Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 85141

Title: Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of TDO2 as a potential therapeutic target

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02492656
Position: Peer Reviewer
Academic degree: BSc, MSc, PhD
Professional title: Emeritus Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2023-04-14

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-04 15:19

Reviewer performed review: 2023-05-08 23:45

Review time: 4 Days and 8 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

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. 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. 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

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

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" 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. 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. Pg 8, line 247. "druggability " is not a word. Pg.11. Heading should read "...Identifying Genes of Interest" 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. Pg. 14, line 366, looks like a typo "promoteds"

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

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

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.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 85141

Title: Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of TDO2 as a potential therapeutic target

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00415501
Position: Peer Reviewer
Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: China

Manuscript submission date: 2023-04-14

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-03 08:05

Reviewer performed review: 2023-05-13 08:10

Review time: 10 Days

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Scientific significance of the conclusion in this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

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.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 85141

Title: Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of TDO2 as a potential therapeutic target

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02492656

Position: Peer Reviewer

Academic degree: BSc, MSc, PhD

Professional title: Emeritus Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2023-04-14

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-06-02 19:18

Reviewer performed review: 2023-06-02 19:36

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This paper has been improved considerably. The English is almost perfect and new insights have been added. It will be important in future experiments to test postulates on the functions of TDO2 in the animal model.