**Peer Review File**
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**Reviewer A**

This review summarized the role of HDAC6 in the development of PF and suggest it as a potential target by negative inhibition. The authors have suggested that HDAC6 inhibitor could be a therapeutic agent by modulating macrophage polarization. However, there is no direct evidence showing the therapeutic effects of tubastatin on IPF in vitro and in vivo and just provided one literature (24) describing the therapeutic effects of tubastatin in peritoneal fibrosis. There are some other references suggesting the role of tubastatin in other types of fibrosis (ie. renal fibrosis). Thus, this reviewer suggests described this section more detail about possible anti-fibrotic role of HDAC6 inhibitor in terms of specific signal, mechanism and molecular changes.

**Reply:**
Thank you for the suggestion. We like to express our sincere thanks to the reviewer for her/his great effort to review the manuscript.

Changes in the text:
This section was revised and modified according to the information showed in the work suggested by the reviewer (Lines 192-233, pages 8-10).

**Reviewer B**

Xiu and colleagues wrote a review about the pathogenetic role of HDAC6 in idiopathic pulmonary fibrosis. I have a few comments.

1. Reviewer recommendation for the abstract:

The authors wrote that M1 macrophages are in charge of wound healing following alveolar epithelial injury, whereas M2 macrophages are in charge of resolving wound repair or terminating the inflammatory response in the lung.

The authors should directly add after this sentence: In fibrotic lung diseases, the wound-repair mechanism is altered causing aberrant tissue remodelling and various studies provide evidence that M2-like macrophages contribute to the abnormal fibrogenesis.

**Reply:**
Thank you for the suggestion.

Changes in the text:
This phrase was modified according to the comment (Lines 28-31, page 2).

2. It is true, that HDAC6 has been widely reported as eminent mediator of TGF-β induced EMT

in vitro, but in human IPF in vivo, AECIIs as well as other epithelial cells are not considered as cells giving rise to myofibroblasts (Rock, J. R.; Barkauskas, C. E.; Cronce, M. J.; Xue, Y.; Harris, J. R.; Liang, J.; Noble, P. W.; Hogan, B. L., Multiple stromal populations contribute to pulmonary fibrosis without evidence for epithelial to mesenchymal transition. Proc. Natl. Acad. Sci. U. S. A. 2011, 108 (52), E1475-83).

Thus, the authors should omit the chapter EMT as a critical factor in IPF pathogenesis. With regard to EMT, the authors should only mention in vitro-studies about TGF-β treated epithelial cells in their review-article.

**Reply:**
Thank you for underlining this deficiency. We omitted the sentence "HDAC6 expression in myofibroblasts has been found to be elevated in IPF". We added some contents "In the context of pulmonary fibrosis in mice, recent research suggests that type II lung epithelial cells expressing the biomarker E-cadherin have the ability to undergo EMT and transform into myofibroblasts (Ji Y, Dou YN, Zhao QW, et al. Paeoniflorin suppresses TGF-β mediated epithelial-mesenchymal transition in pulmonary fibrosis through a Smad-dependent pathway. Acta Pharmacol Sin 2016; 37: 794-804.). Moimas and colleagues demonstrated that ATII cells from IPF patients express markers of senescence and EMT, and exhibit a diminished capacity to transdifferentiate into ATI cells (Moimas S, Salton F, Kosmider B, et al. miR-200 family members reduce senescence and restore idiopathic pulmonary fibrosis type II alveolar epithelial cell transdifferentiation. ERJ Open Res 2019; 5.).

Changes in the text:
This section was revised and modified according to the information showed in the work suggested by the reviewer (Lines 147-153, page 7).

3. The authors stated: "Approximately one-third of pulmonary fibroblasts are epithelial in origin."

This is not the fact in IPF. Do the authors have a reference for this claim?

