In vivo assessment of prevention of lung fibrosis using the pan-PPAR agonist lanifibranor in the TβRIIΔk-fib mouse model of systemic sclerosis.

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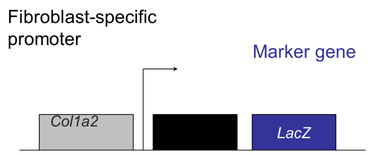
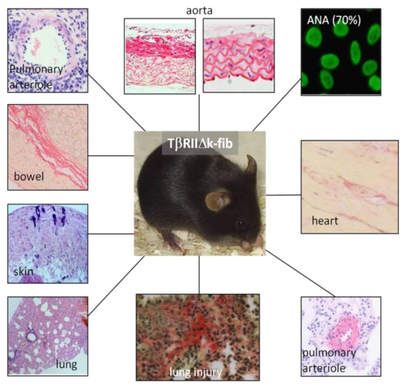
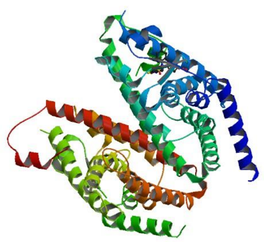
Background/purpose:

The TβRIIΔk-fib transgenic (TG) mouse model of scleroderma carries a fibroblast-specific TGFβ receptor II mutation resulting in balanced up-regulation of TGFβ signalling and replicates key fibrotic and vasculopathic features of scleroderma, including susceptibility to lung fibrosis and pulmonary hypertension.





Published data show an excessive pulmonary fibrotic response persists in TG mice in response to intra-tracheal bleomycin administration when compared to unbuffered saline in TG mice or bleomycin in wildtype (WT) mice (1). In this study, we investigate whether lanifibranor treatment leads to an amelioration of persistent bleomycin-induced lung fibrosis in TβRIIΔk-fib mice.



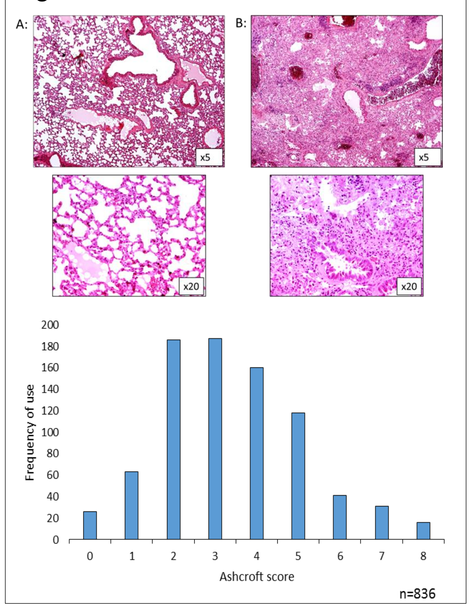
The pan-peroxisome proliferator-activated receptor (PPAR) agonist lanifibranor (formerly known as IVA337) is currently being tested in a phase II clinical trial in scleroderma and has previously been evaluated in 2 mouse models of scleroderma lung fibrosis (2).

Methods:

TG (n=46) and WT mice (n=33) were administered one of two doses of lanifibranor(30 mg/kg or 100 mg/kg) or vehicle administered by daily oral gavage up to 4 weeks. On day 2 bleomycin or unbuffered normal saline (pH 5.3) were administered by oropharyngeal aspiration to trigger lung fibrosis, assessed by histological scoring (Ashcroft score) and biochemical testing of lung homogenates. All procedures were licensed and approved by an animal use ethics committee.

Results:

Figure 1.

