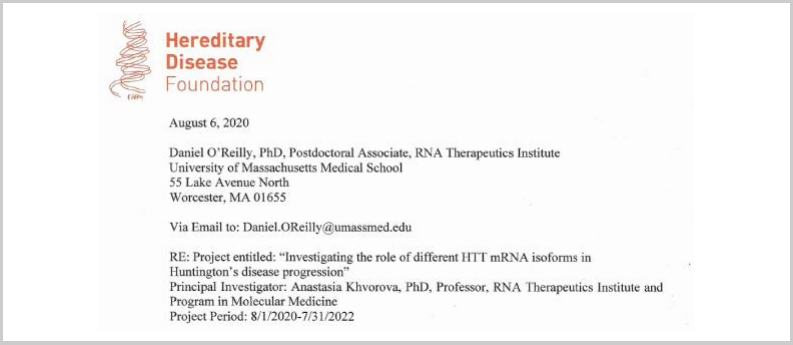
UMPA presents

Postdoc Spotlight Series

National Postdoc Appreciation Week

September 21-25

Let's celebrate us Postdocs!



Hereditary Disease Foundation

August 6, 2020

Daniel O'Reilly, PhD, Postdoctoral Associate, RNA Therapeutics Institute
University of Massachusetts Medical School
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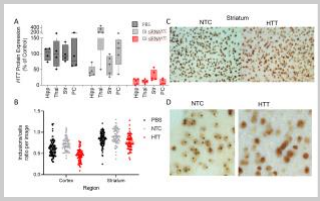
Via Email to: Daniel.OReilly@umassmed.edu

RE: Project entitled: "Investigating the role of different HTT mRNA isoforms in Huntington's disease progression"
Principal Investigator: Anastasia Khvorova, PhD, Professor, RNA Therapeutics Institute and Program in Molecular Medicine
Project Period: 8/1/2020-7/31/2022

Daniel O'Reilly Ph.D.

Khvorova lab

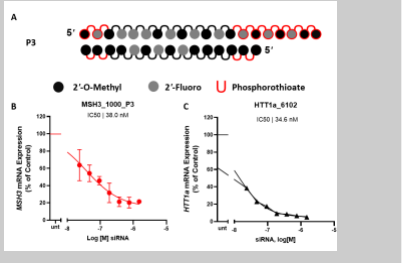
RNA Therapeutics Institute



Aggregate formation even after silencing of HTT mRNA

Dr. Dan O'Reilly is a Postdoctoral research associate, in Professor Anastasia Khvorova's lab, at the RNA Therapeutics Institute. Dan completed his PhD in chemistry in 2019 under the supervision of Professor Masad Damha at McGill University, Montreal, Canada. Dan's work in the Khvorova Lab involves utilizing oligonucleotides (siRNA) as potential treatments for rare diseases. Dan was recently awarded a fellowship from the Hereditary Disease Foundation

Huntington's Disease (HD) is a rare neurodegenerative genetic disorder caused by the expansion of CAG repeats in exon 1 of the huntingtin (*HTT*) gene, resulting in the transcription of mutated *HTT* mRNA and the translation of a mutated protein (mHTT). mHTT is prone to forming nuclear and cytoplasmic aggregates or "inclusions" in neurons. A minor isoform (HTT1a) is also produced. As the disease progresses, neurodegeneration occurs, and patients experience cognitive impairment and chorea. Currently, there is no cure for HD, in part, because the precise mechanisms are not understood.



<u>The goal of this proposal</u> is to systematically evaluate the contribution of somatic expansion of CAG repeats, and the *HTT1a* isoform, to HD *in vivo*. Our lab recently optimized a small interfering RNA (siRNA) chemical architecture – called Di-siRNA – that enables widespread, potent (>95%), and sustained (up to 6 months) gene silencing in rodent and nonhuman primate brain. To date, Di-siRNA compounds have been designed to target and degrade full-length m*HTT* mRNA. However, Di-siRNA have not been designed to target *HTT1a* mRNA. Fortunately, the siRNA sequence of Di-siRNA architecture can be altered to enable modulation of any target gene in the brain.

Our lab has performed extensive screens, and identified hyper-functional, fully chemically-stabilized sequences (compatible with Di-siRNA architecture) that selectively target *HTT1a* (sparing the full-length isoform), and *MSH3* – a key modifier of the somatic expansion of CAG repeats. I will use our Di-siRNA technology to selectively silence *HTT1a*, full-length m*HTT,* and *MSH3*, alone and in combination, in HD mouse models and evaluate the impact on somatic expansion, biochemical readouts (*HTT* mRNA and protein inclusions), and behavioral phenotypes. Mechanistic understanding of the role of *HTT* mRNA isoforms and somatic expansion on HD progression is vital to identifying an optimal therapeutic strategy for HD.