A new dawn for Alzheimer's disease

Dr JoAnne McLaurin describes her groundbreaking array of novel treatments for Alzheimer's disease and her hopes for preventing disease progression in the future

What is the societal and economic burden of dementia in Canada?

According to the Alzheimer Society of Canada, 747,000 Canadians were living with dementia in 2011, which equates to approximately 15 per cent of people over the age of 65 – after which the risk of dementia doubles every five years. Canada has a large number of baby boomers who are reaching this milestone, resulting in the prediction that by 2031 there will be 1.4 million Canadians with dementia if a treatment or prevention strategy is not found. The economic burden of this cognitive disorder is $33 billion per year, including both the direct cost of dementia as well as indirect costs such as lost income. In 2011, caregivers spent in excess of 444 million unpaid hours looking after someone with cognitive impairment, resulting in $11 billion in lost income and the equivalent of 227,760 full-time employees in the workforce.

Your work has been at the forefront of therapy development for Alzheimer's disease, the most common form of dementia. Can you provide an insight into the use of vaccinations and small molecules as treatment?

Current passive immunisation strategies in clinical development by large pharmaceutical companies target the two key pathological proteins in Alzheimer's disease, namely amyloid-beta (Aß) peptide and hyper-phosphorylated tau. These studies were designed to improve the cognitive function of people with mild Alzheimer's disease and protect individuals who are genetically susceptible.

Currently, small molecules are being developed to inhibit various processes involved in Aß plaque formation in the disease. One class of inhibitors being examined by various studies is ß-site APP cleaving enzyme (BACE) inhibitors that prevent the production of Aß from its precursor protein. Other molecules in clinical development target vascular dysfunction in Alzheimer's and enhancement of the brain environment, decreasing further degeneration and improving quality of life.

How did you validate your theory that pathways not rescued after Aß removal are therapeutic targets for the preservation of cognitive function?

We currently utilise transgenic rodent models of Alzheimer's disease that present with many of the cognitive and pathological aspects of human disease. Once Aß is removed by a small molecule inhibitor, we investigate which memory functions, if any, are restored; this highlights areas that require further intervention.

We have also used a microarray approach that looks globally at the genes that are alternately regulated as a function of disease progression and removal of Aß. These analyses have led us to investigate a number of signalling pathways that are dysfunctional in mice and in Alzheimer's patients. For example, the microarray study identified that the pro-opiomelanocortin gene is downregulated in Alzheimer's-like progression in the rodents. We recently demonstrated that a-melanocyte stimulating hormone (a cleavage product of pro-opiomelanocortin) treatment of an Alzheimer's mouse model prevents the loss of inhibitory neurons in the hippocampus, and thus maintains cognitive function.

Have you encountered any particular challenges during your investigations? If so, how did you overcome them?

There are always challenges in research, which is one of the factors that drives scientists to continue looking for answers to our respective problems. During the early stages of drug development someone pointed out that I would need to perform proof-of-concept experiments in animal models of Alzheimer's disease. Having a background in chemistry and biochemistry, rodent models were foreign territory for me. It was a very steep learning curve; luckily I had a very talented technician with many years of experience with rodents, although she also had to learn the cognitive tasks. After 16 years in academia, it would now seem to others that I have always conducted these experiments.

How do you envision your work progressing in the next five years?

Most Alzheimer's disease clinical trials that have been initiated over the last 10-15 years target a single pathway, but none have shown robust efficacy in terms of modifying the outcome of disease. The potential effect of therapies targeted at Aß and tau on cognitive function in mild patients was not seen in moderate patients, suggesting that multiple drug therapies will be necessary as the disease progresses. Our efforts to understand the downstream pathways that are affected by the removal of Aß at different disease stages will highlight potential complementary pathways to target in advanced Alzheimer's patients. Furthermore, our studies to understand the interaction between vascular risk factors and Alzheimer's disease may also identify novel targets for combination therapies.

The small molecule with big potential

World-leading research into Alzheimer's disease at **Sunnybrook Research Institute** and the **University of Toronto**, Canada, has uncovered a small molecule-based therapy with the potential to tackle a host of important diseases

ALZHEIMER'S DISEASE IS the most prevalent form of dementia. The symptoms of this chronic and fatal neurodegenerative condition include memory loss, disorientation, difficulty with language and recognition, mood swings, behavioural issues and withdrawal from social situations, eventually leading to severe decline in mental and physical ability. It is difficult to determine the exact causes of Alzheimer's disease; however, the pathological events that result in neurodegeneration are important targets for research and potential preventive or therapeutic measures.

Dr JoAnne McLaurin from Sunnybrook Research Institute and the University of Toronto, Canada, is an international leader in the development of treatments for Alzheimer's disease using a range of techniques. Her prolific research career has combined academic, clinical and industrial programmes that have transformed understanding of the disease and highlighted several important pathways that might be effectively targeted by the development of new pharmaceuticals.

