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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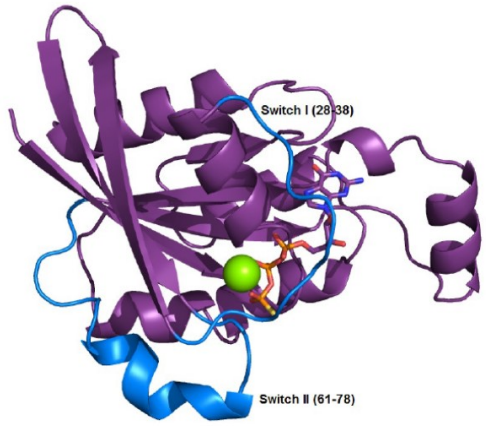
PIRAMID

PROTEIN INTERACTIONS
IN RATIONAL APPROACHES
FOR MEDICINAL
INNOVATIVE DRUGS

Protein Interactions in Rational Approaches for Medicinal Innovative Drugs

RhoA



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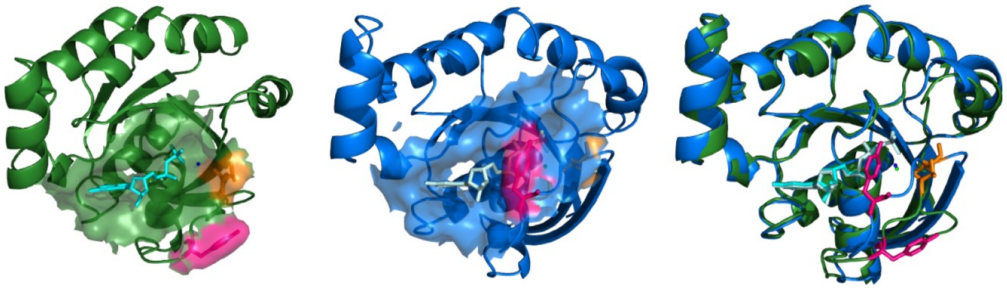
The protein-protein interaction RhoA

There is an increasing body of evidence supporting a causal role of aberrant activity of **small GTPases of the Rho protein family in human diseases** including cancers, neuronal disorders, pulmonary and cardiovascular diseases, thus identifying Rho protein signaling cascades as potential targets for new therapeutic strategies. Unfortunately, because of their smooth and globular structure lacking pockets to which small molecules can bind with high affinity, **Rho proteins are considered as "undruggable" by traditional drug design approaches.**

Rho GTPases (including RhoA, Rac, Cdc42) are critical ubiquitous intracellular signaling molecules that act as binary switches to control many fundamental cellular processes from cytoskeleton organization to gene expression, cell cycle progression, cell motility and contraction. The activity of Rho proteins results from a tightly regulated balance between the GTP-bound, active state and the GDP-bound, inactive state.

By catalyzing the exchange from GDP to GTP, Rho guanine exchange factors (GEFs) are **major regulators of Rho protein activity that relay a variety of upstream signals from growth factors, hormones, neuromediators, cytokines or other soluble messengers and adhesion molecules.** Targeting the interaction of Rho GTPase with its GEFs thus appears as an alternative strategy to block Rho protein signaling and circumvent the low druggability of the GTPase.



RhoA-GDP (PDB 1ftn) RhoA-GTP (PDB 1a2b) Superposition RhoA-GDP et RhoA-GTP

Goals and ambition

The aim of our project is **to develop Rho GEF/GTPase interaction-specific small-molecule inhibitors.** We will use the mechanistic information of Rho GEF/GTPase interaction to conduct a rational design strategy by structure-based molecular modeling simulations using a wide range of methods to get a comprehensive understanding of RhoGEF site(s) essential for Rho GTPase activation. **This strategy will be first applied on the Rho GEF/GTPase pair Arhgef1/RhoA** that we have recently identified as a relevant target for the development of new therapies against high blood pressure and atherosclerosis.

We believe that our project will lead to the discovery of innovative GEF-specific RhoA inhibitors with potential therapeutic applications in hypertension. In addition, our approach may have broad implications for drug discovery efforts targeting Rho GEF/Rho GTPase interactions in other pathophysiological contexts including cancers.

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