

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.

www.piramid-research.fr



PIRAMID Research Program

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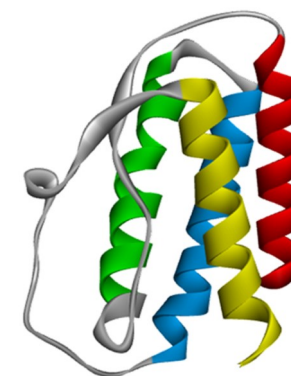
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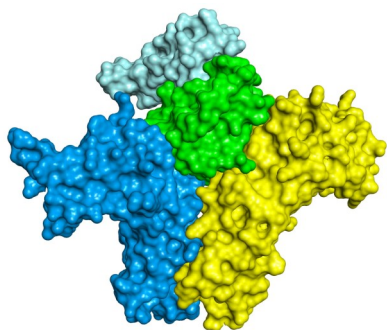
PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

Interleukine 15



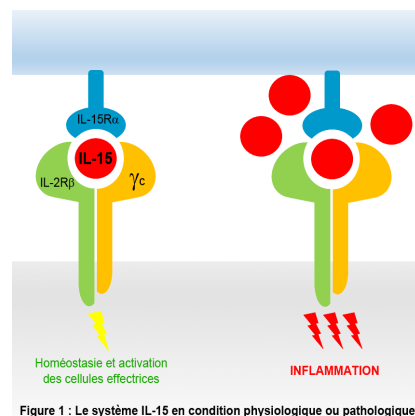
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The protein-protein interaction IL-15

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**.

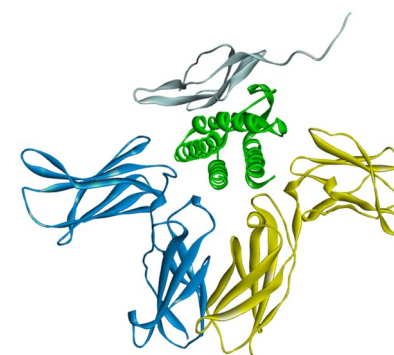
Both IL-2 and IL-15 share particular functions that include the stimulation of **T cell proliferation**, the generation of cytotoxic T lymphocytes and NK cells. This redundancy could be explained by the fact that they share the heterodimeric receptor formed by **the IL-2/15R β (β) and common gamma (γ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



IL-15R α 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 / γ c dimeric receptors on nearby effector NK and 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.

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