The liver is a well-known immunotolerogenic environment \(\rightarrow\) 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) \(\rightarrow\)
  - 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 (IFNa)
- Natural killer cells (NK) are activated by IFNa:
  - Cytolytic response by TRAIL (NKtr) cells
  - Non-cytolytic response by IFNy

#### 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 IFNy
    - 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 (TNFa)

#### 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 (Bbp)
    - 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 (TNFa)
  - Tolerogenic (IL10 and TGFβ)
- Regulatory T cells (Treg), activated by DC* in a TGFβ environment, promote tolerogenic response and persistence of viral infection

### 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.

### References


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**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).