Thesis title : Design of prodrugs of antiviral molecules targeting the central nervous system to treat neurotropic viruses

Proposition : Dr. Karine ALVAREZ
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Team : Replicases Virales : Structure, mechanism and Drug-design (Dir : Dr Bruno Canard).
Thematic Group : Antiviral Medicinal Chemistry, led by Dr Karine Alvarez.
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Keywords : Medicinal chemistry, antivirals, prodrugs, nucleotide analogues, metabolism.

Background to the study:
Viruses responsible for neurological disorders, such as certain Bunya- Corona- or Flaviviruses, are a real public health problem due to the lack of effective antiviral molecules. Neurologically-tropic viral infections are the most difficult to treat, and therapeutic developments are hampered by the problem of delivering the antiviral to the central nervous system (CNS). Nucleotide analogues (NAs) are the main therapeutic arsenal used clinically to treat viral infections, although their delivery to the brain is limited by the passage of the blood-brain barrier (BBB) and the blood-cerebrospinal barrier (BCSFB). Although the delivery of AN to the CNS has been improved by the study of metabolizing enzymes, endogenous cellular transport systems, and the synthesis of conjugates, chemical delivery devices and prodrugs, it is still insufficient. In the current context, there is an urgent need to propose solutions for the design of a new generation of CNS-targeted AN prodrugs. The approach is based on the study of AN distribution, metabolism and physico-chemical properties, in order to better understand the therapeutic challenge of delivering them to the brain.
This multi-disciplinary project covers several areas, two of which will be developed within the framework of this thesis project.

Missions :
One is linked to the study of the metabolism[1] of several antiviral molecules of the NA type, repositioned on Bunya- Corona[2]- and Flavivirus[3] infections, which have shown therapeutic interest and whose understanding will be a major asset for the design of improved ANs. The other axis is linked to the rational design, synthesis and study of new ANs prodrugs to improve CNS targeting.

1) Chazot A. et al. In Review Plos Biology, 2024. The activation chain of the broad-spectrum antiviral Bemnifosbuvir at atomic resolution. 2) Shannon A. et al. NAR, 2023, DOI: 10.1093/nar/gkad1194. An exonuclease-resistant chain-terminating nucleotide analogue targeting the SARS-CoV-2 replicase complex.3) Feracci M. et al. Antivir Res, 2023, DOI:10.1016/J.antiviral.2023.105574. AT-752 multiple sites and activities on the dengue virus replication enzyme NS5.

Candidate profil :
With an engineering or Master's degree, the candidate should have a strong background in organic synthesis (medicinal chemistry), with a motivation to tackle complementary drug-design disciplines such as biophysics, biochemistry and crystallography.

Hosting conditions :
The AFMB laboratory is fully equipped to carry out the project. The team has strong expertise in the synthesis and study of nucleotide analogues targeting viral polymerases (see most recent references 2 and 3). Tools are already in place to study metabolism[1] (enzyme production, analytical monitoring,

crystallogenesis platform). For the synthesis axis, a chemistry laboratory and characterization tools are available. The project will benefit from collaborations in the evaluation of compounds in adapted cellular and animal models.

How to apply :

The offer is posted on the Ecole Doctorale des Sciences Chimiques de Marseille ED-250 website (https://ecole-doctorale-250.univ-amu.fr/fr/sujets-concours-2024).

The application must be returned as soon as possible, for selection of the candidate by May 15 and participation in the Doctoral School competition on May 28 and 29, 2024.

The application must include the following information:

- CV
- Letter of motivation
- E-mail addresses of two referees
- M1 and M2 transcripts (S1 transcript if available)
- Copy of diploma authorizing registration (certificate to be provided at a later date)