

A quantitative framework for immune liver diseases: understanding HBV infection



Universidad de Navarra

Eduardo Asín-Prieto^{1,2}, Zinnia P Parra-Guillen^{1,2}, José David Gómez Mantilla^{1,2,4}, Joris Vandenbossche³, Kim Stuykens³, Xavier Woot de Trixhe³, Juan José Pérez-Ruixo³, Iñaki F. Trocóniz^{1,2}

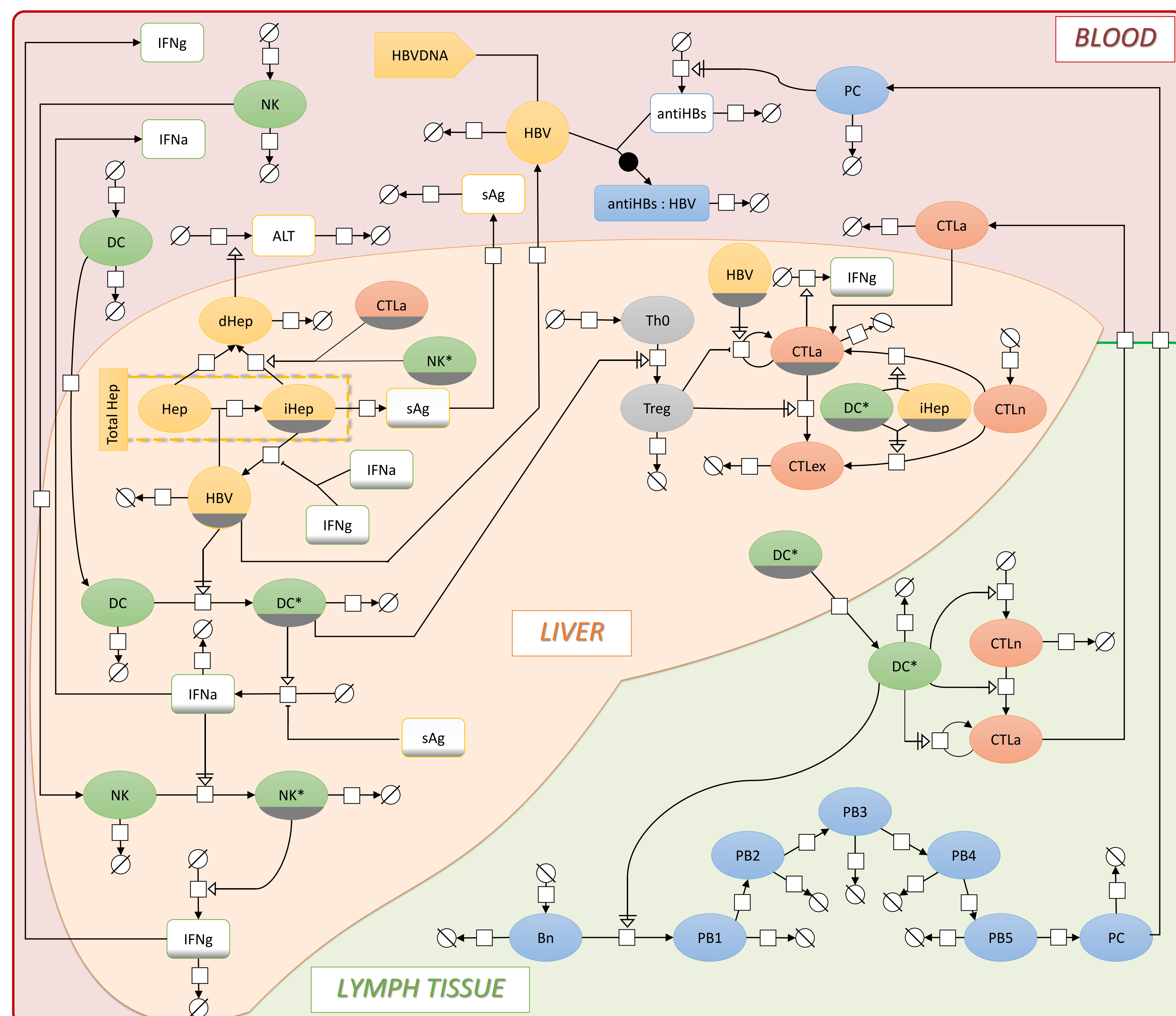
(1) Pharmacometrics & Systems Pharmacology Group, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 31008, Spain; (2) IdiSNA, Navarra Institute for Health Research; Pamplona, Spain; (3) Janssen R&D, Beerse, Belgium; (4) Current affiliation, Boehringer-Ingelheim,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

BACKGROUND AND OBJECTIVE

The **liver** is well-known for its **immunotolerogenic** response, thus providing an adequate niche for the persistence of infectious pathogens such as the hepatitis B virus (HBV) [1]. A **topological model** identifying the key elements of the interaction between the virus and immune system has been previously developed by our group [2].

