PhD thesis proposal

Rational development of small molecule splicing modifiers.

Project description: Specific mRNA splicing correction using small molecules is an emerging field of drug discovery which has already provided innovative therapeutic applications in the context of inherited diseases. In the context of Spinal Muscular Atrophy (Naryshkin NA., Science 2014) and Huntington's disease (Bhattacharyya A., Nat. Comm. 2021), the small molecule acts as a molecular glue between the first particle of the spliceosome and an A_{-1} bulged 5'-splice site to promote specific splicing correction. Even if the mechanism of action of the first small molecule splicing modifiers was elucidated (Campagne S. *et al.*, Nat. Chem. Biol. 2019; Malard F. *et al.*, Nucleic Acids Research 2024) and the concept of 5'-splice site bulge repair was discovered, there are still some open questions to fully understand the gene selectivity of splicing modifiers targeting an A_{-1} bulged 5'-splice site (Ishigami Y. et al., Nature Comm. 2024). In this context, we are looking for a motivated PhD candidate to decipher the molecular details of small molecules RNA interactions in the context of specific splicing correction. During this part of the PhD thesis, the candidate will determine the structure of already known small molecule splicing modifiers bound to specific RNA helices and will investigate the effect of divalent ions on these interactions. Known small molecule splicing modifiers are active on A_{-1} bulged 5'-splice sites and brought novel therapeutic solutions in the context of Spinal Muscular Atrophy and Huntington's diseases. However, mutations at the position -1 into C or U also trigger human diseases. In this context, the PhD candidate will also participate to the group project aiming at diversifying the pool of small molecule splicing modifiers and will discover using state-of-art AI-powered methods novel splicing modifiers acting on U_{-1} and C_{-1} bulged 5'-splice sites. Since many diseases originate from mutations falling at the position -1 of the 5'-splice sites, the overall aim of the project is to further explore the fundamental basis of the small molecule splicing modifier gene specificity but also to rationally design new tools for biomedicine. This PhD project is funded by the ANR EpiCor (to S.C. and JM.C.) and the expected starting date is in Autumn 2025.

Expected candidate's profile: We are seeking for an excellent student who is willing to work at the interface between chemistry, biochemistry, drug discovery, genetics and structural biology in a young and dynamic group of research. Previous experience in structural biology, genetics or bioinformatics will be a nice add-on.

Working environment: The project will be performed in the European Institute for Chemistry and Biology (IECB, Bordeaux) in the SMaRT group (Structure, Mechanism and RNA therapeutics, https://rna-smart.com) under the supervision of Dr. Sébastien Campagne (PI) and Dr. Florian Malard (Postdoc). The SMaRT group is affiliated to the ARNA laboratory (https://arna.cnrs.fr), a structure supported by INSERM, CNRS and University of Bordeaux. The project will be performed in a collaboration with the group of Pr. Jean-Marc Campagne (ENSCM, Montpellier) who's is holding the organic chemistry expertise. The PhD candidate will be embedded in the Sciences de la Vie et Santé (SVS) doctoral school of the University of Bordeaux.

Start date: September/October/November 2025; Duration: 36 months;

How to apply: Send your CV, a cover letter and one or two reference letter(s) to sebastien.campagne@inserm.fr