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Selective translation blockers of SNCA as potential therapies for Parkinson's disease

Aims: The mRNA for alpha-synuclein (a-syn) encodes a uniquely folded version of an iron-responsive element (IRE) RNA stem loop, which binds to Iron-regulatory protein-1 (IRP1) to control iron dependent a-syn translation. We have previously shown that posiphen inhibited SNCA mRNA translation by targeting its '5'untranslated region (UTR) in the micromolar range to lower a-syn levels ex vivo and in vivo.

1. To generate proof-of principle that the5'untranslated region of the SNCA transcript can be a highly useful drug target to identify and advance inhibitors of a-syn.

2. To compare our novel 5'UTR SNCA inhibitors to posiphen

Methods: We conducted a high throughput screen at the Broad Institute and identified and characterized potent and selective SNCA mRNA directed translation blockers (including Syn-516) (PUBCHEM AID 2627). We used SNCA 5'UTR-luciferase reporter constructs, ELISA and western blotting secondary assays, direct RNA binding by Tm calorimetry and 11C labeling and PET imaging in mice to evaluate BBB penetrability.

Results: The Syn-516 blocker probe and 3 additional selective SNCA 5' UTR inhibitors exhibited potent inhibition of a-syn translation. They significantly decreased a-syn levels by more than 50% in primary iPSC derived dopaminergic (DA) neurons. Syn-516 also demonstrated greater efficacy in reducing a-syn in cholinergic neurons expressing the triple SNCA gene. Each inhibitor exhibited substantial direct binding to RNA oligonucleotides encoding the SNCA 5'UTR RNA sequences. Some inhibitors were successfully labelled with 11C and demonstrated BBB penetrability using PET imaging.

Conclusion: We show that the Syn-516 blocker probe and 3 additional selective SNCA 5' UTR inhibitors exhibited comparable and greater efficacy to posiphen to inhibit alpha Syn translation. Our data support rapid further testing of these inhibitors for their ADMET properties for advancement into human clinical trials.

Biography

Catherine M Cahil studied Biology at University College Dublin, Ireland graduating in 1985 with her Batchelors degree. She received her PhD degree in Endocrinology in 1990 at the same institution. After a 3 year postdoctoral fellowship in the Dept. of immunology at the Babraham Research Institute, Cambridge UK, she came to the U.S. where she carried out molecular biology research at the Dana Farber Cancer Institute and several other Harvard affiliated hospitals including Massachusetts General Hospital. She is currently an Assistant Professor of Psychiatry at Harvard Medical School and Co-Directs the Neurochemistry lab at Massachusetts General Hospital with her colleague Dr. Jack Rogers. She has published widely in topics such as cancer and inflammation, diabetes and neurodegenerative diseases including Parkinson's Disease, bringing to the field her interdisciplinary background and new perspectives to this research area.International Advisory Committee on Electromagnetobiology. She has authored 7 international books and 115 research articles.

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