Epigenetic Mechanisms in human memory quantified by non-invasive PET imaging

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Epigenetic Mechanisms in human memory quantified by non-invasive PET imaging

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1

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Research Abstract
? DESCRIPTION (provided by applicant): Histone deacetylase (HDAC) enzymes are zinc-dependent chromatin modifying proteins that have emerged as an important lead in

understanding CNS dysfunction. To date, HDAC expression has been measured in a small number of postmortem brain tissue samples from healthy and diseased patients affected by brain disorders including schizophrenia, depression and Alzheimer's Disease (AD) and provides evidence that altered expression of HDACs in at least cortex, hippocampus and cerebellum, may play a central role in the underpinnings of brain disease. Research in animal models supports that HDAC expression is a critical mediator of neural development, aging, cognition, learning and memory. Further, synthetic small molecules targeting HDACs have been shown to alleviate deficits in neural plasticity and disease-related behavior in animals underscoring the great need to improve understanding of the relationship between HDAC expression, brain function and disease pathogenesis. We have recently achieved a major research goal by resolving a PET imaging agent, [11C]Martinostat that selectively binds to a subset of HDAC enzymes. Our imaging studies to date, including in 7 healthy human volunteers, have identified key features that make [11C]Martinostat a rare and promising CNS HDAC probe including robust brain uptake and high specific binding. Using an AD mouse model, we have collected additional preliminary imaging data demonstrating increased tracer uptake – evidence of increased HDAC expression – in aged AD mice compared to age-matched healthy control animals, a result consistent with invasive protein measurements reported from postmortem human brain. We are extremely excited to take a large step forward in understanding cognitive decline by visualising HDAC in the healthy and dysfunctional human brain. Our lab in Martinos Center is one of few in the world that can directly translate basic science advancements to knowledge of the human system. Together with the our multidisciplinary teams and strong collaborations, we are seeking the support through the R21 mechanism for this high-risk, high-reward study to characterize the density and distribution of key HDACs throughout the brain of aging healthy subjects and in patients with Alzheimer's Disease. Our initial data on [11C]Martinostat in humans age 18-35 years strongly supports the success of our proposal for clinical imaging in healthy older subjects (Aim 1) and in AD patients (Aim 2). PET-MR imaging in humans with [11C]Martinostat will deliver answers to fundamental questions about chromatin modifying enzymes in the living human brain in a way that has not been possible until now. Importantly, using [11C]Martinostat to understand HDAC expression in AD, a profound example of cognitive decline and neurodegeneration, will enable validation of an epigenetic drug target, refine patient selection based on HDAC expression, and facilitate proof of mechanism/target engagement in novel therapeutic trials.

Further information available at:

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