[Mock specific aims for the UC San Diego Certificate in Medical Writing Program]

Specific Aims

In the United States, ten people are diagnosed with dementia every minute.[1] This trend is not isolated to the United States. The health burden of dementia is rising globally, a ramification of demographic aging.[2] Worldwide, the most common form of dementia for individuals aged 45 to 65 years is frontotemporal lobe dementia (FTLD). The clinical phenotypes of FTLD (subtypes A-D) can be distinguished by the cortical distribution of the TAR DNA binding protein TDP-43.[3] Currently, TDP-43 distribution is determined through the histologic evaluation of brain tissue conducted post-mortem. Other technologies such as positron emission tomography (PET) scan with [18F]-2-Flouro-2-deoxy-D-glucose can be used to assess patterns of brain hypometabolism as a proxy for decreased synaptic activity; however, this method stratifies patients by linking areas of glycogen hypometabolism to a clinical phenotype as opposed to a pathological diagnosis. A second method used to diagnose FTLD, brain MRI, depicts structural changes that often overlap with other neurodegenerative diseases. Indeed, current PET scan and MRI technology lack the precision to definitively distinguish FTLD from other forms of dementia resulting in a diagnostic process that is unnecessarily complex, sporadically inaccurate, and always belated as early-stage disease cannot be detected by any known method. Neuroimaging that quickly and accurately diagnoses FTLD at the earliest stages must target biomarkers that typify the core pathophysiology of FTLD; thus far, the discovery of these precision biomarkers has eluded scientists. Moreover, the lack of such biomarkers has stagnated the development of novel pharmaceuticals for FTLD. To overcome this hurdle, scientists *urgently* need a technique that can diagnose FTLD in its nascent stage and track the subsequent neurodegenerative changes.

Our *long-term goal* is to alter the progression of disease for millions of individuals who suffer from FTLD. Our *current objective* is to identify TDP-43 protein structures that are conducive to radioligand targeting. **Our *central hypothesis* is that each FTLD subtype (A-D) has a unique protein fold located between residues A321-Q331 in the carboxy-terminal portion of assembled TDP-43 filaments.** Preliminary research in our lab has uncovered unique protein folds between residues A321-Q331 in two FTLD subtypes: a chevron-shaped fold in subtype A individuals (n = 3) and a double-spiral fold in subtype B individuals (n = 3). Our findings were supported in a recent study by Arseni et al.[4] In addition, these protein folds are adjacent to a section of hydrophobic residues that are exposed, along with the protein fold, at the surface of the TDP-43 filament, making TDP-43 especially conducive to radioligand targeting.[5] The *rationale* for this study is that, once key FTLD biomarkers are identified and radioligands that target these biomarkers are developed, researchers will have a tool to detect FTLD before clinical symptoms appear—a finding that will have implications beyond FTLD.

We intend to rigorously test our central hypothesis and achieve our goals by pursuing *two specific aims*:

1. **Validate the characteristic folds as effective biomarkers for FTLD.** Using a larger cohort, we will verify the structure and location of the protein folds for all four FTLD

subtypes found in assembled TDP-43 between residues A321-Q331. Based on the preliminary data discussed, our *working hypothesis* is compelling: *each FTLD subtype contains a distinctive protein fold in the C-terminal region of TDP-43.*

2. **Identify the optimal radioligands for one or all protein folds found in the four FLTD subtypes.** We intend to use the multimodal feature extraction method developed by Xu et al[3] to identify radioligands with an affinity to the protein folds and hydrophobic regions in the C-terminal portion of TDP-43. Again, based on our preliminary data, our *working hypothesis* is reasoned: *these protein structures, which are advantageously located at the protein surface and nestled adjacent to hydrophobic residues, will be readily targeted by radioligands.*

The *outcome* of these studies will be innovative PET scan technology that can unmask the proteomic shifts responsible for launching the neurodegenerative process in FTLD. These findings will eliminate barriers that have impeded research in FTLD—and the byproduct will be a flurry of diagnostic, therapeutic, and epidemiological studies in FTLD. In addition, the discovery of these biomarkers will expand our understanding of the neuropathology of dementia and influence the future direction of research in the field. Accordingly, our work will have a *positive impact* on millions of patients with this devastating disease.

References:

1. Rajan KB, Weuve J, Barnes LL, et al. Population estimates of people with clinical AD and mild cognitive impairment in the United States (2020-2060). *Alzheimer Dement.* 2021:17(12):1966-1975. doi: 10.1002/alz.12362
2. World Health Organization. 2021 fact sheets on dementia. Updated March 15, 2023. Accessed November 20, 2024. www.who.int./news-room/fact-sheets/detail/dementia.
3. Geser F, Martinez-Lage M, Robinson J, et al. Clinical and pathological continuum of multisystem TDP-43 proteinopathies. *Arch Neurol*. 2009;66(2): 180-189. doi: 10.1001/archneurol.2008.558
4. Arseni D, Chem R Murzin AG, et al. TDP-43 forms amyloid filaments with a distinct fold in type a FTLD-TDP. *Nature.* 2023;620:898-903. doi: 10.1038/s41586-023-06405-w
5. Xu S, Shen L, Zhang M, et al. Surface-based multimodal protein-ligand binding affinity prediction. *Bioinformatics*. 2024;4(7):1-8 doi: 10.1093/bioinformatics/btae413
6. Young PNE, Estarellas M, Coomans E, et al. Imaging biomarkers in neurodegeneration: current and future practices. *Alzheimer's Res Ther*. 2020;12(49):1-17. doi: 10.1186/s13195-020-00612-7