PhD in Medicinal Chemistry/Chemical Biology

ANR FUNDED PROJECT

Titre: RNA targeting for the treatment of Fragile-X syndrome: target validation toward future drug discovery

Key words: RNA, RNA ligands, non-coding RNAs, binding, inhibition

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Host laboratory: Université Côte d'Azur – Institute of Chemistry of Nice in collaboration with Institut de pharmacologie Moléculaire et Cellulaire in Sophia Antipolis.

Project: Neurodevelopmental disorders represent a major public health burden since these diseases result in lifelong cognitive and behavioral deficits. Among them, fragile X syndrome (FXS) is the most common form of inherited intellectual disability (ID) and the leading monogenetic cause of Autism Spectrum Disorders (ASD). FXS is caused by the absence of expression of the Fragile X Messenger Ribonucleoprotein 1 (FMR1) gene, which ultimately leads to the lack of the encoded Fragile X Messenger RibonucleoProtein (FMRP). This latter usually binds to G-quadruplex structures in mRNA and regulates translation of protein targets. Given the absence of any treatment for FXS and the lack of relevant targets, we propose to validate G-quadruplexes in mRNAs as original and promising targets for synthetic RNA binders. To this aim, we will start from previously identified hits, confirm their molecular mechanism of action inside cells using target engagement experiments and increase their biological activity through medicinal chemistry optimization. The most active compounds will then be studied in vitro and in vivo using cellular and animal models mimicking FXS disorder. The main expected result from the development of this project is the validation of RNA G4 targeting approach as a potential treatment for FXS. The most active compounds could represent the first leads that would be further developed toward new drugs against this incurable disease.

Candidate profile: the candidate must have a sound knowledge of organic chemistry, and must have obtained his/her M2 in organic chemistry, medicinal chemistry or chemical biology within the last 2 years. Candidates must also be highly motivated and interested in projects at the chemistry-biology interface.

To apply: send a CV (with contacts of previous supervisors), Master grades and ranking and a cover letter describing your scientific interests and career plans, in English or French, to maria.duca@univ-cotedazur.fr

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