Technology Opportunity

Non-Confidential Summary

A NOVEL TARGET FOR DIAGNOSING AND TREATING DEPRESSION AND AD

Background:

A history of depression can increase the risk of developing Alzheimer disease (AD) in later life, yet how the one leads to the other is unclear. The brains of AD patients often have a higher density of 'plaques' that are composed primarily of the β-amyloid peptide. β-Amyloid is generated following the enzymatic secretase-mediated cleavage of a larger molecule, the Amyloid Precursor Protein (APP).

We used young and old transgenic (Tg) mice that overexpress a human AD-related APP that favours the amyloidogenic processing of APP and observed that the young Tg mice were far **less 'depressed'** than their wildtype littermates, although they already were exhibiting subtle defects in recognition memory. In contrast, the older Tg mice (in which the Aβ peptide and plaque pathology was evident) were significantly **more 'depressed'** than their wildtype littermates. Brain-slice electrophysiology revealed age-dependent (and region-dependent) patterns in the ability of monoamines, e.g. noradrenaline and serotonin, to modulate cortical network inhibition (using a paired-pulse stimulation paradigm). Alterations in the neurochemistry of monoamine systems have been associated with clinical depression.

We then confirmed a shift from α- to β-secretase processing in the older Tg mice, and age- and region-dependent changes in Aβ (thus corroborating the changes in secretase activities). Examining the distribution of fragments of APP in the two age groups, we identified one fragment that could be exerting an influence in the current context. We overexpressed the fragment in mouse hippocampal cells as well as in two human neuronal cell lines, and observed an increase in the expression and activity of the enzyme monoamine oxidase-A (MAO-A), which is historically associated with clinical depression.

We propose that as the processing of APP changes with age, so does its influence on the depression-related enzyme, MAO-A, and on monoaminergic tone, and invariably on the potential for developing a clinical depression.

Additional studies of ours indicate that while some fragments increase MAO-A activity, others decrease MAO-A activity, which suggests age-dependent effects of the distinct fragments. Preliminary results also suggest gender selective differences in the expression of these fragments in AD and depressed subjects. This provides novel insight into what might regulate MAO-A activity and thus provide novel avenues for treating depression in the general population. This might also provide a mechanism for identifying depressed individuals who would be at risk of converting to a mild cognitive impairment or even AD.

Patent status: U.S. Provisional Patent Application No. 61/814,297

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We are looking for a partnership to achieve two goals:

1. Validation of our animal model with results using human blood samples taken from cllinical trials using subjects suffering progressive AD and Depression

2. Assistance with targetting APP fragments identified in causing both increased and decreased levels of MAO-A (ie. generation of soluble peptides and antibodies)

Researcher profiles:

Darrell Mousseau, Ph.D.
Associate Professor
Saskatchewan Research Chair in *Alzheimer's disease and related dementias*

Research interests: Dr. Mousseau has worked on aspects of antidepressants and neurochemistry; on cell signaling cascades in cell death and on the role(s) of typical antipsychotics in this context; on breast cancer metastasis; and on mechanisms of cellular dysfunction in Alzheimer's disease, particularly in the earlier stages of the pathology. His work in Alzheimer's disease spans the seeding effects of growth factors on amyloid fibril behaviour, animal models, and cellular and molecular mechanisms. He collaborates with local as well as national colleagues, and has a strong tie to the University of Alberta, where he obtained his PhD.

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