**Huntington’s Disease**

Huntington’s Disease (HD) is a fatal neurodegenerative disorder that strikes individuals in the prime of life, with onset generally between ages 35 and 50, and extends years before death. Estimates are that at least one in every 10,000 persons in the United States have HD. HD is autosomal dominant, meaning children of existing patients are at 50% risk. To date, no disease-modifying treatments have been developed for HD. Consequently, HD represents a completely unmet medical need, and the development of any therapeutic treatment to benefit affected individuals would have a profound effect. Given the devastating impact of HD on patients and families, an urgent need exists to identify effective treatment approaches. The highly penetrant HD gene leads to neuronal dysfunction and clinical expression of involuntary movements, progressive intellectual decline, and behavioral disturbances. Overt clinical expression of involuntary movements, progressive intellectual decline, and behavioral disturbances. Overt clinical expression of involuntary movements, progressive intellectual decline, and behavioral disturbances.

**Stem Cells**

The complexity of the brain and the impact of HD on multiple cellular pathways suggests that it is unlikely a single drug will prevent or significantly alter the disease. Cell-based approaches offer potential for rescue of pathways damaged by disease. We are performing studies in HD-modeled mice to develop human neural stem cells (hNSCs) as preclinical candidates to treat HD.

**Outcomes of implanting hNSCs into HD mice**

Implanting nestin positive hNSCs into the striatum causes a delay in the disease phenotypes in HD modeled R6/2 mice, including a delay in clasping.

**A SUMO-PIAS1 Balance**

**Potential Therapeutics for Huntington’s Disease**

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**Huntington’s Disease**

Cytosol

- Trafficking
- Aggregation

Nucleus

- SUMO-1/2/3 modification of mHTT

**ApICCT1**

CCT is a molecular chaperone that binds and folds newly synthesized proteins. The apical domain of the first subunit of CCT (ApICCT1) binds to mutant Huntingtin (mHTT) and inhibits aggregation in vitro and in vivo. ApICCT1 can penetrate the cell membrane to reduce intracellular toxic phenotypes, circumventing the need to establish complex methods to express the protein within affected cells. We have engineered viruses and mouse NSCs (mNSCs) to express secreted ApICCT1, combining the ability of ApICCT1 to target mHTT with the neurotrophic support of stem cells.

**Outcomes of implanting mNSC-sApICCT1 into HD mice**

R6/2 HD mice were implanted with mNSC-sApICCT1 in the striatum. Secretion of ApICCT1 in striatum enhances the therapeutic effects of stem cell transplantation. Mice with mNSC-sApICCT1 implantation showed significantly reduced mHTT aggregation (below) and delayed clasping behavior (not shown) compared to NSCs alone and vehicle control.

**Future Directions: Work towards clinical trials**

**A SUMO-PIAS1 Balance**

Diverse cellular processes are impacted by expression, post-translational modification, and accumulation of mHTT. A particular modification called SUMOylation involves covalent attachment of SUMO to specific lysine residues and modulates protein activity and clearance of mHTT.

- We have shown that a single E3 SUMO ligase, PIAS1, is elevated in HD mouse brain and increases both SUMO-1/2/3 modification of mHTT and the accumulation of insoluble HTT species, raising the possibility that changing levels of PIAS1 may provide a selective therapeutic target.

**Reducing PIAS1 rescues HD behavior deficits and reduces mHTT accumulation**

**Sample Figure**

**Engineering Stem Cells to Secrete ApICCT1**

Mouse NSCs engineered to secrete ApICCT1 reduce toxic mHTT aggregation when co-cultured with HD neurons. Aggregation was analyzed with agarose gel electrophoresis (AGE).

**Outcomes of implanting mNSC-sApICCT1 into HD mice**

R6/2 HD mice were implanted with mNSC-sApICCT1 in the striatum. Secretion of ApICCT1 in striatum enhances the therapeutic effects of stem cell transplantation. Mice with mNSC-sApICCT1 implantation showed significantly reduced mHTT aggregation (below) and delayed clasping behavior (not shown) compared to NSCs alone and vehicle control.

**Future Directions:**

What is the mechanism behind PIAS1-mediated rescue/deficits in HD?

**Balance is key!**

**Potential Benefits**

- Neuroprotection
- Neuroregeneration
- Neuronal Survival
- Neuronal Function
- Anti-inflammation

**Potential Detrimental Effects**

- Injury to Neuronal Elements
- Neuronal Death
- Neurodegeneration
- Aggregative Processes
- Neuroinflammation

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