

PROJECT SUMMARY (See instructions):

Title: **Multimodal MRI-based diagnosis and treatment of mild cognitive impairment**

Middle-aged people with mild cognitive impairment (MCI) are at high risk for developing Alzheimer's disease (AD), a condition that slowly destroys memory skills. About 5.2 million Americans are living with AD today and this number is predicted to triple by 2050¹. There is a critical need for early therapies that can arrest the progression from MCI to AD and other dementias, and for objective and sensitive measures of efficacy for interventions. It is highly desirable to develop an integrated approach for non-invasive, neuroimaging-based diagnosis and treatment of MCI. We propose a mechanistic-driven neurocognitive enhancement intervention with the safe drug USP methylene blue (MB) while simultaneously monitoring with advanced multimodal magnetic resonance imaging (MRI) the neural alterations in MCI, leading to a more effective MCI treatment.

MB is a FDA-grandfathered drug safely used for over a hundred years to treat metabolic poisons, such as methemoglobinemia, carbon dioxide and cyanide poisoning in humans². Daily 4 mg/kg oral MB has been used safely for one year in clinical trials. New mechanistic studies showed that oral MB readily enters the brain and has unique energy-enhancing and antioxidant properties and acts in the mitochondria to sustain or enhance ATP energy production, thereby promoting neuronal cell survival and neurocognitive enhancement. MB has been shown to reduce behavioral impairments in animal models of Parkinson's and Alzheimer's diseases. Our lab has shown with MRI that MB increases oxygen consumption, blood flow and evoked responses in the rat brain *in vivo*. We also found that MB treatment reduces MRI-defined lesion and behavioral deficits in animal models of traumatic brain injury and stroke.

As the first step to translate these experimental findings to humans, we are currently carrying out a randomized, double-blinded, placebo-controlled, phase II clinical trial (NCT01836094) to evaluate the effects of a single oral MB dose (280 mg, 4 mg/kg) on memory by using cerebral blood flow, evoked functional MRI (fMRI) and resting-state functional connectivity fMRI on young (~30 years old) healthy volunteers. Our findings suggest that MB has favorable memory effects. No negative adverse event was reported.

This proposal takes the next step to test the hypothesis whether daily oral MB (280 mg, 4 mg/kg) over two weeks will improve memory, cognition and brain functional connectivity in *healthy middle-aged* volunteers and age-matched subjects with *MCI* by using advanced, objective multimodal MRI techniques and standard neuropsychological tests. Our **central hypothesis** is that MB treatment, compared to placebo, will improve memory and cognitive function in both healthy middle-aged and MCI subjects. **Primary** outcome will be task-evoked fMRI readouts and neuropsychological tests to assess episodic memory, working memory and sustained attention. **Secondary** outcome will be resting state functional connectivity fMRI. **Tertiary** outcome will be cerebral blood flow. Data will be collected at baseline and 2 weeks after daily MB or placebo.

RELEVANCE (See instructions):

This proposal arises from a new partnership among three internationally recognized leaders in their perspective fields: Drs. Francisco Gonzalez-Lima, PhD (UT Austin), and Donald Royall, MD (UTHSCSA), and Tim Duong, PhD (UTHSCSA). This clinical trial arose from a number of successful animal studies using methylene performed independently and jointly by Drs. Lima and Duong. Dr. Gonzalez-Lima brings in expertise in methylene blue and neurosciences. Dr. Royall is internationally recognized Alzheimer's researcher and an experienced clinical trialist, having conducted 65+ clinical trials. Dr. Duong brought to the team neuroimaging and brain mapping expertise. The study is innovative in that it involves, in addition to neuropsychological tests, state-of-the-art neurotechnologies and brain mapping methods. We focus on middle age where early intervention is likely more effective. Another strength lies in the translational nature of this work and the use of a safe and readily available drug to improve cognition. This work has a near-term potential for translation to clinical practice. This project leverages the unique resources of the Research Imaging Institute and the Texas Alzheimer's Research and Care Consortium. Success will lead to NIH grants (R01 and U01) to fund larger clinical trials of MCI and AD patients that could ultimately improve health span and quality of life of MCI and AD patients.