Seminar

Thursday, September 20th 2018 at 10:30 am
(Chemistry building, 5th floor, academic room)

MOLECULAR DYNAMICS SIMULATIONS AND VIRTUAL SCREENING OF INTERLEUKIN-15 AND ITS RECEPTORS

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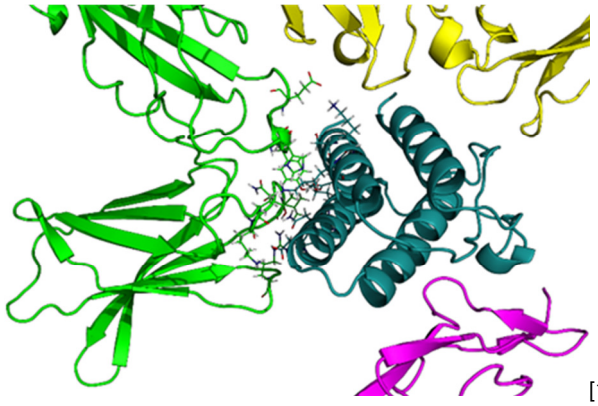
The Interleukin 15 (IL-15) is a cytokine involved in a plethora of different cellular functions. It participates in the development and activation of immune responses. Its functions include the stimulation of memory T cells and NK cell proliferation and activation, as well as the inhibition of the apoptosis in immune cells. IL-15 has therefore clearly appeared as a potential target for several therapeutic applications. [1] The structure of this cytokine is based on a quaternary complex between IL-15 and its α (IL-15Rα), β (IL-15Rβ) and γ (IL-15Rγ) receptors. The key to the functional modulation of IL-15 lies on its interaction with its receptors and, more particularly, with Rβ.
In the framework of a multidisciplinary projects gathering biologists, organic chemist partners and modelers, we present molecular dynamics (MD) and drug design results aiming to design specific inhibitors of IL-15. Since there are not, currently, any known modulators of IL-15, the data obtained from the MD simulations brings novel perspectives. Indeed, we have (i) characterized the structural fluctuations upon various mutations, (ii) determined the key and novel components (amino-acid residues, water molecules) of the IL-15/IL-15Rβ interface and (iii) highlighted/quantified key interactions. Comparison with *in vitro* biological tests validate our model showing a good agreement upon mutations and their impact on cell proliferation/STAT5 activity. Interestingly, a new hotspot residue has been pointed out, which can lead to the discovery of compounds specific to IL-15 (and not to IL-2). The newly identified region has, therefore, been employed to perform a Virtual Screening campaign, starting with the definition of a pharmacophore. These data will be useful for the design of highly specific small organic ligands selectively targeting specifically IL15.



[1] T. A. Waldmann and Y. Tagaya, Annu. Rev. Immunol. 17:19–49 (1999)

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