Master Biologie Moléculaire et Cellulaire 'BMC',
Université Paris Cité - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
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Fiche de Projet de Stage de M2, 2026-2027

Unité INSERM ou CNRS ou Université : INSERM, UVSQ **Intitulé Equipe :** UMR 1357 IMPROVE- « Innovation thérapeutique : de la physiopathologie à l'appliqué dans les pathologies neuro-Musculaires, la rePROduction et le deVÉloppement » **ED d'appartenance :** ED577 – Structure et Dynamique des Systèmes Vivants (Paris Saclay)	**Responsable de l'Equipe :** Aurélie Goyenvalle, PhD, DR Inserm **Responsable du Stage :** Julien Dang, MD, PhD, Praticien Hospitalier Universitaire Service de Néphrologie – CHU Ambroise Paré – APHP **Contacts** Adresse : UFR des sciences de la santé, 2 Avenue de la source de la Bièvre, 78180 Montigny le Bretonneux Email : julien.dang@aphp.fr Tel : 01 49 09 57 11

Titre du projet : Exploring Exon-Skipping Antisense Oligonucleotides (AONs) as a Novel Therapeutic Strategy for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)
The research conducted in our laboratory focuses on developing innovative antisense-based strategies targeting mRNA modulation as potential treatments for neuromuscular and kidney diseases. In particular, our lab has pioneered the use of AAV vectors to mediate exon skipping as a therapy for Duchenne muscular dystrophy (DMD). Antisense strategies show great promise for the therapeutic correction of a variety of genetic disorders. However, they have yet to reach their full potential in the field of nephrology. In this project, we will investigate the therapeutic potential of this exon-skipping strategy (ESS) in Autosomal Dominant Polycystic Kidney Disease (ADPKD). ADPKD is the most common hereditary kidney disease, affecting 1 in 1,000 individuals. It is most often caused by a loss-offunction mutation in the PKD1 gene (70% of cases), which encodes polycystin-1 (PC1). These mutations lead to the formation of numerous large renal cysts that progressively destroy the renal parenchyma, ultimately accounting for 8% of end-stage renal disease cases. Recent data suggest that the loss of the C-terminal portion of PC1 is particularly critical in disease pathogenesis. Its restoration in mice with a bi-allelic, inducible Pkd1 deletion in the renal tubule was sufficient to reduce cyst formation and preserve kidney function. More than 60% of the mutations identified in PKD1 are truncating, leading to the loss of the C-terminal region and a more severe phenotype. We hypothesize that ADPKD could be amenable to an innovative ESS approach using AONs which, as demonstrated in DMD, would produce a shortened but functional form of PC1 by restoring the reading frame and enabling expression of its C-terminal region. Our objective is to establish proof of concept for ESS in a tubule-on-chip model of cystogenesis, using human kidney cyst–derived cell lines from ADPKD patients carrying truncating PKD1 mutations. In this project, the student will employ a wide range of techniques, including cell culture, transfection, RNA extraction, RT-qPCR, western blotting, immunocytochemistry, cell viability and proliferation assays, and others.

Publications de l'équipe relatives au projet de stage (max 5)

1. Blitek M, Gastaldi C, Doisy M, Le Coz O, Tensorer T, Garcia L and Goyenvalle A. The Combined 20-hydroxyecdysone and antisense-mediated exon-skipping improve functional outcomes in a mouse model of Duchenne muscular dystrophy. Nucleic Acid Ther. 2025 2025 Feb 17. doi: 10.1089/nat.2024.0085.
2. Phongsavanh M, Bizot F, Saoudi A, Gastaldi C, Le Coz O, Tensorer T, Brisebard E, Garcia L, Goyenvalle A. Valproic Acid Improves Antisense-Mediated Exon-Skipping Efficacy in mdx Mice. Int J Mol Sci. 2025 Mar 13;26(6):2583. doi: 10.3390/ijms26062583
3. Ferlini A, Goyenvalle A. and Muntoni F. RNA-targeted drugs for neuromuscular diseases. Science 2021 Jan 1;371(6524):29-31.
4. Relizani K, Griffith G, Echevarría L, Zarrouki F, Facchinetti P, Vaillend C, Leumann C, Garcia L and Goyenvalle A. Efficacy and safety profile of tricyclo-DNA oligonucleotides: promising tools toward an antisense therapy for Duchenne muscular dystrophy. Mol Ther Nucleic Acids. 2017 Sep 15;7:144-157.
5. Goyenvalle A, Griffith G, Babbs A, ELAndaloussi S, Ezzat K, Avril A, Dugovic B, Chaussenot R, Ferry A, Voit T, Amthor H, Bühr C, Schürch S, Wood MJA, Davies KE, Vaillend C, Leumann C et Garcia L "Functional correction in muscular dystrophic mice using splice-switching tricyclo-DNA oligomers." Nat. Med. 2015 Mar;21(3):270-5.