ABSTRACT Age is the number one risk factor for neurocognitive disorders (NCDs), conditions that result in reduced intellectual and functional ability, greatly limiting quality of life.[1] Increasing evidence suggests both acute and chronic inflammation contributes to the development of NCDs.[2-4] Acutely, ischemic stroke, a leading disease of morbidity and mortality, confers worse outcomes as age increases.[5] This may be partly due to ischemia-reperfusion/injury (I/RI), in which the cessation of blood flow during stroke and the therapeutic restoration to reduce core (irreversibly damaged tissue) and maximize penumbra (salvageable tissue) actually triggers a rapid influx of both resident and peripheral immune cells such as polymorphonuclear neutrophils (PMN) and monocyte-derived macrophages (MDM).[6, 7] Chronically, low-grade inflammation, known as inflammaging, occurs independent of a specific clinical diagnosis, and is accompanied by changes in the activity and numbers of cells of the innate immune system, such as CNS microglia (MG) that occur independent of a clinical event.[8, 9] Vascular contributions to cognitive impairment and dementia (VCID), the most common subtype of NCD in which stroke is a critical precipitant, are especially prominent in aging.[10] Determining the interactions between inflammatory cell biology (both acute and chronic) and age-related loss of resilience to vascular insults may thus prove crucial in elucidating common links between inflammaging and VCID. In turn, these findings could prove enlightening towards NCD-related disorders as well.

Our multi-PI group has extensive experience in understanding behavior, inflammation, neurodegeneration, stroke, and advanced techniques for imaging of pathology and radiology. Our published work has demonstrated a clear impact of inflammation in infarct size for stroke.[11, 12] The work of others confirms that older mice and humans have worse outcomes despite identical stroke burdens.[13, 14] Consequently, *our working hypothesis is that aging and stroke negatively synergize to worsen neuroinflammatory topography and limit physiologic cerebrovascular reserve, accounting for differences in behavioral outcomes across time in young and old mice despite identical stroke burdens.* We propose to apply a paradigm of inflammatory ischemic stroke in young and aged mice to develop radio-pathologic and behavioral outcome models. We will then confirm the validity of the predictive model in stroke animals by modifying the inflammatory status.

Specific Aim 1: Define and manipulate a stroke I/RI model in young and aged mice as a continuum of radio-pathologic and behavioral outcomes using multi-scale imaging informatics.

1A Build an imaging informatics platform for multi-scale spatio-temporal modeling of vasculature and different cellular biomarkers. We will apply machine learning and advanced mathematical modeling to describe vascular and cellular topology using wide-field brain sections and live-animal imaging of young and old mice subject to a standard 60min stroke.

1B Define I/RI in different ratios of core/penumbra and their radio-pathologic and behavioral outcome trajectories by using different conditions (i) early reperfusion at 30 min (ii) standard 60 min (iii) delayed reperfusion at 90 min, to enable our model to detect the effects of a range of stroke severities on radio-pathology and behavior.

Specific Aim 2: Validate the radio-pathologic model's ability to predict differential contributions of specific inflammatory cell populations to stroke and ensuing behavior by comparing young adult and aged mice subjected to I/RI and ensuing VCID. Eliminate different populations of immune cells using drugs i) MG (PLX 5622) ii) PMN (Combo Antibody depletion) iii) MDM (PLX 73086) to examine the relative contribution of each cell population to radio-pathologic and behavioral outcomes in young adult and aged mice.

The results of our experimental and computational approaches in this OVPR Seed grant will address criticisms in our multi-PI group's recent R01 summary statement. Receipt of this seed funding will enable our group to demonstrate our continuous collaboration, increase our potential for early publication, and obtain preliminary data to apply this model to other NCDs.