

Writing a point-by-point rebuttal

Following the editorial decision, you may be invited to respond to the reviewers' criticisms. The format is a simple point-by-point rebuttal. List each of the points of each reviewer in turn, and under each have your reply to that specific point. Use consistent formatting so that it is easy for the editor to see which are comments and which are replies. I prefer to put comments in italics, have my reply in plain text and quotes indented, as below:

Reviewer 1, comment 1. Although the authors mention in the Introduction the existence of thymus-derived and peripherally induced Treg, they never discuss that these two subpopulations might contribute a major component of Treg diversity. The size of the peripherally induced compartment has been estimated to be 20-30% (using Helios as the marker) or 10% (using neuropilin1 as the marker) of the total Foxp3+ population.

We agree with the reviewer that in the original manuscript we did not adequately discuss the relative contribution of thymic and peripheral Treg cells. To a certain extent we are still unable to do so, as experimental data is lacking. We have added a comment to the introduction as to the relative size of the thymic and peripheral Treg cell populations:

The relative proportion of thymic Treg cells remains unknown, but is estimated at 70-90% using the markers Helios and Neuropilin 1, which are enriched within this population.

Reviewer 1, comment 2. The authors do an excellent job in discussing Treg proliferation, survival and death, and their recent, solid paper on the role of MCL1 forms the basis for this discussion. However, they never consider the possibility that one major subpopulation is actually very long-lived, rarely divides, stable and does not undergo apoptosis.

To our knowledge, there are no studies that strongly support the supposition of a long-lived stable non-dividing Treg cell population, although we are also not aware of any definitive exclusion. It is still worth raising as a possibility, but not one that we can discuss in detail. We have modified the manuscript as follows:

These observations on the bulk central Treg cell population do not exclude the possibility of subsets with distinct homeostatic control mechanisms, including reliance on alternative molecular mediators or on quiescence rather than homeostatic proliferation.

There are two basic ways you can address each comment:

1. "Argue" the point. The preferred route of the author, just explain why this point is invalid or, more generally, shouldn't stand in the way of publication.
2. Experimentally address the point. The preferred route of the editors, who have an insatiable desire for more supplementary figures.

Rule of thumb: If it is ever possible to experimentally address the point rapidly, then do so. Yes, even if the comment was silly and you think you can argue around it. Editors really like to see more data and editors trust reviewers more than they trust authors. Also, this allows you to store up "points" for those comments that you can't address experimentally – editors will be more lenient on you arguing point 11 if you gave data for points 1-10.

Hints

- Do not paraphrase a reviewer's comment. Leave all comments as they are. If a second reviewer has a very similar comment, then your reply can be a rephrased reply or you can write "see response to reviewer 1, comment 3".
- If multiple reviewers have the same comment, the editor is going to take it very seriously. You should too.
- Use editorial instructions to your advantage. If the reviewer asks you to do a six month experiment and the editor requested "return your manuscript within 4 weeks", then you can write something like "this is a potentially interesting strand of research which we will pursue in the future, however it is not possible to generate this data within the 4-week time-frame requested by the editor".
- If the reviewer doesn't understand something, that is your fault. Sometimes reviewer comments simply derive from the reviewer not understanding the system. Avoid arguing that the reviewer is wrong in this case. The reviewer is an example of your target audience, so if the reviewer did not understand something then you failed to explain it clearly enough. Use replies such as "We apologies for the unclear description in the original manuscript. This approach actually...". Then go through your text and expand/clarify this section and give the new text as a quote. The reviewer will be happy and the new text is probably clearer to everyone.
- Don't be a purist. An article is not an artistic vision, is a mode of communication which serves to get your science out to the world. If reviewers and editors want you to change something then do it.