The PIRAMID project, supported by the Région des Pays de la Loire,

aims to design new drugs targeting specifically protein-protein interactions (PPI). PIRAMID is based on the structuring of a new regional network with high added value in basic and applied research, at the interface Molecular Modeling/ Organic chemistry / Biology. Several disciplinary sub-sectors, in the field of molecular modeling, chemistry and biology are thus associated to allow the rational design of original organic ligands specific to the targeted PPI. The combination of the various approaches, carried out at different scales (atomic, molecular, cellular and physiologic) is one of the main originality of PIRAMID, both in terms of approach and importance, considering the skills of the members of the consortium.

Région PAYS DE LA LOIRE

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PIRAMID

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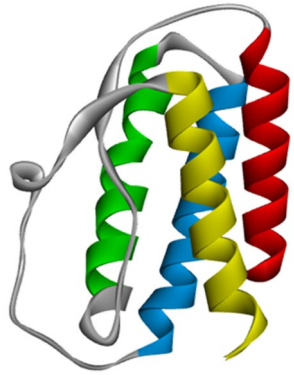
PIRAMID

PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

Interleukine 15



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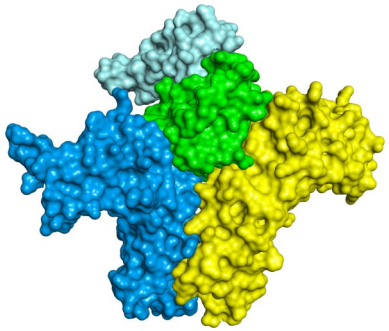

The protein-protein interaction IL-15

Cytokines are key mediators involved in the regulation of the normal immune response. Dysregulation of cytokine expression has a complex role in the pathogenesis of autoimmune diseases. **IL-15**, a cytokine discovered in 1994, belongs to the **IL-2 family**.

Both IL-2 and IL-15 share particular functions that include the stimulation of **T cell proliferation**, the generation of cytotoxic T lymphocytes and NK cells. This redundancy could be explain by the fact that they share the heterodimeric receptor formed by **the IL-2/15Rβ (β) and common gamma (γc) chains.** The specificity of action of IL-15 is conferred by **its alpha receptor chain IL-15Rα,** that is widely expressed in humans and mice independently of β and γc chains.

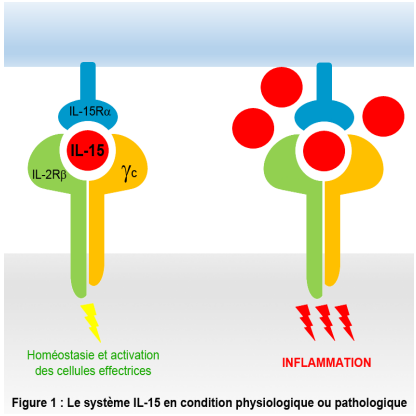

Figure 1 : Le système IL-15 en condition physiologique ou pathologique

IL-15Rα binds to IL-15 with high affinity, retaining IL-15 on the surface of IL-15-producing cells. IL-15 is then **trans-presented to β / γc dimeric receptors on nearby effector NK an T cells, participating to the immunological synapse** (Figure 1). This mechanism is believed to limit exposure to circulating IL-15. Indeed, elevated IL-15 levels have been reported in several **autoimmune diseases**, including psoriasis, rheumatoid arthritis, lupus, sarcoidosis, celiac disease, and inflammatory bowel disease. Thus, **IL-15 uncontrolled expression would undeniably result in the induction of autoimmunity.** This cytokine-mediated inflammation has been translated into the development of novel therapeutic agents.

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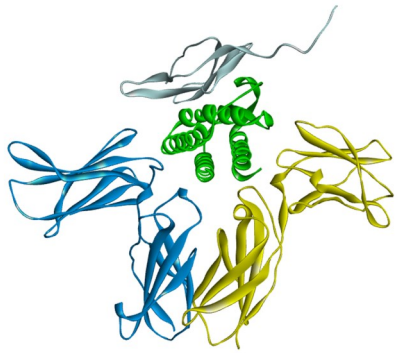
Goals and ambitions

The aim of this project is **the identification of low molecular weight chemical compounds capable of inhibiting the actions of IL-15 overexpressed in the context of autoimmune diseases.** Our multidisciplinary approach is based on experimental biological observations and **combines multi-scale molecular modeling studies, chemical synthesis optimization steps and structure-activity relationships analysis.**



Complexe IL-15

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