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Title: PK/PD profiles of the CXCL8 decoy protein PA401 after intravenous and intratracheal administration in saline and LPS exposed mice

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Body: Neutrophils play a crucial role in acute and chronic lung diseases including ALI, COPD, CF and severe asthma, and their presence in the lung has been correlated to disease severity and progression. Among the mediators of neutrophil recruitment into the lung CXCL8 is considered the major player. CXCL8 exerts its chemotactic activity by binding to glycosaminoglycan (GAG) co-receptors on inflamed cells, thus creating a solid-phase haptotactic gradient and being properly presented to GPC receptors CXCR1/2 on neutrophils. We have engineered higher affinity for GAGs into human CXCL8 obtaining a protein-based competitor for the CXCL8/GAG interaction. By further knocking-out the GPCR domain, we have obtained a decoy protein (PA401) with potent anti-inflammatory characteristics. PA401 has been tested in murine models of lung inflammation induced by lipopolysaccharide (LPS) showing strong dose-dependent neutrophil reduction in bronchoalveolar lavage fluid (BALF) after intravenous (IV) and subcutaneous (SC) administration. In the present study we have compared PA401 activity after IV and intratracheal (IT) administration in the same model, using saline exposed mice as control. PA401 plasma levels were also measured to assess pharmacokinetic profiles. PA401 has strongly reduced BALF neutrophils number after IV and IT administration (up to -76%). The blood cells increase due to LPS exposure was also partly normalized by IV, but not IT treatment, possibly due to the differences in plasma exposure. PA401 is a new biopharmaceutical with a unique mode of action interfering with lung neutrophilic inflammation and with activity after systemic and local delivery to the lung.