Master « Sciences, Technologie, Santé »
Mention « In Silico Drug Design »
2ème année

PROPOSITION DE STAGE
Année Universitaire 2011 – 2012
A envoyer à Mme Pr Camproux :
anne-claude.camproux@univ-paris-diderot.fr

Nom du Responsable du Laboratoire ou de l'Entreprise:

Affiliation administrative (CNRS, INSERM,…) et Numéro d'affiliation de l'unité : David ADELSON

Adresse précise du Laboratoire : The University of Adelaide
North Terrace Campus
Level 2 , Molecular Life Sciences
SA 5005
AUSTRALIA

Nom du Responsable de l'équipe d'accueil (EA) :
E-mail :

Nom du Responsable du stage : Grant BOOKER

Téléphone : +618 8303 3090 Fax :
E-mail : grant.booker@adelaide.edu.au
HDR : oui ou non

Ecole doctorale de rattachement :

Spécialité du stage : Recherche Professionnel

Indiquez par quelques mots clés, l'orientation scientifique du sujet :

Titre du stage :

Antagonists of gankyrin as a treatment for primary liver cancer.

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

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Description du sujet (quelques lignes):

Gankyrin is a protein that is highly over-expressed in primary liver tumour cells. It is composed of 7 ankyrin repeats and acts as a platform upon which other protein assemble to drive cell cycle progression. In particular gankyrin allows cdk4 to associate with the retinoblastoma protein (Rb) and phosphorylation of Rb results in conformational changes that release E2F and cause progression through the G1/S checkpoint for DNA synthesis. Too much gankyrin results in too much cell proliferation. Gankyrin has other roles in the cell but we are concentrating on finding antagonists of the gankyrin-cdk4 interation, as they would shut down cell proliferation in these liver tumour cells.

A crystal structure and NMR structure of gankyrin is available. We have used a truncated version of gankyrin to undertake NMR studies including a ligand titration study using HSQC experiments to confirm the site of cdk4 binding on gankyrin. The crystal structure of cdk4 is available. We have used the structure of a related complex to model the gankyrin-cdk4 complex.

The aim the project is to design constrained peptides that bind gankyrin and complete with cdk4. Peptide synthesis is available through our collaborator in Chemistry, Professor Andrew Abell. These active peptides would then be used to design peptidomimetics that can bind gankyrin but have better properties such as the ability to pass through the cell membrane.

We have the necessary constructs to make protein samples, synthetic peptides, binding assays using Biacore technology, good computing/modeling facilities, 3D visualisation, NMR etc.

Retour par e-mail : anne-claude.camproux@univ-paris-diderot.fr