Project Title: Evaluation of an Acute RNAi-Mediated Therapeutic for Visual Dysfunction Associated with Traumatic Brain Injury

Principal Investigator: Colin Doherty, MD

Organization: St. James’s Hospital

Background: The stress response in the brain following a traumatic brain injury (TBI) is normally manifested by a distinct cessation of water diffusion across the blood-brain barrier (BBB), leading to acute increases in intracranial pressure and cerebral edema. In cases of cerebral edema associated with TBI and blast injury, hyperosmolar and hypertonic saline therapy are among the only interventions for the management of raised intracranial pressure, one of the key mediators of mortality in patients presenting with brain trauma. The osmotic diuretic mannitol is commonly used in the acute phases of injury as it establishes an osmotic gradient between plasma and brain cells, reducing cerebral edema by drawing water across areas of intact BBB into the vascular compartment. Repeated administration of mannitol is problematic however as it may produce abnormal neurological and renal side-effects and its effect is only beneficial for up to 24 hours. In many cases of cerebral edema, very often the worst of the tissue swelling may not be visible for 24-48 hours and in TBI associated with blast injury especially; ancillary tissue injury mechanisms beyond impact bruising and bleeding are initiated sometime after the primary insult and so mannitol and hypertonic saline treatment become almost irrelevant for treatment.

Objective/Hypothesis: Using RNA-interference (RNAi), researchers have shown that administration in mice of siRNAs targeting the tight junction protein claudin-5 results in a transient and size-selective modulation of the BBB to very low molecular weight molecules of up to 800 Daltons for periods of between 24 and 72 hours post injection. Claudin-5 plays a key role in the formation of paracellular pores or channels that function in mediating selective ion permeability at the BBB. Investigators have shown that modulation of the BBB represents a potentially novel therapeutic intervention for patients with TBI, by allowing free diffusion of water within the brain for up to 72 hours after administration. In this context, if mannitol does not produce a decrease in cerebral edema within 24 hours post-injury, claudin-5 siRNA will allow for increased passive diffusion of water from the brain to the blood.

Specific Aims: Pre-clinical: Assess the efficacy to which visual function can be preserved following a controlled cortical injury to the visual cortex region of rodents. Assess the extent to which cerebral edema and neuroinflammation induced by TBI to the visual cortex can be reduced using a novel and acute RNAi-based therapeutic intervention. Evaluate the extent to which visual function can be preserved when cerebral edema is decreased using acute treatment with siRNA. Clinical: Moreover, in order to fully assess edema formation in the visual cortex region of the brain, assess individuals who have suffered cerebral ischemia including in the region of the visual cortex. Using a dedicated research 3 Tesla MRI on the hospital campus, make a full assessment of edema formation in the brains of individuals who have suffered an out of hospital cardiac arrest. This cohort of patients represents an ideal study group due to the homogeneity of edema formation following an ischemic insult. Moreover, investigators will employ novel functional MRI (fMRI) analyses for the first time in a study of this nature. Overall, the specific aims of this project will focus on the development of an acute intervention in cases of cerebral edema, in particular TBI in which associated edema is the leading cause of pathology.

Study Design: Full assessment of the extent to which cerebral edema in the visual cortex induced by TBI can be reduced using systemic injection of siRNA targeting the tight junction component claudin-5. Researchers will assess the acute and long-term effects on optokinetic and visual evoked potential (VEP) responses in mice following RNAi-mediated therapeutic intervention. Investigators will also use fMRI techniques to assess therapeutic outcome in mice and rats receiving either claudin-5 siRNA or a nontargeting control. A clinical component of this project will incorporate MRI and fMRI studies in individuals with cerebral ischemia, in order to obtain a full complement of data relating to edema formation in the visual cortex and the subsequent extent of visual dysfunction.
Relevance: This proposed work has the potential to lead to an acute treatment for edema formation in the visual cortex of military personnel who have suffered a blast injury or indeed a TBI. Given the availability of distinct experimental protocols designed to assess visual dysfunction in rodents and the availability of novel fMRI studies, investigators believe that the findings of our proposed work could lead to a novel, acute, therapeutic strategy for military personnel who have suffered blast injuries. Indeed, any therapeutic control of visual cortex edema formation could have significant long term benefits with regards to visual function.