Postdoctoral position (M/F; 1 yr, renewal 3 yrs) – Cancer Research Center of Toulouse

PROJECT

IRONAML53 – Uncovering and targeting metabolic vulnerabilities of acute myeloid leukemia harboring *TP53* mutations, promoting Darwinian advantages in leukemic evolution and drug resistance

Despite an improvement in the complete response rate obtained after conventional chemotherapy, overall survival of acute myeloid leukemia (AML) patients is still poor, especially for AML harbouring TP53 mutations. This is due to relapses caused by tumor regrowth initiated by chemoresistant leukemic clones. These clones are characterized by an enhanced oxidative metabolism, mitochondrial adaptation and metabolic flexibility. However, how p53-deficiency provides a competitive advantage to AML cells and whether all *TP53* mutations equally impacts metabolism and evolution of AML are currently unsolved questions. Our proposal supports that p53-mediated control of iron metabolism is an essential driver of AML progression and drug resistance. Our plan relies on the complementary expertise of the 4 partners in AML biology, in the p53 pathway, in iron metabolism and in oncometabolism who will utilize diverse multi-omics approaches. The IRONAML53 consortium proposes to study evolutionary biology of Tp53 AML and to demonstrate that distinct *TP53* mutation subtypes differentially influence cellular iron and oxidative metabolism of AML/MDS blasts. We will also investigate whether systemic/environmental iron load promotes TP53-mediated competitive advantages of certain clones during AML evolution pre- and post-treatment through their adaptive metabolic heterogeneity associated with a highest flexibility of their iron metabolism. Here, several risky and innovative aspects are developed including the utilization of Bioreactor-based *in vitro* cell culture system that can constantly maintain metabolite concentration in growth medium and allow a longitudinal study of competitive selection of specific TP53 clone(s). We will establish a novel syngenic model of TP53-driven AML and an *in vivo* tool of iron overload to challenge TP53-Mut mice model. Finally, our project aimed at cracking, at an unprecedented and multilayer level, how distinct *TP53* mutations impinge on mechanisms of drug resistance, relapse and Darwinian evolution of AML by controlling iron metabolism upon metabolic stress and drug exposure. This will provide novel avenues for preclinical investigations to eradicate drug-resistant TP53 clones.

MISSIONS

The postdoctoral fellow will be implicated in a highly collaborative project between the CRCT (JE Sarry, Toulouse), METATOUL (JC Portais, Toulouse), IRCM (L Le Cam, Montpellier) and Cochin (C Peysonneaux, Paris). The postdoctoral fellow will establish unique PDX models (well handled by the CRCT) and novel GEMMs and will study cellular and metabolic mapping of TP53 mutant leukemic blasts and their microenvironment in those models. He/she will be devoted to unravel the role of host iron in the development of selective advantage and chemoresistance of distinct TP53 clones. Her/his work will be done in close collaboration with PhD students and engineers working on the multidisicplianry project. General responsibilities include design, implement and interpret experiments, both independently and in collaboration, and communicate research and findings in a clear and concise manner. The postdoctoral fellow will present the progress of the project during bi-monthly meetings between the different teams, as well as during national and international conferences.

QUALIFICATIONS REQUIRED

- A PhD degree preferably in biochemistry or cell biology and physiology
- Expertise in the field of metabolism and cancer biology will be highly prioritized
- Hands-on experience on *in vivo* (mice/GEMM) experiments, multi-color flow cytometry, and cell culture of mammalian primary cells
- High levels of initiative, autonomy and the ability to assume a high level of responsibility
- Strong interpersonal and mentoring skills needed to effectively deal with students and people of the several collaborating partners

Additional qualifications desired

- Experience in editing and writing original research articles and grant applications is an asset

EMPLOYMENT

Starting beginning of 2023, the job position is funded by an INCA-HRHG grant.
The application should be written in English and include:

1. Letter of motivation with a short description of the applicant's previous research and why the applicant considers her/himself a good match for the position (1-2 pages).
2. Curriculum vitae, including a description of relevant skills and experiences, as well as a full publication list.
3. Names, e-mail addresses and telephone numbers to 2-3 references.

CONTACT

Application should be sent to Jean-Emmanuel Sarry (jean-emmanuel.sarry@inserm.fr).