

THE GRADUATE COLLEGE OF THE  
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

# Christopher Michael Hoover

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE

*Department of Biochemistry & Molecular Biology*

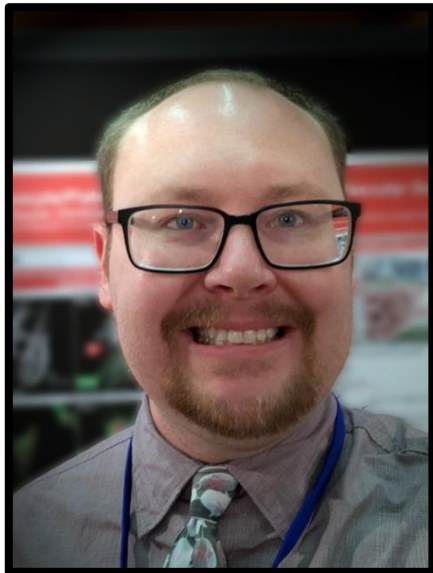
Thursday, May 7<sup>th</sup>, 2020 | 12:00 p.m.  
Zoom Conference Call

Meeting ID: 967 8305 4390

Password: 497517

Link to join the Zoom call at the scheduled time:

<https://ouhsc.zoom.us/j/96783054390?pwd=bU4waWVqN0JnNC96MFYwdFZUWjlrZ09>



## Podoplanin prevents formation of brain aneurysms at midgestation by regulating activity of primitive megakaryocytes

**COMMITTEE IN CHARGE:** Lijun Xia, MD/PhD; Ann Louise Olson, PhD; Augen A. Pioszak, PhD; Guangpu Li, PhD; Courtney T. Griffin, PhD

**ABSTRACT:** The evolution of mammals coincided with the emergence of megakaryocytes and platelets to perform hemostatic functions, replacing less efficient nonmammalian vertebrate nucleated thrombocytes. At midgestation mouse embryos have many circulating primitive megakaryocytes (pMk), that resemble nucleated thrombocytes, throughout the vasculature, though their impact on development is unknown in the less hemostatically-challenged embryonic environment. Embryos lacking podoplanin (PDPN) or its megakaryocyte/platelet receptor CLEC-2 develop spontaneous hemorrhages in the brain, but the nature of vascular defects and underlying mechanisms remain unclear. We hypothesize that PDPN is required to regulate pMk function through CLEC-2 during brain development, in order to protect the rapidly growing vasculature from harmful overactivity. Here we report that loss of PDPN-CLEC-2 resulted in defective angiogenic sprouting and aneurysms in the lower diencephalon at mid-gestation, with increased pMk localization and exhibition of active granule secretion prior to hemorrhage. We find that PDPN is critical to regulating fetal megakaryocyte secretion of  $\alpha$ -granule components, including angiopoietin-1, which in embryos lacking PDPN led to enhanced TIE2 activation in angiogenic sprouts early in aneurysm growth. Platelet inhibitory treatment of the pregnant dam rescued the PDPN-deficient embryo vascular defects. Our data reveal a new role for PDPN in regulating pMk function at midgestation.