Robin Stephens, PhD
Associate Professor
Immunology and Pathology of Malaria

T Helper Plasticity in Balancing Pathology and Protection in Malaria

Dr. Stephens started her career as a parasite immunologist while an undergraduate at Cornell University. After earning a Master's at NYU, and a PhD in Immunology at Washington University, Dr. Stephens trained in malaria immunology at the National Institute for Medical Research in Mill Hill, London (now the Crick Institute). The Stephens lab at the University of Texas Medical Branch is dedicated to understanding protective adaptive immune responses to Plasmodium spp., including lethal cerebral pathology, in order to find novel solutions for vaccination and treatments for malaria.

Abstract: Complete protection from malaria requires both antibody and Th1 cells. Evolution has solved the competing nature of these two responses with the hybrid Th1/Tfh cell (IFN-g+IL-21+CXCR5+), which predominates in response to several persistent infections. In Plasmodium chabaudi infection, IFN-g+ T cells control parasitemia, whereas antibody and IL-21+Bcl6+ T cells effect final clearance, suggesting an evolutionary driver for the hybrid population. We found that CD4-intrinsic Bcl6, Blimp-1, and STAT3 coordinately regulate expression of the Th1 master regulator T-bet, supporting plasticity of CD4 T cells. Bcl6 and Blimp-1 regulate CXCR5 levels, and T-bet, IL-27Ra, and STAT3 modulate cytokines in hybrid Th1/Tfh cells. Infected mice with STAT3 knockout (KO) T cells produced less antibody and more Th1-like IFN-g+IL-21- CXCR5lo effector and memory cells, and were protected from re-infection. Conversely, T-bet KO mice had reduced Th1-bias upon re-infection and prolonged secondary parasitemia. Therefore, each feature of the CD4 T cell population phenotype is uniquely regulated in this persistent infection, and the cytokine profile of memory T cells can be modified to enhance the effectiveness of the secondary response. As some increase in pathology was seen in mice with a shifted Th1/Tfh balance, we are currently investigating the protective and functional capacity of hybrid Th1/Tfh cells to understand if this solution is ultimately maladaptive.