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Nonclinical characterization of the novel IL-1 heterodimeric fusion protein RPH-104

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Abstract

Interleukin-1 (IL-1), a central mediator of innate immunity and inflammation, plays a pivotal role in a broad spectrum of inflammatory diseases. RPH-104 is a novel IL-1 antagonist: a heterodimer comprised of human extracellular portions of IL-1RI and IL-1 receptor accessory protein, each linked to a mutant Fc portion of human IgG1. Aim: The aim of the studies is preclinical characterization of RPH-104. Methodology & Theoretical Orientation: A surface plasmon resonance methods were developed to measure the binding kinetics/affinity of RPH-104 to IL- IL-1IL-1Ra and Fc receptor binding. U937 cells which express IL-1were selected for use in the antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) assays. Potential tissue cross-reactivity (TCR) was assessed with histologically prepared cryo-sections from a selected panel of human and cynomolgus monkey tissues. To facilitate immunohistochemical detection RPH-104 and human IgG1 were conjugated with biotin. To assess the toxicity, toxicokinetics and immunogenicity of RPH-104, a 4 weeks subcutaneous administrations toxicity study in cynomolgus monkey was performed. Findings: RPH-104 binds to IL-in preference to IL-1or IL-Ra. RPH-104 binds to Fc (Fc³RI, Fc?³RIIa, Fc³RIIb, FcRn, Fc³IIIb) receptors overall with a lower affinity than human IgG1. No evidence of RPH-104 ADCC or CDC was shown. TCR study shows similar binding of RPH-104 to cynomolgus monkeys and human tissues. There are no safety issues evident from the cynomolgus monkey GLP (Good Laboratory Practice) 4-week toxicology study. No-observed-adverse-effects-level is considered to be 100 mg/ kg RPH-104. Conclusion & Significance: Overall RPH-104 has shown potent in vitro activity and no safety concerns. This makes RPH-104 a potent candidate as an anti-inflammatory therapeutic for a range of IL-1 mediated clinical indications.

The combined effects of interferon gamma (IFNgamma) and tumor necrosis factor alpha (TNFalpha) stimulation on CXCL10 secretion in primary cells from PTCs and TFC were tested. Furthermore, the effect of PPARgamma activation by TZDs, on CXCL10 secretion and proliferation in these cell types was studied. In primary cultures of TFC and PTCs CXCL10 production was absent under basal conditions; a similar dose-dependent secretion of CXCL10 was induced by IFNgamma in both cell types. TNFalpha alone induced a slight but significant CXCL10 secretion only in PTCs. The stimulation with IFNgamma+TNFalpha induced a synergistic CXCL10 release in both cell types; however, a secretion more than ten times higher was induced in PTCs. Treatment of TFC with TZDs dose-dependently suppressed IFNgamma+TNFalpha-induced CXCL10 release, while TZDs stimulated CXCL10 secretion in PTCs. A significant antiproliferative effect by TZDs was observed only in PTCs. In conclusion, a dysregulation of CXCL10 secretion has been shown in PTCs. In fact, a CXCL10 secretion more than ten times higher has been induced by IFNgamma+TNFalpha in PTCs with respect to TFC. Moreover, TZDs inhibited CXCL10 secretion in TFC and stimulated it in PTCs. The effect of TZDs on CXCL10 was unrelated to the significant antiproliferative effect in PTCs.

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