THE FORUM
For Collaborative Research℠

MAPPED Working Group Update

Jordan Feld, *Toronto Centre for Liver Disease*
Michael Biermer, *Janssen Pharmaceuticals*

Berkeley Public Health

Overview

THE FORUM For Collaborative Research℠

- **MAPPED =** Mechanisms of Action and Patient Populations: Emphasizing Diversity
- **Co-Leads:**
  - Michael Biermer, Janssen Pharmaceuticals
  - Jordan Feld, Toronto Centre for Liver Disease
- **Aims:**
  - *Understand relationship between CHB patient heterogeneity and mechanisms of action*
  - *Establish consensus, if any, on clinical development strategies that account for this dynamic*

Matching the right drug to the right population or perhaps more importantly…
Not matching the right drug to the wrong population!

Working Group Members

THE FORUM
For Collaborative Research℠

Academia	Industry	Forum
Jordan Feld Maura Dandri Maurizia Brunetto Jean-Michel Pawlotsky Pietro Lampertico Chloe Thio MF Yuen Soo Aleman Geoff Dusheiko Harel Dahari	Michael Biermer, Janssen Oliver Lenz, Janssen Grace Dolman, GSK Max Lee, GSK Carey Hwang, Vir Patricia Mendez, Gilead Sue Currie, Virion Andy Luber, Virion	Veronica Miller Mitchell Leus

Working Group Approach

THE FORUM
For Collaborative Research℠

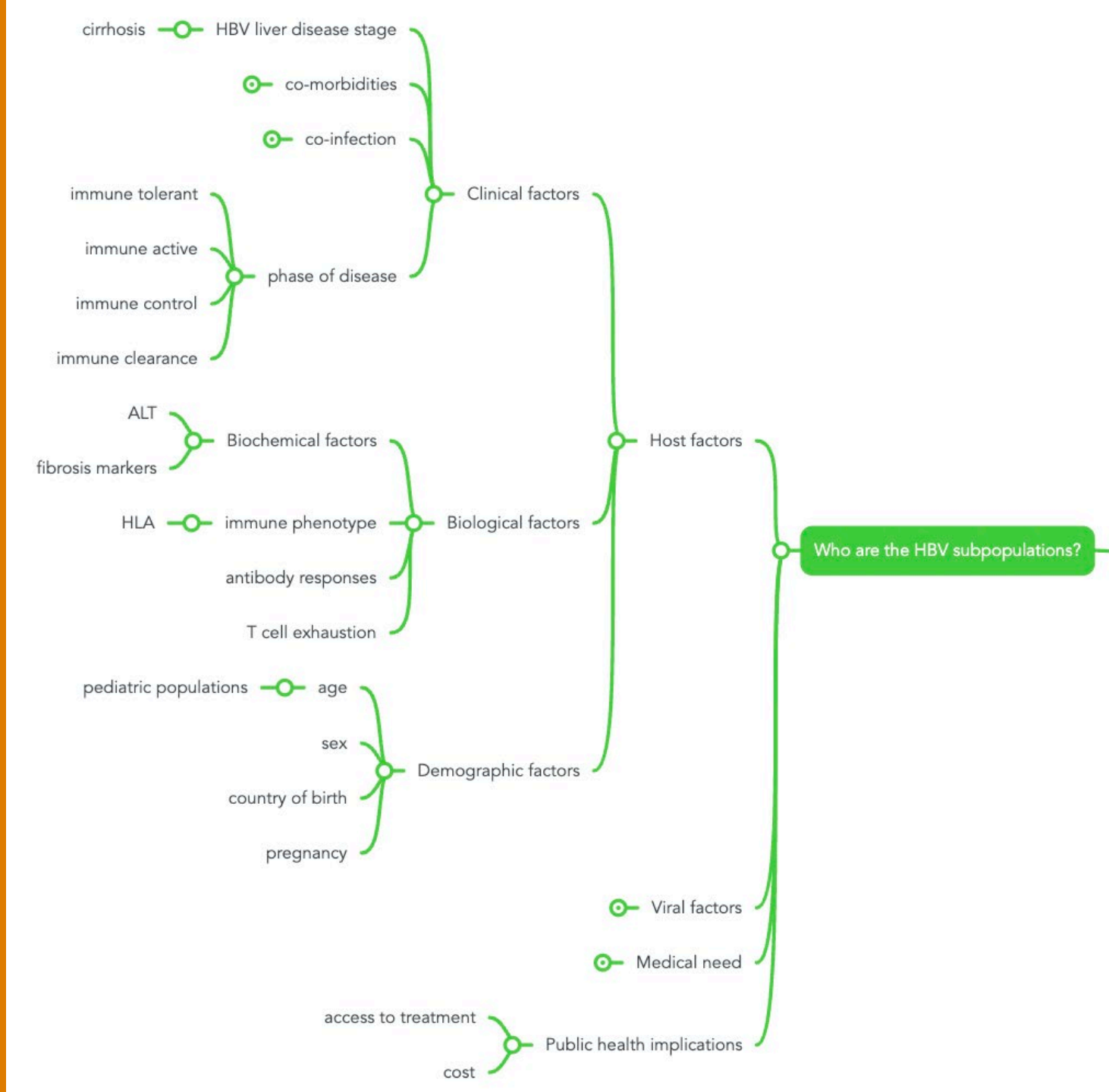
- Convene experts in clinical research and industry
- Utilize “mind-mapping” tool to facilitate discussion
- Began with 4 framing questions
  - Who are the HBV subpopulations?
  - What are the drug classes?
  - Study design considerations?
  - When and how to measure success and failure?

