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Identification of inhibitors for the Lutheran – Laminin interaction by molecular modeling techniques to reduce the vaso-occlusive crises of sickle cell disease

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Drepanocytosis is a genetic blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. In the pathogenesis of vaso-occlusive crises of sickle cell disease, red blood cells bind to the endothelium and promote vaso-occlusion. At the surface of these sickle red blood cells, the over-expressed protein Lutheran strongly interacts with the protein Laminin found on the endothelium. The aim of this study is to identify a protein-protein interaction inhibitor with a high probability of binding to Lutheran for the inhibition of the Lutheran-Laminin interaction. A virtual screening was performed with 395 601 compounds that target Lutheran. Prior validation of a robust docking and scoring protocol was considered on the protein CD80 because this protein has a binding site with similar topological and physico-chemical characteristics; CD80 also has a series of ligands with known binding affinity constants. The protocol that was finally selected consisted of multiple filtering steps based on docked scores, molecular dynamics simulations, post-screening scores, and molecular properties. We were able to identify promising compounds that could reduce the Lutheran-Laminin interaction as measured by our micro-fluidic platform capable of quantifying cell rolling and binding/adhesion.

Biography

Fabrice Gardebien has completed a PhD in Theoretical Chemistry from the University of Pierre and Marie Curie (Paris, France) and Postdoctoral studies from University of Mons (Mons, Belgium). He is interested in predicting protein-ligand interactions by combining molecular modeling techniques (molecular docking and molecular dynamics) and quantum chemistry (ab initio and semi-empirical levels). He is the Director of the DSIMB team based in Reunion Island.

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