Post-doc Position in 2023:
Targeting pre-leukemic stem cells in B-cell acute lymphoblastic leukemia

(*Bastien GERBY, Cancer Research Center of Toulouse, France*)

General problematic: *The cell of origin of B-ALL*

B-cell acute lymphoblastic leukemia (B-ALL) is a multi-step disease characterized by the acquisition of a first oncogenic event such as *ETV6::RUNX1*, *BCR::ABL1 or TCF3::PBX1* fusion genes or specific *PAX5* alterations (such as *PAX5::ELN* or *P80R* point mutation). Genome-wide analyses have been used to draw the genomic landscape and the gene expression profile of B-ALL patients leading to patient stratification and the discovery of new therapeutic opportunities. However, although chemotherapies are efficient at reducing the tumor load by targeting proliferating and metabolically active leukemic cells, the disease relapse, especially in adult B-ALL, points to the presence of resistant cells that escape treatment. Thus, the biological properties of the cell-of-origin of leukemia, including oncogene-induced reprogramming, cell plasticity, sustained self-renewal activity, cell-quiescence and drug-resistance, can affect the treatment and should be considered in the search for new targeted therapies (*Fregona V et al., Cancers (Basel) Review, 2021*).

Research Context: *A unique murine model of B-ALL*

In this context, our research focuses on the characterization and the targeting of pre-leukemic stem cells (pre-LSCs) in B-ALL. We develop cellular and animal models aiming to understand how a primary oncogene in B-ALL such as a chromosomal translocation, reprograms normal B-cells to pre-LSCs as demonstrated in our 2018 PNAS paper. Indeed, we generated the *PAX5::ELN* transgenic mouse model that recapitulates the multi-step process of B-ALL and that represents a prime tool to explore the pre-leukemic phase of the disease before the overt transformation (*Jamrog L et al., PNAS, 2018*). Our recent work indicates that pre-LSCs: (*i*) are restricted in the cell-cycle, (*ii*) are devoid of secondary mutations, (*iii*) are blocked in the B-cell differentiation, (*iv*) are resistant to chemotherapeutic agents, (*v*) up-regulate a stem cell-like molecular programs and (*vi*) sustain the leukemia initiation and transformation. Thus, our work indicates that *PAX5::ELN* reprograms stem cell-like properties in a subset of B-cell progenitors and converts them into quiescent pre-LSCs (*Fregona V et al., submitted*).

Proposed project: *Targeting leukemia initiating activity*

We recently designed a robust protocol for the screening of compounds targeting primary pre-LSC-enriched population. We screened a bank of 1040 natural and synthetic compounds and identified drug candidates that affect their viability. Using further investigations (counter screens on quiescent cells, dose-responses, synthetic lethality assays, RNA-sequencing, transplantation assays), the post-doc candidate will have in charge to identify the most relevant compound that affects the cell-quiescence/resistance, the self-renewal potential and the gene expression profile of PAX5-ELN pre-LSCs. In addition, the candidate will define whether targeting pre-LSC biological properties is relevant in other B-ALL models available in the lab (*PAX5-P80R* and *TCF3::PBX1* mouse models or human B-ALL patient-derived-xenografts (PDXs)).

Candidate profile and application

We are seeking a dynamic and proactive post doc. The candidate should have good experience in mouse models, flow cytometry, as well as in culture of primary cells. Skills in hematopoiesis and in bioinformatics would be very welcome. With our strong help and support, the selected candidate will have to apply in 2023 for a Postdoctoral Fellowship from different institutions (Fondation ARC, Fondation pour la Recherche Médicale, Fondation de France,…). The applicant is invited to send a CV with list of publications, research experiences and referees to Bastien Gerby (bastien.gerby@inserm.fr).

Situation & scientific environment

Our team "*Impact of genetic alterations on leukemia development*" led by Pr. Eric Delabesse is located at the *Cancer Research Center of Toulouse* (CRCT, UMR1037, CNRS UMR5071). The team is composed of 16 people including two PU-PH, three researchers, four engineers, two technicians and five students at the MSc and PhD levels. The laboratory promotes multidisciplinary approaches allowing an efficient investigation and deeper understanding of normal and aberrant hematopoiesis. Combined with clinical studies and genetic profiling of leukemia patients, the

development in our team of cellular and animal models aims to define and target the biological mechanisms by which genetic alterations lead to leukemia development. The projects are supported by grants from INCa, ANR, ARC Foundation, Ligue Contre le Cancer and from the associations “Laurette Fugain”, “111 des arts”, “Cassandra” and “Constance la petite guerrière astronaute”.
As a post-doc, you will have a full access to facilities available in the CRCT (https://www.crct-inserm.fr/en/the-technology-cluster-of-the-crct/) including flow cytometry/cell sorting, bioinformatics, vectorology and genomics platforms.

Webpages of the team:

https://www.crct-inserm.fr/en/characterization-and-targeting-of-pre-leukemic-stem-cells-from-b-acute-lymphoblastic-leukemia/

https://www.crct-inserm.fr/en/igaald_en/

https://www.crct-inserm.fr/en/axis-1-oncogenic-pathways-in-cancer-from-modelization-towards-targeted-therapy/

Contacts:

Project leader: Dr. Bastien Gerby: bastien.gerby@inserm.fr
Team leader: Pr. Eric Delabesse: delabesse.e@chu-toulouse.fr

Selected references:

- Fregona V et al. *Cell quiescence and reprogramming are distinctive features of pre-leukemic stem cells in B-cell acute lymphoblastic leukemia*. Submitted.

- Fregona V et al. *Oncogene-Induced Reprogramming in Acute Lymphoblastic Leukemia: Towards Targeted Therapy of Leukemia Initiating Cells*. Cancers (Basel) Review, 2021 Nov 2, 13(21):5511.

- Duployez N et al. *Germline PAX5 mutation predisposes to familial B acute lymphoblastic leukemia*. Blood, 2021 Mar 11;137(10):1424-1428.

- Jamrog L et al. *PAX5-ELN oncoprotein promotes multistep B-cell acute lymphoblastic leukemia in mice*. Proc Natl Acad Sci USA. 2018 Oct 9;115(41):10357-62.

- Cresson C et al. *PAX5A and PAX5B isoforms are both efficient to drive B-cell differentiation*. Oncotarget. 2018 Aug 28;9(67):32841-54.

- Gerby B et al. *High-throughput screening in niche-based assay identifies compounds to target pre-leukemic stem cells*. J Clin Invest. 2016 Dec 1;126(12):4569-84.

- Gerby B et al. *The SCL, LMO1 and Notch1 oncogenes reprogram T-lymphocyte progenitors into self-renewing cells*. PloS Genetics. 2014 Dec 18;10(12).