2017-01

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Replication fork stability and resistance to PARP inhibitors in homologous recombination (HR)-deficient tumors

General information

Call	2018
Reference	2017-01-CECCALDI
Keyword(s)	Homologous recombination (HR)-deficient tumors CRISPR screen, mass spectrometry, replication fork stability, resistance to PARP inhibitors

Director(s) and team

Thesis director(s)	Raphael Ceccaldi
Research team	Alternative DNA repair in cancer
Research department	U830 – Genetics and Biology of Cancers

Description of the PhD thesis project

Our lab is studying DNA repair mechanisms that are essential for the survival of cancer cells. We are particularly interested in the alternative end joining (alt-EJ) repair pathway, that take place in cancer cells to compensate for the loss of homologous recombination (HR) activity. Unrevealing the function and structure of these mechanisms will facilitate the identification of new targets for the tailored treatment of cancer.

Ovarian carcinomas (OCs) and basal-like breast carcinomas (BLBCs) are associated with a high lethality and mortality. Large-scale genomic studies estimate that half of OCs and BLBCs have alterations in homologous recombination (HR)-dependent DNA repair, which are correlated with sensitivity to certain types of chemotherapeutics such as inhibitors of the poly (ADP-ribose) polymerase (PARPi). However, while initially sensitive to PARPi, HR-deficient (HRD) cancers eventually develop resistance, which greatly reduce patients' survival. Thus, there is a critical need to understand the mechanisms underlying this resistance and to develop alternative curative options.

During the last decade, a number of mechanisms restoring HR capacities and thus inducing resistance to PARPi have been described. Just last year, replication fork (RF) stability came into the spotlight and emerged as a new central mechanism of PARPi resistance in HRD cells. However, little is known about the molecular pathways that control genomic stability at stalled RFs. Here we will employ two independent strategies to uncover new mechanisms of RF stabilization and PARPi resistance in HRD tumors.

This work will have important translational applications, as it will allow the identification of new predictors of PARPi resistance/sensitivity and eventually provide new drug targets which could improve the tailored treatment of HRD tumors

International, interdisciplinary & intersectoral aspects of the project

Our research proposal will benefit from established international collaborations. As such, the successful PhD candidate will have the possibility to collaborate with different research groups to reinforce the robustness of her/his findings.

The intersectorality of our project stems from a collaboration with the industry. Since the measure of DNA resection is essential but current techniques to measure it lack of accuracy, we have built a partnership with the Genomic Vision company to develop more robust and faster ways to quantify DNA resection.

Finally, our project is interdisciplinary since it stands at the crossroads between basic and translational research. Indeed, we will both dissect the molecular mechanisms of RF processing and evaluate the clinical significance of our findings.

Recent publications

1. Kais Z, Rondinelli B, Holmes A, O'Leary C, Kozono D, D'Andrea AD, **Ceccaldi R**. FANCD2 Maintains Fork Stability in BRCA1/2-Deficient Tumors and Promotes Alternative End-Joining DNA Repair. Cell Rep. 2016 Jun 14;15(11):2488-99.

2. **Ceccaldi R**, Sarangi P, D'Andrea AD. New Players and Diverse Functions of the Fanconi Anemia Pathway. Nature Reviews Molecular Cell Biology, 2016 Jun;17(6):337-49.

3. **Ceccaldi R**, Rondinelli B, D'Andrea AD. Repair Pathway Choices and Consequences at the Double-Strand Break. Trends in Cell Biology, 2015 Aug 26. pii: S0962-8924(15)00142-7.

4. **Ceccaldi R**, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin M, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ, Yusufzai T, D'Andrea AD. Homologous recombination (HR)-deficient tumors are hyper-dependent on POLQ-mediated repair. Nature, 2015 Feb 12;518(7538):258-62.

5. **Ceccaldi R**, Parmar K, Mouly E, Delord M, Kim JM, Regairaz M, Pla M, Vasquez N, Zhang QS, Pondarre C, Peffault de Latour R, Gluckman E, Cavazzana-Calvo M, Leblanc T, Larghero J, Grompe M, Socié G, D'Andrea AD, Soulier J. Bone marrow failure in Fanconi anemia is triggered by an exacerbated p53/p21 DNA damage response that impairs hematopoietic stem and progenitor cells. Cell Stem Cell, 2012 Jul 6;11(1):36-49.

Expected profile of the candidate

Prospective applicants should have a strong desire to study molecular biology, biochemistry and genetics. The ideal applicant should further have either experience or interest in proteomics. She/he is eager to learn, has solid capacity for independent and creative thinking. Great communication skills are needed, together with appropriate organizational capacity.