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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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Alterations of Brain Activity regions in Neurological Disorders at rest

Brain investigations by resting-state functional magnetic resonance imaging (rsfMRI), diffusion tensor imaging (DTI), positron emission tomography (PET) and alike have enhanced our knowledge on the organization of large-scale structural and functional brain networks, which consist of spatially distributed, but functionally linked regions that continuously share information with each other. Brain's energy is largely consumed at rest during spontaneous neuronal activity (~20%), while task-related increases in metabolism energy are minor (<5%). Spontaneous ultralow-frequency fluctuations in BOLD-based rsfMRI signals (<0.01Hz) at the level of large-scale neural systems are not noise, but orderly and organized in a series of functional networks that permanently maintain a high level of temporal coherence among brain areas that are structurally segregated and functionally linked in resting state networks (RSNs). Some RSNs are functionally organized as dynamically competing systems both at rest and during tasks. The default mode network (DMN), the most important RSN, is even more active during rest and involved in realization of tasks like memory retrieval, emotional process, and social cognition. Cortical connectivity and activity patterns at rest are reportedly altered in several neurological and psychiatric disorders. Human brain function has been imaged in fMRI thereby accessing both sides of the mind-brain interface (subjective experience and objective observations) have simultaneously been performed. As such, functional neuroimaging moves onto new potential applications like reading the brain states, brain-computer interfaces, lie detection, and so forth. The present review evaluates the most current approaches and findings on early detection and classification of some prevalent cognitive impairments and dementia, particularly among syndromes with relatively similar behavioral effects, on the basis of alterations in brain connectivity and activity patterns at rest explored by fused rsfMRI and PET.

Biography

Radu Mutihac is Chair of Medical Physics, University of Bucharest, and works in Neuroscience, Signal Processing, Microelectronics, and Artificial Intelligence. As postdoc/research associate/visiting professor/full professor he has conducted his research at the University of Bucharest, International Centre for Theoretical Physics (Italy), Ecole Polytechnique (France), Institut Henri Poincaré (France), KU Leuven (Belgium). Data mining and exploratory analysis of neuroimaging time series were addressed during two Fulbright Grants in Neuroscience (Yale University, CT, and University of New Mexico, NM, USA). His research in fused biomedical imaging modalities was carried out at the Johns Hopkins University, National Institutes of Health, and Walter Reed Army Institute of Research, MD, USA. Since 2008, he has been nominated PhD student supervisor in the field of Biophysics and Medical Physics at the University of Bucharest, Romania. He is member of the ISMRM, ESMRMB, OHBM, Romanian US Alumni Association, and fellow of Signal Processing and Neural Networks Society IEEE. He published over 120 scientific papers in reputed peer-reviewed journals, 12 monographs, and contributed with chapters in other 11 textbooks published by renowned scientific publishing houses.

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