

**P055** Enhanced resistance to intracellular pathogen in PI3K-deficient mice due to defective expansion of natural regulatory T cells

**Dong Liu<sup>1</sup>, Aaron Marshall<sup>1</sup>, Klaus Okkenhaug<sup>2</sup>, Bart Vanhaesebroeck<sup>3</sup> Jude Uzonna<sup>1</sup>**

<sup>1</sup>Department of Immunology, University of Manitoba, Canada; <sup>2</sup>The Babraham Institute, Cambridge, UK; <sup>3</sup>Ludwig Institute for Cancer Research, UK

The conventional paradigm holds that the balance between IFN- $\gamma$ -driven type 1 and IL-4-driven type 2 response regulates resistance or susceptibility to many intracellular pathogens including *Leishmania major*. Here, we provide compelling evidence that questions the validity of this concept. We show that mice with defective p110 delta gene expression (p110 $\delta$ -KI) are highly resistant to *L. major*. These mice develop significantly smaller lesion and controlled parasite faster than controls. Paradoxically, both antigen-specific cellular proliferation and the production of Th1 and Th2 cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-4 and IL-10) were dramatically impaired in infected p110 $\delta$ -KI mice. Interestingly, infected p110 $\delta$ -KI mice also had significantly impaired expansion of CD4+CD25+Foxp3+ IL-10-producing regulatory T cells in both their lymphoid organs and at the site of infection. P110 $\delta$ -KI macrophages were more responsive to IFN- $\gamma$  and controlled parasite replication more efficiently than those from WT mice. Taken together, these findings strongly suggest that resistance to *L. major* is most likely regulated by IL-10 produced by natural regulatory cells rather than the magnitude of Th1 (IFN- $\gamma$ ) and Th2 (IL-4) cytokines as is currently believed.