DESIGN AND DEVELOPMENT OF ORGANOMEDICINALS FOR IMAGING AND TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEMENTIA (FTD)

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Background

Frontotemporal Dementia (FTD) is the second most common form of non-Alzheimer's dementia in the population under 65 years old. FTD represents approximately 20% of all dementias and onset normally appears in the mid to late 50s. Clinically FTD is characterized by a progressive neuronal atrophy with behavioral and personality changes. This disease equally impacts men and women and can appear in either sporadic or familial form (40% of FTD cases). FTD can appear alone or in combination with parkinsonism, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and motor neuron disease (MND).

FTD symptoms resemble those of amyotrophic lateral sclerosis (ALS), where there is muscle loss due to degeneration of lower motor neurons and their axons, and loss of upper motor neurons and their corticospinal axonal tracts. In general, ALS patients die within up to 5 years following onset of symptoms.

FTD and ALS overlap in pathogenic mechanism of neuronal degeneration. It is commonly perceived that ALS and FTD are linked clinically, pathologically, and mechanistically, and thus both diseases are now properly recognized as representatives of a combination of broad neurodegenerative disorder, with each presenting in a spectrum of overlapping clinical symptoms.

Discovery of TAR DNA-binding protein 43 (TDP-43) has linked the disease mechanisms for ALS and FTD. TDP-43 is a protein found in both sporadic ALS patients and in the most frequent pathological form of FTD. This protein has been described as a transcriptional repressor, involved with pre-mRNA splicing and translational regulation. It has also been shown to form in amyloid-like aggregates in cells in vitro.

Overall, the pathogenic mechanisms for TDP-43 could result from a combination of both loss of its function and induction of toxicity, therefore indicating that TDP has emerged as a consistent and well-validated pathological biomarker for ALS/FTD.

Technology Summary

PET/SPECT/OPTICAL probe monitoring for TDP-43 pathological inclusions offers a utility both in diagnosis and interrogation of efficacy for therapeutic drugs for treating both ALS and/or FTD.

We have designed a class of small organic molecules targeting C-terminus of TDP-43. We used selected candidates to achieved high enhancement of fluorescent signal after binding to TDP-43 aggregates in

vitro. Our lead compound (and its PET ^{18}F counterpart) was assessed for BBB permeability and pharmacokinetics. Preliminary biodistribution studies revealed transient brain uptake with clearance ration of 2.60. Additionally, radiotracer clears rapidly from liver and kidney.

Advantages :

- BBB permeability, fast clearing from non-target tissues and organs
- Diagnostic biomarker for both neurodegenerative diseases, ALS and FTD
- Imaging of disease progression
- Therapeutic applications

Patents: Pending