Internship proposition 2026-2027

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

Lab: TaRGeT UMR1089 Translational Research in Gene Therapy
Team: Génétique Humaine

Name and position of the supervisor: Yannick LE DANTEC (INSERM Research engineer)
Email of the supervisor: yannick.ledantec@univ-nantes.fr

Candidate (if internship filled):

Title of the internship: Development of a *trans*-splicing pre-mRNA for POIKTMP associated with dominant-negative variants.

Summary of the internship proposal:
Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP) is a rare multisystemic disorder caused primarily by dominant missense pathogenic variants clustered within the fourth and final exon of the *FAM111B* gene (Mercier et al. 2013; Mercier et al. 2015; Vignard et al. 2025).
Recent transcriptomic, proteomic, and functional analyses have confirmed the central role of FAM111B in regulating protein homeostasis through its association with a large ubiquitin-proteasome system (UPS)-type protein complex (Vignard et al. 2025). Under pathological conditions, decreased FAM111B expression leads to dysregulation of pathways related to cell signaling and cytoskeletal dynamics, as well as increased expression of type I interferon-induced genes (Vignard et al. 2025).
One of the therapies being considered is the use of post-transcriptional editing of *FAM111B* gene transcripts via *trans*-splicing of pre-messenger RNA (pre-mRNA). The effectiveness of this approach, which allows for the selective correction of pathogenic *FAM111B* variants responsible for POIKTMP, depends on the identification of an antisense binding domain for the mutated endogenous pre-mRNA. A preliminary screening of binding domains is currently underway in the laboratory using a fluorescent reporter minigene assay (Murauer et al. 2013). The best candidate selected will subsequently be fused to the wild-type (WT) version of the exon to be replaced in order to restore protein expression and function.
In the short and medium term, the objectives will be to establish mechanistic, structural, functional, and safety proofs of concept for the *trans*-splicing of *FAM111B* transcripts in patient-derived fibroblasts, muscle organoids, and a mouse model of the disease. These proofs of concept will provide the necessary foundation for clinical translation.

Mercier, S, S Kury, E Salort-Campana, et al. 2015. Expanding the clinical spectrum of hereditary fibrosing poikiloderma with tendon contractures, myopathy and pulmonary fibrosis due to FAM111B mutations. Orphanet J Rare Dis 10:135.

Mercier, S, S Kury, G Shaboodien, et al. 2013. Mutations in FAM111B cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis. Am J Hum Genet 93:1100-1107.

Murauer, EM, U Koller, S Hainzl, V Wally, JW Bauer. 2013. A reporter-based screen to identify potent 3' trans-splicing molecules for endogenous RNA repair. Hum Gene Ther Methods 24:19-27.

Vignard, V, M Maillasson, A Bigot, et al. 2025. Ubiquitin-proteasome system dysregulation in FAM111B-related poikiloderma and phenotypic spectrum expansion: new case reports and long-term follow-up. EBioMedicine 119:105864.

Profile(s) linked to the project:

X Experimental Biology *(Recherche expérimentale)*
☐ Clinical Research *(Recherche clinique)*
☐ Research in data analysis (Recherche en analyse de données)