Synthesis and Evaluation of Small Molecule Inhibitors of Interleukin (IL)-15: Towards IL-15 vs IL-2 Selectivity

Authors: Jimmy SMADJA; Laurence ARZEL; Agnès QUÉMÉNER; Constantin VITRE; Monique MATHÉ-ALLAINMAT; Didier DUBREUIL; Erwan MORTIER

Interleukin (IL)-15, is a pleiotropic cytokine structurally close to IL-2, both sharing the IL-2Rβ and γc receptor (R) subunits. IL-15 plays important roles in innate and adaptive immunity, supporting the activation and proliferation of NK, NK-T, and CD8+ T cells.1,2

In case of dysregulation, high levels of IL-15 have been detected, leading to abnormal immune responses and autoimmune or inflammatory diseases such as polyarthritis rheumatoid or psoriasis3. Hence, our goal is to synthesize small molecule inhibitors that bind specifically to IL-15 on the IL-2Rβ interface.

Our presentation will describe two new families of IL-15 inhibitors (Figure). Taking advantage of our previous work IL-154, extending modifications were done on our first series called IBI5. On a second time, we applied a similar docking-based virtual screening of compounds libraries on a refined pharmacophore-based on IL-15 specific residues identified on the binding site of IL-15 with IL-2Rβ giving so our second family named IBIS. These series of compounds were evaluated for their capacity to inhibit the binding to IL-15 to its cognate receptor, as well as the down-stream signaling of IL-15-dependent cells and their proliferation.

Figure: Structure-Activity Relationship Study. IBI Family: Modulations of N-triazole (orange), N-Phthalazinone (blue), Linker and Aromatic (yellow) moieties. IBIS Family: Modulations of Aromatic (yellow), Heterocyclic (blue) and Thiophene (orange) moieties.

---