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.

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PIRAMID

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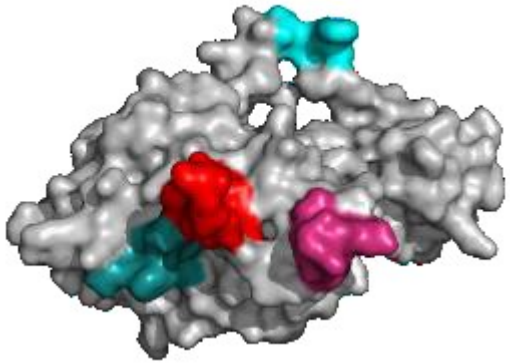
PIRAMID

PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

Rad51



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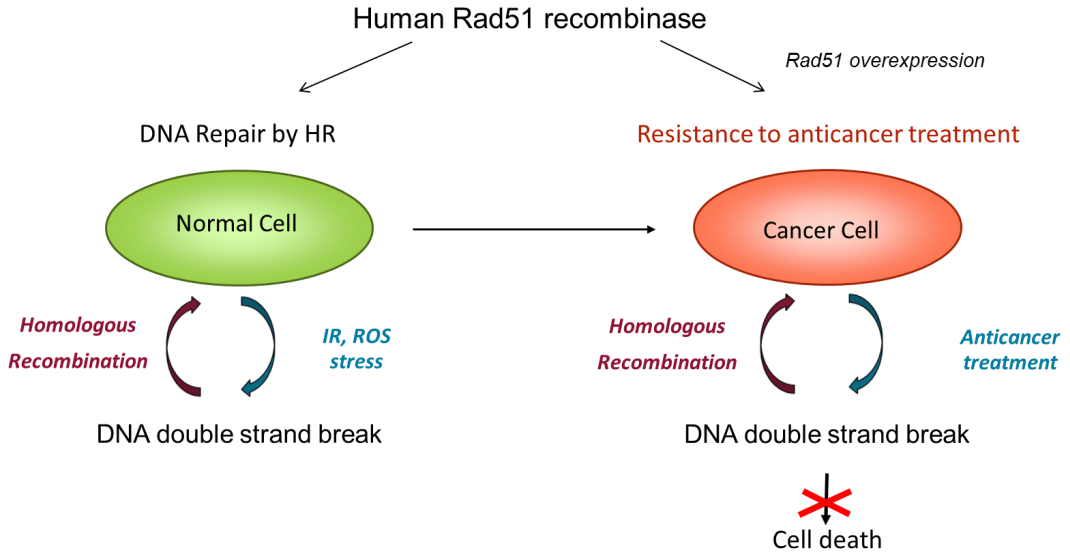
The PPI Rad 51

Anti-cancer therapies frequently encounter induced and intrinsic radio- and chemoresistance. This can be due to some DNA repair pathways which restore the DNA of cancer cells, damaged during radio- or chemotherapies.

These **mechanisms have since emerged as therapeutic targets** of interest to sensitize tumors. Double-strand breaks (DSBs) of DNA are the most deleterious alterations that can be repaired by the homologous recombination (RH) pathway. The **Rad51 protein is the main element of this repair way**. **Deregulation of Rad51** can lead to carcinogenesis and then promote the resistance to treatments. The overexpression of Rad51 indeed leads to a high level of RH associated with genomic instability of the cells that could be at the origin of some cancers .

This **overexpression provides resistance** by promoting the repair of treatment-induced DSBs. It has been shown that the survival of cancer patients expressing a higher level of Rad51 is shorter and that a decrease in the amount of Rad51 by antisense or ribozyme treatment increases the efficiency of cancer treatment by radiotherapy.



Small molecule inhibitors of Rad 51 activity

Rad51 is therefore today a relevant target to modulate HR and thus potentiate antitumor treatments. Molecules exhibiting anti-recombinase activities are increasingly attractive and several Rad51 small molecules have been identified over the last decade (Mol Cancer Ther., 2016, 15, 2665). These **inhibitors may interfere with protein-protein interactions** that are directly involved in some steps of Rad51 activity and thus lead to limit the RH repair pathway. Among these potential inhibitors, a Japanese team has shown that a small molecule, DIDS (4,4'-Diisothiocyano-2,2'-stilbene disulfonic acid) identified from libraries screening, was able to block Rad51 recombinase activity during HR .

Goals and ambitions

Our project consists to develop new analogues, as potential inhibitors of Rad51 with protein-protein interface recognition. **The multidisciplinary approach** combining biologists (UFIP, UMR 6286, Nantes), organic chemists and molecular modeling chemists (CEISAM UMR 6230, Symbiose and MoDES teams, Nantes) open the way to rationally synthesize and then evaluate small molecules in an *in vitro* and *in vivo* context. The results thus obtained can **offer therapeutic interest developing novel sensitizing agents for anticancer therapies** but also fundamental interest in better **understanding of the mechanism** of DNA repair by HR.