**Abstract S133 Table 1** Demographics and clinical characteristics according to $\beta_2$-adrenergic receptor genotype

| | Gly-Gly | Arg-Gly | Arg-Arg | |
|---|---|---|---|---|
| | n = 105 | n = 88 | n = 3 | p value |
| Age (years) | 46 (43–49) | 46 (43–49) | 45 (39–52) | 0.97 |
| $FEV_1$ | | | | |
| (% predicted) | 86 (82–90) | 85 (81–89) | 88 (82–94) | 0.72 |
| $FEF_{25-75}$ | | | | |
| (% predicted) | 59 (53–65) | 57 (51–63) | 58 (49–66) | 0.85 |
| $FEV_1$/FVC | 0.72 (0.70–0.75) | 0.71 (0.68–0.74) | 0.74 (0.70–0.77) | 0.49 |
| ICS Dose | | | | |
| (BDP equivalent, µg/day) | 800 (800–1500) | 800 (680–2000) | 800 (400–1250) | 0.65 |
| LABA (%) | 76 | 74 | 60 | 0.21 |
| ACQ-6 | 1.78 (1.53–2.03) | 1.53 (1.28–1.78) | 1.93 (1.36–2.50) | 0.23 |

Data presented as mean (95% CI) except for ICS dose which is presented as median (IQR)

**Methods** In this cross-sectional study, demographics, medication and spirometry were prospectively recorded from patients attending a secondary care asthma clinic who were also genotyped and completed the Asthma Control Questionnaire (ACQ-6).

**Results** A total of 223 patients prescribed ICS were included in the analysis. Overall mean age was 46 years, $FEV_1$ 86%, median ICS dose 800 µg/day and 73% were prescribed LABA. There were no differences in terms of spirometry and ACQ-6 between the three genotypes (Table 1). In patients who were prescribed LABA there was no difference in ACQ-6 comparing patients with no Arg copies (n = 80, ACQ-6 1.82) versus those with one or two Arg copies (n = 83, ACQ-6 1.70). Moreover salbutamol reliever use was no different.

**Conclusion** Gly16Arg polymorphism was not associated with impaired asthma control in ICS treated adult asthmatics irrespective of LABA exposure.

## REFERENCES

1 Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta (2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol*. 2009 Dec;124(6):1188-94 e3

# Basic mechanisms of IPF

## S134 KINASE SELECTIVITY PROFILES OF NINTEDANIB AND IMATINIB

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**Introduction** Tyrosine kinase inhibition has shown inconsistent success in the treatment of idiopathic pulmonary fibrosis (IPF). While a study of imatinib showed no impact on survival or lung function in a placebo-controlled study, two recently announced placebo-controlled phase 3 trials of nintedanib demonstrated statistically significant impact on forced vital capacity. Comparing the kinase target profiles could inform future target selection for drugs in IPF.

**Methods** *In vitro* kinase selectivity data of nintedanib and imatinib were collected using the kinomescan platform (DiscoveRx Inc). Binding data (% binding) for 451 human kinases (~80% of the human kinome) were initially collected at a single concentration (10 uM). For kinases that displayed significant binding, potencies ($K_D$) were measured in dose-response format.

**Results** At a common concentration of 100 nM, imatinib and nintedanib bound to 12 and 50 kinases, respectively. Maximal drug concentrations ($C_{max}$) observed in patients were used to project therapeutically relevant kinase inhibition for both drugs. Using these criteria, nintedanib binds 44 kinases at drug levels seen in patients ($K_D < C_{max}$ of 64 nM). Imatinib binds 34 kinases at drug levels seen in patients ($K_D < C_{max}$ of 7500 nM). 14 kinases were bound by both compounds, including PDGFRA, PDGFRB and VEGFR2.

**Conclusions** Our results suggest that nintedanib and imatinib have partially overlapping inhibition profiles; the kinases that are targeted by both agents are unlikely to be responsible for efficacy differences. Further work is required to identify which of the remaining kinase target (s) are responsible for efficacy in IPF and could therefore represent targets for follow-up compounds.

## S135 DOES CD248 HAVE A ROLE IN IPF?

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Idiopathic pulmonary fibrosis (IPF) has a complex pathophysiology withepithelial-mesenchymal transition (EMT) thought to be important to the pathogenesis of fibrotic lesions. CD248 is a membrane bound receptor that has collagen and lectins as ligands and is a stromal cell marker, whose expression is up-regulated postnatally during tissue inflammation andre-modelling. A role of CD248 is emerging in kidney fibrosis, but its function in the lung is unknown. We hypothesised that CD248 is a mesenchymal marker of IPF severity and that CD248 contributes to IPF pathogenesis.

**Methods** CD248 expression was investigated in 23 IPF patient lung samples using immunohistochemistry (IHC) and qualitatively scored. Expression was assessed in cultured normal human lung fibroblasts (NHLFs), A549 cells, IPF derived fibroblasts and normal human primary ATIIs, treated with or without TGF-$\beta$1 and PDGF-BB, using flow cytometry and qRT-PCR. siRNA CD248 knock down (KD) on NHLF mesenchymal marker expression and proliferation was evaluated using qRT-PCR and BrdU assays.

**Results** IHC revealed strong CD248 expression by fibroblasts in both fibrotic areas and physiological structures of IPF lung tissue (pericytes and pleural tissue). Expression was greatest in samples from lung transplant explants. *In vitro*, CD248 protein levels were significantly greater in IPF derived lung fibroblasts vs NHLFs ($p < 0.01$). CD248 KD significantly reduced proliferation of control, PDGF-BB and/or TGF-$\beta$1 treated NHLFs ($p < 0.001$), but collagen and $\alpha$SMA mRNA levels were unaffected ($p > 0.05$). The alveolar epithelium did not express CD248 on the protein level and minimal CD248 mRNA levels were detected in cultured A549 cells and ATIIs, which remained unchanged during TGF-$\beta$1 induced EMT.

**Summary** CD248 expression is elevated in the lungs of IPF patients especially in severe disease. CD248 expression appears specific for fibroblasts compared to epithelial cells and does not change during EMT. CD248 KD reduced fibroblast proliferation, but not myofibroblast differentiation.

We conclude that CD248 over-expression is involved in the pathogenesis of IPF – and that it has potential as a marker of mesenchymal/fibroblast lineage. Given that CD248 ligands are collagen type I, IV and fibronectin, we hypothesise that CD248 signalling represents a novel matrix-fibroblast interaction that may be a potential therapeutic target in IPF.



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