THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Ryan A. Zander

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Friday, July 1, 2016 | 10:00 a.m.
Biomedical Research Center Room 109

Immunoregulation of Plasmodium-specific CD4 T cells

Committee in Charge: Noah Butler, Ph.D. Chair; Mark Lang, Ph.D.; Daniel J.J. Carr, Ph.D.; Bob Axtell, Ph.D.; Kent Teague, Ph.D.

ABSTRACT: *Plasmodium* parasites are transmitted by *Anopheles* mosquitoes and cause the disease malaria. Malaria remains a global public health crisis that claims over 400,000 deaths annually. Despite the importance of CD4 T cell and B cell-secreted antibody responses in controlling parasite replication during the blood-stage of the infection, the cellular and molecular circuits that regulate the differentiation and function of these critical cell subsets remain poorly defined. Herein, we identified that human and rodent CD4 T cells exhibit atypical expression of the co-stimulatory receptor OX40 during malaria. Therapeutically targeting OX40 during experimental malaria promotes the accumulation of multiple functionally distinct CD4 T helper cell subsets, enhances the protective capacity and B cell helper function of parasite-specific CD4 T cells, and promotes efficient immune-mediated clearance of *Plasmodium* parasites. Strikingly, the effects of signaling through OX40 are modified following simultaneous blockade of the PD-1 co-inhibitory receptor, resulting in excessive type II interferon (IFN-γ) production that directly limits helper T cell-mediated support of humoral immunity. Importantly, our data highlight a previously unrecognized role for IFN-γ in suppressing protective humoral responses during malaria. Taken together, our results identify that a host-specific factor (OX40) can be targeted to enhance *Plasmodium* parasite control and reveal previously unknown mechanisms of how crosstalk between co-inhibitory and co-stimulatory pathways impacts parasite-specific CD4 T cell activity and control of *Plasmodium* infection. Additionally, using genetic and biochemical approaches, we show that excessive type I interferon (IFNα/β) limits T follicular helper cell accumulation and constrains anti-malarial humoral immunity. Mechanistically we show that CD4 T cell-intrinsic IFNα/β signaling promotes the formation of parasite-specific CD4 T regulatory 1 (Tr1) cells that co-express IFN-γ and interleukin (IL)-10. Moreover, the secreted effector cytokines of Tr1 cells, IL-10 and IFN-γ collaborate to restrict T follicular helper cell accumulation, limit parasite-specific antibody responses, and diminish parasite control. Collectively, work in this dissertation provides new insight into how *Plasmodium*-induced inflammation and regulatory networks impact CD4 T cell activity and humoral

immunity during malaria. These findings have important implications for strategies that aim to bolster parasite-specific CD4 T cell and B cell-secreted antibody responses during malaria.