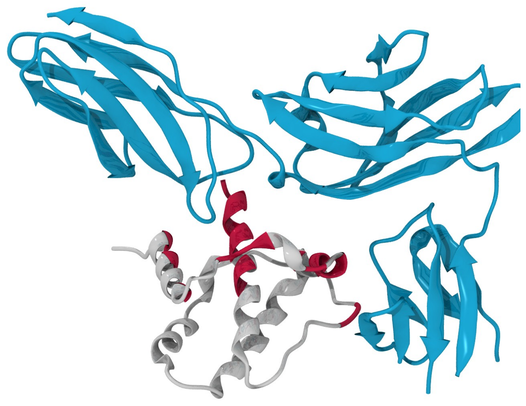
Establishing a docking protocol to find relevant ligand poses in order to target the IL-3/IL-3Rα interaction

Lucas ROUAUD*, Jade FOGHA*, Alexandre G. DE BREVERN*, Julien DIHARCE*#

*Université Paris Cité and Université des Antilles and Université de La Réunion, BIGR, UMR UPC Inserm S_1134, Hôpital Broussais, 8 Rue Maria Helena Vieira Da Silva, 75 014 Paris
#julien.diharce@u-paris.fr



Interaction between IL-3 (white) and its α receptor (blue). Interaction on the IL-3 protein are highlights in red. This structure is available on the PDB with the accession code 5UWC.

INTRODUCTION

Atopies are hypersensitivity of genetic origin, which induced an over-reaction to a, *a priori*, inoffensive substance, also possibly described as allergies. These sensibilities induced the apparition of disease like eczema, asthma, or conjunctivitis. In the organism, it's translated by an over-production of cytokines, which are inflammation mediators. These proteins are members of a huge family which have some commons characteristics like their low molecular weight or their local action[1]. One of its subfamily is the β commons, composed of three members which have in commons a part of the same receptor (the β subunit).

In these study, we are interested in IL-3, which interact with its receptor IL-3R (composed of an α and β subunit)[2]. Actually, it's been showed that this complex is implied in atopic disease. Inhibition of the interaction of IL-3 with its receptor could be a therapeutic target to treat these conditions[3]. For this purpose, we are going to use bioinformatics methods like molecular dynamics and docking to find good ligands targeting this interface.

METHODS

Finding all potential conformation of IL-3:

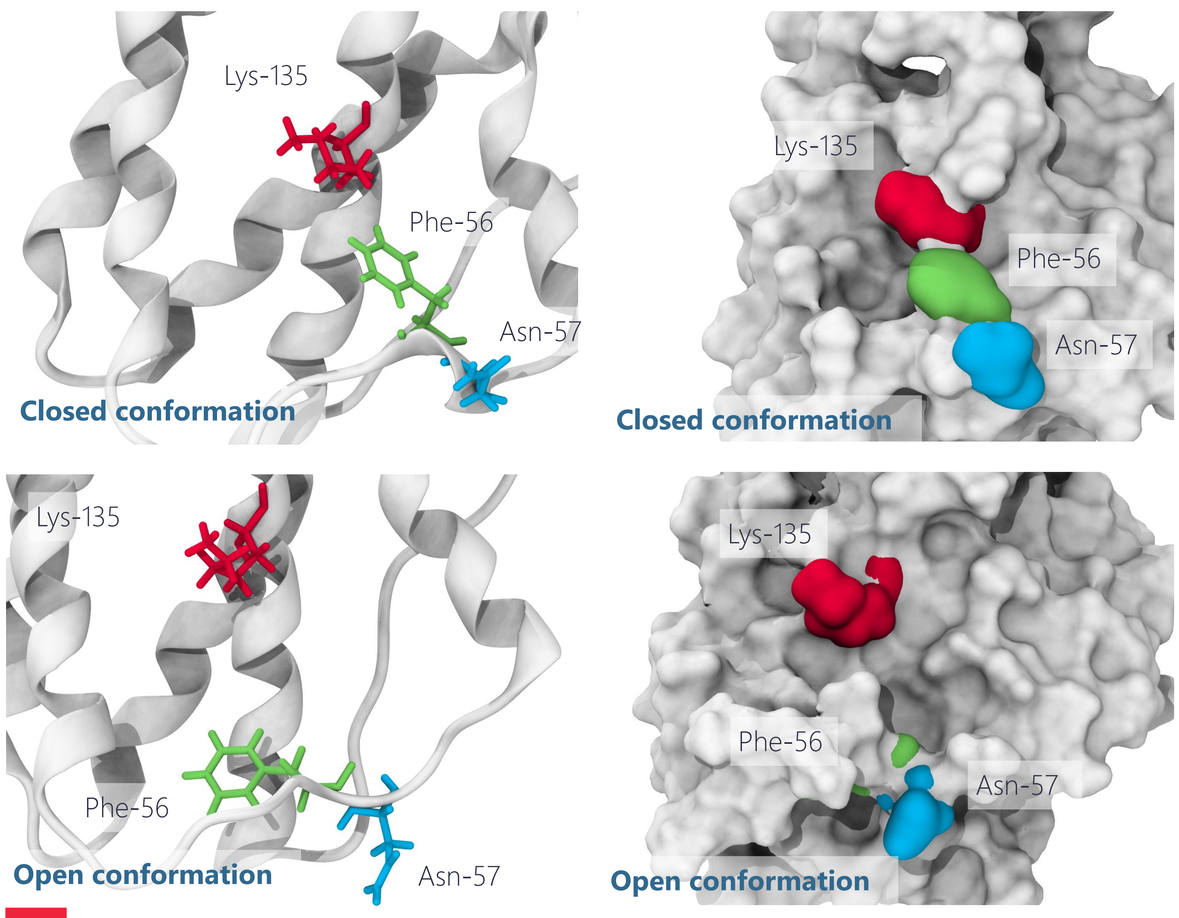
- Completing the existing structure by comparative modelling (11 missing residues in the N-ter and 2 engineered mutations, using Modeller[4]).
- Protonation at pH 7 (H++[5]).
- 3 replica Molecular dynamics simulation using TIP3P water[6] and charmm36[7] (Gromacs[8]):
  - Protocol of minimisation, equilibration and produc-tion of 400 ns.

