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RORC2 inverse agonists suppress human Th17 and Tc17 cell differentiation and IL-17 expression by IL-17-producing T cells

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Th17 cells are CD4+ T helper cells characterized by their expression of IL-17A, IL-17F, IL-22, CCR6 and RORγt. Animal studies demonstrated that IL-17 and Th17 cells are critical for the pathogenesis of autoimmune disease models such as experimental autoimmune encephalomyelitis (EAE), inflammatory bowel disease (IBD) and collagen-induced arthritis (CIA). In humans, IL-17 and Th17 cells are correlated with rheumatoid arthritis, psoriasis and inflammatory bowel disease. Neutralizing anti-IL-17 and anti-IL-17 receptor monoclonal antibodies have demonstrated remarkable clinical efficacy in psoriasis patients. Thus, targeting Th17 cells is believed to be an important intervention for several autoimmune diseases. RORC2 has been shown to be the master transcription factor for the differentiation of Th17 cells. We have discovered several novel small molecule inverse agonists of RORC2. These compounds inhibit the differentiation of human Th17 cells and Tc17 cells from naïve CD4+ T cells and CD8+ T cells, respectively. Importantly, they also significantly inhibit IL-17 expression by differentiated Th17 cells and Tc17 cells. These inverse agonists suppress in vivo Th17 cell differentiation in mouse models. Collectively, these data support the use of RORC2 inverse agonists for the treatment of human autoimmune diseases.

Biography

Jianfei Yang is a senior scientist and a project leader for a Th17 cell target 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 15 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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