A PROMISING THERAPEUTIC

The brain of an Alzheimer's disease patient contains senile plaques, which are large fibrous accumulations of amyloid-beta (Aß) peptides that disrupt neuronal communication. McLaurin's most important discovery to date is the identification of a small molecule, *scyllo*-inositol, which is able to block the formation of Aß plaques and promote neuronal survival. Its mechanism of action is to bind and stabilise Aß molecules, preventing their polymerisation and subsequent assembly into fibrils that comprise senile plaques.

McLaurin tested the efficacy of *scyllo*-inositol on a TgCRND8 Alzheimer's mouse model that overexpresses the human amyloid precursor protein APP, which is cleaved to produce Aß. These mice have amyloid deposits by 12 weeks of age, leading to Alzheimer's-like cognitive decline and early death. When McLaurin gave the rodents a preventive dose of *scyllo*-inositol from six weeks of age, the mice showed a significant improvement in their cognitive deficits, reduction of amyloid plaques and of *myo*-inositol levels throughout the brain and greatly improved survival rates.

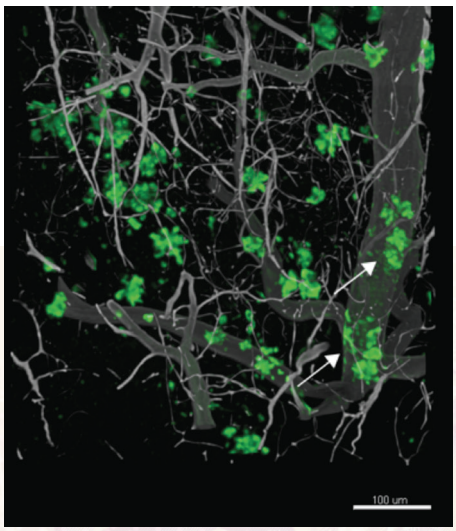
Typically, Alzheimer's disease begins around 10-20 years before the appearance of clinical symptoms and diagnosis, so McLaurin and her team investigated *scyllo*-inositol as a treatment. They administered the small molecule to five-month-old TgCRND8 mice that already had Aß plaque deposits, and found that after one month the treated mice had significantly lower levels of plaque than untreated littermates, thereby restoring cognitive ability.

Most Alzheimer's disease patients also accumulate Aß around the blood vessels in the brain, which McLaurin's team showed prevented normal function. "With age, Alzheimer's and ischaemic strokes become increasingly coincident," she elucidates. "Up to 90 per cent of Alzheimer's patients have two or more 'silent' strokes. While these infarcts are believed to be independent of the progressive accumulation of cerebrovascular amyloid, and may only cause subtle deficits in the absence of the disease, they have been shown to significantly accelerate cognitive decline in Alzheimer's patients." Moreover, McLaurin recently discovered that *scyllo*-inositol treatment of TgCRND8 mice was able to remove the Aß vascular deposits and rescue both the structural and functional impairment of the vessels, highlighting the drug's potential for slowing vascular-mediated cognitive decline in Alzheimer's.

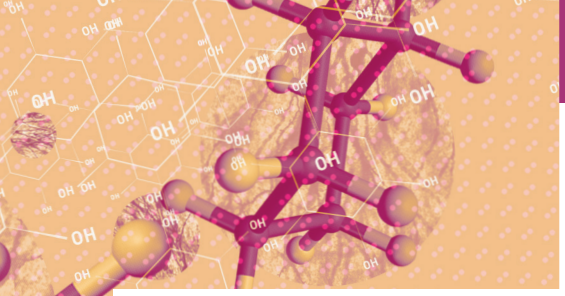
THE NEXT STAGE

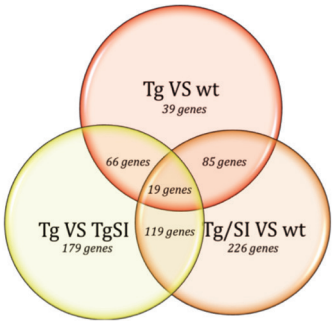
The promising results from mice enabled McLaurin to progress *scyllo*-inositol forward for clinical human trials in collaboration with Transition Therapeutics Inc., a Canadian biotechnology company. A phase II trial of patients with probable Alzheimer's disease was able to establish the safety profile of the drug; however, adverse effects meant that the study was not able to determine disease-modifying effects in patients.

During the trial, clinical trialists noticed that *scyllo*-inositol appeared to decrease the emergence and severity of neuropsychiatric



Maximum intensity projection of a region from the motor cortex of a six-month-old TgCRND8 mouse with the microvasculature visualised (grey). Methoxy X04, an amyloid-imaging agent, was used for visualisation of parenchymal amyloid plaques and cerebrovascular amyloid (green). Arrows are pointing to cerebrovascular amyloid.