Docking:

- Extracting ligands from the *Chimiothèque Nationale Essentielle*.
- Preparing the ligands (GYPSUM-DL[9]).
- Testing different software like Autodock VINA 2009[10], SMINA[11], PLANTS[12], Autodock VINA 2021[13], with VINARDO[14] socring function and rXDOCK[15].

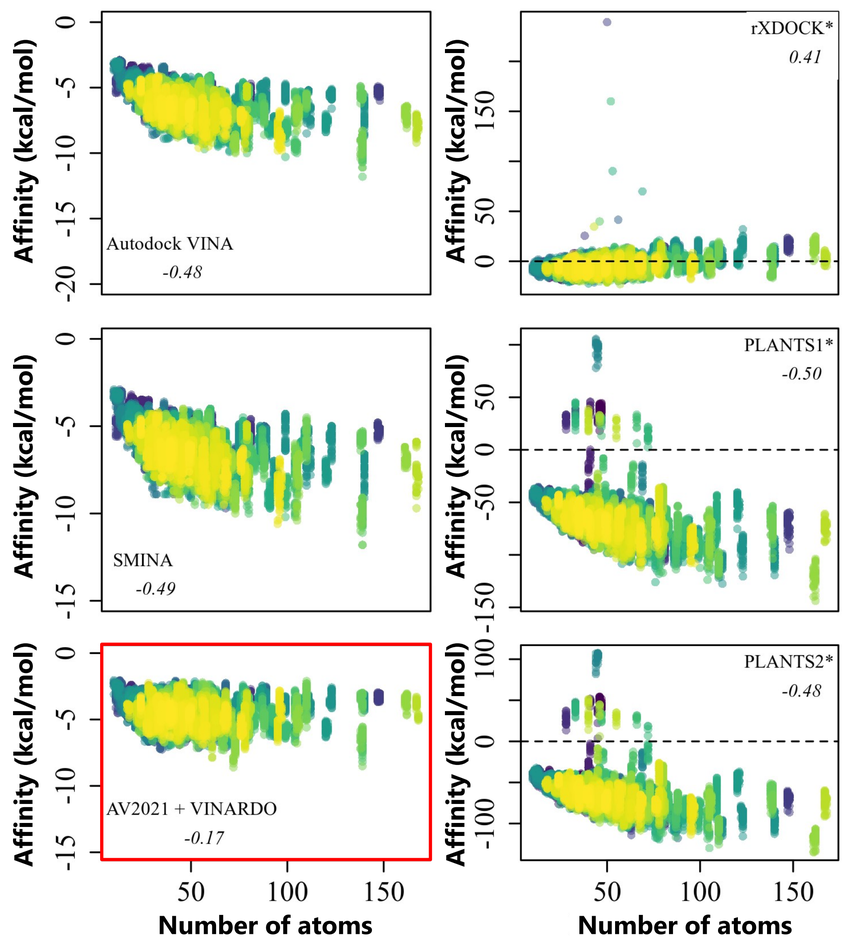
RESULTS

1) Sampling obtained from molecular dynamics simulations



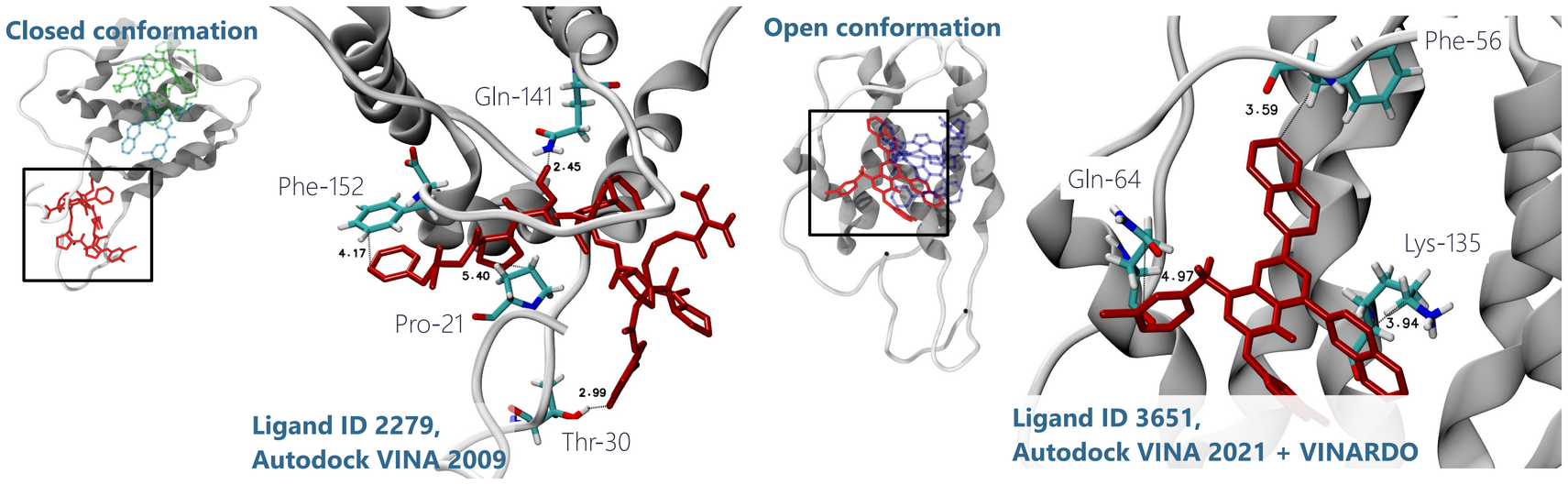
Up = initial conformation; down = open conformation. The area of interaction between IL-3 and its receptor change: this new conformation is is induced by the loss of the cation-pi interactions between K135 and F56. ***So, we have two conformations of interest to use.***

2) Tests of the several softwares



Plots of the affinity in function of the number of atoms. Correlation are indicated under the selected methods. All methods, except Autodock VINA 2021 using VINARDO scoring function, have a high correlation between the compute affinity and the number of atoms. ***The best software and the score function is Autodock VINA 2021 (AV2021) with the VINARDO scoring function.***

3) Virtual screening of the CNE on the two conformations



Bad position in the closed cavity. This position is the top 10 of best ligands. ***This pose is bad as far as the ligand is too big and do not interact with the area of interest (far away from the site).***

Top left is IL-3 into its globality. We can see two other ligand in the area of interest.

Good position on the open cavity. Ligand is in the TOP 10 best pose, interaction with the area of interaction between IL-3 and its receptor. ***So, this ligand is a potential candidate.***

Top left is IL-3 into its globality. We can see two other ligand in the area of interest.

CONCLUSION

During this project, a new conformation of IL-3 have been found, showing a rearrangement of the interaction area between IL-3 and IL-3Rα. Next, promising pose have also been found while finding that the best software is Autodock VINA 2021 with the score function VINARDO. Overall, while there is still work to do, like testing other ligands on bigger databases with chemical property selection (like hydrophobicity...), the results presented here are promising.

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