Tau-directed catalytic antibodies

https://www.neurodegenerationresearch.eu/survey/tau-directed-catalytic-antibodies/

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Country

USA

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Tau-directed catalytic antibodies

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1

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Catalytic Antibodies, tau Proteins, Amyloid, Light-Chain Immunoglobulins, tau aggregation

Research Abstract
? DESCRIPTION (provided by applicant): The tau protein and amyloid ? (A?) peptide form ?-sheet aggregates that provide central contributions in the pathogenesis of Alzheimer's disease. We suggest this hypothesis: ""Specific catalytic antibodies (catabodies) directed to the aggregation-inducing epitopes of tau and other amyloids are produced innately by B lymphocytes as a first-line defense function that evolved by Darwinian selection for retardation of age- associated amyloidosis."" Supporting information includes findings of IgM class catabodies from healthy humans without amyloidosis that hydrolyze tau. Clinical translation of the catabody field has been delayed because of low-to-modest catalytic rates. We recently

documented the immunological principles governing expression of high level catalysis by innate catabodies to A? and transthyretin amyloid. Our objective is to apply these novel principles to prepare rapid monoclonal catabodies that hydrolyze tau specifically and hold potential for clearing brain tau aggregates without harmful microglial activation. We will isolate tau-specific catabodies from human IgM+ B cells and an immunoglobulin light chain variable (IgVL) domain library. The IgM and IgVL scaffolds support expression of amyloid-specific catalysis at levels superior to traditional antigen-binding IgGs. Tau-specific catabodies will be isolated by selection using an electrophilic analog of oligomeric tau to permit permit specific epitope binding in coordination with covalent electrophile binding to the nucleophilic catalytic site of catabodies. Selected catabodies will be analyzed for hydrolytic and binding activities directed to various tau aggregation states, post-translationally modified tau, irrelevant amyloids and irrelevant non-amyloidogenic proteins. Catabody dissolution of tau aggregates without dependence on microglia will be shown. Catabodies do not form stable immune complexes, minimizing the risk of harmful microglial activation. We will compare activation of microglial inflammatory mediator release and phagocytosis by catabodies and reference tau-binding IgGs. Extracellular tau is thought to seed transneuronal spread of taupathy in the brain. A cell culture model will be applied to test whether catabody-mediated extracellular tau removal inhibits transcellular spread of taupathy. Brain penetrating catabody constructs will be prepared by attachment to single chain Fv moieties that bind the transferrin receptor or a peptide tag that binds the lipoprotein receptor 1 expressed by cells lining the blood-brain barrier. Entry of the catabodies into the brain and catabody half-life will be determined in mice by pharmacokinetic and microscopy methods. If the catabodies do not induce microglial activation, increased brain delivery of catabodies for thorough and safe tau clearance will be feasible. The project will provide a basis for future study of the therapeutic potential of tau- directed catabodies alone or in combination with available A?-directed catabodies.

Further information available at:

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