PROJECT 1

DoS: Matteo Iannacone

Title: Study the dynamics of HBsAg-specific B cells in mouse model of HBV pathogenesis

Curriculum: BAIO

Link to OSR/UniSR personal page:
https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/dynamics-of-immune-responses.html

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

Hepatitis B virus (HBV) is a noncytopathic, hepatotropic DNA virus with the potential to cause a persistent infection ultimately leading to cirrhosis and hepatocellular carcinoma. It is widely assumed that innate immune responses are poorly triggered by HBV infection, and that cellular and humoral adaptive responses mediate resolution of acute infection. $CD4^+$ T cells promote induction and maintenance of both $CD8^+$ T cells and neutralizing antibodies (nAbs); effector $CD8^+$ T cells contribute to viral clearance by secreting antiviral cytokines and killing infected hepatocytes; nAbs contain viral spread and prevent reinfection. HBV persists in the majority of neonatal/perinatal infections and in a small minority of adult-onset infections, reflecting the failure of one or more of the abovementioned aspects of the immune response. *Dissecting where, when and how adaptive immune cells are activated and differentiate into antiviral or dysfunctional cells is, therefore, of paramount importance to understand HBV pathogenesis*.

Whereas much is known about HBV-specific T cell responses, the lack of reliable techniques to detect and isolate HBV-specific B cells has limited the study of the mechanisms that drive HBV-specific B cell responses. To overcome this problem, our lab developed an HBV-specific B cell receptors (BCR) transgenic mouse, whose B cells specifically recognize the HBV surface antigen (HBsAg). By using these newly generated mice, we found that HBs-specific B cells acquire a germinal centre-like phenotype in the liver, like in second lymphoid organs, and displayed plasma cells features.

The aim of the PhD project will be to investigate where, when and how HBV-specific B cells recognize cognate antigen, become activated and differentiate in antiviral or dysfunctional cells. The cellular and molecular mechanisms, e.g. the involvement of CD4+ T cells or the role of the microbiome, responsible for B cell activation will be also investigated. Finally, the PhD student will study the role of B cells in HBV pathogenesis and define their eventual cross-talk with other immune cells (e.g. HBV-specific CD8+ T cells). The project will combine high-dimensional flow cytometry, single-cell RNA-sequencing analyses, static and dynamic imaging and dedicated mouse models of HBV pathogenesis to provide a comprehensive understanding of B cell responses to HBV.

Skills to be acquired by the student:

Besides becoming proficient in the many techniques required by the research project, the successful student should develop project management and organization skills, learn how to design and interpret experiments, learn how to set priorities, develop excellent writing and oral communication skills, as well as leadership, networking and interpersonal skills.

References (max. 3)

1. De Simone G*, Andreata F*, Bleriot C*, Fumagalli V*, Laura C, Garcia-Manteiga JM, Di Lucia P, Gilotto S, Ficht X, De Ponti F, Bono E, Giustini L, Ambrosi G, Mainetti M, Zordan P, Bénéchet AP, Ravà M, Chakarov S, Moalli F, Bajenoff M, Guidotti LG, Ginhoux F, Iannacone M✉ (2021) Identification of a Kupffer cell subset capable of reverting the T cell dysfunction induced by hepatocellular priming. ***Immunity**, in-press article* (*co-first authors)

2. Fumagalli V*, Di Lucia P, Venzin V, Bono EB, Jordan R, Frey CR, Delaney W, Chisari FV, Guidotti LG#, Iannacone M#✉. Serum HBsAg clearance has minimal impact on CD8+ T cell responses in mouse models of HBV infection. ***J Exp Med**, 217:11* (*first author; #co-last authors)

3. Benechet AP*, De Simone G*, Di Lucia P, Cilenti F, Barbiera G, Le Bert N, Moalli F, Lusito E, Fumagalli V, Bianchessi V, Zordan P, Bono E, Giustini L, Bonilla WD, Bleriot C, Kunasegaran K, Gonzalez-Aseguinolaza G, Pinschewer DD, Kennedy PTF, Naldini L, Kuka M, Ginhoux F, Cantore A, Bertoletti A, Ostuni R#, Guidotti LG#, Iannacone M#✉ (2019) Dynamics and genomic landscape of $CD8^+$ T cells undergoing hepatic priming. ***Nature**, 574:200* (*co-first authors; #co-last authors)