

# Loydie Jerome-Majewska- Scientific Summary

**Project Title:** Impact of Spliceosomal Defects on Early Brain Development

**Statement of Purpose:** We will use mouse models of human diseases caused by mutations in genes involved in pre-mRNA splicing to understand the effect of splicing defects on early embryonic brain development.

**Project Summary:**

Pre-mRNA splicing is an essential molecular process in most eukaryotic organisms. Following transcription, intronic sequences must be removed in order to produce translatable mRNA molecules. Alternative splicing, is thought to be particularly important in the normal developing brain, where it increases transcriptomic diversity. Aberrant splicing contributes to disease and cancer. Mutations in at least 8 genes that encode core components of the spliceosome – the large protein complex responsible for the splicing process - are known to cause developmental disorders that include microcephaly, autism, sensorineural hearing loss, eye anomalies, psychomotor delay and intellectual disability.

Our group has been involved in identifying several of those mutations in human patients and is currently poised to study their downstream effects in a mouse model system: Mandibulofacial dysostosis and microcephaly syndrome (caused by mutations in the gene EFTUD2), Nager syndrome (mutations in SF3B4), and cerebro-costal mandibular syndrome (mutations in SNRPB). We used CRISPR-cas9 genome editing to generate mouse models of the above three diseases. We have established that the mutant animals exhibit developmental abnormalities as early as embryonic day 9.5. In this proposal, we will focus on the effect of the spliceosomal mutations on the developing brain. We will identify both differences and similarities across the three distinct disorders. Focusing on the similarities, we will aim to understand common splicing aberrations that are likely to be universally important to neurodevelopment and hence pertinent to a wider range of neurodevelopmental disorders. In addition to classical experimental approaches, I propose to use RNA-sequencing and single-cell RNA sequencing to profile splicing defects in the structures of interest and identify transcriptomic changes in specific sub-populations of cells. The long-term goal of this research program is to identify pathways that can be used as therapeutic targets in neurodevelopmental disorders. I have many years of experience in using mouse models to study early embryonic development, with particular emphasis on craniofacial and neurodevelopmental defects. Our experience and the availability of mouse lines that have already been created puts us in a unique position to understand the role of pre-mRNA splicing in both hereditary disease and normal neurodevelopment.