Washington University in St. Louis
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# MICRORNA-INDUCED DIRECT CONVERSION OF HUMAN ADULT FIBROBLASTS INTO NEURONS

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**Background:** Studying late-onset neurodegenerative disorders using patient-specific neurons is one of the primary goals of precision medicine. The ability to generate human neurons that mimic the neurons of elderly individuals will provide an instrumental platform to model and study adult-onset neurodegenerative disorders. Furthermore, because neurological disorders often affect discrete subtypes of neurons, it is necessary to generate specific subtypes of human neurons for disease-modeling purposes. Huntington's disease (HD) is a fatal neurodegenerative disorder that deteriorates a person's physical and mental abilities characterized by progressive neurodegeneration of striatal medium spiny neurons (MSNs). There are approximately 30,000 symptomatic Americans and over 200,000 at-risk of inheriting the disease. HD is caused by an abnormal expansion of CAG codons in the Huntingtin (*HTT*) gene where the CAG length correlates with the severity of the disease. Symptoms normally occur midlife during prime working years and in 10% of cases occur in children or adolescents. Currently, there is no cure and medications only manage HD symptoms. Modeling HD with patient-derived neurons has been challenging as MSNs from induced pluripotent stem cells (iPSCs) do not robustly recapitulate HD-associated phenotypes detected in adult neurons.

Figure 1. Direct Neuronal Reprogramming

**Technology Description:** Scientists at Washington University School of Medicine have developed a novel method to directly convert fibroblasts into neurons via microRNAs (miRNAs) (Figure 1). Brain-enriched miRNAs, miR-9/9* and miR-124, target multiple components of chromatin remodeling complexes when ectopically expressed in human adult fibroblasts and induce the direct cell fate switch from fibroblasts to neurons through an extensive reconfiguration of the chromatin landscape. Additional terminal selector transcription factor genes can be combined to guide the miRNA-mediated neuronal state to specific neuronal subtypes such as striatal neurons, spinal cord motor neurons, and cortical neurons whereas the subtype-defining transcription factors alone do not display reprogramming activities alone in human adult fibroblasts (Figure 1). The synergism between miRNAs and transcription factors provides a highly efficient and subtype-specific conversion method resulting in neurons that preserve the epigenetic memory of cellular "age" of the fibroblast donor, as observed by genetic and epigenetic indicators. This is particularly beneficial toward the study of adult-onset neurodegenerative diseases compared to utilizing cellular rejuvenated iPSCs. MiRNA-mediated direct conversion is also advantageous due to the specificity, speed, and efficiency of the reprogramming process in human adult fibroblasts.

**Key Advantages:**

- Direct neuronal reprograming of fibroblasts

- Rapid reprograming compared with iPSC-based methods
- Reprogrammed cells display gene expression analogous to endogenous neurons

- Cellular age maintained
- Optimal platform for studying late-onset neurodegenerative diseases

**Related Publications:**


- Striatal neurons directly converted from Huntington's disease patient fibroblasts recapitulate age-associated disease phenotypes. *Nature Neuroscience*. 2018. 21, 341-352 PMCID: PMC5857213
- MicroRNA-based conversion of human fibroblasts into striatal medium spiny neurons. *Nature Protocols.* 2015. 10, 1543-1555. PMID: 26379228
- Generation of human striatal neurons by microRNA-dependent direct conversion of fibroblasts. 2014. *Neuron.* 84, 311-323. PMCID: PMC4223654
- MicroRNA-mediated conversion of human fibroblasts to neurons. 2011. *Nature*. 476, 228-231.


**Patents: Pending**

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| Licensing Contact | Application Space | WUSTL Case# |
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