PhD Studentship - Evaluation of the integration profile of AAVs to develop next generation vectors with improved persistence and safety profile

Whitelab Genomics / INSERM U951 Genethon

Description:

The recent FDA approvals of gene therapies for rare eye and motor neurons genetic diseases are just an example of how adeno-associated virus (AAV) vectors are dramatically changing patients' lives. Rare metabolic conditions are another category of diseases that attracted the utmost attention. Early reports of liver gene transfer in preclinical models indicated long-term stability of gene transfer. While in haemophilia B patients, 10-year gene transfer stability was reported, these results were only partially confirmed in haemophilia A where reduced efficacy was reported at long-term. These results suggest that disease-specific conditions may affect the AAV genome stability in hepatocytes and are associated with reduced persistence. Random integration is another consequence of long-term persistence of AAV vector genomes and may represents an underestimated risk.

This project aims at the consolidation of the knowledge existing on the molecular signatures of long-term persistence of AAV vectors in the host nuclei in healthy and diseased liver. Specifically, persistence, genome integrity of the AAV vector and random integration will be assessed using state-of-the-art and in-house developed NGS assays. The generated experimental results will be integrated into a biological knowledge graph and artificial intelligence algorithms will be harnessed to identify and overcome the limitations of the technical approaches used in the past for this purpose, and to improve AAV vector selection/generation. Genetic animal models of liver disease, available at the host laboratory will be used to evaluate how transgene expression stability is affected by hepatocyte metabolism impairment. The knowledge accumulated during this project will be used to create next-generation transgene expression cassette for AAV gene therapy approaches with improved persistence and reduced insertional risk. Importantly, this new generation of vectors, will represent a unique tool to address both genetic and diet-induced metabolic diseases associated with liver degeneration, a crucial medical need in developing countries.

Person specification: Applicants must hold a Master's degree in biology/bioinformatics. Experience with gene therapy and/or genomic integrations of vector genomes in the host is a significant advantage.

Closing Date and Start Date: November 2020

Value of award: Funding for the PhD fellowship is provided through the ''Paris Region PhD 2020'' program.

Eligibility: No eligibility criteria

Contacts: Prospective candidates are strongly encouraged to email Dr. Julien Cottineau jcottineau@whitelabgx.com, Dr. Kevin Cheeseman kcheeseman@whitelabgx.com and Dr. Giuseppe Ronzitti giuseppe.ronzitti@inserm.fr. Please attach your CV, full transcript of results (listing all subjects taken and their corresponding grades/marks) and a cover letter stating how the project meets your research interests.