Bleomycin-induced IPF in the DIO mouse: a new translational model to evaluate drugs targeting IPF

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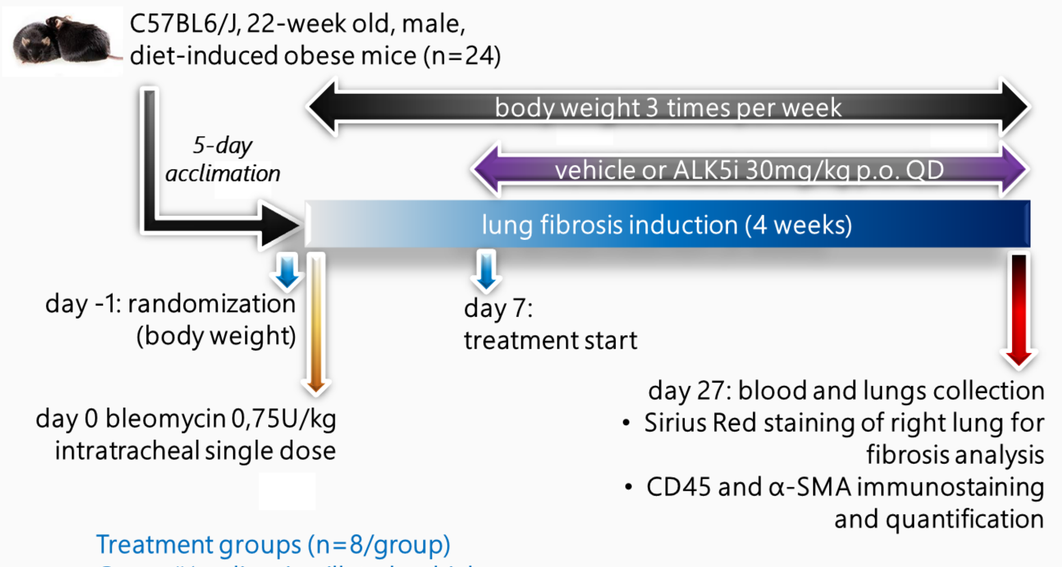
BACKGROUND:

Bleomycin-induced IPF in lean C57BL6/J mouse is a challenging animal model with several limitations for drug efficacy studies.
Observational studies suggest a significant link between obesity and IPF in humans. Diet-induced obese (DIO) mice have higher levels of Angiotensin II, which is know to be pro-inflammatory and pro-fibrotic. Hence, the DIO mouse model has the potential to better respond to bleomycin challenge. We then evaluated the effects of bleomycin in DIO mice treated without or with the anti-fibrotic drug ALK5 inhibitor.

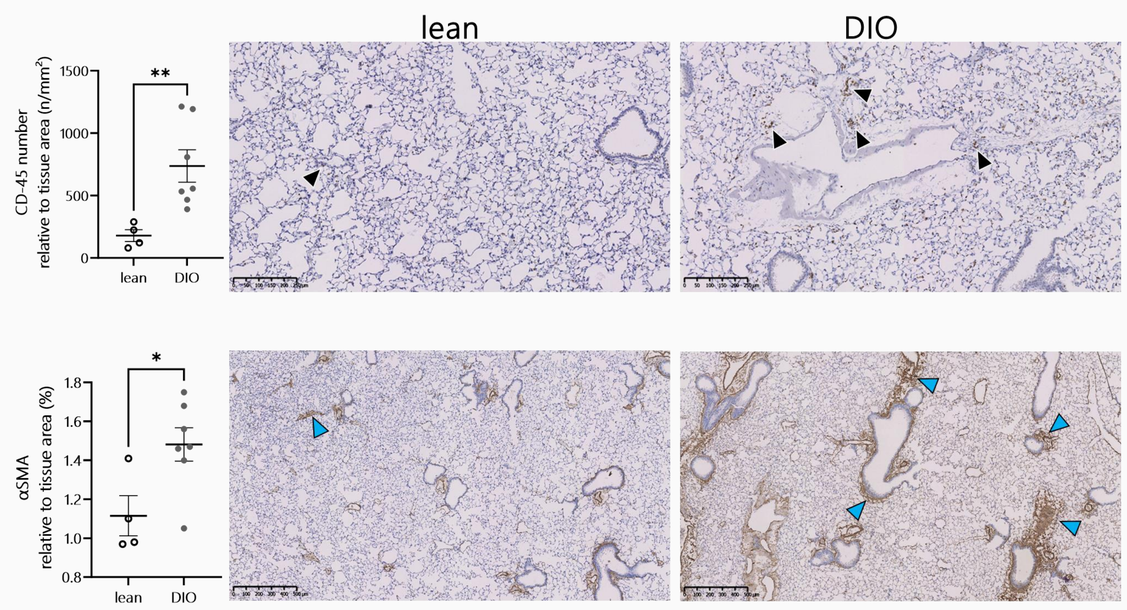
METHODS:

