Transgenic Rat Model of Cerebral Amyloid Angiopathy

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Research Abstract
? DESCRIPTION (provided by applicant): Cerebrovascular accumulation of the amyloid ß-protein (Aß), a condition known as cerebral amyloid angiopathy (CAA), is an important cause of vascular cognitive impairment (VCI) and a common pathological feature of patients with Alzheimer’s disease (AD). In addition, several related familial CAA disorders result from mutations that reside within the Aß peptide sequence of AßPP gene including Dutch-type

(E22Q) and Iowa- type (D23N). Evidence continues to accumulate indicating that cerebral microvascular amyloid can promote small vessel pathology, neuroinflammation and cognitive deficits in patients with AD and related CAA disorders. Previously, we generated unique transgenic mice that produce Dutch/Iowa CAA mutant human Aß in brain, designated Tg-SwDI, that develop early-onset and prominent subcortical fibrillar cerebral microvascular Aß deposition. Despite the value and unique insight that Tg-SwDI mice have provided in the study of subcortical small vessel CAA, associated pathologies and cognitive impairment there remains significant shortcomings with the use of this model. For example, in contrast to humans and higher animals, mice possess small brains with little white matter thus limiting neuroimaging capabilities and the study of important vascular mediated changes in these regions. In addition, the study of cognitive abilities in mice are much more restricted compared to higher species. Thus, there is an important need for better models to further our understanding of the impact of small vessel CAA on brain pathology and function. In light of the limitations of current mouse models, advances in the production of transgenic rats provide the opportunity to develop a more appropriate and reproducible species to model small vessel CAA. Thus, the overall hypothesis and aim of this exploratory R21 proposal is that the generation and characterization of novel transgenic rats will provide a superior model to study the impact of subcortical small vessel CAA on brain pathology and cognitive function. To accomplish this goal we propose to generate novel transgenic rats expressing Dutch/Iowa CAA mutant Aß in brain and subsequently 1) conduct temporal biochemical and pathological characterization; 2) determine the consequences of small vessel CAA on cognitive functions; and 3) perform neuroimaging studies to determine the impact of small vessel CAA on brain pathology using microMRI. Here, we take the unorthodox approach of submitting a multi-PI exploratory proposal that will bring together three collaborative investigators with distinct, but highly complimentary, expertise to generate and characterize novel transgenic rats for CAA. The investigators range in expertise from production of numerous transgenic mouse models and biochemical and pathological characterization (Dr. Van Nostrand), advanced behavioral and cognitive characterization of rodents (Dr. Robinson) and high-resolution neuroimaging morphometric analysis of rodent models (Dr. Benveniste). The aim of our group is to generate a superior model for the study of small vessel CAA and provide a much needed, more advanced and invaluable animal model of this condition to the research community for investigating pathogenic mechanisms and to evaluate potential diagnostic and therapeutic interventions with relevant cognitive and neuropathological endpoints.

Further information available at:

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