THE FORUM
For Collaborative Research℠

Immune Monitoring Working Group

Adam Gehring

Toronto Centre for Liver Disease

Berkeley Public Health

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- **Title:** Immunological biomarker discovery in cure regimens for chronic hepatitis B virus infection
- **Members:**
  - Adam J. Gehring
  - Patricia Mendez
  - Kirsten Richter
  - Hildegund Ertl
  - Eric F. Donaldson
  - Poonam Mishra
  - Mala Maini
  - Andre Boonstra
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Seminar

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Immunological biomarker discovery in cure regimens for chronic hepatitis B virus infection †

Adam J. Gehring[1,2,*], Patricia Mendez[3], Kirsten Richter[4], Hildegund Ertl[5], Eric F. Donaldson[6], Poonam Mishra[6], Mala Maini[7], Andre Boonstra[8], Georg Lauer[9], An de Creus[10], Kathleen Whitaker[11], Sara Ferrando Martinez[12,13], Jessica Weber[14], Emily Gainor[14], Veronica Miller[14]

Summary

There have been unprecedented advances in the identification of new treatment targets for chronic hepatitis B that are being developed with the goal of achieving functional cure in patients who would otherwise require lifelong nucleoside analogue treatment. Many of the new investigational therapies either directly target the immune system or are anticipated to impact immunity indirectly through modulation of the viral lifecycle and antigen production. While new viral biomarkers (HBV RNA, HBcAg, small, middle, large HBs isoforms) are proceeding through validation steps in clinical studies, immunological biomarkers are non-existent outside of clinical assays for antibodies to HBs, HBc and HBe. To develop clinically applicable immunological biomarkers to measure mechanisms of action, inform logical combination strategies, and guide clinical management for use and discontinuation of immune-targeting drugs, immune assays must be incorporated into phase I/II clinical trials. This paper will discuss the importance of sample collection, the assays available for immunological analyses, their advantages/disadvantages and suggestions for their implementation in clinical trials. Careful consideration must be given to ensure appropriate immunological studies are included as a primary component of the trial with deeper immunological analysis provided by ancillary studies. Standardising immunological assays and data obtained from clinical trials will identify biomarkers that can be deployed in the clinic, independently of specialised immunology laboratories.

Keywords: Hepatitis B; clinical trial; immunology; drug development; therapy; viral hepatitis.

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Introduction

As an increasing number of therapeutic approaches involving the immune system are being investigated, individually or in combination treatments, the need for "fit for purpose" immunologic assays and data is urgent. Meeting this challenge requires standardisation of assays across diverse laboratories and collaboration among laboratory experts, immunologists, drug developers, regulators and the HBV research community to validate them for clinical research. A critical first step is to select, integrate and harmonise assays to monitor immune responses, potential immune-mediated toxicity, and target engagement in clinical trials. The Immune Monitoring Working Group of the HBV Forum, a project of the Forum for Collaborative Research, provides a neutral and independent setting to explore the current status and future directions of approaches to monitor immunomodulators in the setting of novel therapies being tested for finite treatment of chronic hepatitis B (CHB).

The purpose of this paper is to provide recommendations for both clinical trial sponsors and immunologists regarding the incorporation of immunological assays into the clinical research setting, where available biospecimens do not always meet expectations for the breadth and depth of analysis. The long-term goal is to standardise these techniques and biomarkers across diverse laboratories so that they will have prognostic or diagnostic value and can be used for the stratification of trial participants, to determine the effectiveness of novel HBV therapies and to guide potential combination therapeutic approaches.

General background

Functional HBV cure can only be achieved through the elimination or silencing of the HBV replication template, covalently closed circular DNA (cccDNA), in infected hepatocytes.[1] The immune system naturally achieves this via the coordinated action of innate and adaptive immune cells. HBV-specific CD4 T cells, CD8 T cells and B cells are critical for resolution of acute infection,[2–4] providing the rationale for the induction of an effective, broad anti-HBV-specific response as a therapeutic

[1]*Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, University Health Network, Toronto, Ontario, Canada;* [2]*Department of Immunology, University of Toronto, Toronto, Ontario, Canada;* [3]*Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404, USA;* [4]*F. Hoffmann-La Roche, Roche Innovation Center Basel, Grenzacher Strasse 124, CH-4070 Basel, Switzerland;* [5]*The Wistar Institute, Philadelphia, PA 19104, USA;* [6]*Division of Antivirals, Center for Drug Evaluation and Research, US Food and Drug Administration, USA;* [7]*Division of Infection and Immunity, University College London, London, UK;* [8]*Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, The Netherlands;* [9]*Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA;* [10]*Janssen Pharmaceuticals, Beerse, Belgium;* [11]*Division of Microbiology Devices Office of In Vitro Diagnostics and*

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