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# RORγt inverse agonists suppress Th17 cell differentiation *in vivo*

**Jianfei Yang**
*Tempero Pharmaceuticals, a GSK Company, USA*

## Abstract

Th17 cells play a critical role in the pathogenesis of autoimmune diseases. Differentiation of Th17 cells requires the nuclear receptor RORt, and inhibition of RORt by small molecule inhibitors prevents Th17 cell differentiation *in vitro*. RORt inhibitors also modulate RORt activity *invivo* as demonstrated by a significant reduction in the severity of experimental autoimmune encephalomyelitis. However, the effect of RORt small molecule inhibitors on the *in vivo* generation of Th17 cells has not yet been clearly demonstrated. Here we report a novel, potent, and selective RORt inverse agonist TMP778 and demonstrate its role in the *in vivo* differentiation of Th17 cells. TMP778 blocks both human and mouse Th17 cell differentiation *in vitro*. *In vivo*, administration of TMP778 to C57BL/6 mice immunized with myelin oligodendrocyte peptide 35-55 ($MOG_{35-55}$)blocked MOG-specific IL-17A expression. In addition, expression of Th17 signature genes (*Il17a, Il17f, Il22,* and *CCL20*) as well as *Ifn* was inhibited. Further, IL-17-producing $CD4^+$ T cells were significantly reduced in IL-17-IRES-GFP transgenic mice administrated TMP778 after immunization with $MOG_{35-55}$. Thus, our studies demonstrate that RORt inverse agonist TMP778 suppress Th17 differentiation *in vivo*.

## Biography

Jianfei Yang is a PrincipalScientist and a Project Leader of a Th17 cell-related project at Tempero Pharmaceuticals, a GSK company, in Cambridge, MA, USA. He received a PhD in Pathology from Niigata University in Japan in 1997. He then obtained postdoctoral training in Dr. Ken Murphy's lab at HHMI and Washington University. In the past 16 year, he has been studying the role of $CD4^+$ T helper cells in immunity and diseases. He has more than 10 years of experience in autoimmune disease research and pharmaceutical drug development. He has published numerous papers and patents.