

Manuscript Assessment Report

Paper title: *DE2300c5: a potential therapeutic treatment for hyponatremia*

Submitted by: xxxxx

Date prepared: January, 2020

Congratulations on taking this step toward your publication goals!

This report provides feedback on the clarity, consistency and effectiveness of the presentation of your manuscript. It starts with a Manuscript Summary and Recommendations section that provides a general overview of how effective and clear we consider the manuscript to be, as well as a list of the Top 3 Recommendations to consider prior to journal submission. The remainder of this report contains detailed checklists and additional comments that result from our assessment of each section of your manuscript.

✓ : The presentation of this aspect of the paper generally seems strong.

X: We recommend significant changes to the presentation of this aspect of the paper.

If an item has neither a ✓ nor a X, then the item does not apply to your manuscript. Further explanation and suggested revisions will be included in the comments.

How to use this report

- Focusing particularly on aspects of the paper marked with an X, determine whether you think each comment calls for changes to be made to the presentation of the manuscript, and if so, implement those changes. Please note that a ✓ is not required for each item of the checklist for the manuscript to be accepted for publication by a journal.
- Please remember that our comments represent opinion, and they reflect our understanding of the current text. We are not acting on behalf of any particular journal, and our primary focus is on the clarity and effectiveness of the current text. As such, the comments should not serve as the sole basis for significant decisions such as further experimental or analytical work, journal submission or significant rewriting.
- Contact us if you need help with other services (such as Editing, Formatting, or Figure Formatting) to prepare your paper for submission to a journal.
- Submit the final manuscript to the journal of your choice.

Manuscript Summary and Recommendations

The study presented in this manuscript aimed to identify agents able to inhibit 11β -HSD2 as a potential means of treating hyponatremia and found that DE2300c5, a compound with the required physiological and structural characteristics, was able to increase intracellular sodium levels in renal cortical cells. Overall, the paper was written well, and the results of the evaluation of candidate compounds in particular were presented clearly and effectively. We have identified three recommendations that we think would be particularly helpful in revising the paper further.

1. The Abstract and Introduction would both benefit from the inclusion of additional background information on hyponatremia (causes, symptoms, underlying biology, treatment options), to help establish the main question addressed by the study. Similarly, additional information can be provided on the identity and properties of DE2300c5 and the role of miR-401 in sodium homeostasis if directly relevant.
2. The article contains insufficient reference to the literature (including recently published, international studies). There are statements made throughout the paper that do not provide citations to the original sources. These uncited statements in the Discussion make it difficult to know whether the statement is referring to the present results or the published literature. Ultimately, this makes it harder for the reader to assess the novelty and potential implications of the findings.
3. The Methods section does not appear to provide sufficient detail (e.g., concentrations, control conditions, particular assays, and equipment used) that would allow a competent person to replicate the study and reproduce the results. Providing these details in the main text would address this issue, and this should involve moving the descriptions of these critical methods from the supplementary material to the main text.

1. Title

Most people who encounter your paper will only read the Title. Therefore, to attract the desired target audience, the title should be concise and enticing, yet specific enough to clearly communicate what the paper is about.

Yes	No	
	X	The title accurately and succinctly describes the main novel outcome of the study, or the main message from the manuscript.
	X	The title is specific, and includes all appropriate key terms to alert readers to the content.

- 1.1) The current title essentially reports the name of a novel compound and a potential therapeutic use that was not directly assessed in this study. A more explicit title that describes what happened in the context of this particular study would be more useful for readers, for example, highlighting the action and not the name of this compound or focusing on the identification and in vitro characterization of this compound.
- 1.2) As described in the previous comment, the level of specificity in the title could be adjusted as it currently refers to a very specific, yet unknown, compound and a general physiological condition. We suggest changing the title to a statement that describes what happened in the study and might include the key terms "11 β -hydroxysteroid dehydrogenase type 2", "inhibition"/"inhibitor", and "sodium levels".

2. Abstract

The Abstract should provide a concise and self-contained description of the most relevant previous understanding, the problem/question to be addressed in the paper, the overall approach and the most important results, the main conclusion, and a broader consideration of what the conclusions tell us or where they lead us next.

Yes	No	
	X	The abstract includes sufficient background information to support the study's rationale.
	X	The abstract includes a clearly stated objective
✓		The abstract contains sufficient description of the overall approach, including key methods if useful.
	X	The abstract contains sufficient description of key results.
	X	The abstract clearly states the conclusions of the study.

✓		The abstract is internally consistent, and consistent with the rest of the manuscript in terms of message.
	✗	The abstract is well organized and concise.
		If a target journal was indicated to us, the abstract has been formatted for the journal in terms of headings and total word count

- 2.1) A more explicit description of hyponatremia and disruptions in sodium homeostasis, the conditions under which this occurs and associated problems, and the currently available treatments could be added to support the overall rationale. The inclusion of additional material needs to take into account word count limits based on the journal that the paper is submitted to. Therefore, including concise statements in other parts of the Abstract and removing extraneous information will help in this respect.
- 2.2) The components that constitute the overall objective are in the Abstract but are spread across sentences. We suggest including a single concise statement that captures this objective.
- 2.3) The role of miR-401 in this context is not described, and therefore, the implications of the final key result presented in the Abstract are difficult to assess. Either an explanation can be provided or this statement could be removed from the Abstract.
- 2.4) The Abstract states that the results indicate that DE2300c5 represents an effective treatment for hyponatremia. This was not actually assessed in the current study. The conclusion of the study could be stated in terms of the methods used and results obtained in this study (i.e., identification and characterization of a selective 11β-HSD2 inhibitor that increased intracellular sodium levels).
- 2.5) Based on the above comments, a slight restructuring of the Abstract and potentially including subheadings (depending on the journal that the paper is submitted to) would help to emphasize the critical aspects of the study in a concise manner.

3. Introduction

The aim of the introductory paragraphs is to clearly and concisely establish the context of the main question that the paper is trying to answer, how the paper relates to previous research in the field, and why it is important – the ‘hook’ that shows the readers why they should care. Optionally, the Introduction can very briefly describe the methodology that is used and the rationale for choosing it, and the main conclusions.

Yes	No	
	✗	The Introduction provides sufficient background and context for the study, with citations.
	✗	The text describes recently published international studies that relate to the topic.

✓		The rationale for the study is clearly defined, for example in terms of an unanswered question and why that question is important.
	X	The section flows logically from general background information, to specific background information, to the study itself.
✓		The objective/hypothesis is clearly stated near the end, and is consistent with the research performed.
✓		If useful, the section ends with an introduction to the approach and/or summarizes the main findings.

Comments:

- 3.1) As noted above, there is a lack of relevant citations throughout this section. Furthermore, although the information included in the Introduction is relevant, there is an opportunity to provide additional background information relevant to hyponatremia and currently available treatments.
- 3.2) The inclusion of additional background information and the relevant citations would remedy this issue.
- 3.3) The Introduction begins with a mechanistic description of particular physiological processes. This information would be more useful if preceded by more foundational information that places the problem in a larger context, for example, by restructuring the introduction to move from a broad and more general background to the specifics directly relevant to the current study.

[Rest of the section-by-section details of the report deleted]