Identification of new drugs to counteract anti-spike IgG-induced hyperinflammation in severe COVID19


DOI: https://doi.org/10.26508/lsa.202302106

Corresponding author(s): Jeroen den Dunnen, Amsterdam University Medical Centers and Menno de Winther, Amsterdam UMC

Review Timeline:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission Date</td>
<td>2023-04-21</td>
</tr>
<tr>
<td>Editorial Decision</td>
<td>2023-06-30</td>
</tr>
<tr>
<td>Revision Received</td>
<td>2023-07-21</td>
</tr>
<tr>
<td>Editorial Decision</td>
<td>2023-08-18</td>
</tr>
<tr>
<td>Revision Received</td>
<td>2023-08-24</td>
</tr>
<tr>
<td>Accepted</td>
<td>2023-08-29</td>
</tr>
</tbody>
</table>

Scientific Editor: Eric Sawey, PhD

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)
Dear Dr. den Dunnen,

Thank you for submitting your manuscript entitled "Identification of new drugs to counteract anti-spike IgG-induced hyperinflammation in severe COVID19" to Life Science Alliance. The manuscript was assessed by an expert reviewer, whose comments are appended to this letter. We invite you to submit a revised manuscript addressing the Reviewer comments. In addition, please further contextualize these findings and mention that this identified inhibitor was not tested against live virus at this stage.

To upload the revised version of your manuscript, please log in to your account: https://lsa.msubmit.net/cgi-bin/main.plex

You will be guided to complete the submission of your revised manuscript and to fill in all necessary information. Please get in touch in case you do not know or remember your login name.

While you are revising your manuscript, please also attend to the below editorial points to help expedite the publication of your manuscript. Please direct any editorial questions to the journal office.

The typical timeframe for revisions is three months. Please note that papers are generally considered through only one revision cycle, so strong support from the referees on the revised version is needed for acceptance.

When submitting the revision, please include a letter addressing the reviewers comments point by point.

We hope that the comments below will prove constructive as your work progresses.

Thank you for this interesting contribution to Life Science Alliance. We are looking forward to receiving your revised manuscript.

Sincerely,

Eric Sawey, PhD
Executive Editor
Life Science Alliance
http://www.lsajournal.org

---

A. THESE ITEMS ARE REQUIRED FOR REVISIONS

-- A letter addressing the reviewers' comments point by point.

-- An editable version of the final text (.DOC or .DOCX) is needed for copyediting (no PDFs).

-- High-resolution figure, supplementary figure and video files uploaded as individual files: See our detailed guidelines for preparing your production-ready images, https://www.life-science-alliance.org/authors

-- Summary blurb (enter in submission system): A short text summarizing in a single sentence the study (max. 200 characters including spaces). This text is used in conjunction with the titles of papers, hence should be informative and complementary to the title and running title. It should describe the context and significance of the findings for a general readership; it should be written in the present tense and refer to the work in the third person. Author names should not be mentioned.

-- By submitting a revision, you attest that you are aware of our payment policies found here: https://www.life-science-alliance.org/copyright-license-fee

B. MANUSCRIPT ORGANIZATION AND FORMATTING:
Full guidelines are available on our Instructions for Authors page, https://www.life-science-alliance.org/authors

We encourage our authors to provide original source data, particularly uncropped/-processed electrophoretic blots and spreadsheets for the main figures of the manuscript. If you would like to add source data, we would welcome one PDF/Excel-file per figure for this information. These files will be linked online as supplementary "Source Data" files.

***IMPORTANT: It is Life Science Alliance policy that if requested, original data images must be made available. Failure to provide original images upon request will result in unavoidable delays in publication. Please ensure that you have access to all original microscopy and blot data images before submitting your revision.***

Reviewer #1 (Comments to the Authors (Required)):

The authors have previously shown that high levels of anti-spike IgG with aberrant Fc tail glycosylation leads to hyperinflammation, greatly increasing the severity of COVID-19. The authors have identified a need for immune-regulatory therapeutics that counteract excessive inflammation while simultaneously minimizing inhibition of antiviral immunity. The authors developed an in vitro assay to screen for such drugs. Using this assay the authors identified entospletinib, an SYK inhibitor, as a promising drug candidate. They showed that entospletinib can counteract anti-spike-induced endothelial dysfunction and thrombus formation, markers of hyperinflammation. The authors also showed that entospletinib was effective against spikes from different SARS-CoV-2 variants.

