Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : Institut du Cerveau et de la Moelle épinière
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2. Internship project title:

Assessment of the contribution of a long non-coding RNA in Parkinson's Disease : preliminary loss of function study in human dopaminergic neurons *in vitro*.

3. Internship Description :

Most neurodegenerative diseases are associated with the dysfunction and/or degeneration of specific cell types. In the case of Parkinson's Disease (PD), the onset of symptoms occurs when a large proportion of the dopaminergic (DA) neurons in the *substantia nigra pars compacta* (SNpc) are already lost, leading to a significant alteration of the basal ganglia circuitry. Exploring and understanding the molecular mechanisms driving the PD associated cell- and tissue-selectivity constitutes therefore a key challenge in order to fully apprehend the physiopathology of the disease.

In addition, genome-wide association studies (GWAS) on large cohorts of patients have shown a prominent role of genetic factors in the etiopathology of PD. Importantly, only 10% of the cases represent familial monogenic forms of the disease, such that most of the sporadic forms of PD remain unexplained. Today, 41 loci of risk factors associated with single nucleotide polymorphisms (SNPs) have been identified and the subsequent functional studies mainly focus on candidate genes that encode proteins. Yet, protein-coding genes hardly account for 2% of the transcribed genome, and the vast majority of PD associated SNPs fall into non-coding regions that potentially harbor transcriptional/translational regulatory functions. This calls into question the ability of current studies based on protein coding genes to reflect the whole complexity of PD. Acquiring knowledge of the function of non-coding elements in a PD-relevant human cell type would thus represent a major breakthrough for understanding this and other pathophysiologies and, hence, developing new therapies.

In the laboratory, we use high throughput genome analyses to characterize in human iPS-derived DA neurons a category of non-coding elements that are understudied in human diseases, the long non-coding RNAs (lncRNAs). LncRNAs are increasingly scrutinized for their multiple regulatory functions

from the epigenetic to the post-translational levels, and for their involvement in crucial developmental and cellular processes, such as neuronal differentiation and maturation. Moreover, recent developments suggest that lncRNAs constitute repertoires displaying much greater cell specificity than protein-coding genes. Altogether, these data make lncRNAs ideal candidate determinants of cellular specificity, providing an unprecedented opportunity for the investigation of their role in human diseases associated with specific cell-types. In this context, a growing body of literature associates lncRNAs to a large variety of human diseases, including neurodegenerative disorders, notably by revealing their putative contribution as genetic risk factors. Therefore, in the context of PD, we anticipate that these non-coding elements will turn out to constitute molecular signatures governing DA neurons specificity, and by extension, intrinsic vulnerability.

In this context, we have identified candidate lncRNAs harboring PD-associated polymorphisms: they represent promising new candidates to study the molecular basis of PD. We propose to analyze the function of one candidate lncRNA in DA neurons, using gain/loss-of function strategies. Thus, the M2 student will 1) analyse the candidate lncRNA expression during the differentiation of iPS cells and LUHMES cells into dopaminergic neurons; 2) perform Knock down experiments and 3) study the effect of the KD on the dopaminergic differentiation, the cell survival following application of a mitochondrial stress and their transcriptome.