

Dr. Jose Luchsinger

In line with the stated goals of PA-14-047, midcareer investigator award in patient oriented research (parent K24), the goals of this application are to allow me to devote more time to augment my capabilities in Patient-Oriented Research (POR), with a focus on Alzheimer's disease (AD) biomarkers for use in AD risk factor and prevention research, and to provide mentoring to junior clinical investigators in the conduct of POR, with a focus on research in AD risk factors and prevention. Many studies have shown associations of diabetes with AD. However, whether diabetes causes AD neuropathology remains unclear. In order to answer this question I will leverage a recent R01 award (Diabetes Status and Brain Amyloid in Middle Aged Hispanics; 1R01AG050440-01A1; 09/01/15-05/31/20). This 5-year R01 project will conduct Amyloid β ($A\beta$) positron emission tomography (PET) imaging with ^{18}F -Florbetaben in 150 late middle-aged persons in order to examine in-vivo the cross-sectional and longitudinal association of diabetes status and glycemia with AD. I propose to complement the new R01 by adding plasma-based biomarkers, and by piloting Tau imaging to further the study of mechanisms linking diabetes to AD. The new R01 and the proposed K24 research project will be integrated with the proposed mentoring and training program. The primary research aim of this award is to examine the association of soluble receptor of advanced glycosylation end-product (sRAGE) with plasma and brain cortical fibrillar Amyloid β ($A\beta$). I will also examine whether these associations mediate the association of glycemia (examined continuously with HbA1c) and diabetes status (Normal glucose tolerance [NGT], pre-diabetes, diabetes), with brain $A\beta$. The secondary research aims are to explore the plasma lipidomic profile predictive of brain $A\beta$ and whether this profile mediates the association of glycemia and diabetes status with brain $A\beta$, and to conduct a pilot study of tau imaging using ^{18}F -THK-5351 PET comparing persons with NGT (n=5) and diabetes (n=5) to demonstrate feasibility in preparation for an independent grant application. The mentoring aims of the application are: 1) To train early investigators on POR in the cognitive complications of diabetes and related conditions, the potential mechanisms linking these conditions to AD, and methods to study these associations; 2) Mentees will have access to the training resources of the applicant related to lipidomics; 3) Early investigators will learn about the importance of tau as an AD mechanism, methods to ascertain it, and will have access to the training resources of the application. The training aims of the application are: 1) To train in the potential application of blood based AD biomarkers to research in AD risk factors and prevention, with an initial focus on diabetes and related conditions; 2) To acquire new knowledge in lipidomics and how it can be applied to the study of risk factors for AD and its prevention and treatment (I will also seek training in genomics and proteomics); 3) to learn the application of Tau imaging to research in risk factors for AD.