Elucidating the role of Glut1 in neural development and disease.

The development of the brain depends upon the precise regulation and organization of neural progenitor cells (NPCs). NPCs are the building blocks of the brain and generate the billions of neurons and glia that form our incredibly complex and sophisticated brains. Perturbations in the regulation and character of NPC populations have been linked to neurodevelopmental disorders (NDDs), including Autism, ADHD, and epilepsy.

Our research group uses a combination of mouse and human models to study the role of NDD genes during early brain development. Our previous study focused on the high-risk Autism gene, Foxp1. We found that loss of Foxp1 in early NPCs leads to the upregulation of many genes associated with glycolysis, including Slc2a1. This shift in glycolysis gene expression is associated with a premature transition of NPCs towards differentiation *(Buth, Dyevich et al., EMBO Reports, 2024).*

We have shown that mouse and human NPCs express *Slc2a1*, which encodes glucose transporter 1 (Glut1). During mouse neurogenesis, Glut1 is increasingly expressed in NPCs as they begin to generate neurons. Using conditional mouse genetics, we have selectively removed Glut1 from NPCs in the developing cortex. We have demonstrated that loss of Glut1 results in an increase of NPCs in the early cortex, at the expense of neuron generation. Furthermore, the type of neuron being generated is altered, such that there is an increase in the number of early-born neurons at late stages of embryogenesis. These changes in progenitor character coincide with metabolic changes that may be influencing the cell fate decisions of NPCs. Processes such as the Pentose Phosphate Pathway and nucleotide synthesis are prevalent in early NPCs lacking Glut1, whereas the TCA cycle and anaerobic glycolysis are disrupted.

To begin to model GLUT1-deficiency syndrome (GLUT1-DS) in a human model, we generated human embryonic stem cell lines missing one or two copies of the GLUT1 gene. We then generate 3-dimensional cerebral organoids to determine how the loss of one or two copies of GLUT1 impacts the early stages of brain development. Preliminary studies have shown that loss of GLUT1 impacts the morphology of organoids, and this is associated with changes in cell cycle dynamics, as discussed by Dr Hudson Freeze. This study demonstrates the power of *in vitro* organoid system in modeling human disorders and testing the efficacy and mechanism of potential treatments.