INSTITUT DE RECHERCHE SAINT-LOUIS
Hématologie | Immunologie | Oncologie

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CALL FOR A POST-DOCTORAL FELLOW IN ACUTE MYELOID LEUKEMIA RESEARCH

Project title: ***In vivo*** **humanized bone marrow functional screening to identify microenvironment-related therapeutic targets in Acute Myeloid Leukemia (AML).**

Host team and institute: **INSERM U944 - Institut de Recherche Saint-Louis – Genomes and Cell Biology of Diseases.**

Websites: https://gencelldis.fr/, https://irsl.univ-paris-diderot.fr/ , http://www.jeanbernard.univ-paris-diderot.fr/fr/

Address: Centre Jean Bernard – Hôpital Saint-Louis - 16, rue de la grange aux belles, 75010, Paris.

Saint-Louis Research Institute was initially created in 1958 by Jean Bernard and Jean Dausset (Nobel Price), aiming to achieve excellence in both research and teaching, in the fields of **hematology, oncology, cell biology, immunology, virology, genetics and therapeutic biotechnologies.** Our research institute is located in the **center of Paris within the Saint-Louis campus**, and thus benefits from a close relationship and collaboration with Saint-Louis hospital. The institute is affiliated to the **doctoral school of "Hematology, Oncology & Biotherapies"** and hosts the **"European School of Hematology",** thus participating to the **training of over 2000 researchers and clinicians every year.** Since 2020, Saint-Louis Research Institute is also the home of the ambitious **"National Leukemia Institute THEMA"**, which seeks to develop public-private partnerships to cure leukemia in 10 years.

Our research unit (UMR U944: genomes, cellular biology & therapeutics), has an **internationally recognized research program with world-renowned leukemia researchers**, such as Jean Soulier, Hugues de Thé and Alexandre Puissant. Consequently, intellectual interactions among our department members are fostered by a number of **weekly research seminars**. Our research unit is now composed of 6 research groups whose research encompasses a broad spectrum of fields, including basic virology, cell biology, cancer genomics, cancer biology and leukemia research, yeast biology, functional studies of post-translational modifications and chromosome biology. Most of the studies carried out by our team bridge several of those fields and have implications in translational research, together with the clinical groups of Saint-Louis hospital. The team works in **close partnership with Saint-Louis Hospital Clinical Investigations Center (INSERM-CIC 1427)** to accelerate the clinical translation of our lab discoveries.

Our team benefits from a **large dedicated laboratory bench space**, with adjacent office space. Saint-Louis Research Institute also benefits from a privileged access to a **large variety of institutional core facilities**, including a fully equipped animal facility offering excellent technical support and all the necessary equipment (Visualsonics Vevo 770 ultrasound, Caliper Xenogen IVIS Spectrum systems for optical imaging, MS9 (Melet Schlosing Laboratories) for blood count, mice irradiator), a Fluorescence Activated Cell Sorting and flow cytometry facility, a sequencing facility (MiSeq, HiSeq and NextSeq), and an imaging facility (Confocal, Bi-Photon and Light Microscopy).

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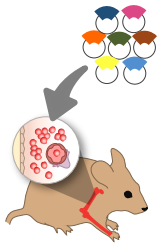
Available position: An EHA funded **two-years post-doctoral position** (possible extension of three extra years) will be opened in **March 2021** in a young dynamic team led by Dr Lina BENAJIBA, a physician-scientist focusing on target identification and drug discovery in Acute Myeloid Leukemia.
We are looking for a **highly motivated and dynamic** fellow wishing to complete his post-doctoral training in a young and international team, hosted by an internationally renowned INSERM Unit. The candidate must appreciate teamwork and have good interpersonal skills, be rigorous in his/her work and have good organizational skills. Experience in **molecular/cellular biology and murine models** is required. Experience in ***in vivo* imaging** would be an asset. Applicants should hold a **PhD degree in Biochemistry/Cellular Biology/Molecular Biology/Oncology/Hematology or related disciplines** (or have recently submitted their thesis with scheduled defense) and have published (or about to publish) in a peer reviewed journal.

Project description: Despite the significant progress made in understanding **Acute Myeloid Leukemia (AML) pathogenesis** over the last decades, our clinical progress in treating this disease has lagged behind. Developing new translational research strategies focused on the identification of druggable oncogenic targets is critical to pave the road for successful AML treatment. Leukemia development and chemoresistance are complex processes that do not depend only on the intrinsic accumulation of genetic alterations in hematopoietic progenitor cells. Recent findings have demonstrated the **key role of the bone marrow (BM) niche** in sustaining AML and regulating drug resistance. **Concomitant "seed" and "soil" targeting** may thus eradicate AML leukemic stem cells and improve patient's survival.

