cccDNA minichromosome studies
  - 1) **harmonize** the different methodologies used to quantify cccDNA;
  - 2) develop new strategies to improve specificity and sensitivity of cccDNA measurements (i.e. testing new nucleases or using digital PCR procedures)
  - 3) *in-situ* assays of cccDNA should be developed and validated in different labs, as per ICE-HBV working group project with UKE Hamburg, ANRS and DZIF.

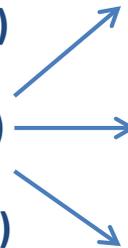
# Concerted harmonization efforts of HBV cccDNA quantification



endorsed by:



Hamburg (M. Dandri lab)  
Lyon (F. Zoulim lab)  
Indianapolis (H. Guo lab)  
Munich (Protzer lab)  
Heidelberg (S. Urban lab)  
Foster City (Gilead)



Jianming Hu (US)  
Peter Revill (AUS)  
Stephen Locarnini (AUS)  
Jake Liang (US)  
Koichi Watashi (Japan)  
Hung-Chih Yang's lab (Taiwan)  
Dieter Glebe (Germany)  
Anna Kramvis (Africa)  
Sofia Perez-del-Pulgar / X. Forns (Spain)

... (Presented by Dr. Lena Allweiss  
HBV meeting, Washington DC, Sep 2017)



# We will facilitate new standardisation projects

- Serum markers (secreted RNA, HBcrAg)
- Cell culture models (iPSCs, organoids)
- New *in vivo* models
- Standardized HBV peptide libraries and tetramers
- POC diagnostics

Let's work together to make this happen!

# Stakeholders' Consultations on Strategic Priorities

4 consultations with 152 stakeholders, 21 countries, 5 continents, 27 companies

- HBV Forum meeting, October 2017, Washington D.C.
- Sao Paulo (World Hepatitis Summit), November 2017
- Australia Stakeholders, 13 November 2017
- Senior Advisors, at HepDART

=> 4-year scientific strategy publication in 2018!

# Let's engage!

ICE-HBV  
International Coalition to Eliminate HBV

CONTACT US SEARCH

ABOUT ▾ HEP B CURE ▾ ACTIVITIES ▾ EVENTS PUBLICATIONS

Over 250 million people worldwide are chronically infected with hepatitis B virus (HBV) and even though a prophylactic vaccine and effective antiviral therapies are available, no cure currently exists.

**How can we cure HBV?**

The ultimate aim of HBV cure regimens should be the eradication of the virus. However, functional cure may be a more realistic goal. A combination of strategies which target the viral replication cycle and enhance the immune response will most likely be required.

**Why do we need to cure HBV?**

The World Health Organization has stated that viral hepatitis is an international public health challenge comparable to other major communicable diseases, including HIV, tuberculosis and malaria. Chronic HBV infection results in 686,000 deaths per year from cirrhosis and liver cancer.

Find out more: [Download our Brochure](#)

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[www.ICE-HBV.org](http://www.ICE-HBV.org)

 [@ICE\\_HBV](https://twitter.com/ICE_HBV)

[info@ice-hbv.org](mailto:info@ice-hbv.org)

# Acknowledgements

## ICE-HBV Governing Board

Frank Chisari

Peter Revill

Fabien Zoulim

Joan Block

Massimo Levrero

Jake Liang

Stephen Locarnini

John Tavis

Capucine Penicaud (Ex-Officio)

## ICE-HBV Scientific Working Groups & Senior Advisors & Stakeholders Group



AUSTRALIAN CENTRE FOR  
HEPATITIS VIROLOGY



Aurelie Pailhe  
Ventzislava Petrov-Sanchez



The logo for the HBV 2019 International Meeting. It features a stylized red and blue graphic on the left, followed by the text "HBV 2019" in a large, bold, purple font, and "INTERNATIONAL MEETING" in a smaller, black font below it.

# HBV 2019

INTERNATIONAL MEETING

- Convenors: Peter Revill and Wenhui Li

- Location:

