In silico simulation of a clinical trial with anti-CTLA-4 and anti-PD-L1 immunotherapies in metastatic breast cancer using a systems pharmacology model

Hanwen Wang, Oleg Milberg, Imke H. Bartelink, Paolo Vicini, Bing Wang, Rajesh Narwal, Lorin Roskos, Cesar A. Santa-Maria and Aleksander S. Popel

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Review timeline
Original submission: 27 February 2019
Revised submission: 10 April 2019
Final acceptance: 24 April 2019

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Note: This manuscript was transferred from another Royal Society journal with peer review.

Review History
RSOS-190366.R0 (Original submission)

Review form: Reviewer 1

Is the manuscript scientifically sound in its present form?
Yes

Are the interpretations and conclusions justified by the results?
Yes

Is the language acceptable?
Yes

Is it clear how to access all supporting data?
Yes
Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

**Recommendation?**
Major revision is needed (please make suggestions in comments)

**Comments to the Author(s)**
In this work, Wang and colleagues present an ordinary based equation system to investigate the relationship between the tumor response to checkpoint blockade therapy and antigen intensity, including their individual and combined effects on the immune system.

The work is well written and the results are clearly presented. All the equations are presented and one can be able to reproduce the work.

On the other hand, there are some critical points that need to be addressed before the manuscript is acceptable for publications.

**Major points:**

1) Authors failed to discuss other methodologies that were adopted to model the complex immune system behaviour both alone and in response to induced artificial immunity. There are a lot of these examples, especially in tumor immunology. Some are based on agent based modeling approaches. Others are based on complex differential equation systems, also based on enzymatic kinetics.

See for example:

*) Induction of T cell memory by a dendritic cell vaccine: a computational model. Bioinformatics, 30(13):1884-1891, 2014. (doi:10.1093/bioinformatics/btu059)

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It is useful if the authors add to the discussion session a paragraph or two reviewing these important works in the field.

2) Authors failed to discuss the advantage and the disadvantages of their methodology. ODE systems are good when dealing with populations. But they fail to address important aspects when immune system is modelled. For example, specificity and immune system repertoire are not taken into account. Moreover, different types of lymphocytes subpopulation are not considered at all. See for example CD4(Th1, Th2, Th17), CD8. Authors should mention these in the discussion session.
08-Apr-2019

Dear Mr Wang,

The editors assigned to your paper ("In silico simulation of a clinical trial with anti-CTLA-4 and anti-PD-L1 immunotherapies in breast cancer using a systems pharmacology model") have now received comments from reviewers. We would like you to revise your paper in accordance with the referee and Associate Editor suggestions which can be found below (not including confidential reports to the Editor). Please note this decision does not guarantee eventual acceptance.

Please submit a copy of your revised paper before 01-May-2019. Please note that the revision deadline will expire at 00.00am on this date. If we do not hear from you within this time then it will be assumed that the paper has been withdrawn. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office in advance. We do not allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Editors, your manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available, we may invite new reviewers.

To revise your manuscript, log into http://mc.manuscriptcentral.com/rsos and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. Revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you must respond to the comments made by the referees and upload a file "Response to Referees" in "Section 6 - File Upload". Please use this to document how you have responded to the comments, and the adjustments you have made. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response.

In addition to addressing all of the reviewers' and editor's comments please also ensure that your revised manuscript contains the following sections as appropriate before the reference list:

- Ethics statement (if applicable)
  If your study uses humans or animals please include details of the ethical approval received, including the name of the committee that granted approval. For human studies please also detail whether informed consent was obtained. For field studies on animals please include details of all permissions, licences and/or approvals granted to carry out the fieldwork.

- Data accessibility
  It is a condition of publication that all supporting data are made available either as supplementary information or preferably in a suitable permanent repository. The data accessibility section should state where the article's supporting data can be accessed. This section should also include details, where possible of where to access other relevant research materials such as statistical tools, protocols, software etc can be accessed. If the data have been deposited in an external repository this section should list the database, accession number and link to the DOI for all data from the article that have been made publicly available. Data sets that have been deposited in an external repository and have a DOI should also be appropriately cited in the manuscript and included in the reference list.
If you wish to submit your supporting data or code to Dryad (http://datadryad.org/), or modify your current submission to dryad, please use the following link: http://datadryad.org/submit?journalID=RSOS&manu=RSOS-190366

- Competing interests
Please declare any financial or non-financial competing interests, or state that you have no competing interests.

