THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

STEFANO TARANTINI

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF PHYSIOLOGY

Wednesday, November 30, 2016, 2:00 p.m.
Biomedical Research Center, Room 109

MICROVASCULAR MECHANISMS CONTRIBUTING TO COGNITIVE DECLINE IN AGING: ROLE OF NEUROVASCULAR UNCOUPLING AND CEREBRAL MICROHEMORRHAGES

COMMITTEE IN CHARGE: Zoltan Ungvari, M.D., Ph.D., Chair; Anna Csiszar, M.D., Ph.D.; William E. Sonntag, Ph.D.; Ferenc Deak M.D., Ph.D.; Robert Foreman, Ph.D;, Willard Freeman, Ph.D.; Courtney Griffin, Ph.D.

ABSTRACT: Growing evidence from epidemiological, clinical and experimental studies indicate that aging-induced impairment of neurovascular coupling (NVC) responses and cerebral microhemorrhages (CMHs) contribute to the pathogenesis of cognitive impairment and dementia in the elderly. Understanding and targeting the age-related pathophysiological mechanisms that underlie NVC impairment and CMHs are expected to have a major role in mitigating vascular contributions to cognitive impairment and dementia (VCID) thereby preserving brain health in older individuals. Our overarching hypothesis is that age-related

oxidative stress and IGF-1 deficiency compromise the functional and structural integrity of the cerebral microcirculation, promoting both NVC impairment and development of CMHs, exacerbating cognitive decline. Our studies, which are illustrated and discussed in this dissertation, tested predictions based on this hypothesis. Murine models of aging and IGF-1 deficiency were used to measure NVC responses, cognitive function, age-related alterations of cerebrovascular function and phenotype, and clinically relevant models of CMH on older animals. On the basis of our findings a novel integrated model for the pathomechanism of NVC impairment and CMHs in aging is proposed. We demonstrate that aging and age-related IGF-1 deficiency affect both astrocytes and microvascular endothelial and smooth muscle cells. Functional and phenotypic impairment of astrocytes and endothelial cells are responsible for neurovascular uncoupling. Functional and phenotypic impairment of microvascular smooth muscle cells compromise the structural integrity of the cerebral microcirculation, impair microvascular adaptation to hypertension and promote microvascular damage. Our studies identify IGF-1 deficiency and oxidative stress as potential common mechanisms in the pathogenesis of neurovascular uncoupling and CMHs in aging. Our pre-clinical studies point to potential benefits of pharmacological interventions promoting microvascular health for prevention of age-related cognitive decline. Specifically, we provided proof-of-concept that treatments specifically targeting mitochondria to reduce mtROS production could be developed for microvascular protection in aging.