Ph.D. Position in the Department of Translational Medecine and Neurogenetics at the IGBMC in Strasbourg, France.

Our team have worked on deciphering the pathophysiology of **neurodevelopmental disorders with cognitive deficits**. Our interest have mostly focused on **Down syndrome (DS) (Trisomy 21)**. Using behavioral tests for learning and memory, molecular and genetic analyses, we have identified genes and pathways involved in DS cognition and generated a phenotype-genotype map and found epistatic interactions occurring between trisomic genes. We have also validated several drug to improve cognition in preclinical models.

We are looking for a motivated student with a Master in Biology, Neurosciences or Genetics to join our team and work on a PhD project involving two genes, Cbs (Lopes Pereira et al. 2009; Marechal et al. 2019) and Dyrk1a (Duchon and Herault, 2016; Nguyen et al. 2018) (See project description below) that are involved in DS cognitive deficits. For this, the candidate will combine genetic and pharmacological approaches with mouse and/or unique rat models and with expression analysis based on neuronal single cell analysis (RNAseq) using mouse tissue or cell cultures to understand the nature of the molecular interaction between Cbs and Dyrk1a.

The candidate will learn basic techniques in mouse genetics and phenotyping (maintenance of colonies, genotyping, Behavioral and physiological analyses), in molecular biology (DNA, RNA and protein extraction and analysis) and cell biology (primary neuronal cells cultures, immunofluorescence, classical and confocal microscopy). He or she will also benefit from a training in new techniques of genomic and transcriptional analyses (RNAseq, single cells, and proteome analysis) and will have the occasion to collaborate with French and European partners.

The candidate must hold a **Master degree in Science or equivalent** (5 years of higher education) and will have to start their PhD between October and the end of the year. The PhD is funded by the **IMCBio International PhD program**. The candidate should apply to this program via the following link: http://imcbio-phdprogram.unistra.fr/
The registration for the 2020 call is open until February 23, 2020, noon (Paris time).

Research Unit

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PhD subject

Title: Deciphering genetic interactions of Chromosome 21 genes involved in the cognitive deficits observed in Down syndrome

Description:

Trisomy 21 (T21) (Down syndrome, DS), due to the presence of 3 copies of chromosome 21 (Hsa21), is the first genetic cause of intellectual disability (ID). There is currently no drug treatment for ID. Several studies using trisomic mouse models and aimed to understand the impact of the overexpression of Hsa21 genes suggest that a restricted number of genes could be responsible for the ID. One of them, *CBS,* code for the cystathionine β-synthase enzyme which is implicated in cysteine synthesis and in the production of hydrogen sulfide (H2S), a neuromodulator. We have shown that *CBS* overexpression was responsible for the memory deficit observed in a partial trisomic mouse model (1, 2), making CBS a target for drug treatment. But we also found an epistatic interaction of *CBS* with another ID gene, *DYRK1A*, for which several inhibitors are currently tested in clinical trials (3). Moreover, we found that *CBS* expression is also modulated by a yet unidentified Hsa21 gene. The goal of the PhD thesis is to characterize the functional relationship between CBS and DYRK1A and to identify the gene that modifies *CBS* expression. Taking advantage of combinations of mouse models with partial trisomies and transgenic overexpressing CBS or DYRK1A, the student will combine behavioral, cellular and molecular approaches to identify neurological systems and molecular pathways that are affected by overdosage of those proteins. Understanding the interplay between proteins involved in DS ID is crucial for developing the best therapeutic approach in this pathology.

Key words: Trisomy 21, Intellectual disability, CBS, DYRK1A

1. Lopes Pereira et al. A new mouse model for the trisomy of the Abcg1–U2af1 region reveals the complexity of the combinatorial genetic code of Down syndrome. *Human Molecular Genetics.* 18: 4756–4769 (2009).

2. Maréchal et al. *Cbs* overdosage is necessary and sufficient to induce cognitive phenotypes in mouse models of Down syndrome and interacts genetically with *Dyrk1a*. *Human Molecular Genetics.* 28: 1561–1577 (2019).

3. De la Torre et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): a double-blind, randomised, placebo-controlled, phase 2 trial. L*ancet Neurol*. 15: 1474-4422 (2016).