C57Bl6/J DIO mice, male, 22-week-old (16 weeks on 60% high fat diet) were randomized based on their body weight after a 5-day acclimation.
On day 0, bleomycin (0.75U/kg) was administered with an intratracheal single dose. At day 7 after bleomycin administration, DIO mice were then treated until day 27 with vehicle or ALK5i (SB525334) 30mg/kg p.o. QD. Blood and lungs were then collected. Formalin-fixed lung was used for histology analysis (Sirius Red staining, CD45 and α –SMA immunostaining and AI-based digital pathology).



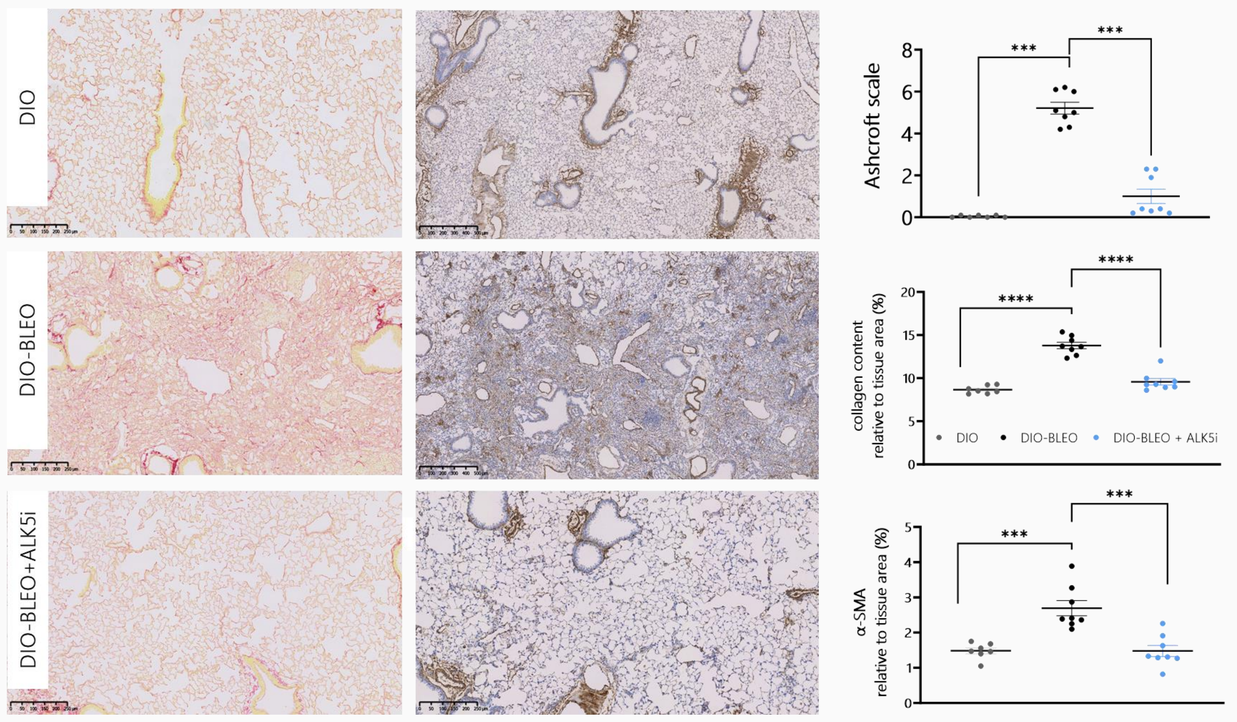
RESULTS:

