Single-Domain Antibodies (sdAbs) Against Tau and A-syn as Therapeutic and Diagnostic Tools for Neurodegenerative Diseases

The unique structural and biological features of the sdAbs provide a highly effective way of treating Alzheimer's and Parkinson's diseases

Technology Overview

The Sigurdsson Lab has pioneered targeting the tau protein with immunotherapy. These findings have been confirmed and extended by multiple groups, leading to about a dozen ongoing clinical trials on tau immunotherapy with several additional trials likely to commence in the near future. We have preliminary data supporting the therapeutic and diagnostic potential of the anti-tau and anti-α-synuclein sdAb clones. Our tau single domain antibodies (sdAbs) recognize tau pathology in human tauopathy brains and prevent toxicity and clear Alzheimer's brain derived tau proteins in mouse and human tauopathy cultures. Likewise, in Drosophila tauopathy models, sdAbs prevent tauopathy-induced mortality and other tauopathy features. *In vivo* studies in tauopathy and synucleinopathy mice have shown significant target engagement in the brain, as assessed by confocal imaging and brain microdialysis. In addition, gene therapy with anti-α-synuclein sdAb shows brain clearance of insoluble α-synuclein. On the diagnostic front, *in vivo* imaging shown strong correlation of brain signal from the intravenously injected sdAb probes with the pathological tau or α-synuclein, respectively.

Background

The Sigurdsson lab has identified about 50 anti-tau sdAb clones and a similar number of anti-α-synuclein sdAb clones with varying binding properties to different forms of tau and α-synuclein that have unique sequences of their binding regions (CDRs). The sdAbs were selected based on their tau and alpha-synuclein binding properties from a phage display library generated from peripheral blood mononuclear cells of llamas immunized with tau or alphasynuclein immunogens, respectively. Additional clones could be generated with further panning from these separate biological materials. Initial characterization of some of these clones supports their therapeutic and diagnostic potential.

Several tau and α-synuclein immunotherapies have advanced to clinical trials, with all the passive approaches using whole antibodies. sdAbs, which are ten times smaller than antibodies, have not been well studied. However, their distinct properties provide certain advantages that justify exploring their therapeutic and diagnostic potential. In particular, their small size provides unique benefits over the larger whole antibodies, primarily because of greater access into the brain and to their protein target, and to some extent due to their binding to novel epitopes.

Future Work

Category

Life Sciences/Diagnostics

Life Sciences/Neuroscience

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Further characterizing on the binding of the sdAbs in various animal and human tissues is underway. Other work includes in vivo two-photon/calcium imaging, microdialysis, proteomics and behavioral studies to clarify the kinetics, mechanisms, and functional consequences of sdAb therapies. Another goal is to crystallize lead sdAbs and engineer them to modify their pharmacokinetics and pharmacodynamics.

Benefits

- **sdAbs are ten times smaller than antibodies** It is hypothesized that their small size will provide unique therapeutic and diagnostic benefits over the larger whole antibodies, primarily because of greater access into the brain and to their protein target, and to some extent due to their binding to novel cryptic epitopes that the larger antibodies cannot access.
- **They are more amenable for gene therapy and to scale up and engineer** than whole antibodies or single chain variable antibody fragments (scFvs).

Applications

- Therapeutic and diagnostic tools for the treatment of:
  - Alzheimer's disease
  - Parkinson's disease

Intellectual Property

Utility patents 16/971,157 and 16/969,835 pending