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**Suberanilohydroxamic Acid (SAHA) Inhibits Collagen deposition in a Transforming Growth Factor  $\beta_1$ -driven Precision Cut Lung Slice (PCLS) model of Pulmonary Fibrosis.**

Oliver J Brand, Alice Pasini, Anthony Habgood, Alan J Knox, Gisli Jenkins, Linhua Pang

**Introduction and Objectives:** Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive interstitial lung disease that is refractory to current treatment options. Transforming growth factor (TGF)- $\beta_1$  is a key pro-fibrotic cytokine that plays a crucial role in IPF pathogenesis. Our group previously demonstrated distinct epigenetic modifications involved in repression of the antifibrotic gene cyclooxygenase-2 (COX-2) in fibroblasts from IPF (F-IPF) lungs compared with fibroblasts from non-fibrotic lungs (F-NL). Epigenetic drugs capable of inhibiting DNA and histone modifications may, therefore, represent a putative novel therapy. The aim of this study was to investigate the ability of 4 epigenetic inhibitors to regulate TGF- $\beta$ -driven fibrosis in *ex vivo* mouse lung.

**Methods:** A precision-cut lung slice (PCLS) model of fibrosis was established using the previously described [1] CC10-tTS-rtTA-TGF $\beta_1$  transgenic (tgTGF- $\beta_1$ ) mouse. The model was first assessed by investigating PCLS overexpression of TGF- $\beta_1$  in response to stimulation of the transgene by doxycycline treatment. Gene expression of COX-2 and fibrotic markers including collagen were assessed after 4 days of treatment. The anti-fibrotic potential of 4 epigenetic inhibitors; BIX01294 (BIX, inhibitor of G9a histone methyltransferase), 3-deazaneplanocin A (DZNep, inhibitor of EZH2 histone methyltransferase), SAHA (inhibitor of histone deacetylases, HDACs) and Decitabine (DAC, DNA demethylating agent) was investigated. Viability of PCLS was assessed by MTT and Prestoblu<sup>®</sup> viability assay.

**Results:** Treatment of PCLS from tgTGF- $\beta_1$  mice with doxycycline induced a concentration-dependent increase in global TGF- $\beta_1$ , pro-fibrotic markers including collagen and pro-inflammatory COX-2, which was comparable to recombinant TGF- $\beta_1$  treatment. Treatment with three of the epigenetic inhibitors BIX01294, DZNep and DAC did not reduce the pro-fibrotic response following doxycycline treatment. However SAHA demonstrated a significant suppressive effect on COX-2 and collagen expression, while not directly affecting TGF- $\beta_1$  transgene expression.

**Conclusions:** The data suggests that SAHA has the potential to reduce fibrosis in a TGF- $\beta_1$  driven model of pulmonary fibrosis. Further work is currently underway to assess the anti-fibrotic potential of this drug in tgTGF- $\beta_1$  animals.

## Reference

[1] Lee CG, Cho SJ, Kang MJ et al. Early Growth Response Gene 1-mediated Apoptosis Is Essential for Transforming Growth Factor  $\beta_1$ -induced Pulmonary Fibrosis. *J Exp Med.* 2004; 200(3):377-389.