ÉCOLE DOCTORALE UNIVERSITÉ PARIS-EST
Sciences de la Vie et de la Santé

Campagne de recrutement 2020

Titre du projet de Thèse
Structural approaches of vaccine antigens to improve T and B cell immune responses induced by the targeting of Langerhans cells Approches structurelles des antigènes vaccinaux pour améliorer les réponses immunitaires des cellules T et B induites par le ciblage des cellules de Langerhans

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Unité / laboratoire d'accueil

Intitulé de l'unité/laboratoire :
Inserm U955 (Institut Mondor de Recherche Biomédicale, IMRB)
Équipe 16 « From Pathophysiology Towards Immune-Based Interventions in HIV Infection ", Labex VRI (Vaccine Research Institute)

Nom du Directeur de l'unité / laboratoire d'accueil :
Jorge Boczkowski / Yves Levy

Contexte scientifique du projet et objectifs (0,5 page maximum)

Arial 11, interligne simple

The main avenue for the development of an HIV-1 vaccine remains the induction of protective antibodies. A rationale approach is to target antigen to specific receptors on dendritic cells *via* fused monoclonal antibodies (mAb). We recently showed that targeting HIV-1 Envelop to mouse skin Langerhans cells (LC) induces the expansion of vaccine-specific B cells, that express germinal center (GC) markers. The development of these immunization strategies in humans requires a better understanding of early immune events driven by human LC. Our *in vitro* investigations revealed that targeted human LC are prompted to induce the differentiation of Tfh cells and activation of naïve and antigen-specific memory B-cells (submitted Ms). Therefore, studies of our group and others strongly suggest that targeting human Langerin appears to be as a promising strategy to bring vaccine antigens to GC and initiate cellular immune responses. Our hypothesis is that structural modifications of the vaccine antigens might improve antigen presentation by LC and functional responses of Tfh and B cells. The PhD student will down-select new and improved HIV-1 envelopes fused with anti-Langerin mAbs and investigate either their processing by *in vitro* cultured human LCs or their immunogenicity in mouse models. This will be done as followed: i) design and production of either monomeric versus trimeric stabilized Envelops or mosaic forms of this antigen, ii) cultures of human LC following procedures of the lab, with immunofluorescent studies of the capture of vaccine candidates by LC, iii) coculture with naïve T cells and memory B cells and immune profiling of activated responses (Flow cytometry, B-cell ELISpot, Luminex and transcriptomics), iv) antiviral functional of produced IgG using in-house produced virus and v) immunization of transgenic mice and study of the GC-B cell reactions. Overall, this program will decipher best-in-class HIV-1 Envelop that will be forwarded to immunological analysis in knock-in mice models expressing a B cell repertoire for testing the generation of broadly neutralizing antibodies. Results will be further assessed by post-doctoral fellows investigating the DC-targeting concepts with surface antigens from emerging virus (SARS-Cov2, Nipah).

Compétences requises du candidat (5 lignes maximum)

Arial 11, interligne simple

The project leader masters with his/her knowledge anti-infectious immunology and/or vaccine development. His/her skills include molecular biology techniques, primary cell culture, and immunological analyzes (polychromatic flow cytometry, ELISpot, ELISA). Experience with mouse immunizations is a plus. While being curious, interactive with members of the lab, the candidate should demonstrate intellectual rigor and good communication skills.

Publications de l'équipe d'accueil de ces 5 derniers années en lien avec le projet (5 publications maximum)

1. Bouteau A, Kervevan J, Su Q, Zurawski SM, Contreras V, Dereuddre-Bosquet N, Le Grand R, Zurawski G, Cardinaud S, Lévy Y & Igyártó BZ (2019) DC subsets regulate humoral immune responses by supporting the differentiation of distinct TFH cells. Front. Immunol. 10: 1–15
2. Cheng L, Wang Q, Li G, Banga R, Ma J, Yu H, Yasui F, Zhang Z, Pantaleo G, Perreau M, Zurawski S, Zurawski G, Lévy Y & Su L (2018) TLR3 agonist and CD40-targeting vaccination induces immune responses and reduces HIV-1 reservoirs. J. Clin. Invest. 128: 4387–4396
3. Zurawski G, Shen X, Zurawski S, Tomaras GD, Montefiori DC, Roederer M, Ferrari G, Lacabaratz C, Klucar P, Wang Z, Foulds KE, Kao S-F, Yu X, Sato A, Yates NL, LaBranche C, Stanfield-Oakley S, Kibler K, Jacobs B, Salazar A, Self S, Fulp W, Gottardo R, Galmin L, Weiss D, Cristillo A, Pantaleo G & Lévy Y (2017) Superiority in Rhesus Macaques of Targeting HIV-1 Env gp140 to CD40 versus LOX-1 in Combination with Replication-Competent NYVAC-KC for Induction of Env-Specific Antibody and T Cell Responses. J. Virol. 91: 1–20
4. Salabert N, Todorova B, Martinon F, Boisgard R, Zurawski G, Zurawski S, Dereuddre-Bosquet N, Cosma A, Kortulewski T, Banchereau J, Lévy Y, Le Grand R & Chapon C (2015) Intradermal injection of an anti-Langerin-HIVGag fusion vaccine targets epidermal Langerhans cells in non-human primates and can be tracked in vivo. Eur. J. Immunol. Dec 17: 1–40
5. Epaulard O, Adam L, Poux C, Zurawski G, Salabert N, Rosenbaum P, Dereuddre-Bosquet N, Zurawski S, Flamar A-L, Oh S, Romain G, Chapon C, Banchereau J, Levy Y, Le Grand R, Martinon F & Lévy Y (2014) Macrophage- and Neutrophil-Derived TNF- Instructs Skin Langerhans Cells To Prime Antiviral Immune Responses. J. Immunol. 193: 2416–2426