



Pasini, Alice and Brand, Oliver J. and Jenkins, Gisli and Knox, Alan J. and Pang, Linhua (2016) Effect of epigenetic inhibitors on lung fibroblast phenotype change in idiopathic pulmonary fibrosis. In: British Thoracic Society Winter Meeting 2016, 7-9 Dec 2016, London. (Unpublished)

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## Effect of Epigenetic Inhibitors on Lung Fibroblast Phenotype Change in Idiopathic Pulmonary Fibrosis

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**Introduction and objectives** Idiopathic Pulmonary Fibrosis (IPF) is a fatal interstitial lung disease with unknown aetiology. Lung myofibroblasts (activated fibroblasts) are the major effector cells in the pathogenesis of IPF. Transforming growth factor- $\beta$  (TGF- $\beta$ 1) is a potent activator of fibroblasts. Lack of effective treatment options necessitates novel therapeutic approaches. Epigenetic drugs, by inhibiting chromatin modifying enzymes involved in gene expression control, represent promising agents capable of modulating the cellular phenotype.

We previously demonstrated that the cyclooxygenase-2 (*COX-2*) gene is epigenetically silenced in lung fibroblasts from IPF patients (F-IPF)[1] and epigenetic inhibitors and restore *COX-2* expression. However, whether epigenetic inhibitors can alter fibroblast phenotype remains unknown. This study aimed to investigate the effect of four different epigenetic enzyme inhibitors on fibroblast phenotype change in IPF.

**Methods** F-IPF and fibroblasts from non-fibrotic lung (F-NL) treated with TGF- $\beta$ 1 were cultured to test the effects of the epigenetic inhibitors BIX01294 (BIX, G9a histone methyltransferase inhibitor), 3-deazaneplanocin A (DZNep, EZH2 histone methyltransferase inhibitor), SAHA (histone deacetylases inhibitor) and Decitabine (DAC, DNA demethylating agent), in comparison with the *COX-2* products prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The expression of *COX-2* and myofibroblast markers collagen 1 (COL1) and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) was assessed. The *COX-2* DNA promoter methylation level was analysed by bisulfite sequencing.

**Results** TGF- $\beta$ 1 induced a myofibroblast phenotype in F-NL characterised by COL1 and  $\alpha$ -SMA upregulation and *COX-2* downregulation, similar to F-IPF. PGE<sub>2</sub> and SAHA were able to maintain/restore *COX-2* expression in TGF- $\beta$ 1-induced myofibroblasts and F-IPF. DAC demonstrated similar effect in TGF- $\beta$ 1 treated F-NL only. SAHA also reduced COL1 and  $\alpha$ -SMA expression. But DZNep and BIX showed no effect. No differences in the *COX-2* promoter methylation was detected between F-NL and F-IPF.

**Conclusions** Among the epigenetic inhibitors tested, SAHA shows a promising antifibrotic effect by inhibiting fibroblast activation and the underlying molecular mechanisms are currently under investigation.

**Reference** [1] Coward WR , Feghali-Bostwick CA, Jenkins G et al. A central role for G9a and EZH2 in the epigenetic silencing of cyclooxygenase-2 in idiopathic pulmonary fibrosis. *FASEB J.* 2014;28(7):3183-96.