

THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Valerie Lewis

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



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Biomedical Science Building Room 433

Molecular characterization of CXorf21 provides further insight into sex disparities in both innate immunity and SLE pathogenesis

COMMITTEE IN CHARGE: Robert Hal Scofield, MD, Chair; Robert C. Axtell, PhD; Kristi Koelsch, PhD; Christopher J. Lessard, PhD; Yuechueng Liu, PhD; Zhizhuang Joe Zhao, PhD

ABSTRACT: Systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) are both complex autoimmune disorders characterized by B cell hyperactivity resulting in autoantibody and cytokine production. Approximately 90% of SLE or pSS patients are female and this relationship holds true in all racial and ethnic groups studied. The etiology behind what drives this sex-bias still is unknown. This project addresses the theory that an X-chromosome gene dose effect or simply the number of X chromosomes increases susceptibility to SLE and pSS. Thus, the hypothesis is that this disparate gene expression between men and women contributes directly or indirectly to immune functions, and ultimately results in the gender bias found in lupus and pSS. Our published data support this theory showing that men with Klinefelter's syndrome and trisomy X women are overrepresented in SLE by roughly 11- and 2.5-fold and in pSS 13-fold and 3-fold, respectively. We began by studying Chromosome X open reading frame 21 (CXorf21), a gene identified as a novel SLE-associated risk allele and postulated to contribute to the X-chromosome gene dose effect. Our data reveals that CXorf21 mRNA and protein expression in monocytes, B cells, and dendritic cells are elevated in female cells compared to male cells. We also found CXorf21 mRNA expression is higher in both male and female cells from SLE patients compared to control subjects. CXorf21 knockdown abrogated TLR7 and NOD1-driven increased IFNA1 and NFkB1 mRNA expression. Additionally, we found that CXorf21 knockdown reduced TLR7-mediated secretion of both TNF-alpha and IL-6 and increased lysosomal pH in female monocytes. A comparison of female immune cells with elevated CXorf21 expression to male samples showed that female subjects had lower endolysosomal pH. Thus far, we have yet to determine the exact mechanism by which CXorf21 regulates the described immune response, but these data make a compelling case that this X-linked gene protein product, CXorf21, is a major contributor to the X-chromosome gene dose effect and female bias immune responses observed in TLR7 and NOD1 signaling pathways, distinct clinical manifestations observed in SLE and pSS pathogenesis.