Internship proposition

(One-page max)

Master 2 GP Medicine 4R (Repair, Replace, Regenerate, Reprogram)

Lab: TaRGeT, INSERM UMR 1089

Team: Next Generation Disease Models

Name and position of the supervisor: Jean-Baptiste Dupont, chercheur ATIP Avenir

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Candidate (if internship filled): Ninon Carlet

Title of the internship: Development of immunocompetent skeletal muscle organoids for the prediction of anti-AAV immune responses in gene therapy protocols

Summary of the internship proposal:

Gene therapy using recombinant adeno-associated viral vectors (rAAV) promises to become one of the most widespread biomedicine strategies in the coming years, for a wide range of diseases, particularly neuromuscular diseases. Although these innovative biotherapies have demonstrated their efficacy and great therapeutic potential, there are still scientific and technological hurdles to be overcome in terms of their immunogenicity. Since the switch from local injections to systemic injections with increasing doses of vector, adverse reactions linked to activation of the immune system have been reported in patients, leading in some cases to the suspension of clinical trials. These effects had not previously been described in preclinical study models. These effects had not previously been described in preclinical study models. Several types of immune response have been reported in gene transfer protocols when they are transposed from animal models to the patient: (i) non-specific innate immunity linked to recognition of the vectors as 'modified viruses', and (ii) the adaptive immune response specific to the capsid and/or the transgene product. To better characterize these phenomena and develop innovative immunomodulation strategies, new preclinical models reproducing the adverse reactions observed in patients are urgently required. In particular, organoids derived from induced pluripotent stem cells (iPSCs) offer the advantage to come directly from the patients, reproduce structural and functional features of given tissues, and to be used in high-throughput screening experiments. Our lab has initiated a global effort to develop a preclinical gene therapy testing platform based on hiPSC-derived organoids as a complement to *in vivo* experimentation. In this context, the main purpose of the internship is to generate skeletal muscle organoids populated with human peripheral blood mononucleated cells (PBMCs) from donors seropositive for specific rAAV serotypes. This will be used to investigate the impact of the different immune cell populations on rAAV transduction efficiency, and on the structure and function of skeletal muscle organoids.

Profile(s) linked to the project:

☑ Experimental Biology *(Recherche expérimentale)*

☐ Clinical Research *(Recherche clinique)*