# Cerebrovascular diseases, a well-established risk factor for dementia, are among the most common diseases in aging societies, the third leading cause of mortality in Western countries and the major cause of long-term disability, with enormous physical, psychological and financial impact on patients, families and the health care system.1 Current evidence suggests that 25–33% of stroke survivors develop post-stroke cognitive impairment (PSCI) or dementia, and nearly half of patients diagnosed with Alzheimer disease (AD) dementia have mixed pathologies, commonly AD pathologies and vascular dementia (VaD).2 White-matter lesions (WML) are known to play a major role in cognitive impairment and dementia among stroke survivors and the elderly in general and may indicate small-vessel disease (SVD), demyelination or inflammatory processes.3 Drugs that might enhance learning or neuronal repair could protect from this devastating outcome and help prevent recurrent cerebrovascular events.

Recovery after brain injury shares molecular, cellular and neuropsychological principles with mechanisms of learning and memory. Based on these similarities, manipulations that enhance synaptic plasticity could accelerate recovery of function after stroke.4

In this project, we aim to harness a recently proven molecular mechanism that underlies post-stroke recovery as treatment for stroke survivors who develop PSCI. We will focus on the C-C chemokine receptor 5 (CCR5), a pro-inflammatory receptor that is uniquely expressed in cortical neurons after stroke.5 Inhibition of CCR5 signaling has been shown to enhance learning, memory and plasticity processes in hippocampal and cortical circuits.6

Several very recent preclinical experiments and observational studies in patients after stroke suggest that the commercially available medication Maraviroc, a CCR5 antagonist approved for patients infected with HIV-1,may augment learning skills and cognitive performance by acting on unique molecular components for novel learning.

CCR5 is a seven-transmembrane G protein–coupled receptor that mediates cellular entry of the HIV virus. In individuals with a naturally occurring 32-base-pair deletion within the CCR5 gene (CCR5-Δ32), the mutation7 leads to a nonfunctional gene product that does not reach the cell surface; individuals with a homozygous CCR5Δ32 deletion are protected from HIV-1 infection.7 The CCR5 receptor is expressed in microglia, astrocytes and neurons in many regions of the brain. Together with our colleagues, we have recently shown5 that this receptor is involved in learning and memory: (1) CCR5 deficiency results in enhancements in hippocampal learning and memory and in experience-dependent sensory plasticity, and (2) CCR5 overexpression leads to learning and memory deficits. Decreasing the function of CCR5 increases MAPK/CREB signaling, long-term potentiation, hippocampus-dependent memory and neocortical experience-dependent plasticity.5,6 Ligand binding to CCR5 is known to modulate several parallel signaling cascades implicated in learning and memory, including the suppression of adenyl cyclase as well as the activation of the PI3K/AKT and P44/42 MAPK signaling. These findings support the application of brain-permeable CCR5 antagonists, not only as a combination drug in antiretroviral therapy but also as a treatment for cognitive deficits caused by HIV. In addition, the studies suggest that the receptor is a novel target to augment learning and memory in those with cognitive and motor deficits in relation to training.

In several preclinical models of stroke and traumatic brain injury, our colleagues suggest that Maraviroc may lead to better motor and cognitive outcomes, presumably due to enhanced learning.6 Stroke induces CCR5 expression in neurons in the first month after onset in a mouse model. Knockdown of CCR5 in the motor cortex of adult mice improves recovery after stroke.

We have recently tested the effects of the naturally occurring CCR5-Δ32 mutation in a large clinical post-stroke population (TABASCO—an exclusive prospective cohort of 575 first-ever stroke patients, free of dementia at baseline, whom we have followed for several years); about 15% of these patients, mostly Ashkenazi Jewish individuals, were carriers of the mutation. This group showed significantly better cognitive and functional outcome 2 years post-stroke.5

Proposed mechanisms of action for Maraviroc in PSCI may combine two processes: (1) neuromodulation, or improving synaptic plasticity, and (2) reducing inflammatory reactions that appear after the ischemic insult as well as chronic inflammation involved in neurodegenerative processes. Evidence is emerging that chemokine receptors are involved in neuronal death and hence neurodegenerative diseases. Chemokines may induce neuronal death either indirectly (e.g., through activation of microglia-killing mechanisms) or directly through activation of neuronal chemokine receptors.8 Immuno-histochemical analysis of tissue from human brains with AD have revealed the expression of CCR5 and its ligands in the cortex and hippocampus as well as increased expression on some reactive microglia.9 Likewise, CCR5 ligand, MIP-1a/CCL3, was reported as predominantly located in neurons and weakly located in some microglia, particularly in the white matter of both AD and control brains, and many CCR5-reactive microglia and MIP-1a/CCL3-reactive astrocytes were found to be associated with amyloid deposits.9

Correspondingly, Maraviroc has already been reported to improve cognitive function in chronic HIV-infected patients experiencing HIV-associated cognitive impairment.10,11 HIV-associated dementia (HAD) is a progressive neurological disorder that affects 20–30% of patients with advanced HIV disease.12 HAD presents as a subcortical dementia, in which cognitive decline and motor slowing are the predominant characteristics. Moreover, recent data in humans suggest an anti-atherogenic effect: Maraviroc led to significant improvements in endothelial function and carotid atherosclerosis,13 symptoms that usually accompany VaD; inflammatory and membrane-adhesion molecules also upregulated in the cerebral microvasculature in AD.

Maraviroc (Selzentry, Pfizer) is the only CCR5 antagonist currently approved by the U.S. Food and Drug Administration (FDA), the European Commission and Health Canada for treatment of patients infected with R5-tropic HIV-1. The drug is a small molecule metabolized by CYP3A4, with a good pharmacokinetic profile, relatively low protein binding and high bioavailability when given at standard doses twice a day. Maraviroc appears to be well tolerated, but the dose may have to be adjusted when given with CYP3A4 inducers or inhibitors, primarily drugs that are also used for HIV therapy, but also for several anticonvulsants. Patients who are taking these medications will not be entered in the proposed trial. The drug should be used cautiously in patients with a history of orthostatic hypotension and patients with preexisting liver dysfunction or coinfection with hepatitis B or C (these patients will not be included in the proposed trial). Maraviroc does not appear to cause clinically significant changes in concentrations of other medications (data from Micromedex). It is moderately lipophilic, so it can penetrate the blood-brain barrier. At a single dose of 150 mg or 300 mg, time to maximum concentration occurred by 2 hours post-treatment in humans. The terminal half-life is 14–18 hours, so a single dose used in the proposed protocol should be adequate, rather than the BID treatment for AIDS. Despite low cerebrospinal fluid (CSF) concentrations, the drug suppresses CSF viral load. It potently inhibits downstream CCR5 signaling and does not induce CCR5 internalization, suggesting that the drug is a functional CCR5 antagonist.

The human and animal data point to this receptor system as a valid target for future clinical trials aimed to slow VaD progression. Patients experiencing PSCI with high WML load represent a high-risk group for both recurrent stroke and dementia, thus presenting a unique subgroup of patients that may specifically benefit from our proposed intervention: a pioneer proof-of-concept randomized, placebo-controlled phase IIa clinical trial to determine if Maraviroc is able to be repurposed as a safe and effective treatment for preventing cognitive deterioration in recent subcortical stroke patients experiencing PSCI, with WML and SVD. Consistent blocking of CCR5 may prevent the deleterious consequences of another lesion/event and deterioration of the current processes by protecting both blood vessels and neurons.

If successful, the results of this work could lead to large-scale clinical trials of Maraviroc as a novel, readily available, therapeutic avenue to reduce the burden of post-stroke dementia and vascular-AD pathologies.