Venn diagram of the comparisons between transgenic and non-transgenic mice treated or untreated with *scyllo*-inositol showing the number of genes that were differentially regulated.

symptoms, specifically agitation and aggression, which are seen in the majority of Alzheimer's patients. Current treatments of neuropsychiatric symptoms can have serious side effects; therefore, Transition Therapeutics Inc. is undertaking phase II clinical trials in Alzheimer's disease patients experiencing moderate levels of agitation or aggression to ameliorate these symptoms. McLaurin hopes this trial will help both patients and their caregivers: "If *scyllo*-inositol treatment reduces or prevents the emergence of neuropsychiatric symptoms, then both patients and caregivers will have an improved quality of life. Since emergence of neuropsychiatric symptoms tends to correlate with admission to long-term care facilities, successful treatment may enable patients to live at home for longer, resulting in enhancement of quality of life and a lower burden of medical cost." It was also suggested that these findings could be translated to people with bipolar disorder whom have previously been treated with other *myo*-inositol lowering therapeutics.

BROAD POSSIBILITIES

Down's syndrome is caused by the presence of an extra copy of chromosome 21, which means that genes on this chromosome are typically overexpressed. The APP gene is located on chromosome 21, and overexpression is believed to play a role in synaptic dysfunction and cognitive disability in Down's syndrome. The excess levels of APP also lead to an overproduction of Aß that can often result in early-onset Alzheimer's in these patients. Phase IIa clinical trials using *scyllo*-inositol demonstrated the safety and pharmacokinetics in young adults with Down's syndrome who do not have Alzheimer's disease, with the aim of improving their cognitive abilities and preventing dementia by decreasing amyloid and *myo*-inositol levels in the brain.

Another focus for McLaurin's group has been treatment of other neurodegenerative diseases, such as Huntington's disease, caused by the aggregation of mutated huntingtin protein. McLaurin explains that Huntington's and Alzheimer's diseases share some similarities: "Huntington's disease causes a decline in cognitive function such as reasoning skills, memory and judgment, and changes in the brain lead to alterations in mood as well as anger and irritability". Accumulation of aberrant protein in the brain occurs in both Alzheimer's and Huntington's diseases; therefore, McLaurin treated cultured cells overexpressing mutant huntingtin with *scyllo*-inositol and found that its modulatory effects on protein accumulation led to a reduction in mutant huntingtin protein levels. This work supports further development of *scyllo*-inositol as a potential therapeutic in Huntington's disease.

The Alzheimer's disease clinical trial data also suggested a host of other potential disease targets for *scyllo*-inositol. The drug gave patients a dose-dependent decrease in uric acid, which could be translated to a number of diseases associated with hyperuricaemia, for example: gout, renal diseases, cardiovascular diseases and metabolic syndrome. *Scyllo*-inositol also has anticonvulsant properties, significantly reducing the duration of seizures; it could thus also be used as a potential treatment in epilepsy. The possible applications of *scyllo*-inositol are extensive, and although still under investigation, any one of these avenues could have a huge impact on the future of treatments for neurological disorders and, potentially, our understanding of the common underlying mechanisms across a range of conditions that could be targeted by a broad spectrum drug to improve overall health.

THE FUTURE OF ALZHEIMER'S DISEASE TREATMENT

The majority of recent Alzheimer's disease treatments have been aimed at reducing Aß accumulation; however, McLaurin has previously shown that simply removing these senile plaques is not sufficient to cure advanced disease. Alzheimer's disease develops over many decades, long before any overt symptoms are present; so by the time it is diagnosed, the damage to the brain may be too extensive to be cured with a single therapy. In addition to working on preventive measures for families at risk of Alzheimer's, McLaurin is keen to uncover more efficacious treatments for patients who already have moderate disease progression. To achieve this, she is monitoring which molecular pathways or particular regions of the brain are not rescued after the removal of Aß to identify targets for designing new therapeutic interventions to slow or reverse Alzheimer's progression.

COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE

OBJECTIVES

To develop and evaluate novel treatments for Alzheimer's disease, focusing specifically on the potential of the small molecule *scyllo*-inositol, which is undergoing clinical trials.

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DR JOANNE MCLAURIN graduated in 1983 with a BSc in Chemistry from Queen's University, Canada, after which she obtained an MSc (1988) and PhD (1992) in Clinical Biochemistry from the University of Toronto. McLaurin's research focuses on the development of potential therapeutics to target protein-misfolding disorders, in particular Alzheimer's disease. Stemming from the basic research of protein-lipid interactions, her laboratory identified a family of naturally occurring compounds that inhibit the formation of toxic soluble aggregates in Alzheimer's disease. These molecules underwent preclinical studies to demonstrate efficacy and are being evaluated in clinical trials. This work is being expanded to examine other neurodegenerative disorders to investigate the possibility of a universal anti-aggregant small molecule, *scyllo*-inositol.

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