EPIS - Epigenetic PET imaging in substance use disorder patients

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Background: Millions of people in the United States and all over the world are affected by substance use disorders. There is growing evidence suggesting that the epigenetic processes may play a role in the substance-induced gene regulations and behavior. To date, studies in animals have demonstrated that epigenetic enzymes could induce histone-related epigenetic changes after the use of substances of abuse. We plan to use novel imaging methods to apply to the analysis of the epigenetics in drug addiction. The development of techniques for visualizing epigenetics *in vivo* represents a key step in understanding both the normal function and pathophysiology of the epigenetic enzymes in brain. Moreover, these techniques will accelerate the discovery of small molecule therapeutics for substance use disorders.

I am starting a new project for my independent research, Epigenetic Positron emission tomography (PET) Imaging in Substance use disorder (SUD) patients (EPIS). My goal for the EPIS program is the development and application of novel PET imaging probes for SUD research. Over the past seven years, we have developed the first, non-invasive epigenetic PET imaging agent targeting histone deacetylases (HDACs), termed [11C]Martinostat, that will facilitate investigating the relationship between HDAC expression and SUD. [11C]Martinostat was approved by the FDA for first-in-man studies (IND # 123154) and we have imaged healthy controls with [11C]Martinostat. Currently we are the only group could measure HDAC in the living human brain. We will start imaging alcohol use disorder patients late this year with the support from NIAAA. As another important component of the EPIS program, we are also working on developing new PET imaging probes targeting other epigenetic enzymes, such as bromodomain and sirtuins.

Methods: After consenting and pre-scan preparation, each subject was administered [11C]Martinostat, normally 5 mCi, in a homogenous solution of 10% ethanol and 90% isotonic saline intravenously (via catheter) and each subject was imaged during a 90-minute MR-PET session. One MR pulse sequence was utilized concomitant with PET data acquisition to capture subject-specific neuroanatomy, specifically, a high-resolution structural scan via multiplanar magnetization prepared rapidly acquired gradient echo (MPRAGE). PET images were corrected for motion using a recently developed MR-based method or a frame-to-frame registration process with a mutual information cost function. The motion corrected volumes were implicitly co-registered to the anatomic MR scans.