Please complete and return via email only (gdip.hres@utoronto.ca) by September 4, 2018 (forms received after this date will not be posted).

Supervisor Information

Name: Carmela Tartaglia
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Degree(s): MD
SGS Department: IMS

Academic Rank: Associate Professor
Field of Research: Biomarkers of neurodegenerative disease (Imaging)

Research Institution Affiliation (if applicable): Centre for Research in Neurodegenerative Diseases

Allocation of student contact time: 7
(number of hours per week YOU are available to the student for any concerns or to review progress)
**Title:** Multimodal Assessment For Predicting Specific Pathological Substrate in FTLD

Description (max 500 words):

Frontotemporal dementia describes a group of clinical syndromes united by underlying frontotemporal lobar degeneration (FTLD) pathology. The clinical syndromes associated with FTLD are heterogeneous and are based on whether the patients present with behavioral, language and/or motor impairments. The FTLD-related syndromes determined by the regional distribution of pathology are: behavioral variant FTD, semantic variant primary progressive aphasia (PPA), non-fluent variant PPA, FTD-motor neuron disease (FTD-MND), progressive supranuclear palsy (PSP), and Corticobasal syndrome (CBS). The underlying pathology in FTLD is divided primarily between abnormal accumulations of Tau (FTLD-Tau) and TDP-43 (FTLD-TDP).

There is increasing evidence that at the time of clinical manifestation of neurodegenerative disease, significant irreversible brain damage is already present. As such, there is a dire need for early interventions to halt, or at least slow disease progression, and thus early diagnosis is paramount. Being able to detect in vivo the underlying pathology has proven challenging but the recent discovery of Positron Emission Tomography (PET) tau-specific ligands is going to help make protein-specific treatments a reality. The PET tau ligands will facilitate in vivo diagnosis of tauopathies and so facilitate their differentiation from the other proteinopathies. One of the ligands is the PET tracer $[^{18}F]$T807. It has high affinity and selectivity to paired helical filament (PHF)-tau in vivo and immunohistochemistry stained sections revealed good overlap with PHF-tau staining but not amyloid-beta aggregates in AD brain slices. The relationship between PET tau ligand binding and cerebrospinal fluid (CSF) markers and MRI markers is yet unknown. There is preliminary data that atrophy on MRI correlates with $[^{18}F]$T807 signal and thus presumed tau pathology but its relationship to other MRI parameters such as connectivity, tractography or detailed volumetrics is unknown. As well, there is no data on correlation of PET tau ligand and CSF tau, phosphorylated tau and even beta-amyloid.

The ultimate goal of this study is to establish diagnostic tools to make an accurate ante-mortem clinical and pathological diagnosis of patients with clinical FTLD syndromes.

We hypothesize that clinical, imaging and CSF biomarker features, within or across syndromes when combined, provide evidence for a particular pathological subtype and thus allow in vivo pathological diagnosis. Specifically, we hypothesize that: (A) imaging patterns (volumetrics, diffusion tensor metrics, and connectivity analyses) and PET $[^{18}F]$T807 will be significantly different in FTLD-Tau and FTLD-TDP; (B) combination of multimodal information (imaging and CSF) will allow differentiation of FTLD-TDP from FTLD-Tau. We hypothesize that MRI biomarkers of connectivity, volumetrics and tractography of specific tracts implicated in PET $[^{18}F]$T807 positive patients as well as CSF Total tau and ptau will be related to PET $[^{18}F]$T807 tracer binding. Our specific aims are:

**AIM 1:** Determine the imaging and CSF protein biomarker profiles that best differentiate FTLD-Tau from FTLD-TDP based on PET $[^{18}F]$T807 binding and known pathological-syndrome associations, i.e. PSP with tau pathology and semantic variant PPA and FTD-MND with TDP-43 pathology.

**AIM 2:** In PSP, and other PET $[^{18}F]$T807 positive patients, correlate PET $[^{18}F]$T807 signal with CSF tau, ptau and MRI parameters including resting state, tractography and volumetrics.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?
Do you expect this work will be published within the 20 months?

☐ YES  ☐ NO  X ☐ Uncertain
**Student’s roles and responsibilities** (please be as specific as possible):

Help in data collection and data analysis. Will likely have to learn some image processing. A Post-doc in my lab will serve as mentor and provide training.

*Please indicate who will serve as the student’s direct report for daily oversight (PI, PhD student, technician, etc...):*