PROPOSITION SUJET DE THESE

Concours d'attribution des Contrats Doctoraux 2017 - 2020

A renvoyer par email **format PdF** à edsvs-direction@univ-amu.fr

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PRESENTATION DU SUJET (1/2 page maximum avec courte bibliographie)
Titre en anglais: Targeting of the PTK7 tyrosine kinase receptor in breast cancer
Spécialité: cancer research
Liens URL éventuel du sujet: http://crcm.marseille.inserm.fr/en/jobs

Despite undeniable therapeutic advances in recent decades, some breast cancers remain medical and scientific challenges. This is the case of triple negative breast cancers so called because of the lack of expression of HER2 and hormone receptors, making patients ineligible for targeted therapies. The search for therapeutic targets in these very aggressive cancers thus remains a priority.

The team of Jean-Paul Borg has shown that the PTK7 tyrosine kinase receptor belonging to the Wnt/planar cell polarity pathway is overexpressed in many cancers, including triple-negative breast cancers, and associated with poor prognosis and metastasis development. A characteristic of PTK7 is the absence of catalytic activity of its kinase domain, making the use of kinase inhibitors inaccessible. PTK7 is currently only targeted by an antibody-drug conjugate currently in early clinical development. This approach is interesting but does not clear PTK7 from the tumor cell. In this thesis project, the teams propose to target PTK7 by

a recently described PROTAC (Proteolysis Targeting Chimera) approach promoting the degradation of proteins of interest by the proteasome. This technology has been shown to be effective in removing oncoproteins in tumor cells (BCR-ABL in acute myeloid leukemia). The project will consist first in the production and purification of the PTK7 kinase domain. Second, thanks to a screen of libraries developed by the Xavier Morelli/Yves Collette team expert in structural biology and chemistry and assays developed for drug design (isothermal titration calorimetry and thermal shift assay), the student will identify chemical compounds specific for PTK7 that will be functionalized to recruit an E3 ubiquitin ligase capable of degrading the receptor. Third, these compounds will be tested *in vitro* and *in vivo* using models of breast cancer cells developed at the CRCM.

Daulat A.M. and Borg J.-P. Wnt/Planar Cell Polarity signaling: new opportunities for cancer treatment. (2017) ***Trends in Cancer**,* 7: 113-125.
Lhoumeau A.-C., Arcangeli M.-L., Giordano M., Orsoni J.-C., Lembo F., Bardin F., Marchetto M., Aurrand-Lions M. and Borg J.-P. *Ptk7* deficient mice have decreased hematopoietic stem cell pools as a result of deregulated proliferation and migration. (2016) ***J. Immunology***, 196: 4367-77.
Lhoumeau A.-C., Prébet T., S. Martinez, and Borg J.-P. PTK7 tyrosine kinase receptor family. (2015) *"The Receptor Tyrosine Kinase Handbook"*, Humana press 539-558.
Martinez S., Scerbo P., Giordano M., Daulat A.M., Lhoumeau A.-C., Thomé V., Kodjabachian L. and Borg J.-P. (2015) The PTK7 and ROR2 receptors interact in the vertebrate WNT/PCP pathway. ***J. Biol. Chem.**,* 290: 30562-72.
Lhoumeau A.-C., Martinez S., Monges G., Castellano R., Poizat F., Saillard C., Viens P., Raoul J.-L., Prebet T., Aurrand-Lions M., Borg J.-P and Gonçalves A. Overexpression of the promigratory and prometastatic PTK7 receptor has an adverse clinical outcome in colorectal cancer. (2015) ***PLoS ONE***, 10: e0123768.
Milhas S., et al. Protein-protein interaction inhibition (2P2I)-oriented chemical library accelerates hit discovery (2016). ACS Chem. Bio. Aug 19;11(8):2140-8.
Raux, B., et al. Exploring Selectivity of the First Bromo and Extra-Terminal (BET) Bromodomain Inhibition (2016). J. Med. Chem. Feb 25;59(4):1634-41.
Basse, M.J., et al. 2P2Idb v2: update of a structural database dedicated to orthosteric modulation of protein–protein interactions (2016). Database Mar 15;2016. pii: baw007.

Informations complémentaires

This student will be involved in an interdisciplinary biology-chemistry program developed in close collaboration with academic (proteomics, drug design) and industrial (IPC drug discovery) platforms set up at CRCM and Institut Paoli-Calmettes.