# MODELING HUNTINGTONS DISEASE WITH STRIATAL NEURONS DIRECTLY CONVERTED FROM PATIENT FIBROBLASTS

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MODELING HUNTINGTONS DISEASE WITH STRIATAL NEURONS DIRECTLY CONVERTED FROM PATIENT FIBROBLASTS

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**Research Abstract**

PROJECT SUMMARY Huntington’s disease (HD) is an inherited neurological disorder that typically manifests in midlife. Although the genetic etiology of HD is known, the molecular mechanism that contributes to neuronal death are still poorly understood. HD is characterized

by two cellular hallmarks, i) the presence of misfolded and aggregated protein inclusions, generally thought to be toxic, and ii) massive degeneration of striatal medium spiny neurons (MSNs), a neuronal subpopulation critical for motor control. Due to the inaccessibility of human neurons, most of our understanding of the mechanism of HD pathogenesis has been studied in the context of non-human models. Recently, the ability to convert or reprogram easily accessible human cells, such as skin fibroblasts into neurons, have prompted many research groups to develop protocols to reprogram fibroblasts into various neuronal subtypes in the hope of one day reprogramming patient-specific cells and modeling neurological diseases in vitro. There are currently two distinct methods to generate human MSNs. The first relies on the induction of fibroblasts into pluripotent stem cells (iPSCs) and the subsequent differentiation of these cells into MSNs. The second, developed by us, takes advantage of brain-enriched microRNAs to directly (bypassing the induction of pluripotency) convert human adult fibroblasts to MSNs. Although the advantages of direct reprogramming are still not entirely clear, one unique benefit of this approach might be the ability to retain age- related cellular signatures in the converted cells. Defects accumulated in normal aging contribute to the onset of many neurological disorders, including HD, and we therefore believe direct reprogramming strategies might be better suited for modeling the pathogenesis of HD. In this proposal, we seek to employ directly reprogrammed MSNs to study the contribution of aging to triggering cell death and protein aggregation in HD. In our prelimary studies, we demonstrated that our microRNA-based approach can reprogram fibroblast from HD patients into MSNs with similar efficiencies despite of individual age. Additionally, we found that HD MSNs are more susceptible to cell death with time in culture than MSNs reprogrammed from age-matched healthy controls. Moreover, unlike other studies that model HD with iPSCs, our reprogrammed MSNs exhibit aggregated protein inclusions, suggesting that age-related factors contribute to the formation of aggregates. In the first aim of this proposal, we will rejuvenate fibroblasts from adult symptomatic HD patients by first inducing these cells into iPSCs and later re-differentiating them back into fibroblasts. Conversely, in the second aim we will accelerate the aging of adult symptomatic HD fibroblasts by forcing the expression of Progerin, a factor shown to induce cellular aging. Rejuvenated and aged fibroblasts will be converted into MSNs by miRNA- based reprogrammed, assayed for protein aggregation and cellular death and compared to normal aged MSNs reprogrammed from adult HD patients. Together, these experiments will determine if age-related cellular changes triggers protein aggregation and broaden our understanding of the pathogenic mechanisms in HD.

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