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Discovery of a novel, high affinity, small molecule alpha-v beta-6 integrin inhibitor for the treatment of idiopathic pulmonary fibrosis

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Introduction: Fibrosis is the formation of scar tissue due to injury or long-term inflammation and is a leading cause of morbidity and mortality in disorders that include idiopathic pulmonary fibrosis (IPF). The alpha-v beta-6 (αvβ6) integrin has been identified as playing a key role in the activation of transforming growth factor-β (TGFβ) that is hypothesised to be pivotal in the development of IPF [1]. Therefore, a drug discovery programme within GlaxoSmithKline to identify small molecule αvβ6 selective RGD-mimetics was initiated.

Method: As part of a medicinal chemistry programme GSK3008348 [2] was identified and profiled in a range of pre-clinical *in vitro* (radioligand binding [3], flow cytometry [4], functional TGFβ [5] and high content screening assays) and *in vivo* (bleomycin-induced lung injury mouse model (20 and 60 IU bleomycin treated male C57/Bl6 mice)) systems.

Results: GSK3008348 (1% DMSO) was shown to bind to the αvβ6 with high affinity (pK_D 11.3±0.07, mean±SEM, n=6 donors) in membrane preparations generated from IPF human lung tissue. In primary human lung epithelial cells GSK3008348 (0.1% DMSO) induced rapid internalisation of αvβ6 ($t_{1/2}$2.6±0.5 min, mean±SEM, n=4) followed by a slow return of the integrin to the cell surface ($t_{1/2}$ 11.0±1.9 h, mean±SEM, n=4). It was shown that αvβ6 is degraded in lysosomes post-internalisation by GSK3008348 that would suggest the slow return of integrin to the surface and sustained duration of action is a consequence of new αvβ6 synthesis. GSK3008348 (1 mg/kg i.n. saline) was shown to engage with αvβ6 and inhibit the activation of TGFβ with a prolonged duration of action using *in vivo* mouse bleomycin lung fibrosis models measuring αvβ6 engagement (SPECT imaging [6]) and TGFβ signalling (pSMAD2 lung levels).

Conclusion: In summary, GSK3008348 displays the desirable pharmacological characteristics required for targeting a prolonged inhibition of TGFβ activation in the IPF lung via blockade of the αvβ6 integrin and is currently in Phase I trials for IPF [7].

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