

Thierry Roger – abstract

Harnessing innate immune training to improve sepsis management

Sepsis is one of the leading causes of mortality worldwide. So far, immunotherapies tested in clinical trials have been unsuccessful. Trained immunity refers to the capacity of the innate immune system to recall and adapt to an initial challenge to mount an improved response to a secondary challenge. Contrary to adaptive immune memory, trained immunity is not antigen specific, suggestive of wide-ranging effects. We recently reported that trained immunity confers broad-spectrum protection against bacterial infections. Furthermore, challenging the paradigm that innate immune system-mediated adaptation to infections cannot be inherited, we reported intergenerational and transgenerational transmission of trained immunity conferring heterologous resistance to infections (Ciarlo et al. *J Infect Dis.* 2020; Théroude et al. *Front Immunol.* 2021, Katzmarski et al. *Nat Immunol.* 2021). Deeper understanding of trained immunity could bring invaluable information in the fields of infectious diseases and sepsis. Based on strong preliminary results, our general working hypothesis is that trained immunity has persistent effects, declines with age, and modulates metabolic pathways to protect from sepsis. During this project, we will tackle three aims using preclinical mouse models mastered in the laboratory and through clinical studies: 1) the first aim is to characterize the persistence of trained immunity protecting from lethal infections and to characterize the underlying cellular and molecular mechanisms, 2) the second aim is to define whether the efficacy of trained immunity declines with age, and if so whether this impacts the response to vaccines and infections, and 3) the third aim is to use trained immunity to identify biomarkers and/or metabolic pathways targetable during sepsis. Altogether, this project will generate data essential to our comprehension of trained immunity, and will strengthen our knowledge onto the impact of trained immunity on lethal infections. On the long-term, therapies directed at trained immunity might offer new treatment options to improve vaccine efficacy or normalize dysregulated host responses in sterile and infectious pathologies.