CSC-RUB PhD Project Proposal

Title: Molecular regulation in cortical neurogenesis and neuronal reprogramming

Sector of research: Neuroscience, developmental neurobiology, neural stem cells

Degree awarded: PhD in Neuroscience

Keywords: brain development, neural stem cell, neurogenesis, neuronal reprogramming, neurodevelopmental disorder, brain repair, molecular genetics, transcriptional and epigenetic regulation.

Supervisor of PhD project:

Dr. Tran Tuoc & Prof. Huu Phuc Nguyen, Dept. Human Genetics ; e-mail: tran.tuoc@rub.de

Research focus of supervisor: Our long-term interest is to investigate how the degenerated, injured brain and neurological disorders can recover. In the long run, we believe that understanding the intrinsic factors, including chromatin/epigenetic programs, that instruct neuronal fates, will greatly help cell replacement therapy for neurodegenerative diseases by manipulating these factors and thus inducing neuronal generation. Toward our goals, we are interested in elucidating the molecular features of the evolutionarily and clinically important basal progenitors (BPs), including the basal radial glia (bRGs) and intermediate progenitors (bIPs) in developing brain. Recent findings in our laboratory have unraveled a number of key BP-enriched chromatin and epigenetic factors, which play essential roles in cortical neurogenesis. Furthermore, with the advent of next-generation sequencing (NGS), genes encoding for such BP-enriched factors in human neurological disorders have been discovered. By combining a genome-editing technique with genomic & proteomic approaches, the knowledge gained from our study should significantly improve our understanding of the genetic and molecular regulation of brain development, as well as the etiology of brain malformations.

Publications: {selection of five relevant papers}

1. Kerimoglu et al. H3 acetylation selectively promotes basal progenitor proliferation and neocortex expansion. Science advances. 2021;7(38). PubMed: 34524839.
2. Ulmke et al. Molecular Profiling Reveals Involvement of ESCO2 in Intermediate Progenitor Cell Maintenance in the Developing Mouse Cortex. Stem Cell Reports. 2021. PubMed: 33798452.
3. Nguyen et al. Epigenetic Regulation by BAF Complexes Limits Neural Stem Cell Proliferation by Suppressing Wnt Signaling in Late Embryonic Development. Stem Cell Reports. 2018;10(6):1734-50. PubMed: 29779894.
4. Narayanan et al. Loss of BAF (mSWI/SNF) Complexes Causes Global Transcriptional and Chromatin State Changes in Forebrain Development. Cell Rep. 2015;13(9):1842-54. PubMed: 26655900.
5. Tuoc et al. Chromatin Regulation by BAF170 Controls Cerebral Cortical Size and Thickness. Developmental Cell. 2013;25(3):256-69. PubMed: 23643363.

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Summary of research plan

Background:

Recent advances have uncovered specific molecular and cellular features of cortical neural stem cells (NSCs) that might contribute to the cortical neurogenesis. Interspecies comparisons have revealed specific proliferative characteristics of the two main types of NSCs: the apical progenitors (APs) and basal progenitors (BPs), which are located in two forebrain germinative zones: the ventricular zone and the subventricular zone, respectively. In particular, BPs appear to play decisive roles in the cortical neurogenesis, size expansion and cortical folding of evolutionarily advanced species. Although some BP-specific molecular determinants have recently been identified, we know little about how distinct transcriptional programs act in concert with epigenetic modulators to control the specification of BPs during cortical ontogenesis and evolution.

Study objective:

1. To examine the epigenome and gene expression signatures of basal progenitors (BPs) and their subtypes in the developing cortex of evolutionarily distinct species, including rodent and human.
2. To identify novel factors and epigenetic programs that control BP genesis, and cortical neurogenesis.
3. The functions of above factors and their target genes will be elucidated partly by using spatiotemporal-specific (epi)genome editing tools such as Cre/LoxP based, chemically/light inducible- systems in developing mouse cortex or in cerebral organoids.
4. To establish protocols for the basal progenitor reprogramming from other cell sources for treatment of brain injury and stroke in rodent models.

Expected Results: Our study implicates that manipulation of the endogenous expression level of above factors may provide a means to generate larger numbers of neurons for potential treatment for neurogenerative disorders or repairing the injured brain.

Methods: Cultures (NSC, cerebral organoid), neuronal reprograming, Cell sorting, NGS (RNA-seq, ChIP-seq, ATAC-seq, HiC-seq), Galaxy-based bioinformatic analysis, ICC/IHC, Confocal microscopy, Crispr-Cas based epi(genome) editing, mouse in utero/in oviduct electroporation

Candidate Requirements: Completion of MSc, diploma or equivalent degree in biology, biochemistry, or natural sciences; good English language skills.

Motivation for CSC application (max 250 words): While your living expense, health insurance and administration fees of university are covered by your scholarship program, we will supervise your work and provide you with laboratory space, network resources and all facilities and supplies required for your research. We will assist for your integration into the Ruhr University Research School, for interdisciplinary skills development etc…