Development of PROTAC molecules to treat parasitic diseases

M2 Internship (6 months)

Scientific context

The global prevalence of nematode infections in humans and animals causes severe diseases and agricultural losses, posing substantial health and economic challenges. Current treatments are based on anthelmintic drugs, whose efficacy is compromised by the emergence of drug-resistance, with no alternatives expected soon. The project's originality lies in the choice of targeting nuclear receptors (NRs) regulating infectious processes in several parasitic nematodes. Inhibiting NRs would block the infective larval stage, preventing the parasite from settling in its host. No existing drugs specifically target this critical stage, making NRs an unprecedented and promising therapeutic target, distinct from current anthelmintic approaches, to prevent infection by parasitic nematodes in humans and animals. The project is based on our discovery of an interactant with high specificity and affinity to NRs from several parasitic nematodes, that will serve as a lead compound for the development of NRs degraders using the innovative PROTAC technology. PROTACs are heterobifunctional molecules composed of a ligand recruiting the target protein (the NR) and another binding to an E3 ubiquitin ligase (e.g. VHL that is conserved in mammals and parasitic worms), connected by a linker. This proximity induces the ubiquitination of the target protein, leading to its proteasomal degradation.

Objectives

The M2 student will participate to the synthesis of two to three PROTAC molecules in the IBMM team.
The M2 student will be in charge of the production of the ligand binding domain (LBD) of the NRs of interest and the VHL protein in complex with Elongins B/C in bacterial system and their purification using the AKTA systems available at the CBS, using the established protocols.
The student will conduct a series of biochemical and biophysical experiments to study the interaction of these proteins from different parasitic nematodes with project-developed PROTAC molecules, either in binary and ternary complexes. This will provide a great opportunity to learn different techniques, such as thermal shift assay, fluorescence anisotropy, and isothermal titration calorimetry. All the methods are available at the CBS.
Additionally, the student will be involved in the crystallographic aspect of the project, aiming to determine the tri-dimensional structure of the ternary complex involving the LBDs, the VHL complex and a PROTAC molecule, or the binary complexes (LBD-PROTAC and VHL-PROTAC), thanks to the crystallization facility of the CBS. The student will be mainly involved in the crystallogenesis part.
Last but not least, this training experience could also provide a pathway for the student to be further involved in the project through a PhD (an ANR funding is available).

Supervision

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Skills required

Knowledge of biochemistry and possibly protein crystallography, modelling or organic synthesis

Collaborations

R. Betous (INTHERES, Toulouse) for cellular assays
C. Martin (MNHN, Paris) for in vivo testing