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Drug discovery paradigm targets Tau protein aggregation linked to the Alzheimer's disease

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Dementia and other tauopathies, most notably Alzheimer's disease, embody a class of neurodegenerative diseases associated with the aggregation of the Tau protein in the human brain. These diseases represent one of the leading causes of death and disability in the elderly population in the western world, with no current effective therapy.

An international team of scientists led by Dr. Gergely Tóth at University of Cambridge (UK) and at Hungarian Academy of Sciences (Hungary), with Professor Eckhard Mandelkow at Deutsches Zentrum fu?r Neurodegenerative Erkrankungen (Germany) in collaboration with Novalix (France) and Elan Pharmaceuticals (USA) reported the development of a novel therapeutic approach to target the monomeric Tau protein by small molecule drug candidates to maintain the protein's native function and reduce its misfolding and aggregation, which is linked to the onset of these diseases. The study was recently published in *Current Alzheimers Research* (CAR) and was selected as Editor's Choice by Prof. D. K. Lahiri's, (Editor-in-Chief,)

The Tau protein is an intrinsically disordered protein (IDP), a class of proteins that lack stable 3D structure. Because of this, targeting it using small molecules has been challenging. To tackle this challenge, the scientific team applied a unique binding screening methodology, applied by Novalix, to detect the binding between small molecules and Tau. This led to the identification of a diverse set of novel fragment and lead-like small molecules capable of binding Tau, a part of which reduced the aggregation of Tau in vitro and in a cellular model of Tauopathies.

The study demonstrated for the first time that monomeric Tau can be a viable receptor of small drug-like molecules, and supports the potential and practical feasibility of the therapeutic strategy to target early phases of the aggregation pathway of Tau and potentially other IDPs by small molecules, thereby eliminating the formation of potential toxic misfolded protein species. The researchers suggest that the presented drug discovery paradigm has general applicability, "the drug discovery approach that we present can be applied to other IDPs linked to other misfolding diseases such as Alzheimer's and Parkinson's diseases".

More information: Marcus Pickhardt et al. Identification of Small Molecule Inhibitors of Tau Aggregation by Targeting Monomeric Tau As a Potential Therapeutic Approach for Tauopathies, *Current Alzheimer Research* (2015). DOI: 10.2174/1567205012091510191049 51

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