Applicazione per Nuovo Assegno di Ricerca

Titolo: In silico studies of PROTACS directed to trypanothione reductase enzyme

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Progetto di ricerca

Background

The activity planned for this research project is part of the FISR2019_03796 project entitled: "*PROLEISH (proteolysis targeting chimeras (PROTACs) to treat leishmaniasis)*", Scientific coordinator and holder of the funds: Prof. Maria Laura Bolognesi.
PROLEISH aims to develop innovative therapeutic tools for the pharmacological treatment of leishmaniasis. Leishmaniasis is a protozoal disease with high morbidity and mortality rates.[1] The disease is endemic in tropical and subtropical areas, but is also widespread in southern Europe.[2] The seriousness of the epidemiological picture is worsened by the absence of effective drugs. The limited efficacy, toxic side effects, inadequate administration methods, and the development of resistance, represent the main limitations for current therapies and call for the development of novel drugs.[3]

Descrizione del progetto

The ambitious goal of the PROLEISH project is the development of first-in-class of *Proteolysis Targeting Chimeras* (PROTAC) to be potentially applied to leishmaniasis. In particular, PROLEISH aims to develop chimeras directed at the enzyme trypanothione reductase (TR), which is a well-validated and extensively studied anti-leshmania target.[4] PROTACs are small molecules whose structure can be conceptually divided into three parts: a moiety that binds the target protein, a moiety able to be recruited by an E3 ubiquitin ligase, and a linker that connects the aforementioned scaffolds. Through the formation of the ternary target-PROTAC-ligase E3 complex, the PROTAC induces the ubiquitination of the target mediated by the E3 ligase and the consequent selective degradation by the proteasome.

Piano formativo

The research project is aimed at the application of computational methods in pharmaceutical chemistry for the design and development of potential PROTACs directed towards the protozoan TR enzyme. In particular, the hired research fellow will perform molecular docking studies combined with molecular dynamics simulations in order to characterize the binding mode of the moieties of the PROTACs responsible for binding the TR enzyme and E3 ligase. Docking studies will be carried out using the TR structures of *Leishmania Infantum* resolved by means of X-ray crystallography, while suitable homology models will be employed for the protozoan E3 ligase. In parallel, the hired research fellow will carry out protein-protein docking simulations aimed at identifying a possible binding mode between TR and the E3 ligase. This information will be instrumental for optimizing the size of the linker and therefore for the effective formation of the TR-PROTAC-ligase E3 ternary complex.

References

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