**Reply:**
Thank you for the suggestion. The following are specific contents of the references.

a) Many vimentin-positive cells are identified in injured lungs, approximately a third of which are also X-gal-positive (Kim KK, Kugler MC, Wolters PJ, et al. Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. Proc Natl Acad Sci U S A 2006; 103: 13180-5).
b) In vivo, we estimate that approximately one third of the S100A4+ lung fibroblasts derive from the lung epithelium 2 weeks after bleomycin administration (Tanjore H, Xu XC, Polosukhin VV, et al. Contribution of epithelial-derived fibroblasts to bleomycin-induced lung fibrosis. Am J Respir Crit Care Med 2009; 180: 657-65).

Changes in the text:
We have added two references as explained above (Line 67, page 3).

4. In general, "many observations and claims about HDAC6" described in this review are not

underscored by references!

**Reply:**
Thank you for the suggestion. Hopefully this reviewer can point out the shortcomings specifically if possible. We'll do our best to revise the manuscript.

Changes in the text:
We added some contents and references as explained (Lines 115-138, pages 5-6; Lines 147-153, page 7; Lines 216-233, pages 9-10; Lines 237-241, pages 10-11).

5. Line 121: The authors wrote “NF-B”…This reviewer thinks that they mean NF-kappa-B.

Lines 46, 216, 231 and 268: The authors wrote “nidanib.” This reviewer thinks that they mean nintedanib.

In general, some English editing is needed. The manuscript text does reveal in part poorly-written English sentences (wording / syntactic mistakes) and many spelling mistakes. The authors should perform a careful stylistic and syntactic revision to improve the clarity of the manuscript.

One example: Lines 99-104: The authors wrote: “To restore organ integrity, initiate the repair process of early acute inflammation, which causes leukocytes to infiltrate, activate, and accumulate in injured tissues, and infiltrating leukocytes not only stimulate fibroblasts, but also make collagen on their own to induce tissue fibrosis.”

Please rewrite this sentence, or rewrite this issue in 2 sentences.

**Reply:**
Thank you for the suggestion. We performed a careful stylistic and syntactic revision to improve the clarity of the manuscript.

Changes in the text:
The correct expression “NF-kappa-B” has been modified (Line 135, page 6).
The correct expression “nintedanib” has been modified (Line 54, 257, 272, 315).
This phrase was modified according to the comment (Lines 111-115, page 5).

6. Line 139: The authors wrote: “acetylated α-tubulin can be utilized as a marker for EMT,…” This sentence should be rewritten. This reviewer would write: The acetylation status of α-tubulin might be used as a marker for EMT. In detail, a low acetylation status of α-tubulin in epithelial cells might be indicative of EMT.

**Reply:**
Thank you for the suggestion.

Changes in the text:
This phrase was modified according to the comment (Lines 153-155 page 7).
7. Lines 226-230: The authors wrote: “Because epigenetic changes are linked to IPF, HDAC6 inhibitors have recently been found to reduce fibrotic remodeling in vitro and in vivo. TGF-β1 has been shown to play a critical role in the pathogenesis of pulmonary fibrosis, and the HDAC6 inhibitor Tubastatin inhibits TGF-β1 induced collagen expression by inhibiting the PI3K-AKT-HIF-1-VEGF pathway, which is consistent with the novel tyrosine kinase.”

Please omit the final subclause: “which is consistent with the novel tyrosine kinase.”

**Reply:**
Thank you for the suggestion. We have modified our text as advised.

Changes in the text:
This phrase was modified according to the comment (Line 184, page 8).

8. This review is not written in a fancy fashion. The review is written incoherently. Many observations are simply listed and the connection is difficult to see.

**Reply:**
Thank you for underlining this deficiency. Sorry for the confusion, we believe that HDAC6 is playing multiple roles in the process of IPF, and the idea of this paper is that HDAC6 can have a regulatory effect on the expression of multiple inflammatory cytokines during the inflammatory phase, and in the fibrotic phase, it improves lung fibrosis through EMT and targeting the TGFβ-PI3K-Akt pathway. Finally, there are some possible mechanisms of HDAC6 on fibrosis, regulating macrophage polarization and participating in IPF through the classical pathway TGF-β-Smad signaling.

Changes in the text:
We modified some expressions throughout the text according to the comment (Lines 147-153, page 7; Lines 216-233, pages 9-10; Lines 237-241, pages 10-11; Lines 263-303, pages 12-13).