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Embryonic stem cells cross-correct for defects found in a mutant mouse model for the neurodegenerative disorder known as Batten Disease

Megan McFerson and Mark Kirk

Our research focuses on a class of hereditary diseases called the neuronal ceroid-lipofuscinoses (NCLs), also known as Batten Disease. The NCLs are a group of autosomal, recessively inherited, progressive neurodegenerative disorders characterized by the accumulation of autofluorescent lipopigment in various tissues, including the retina and CNS. We are focusing on Early Infantile NCL, caused by a mutation in the Cln1 gene. Cln1 is the gene responsible for production of the lysosomal enzyme Palmitoyl Protein Thioesterease-1. PPT-1 breaks down lipopigments, so when it is mutated lipopigments accumulate in lysosomes. We are working on a mouse model with the Cln1 gene knocked out whose brains show an accumulation of autofluorescent lysosomal lipopigment. Our goal is to use murine embryonic stem cells to cross-correct for defects in the Cln1 mice. We anesthetized 7-10 day postnatal Cln1 knockout mice, removed their brains, and made 400 micrometer thick slices of their brains. We maintained the slices on porous membranes for 7 days as organotypic slice cultures, and then transplanted B5 mouse embryonic stem cells onto the slices. Since the B5 cells are EGFP-expressing, they appear green under a fluorescent microscope. After several days we looked at the slices under a fluorescent microscope and tracked movement and proliferation of the stem cells. We continued to monitor the slices for a couple of weeks to track the cells and to test for any reduction in accumulation of the lysosomal storage bodies. Preliminary results show brain slices of Cln1 knockout mice transplanted with B5 stem cells show a reduction in the number of lysosomal lipopigments. In the future, we will transfect stem cells with the PPT-1 gene under the control of a regulated promoter, resulting in neural stem cells that will produce the PPT-1 enzyme on demand. We hope that these stem cells will be able to produce PPT-1 to reduce and possibly eliminate all the lysosomal storage bodies in the deficient cells, thus preventing cell death.