THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Jaanam Gopalakrishnan

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Pathology

Wednesday, April 21, 2021 | 1: 15p.m CST
Zoom Meeting ID: 945 1346 9747 | Passcode: 977538
https://omrf.zoom.us/j/94513469747?pwd=eno2cHBkSXJwdXhPV3QvbE5aM1BZUT09

Identification and Functional Validation of Causal Variants Spanning Systemic Lupus Erythematosus Risk Haplotypes.

COMMITTEE IN CHARGE: Patrick M. Gaffney, M.D., Christopher J. Lessard, PhD., A. Darise Farris, PhD., Scott M. Plafker, PhD., Priyabrata Mukherjee, PhD., Zhizhuang Joe Zhao, PhD.

ABSTRACT: Systemic Lupus Erythematosus (SLE) is a debilitating autoimmune disease characterized by innate and adaptive immune dysfunctions. Genome-wide association studies (GWAS) have identified genetic polymorphisms in ubiquitin-conjugating enzyme E2 L3 (*UBE2L3)* and Tumor Necrosis Factor Alpha-Induced Protein 3 (*TNFAIP3*) to be associated with SLE susceptibility. The presence of the *UBE2L3* risk haplotype results in increased *UBE2L3*-encoded UbcH7 protein expression whereas the *TNFAIP3* risk haplotype results in reduced *TNFAIP3*-encoded A20 protein expression. Both UbcH7 and A20 are involved in the ubiquitin signaling pathway, and their dysregulated expression leads to increased NFκB activation, inflammatory

responses and susceptibility to SLE. Despite the usefulness of GWAS in identifying SLE susceptibility loci spanning *UBE2L3* and *TNFAIP*3, the precise causal variants responsible for these statistically significant associations remain unexplored. Our study is aimed at the identification and functional characterization of causal variants among the single nucleotide polymorphisms (SNPs) residing in the *UBE2L3* and *TNFAIP3* risk haplotypes. We systematically evaluated seven risk variants in the *UBE2L3* haplotype to identify four variants in the *UBE2L3* and *YDJC* promoters as plausible causal variants. The risk variants were found to drive hypermorphic *UBE2L3* expression by strengthening a YY1-mediated long-range interaction between the *UBE2L3* and *YDJC* promoter elements. In the *TNFAIP3* risk haplotype, we characterized a RelA/p65-dependent enhancer element upstream of *TNFAIP3* that exhibited CEBPB-dependent allele-specific enhancer activation. The risk alleles of rs10499197 and rs9494868 were identified to be responsible for modulating this upstream enhancer function. Overall, this dissertation provides mechanistic insights on how SLE risk haplotypes modulate *UBE2L3* or *TNFAIP3* expression, focusing the critical role of causal variants in SLE pathogenesis.