Chobanian & Avedisian School of Medicine
Graduate Medical Sciences

72 E Concord St. L309 | Boston, MA 02118 | GMSRegistrar@bu.edu

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

CANDIDATE:	**Ryan McCann**
DEPARTMENT OR PROGRAM:	**Neuroscience**
TITLE OF DISSERTATION:	**"An Extracellular Vesicle Therapeutic Attenuates Inflammation and Damage in a Rhesus Monkey Model of Cortical Injury"**
DATE, TIME, AND PLACE:	**Thursday, November 13, 2025** **Boston University Chobanian & Avedisian School of Medicine** **Graduate Medical Sciences** **72 E Concord Street, Room L-1008** **Boston, MA 02118**

EXAMINING COMMITTEE

FIRST READER:	**Dr. Tara Moore**
SECOND READER:	**Dr. Maria Medalla**
CHAIR OF THE EXAMINING COMMITTEE:	**Dr. Vasileios "Basilis" Zikopoulos** **Email: zikopoul@bu.edu**
ADDITIONAL COMMITTEE MEMBER:	**Dr. Ella Zeldich**
ADDITIONAL COMMITTEE MEMBER:	**Dr. Aurelie Ledreux**
PROXY MEMBER:	**Dr. Farzad Mortazavi**

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

ALL MEMBERS OF THE CHOBANIAN & AVEDISIAN SCHOOL OF MEDICINE FACULTY ARE INVITED TO ATTEND.

AN EXTRACELLULAR VESICLE THERAPEUTIC ATTENUATES INFLAMMATION AND DAMAGE IN A RHESUS MONKEY MODEL OF CORTICAL INJURY

RYAN MCCANN

Boston University Aram V. Chobanian & Edward Avedisian School of Medicine, 2026

Major Professor: Tara L Moore, Professor of Anatomy and Neurobiology

ABSTRACT

Cortical injury in the aged brain leads to acute cell death and inflammation, which trigger chronic secondary neurodegeneration resulting in long-term cognitive and motor deficits. There are no U.S. Food and Drug Administration (FDA)-approved therapeutics that address cortical injury pathologies. Recent studies in rodents and pigs have identified mesenchymal stromal cell-derived extracellular vesicles (MSC-EVs) as a promising therapeutic for cortical injury, reducing inflammation and enhancing neuroprotection. We have used MSC-EV treatment in a Rhesus monkey model of primary motor cortex injury which impairs fine motor function of the hand. When treated with MSC-EVs 24 hours and 2 weeks following injury, monkeys recovered pre-injury levels of function within the first 3-5 weeks post-injury, while untreated monkeys had an incomplete recovery. Analysis of brain tissue harvested 16 weeks post-injury found that MSC-EVs promoted homeostatic microglial phenotypes, neuronal plasticity, and myelin maintenance. These findings demonstrated the efficacy of MSC-EVs, but at which stage of recovery MSC-EVs acted remains unclear. Here, we assessed the progression of biomarkers of inflammation and damage across recovery and examined the brain at an earlier timepoint, 6-weeks post

injury. The current study addresses the hypothesis that in the early stages of recovery, MSC-EVs attenuate the inflammatory response and reduce tissue damage. We first assessed how MSC-EVs affect the temporal progression of the inflammatory response, using a multiplex protein quantification platform (Olink) on plasma and cerebrospinal fluid (CSF) collected across recovery (pre-injury, 24 hours, 2-, 4-, and 6-weeks post-injury). MSC-EV treatment decreased inflammatory proteins in plasma 2 weeks following injury, with reductions in pro-inflammatory proteins persisting throughout recovery. Assessments of brain tissue revealed that at 6-weeks post-injury, MSC-EV treatment increased homeostatic microglial phenotypes, supporting an early shift towards an anti-inflammatory environment. Next, we assessed if MSC-EV treatment affected the progression, clearance and resolution of neurodegeneration across recovery. MSC-EV treatment was associated with increased levels of neurofilament-light (NF-L) chain, an axonal damage biomarker, in CSF after, coupled with increased neuronal structural integrity markers (MAP2) in brain tissue, suggesting an MSC-EV-mediated clearance of neuronal debris. MSC-EV treatment was also associated with a decrease in Galectin-3, presumably phagocytically active, microglia. Finally, to identify potential mechanisms of action, we performed lipidomic and metabolomic analyses of MSC-EV contents. We found sex-differences in MSC-EV cargo, female EVs were enriched in sugars, while male EVs were enriched in nitrogen-rich compounds. MSC-EVs cargo were related to cellular energy metabolism, supporting its potential role in metabolic efficiency in aging and after injury. Overall, these findings present a role of MSC-EVs in the early resolution of inflammation following cortical injury, creating a neuroprotective environment that supports recovery of motor function.