# An immune quantitative network aimed for viral hepatitis B

Eduardo Asín-Prieto[1-2], Zinnia P Parra-Guillen[1-2], José David Gómez Mantilla[1,2,4], Joris Vandenbossche[3], Kim Stuykens[3], Xavier Woot de Trixhe[3], Juan José Perez-Ruixo[3], Iñaki F. Trocóniz[1,2]

(1) Pharmacometrics & Systems Pharmacology Group, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 31008, Spain; (2) IdiSNA, Navarra Institute for Health Research; Pamplona, Spain; (3) Janssen R&D, Beerse, Belgium; (4) *Current affiliation*, Boehringer Ingelheim. Ingelheim am Rhein, Germany

## BACKGROUND AND OBJECTIVES

- The **liver** is a well-known immunotolerogenic environment → liver infectious pathogens persistence such as the **hepatitis B virus** (HBV).
- A good understanding of viral dynamics and its interaction with the **immune system** is essential to identify key biomarkers, potential therapeutic target and predict responses to current or future therapeutic approaches.
- Different efforts have been undertaken to model individual aspects of the immune response and its interplay with the virus[1–3]. However, little has been done to integrate this information into **multiscale QSP models**. The FIRM represents an **integrative effort** of different sub-models in lung immunology[4].

**Aim**: To provide a comprehensive overview and **topological representation** of a model able to characterize the **full immune response against HBV**.

## TOPOLOGICAL REPRESENTATION

The full model has been divided into five interconnected sub-models:

### VIRAL DYNAMICS

- Hepatitis B virus (**HBV**) produce infected hepatocytes (**iHep**) by infecting healthy hepatocytes (**Hep**)
  - ↳ production of **HBV** and viral proteins (**sAg**)
- **Hep** and **iHep** undergo natural death into dead hepatocytes (**dHep**)
  - ↳ production of alanine transaminase (**ALT**) → biomarker of liver tissue damage

### INNATE IMMUNE RESPONSE

- Dendritic cells (**DC**) trigger the immune response by recognition of **HBV**
  - ↳ Plasmacytoid DC (**pDC**), fraction of activated DC (**DC***), produce type I interferon (**IFNα**)
- Natural killer cells (**NK**) are activated by **IFNα**:
  - Cytolytic response by **TRAIL** (**NKtr** cells)
  - Non-cytolytic response by **IFNγ**

### CELLULAR ADAPTIVE RESPONSE

- Cellular response is crucial to eliminate the virus
- After activation of CD8 T cells (**CTL**) by **DC*** (migrating from liver) and proliferation:
  - Inhibition of viral replication by **IFNγ**
  - Enhancement of **iHep** elimination by **TRAIL**
- Specific memory CTL (**CTLm**) remain in order to act in case of re-exposure to the virus
- T cell exhaustion (**CTLex**) by liver environment: high viral load (**HBV**) and tolerogenic interleukins (**IL10** or **TGFβ**). Reversible by proinflammatory signals (**TNFα**)

### HUMORAL ADAPTIVE RESPONSE

- Humoral response helps to eliminate viral components and control viral infection
- After **B** cell activation by **DC*** and proliferation:
  - **IgM** produced by plasmablast cells (**Bpb**)
    - ↓ selection and recombination
  - **IgG** produced by plasmacells (**Bpc**)
  - Specific memory B cells (**Bm**)

### IMMUNOREGULATORY RESPONSE

- Kupffer cells (**KC**, liver resident macrophages) might present a differential phenotype based on liver environment (titres of viral components):
  - Pro-inflammatory (**TNFα**)
  - Tolerogenic (**IL10** and **TGFβ**)
- Regulatory T cells (**Treg**), activated by **DC*** in a **TGFβ** environment, promote tolerogenic response and persistence of viral infection

