Soluble BAFF Inhibition by small molecules: Virtual Screening drug discovery driven by genetics

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Appropriate biological target identification is the fundamental step in drug discovery process. Human genetic support is a key indication for identifying targets that are more likely to obtain approval than pharmacological targets without genomic data [1,2]. In a recent study, we have been demonstrated that a variant in the TNFSF13B gene (called BAFF-Var) encoding the cytokine B-cell-activating-factor (BAFF), is associated with an increased risk of Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE), as well as soluble BAFF (sBAFF), B lymphocytes and immunoglobulins [3]. This proof of principle supports the role of human genetics in the drug discovery process and potential clinical relevance, either by validating a therapeutic target and by revealing subjects who are more likely to respond to available treatments. BAFF is a cytokine that belongs to the Tumor Necrosis Factor family, which can be cleaved by furin generating a soluble protein (sBAFF)[4,5] and binds three receptors BAFFR (BR3), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), and BCMA (B cell maturation antigen). Each receptor has different binding affinities for sBAFF, in particular BAFFR binds only sBAFF with a greater affinity than the other two. This is the only BAFF receptor able to activate the alternative nuclear factor kappa B (NF-kB) pathway [6]. BAFF is already a drug target for SLE: Belimumab, a specific antibody, that binds to sBAFF, was approved as first drug for the treatment of autoantibody-positive patients with SLE [7]. Other biological BAFF inhibitors are under clinical trial for autoimmune diseases, but unfortunately no small sBAFF inhibitor molecule has been identified yet. To identify novel small molecules that can interact pharmacologically with sBAFF, we designed and applied a Virtual Screening (VS) protocol [8]. Starting from different databases of commercial molecules (Asinex and Sigma Aldrich Diverse Collection about 276,000 compounds) and applying in silico filters (pharmacophore model, docking studies, ADME-Tox prediction), we selected only 218 small molecules able to bind sBAFF and with appropriate properties to become potential oral drugs. All compounds were purchased and tested in MTT assay using B-lymphoid Raji cells at single concentration (30uM). Among them, 8 compounds revealed a best reduction in cell proliferation and were further validated. The test of the 8 compounds based on a curve model for in vitro cell cytotoxicity (120uM, 60uM, 30uM, 15uM, 7,5uM, 3,75uM) showed no toxicity effect at standard 30uM concentration. Contemporaneously, a BAFF responsive cell line through stable transfection of the hybrid receptor (BAFFR-TNFR1A) into COS1 cells has been developed to validate the 8 active compounds in presence and absence of sBAFF [9]. Only 3 compounds showed activity at single concentration (10uM), with 2 of them responding in dose a response mode. These latter 2 hit
compounds represent a novel starting point for further rational design of potent inhibitors against BAFF.

References:


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