- Authors’ contributions
All submissions, other than those with a single author, must include an Authors’ Contributions section which individually lists the specific contribution of each author. The list of Authors should meet all of the following criteria; 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

All contributors who do not meet all of these criteria should be included in the acknowledgements.

We suggest the following format:
AB carried out the molecular lab work, participated in data analysis, carried out sequence alignments, participated in the design of the study and drafted the manuscript; CD carried out the statistical analyses; EF collected field data; GH conceived of the study, designed the study, coordinated the study and helped draft the manuscript. All authors gave final approval for publication.

- Acknowledgements
Please acknowledge anyone who contributed to the study but did not meet the authorship criteria.

- Funding statement
Please list the source of funding for each author.

Once again, thank you for submitting your manuscript to Royal Society Open Science and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Kind regards,
Royal Society Open Science Editorial Office
Royal Society Open Science
openscience@royalsociety.org

on behalf of Dr Marco Viceconti (Associate Editor) and Professor Pietro Cicuta (Subject Editor)
openscience@royalsociety.org

Comments to Author:
Reviewers' Comments to Author:
Reviewer: 1

Comments to the Author(s)
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Author’s Response to Decision Letter for (RSOS-190366.R0)

See Appendix A.
Decision letter (RSOS-190366.R1)

24-Apr-2019

Dear Mr Wang,

I am pleased to inform you that your manuscript entitled "In silico simulation of a clinical trial with anti-CTLA-4 and anti-PD-L1 immunotherapies in breast cancer using a systems pharmacology model" is now accepted for publication in Royal Society Open Science.

You can expect to receive a proof of your article in the near future. Please contact the editorial office (openscience_proofs@royalsociety.org and openscience@royalsociety.org) to let us know if you are likely to be away from e-mail contact. Due to rapid publication and an extremely tight schedule, if comments are not received, your paper may experience a delay in publication.

Royal Society Open Science operates under a continuous publication model (http://bit.ly/cpFAQ). Your article will be published straight into the next open issue and this will be the final version of the paper. As such, it can be cited immediately by other researchers. As the issue version of your paper will be the only version to be published I would advise you to check your proofs thoroughly as changes cannot be made once the paper is published.

On behalf of the Editors of Royal Society Open Science, we look forward to your continued contributions to the Journal.

Kind regards,

Andrew Dunn
Royal Society Open Science Editorial Office
Royal Society Open Science
openscience@royalsociety.org

on behalf of Dr Marco Viceconti (Associate Editor) and Pietro Cicuta (Subject Editor)
openscience@royalsociety.org

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Appendix A

09-Apr-2019

Dear Editors:

Thank you for your email dated 8 Apr 2019 enclosing the reviewer’s comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given below. Changes to the manuscript are made using track changes mode.

We hope the revised version is now suitable for publication and look forward to hearing from you.

Sincerely,

Hanwen Wang
hwang163@jhu.edu

Response to Reviewer 1:

We thank the reviewer for the review of our paper and constructive comments. We have answered each point below.

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It is useful if the authors add to the discussion session a paragraph or two reviewing these important works in the field.

Response: We added a paragraph regarding the other model types in tumor immunology, including the suggested examples, and their potential applications in the Discussion section (please see the last paragraph in Discussion, page 13).

2. Authors failed to discuss the advantage and the disadvantages of their methodology. ODE systems are good when dealing with populations. But they fail to address important aspects when immune system is modelled. For example, specificity and immune system repertoire are not taken into account. Moreover, different types of lymphocytes subpopulation are not considered at all. See for example CD4(Th1, Th2, Th17), CD8. Authors should mention these in the discussion session.
Response: The limitations of ODE-based models are also added to the last paragraph in the Discussion section. Although we tried to capture the heterogeneity of tumor microenvironment by adding tumor species expressing different types of checkpoint ligands and receptors, the modeling of spatial distribution and the immune repertoire may require other approaches such as agent-based modeling. Also for simplicity, only the major species of interest are included in the current model (please see the last paragraph in the Discussion, page 13).