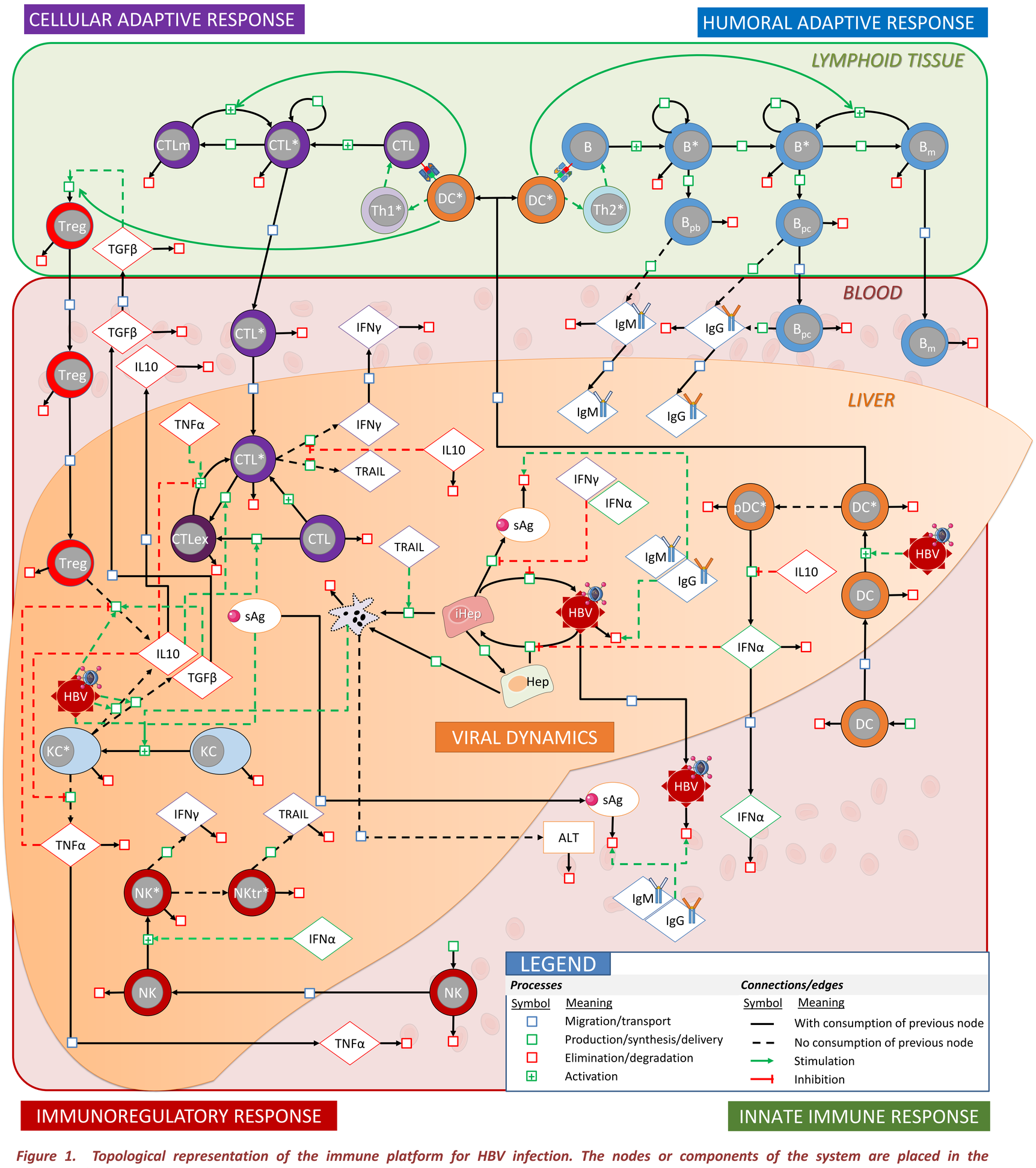


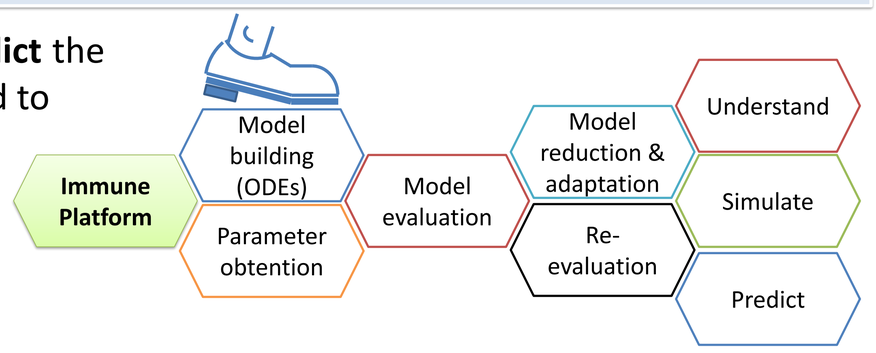

*Figure 1. Topological representation of the immune platform for HBV infection. The nodes or components of the system are placed in the corresponding compartment or physiologic space (lymphoid tissue, blood or liver).*

## CONCLUSIONS

An **immune platform** has been developed, which will be able to help **understand, simulate and predict** the response of and to different therapeutic agents against **HBV**. The resulting immune model can be used to

**(i)** **understand the mechanism of action** of different agents and their effects (in terms of efficacy and safety),
**(ii)** **identify predictive biomarkers** and/or
**(iii)** **optimise dose and dosing regimens and experimental designs** of both in vitro and in vivo studies and clinical trials.

Finally, the developed model has the potential to be extrapolated to other immune diseases.

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