New IL-36 cytokine receptor inhibitors

Pavel Davidovich¹, Vasilisa Aksenova¹, Seamus Martin¹,²

¹Laboratory of Cell Biotechnology, St. Petersburg State Technological Institute, 26 Moskovskii av., 197101, St. Petersburg, Russia.
²Molecular Cell Biology Laboratory, Trinity College, Dublin 2, Ireland.

A number of potential small molecule antagonists of IL-36 cytokine receptor were identified using in silico screening method.

IL-36 family cytokines (α, β and γ) have been implicated to play a key role in skin inflammatory diseases, such as psoriasis. Upon activation, IL-36 cytokines interact with their receptor and initiate the production of a range of pro-inflammatory cytokines and chemokines. Similar to most members of the IL-1 family, IL-36 cytokines require proteolytic processing for activation [1]. Thus, one therapeutic approach for blocking IL-36 activation is to inhibit the proteases responsible for activating IL-36 family cytokines, but unfortunately they are not identified yet. An alternative approach is to antagonize the interaction between IL-36 and the IL-36 receptor. Earlier it was shown that IL-36β and IL-36α bind the same receptor (IL-1RII) as its family member IL-1β.

In current work in silico screening for small molecule IL-1RII antagonist identification was made with LeadFinder (LF) and AutoDock (AD) packages under default computation parameters. The D3 domain from 3O4O.pdb structure of the IL-1RII was used for screening (the structure is resolved by X-ray diffraction at 2.50 Å resolution). D3 domain is responsible for interaction with the processed part of IL-1 family proteins. The water molecules and co-crystallized anions were removed from the protein model. Hydrogens were added to the resolved structure and their positions refined using Gromacs software package. The 20×20×20 Å box centered to the coordinates of the IL-1−IL-1RII binding interface was used for energy grid maps calculation with 0.300 Å grid spacing. Small molecules were treated as flexible and protein − as rigid.

A set of approximately 50000 compounds from the high diversity St. Petersburg State Technological Institute library was screened using in silico method. The ligand protonation states were accounted at the pH 7.0. For the accuracy increase each compound was represented in 15 most favored conformations generated by Omega with mmff94 force field.

A set of 20 promising IL-1RII antagonist molecules were identified during VS with the calculated inhibition constant Ki in the range of 1÷8·10⁻⁸. The binding specificity and their physico-chemical properties of the representative compounds are discussed in the report.
