G. Friocourt is looking for a highly motivated student to do a **PhD on the study of cellular consequences of Cystathionine β-Synthase overexpression in intellectual deficiency in Down syndrome and validation of the therapeutic potential of new candidate drugs**

**Socio-economic and scientific context**:

Down syndrome (DS), which is characterized by a partial or complete triplication of chromosome 21 has an incidence that remains between one in 730 to 1 000 live births depending on the country. Although early management of children and educational therapy are now provided, there is to date no available pharmacotherapy that could lessen the level of cognitive impairment. As this would have substantial social consequences, much effort is being made to identify the dosage-sensitive genes underlying the intellectual deficiency in DS. So far, the kinase DYRK1A has been the main target for therapeutic intervention with the identification of a few compounds inhibiting its protein kinase activity, improving cognition in DS mouse models but with limited success in patients. Another gene of interest, *CBS*, encodes cystathionine β-synthase, an enzyme of the transsulfuration pathway that is involved in the synthesis of cysteine and glutathione at the expense of methionine. Inhibitors of this enzyme would thus be good candidate drugs to alleviate, at least partly, cognitive deficits of DS patients. We have recently developed a yeast model overexpressing *CYS4*, the yeast homolog of CBS, and screened FDA-approved molecules. Using this strategy, we identified 3 drugs already in use for other pathologies, which are able to counteract the cellular consequences of *CYS4*-overexpression. One of this molecule was tested in *Cbs*-overexpressing mice and was able to suppress their defects in the object recognition test (Maréchal *et al.*, Hum Mol Genet 2019).

**Working hypothesis and aims**:

The impact of *CBS* overexpression on cognitive functioning has been so far unclear. Our data show that in yeast, *CYS4* overexpression leads to pH acidification and vesicular trafficking defects. We now aim at validating these observations on different cellular and mouse models which are closer to the pathology of interest with 3 different objectives: (i) determine whether these defects are also found in the mouse model expressing 3 copies of *Cbs* as well as in cellular models for DS, which would unravel new hypotheses to explain intellectual deficiency associated with *CBS* triplication; (ii) validate the therapeutic potential of our 3 candidate drugs in the above-mentioned mouse and cellular models, in particular by testing their effect on pH and vesicular trafficking and iii) investigate the genetic relationship between CBS and DYRK1A, in order to better adapt the therapeutic strategies targeting the triplication of these two genes.

**Main milestones of the thesis**:

As there is no good mouse model for DS, we will first determine whether fibroblasts or neurons from *Cbs*-triplicated mice have defects in pH homeostasis and vesicular trafficking. Then we will use two different cellular models of DS, fibroblasts from patients and neurons derived from iPS (induced pluripotent stem) cells to validate these observations, not only in a cellular context of trisomy of the whole chromosome 21, but also in a neuronal context. The

second main milestone of the PhD will be to validate the therapeutic potential of our 3 candidate drugs. As these 3 molecules restore in a dose-dependent manner the pH defects of *CYS4*-overexpressing yeast cells, we will test their effect on cellular pH, vesicular trafficking as well as on the level of the different metabolites of the transsulfuration pathway in both treated versus non treated Cbs-triplicated mice and in DS cellular models. The third objective of the PhD will be to further characterize the genetic relationship between *CBS* and *DYRK1A*, two genes present on chromosome 21 and thus triplicated in DS, and important for neurodevelopment and cognitive aspects. Our preliminary results suggest that their effects may be additive, further reinforcing the idea of developing combined therapeutic strategies targeting the effects of the overexpression of these two genes.

**Eligibility Criteria**

The candidate must have solid theoretical and practical skills in molecular biology (subcloning, RT-qPCR, mutagenesis), in cell culture (fibroblasts, primary neuronal cultures, iPS...), as well as in immunolabelling of mouse sections (IHC, IF...). The candidate must have a solid motivation to do a PhD, good skills for data analysis, communication and a great scientific and technic rigor.

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