The goal of the proposed work is to **define and validate novel niche-leukemic crosstalk-induced dependencies using high-throughput functional screening methods**. Driven in large part by therapeutic considerations, our team developed a physiologically-relevant *in vivo* model: an **ectopic humanized BM-AML organoid specifically engineered for large scale target discovery**.



The first part of this proposal will combine **powerful large scale *in vivo* functional screening** approaches within this innovative AML model, aiming to discover novel therapeutic gene candidates. We will then aim at **validating** the identified targets and conduct the necessary steps towards **translating** our findings to clinic, including identification of novel **biomarkers of response** to treatments and **synergy studies**. Finally, we will shed light on the **mechanistic underpinnings of the BM-leukemia crosstalk** using **transcriptomic-, epigenomic- and microscopy-based approaches.** *In vitro* **co-culture systems** of fluorescently labeled niche and leukemia cells, combined to RNA-interference screening will be used to decipher pathways involved in communications between leukemia and stroma.
Overall, the proposed research project provides a framework for defining and understanding AML microenvironment-related specific dependencies, and a path towards the discovery and preclinical validation of promising therapeutic targets in AML. Our discoveries may therefore contribute to novel and more efficacious treatments for this highly aggressive and lethal disease.

Key words: large-scale shRNA screen, humanized mouse model, omics (genomics, transcriptomics, epigenomics), *in vivo* imaging, acute myeloid leukemia, bone marrow, microenvironment, tumor-stroma crosstalk, therapeutic targets.

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

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Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

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Selected publications:

1. Su A, Ling F, Vaganay C, Sodaro G, Benaksas C, Dal Bello R, Forget A, Pardieu B, Lin KH, Rutter JC, Bassil CF, Fortin G, Pasanisi J, Antony-Debré I, Alexe G, Benoist JF, Pruvost A, Pikman Y, Qi J, Schlageter MH, Micol JB, Roti G, Cluzeau T, Dombret H, Preudhomme C, Fenouille N, Benajiba L, Golan H, Stegmaier K, Lobry C*, Wood KC*, Itzykson R*, Puissant A*. The folate cycle enzyme MTHFR is a critical regulator of cell response to MYC-targeting therapies. **Cancer Discov. 2020** in press IF 26.4

2. Benajiba L, Alexe G, Su A, Raffoux E, Soulier J, Hemann MT, Hermine O, Itzykson R, Stegmaier K and Puissant A. Creatine kinase pathway inhibition alters GSK3 and WNT signaling in EVI1-positive AML. **Leukemia. 2019**;33:800-804. IF 9.9

3. Benajiba L*, Wagner FF*, Campbell AJ, Weiwer M, Sacher JR, Gale JP, Ross L, Puissant A, Alexe G, Conway A, Back M, Pikman Y, Galinsky I, DeAngelo DJ, Stone RM, Kaya T, Shi X, Robers MB, Machleidt T, Wilkinson J, Hermine O, Kung A, Stein AJ, Lakshminarasimhan D, Hemann MT, Scolnick E, Zhang YL, Pan JQ, Stegmaier K and Holson EB. Exploiting an Asp-Glu "switch" in glycogen synthase kinase 3 to design paralog-selective inhibitors for use in acute myeloid leukemia. **Sci Transl Med. 2018**;10. IF 17.2

4. Fenouille N*, Bassil CF*, Ben-Sahra I, Benajiba L, Alexe G, Ramos A, Pikman Y, Conway AS, Burgess MR, Li Q, Luciano F, Auberger P, Galinsky I, DeAngelo DJ, Stone RM, Zhang Y, Perkins AS, Shannon K, Hemann MT, Puissant A and Stegmaier K. The creatine kinase pathway is a metabolic vulnerability in EVI1-positive acute myeloid leukemia. **Nat Med. 2017**;23:301-313. IF 30.6

5. Benajiba L, Salvado C, Dalle JH, Jubert C, Galambrun C, Soulier J, Socie G and Peffault de Latour R. HLA-matched related-donor HSCT in Fanconi anemia patients conditioned with cyclophosphamide and fludarabine. **Blood. 2015**;125:417-8. IF 16.6

Application & Contact: ***Applications must be sent to*** lina.benajiba@inserm.fr **as a single PDF file including:**

- Cover letter explaining the candidate's interest in joining the lab and his/her future career development expectations (max 1 page)
- Curriculum Vitae including academic track, main technical skills, main past achievements and scientific productions
- Contact details of three past supervisors who can be contacted for recommendation letters