Design of Novel Ligands for Thymic Stromal Lymphoetin

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Thymic stromal lymphopoietin (TSLP) is a member of IL-2 cytokine family. Structurally similar to IL-7-like, TSLP plays an important role in pathophysiology of several allergic conditons such as the triad atopic diseases (asthma, atopic dermatitis and atopic rhinitis) [1]. Intracellular signalling proceeds through binding of TSLP to its cognate TSLP receptor (TSLPR) and IL-7♋ to regulate T-cell development and homoeostasis [2,3].

The importance of targeting TSLP has been revealed by Phase II trial conducted using TSLP blocking antibody, Tezepelumab for reducing allergen sensitivity and inflammation. However, due to lack of oral bioavailability and high production cost, development of small molecule inhibitors that could disrupt this protein-protein complex could be a parallel approach [3].

The objective of this study is to analyze the TSLP-TSLPR-IL-7 complex and identify compounds that disrupt the protein-protein interface. As there are no known small-molecule inhibitor till date, we identify important interactions in the binding site using molecular interaction fields (MIFs) [4]. The feature-based MIFs helps us to determine energetically favorable interaction (hotspots) using different probes such as hydrophobic moieties ("DRY"), for H-bond donors with and without charges (N1+, N1 , N2) and for acceptors (O-, O). This analysis results in a structure-based 3D pharmacophore in LigandScout [5] suitable for virtual screening. Probability density maps (dynophores) are developed for recently published ligands [6] to further characterize ligand binding for this promising and novel target.

References

[1] *Verstraete K, van Schie L. Structural basis of the proinflammatory signaling complex mediated by TSLP. Nat Struct Mol Biol. 2014 Apr;21(4):375-82.*
[2] *Ito T, Liu YJ. Cellular and molecular mechanisms of TSLP function in human allergic disorders--TSLP programs the "Th2 code" in dendritic cells. Allergol Int. 2012 Mar;61(1):35-43.*
[3] *Verstraete K, Peelman F. Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. Nat Commun. 2017 Apr 3;8:14937.*
[4] *Molecular Operating Environment (MOE), 2015.10; Chemical Computing Group Inc.*
[5] *Wolber G, and Langer T. LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters. J. Chem. Inf. Model., 2005, 45 (1), pp 160–169.*
[6] *Van Rompaey D, Verstraete K. Virtual screening for inhibitors of the human TSLP:TSLPR*