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

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Statement of the Problem: 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-1α, IL-1β, IL-1Ra and Fc receptor binding. U937 cells which express IL-1α were 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-1β in preference to IL-1α or IL-Ra. RPH-104 binds to Fc (FcγRI, FcγRIIa, FcγRIIb, FcRn, FcγIIIb) 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.

Recent Publications

1. Dinarello C A, Simon A, van der Meer J W M (2012) Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov. 11(8):633-652.
2. Mistry A, Savic S, van der Hilst J C H (2017) Interleukin-1 blockade: An update on emerging indications. BioDrugs. 31(3):207-221.
3. Beck A, Reichert J M (2011) Therapeutic Fc-fusion proteins and peptides as successful alternatives to antibodies. MAbs. 3(5):415-416.
4. Levin D, Golding B, Strome S E, Sauna Z E (2015) Fc fusion as a platform technology: Potential for modulating immunogenicity. Trends Biotechnol. 33(1):27-34

Biography

Anastasia Dmitrieva has 2 years of laboratory working experience (newly derived recombinant rubella vaccine development and characterization) and 4 years experience in nonclinical studies sphere. She has organized conduction of more than 40 nonclinical studies of different medicine group: small molecules, fusion proteins, monoclonal antibodies, biosimilars, and generics. Her activities include scientific support as well as new drug and biologics license application documents review. Her area of scientific interest includes Immunology, Immune-Oncology, Biology, Virology and Pharmacology.

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