A quantitative framework for immune liver diseases: understanding HBV infection

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Objectives: 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]. The objective of this work is to build a multiscale quantitative system pharmacology (QSP) model to characterize the immune response against HBV.

Methods: Ordinary differential equations (ODE) were implemented in Matlab/Simbiology R2017a using zero-, first-, and second-order processes. Inhibitory and stimulatory effects were integrated using standard pharmacodynamic models. Model parameters were obtained or computed from human in vivo or in vitro studies where the interactions between components had been quantitatively characterized. Data were digitalized using WebPlotDigitalizer v3.8 and analyzed in R v3.3.2 and NONMEM7.3.

Results: An ODE-based model (>30 equations) has been successfully developed from a molecular to organ level. The model was able to reproduce the HBV-related immune response in terms of chronology and plausibility of 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 immunoregulatory system in the establishment of a chronic infection.

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.