1 Before bleomycin administration, lungs of DIO mice have a pro-inflammatory and a pro-fibrotic profile compared to lean mice



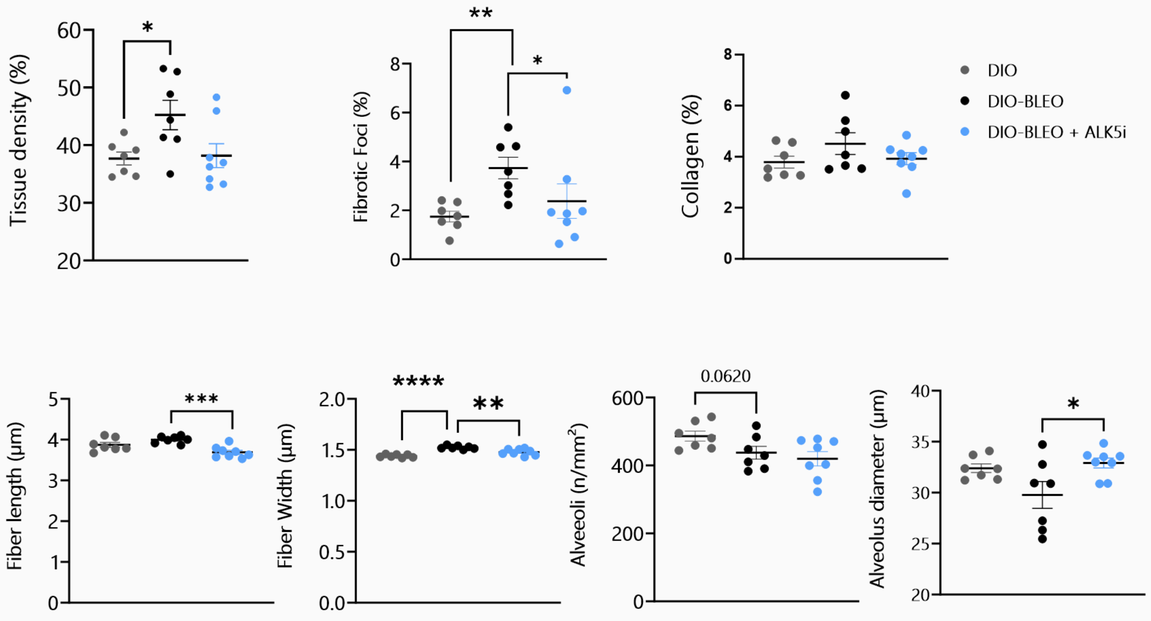
Representative pictures for CD45 (black arrows) and α-SMA (blue arrows) immunostaining and quantification in lungs of lean or DIO mice before bleomycin administration. **p<0.05 and **p<0.01 lean vs. DIO.*

2 Bleomycin strongly raises Ashcroft scale and lung fibrosis in DIO mice. Both parameters are significantly improved by ALK5 inhibition



