Master « In Silico Drug Design »

Second Year

OFFER AN INTERNSHIP
Academic Year 2016/2017

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Specialty training : Research ☒ Professional ☐

a few key words to describe the subject of training : CYP26 inhibitors, virtual screening, pharmacophore, homology modeling, docking

Title of internship: Identification of potent and selective CYP26 inhibitors based on homology modeling and virtual screening.

this subject is a first step towards a thesis: Yes - No

Short texte describing your project

All-trans-retinoic acid (ATRA), a natural metabolite of vitamin A, present in the multitude of human tissues, plays a crucial role in the regulation of cellular differentiation, proliferation and gene expression. ATRA deficiency is associated with diseases such as acne, psoriasis, ichthyosis and cancer. Recently, the cytochrome CYP26 has been reported to be specifically involved for retinoic acid metabolism and it is expected that blocking CYP26 could be beneficial for the therapeutic efficacy of ATRA. Therefore, the objective of the project is to identify potent CYP26 inhibitors based on computational approaches.

Material and methods.
The CYP26 family consist of 3 isoforms (CYP26A1, CYP26B1 and CYP26C1). Both CYP26A1 and CYP26B1 are efficient all trans retinoic acid (ATRA) hydroxylases, whereas CYP26C1 appears to prefer 9-cisRA as a substrate. So, design selective compounds for each enzyme would be a challenge that will be managed in several steps:

- No crystal structure of CYP26 enzymes is available yet, so homology models for the 3 isoforms will be developed.
- Some CYP26A1 ligands are known and will be considered to do a virtual screening on a database for more than 35 millions compounds that can be synthesized or bought at different chemical providers. It will allow selecting a set of molecules that share similar physicochemical properties to known CYP26A1 ligands.

- Finally the set of selected molecules will be docked using molecular modeling tools into the three CYP26A1 isoforms in order to suggest the molecules (hits) that have the better binding affinity for each isoform and higher selectivity.

Results expected

With this computational study, it is expected to to obtain potent and selective hits for CYP26A1, CYP26B1 and CYP26C1. After discussion with the chemists and biologist, some of these compounds will be tested in vitro for validation. Such strategy would allow to suggest new specific retinoic acid metabolism blocking agents that would be of interest in embryonic stem cell manipulation and regenerative medicine and a number of skin diseases. In this project, the student will be in close collaboration with chemists and biologists from the institute as well as with Pr. Taboureau for technical supervision in a regular visio-conference meeting.

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