MASTER « *In Silico* Drug Design »

2ème année

PROPOSITION DE STAGE
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HDR : non / oui

Ecole doctorale de rattachement : ED 393

Spécialité du stage : Recherche ☒ Professionnel ☐

Indiquez par quelques mots clés, l'orientation scientifique du sujet : structural bioinformatic, molecular dynamics simulations.

Titre du stage : Effect of the sequence variations between HIV-1 and HIV-2 proteases on their structure and their flexibility.

Ce sujet constitue-t-il un premier pas vers un travail de thèse : ~~Oui~~ - **Non**

Description du sujet (quelques lignes):

HIV-2 is a retrovirus discovered a few years after HIV-1. HIV-2 infections are restricted mainly to West Africa. HIV-1 and HIV-2 are currently treated with the same therapeutic arsenal, which consists of drugs targeting integrase, reverse transcriptase, fusion protein and protease (PR). However, HIV-2 is naturally resistant to all non-nucleoside inhibitors of reverse transcriptase or fusion inhibitors. HIV-2 has also demonstrated reduced susceptibility to protease inhibitors (PIs) [1–4].

PR is an effective therapeutic target for treating HIV infection because of its essential role in hydrolysing the viral precursor polyprotein during infectious viral particle maturation. From the nine FDA (Food and Drug Administration)-approved PR Inhibitors (PIs) available for HIV-1 therapy, only three of these are

commonly recommended for the treatment of HIV-2 infection [1-3]. Greater understanding of the structural mechanisms underlying HIV-2 resistance to PIs is important for the development of new efficacious anti-HIV-2 drugs.

In this aim, we previously performed a comparison of PR1 and PR2 structures bound to diverse ligands. We showed that substitutions between PR1 and PR2 induced structural changes at some regions, particularly in an external loop (elbow), in two beta-sheets (fulcrum and cantilever), and in the α-helix [5]. In addition, a comparison between PR1 and PR2 pockets showed that sequence variations between PR1 and PR2 modify the properties of the PI-binding pocket that could impact the PI binding, the PR2 flexibility that could partially explain the PR2 resistance against PIs [6].

This new project will focus on the more detailed comparison of PR1 and PR2 to better understand the specificities of PR-2 against inhibitors. In this project two comparisons will be performed. The first comparison of PR1 and PR2 structures would be based on crystallographic structures of the two PRs extracted from the PDB using SA-conf tool [7]. The second comparison will consist to compare the flexibility of the two PR2 using molecular dynamics simulation by focusing on the elbow, cantilever, and fulcrum regions.

1. Brower ET, Bacha UM, Kawasaki Y, Freire E. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. Chem. Biol. Drug Des. 71:298–305, 2008.

2. Raugi DN, Smith RA, Gottlieb GS. & for the University of Washington-Dakar HIV-2 Study Group. Four Amino Acid Changes in HIV-2 Protease Confer Class-Wide Sensitivity to Protease Inhibitors. J. Virol. 90:1062–1069, 2016.

3. Bénard A, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. AIDS. 23:1171–1179, 2009.

4. Ren J, et al. Structure of HIV-2 reverse transcriptase at 2.35-A resolution and the mechanism of resistance to non- nucleoside inhibitors. PNAS U. S. A. 99:14410–1441, 2002.

5. Triki et al., Exploration of the effect of sequence variations located inside the binding pocket of HIV-1 and HIV-2 proteases. Sci Rep. 8: 5789, 2018.

6. Triki et al., Exploration of effects of sequence variations between HIV-1 and HIV-2 proteases on their three-dimensional structures. Amino Acid Journal, in submission

7. Regad et al., Exploring the potential of a structural alphabet-based tool for mining multiple target conformations and target flexibility insight. PLoS One. 12: e0182972, 2017.