THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

# Maulin M. Patel

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

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GRADUATE COLLEGE
*Department of Cell Biology*

Friday, November 30, 2018
Biomedical Research Center, Room 109
2 - 3 pm

## *Role of ADTRP (Androgen-Dependent Tissue Factor Pathway Inhibitor Regulating Protein) in Vascular Development and Function*

COMMITTEE IN CHARGE: Florea Lupu, PhD (Chair); Lorin E. Olson, PhD; Sathish R. Srinivasan, PhD; Eric W. Howard, PhD; Lijun Xia, M.D., Ph.D.

ABSTRACT: **Background**-—The physiological function of ADTRP (androgen-dependent tissue factor pathway inhibitor regulating protein) is unknown. We previously identified ADTRP as coregulating with and supporting the anticoagulant activity of tissue factor pathway inhibitor in endothelial cells *in vitro*. Here, we studied the role of ADTRP *in vivo*, specifically related to vascular development, stability, and function. **Methods and Results**-—Genetic inhibition of Adtrp produced vascular malformations in the low-pressure vasculature of zebrafish embryos and newborn mice: dilation/tortuosity, perivascular inflammation, extravascular proteolysis, increased permeability, and microhemorrhages, which produced partially penetrant lethality. Vascular leakiness correlated with decreased endothelial cell junction components VE-cadherin and claudin-5. Changes in hemostasis in young adults comprised modest decrease of tissue factor pathway inhibitor antigen and activity and increased tail bleeding time and volume. Cell-based reporter assays revealed that ADTRP negatively regulates canonical Wnt signaling, affecting membrane events downstream of low-density lipoprotein receptor related protein 6 (LRP6) and upstream of glycogen synthase kinase 3 beta (GSK-3β). ADTRP deficiency increased aberrant/ectopic Wnt/b-catenin signaling *in vivo* in newborn mice and zebrafish embryos, and upregulated matrix metallopeptidase (MMP)-9 in endothelial cells and mast cells (MCs). Vascular lesions in newborn *Adtrp*$^{-/-}$ pups displayed accumulation of MCs, decreased extracellular matrix content, and deficient perivascular cell coverage. Wnt-pathway inhibition reversed the increased *mmp9* in zebrafish embryos, demonstrating that *mmp9* expression induced by Adtrp deficiency was downstream of canonical Wnt signaling. **Conclusions**-—Our studies demonstrate that ADTRP plays a major role in vascular development and function, most likely through expression in endothelial cells and/or perivascular cells of Wnt-regulated genes that control vascular stability and integrity.