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Drug discovery for Alzheimer's disease: A focus on small molecule able to disrupt PrPC - Aβos binding, to block PrPC-dependent cognitive defects

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Alzheimer's disease (AD) is characterized by a severe loss of memory function. It has been proposed that AD associated memory loss is caused by soluble amyloid-beta oligomers (OS), especially during early stages of AD before significant neuronal cell death has occurred. It has been shown that PrPC mediates the toxic effect of Aβ oligomers and is required for Aβ oligomer-induced suppression of synaptic plasticity, synapse damage, and neuronal cell death Aβos binding to PrPC results in Fyn activation which leads to NR2B subunit of NMDARs phosphorylation and in tau hyperphosphorylation, the second pathological hallmarks of AD. Treatment with PrPC antibodies against the Aβ oligomer binding site prevents the inhibition of long-term potentiation and reverses cognitive deficits in AD transgenic mice. Copper ion (Cu^{2+}) is another important plyer in this scenario. In fact, the PrPC in its copper-loaded state binds to the NMDAR complex to allosterically reduce its glycine affinity, thereby increasing desensitization. When copper is chelated (i.e., by BCS or monomeric Aβ1–42) or when PrPC is absent or functionally compromised (by GPI anchor cleavage or binding to Aβ oligomers), glycine affinity is enhanced, reducing receptor desensitization and producing pathologically large, steady-state currents that contribute to neuronal damage. There has been considerable interest in identification of compounds that bind to PrPC, stabilizing its native fold and thereby acting as pharmacological chaperones to block prion propagation and pathogenesis. However, compounds binding PrPC could also inhibit the binding of toxic species and may have a role in treating AD. The work outlined here details investigations into a group of around 100 compounds. These were screened in HEK 293 and N2a differentiate cells, wild type expressing PrPC in order to establish and optimize their *in vitro* ability to disrupt Aβ1-42-PrPC binding, establish their structure-activity relationship and identify a lead compound.

Recent Publications

1. Chen RJ, et al. (2013) Alzheimer's Amyloid β Oligomers Rescue Cellular Prion Protein Induced Tau Reduction via the Fyn Pathway. ACS Chem Neurosci. 18;4(9):1287-96.
2. LM Smith, et al. (2017) Binding Sites for Amyloid-β Oligomers and Synaptic Toxicity. Cold Spring Harb Perspect Med. Cold Spring Harb Perspect Med. 7(5).
3. M Larson, et al. (2012) The Complex PrPC-Fyn Couples Human Oligomeric Aβ with Pathological Tau Changes in Alzheimer's Disease. The Journal of Neuroscience 32:16857–16871.
4. Chung E et al. (2010) Anti-PrPC monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer's disease model mouse. BMC Neurosci. 14(11):130.
5. You H, et al. (2012) Aβ neurotoxicity depends on interactions between copper ions, prion protein, and N-methyl-D-aspartate receptors. Proc Natl Acad Sci USA 109(5):1737-42.

Biography

Imane Ghafir El Idrissi is a third year PhD student in Pharmaceutical and Medical Biomolecular Sciences at the University of Bari, Italy. Her thesis is entitled as "Role of Prion protein and Involvement of metal ions in the onset of Alzheimer's disease". On 5th February 2018, she has been awarded with a scholarship in the call for PhD mobility for study/research at University of Sheffield (UK) within the framework of the GLOBAL-DOC project. From October 2014 to September 2018, she is involved in a Marie Skłodowska-Curie Action: Industry Academia Partnerships and Pathways (IAPP) Grant Agreement 612347 title D3i4AD and she spent one year in Sheffield (UK), from October 2015 to March 2016 and from November 2016 to June 2017, during which she developed a cell-based assay, by using HEK 293 cells, useful for a high-throughput screening of small molecules able to disrupt the binding of Aβ1-42 to PrPC, under the supervision of Prof Beining Chen and Prof Nicola Antonio Colabufo.

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