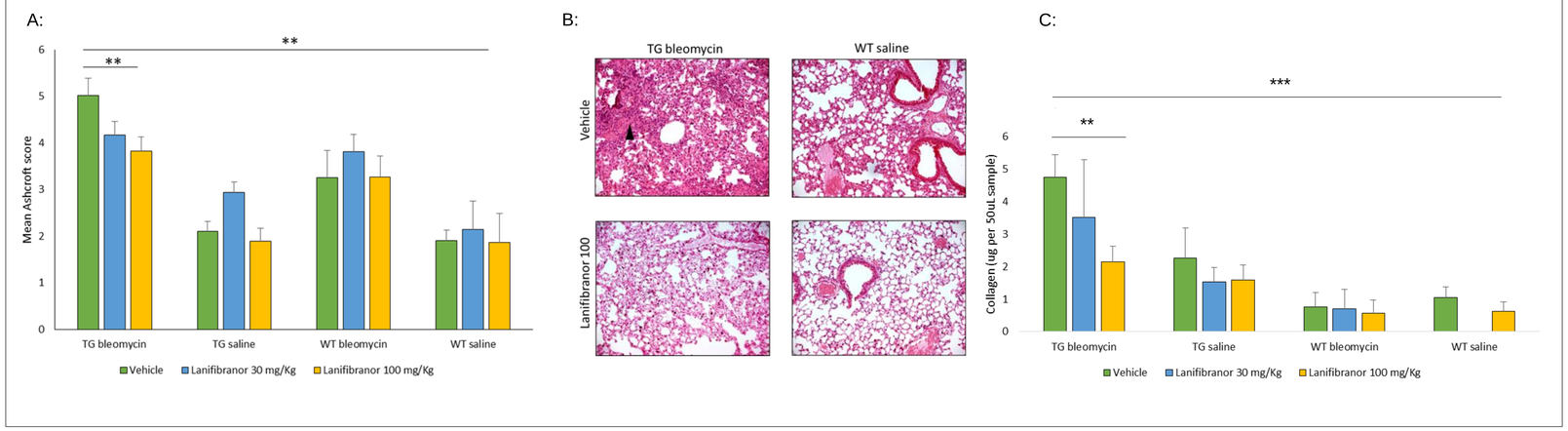


To avoid variability in Ashcroft scoring due to heterogeneity in fibrosis of lung parenchyma, multiple fields were examined and multiple cuts examined per sample. As a result, in this experiment, all scores between 0 (figure 1A) and 8 (figure 1B) were utilised, the mode score was 3 (figure 1; histogram).

TG mice treated with higher dose lanifibranor demonstrated significantly greater protection from lung fibrosis than those treated with vehicle or lower dose lanifibranor, for instance: mean Ashcroft score TG-bleo IVA100 3.82 ±0.31; TG-bleo vehicle 5.01±0.38; p<0.01, presented in figure 2A. Treatment with lanifibranor in WT animals was less effective at preventing fibrosis (WT-bleo IVA100 3.27±0.44; WT-bleo vehicle 3.25±0.59; not significant), suggesting that the pro-fibrotic phenotype **due to TGF-β upregulation** in this model is substantially ameliorated by lanifibranor. There is 1.2 fold difference between TG and WT in the bleomycin group without lanifibranor (4.4 and 3.2) and 0.3 fold difference with lanifibranor (3.8 and 3.5). This represents **75% inhibition** of the TG effect caused by lanifibranor.

Representative H&E images from the key discriminator groups are shown in figure 2B; collagen deposition was quantified using the Sircol assay and this method reproduced the results represented histologically (2C). There is no significant effect on WT mice after 21 days from oropharyngeal aspiration of bleomycin when compared to saline. There remains a dose dependent significant reduction in collagen deposition in transgenic mice given bleomycin aspiration compared with preventative lanifibranor before bleomycin aspiration.

Figure 2.



Conclusions:

- Treatment with 100 mg/kg lanifibranor ameliorates lung fibrosis in the TβRIIΔk-fib mouse model of scleroderma.
- This model, which demonstrates severe and persistent fibrosis compared to WT mice, provides mechanistic support for trials of lanifibranor in scleroderma including cases with pulmonary involvement.

References:
Hoyles RK et al; Arthritis Rheum. 2008;58:1175-88.
Avouac J et al; Ann Rheum Dis. 2017;76:1931-1940