

Abstract N°: 3230**Characterisation of GSK1070806, an anti-IL-18 monoclonal antibody**

Marieta Ruseva^{*1}, Marian Rocha del Cura¹, Helen Payne¹, Joseph Mabbitt¹, Shahid Mehmood¹, Stephanie Lehmann², Iain Uings¹

¹GSK, United Kingdom, ²GSK, Germany

Introduction:

Interleukin 18 (IL-18) is a pleotropic pro-inflammatory immune modulator that functions in a highly context dependent manner depending on the local cytokine environment. Levels of IL-18 are elevated in a wide range of human diseases (including atopic dermatitis, inflammatory bowel disease, and rheumatoid arthritis) suggesting that neutralising IL-18 activity has considerable therapeutic potential in many indications.

In vivo, the functional activity of IL-18 is regulated by an endogenous antagonist - the IL-18 binding protein (IL-18 BP) - that circulates at higher levels than the cytokine and regulates its activity by inhibiting the interaction of IL18 with its cognate receptor, the IL-18Ra. Levels of IL-18BP are also altered in many disease states, making assessment of the contribution of IL-18 bioactivity to pathophysiology challenging.

Results:

GSK1070806 is a humanised IgG1 monoclonal antibody that binds to IL-18 with high affinity in surface plasmon resonance studies (42pM). GSK1070806 blocked production of interferon- γ (IFN γ) and IFN γ -mediated downstream signalling from IL-18 stimulated KG-1 cells confirming that it is a neutralising antibody.

In surface plasmon resonance experiments, the affinity of the interaction between IL-18BP and free IL18 was the same as the affinity of the interaction between IL-18BP and the IL18-GSK1070806 complex. Hydrogendeuterium exchange mass spectrometry confirmed that the binding sites on IL18 for the IL-18 BP and for GSK1070806 are independent and not overlapping.

GSK1070806 did not interfere with the binding of IL-18 to the IL-18R α , which is consistent with the lack of impact on IL-18 BP binding. GSK1070806 therefore appears to neutralise IL-18 activity by preventing activation of the signalling chain of the receptor, the IL-18R β .

Conclusion:

GSK1070806 is therefore a potent neutralising anti-IL18 antibody with considerable therapeutic potential in a range of inflammatory disease. The antibody has been previously evaluated in healthy and obese subjects, patients with type 2 diabetes and patients undergoing renal transplantation. GSK1070806 has been recently assessed in a Phase 1B clinical study in patients with moderate-to severe atopic dermatitis.

