

### Endosomal Fusion of pH-Dependent Enveloped Viruses Requires Ion Channel TRPM7



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**Editorial note:** This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

## REVIEWERS' COMMENTS

### Reviewer #1 (Remarks to the Author):

In their manuscript entitled “Endosomal Fusion of pH-Dependent Enveloped Viruses Requires Ion Channel TRPM7”, Doyle et al. have made several changes and arguments addressing previous concerns raised by this referee. Overall, most of my major concerns have been addressed. Below, I have included several minor textual changes that would improve the clarity and readability of the manuscript in its current form:

In the first mention of TPC channels (related to Fig. 1e and g), the authors should include a sentence rationalizing the study of these channels to the reader. I assume it is to test the selectivity of the TRPM7 effect, but this should be explicitly mentioned.

At the end of the section related to Trpm7-/- primary macrophages that summarizes all of the data so far: the authors should make a mention of the selectivity of the effect (i.e. Rabies is not affected, minor effect on VSV-G). Additionally, the last sentence referring to Figures at the end of the manuscript (Fig. 7 and 8) would be best left for the Discussion.

Extended Data Figure 6 is out of order. Firstly, 6d is mentioned, then 6b, followed by 6c. The first part of the figure (6a) is not mentioned at all, yet it contains a loading control for the blot shown in Figure 5b. The authors should include the loading control itself in the main figure (Fig. 5b) and reorganized Extended Data Figure 6 to follow the text.

### Reviewer #4 (Remarks to the Author):

Concerns appear to be addressed

## Response to Reviewers

We thank the reviewers for their thoughtful comments and suggestions. We have addressed all points as detailed below.

### Reviewer #1:

1. Rationale for studying TPC channels: We have added the following sentence when first mentioning TPC channels (Fig. 1e and g): "To assess the selectivity of the TRPM7 effect, we tested whether TPC channels also regulated enveloped virus infections in a manner similar to TRPM7."
2. Selectivity of effect in *Trpm7*<sup>-/-</sup> primary macrophages section: We have added the following statement at the end of this section: "These results indicate that TRPM7 is expendable for VSV and Rabies infection but has a crucial role in infection by other clinically relevant enveloped viruses (i.e. Lassa, LCMV, and Ebola)."
3. Moving reference to Figures 7 and 8: We have moved the sentence referring to Figures 7 and 8 to the Discussion section as suggested.
4. Extended Data Figure 6: We have reordered Extended Data Figure 6 to match the text order. Additionally, we have moved the loading control from Extended Data Figure 6a to main Figure 5b as suggested.

### Reviewer #4:

The reviewer indicated that all concerns were addressed. We thank the reviewer for their careful evaluation of our manuscript.

These changes have further improved the clarity and flow of our manuscript. We thank the reviewers and editors for their valuable input throughout this process.