

Image TDP-43

Imaging heterogeneous TDP-43 neuropathologies

A diverse range of human neurodegenerative diseases with severe clinical phenotypes are associated with the abnormal accumulation of the transactive response DNA binding protein 43 kDa (TDP-43). TDP-43 is an RNA and DNA binding protein and is associated with a sizeable number of cellular functions, including RNA processing, RNA transport, DNA damage repair, synaptic plasticity and organellar homeostasis. Abnormal accumulation of TDP-43 is generally associated with a loss of TDP-43 function.

The prevalence and heterogeneity of TDP-43 neuropathologies is a new and rapidly expanding area of neurobiological research. One of the major clinical limitations in understanding and diagnosing TDP-43-related proteinopathies is the lack of suitable PET tracers for imaging TDP-43 accumulation in vivo. We propose to address this clinical need by: a) better characterizing the diverse forms of TDP-43 that accumulate in different diseases and b) collaborating with AC Immune to accelerate development of potential PET ligands that discriminate between different forms of TDP-43.

Our team has already pioneered and mastered the methodologies needed to succeed in these important goals. Crucially, AC Immune has identified small molecular weight compounds from its Morphomer™ library that provide a basis from which they will be developing clinical candidates to be used as a PET tracer for TDP-43-related neuropathology. We will test the initially identified compounds for their ability to bind biochemically and structurally defined forms of TDP-43 and to identify abnormal accumulates of TDP-43 in model systems and postmortem human brain samples. We will also conduct trials with one or more of AC Immune's clinical candidate TDP-43 PET imaging agents in human patients with familial forms of FTD. These activities will contribute greatly to the development of a first-in-class TDP-43-targeted imaging agent, thereby addressing an unmet need to expand current methods available for the in vivo classification of neurodegenerative processes.

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