CSC-RUB PhD Project Proposal

Title: Molecular mechanisms cause primary microcephaly in human and mouse

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: The development of the human cortex is a complex and tightly regulated process. During cortical development, distinct cell types proliferate, differentiate, migrate, and integrate to form a highly complex structure that provides the structural basis for the sensory perception, cognitive function, and mental ability of higher primates. Disruptions in any of the abovementioned cellular processes lead to malformations in cortical development (MCD), which are common causes of neurodevelopmental delay or disability. Recent advances in genetic tools and sequencing technologies have expanded our understanding of the genetic causes of neurodevelopmental disorders, such as microcephaly. Nonetheless, the mechanisms underlying MCD are still poorly understood.

Study objective: By screening a panel of patients with a wide range of brain malformations, we identified microcephalic individuals harboring *de novo* mutations in the genes encoding EXOSC10, which is a core subunit of the RNA-decay exosome complex, and NSD2, which is a H3K36 methyltransferase. By combining a genome-editing technique with genomic and proteomic approaches, we herein propose to:

1. generate *EXOSC10* and *NSD2* mouse mutants and characterize their cortical phenotypes
2. study the *EXOSC10*- and *NSD2*-dependent mechanisms that control cortical neurogenesis; and
3. elucidate how the identified *de novo* mutations influence the functions of *EXOSC10* and *NSD2* during cortical neurogenesis and ultimately cause microcephaly.

Expected Results: This study should provide valuable insights into the EXOSC10- and NSD2-mediated mechanisms that control cortical neurogenesis in mouse and human.

Methods: Cultures (NSC, cerebral organoid), Cell sorting, NGS (RNA-seq, RIP-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…