

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 80255

**Title:** Unveiling the biological role of sphingosine 1 phosphate ( S1P ) receptor modulators in inflammatory bowel diseases

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03259512

**Position:** Peer Reviewer

**Academic degree:** MSc, PhD

**Professional title:** Assistant Professor, Lecturer

**Reviewer's Country/Territory:** Australia

**Author's Country/Territory:** Greece

**Manuscript submission date:** 2022-09-20

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-09-20 21:53

**Reviewer performed review:** 2022-09-21 00:06

**Review time:** 2 Hours

|                           |   |
|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Re-review</b>          | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |

|                                     |   |
|-------------------------------------|---|
| <b>Peer-reviewer<br/>statements</b> | Peer-Review: [ <b>Y</b> ] Anonymous [ ] Anonymous<br>Conflicts-of-Interest: [ ] Yes [ <b>Y</b> ] No |
|-------------------------------------|---|

## SPECIFIC COMMENTS TO AUTHORS

The review is focused on discussion of effective therapeutic compounds against inflammatory bowel disease (IBD). The compounds target Sphingosine-1- phosphate (S1P) receptors and constitute a class of oral small-molecule drugs, which are currently in clinical development for IBD and have shown promising effects on disease amelioration. The review is interesting and addresses a novel topic. However, there are several issues to address. 1. Introduction does not reflect the current field of S1P receptor role in the regulation of gastrointestinal diseases. It is very general and does not provide a specific targets or mention specific substances that will be discussed. For instance, authors did not describe the role of S1P in the regulation of diverse biological process (references should be provided/extended). Introduction also does not direct the reader to other large reviews that provide more detailed description and discussion of this filed. For instance, these review were not mentioned ( <https://pubmed.ncbi.nlm.nih.gov/32085881/> ; <https://pubmed.ncbi.nlm.nih.gov/35158806/> ; <https://pubmed.ncbi.nlm.nih.gov/31863815/> ). 2. Authors wrote in the Introduction “ ... small-molecule drugs being” – which ones? It is reasonable to list those in clinical trials. 3. The first large subsection is focused in lymphocyte trafficking, however, it is not reflected in the Abstract properly. Authors did not indicate that they will be discussing the role of T cell subtypes, including Th17, Treg etc. Therefore, the abstract should be improved. 4. Th1/Th17 was mentioned 32 times in the text, however it is not indicated as a keyword. Therefore, keyword list should be extended. 5. The authors also should cite the more recent reviews in the field. For instance, they cite Nielsen et al., 2017

( ref #63), although there are more recent paper in the field from 2020 (<https://pubmed.ncbi.nlm.nih.gov/32085881/>);  
<https://pubmed.ncbi.nlm.nih.gov/31863815/> ) and 2022  
<https://pubmed.ncbi.nlm.nih.gov/35158806/> 6. Authors could separate the Figure 1 into two figures. The second figure could provide a more comprehensive presentation of drugs targeting different S1P receptors. Figure 1 is confusing, it is unclear which drugs target S1P1, or S1P2 etc. 7. Conclusions are too general and do not provide clear author-based support for any of the tested drugs. It does not provide a clear message – which S1P-binding drugs are more promising than others? The whole conclusion is too vacuous and should be re-written, indicating the exact names of the drugs that have higher chances to be used as an IBD treatment (if any).

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**Peer-review model:** Single blind

**Reviewer's code:** 06369714

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Doctor, Lecturer, Senior Postdoctoral Fellow

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Greece

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-10-13 00:43

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**Review time:** 12 Days and 7 Hours

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| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish                                     |
| <b>Language quality</b>   | <input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/><br><input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection                                      |
| <b>Re-review</b>          | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  |

**Peer-reviewer  
statements**Peer-Review: [☒] Anonymous [☐] OnymousConflicts-of-Interest: [☐] Yes [☒] No**SPECIFIC COMMENTS TO AUTHORS**

This paper mini-reviewed recent literature on S1P in IBD pathogenesis and S1P targetted small-molecule drugs' therapeutic effects on IBD. Comments are below: 1. This is an important and novel piece of work. However, the English grammatical errors detract from the quality of the paper and makes it difficult to read. Please polish the English language furtherly. 2. The introduction, especially the immunological part, is tedious and obscure to follow, recommended adding an explicit schematic figure other than just Fig1.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 03259512

**Position:** Peer Reviewer

**Academic degree:** MSc, PhD

**Professional title:** Assistant Professor, Lecturer

**Reviewer's Country/Territory:** Australia

**Author's Country/Territory:** Greece

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**Reviewer chosen by:** Han Zhang

**Reviewer accepted review:** 2022-11-18 03:25

**Reviewer performed review:** 2022-11-18 03:29

**Review time:** 1 Hour

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|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Peer-reviewer</b>      | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous   |



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statements

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

#### **SPECIFIC COMMENTS TO AUTHORS**

The revised manuscript has been improved. All my questions/comments have been addressed.