

THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

James Quinn



FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

Department of Microbiology & Immunology

Thursday, September 26, 2019 | 10:00 am

Biomedical Research Center, Room 109

Characterizing and Assessing the Role of Follicular T Helper Cells and BCL6 in Th17- EAE Disease Progression

COMMITTEE IN CHARGE: Robert C. Axtell, PhD, Daniel J. Carr, PhD, Mark L. Lang, PhD, Lauren A. Zenewicz, PhD, Christopher J. Lessard, PhD

ABSTRACT: Multiple sclerosis (MS) is a severe autoimmune disorder of the central nervous system (CNS). While both T cells and B cells are implicated in pathology, it remains unclear how these two populations cooperate to drive disease. T helper 17 cells (Th17) and T follicular helper (TFH) cells are two T cell subsets that have been implicated in promoting B cell activities in MS and the animal model, experimental autoimmune encephalomyelitis (EAE). The work described in this dissertation sought to understand the mechanistic interplay between B cells, Th17 cells, and TFH cells during CNS autoimmune disease.

In the first chapter, we demonstrated that pathogenic Th17 cells and TFH cells cooperate to drive an inflammatory B cell response in the CNS during neuro-inflammation. Specifically, we found that Th17 cells infiltrate the CNS and induce a second wave of infiltrating TFH cells which promote disease through a B cell-dependent mechanism. We also determined that TFH trafficking into the CNS is mediated by the chemokine CXCL13. Notably, we succeeded in reducing disease severity in these mice by blocking TFH trafficking to the CNS through a CXCL13 antibody therapy.

Additionally, we identified a novel role for the transcription factor BCL6 in the pathogenicity of Th17 cells in EAE. BCL6 is known as the master regulator of TFH differentiation. In the absence of BCL6, we found Th17 differentiation was skewed towards a nonpathogenic phenotype with increased secretion of the anti-inflammatory cytokine IL-10 and reduction of the inflammatory cytokine IL-17. This loss of pathogenicity was confirmed *in vivo* when the BCL6-deficient Th17 cells failed to induce disease upon transfer into recipient mice. This work demonstrates a previously unknown role for BCL6 in Th17 differentiation and an important pathological mechanism of neuro-inflammation.

Overall, this work helps to elucidate the relationship between Th17 cells, TFH cells, and B cells during neuro-autoimmune diseases. Going forward, this work also identifies several new potential therapeutic targets for the treatment of MS.