POST-DOCTORAL POSITION IN MONTPELLIER (FRANCE)

Epigenetic control of metabolic genes by the p53 pathway

Offer description: 2 years post-doc position in the laboratory of Dr. Laurent Le Cam at Montpellier Cancer Center (Montpellier, FRANCE) in the fields of Metabolism and Epigenetics.

Background: Our current research aims at exploring the interplay between transcriptional networks, chromatin organization and cellular metabolism, and at investigating how perturbations of these networks lead to human diseases and influence aging. We have a particular interest in the molecular cascade implicating the p53 tumor suppressor and the mechanisms by which essential components of this pathway control cellular metabolism. Using integrated approaches combining mouse genetics, metabolomics, genomics, and computational modeling, we intend to understand how modulation of these metabolic networks contribute to normal tissue homeostasis, metabolic disorders and cancer progression.

Highlights: In the past 5 years, we identified new mechanisms of regulation of amino-acid, lipid and pyruvate metabolism by key components of the p53 pathway, including E4F1, MDM2 and p53. Altogether, our data highlight the under-estimated complexity of these metabolic networks and clearly show that their perturbation contribute not only to cancer development but also to developmental defects and to metabolic disorders. Some of our studies on these metabolic networks also provide a strong rationale for the development of new therapeutic strategies for specific cancer subtypes.

1- Cissé M. et al. (2020) Targeting MDM2-dependent serine metabolism as a new therapeutic strategy for liposarcoma. ***Science Transational Medecine***. In press
2- Arena G. et al. (2018) Mitochondrial MDM2 regulates respiratory complex I activity independently of p53. ***Mol. Cell.*** Feb 15;69(4):594-609.
3- Riscal R. et al. (2016). Chromatin-bound MDM2 regulates serine metabolism and redox homeostasis independently of p53. ***Mol. Cell***. Jun 16;62(6):890-902
4- Lacroix M.*, Rodier G.*, Kirsh O.* et al. (2016) The transcription factor E4F1 controls a transcriptional program essential for pyruvate dehydrogenase activity. ***Proc Natl Acad Sci U S A.*** 113(39):10998-1003
5- Goguet-Rubio P.*, Seyran B.* et al. (2016) E4F1-mediated control of pyruvate dehydrogenase activity is essential for normal skin homeostasis. ***Proc Natl Acad Sci U S A.*** 113(39):11004-9.
6- Rodier G.*, #, Kirsh O.* et al. (2015) The transcription factor E4F1 coordinates CHK1-dependent checkpoint and mitochondrial functions. ***Cell Reports*** Apr 14;11(2):220-33.

Objectives and profile of the applicants: To identify new molecular mechanisms by which key components of the p53 pathway influence the expression of important metabolic genes, we plan to extensively characterize several metabolic tissues (liver, adipose tissue, muscles) and primary cells isolated from our genetically-engineered mouse models harboring defined genetic alterations of *E4f1*, *Mdm2*, and *Trp53*, using a combination of RNA-seq, ChIP-seq, ATAC-seq and HiChIP approaches. This strategy should allow us to understand how key components of the p53 pathway control chromatin accessibility and DNA long-range contacts that influence the expression of their metabolic targets. The applicants must have a recognized expertise in the field of epigenetics and a strong background in computational biology in order to integrate multi-omics datasets. A previous experience in the field of metabolism would be an added value but is not mandatory. This project is currently supported by the ARC foundation and the French National Cancer Institute (INCa).

For more informations, please visit our website : http://www.ircm.fr/

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