Overall, this was a very well-written manuscript. The problem and approach were laid out very succinctly in the introduction. The figures in the results section were well-designed and easy to follow. The main points are well supported by the data and the results warrant the conclusions.

One minor comment I have would be to try and use the same scale for the graphs in Fig.1 and Fig. 2 whenever possible, to make comparisons easier for the reader.
Response to the reviewers’ comments

LSA-2023-02106-T

We thank the reviewer for the feedback and comments and are glad to hear from the editor that they consider this work of interest for publication in Life Science Alliance.

Reviewer #1

The authors have previously shown that high levels of anti-spike IgG with aberrant Fc tail glycosylation leads to hyperinflammation, greatly increasing the severity of COVID-19. The authors have identified a need for immune-regulatory therapeutics that counteract excessive inflammation while simultaneously minimizing inhibition of antiviral immunity. The authors developed an in vitro assay to screen for such drugs. Using this assay the authors identified entospletinib, an SYK inhibitor, as a promising drug candidate. They showed that entospletinib can counteract anti-spike-induced endothelial dysfunction and thrombus formation, markers of hyperinflammation. The authors also showed that entospletinib was effective against spikes from different SARS-CoV-2 variants.

Overall, this was a very well-written manuscript. The problem and approach were laid out very succinctly in the introduction. The figures in the results section were well-designed and easy to follow. The main points are well supported by the data and the results warrant the conclusions.

One minor comment I have would be to try and use the same scale for the graphs in Fig.1 and Fig. 2 whenever possible, to make comparisons easier for the reader.

We thank the reviewer for this positive feedback and for the suggestion to change the scales. To allow an easier evaluation of the data despite the relatively large donor to donor differences we have included a scale showing the percentage of inhibition for each EC50 graph. Furthermore, we have adjusted the scale units for every scale in Figure 1 and 2 to a more uniform format showing all values in ng/ml. We hope these changes improved the design allowing a better comparison of the curves.
August 18, 2023

RE: Life Science Alliance Manuscript #LSA-2023-02106-TR

Dr. Jeroen den Dunnen
Amsterdam University Medical Centers
Center for Experimental and Molecular Medicine (CEMM)
Meibergdreef 9
Amsterdam 1105 AZ
Netherlands

Dear Dr. den Dunnen,

Thank you for submitting your revised manuscript entitled "Identification of new drugs to counteract anti-spike IgG-induced hyperinflammation in severe COVID19". We would be happy to publish your paper in Life Science Alliance pending final revisions necessary to meet our formatting guidelines.

Along with points mentioned below, please tend to the following:
- please add ORCID ID for corresponding (and secondary corresponding) author--you should have received instructions on how to do so
- please upload all figure files as individual ones, including the supplementary figure files
- all figure legends should only appear in the main manuscript file
- please add your main, supplementary figure, and table legends to the main manuscript text after the references section;
- please add a callout for Fig 5A, Fig 5B to your main manuscript text;
- please upload your Tables in editable .doc or excel format; -Tables should be numbered consecutively with Arabic numerals (1, 2, 3, 4); They can be included at the bottom of the main manuscript file or be sent as separate files.

If you are planning a press release on your work, please inform us immediately to allow informing our production team and scheduling a release date.

LSA now encourages authors to provide a 30-60 second video where the study is briefly explained. We will use these videos on social media to promote the published paper and the presenting author (for examples, see https://twitter.com/LSAjournal/timelines/1437405065917124608). Corresponding or first-authors are welcome to submit the video. Please submit only one video per manuscript. The video can be emailed to contact@life-science-alliance.org

To upload the final version of your manuscript, please log in to your account: https://lsa.msubmit.net/cgi-bin/main.plex
You will be guided to complete the submission of your revised manuscript and to fill in all necessary information. Please get in touch in case you do not know or remember your login name.

