Russell SE, Stefanska AM, Kubica M, Horan RM, Mantovani A, Garlanda C, Fallon PG, Walsh PT. (2013). Toll IL-1R8/single Ig IL-1-related receptor regulates psoriasiform inflammation through direct inhibition of innate IL-17A expression by γδ T cells. *J Immunol*. Sep 15;191(6):3337-46.

Expression of the orphan receptor Toll IL-1R8/single Ig IL-1-related receptor has been reported to be reduced in the peripheral blood of psoriatic arthritis patients. However whether TIR8/SIGIRR activity plays a specific role in regulating psoriatic inflammation is unknown. We report that Tir8/Sigirr-deficient mice develop more severe psoriatic inflammation in both the chemical (Aldara)- and cytokine (rIL-23)-induced models of psoriasis. Increased disease severity was associated with enhanced infiltration of $V\gamma4^+$ γδ T cells that express significantly elevated levels of IL-17A. Critically, we also demonstrate that TIR8/SIGIRR activity directly suppressed innate IL-17A expression by γδ T cells in vitro and in vivo. Importantly, treatment of Tir8/$Sigirr^{-/-}$ mice with an IL-17A neutralization Ab reversed the enhanced disease severity observed in these mice. This study identifies TIR8/SIGIRR as a novel intrinsic negative regulator of innate IL-17A expression and characterizes a novel mechanism involved in the regulation of psoriatic inflammation.