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**Available projects for 2020-21**

- Amyloid

Central to the development of Alzheimer disease (AD) pathology, the transmembrane amyloid precursor protein (APP) is sequentially cleaved by the β-site APP cleaving enzyme 1 (BACE1) and g-secretase enzymes into amyloid-beta (Aβ) peptides of varying length (e.g. Aβ38, Aβ40, Aβ42). Notably, the subsequent accumulation of Aβ42 into "plaques" has been the traditional viewpoint as to how amyloid deposition in the brain leads to cognitive decline. At the molecular level, emerging basic Research & Development now indicates that imbalances in amyloid clearance represent an important new paradigm to better understand amyloid homeostasis in both health and disease.
Recently published in Nature Communications, we discovered a novel enzymatic activity for BACE1 whereby it can degrade plaque-forming peptides (e.g. Aβ42) into non-toxic Aβ34, a novel APP intermediate first described by our laboratory.
The novel enzymatic activity for BACE1 will be used as the basis to design more selective next-generation BACE1 inhibitors. There is a fundamental need to better understand how current inhibitors impact (i) the balance between BACE1's amyloidogenic (e.g. APP à Aβ40 and Aβ42) and amyloidolytic activities (e.g. Aβ40 or Aβ42 à Aβ34), as well as (ii) the generation of N-terminally truncated Aβ species which may enhance the toxicity of non-truncated Aβ species when "seeded" in combination. Targeting specific morphologies of "seeded combinations" with selective drugs may represent an attractive strategy to interfere with the disease process at preclinical AD and mild cognitive impairment (MCI) stages.

- An 8-amino acid Ab42-oligomer Interacting Peptide (AIP) as a novel anti-amyloid strategy

To combat the rapidly growing incidence of AD across Canada, we have developed a unique 8-amino acid Ab42-oligomer Interacting Peptide (AIP) as a novel anti-amyloid strategy for prevention of the disease. In a step-wise fashion our lead candidate has successfully advanced from test tubes (in vitro characterization of AIP) to flies (in vivo rescue of human Ab42-mediated toxicity via AIP-supplemented food) to wildtype mice (proven that protease-resistant D-amino acid AIP (D-AIP) is metabolically stable and can cross the blood brain barrier in vivo). Based upon these promising published and unpublished outcomes, the unique ability of our lead D-AIP candidate to "trap" and neutralize toxic Ab oligomers needs to be tested in two transgenic mouse models of AD. Firmly aligned with CIHR's priorities, this proposal will examine the effect of promising AIP-based compounds on amyloid and/or tau pathologies in advanced rodent models of AD, as well as their potential to disaggregate existing amyloid fibrils.