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

cnrs · Inserm La science pour la santé From science to health

PIRAMID

PIRAMID Research Program

Laboratoire CEISAM
Faculté des Sciences et Techniques
2 rue de la Houssinière
44322 NANTES

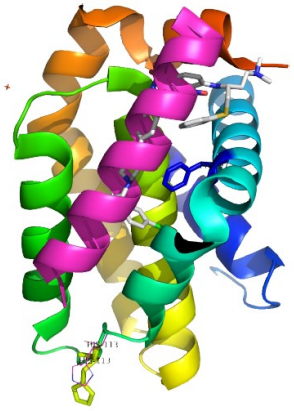
Email : veronique.aubert@univ-nantes.fr
Web Site : www.piramid-research.fr

PIRAMID

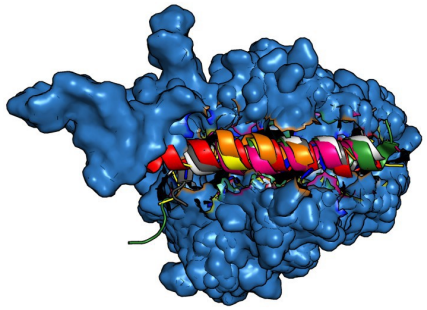
PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

BCL-xL



www.piramid-research.fr

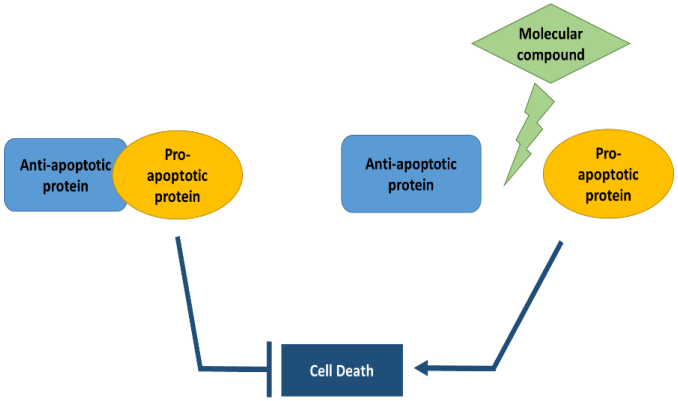


BCL-xL interaction

The protein-protein interaction BCL-xL

The ability to overcome stresses generated during **carcinogenesis** is one of the main traits of cancer cells. As a consequence, **tumor cells are often resistant to conventional chemotherapies,** and it is therefore of importance to lessen those resistances to improve therapeutic efficacy.

Among the different strategies studied in this way, one is to develop small compounds to interfere with protein interactions that control apoptosis, a cell death **process regulated by the cell and its environment**.

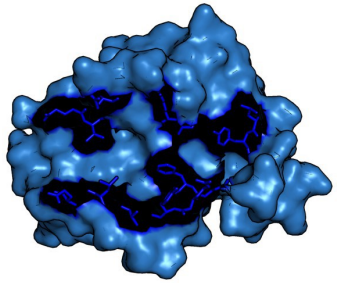


Members of Bcl2 family are the key players of this process, which involves **hementanti-apoptotic proteins** (Bcl2, Bcl-xL, Mcl1….) **and pro-apoptotic proteins** (Bax, Puma, Bim….).

The balance between pro-death and pro-life proteins and the interactions they engage together will define the fate of the cell (figure 1).

Goals and ambitions

We have shown that **Puma is essential to trigger apoptotic cell death,** but the interaction between Puma and Bcl-xL is also extremely resistant to chemical compounds currently available. The purpose of this project is to **design molecules able to break efficiently this interaction to trigger a full-blown apoptotic process**. As a final goal, this compound should give a significant clinical benefit when combined with conventional chemotherapies.



BCL-xL/PUMA