Dear Editor Li Ma,

We would like to thank you and the reviewers for thoroughly reviewing our manuscript and making many thoughtful comments. We have revised the manuscript to address reviewers' comments. Here are our point-by-point responses:

Reviewer #1:

Specific Comments to Authors: The authors used public datasets to identify differentially expressed genes between IPF patients and healthy donors. Potential targets were considered based on multiple bioinformatics conditions, especially the correlation between hub genes and carbon monoxide diffusing capacity, forced vital capacity, and patient survival rate. Validating a potential therapeutic target involves a comprehensive assessment of its functional relevance, as well as evaluating its effects in relevant preclinical models and, eventually, in clinical trials. This process typically involves studying the target's mechanisms of action, its role in disease progression, and the development of specific inhibitors or modulators to assess their efficacy and safety. The introduction is relevant and theory-based. Sufficient information about the previous study findings is presented for readers to follow the present study rationale and procedures. Overall, this is a clear, concise, and well-written manuscript. Biomarkers in IPF can serve as indicators of disease presence, progression, and response to therapy. They can also provide insights into the underlying mechanisms of the disease.

Response: We are very grateful to your comments on the manuscript.

Reviewer #2:

Specific Comments to Authors: This is a generally well written paper that suggests a key role for trytophan dioxygenase 2 (TDO2) in the development of idiopathic pulmonary fibrosis (IPF). This research is being carried out in a significant field where little can be offered to individuals afflicted with IPF. There are a number of questions and comments raised by this work.

Response: We would like to thank the reviewer for his/her enthusiasm for our work

and the constructive criticism that significantly improved our manuscript.

Comment 1: On Page 1, the authors refer to IPF as caused by cigarette smoking. There also is reference to IPF being "caused" by "environmental risk factors". All this is true, but if the cause has been established, the disease is no longer "idiopathic". This obviously is a semantic issue, but the authors need to recognize this, and when they study DNA from the IPF bank are the tissues from "idiopathic pulmonary fibrosis" (cause unknown) of from "interstitial pulmonary fibrosis" an IPF where the cause may very well be established? The genetic profiles may very well be different.

Response: We really appreciate your important comments. To avoid semantic issue, we have changed the relevant sentences to “Smoking exacerbates the loss of lung function in patients with IPF” and deleted the sentence “It is generally accepted that IPF is caused by multiple interacting genetic and environmental risk factors, with repetitive local microlesions of aging alveolar epithelium being the predominant factor”.

Comment 2:

On page 2, line 37, the authors refer to "...injuries (that) induce abnormal epithelial-fibroblast communication." No references were offered to show these "communications", but there are at least two such references in the older literature demonstrating just what the authors are saying. They might consider adding these. "Brody, A. R., and Craighead, J. E. Interstitial associations of cells lining air spaces in human pulmonary fibrosis. Virchows Arch. A. of Pathol., Anat. and Histol. 372:39, 1976", and Brody, A. R., Soler, P., Basset, F., Haschek, W., Witschi, H. Epithelial-mesenchymal association of cells in human pulmonary fibrosis and in BHT-oxygen induced fibrosis in mice. Exp. Lung. Res. 2:207-220, 1981"

Response: We are very thankful for the reviewer’s suggestion, which greatly enriched the content of the article. We have added related literature to enrich the content. (Please

refer to line 80 in the manuscript text).

Comment 3:

3) Pg. 2; line 55. "it provided..." What "It" may be is not clear, and while the idea is to

provide evidence of a "...new perspective on the treatment..", this has not yet been realized as the remainder of the sentence makes clear.

Response: We are very sorry that we have not been able to express our meaning clearly. “It” means “these novel genes”, and we wanted to provide the idea "These novel genes may be potential targets for treating IPF". This sentence is redundant, so we decided to delete it.

Comment 4: Line 60 states "... the severity of IPF was alleviated." There is no evidence presented in this paper that the disease IPF has been "alleviated". There are some data on fibroblasts that respond to treatment, but this is not treatment of a disease.

Response: Thanks for the comments. We have modified the sentence to “TGF-β-induced fibroblast activation was effectively inhibited”.

