KINASES, PROTEIN PHOSPHORYLATION AND CANCER JUNIOR GROUP

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OVERVIEW

Rational and precise targeting of oncogene driven signalling is a crucial and yet outstanding challenge in cancer research today. Understanding the structural and molecular bases of oncogene activation and signalling is key for the design and development of better therapeutics. Our research focuses on the structural and molecular understanding of protein kinase function: how protein kinases are activated and regulated by post-translational modifications and allosteric inputs, and how they assemble into macromolecular protein complexes to transmit signals inside the cell. We put a special emphasis on how these mechanisms are corrupted in cancer and disease due to oncogenic mutations and other oncogenic insults. Crucially, such atomic and molecular information can be translated into the design and development of more potent and specific protein kinase inhibitors, eventually leading to more effective drugs for the treatment of cancer patients.

"Understanding protein kinase function and inhibition for better cancer therapeutics."

Graduate Student
Nicolás Cuesta (since July)

Visiting Graduate Student
Alba Morán (until June, *Universidad Autónoma*)

Visiting Master Student
Moustafa Ahmed Shehata (since July, Cairo University)

RESEARCH HIGHLIGHTS

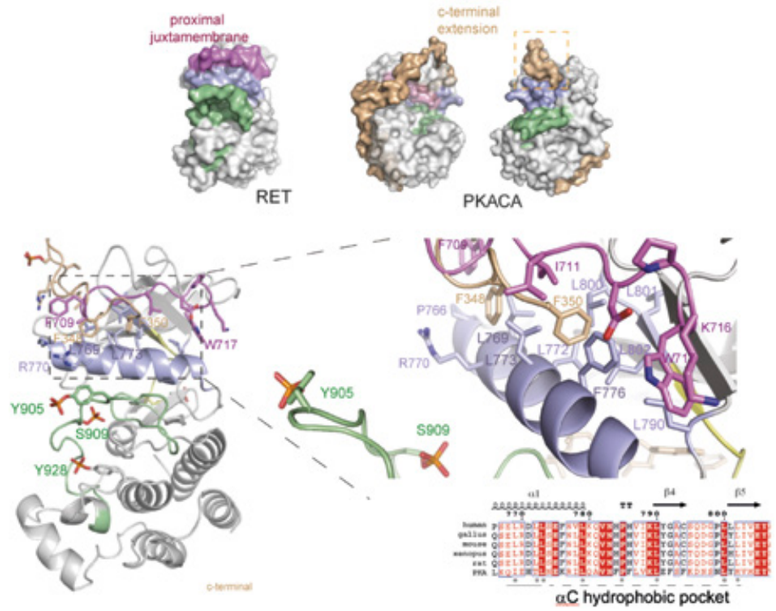

Figure Structural identification of a RET αC hydrophobic PIF-like allosteric pocket based on the superimposition of the RET (PDB code 5FM3) and PKACA (1ATP) crystal structures, and the resemblance of the c-terminal FxxF hydrophobic motifs of RET (FTRF) and PKACA (FTRF).

During 2018, we have set up the different experimental systems and techniques needed for the adequate functioning of the lab and have established 3 main research lines:

- → Structural and molecular determinants of RET catalytic activity and signalling, both *in cis* by intrinsic elements and *in trans* by effector kinases and adaptor proteins.
- → Structure-function studies of RET oncogenic variants, i.e. point mutations targeting the kinase domain and oncogenic fusions generated by DNA-rearrangements.
- → Structure-based drug-discovery of (allosteric) RET inhibitors.

Furthermore, upon invitation by the journal *Endocrine-Related Cancer*, we contributed to a special issue to commemorate the 25th anniversary of the discovery of the RET proto-oncogene as the cause of Multiple Endocrine Neoplasia type 2 (see publication list). ■

PUBLICATIONS

- Plaza-Menacho I (2018). Structure and function of RET in multiple endocrine neoplasia type 2. *Endocr Relat Cancer* 25, T79-T90.
- Redaelli S, Plaza-Menacho I, Mologni L (2018). Novel targeted therapeutics for MEN2. *Endocr Relat Cancer* 2, T53-T68.