1st Conference Call - March 2023

THE FORUM
For Collaborative Research℠

- Categorized CHB subpopulations:
  - Host factors
    - Clinical factors (phase of disease, co-infection, cirrhosis)
    - Biological factors (biochemical response, immune phenotype)
    - Demographic factors (country of origin, age)
  - Viral factors (viral markers)
  - Medical need (predictors of response, risk/benefit)
  - Public health implications (stigma, quality of life, access to treatment, cost)

Mind Mapping Example



Major Learning:

CHB is highly heterogeneous with an exhaustive list of variables to account for in clinical development.

2nd Conference Call – April 2023

- Trial design considerations for Phase 2 trials
  - Contribution of component
  - Virtual control arms
  - Adaptive population enrichment
  - Master protocols
  - Platform trials
- 2 general clinical development strategies
  - Start with broad study population → narrow based off treatment response
  - Multiple smaller trials in specific subpopulations

Major Learning:

Multiple approaches to Phase 2 trials – pros and cons to each approach.

3rd Conference Call – May 2023

- Key assumptions critical to trial design
  - Types of therapy required – immunological vs virological
  - Groups – phase of disease, on or off NA
  - Endpoints – biomarkers, follow-up time
- Varying degrees of confidence

3rd Conference Call – May 2023

THE FORUM
For Collaborative Research℠

- Examples of assumptions made when designing trials
  - Chance for an HBV specific T-cell response is higher in young/treatment naïve/HBeAg pos. patients
  - Exhaustion of HBV specific T-cells is correlated with duration of infection
  - HBsAg in HBeAg negative is mainly coming from integrants
  - After long term NA treatment majority of infected hepatocytes is transcriptionally silenced
  - Killing of infected hepatocytes is needed to achieve functional cure
  - Stop-Nuc does not work in Asian cohorts
  - You cannot stop NA when HBeAg is positive

Major Learning:

Functional cure trial design necessitates making certain assumptions, with varying degrees of confidence.

Challenges and Lessons Learned

THE FORUM
For Collaborative Research℠

- Critically important consideration for optimal trial design
- Limited consensus – multiple approaches with pros and cons to all
- Many points with limited or inconclusive data…we don't have all the answers!
- Consensus is difficult to achieve - may not be required but some consensus on key assumptions likely to benefit the field as a whole

Panel Discussion

Assumptions and considerations in clinical development programs.