Internship Proposal

Project's title:
Impact of the delay between prime and boost immunization on the dynamics of innate and adaptive immune responses and their interactions.

Supervisor's name:
Anne-Sophie BEIGNON

Welcoming institution and team (short presentation in 10 lines maximum)
The host laboratory is a new research center, ImVA, (directed by Dr Roger Le Grand).

It gathers together more than 100 scientists working on common scientific challenges related to innate and adaptive immunity in the context of viral infections, vaccine development, and regulation of autoimmune disorders.

ImVA is a mixed research unit (UMR1184) involving CEA, INSERM, Université Paris-Sud and a strong partnership with the Institut Pasteur.

Research programs are supported by outstanding technological platforms, inc. *in vivo* imaging, mass cytometry, computational biology, non-human primate models, and pharmacology.

It is located at CEA in Fontenay-aux-Roses. This is close to Paris, about 20 min by public transportation, in the south suburb.

IDOH co-supervisor : (if you have already identified someone, please indicate the name of the IDOH co-supervisor. If not, please let it empty and we (the IDOH Coordinating office) will identify someone) :

Summary of the project (1 page max):
Prime/boost strategies are widely used to increase the frequency of responders among vaccinees and vaccine coverage. They also modulate immunity. However the cellular and molecular mechanisms at play are insufficiently known and understood to allow the rational design of prime/boost vaccination. We study the modes of action of vaccines, especially in the context of prime/boost immunizations, with the ultimate goal to optimize, and even predict, the best time to boost.

Using macaques immunized with the attenuated vaccinia virus, MVA, we analyze the dynamics of innate and adaptive immune responses to a 1st and a 2nd MVA injection,

and their interactions. We also compare different delays between prime and boost and their impacts on innate response at the time of the boost and on secondary memory immune responses.

Our preliminary data showed that the vaccine schedule strongly impacted the quality of the vaccine specific Ab response. Animals boosted early, 2 weeks post-prime, and later, 2 months post-prime, mounted a similar anti-MVA binding IgG response. However, only those boosted later developed specific IgA and Abs showing a neutralizing activity. In addition, we want to compare and contrast memory B cells, inc. vaccine specific B cells, and plasmablasts/plasma cells (PB/PC), as well as TFH, from these 2 groups of animals. Single cell mass cytometry data have already been generated. We have also developed the computational tools to analyze longitudinal mass cytometry data.

The goal of this internship is (1) to complete the comprehensive characterization and comparison of Ab features (*e.g.* affinity, isotype) and Ab functions (beyond neutralization, *e.g.* FcR binding dependent functions) after an early *versus* a later boost; (2) to analyze the dynamics of the primary and secondary B cells and PB/PC responses after an early *versus* a later boost; and (3) to integrate the multi-dimensional analysis of the Ab response with the single cell analysis of B cells and PB/PC.

Supervisor's Significant publications (5 maximum)

1. Palgen JL, Tchitchek N, Elhmouzi-Younes J, Delandre S, Namet I, Rosenbaum P, Dereuddre-Bosquet N, Martinon F, Cosma A, Levy Y, Le Grand R, Beignon AS. Prime and Boost Vaccination Elicit a Distinct Innate Myeloid Cell Immune Response. **Scientific Reports**, in press
2. Gautreau G, Pejoski D, Le Grand R, Cosma A, Beignon AS, Tchitchek N. SPADEVizR: an R package for visualization, analysis and integration of SPADE results. **Bioinformatics**. 2017 Mar 1;33(5):779-781.
3. Elhmouzi-Younes J*, Palgen JL*, Tchitchek N, Delandre S, Namet I, Bodinham CL, Pizzoferro K, Lewis DJM, Le Grand R, Cosma A, Beignon AS. In depth comparative phenotyping of blood innate myeloid leukocytes from healthy humans and macaques using mass cytometry. **Cytometry A**. 2017 Oct;91(10):969-982
4. Platon L, Pejoski D, Gautreau G, Targat B, Le Grand R, Beignon AS, Tchitchek N. A computational approach for phenotypic comparisons of cell populations in high-dimensional cytometry data. **Methods**. 2018 Jan 1;132:66-75.
5. Pejoski D, Tchitchek N, Rodriguez Pozo A, Elhmouzi-Younes J, Yousfi-Bogniaho R, Rogez-Kreuz C, Clayette P, Dereuddre-Bosquet N, Lévy Y, Cosma A, Le Grand R, Beignon AS. Identification of Vaccine-Altered Circulating B Cell Phenotypes Using Mass Cytometry and a Two-Step Clustering Analysis. **J Immunol**. 2016 Jun 1;196(11):4814-31.