Master « Sciences, Technologie, Santé »
Mention « In Silico Drug Design »
Second Year

OFFER AN INTERNSHIP
Academic Year 2013 – 2014
Send to Mrs Pr Camproux :
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Name of the head of laboratory or company: Nathalie REUTER

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Specialty training : Research ☒ Professional ☐

a few key words to describe the subject of training :

neutrophil serine proteases, *in vitro* HTS, *in silico* structural characterization

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Title of internship:

Docking of low molecular weight compounds in the active site of human Proteinase 3

this subject is a first step towards a thesis: ~~Yes~~ - No *(no PhD grant available at the moment)*

Short texte describing your project

Serine proteinases of polymorphonuclear neutrophils (PMN), including proteinase 3 (PR3), human neutrophil elastase (hNE) and cathepsin G, have been considered for a long time as deleterious mediators able to degrade connective tissues. These proteinases are involved in proteolytic events associated with inflammation and are therapeutic targets in a number of chronic inflammatory diseases. Moreover, and although much progress has been made in the last years in understanding the structure-function relationship of PR3, the field would immensely benefit from new specific compounds that could be used for *in vitro* studies of PR3. We have results of an *in vitro* HTS on PR3 yielding about 40 hits showing 40% or more inhibition of the protease's activity. These hits are currently being closely investigated in our lab.

The goal of the proposed project is to structurally characterize the binding of these 40 compounds (or a subset of these) to PR3 using docking. The student will thus have to set up a protocol for docking the low molecular weight compounds (LMWC) in the X-ray structure of PR3. There exist several X-ray structures of enzymes homologous to Proteinase 3 showing protease inhibitors that are covalently bound to the target enzymes. We therefore suspect that some of the compounds from the HTS might bind covalently to PR3. The docking protocol will need to take this aspect into account.

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