

Lab: TaRGeT, INSERM UMR 1089

Team: Immunology

Name and position of the supervisor: Malo Journou, Postdoctoral Researcher Nantes Université

Email of the supervisor: malo.journou@univ-nantes.fr

Candidate (if internship filled): NA

Title of the internship: Genome engineering of recombinant adeno-associated virus to evade the immune system.

Summary of the internship proposal:

Gene therapy offers innovative techniques for treating genetic disorders. Recombinant adeno-associated virus (rAAV) is a key tool, demonstrating high efficiency in gene delivery and maintaining long-term expression in organs such as the liver, heart and skeletal muscle. Successful preclinical and clinical studies have led to FDA and EMA approvals of rAAV-based therapies. However, systemic administration of high doses can induce non-specific innate immune responses, largely due to recognition of the capsid and vector genome, as well as adaptive immune responses targeting the capsid and/or transgene product. In particular, activation of TLR9 pathway by recognition of CpG-rich regions in the transgene, including the inverted terminal repeats (ITR), has been associated with the activation of the immune response. This response has been associated with elevated liver transaminases and loss of transgene expression in some patients. Improvement of AAV vectors is essential to reduce these immune responses. The project will focus on the depletion of CpG-rich regions in the ITR, promoters and transgenes and to test these modified transgene constructs in vitro and evaluate their impact on immune responses in rodents.

Techniques: cloning (bacterial culture, enzymatic digestion, gel electrophoresis, ligation), cell culture, plasmid transfection, flow cytometry.

Profile(s) linked to the project:

- ☒ Experimental Biology (*Recherche expérimentale*)
- ☐ Clinical Research (*Recherche clinique*)