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

UNIVERSITÉ DE NANTES · Le Mans Université · université angers

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PIRAMID

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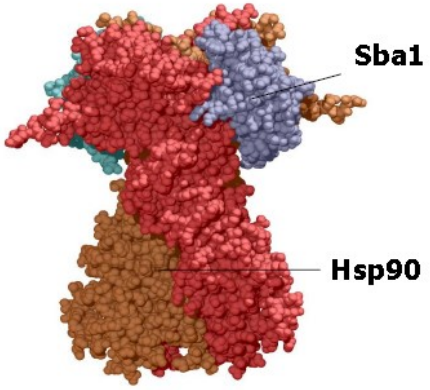
PIRAMID

PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

Hsp90



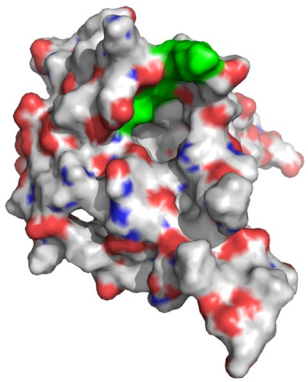
www.piramid-research.fr

The protein-protein interaction Hsp90

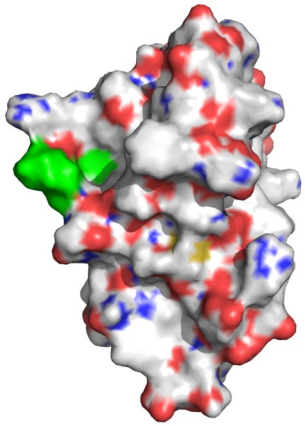
Fungal diseases result in approximately 11 million life-threatening infections annually. Current treatment strategies for these infections are limited by **antifungal resistance, toxicity and drug interactions.**

Fungal Hsp90 chaperone is a major regulator of cell wall integrity and virulence. Genetic impairment of Hsp90 function **reduces tolerance to stress** and **abrogates drug resistance** to the two main classes of antifungals (azoles and echinocandins).

Inhibition of Hsp90 by geldanamycin restores susceptibility of *C. albicans* strains resistant to azoles and echinocandins but such ATP inhibitors **appear to have limited therapeutic potential on their own** as they exhibit *in vivo* toxicity because of their non-selectivity.



C. albicans sba1

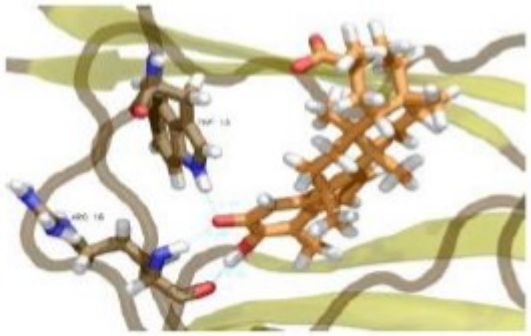


Human p23

Goals and ambitions

This project proposes an **innovative and original strategy in medical mycology to selectively inhibit yeast Hsp90 by targeting its interactions with associated proteins**. The aim is to **identify** *in silico* and *in vitro* small molecules or hits able to disrupt the protein-protein interactions (PPIs).

This approach will be carried out thanks to an **interdisciplinary consortium**, gathering biologists, organic and computational chemists. Therefore, the goal of the fundamental and multidisciplinary project will be **the identification of new drug candidates** with selective antifungal activity and being able to bypass resistance to the most widely used antifungal drugs.



Sba1-celastrol interface