OBJECTIVE: to build a **multiscale quantitative system pharmacology (QSP) model** to **characterize the immune response against HBV** using literature data.

RESULTS



An **ODE-based model** (35 equations) has been successfully developed from a molecular to organ level.

- The **biological framework** has been divided into **5 sub-models**: **HBV viral dynamics**, **innate immune response**, **humoral adaptive response**, **cellular adaptive response** and **regulatory response**.
- **3 compartments** were identified and all components were located appropriately: **LIVER**, **LYMPH TISSUE** and **BLOOD**.

Figure 1 represents the structure of the model showing the main components identified for each of the sub-models, the nature of the relations between them and the localization in its specific compartment, according to the SBGN notation [3].

The model was able to **reproduce** the HBV-related immune response in terms of **chronology** and **plausibility** of the most relevant component levels during an **acute process**.

Simulations highlight the limited contribution of the innate response to the control of the disease, but its central role triggering the adaptive response, together with the role of the immuno-regulatory system in the establishment of a **chronic infection**.

Figure 1. Topological representation of the quantitative framework for immune liver diseases describing hepatitis B viral dynamics and the immune response QSP model following the Systems Biology Graphical Notation (SBGN) [3] with minor customizations.

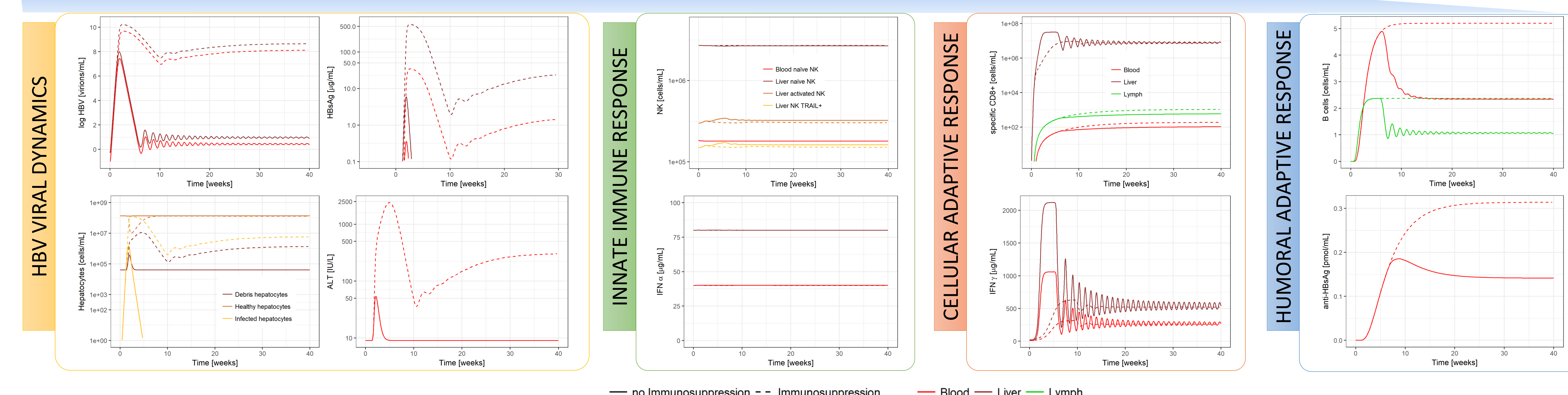


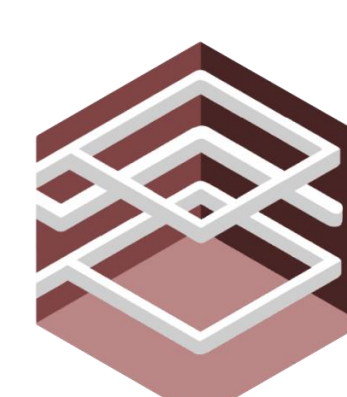
Figure 2. Simulations for the most relevant components of each of the main submodels of the HBV immune response QSP model.

CONCLUSIONS

A **multiscale QSP model** characterising the **HBV immune-related response** has been developed. The model developed provides an adequate quantitative framework to (i) **understand** the role and contribution of the innate, cellular and humoral immune response to the viral eradication, and (ii) **explore** the mechanism of action of different agents and their effects in terms of efficacy and safety.

REFERENCES

- [1] Bogdanos D, et al. Compr. Physiol. 3(2): 567-598, 2013.
- [2] Asin-Prieto et al. PAGE 26 (2017) Abstr 7327.
- [3] Sorokin A, et al. J. Integr. Bioinform. 12(2): 264, 2012.



Pharmacometrics & Systems Pharmacology



www.unav.edu/psp



PHARMACEUTICAL COMPANIES OF Johnson & Johnson

For further information: easin@unav.es

AIM

EXPERIMENTAL DEVELOPMENT

APPLICATION

Immune Platform

Model building (ODEs)

Parameter obtention

Model refinement & evaluation

Model reduction & adaptation

Re-evaluation

Understand

Simulate

Predict