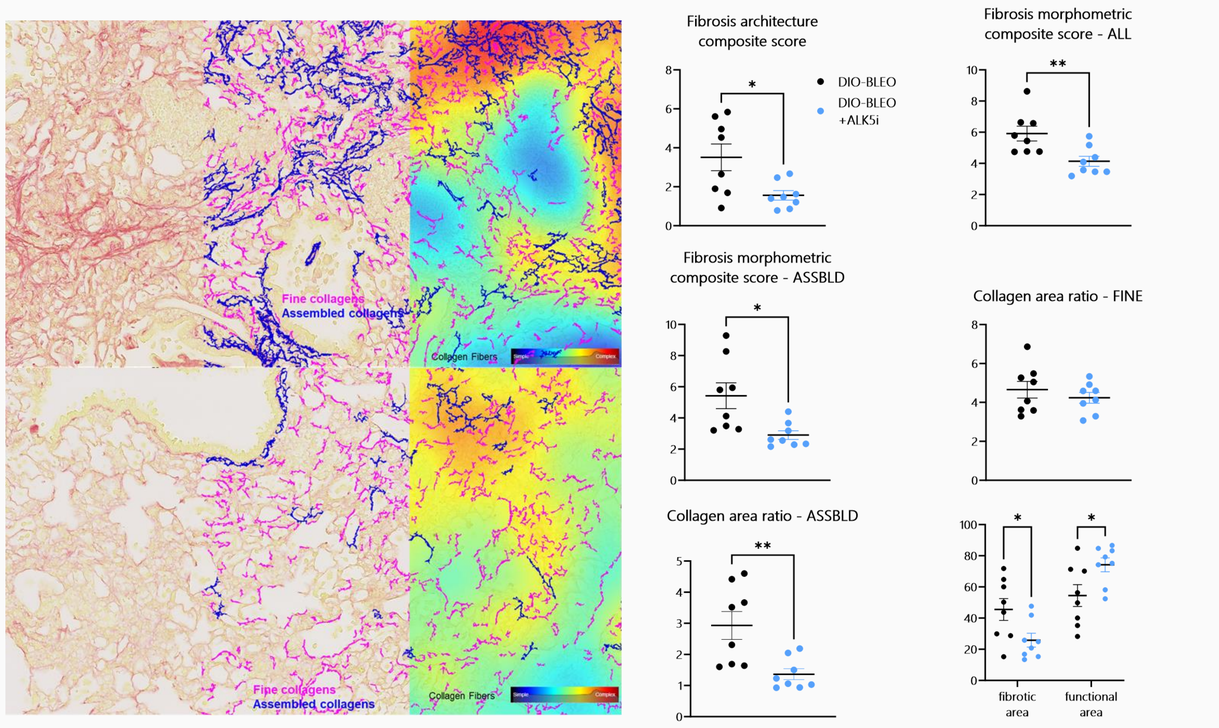
Representative pictures for Sirius Red staining (left panel), α-SMA immunohistochemistry (middle panel), Ashcroft scale, collagen content and % α-SMA immunostaining (right panel) in DIO mice administered with saline (DIO), bleomycin and treated with vehicle (DIO-BLEO) or ALK5i (DIO-BLEO+ALK5i).
****p<0.001 and ****p<0.0001 DIO vs. DIO-BLEO or DIO-BLEO vs. DIO-BLEO+ALK5i*

3 Biocellvia morphometric digital pathology confirms anti-fibrotic effects of ALK5 inhibition and its potential benefit on emphysema



Tissue density, fibrotic foci and collagen (upper panel), collagen fiber length and width, number of alveoli and alveolus diameter (lower panel) assessed with MorphoQuant™.
**p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001 DIO vs. DIO-BLEO or DIO-BLEO vs. DIO-BLEO+ALK5i*

4 PharmaNest quantitative digital pathology demonstrates that ALK5 inhibition markedly reduces fibrosis scores and complex collagen fibers



Representative pictures showing the three panels illustrating both original Sirius Red images and image analysis layers (left panel), fibrosis composite scores, fine and assembled (ASSBLD) collagen area ratios, fibrotic and functional areas (right panel) assessed with PharmaNest quantitative digital pathology. **p<0.05 and **p<0.01 DIO-BLEO vs. DIO-BLEO + ALK5i*

CONCLUSION

- ALK5 inhibition significantly improves Ashcroft scale and lung fibrosis in bleomycin-induced IPF in DIO mice, as confirmed with AI-based digital pathology.
- Our data demonstrate that bleomycin-induced IPF in the DIO mouse represents a new translational model to evaluate drugs targeting IPF.

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