Team : Endocrine resistance, methylation and breast cancer
Cancer Center Research in Lyon, Center Leon Bérard
28 rue Laennec, 69008 Lyon, France

Open position for a post-doctoral fellow for 3 years to work on DNA repair and PRMTs

Environment: A post-doctoral position supervised by Dr Le Romancer is available in the team co-directed by Muriel Le Romancer and Olivier Trédan at the CRCL.
The CRCL located on the site of the Léon Bérard Comprehensive Cancer Center (CLB), is directed by P. Mehlen and encompasses 24 teams and 11 platforms dedicated to cancer biology. The team "Endocrine resistance, methylation and breast cancer" co-directed by Dr Le Romancer and Trédan aims at deciphering the molecular mechanisms involved in resistance to treatment in breast cancer to identify new therapeutic targets and new drugs. In our team, complementarity between researchers and clinicians is an undeniable asset to transfer results from bench to bedside.

Description of the METEOR project:

The arginine methyltransferases PRMT1 and PRMT5 play a key role in the repair process of DNA double-strand breaks by methylating protein players involved in the initiation of repair mechanisms such as BRCA1 and MRE11 for homologous recombination (HR) or 53BP1 and RUVBL1 for non-homologous end joining (NHEJ). In this context, we hypothesized that targeting PRMT1 and PRMT5 with inhibitors of their enzymatic activity could sensitize the response to chemotherapies inducing double-strand breaks. Our results show that PRMT1 and PRMT5 are recruited to double-strand breaks and that their inhibition impairs tumor growth and potentiates the effect of chemotherapies. Using a reporter system based on the induction of localized double-strand breaks by CRISPR/Cas9, we have shown that in BRCA WT models, PRMT inhibitors (PRMTi) act by preferentially blocking the HR repair pathway. This result is very promising as it suggests major clinical applications in combination with inhibitors of poly (ADP-ribose) polymerase (PARPi), an enzyme activating accessory DNA repair pathways such as the Alt-NHEJ pathway. Based on the principle of synthetic lethality, PARPi, such as olaparib, has recently been approved to treat TNBC patients with germline BRCA mutations. However, tumors often develop resistance to PARPi, particularly through the re-establishment of a functional HR pathway. It is thus important to develop new strategies to potentiate the effect of PARPi on BRCA mutated tumors and to extend their use to BRCA WT TNBC. We therefore propose to use PRMTi in combination with PARPi on TNBC tumors without BRCA mutation, as well as on BRCA mutated and PARPi-resistant tumors.

This project should allow us to propose new treatment combinations that we can eventually try in the clinic as PRMTi are being evaluated.

Skills required: We are looking for a talented and motivated candidate with a solid experience in molecular biology and cancer research. Experience in Crispr/Cas9 screen is required and experience in DNA repair and in mice xenografts would be an advantage.
The candidate should be organized, innovative, autonomous and capable of project management,
The candidate is expected to present results at international conferences and to write publications. Fluent english is required.

Contract: The position is a full time 3-year fellowship, starting in summer 2023. The salary will be adapted to the experience of the candidate.

Application: Please send a cover letter with a summary of your previous research activities, a resumé and supporting letters with contact details of two referees.

For more information on the CRCL and the team, see: https://www.crcl.fr
All applications must be sent to: muriel.leromancer@lyon.unicancer.fr

Recent publications

-Omarjee S, Jacquemetton J, Poulard C, Rochel N, Dejaegere A, Chebaro Y, Treilleux I, Marangoni E, Corbo L and Le Romancer M. The molecular mechanisms underlying the ERα-36-mediated signaling in breast cancer. Oncogene 2017 May 4;36(18):2503-2514.
-Lattouf H, Kassem L, Jacquemetton J, Choucair A, Poulard C, Trédan O, Corbo L, Diab-Assaf M, Hussein N, Treilleux I and Le Romancer M. LKB1 regulates PRMT5 activity in breast cancer. Int J Cancer, 2019, 144(3):595-606.
-Poulard C, Jacquemetton J, Trédan O, Cohen P, Treilleux I, Marangoni E and Le Romancer M. Oestrogen non-genomic signalling is activated in tamoxifen-resistant breast cancer. International Journal of Molecular Sciences, 2019, PMID 31195751.
-Choucair A, Pham TH, Omarjee S, Jacquemetton J, Kassem L, Trédan O, Rambaud J, Marangoni E, Corbo L, Treilleux I and Le Romancer M. The arginine methyltransferase PRMT1 regulates IGF-1 signaling in breast cancer. Oncogene, 2019,
Konan HP, Kassem L, Omarjee S, Surmieliova-Garnes A, Jacquemetton J, Cascales E, Rezza A, Trédan O, Treilleux I, Poulard C, Le Romancer M. ERα-36 regulates progesterone signaling in breast cancer. Breast cancer research. 2020 May 19;22(1):50.
-Malbeteau L, Poulard C, Languilaire C, Mikaelian Y, Flamant F, Le Romancer M*, Corbo L*. PRMT1 is critical for the transcriptional activity and the stability of the progesterone receptor. iScience. 2020 Jun 4;23(6):101236.* corresponding author
-Jacquemetton J, Kassem L, Poulard C, Dahmani A, De Plater L, Montaudon E, Sourd L, Morisset L, El Botty R, Chateau-Joubert S, Vacher S, Bièche I, Treilleux I, Trédan O, Marangoni E and Le Romancer M. Analysis of genomic and non-genomic signalling of oestrogen receptor in PDX models of breast cancer treated with a combination of the PI3K inhibitor Alpelisib (BYL719) and fulvestrant. Breast Cancer Research, 2021, May 21;23(1):57.
-Malbeteau L, Jacquemetton J, Languilaire C, Corbo L, Le Romancer M, Poulard C. PRMT1, a Key Modulator of Unliganded Progesterone Receptor Signaling in Breast Cancer. Int J Mol Sci. 2022, 23;23(17):9509.
Poulard C, Noureddine LM, Pruvost L, Le Romancer M. Structure, Activity, and Function of the Protein Lysine Methyltransferase G9a. Life. 2021 Oct 14;11(10):1082.
-Thiebaut C, Eve L, Poulard C, Le Romancer M. Structure, Activity, and Function of PRMT1. Life 2021 Oct 27;11(11):1147.
-Thiebaut C, Vlaeminck-Guillem V, Trédan O, Poulard C and Le Romancer M. Non-genomic signaling of steroid receptors in cancer. Mol Cell Endo. 2021 Dec 1;538:111453.23;23(17):9509.
-Malbeteau L, Pham Thuy H, Eve L, Stallcup MR, Poulard C and Le Romancer M. How protein methylation regulate steroid receptors function. 2022, Endocrine Reviews, 2022 Jan 12;43(1):160-197.