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DEFENSE OF THE DOCTORAL

DISSERTATION

"Revealing New Perspectives on Dementia Pathogenesis with Contemporary Methods: Single-Cell RNA Sequencing Analysis and the IntelliCage"

by

Hoa Pham

M.D./Ph.D. Program

B.A. 2013, Columbia University, New York, NY

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Friday, April 17th, 2020
12:30 P.M.
WebEx

ABSTRACT

Model organisms mimicking the pathogenesis of human diseases are useful for identifying pathogenic mechanisms and testing therapeutic efficacy of compounds targeting them. Models of Alzheimer's disease and related dementias aim to reproduce the brain pathology associated with these neurodegenerative disorders. Transgenic models, which involve random insertion of disease-causing genes under the control of artificial promoters, are efficient means of doing so. There are confounding factors associated with transgenic approaches, however, including target gene overexpression, dysregulation of endogenous gene expression at transgenes' integration sites, and limitations in mimicking loss-of-function mechanisms. Furthermore, the choice of species is important, and there are anatomical, physiological, and cognitive reasons for favoring the rat over the mouse, which has been the standard for models of neurodegeneration and dementia. In this thesis, we report a potential mismatch between physiological and transgenic cell-type-specific expression of dementia-related genes based on analysis of preexisting, publicly available single-cell RNA sequencing data from wildtype mouse hippocampal tissue, which may support the locus-specific "knock-in" approach to genome modification. Notably, microglia had the highest expression of *Itm2b* (or *Bri2*), a gene associated with familial British and Danish dementias (FBD and FDD), with low co-expression of *Prnp*, the gene physiologically associated with a promoter used in transgenic FDD mouse models. We also report an initial assessment of the spatial learning, reversal, and sequencing task capabilities of novel knock-in Long-Evans rats with humanizing mutations in the Aβ-coding region of *App*, which encodes amyloid precursor protein (*App*$^{h/h}$ rats), using the IntelliCage, an automated operant social home cage system, at 6-8 weeks of age, then again at 4-5 months of age. These rats were previously generated as control organisms for studies on neurodegeneration involving other novel knock-in rat models from our lab. *App*$^{h/h}$ rats of either sex can acquire place learning and reversal tasks, and quickly change their place preferences within minutes by 6-8 weeks of age, with improvement at 4-5 months of age. They can also acquire a simple diagonal sequencing task by 6-8 weeks of age and a more advanced serial reversal task involving alternating diagonals by 4-5 months of age, though not robustly.