ANNOUNCEMENT OF FINAL ORAL EXAMINATION
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CANDIDATE: Megan Varnum

DEPARTMENT OR PROGRAM: Pharmacology

TITLE OF DISSERTATION: “An Anti-Inflammatory Glycoprotein, CD200, Restores Neurogenesis and Enhances Amyloid Phagocytosis in a Mouse Model of Alzheimer’s Disease”

DATE, TIME, AND PLACE: Thursday, July 30, 2015 at 9:00a.m.
Boston University School of Medicine
72 E. Concord Street (Room L 112)
Boston, MA 02118

EXAMINING COMMITTEE

FIRST READER: Dr. Tsuneya Ikezu
SECOND READER: Dr. Susan Leeman
THIRD READER: 
CHAIRMAN OF THE EXAMINING COMMITTEE: Dr. Benjamin Wolozin Email: bwolozin@bu.edu

ADDITIONAL COMMITTEE MEMBERS: Dr. Carmela Abraham
Dr. Joseph El Khoury

Members of the committee are asked to confirm attendance by replying directly to the Chairman of the Examining Committee.

ALL MEMBERS OF THE SCHOOL OF MEDICINE FACULTY ARE INVITED TO ATTEND.
AN ANTI-INFLAMMATORY GLYCOPROTEIN, CD200, RESTORES NEUROGENESIS AND ENHANCES AMYLOID PHAGOCYTOSIS IN A MOUSE MODEL OF ALZHEIMER’S DISEASE

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Boston University School of Medicine, 2015

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ABSTRACT

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by the accumulation of amyloid-β peptide (Aβ) in the brain and intraneuronal hyperphosphorylated tau. Microglia in the brain adopt M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes similar to peripheral monocytes. M1 microglia negatively affect neurogenesis and have reduced phagocytic capabilities whereas M2 microglia can enhance neurogenesis and support phagocytosis. Cluster of Differentiation-200 (CD200) is an anti-inflammatory glycoprotein physiologically expressed on neurons and lymphocytes, and its receptors (CD200R1 and CD200R3) are expressed on glia. Both AD patients and mouse models of AD show an age-related or Aβ-induced reduction in neural CD200 that may contribute to M1-skewing of microglia in AD. We hypothesize that CD200 skews microglia to an M2 phenotype, and that genetic over-expression of CD200 in transgenic mice expressing the Swedish familial AD mutation of human β-amyloid precursor protein (APP mice) can restore neurogenesis and enhance Aβ clearance in the hippocampus. In this study, we constructed a tetracycline-controlled transactivator-inducible adeno-associated virus serotype 2/1 expressing full-length CD200 (AAV2/1-CD200) or green fluorescent protein (AAV2/1-
GFP). These were bilaterally injected into the hippocampi at 6 months of age, and mice were sacrificed at 12 months of age. AAV2/1-GFP-injected APP mice showed a reduction in number of proliferating neural stem cells (NSCs) by 65.0% and differentiating NSCs by 70.5% in the dentate gyrus compared to wild-type controls. AAV2/1-CD200 restored these neurogenic deficits to those of wild-type mouse levels. AAV2/1-CD200 reduced diffuse Aβ plaques in the hippocampal region by 65.5% compared to AAV2/1-GFP-injected APP mice, but did not alter thioflavin-S-positive compact plaques as measured by protein and immunohistochemical assays. *In vitro* studies demonstrated that CD200-stimulated microglia co-cultured in transwells increased differentiation and complexity of neural stem cells. CD200 also directly enhanced Aβ phagocytosis by microglia. CD200 enhanced expression of the adaptor protein TYRO protein tyrosine kinase binding protein (TYROBP), suggesting this may be the mechanism by which CD200 enhances phagocytosis of Aβ. Overall, the data presented here indicate that CD200 is a plausible therapeutic agent in patients with AD to enhance neural differentiation and microglial-mediated clearance of Aβ.