JOB DESCRIPTION

Job Title : **Post-doctoral position on Huntington's disease**

Job Summary :
(English, max 1000 characters)

A two-year post-doctoral position is available in the Laboratory of Cognitive and Adaptive Neurosciences (LNCA) in Strasbourg to study the relationship between metabolic and epigenetic alterations in Huntington's disease (HD), a neurodegenerative disease leading to motor, cognitive and psychiatric symptoms and affecting primarily the striatum. No cure is currently available for this disease and it is therefore essential to better decipher the pathological mechanism. Epigenetic regulations and energy metabolism are two critical processes early impaired in HD. Limited glucose uptake is a primary, initial mechanism contributing to impaired energy metabolism in HD striatum. Remarkably, early decrease of histone acetylation and transcription at striatal neuronal genes is also a hallmark of HD striatum. Seminal findings showed that energy cell status and histone acetylation interplay, suggesting possible link between altered epigenetic regulations and energy metabolism in HD. Building on our expertise on epigenetics in HD, we aim to investigate this intriguing hypothesis. Expected results should provide novel mechanistic insights, which might then lead to the identification of new therapeutic targets or strategies.

Job Description :
(*English, detailed information – max 3000 characters*)
WARNING: Pleases indicate the name of the research lab, group leader and supervisor.

The acetyl-CoA synthetase Acss2, a key metabolic intermediate, has been linked to histone acetylation regulation. Upon energy stress, including glucose deprivation, Acss2 translocates into the nucleus, where it converts nuclear acetate to acetyl-CoA, thereby increasing H3K27ac and transcription of metabolic genes, which ultimately promotes cell survival. Acss2 is also a critical regulator of learning and memory genes. It can provide acetyl-CoA for histone acetylation (H3K27ac) at neural activity-regulated genes, thereby promoting learning and memory. The mechanism involves recruitment of Acss2 at CBP-enriched chromatin regions, which increases H3K27ac and facilitates the induction of learning/memory genes. Our recent RNAseq and ChIPseq data on HD mouse striatum show that the regulation of these genes is impaired. Since HD neurons also suffer from metabolic stress, Acss2 may be recruited at metabolic genes, possibly at the expense of learning/memory genes. To explore this hypothesis, **1)** we will assess whether Acss2-mediated regulation is impaired in HD mouse striatum, using mouse models, classical molecular biology and imaging techniques. RNAseq and ChIPseq experiments will also be performed. **2)** We will investigate whether oversexpression of Acss2 (through AAV delivery) rescues molecular and functional phenotypes of HD mice.

Position available at LNCA/University of Strasbourg (UMR7364 head Jean-Christophe Cassel), under the supervision of Dr. Karine Merienne

Related Publications:
- Achour, M. *et al.* Neuronal identity genes regulated by super-enhancers are preferentially down-regulated in the striatum of Huntington's disease mice. *Hum Mol Genet* **24**, 3481-3496, doi:10.1093/hmg/ddv099 (2015).
- Le Gras, S. *et al.* Altered enhancer transcription underlies Huntington's disease striatal transcriptional signature. *Sci Rep* **7**, 42875, doi:10.1038/srep42875 (2017).
- Francelle, L., Lotz, C., Outeiro, T., Brouillet, E. & Merienne, K. Contribution of Neuroepigenetics to Huntington's Disease. *Front Hum Neurosci* **11**, 17, doi:10.3389/fnhum.2017.00017 (2017).

- Chatterjee, S. *et al.* Reinstating plasticity and memory in a tauopathy mouse model with an acetyltransferase activator. *EMBO Mol Med* **10**, doi:10.15252/emmm.201708587 (2018).
- Merienne, N. *et al.* New method for cell-type specific gene expression profiling in adult mouse brain reveals normal and disease-state signatures. *Cell Rep* **26**, 2477-2493, doi:10.1016/j.celrep.2019.02.003 (2019)

Main research field :

WARNING: Please select, trying to be specific, using 'Other' or 'All' will decrease your Job Vacancy visibility

Biological sciences / Medical sciences / Neurosciences

Offer Requirements :

Prior experience in molecular biology is required. Skills in functional genomics/bioinformatics and/or mouse behavior will be an asset.

Eligibility criteria :

PhD in biological sciences required

Highly motivated candidates should send their application (motivation letter, CV, and at least two recommendation letters) to Karine Merienne (karine.merienne@unistra.fr).

JOB DETAIL

Type of contract : CDD

Status : Post-doc

Company / Institute : LNCA/ Strasbourg university UMR 7364

Country : France

City : Strasbourg

Postal Code : 67000

Street : 12 rue Goethe

APPLICATION DETAILS (mandatory)

Provisional start date : 01/10/2019

Application e-mail : karine.merienne@unistra.fr

WARNING: This is the contact e-mail for applicants