Comment 5: Pg 8, line 247. "druggability " is not a word.

Response: We have revised this sentence to “…has potential drug effect” in line 489.

Comment 6: Pg.11. Heading should read "...Identifying Genes of Interest".

Response: Thank you for the reviewer comments, we have revised this heading.

Comment 7: Pg 13, Line 339. There is no evidence that "...in vitro data reveal that reducing TDO2 expression can alleviate pulmonary fibrosis...". This paper actually has a number of statements like this that reach far beyond what their data show.

Response: We are very sorry that we overstated the results. We rechecked the full text and corrected the relevant sentences.

Comment 8: Pg. 14, line 366, looks like a typo "promoteds"

Response: The reviewer is correct. We have corrected the typo.

Comment 9: Pg. 15. line 376 is an example of where the authors are assuming that they have uncovered more than they actually have. "... the potential regulatory pathway of TDO2 in IPF was discovered..." needs to be qualified to something like " a regulatory pathway that may have the potential to regulate expression of TDO2 is proposed here...".

Response: Thank you for the important suggestions and comments. We have made appropriate changes in these sentences according to reviewer's suggestion.

Comment 10: Pg.16. line 419; the authors conclude that "..the fibrosis was relieved." There is no evidence that any fibrosis has been stemmed or treated in any way. Blocking TGFbeta production is an interesting and important finding but does not show "relief" of fibrosis.

Response: We are very sorry that we overstated the results. We have revised the sentence in line 414.

Comment 11: And in line 420, the authors need to say that TDO2 appears that it might become an effective treatment for IPF.

Response: Thank you for the important suggestions and comments. We have revised the sentence in line 510.

Comment 12: In line 421. the authors, again need to couch their enthusiasm in the context of "potential" therapies. It is disappointing to eventually learn that the bleomycin-exposed mice were not treated with any of the TDO2 blockers as the cells were. Actually it's quite confusing to try to understand what the investigators did with this well known model of interstitial pulmonary fibrosis. Apparently, mice were treated with bleomycin and 21 days later were sacrificed and the lungs homogenized. This animal experiment apparently was carried out only one time, and data shown are in Fig. 5. The reader does not know how reproducible these findings are should another group of animals be exposed or if this one group were to receive more or less bleomycin. Was there any histopathology with which to correlate the gene expression

data? In general, the animal experiments are lost among the large amount of data from the human lungs. In conclusion; this work could be potentially very important if the role of TDO2 can be confirmed as proposed by these investigators. More complete work with the animal model could go a long way toward this end since the TDO2 gene was apparently upregulated by bleomycin treatment.

Response: Reviewer's comments have important guiding significance for our further research. We thank you for the critical comments and helpful suggestions. We have taken all these comments and suggestions into account, and have made major corrections in this revised manuscript. At present, there are no conditions available to conduct experiments on mice exposed to bleomycin and treated with some TDO2 blocker. Once conditions improve, we will conduct experiments on TDO2 in animals and publish our results. This article is important for students' graduation, and we hope to receive your understanding. The representative images of rat body weight, survival rate, lung wet-to-dry weight ratio, lung hydroxyproline content, mouse HE staining and Masson's trichrome-stained of lung sections are more conducive to increasing the persuasiveness of our results, which will be further studied in the future. We repeated the detection of the TDO2 gene multiple times, and it was consistently found to be highly expressed in the bleomycin group. We will add a discussion that whether exposure to more or less bleomycin has an impact on the results in subsequent discussions, which will improve the reproducibility of the data. We add this relevant discussion in the Discussion according to reviewer's nice comments.

EDITORIAL OFFICE'S COMMENTS:

I recommend transfer to World Journal of Cardiology. I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Cardiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for

Manuscript Revision by Authors. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/. Uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response: Thanks for you advise. We have used the professional English language editing companies as you recommend. We have improved the highlights of the latest cutting-edge research results and organized decomposable Figures into a single PowerPoint file “**85141-Figures.pptx**”.

Thank you for your consideration of our manuscript.

Yours sincerely,

Yanmei Yang, Ph.D.