To avoid unnecessary delays in the acceptance and publication of your paper, please read the following information carefully.

A. FINAL FILES:

These items are required for acceptance.

- An editable version of the final text (.DOC or .DOCX) is needed for copyediting (no PDFs).
- High-resolution figure, supplementary figure and video files uploaded as individual files: See our detailed guidelines for preparing your production-ready images, https://www.life-science-alliance.org/authors
- Summary blurb (enter in submission system): A short text summarizing in a single sentence the study (max. 200 characters including spaces). This text is used in conjunction with the titles of papers, hence should be informative and complementary to the title. It should describe the context and significance of the findings for a general readership; it should be written in the present tense and refer to the work in the third person. Author names should not be mentioned.

B. MANUSCRIPT ORGANIZATION AND Formatting:

Full guidelines are available on our Instructions for Authors page, https://www.life-science-alliance.org/authors

We encourage our authors to provide original source data, particularly uncropped/-processed electrophoretic blots and spreadsheets for the main figures of the manuscript. If you would like to add source data, we would welcome one PDF/Excel-file
per figure for this information. These files will be linked online as supplementary "Source Data" files.

**Submission of a paper that does not conform to Life Science Alliance guidelines will delay the acceptance of your manuscript.**

**It is Life Science Alliance policy that if requested, original data images must be made available to the editors. Failure to provide original images upon request will result in unavoidable delays in publication. Please ensure that you have access to all original data images prior to final submission.**

**The license to publish form must be signed before your manuscript can be sent to production. A link to the electronic license to publish form will be sent to the corresponding author only. Please take a moment to check your funder requirements.**

**Reviews, decision letters, and point-by-point responses associated with peer-review at Life Science Alliance will be published online, alongside the manuscript. If you do want to opt out of having the reviewer reports and your point-by-point responses displayed, please let us know immediately.**

Thank you for your attention to these final processing requirements. Please revise and format the manuscript and upload materials within 7 days.

Thank you for this interesting contribution, we look forward to publishing your paper in Life Science Alliance.

Sincerely,

Eric Sawey, PhD
Executive Editor
Life Science Alliance
http://www.lsajournal.org

Reviewer #1 (Comments to the Authors (Required)):

The authors have adequately responded to my concerns. I recommend this manuscript for publication.
Dear Dr. den Dunnen,

Thank you for submitting your Research Article entitled "Identification of new drugs to counteract anti-spike IgG-induced hyperinflammation in severe COVID19". It is a pleasure to let you know that your manuscript is now accepted for publication in Life Science Alliance. Congratulations on this interesting work.

The final published version of your manuscript will be deposited by us to PubMed Central upon online publication.

Your manuscript will now progress through copyediting and proofing. It is journal policy that authors provide original data upon request.

Reviews, decision letters, and point-by-point responses associated with peer-review at Life Science Alliance will be published online, alongside the manuscript. If you do want to opt out of having the reviewer reports and your point-by-point responses displayed, please let us know immediately.

***IMPORTANT: If you will be unreachable at any time, please provide us with the email address of an alternate author. Failure to respond to routine queries may lead to unavoidable delays in publication.***

Scheduling details will be available from our production department. You will receive proofs shortly before the publication date. Only essential corrections can be made at the proof stage so if there are any minor final changes you wish to make to the manuscript, please let the journal office know now.

DISTRIBUTION OF MATERIALS:
Authors are required to distribute freely any materials used in experiments published in Life Science Alliance. Authors are encouraged to deposit materials used in their studies to the appropriate repositories for distribution to researchers.

You can contact the journal office with any questions, contact@life-science-alliance.org

Again, congratulations on a very nice paper. I hope you found the review process to be constructive and are pleased with how the manuscript was handled editorially. We look forward to future exciting submissions from your lab.

Sincerely,

Eric Sawey, PhD
Executive Editor
Life Science Alliance
http://www.lsajournal.org