THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Jenna Guthmiller

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Microbiology and Immunology

Friday, May 5, 2017, 10 a.m.
Biomedical Research Center, Room 109

Immunoregulation of Anti-Plasmodum Humoral Immunity

COMMITTEE IN CHARGE: Noah S. Butler, Ph.D., Co-Chair, William H. Hildebrand, Ph.D., Co-Chair, Mark L. Lang, Ph.D., Lauren A. Zenewicz, Ph.D., Paul. W. Kincade, Ph.D., Scott M. Plafker, Ph.D.

ABSTRACT: *Plasmodium* infections are responsible for the disease malaria. Despite decades of research, no highly efficacious vaccine exists to combat *Plasmodium* infection and prevent malaria. The lack of protective immunity following either natural infection or vaccination is due in part to the short-lived nature of anti- *Plasmodium* antibody responses. Short-lived antibody responses are primarily the result of the expansion and activity of short-lived antibody secreting cells known as plasmablasts. Long-lived humoral immunity mediated by memory B cells and plasma cells generally largely derives from germinal center (GC) reactions. However, the molecular and cellular pathways that regulate B cell activation and the balance between plasmablast versus GC reactions during *Plasmodium* infection are poorly defined. The work within this dissertation identified mechanisms that regulate GC responses and that promote the preferential accumulation of plasmablasts during experimental malaria.

We identified that the anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokine IFN-γ acted reciprocally and in a B cell-intrinsic manner to regulate expression of T-bet in B cells. IL-10 signaling in B cells promoted GC B cells, protective anti-*Plasmodium* antibody responses, and parasite control and clearance. Conversely, B cell-intrinsic IFN-γ signaling and T-bet expression impaired GC B cell responses and protective anti-*Plasmodium* antibody responses. IL-10 additionally promoted the number and function of T follicular helper cells, which promote the selection of GC B cells that differentiate into long-lived plasma cells. Thus, IL-10 is essential for GC responses and protective antibody responses.

We further identified that B cell-intrinsic IFN-γ signaling and T-bet expression preferentially stimulated short-lived plasmablast responses. Adoptive transfer of *Plasmodium* infection-induced plasmablast populations into infection-matched mice had no impact on parasite control and instead suppressed germinal center derived antibody responses via expression of the co-inhibitory ligand PD-L1. Moreover, antibodies secreted by plasmablasts were largely not targeted against *Plasmodium* parasites.

Rather, plasmablast reactions were a result of polyclonal B cell activation. Therefore, *Plasmodium* infection induced IFN-γ promotes the accumulation of non-protective, immunosuppressive plasmablasts. Collectively, the work within this dissertation defines the role of IL-10 and IFN-γ in regulating humoral immunity and reveals targets to improve humoral immunity against *Plasmodium* infection.