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RORyt inverse agonists suppress Th17 cell differentiation in vivo

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Th17 cells play a critical role in the pathogenesis of autoimmune diseases. Differentiation of Th17 cells requires the nuclear receptor RORyt, and inhibition of RORyt by small molecule inhibitors prevents Th17 cell differentiation *in vitro*. RORyt inhibitors also modulate RORyt activity *in vivo* as demonstrated by a significant reduction in the severity of experimental autoimmune encephalomyelitis. However, the effect of RORyt 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 RORyt 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 (MOG₃₅₋₅₅) blocked MOG-specific IL-17A expression. In addition, expression of Th17 signature genes (*Il17a, Il17f, Il22, and CCL20*) as well as *Ifny* was inhibited. Further, IL-17-producing CD4⁺ T cells were significantly reduced in IL-17-IRES-GFP transgenic mice administrated TMP778 after immunization with MOG₃₅₋₅₅. Thus, our studies demonstrate that RORyt inverse agonist TMP778 suppress Th17 differentiation *in vivo*.

Biography

Jianfei Yang is a Principal Scientist and a Project Leader of a Th17 cell-related project at Tempero Pharmaceuticals, a GSK company, in Cambridge, MA, USA. He received a Ph.D. 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.

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