MASTER « *In Silico* Drug Design »

2ème année

PROPOSITION DE STAGE
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HDR : oui ou non

Ecole doctorale de rattachement :

Spécialité du stage : Recherche ☒ Professionnel ☐

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

Docking, inhibitors,

Titre du stage :

In silico design of anti-inflammatory and anticancer inhibitors
targeted to vascular adhesion protein-1 and Siglec-9

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

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Description du sujet (quelques lignes):

Background: Sialic acid-binding immunoglobulin (Ig)-like lectin 9 (Siglec-9), which is expressed on leukocyte surface, regulates the innate and adaptive immune systems by recognizing sialic acids on the surface sialoglycans of its binding partners. Siglec-9 forms multivalent interactions with vascular adhesion protein-1 (hVAP-1; also called primary amine oxidase (hAOC3), which is translocated onto the luminal surface of endothelium upon inflammation and, thus, a peptide derived from the C22 domain of Siglec-9 can be used as tracers in positron emission tomography (PET) to detect inflammation in vivo (Aalto 2011). Furthermore, the V domain of Siglec-9 interacts with the sialic acids of the hVAP-1 attached glycans (Elovaara 2016). Inhibitors blocking the Siglec-9/hVAP-1 interactions could be used in treating acute and chronic inflammatory conditions and cancers (Reviewed Salmi and Jalkanen, 2017). Furthermore, the V domain of Siglec-9 also interacts with

Tamm–Horsfall glycoprotein (THP) in urinary track infections (Patras et al., (2017) and cancer-associated proteins, MUC1 (Beatson 2016), MUC16 (Belisle 2010) and Lectin Galactoside-Binding Soluble 3 Binding Protein (LGALS3BP) (Läubli 2014), which makes the sialic acid–Siglec axis an emerging target to prevent infectious diseases, inflammation, autoimmune diseases and cancer. Furthermore, the genetic variation in Siglec-9 carries a risk factor for several diseases but also might have beneficial effect in response to cancer therapies (Läubli 2014).

Objectives and plan: Smaller Siglec-9 peptides with the conserved WRG sequence are designed and 3D peptide/ hVAP-1 complexes created by molecular docking. For the designed peptides, the binding and inhibition properties are experimentally analyzed.–Furthermore, 3D complex for the V domain with its sialic acid ligands are modeled by docking and used as basis for the in silico design of novel sialic acid mimetics that block the hVAP-1/Siglec-9 interactions. To design a dual inhibitor blocking both hVAP-1 and Siglec-9, Siglec-9 peptide with the highest inhibitory potential is combined with the best sialic acid mimetics. The designed dual inhibitors are docked into hVAP-1 and Siglec-9.

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