

## **Opportunities and challenges of circulating biomarkers in neuroblastoma**

Ricky M. Trigg, Jacqui A. Shaw and Suzanne D. Turner

### **Article citation details**

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### **Review timeline**

Original submission: 5 March 2019

Revised submission: 16 April 2019

Final acceptance: 23 April 2019

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

## Review History

### RSOB-19-0056.R0 (Original submission)

#### Review form: Reviewer 1

#### **Recommendation**

Accept with minor revision (please list in comments)

#### **Are each of the following suitable for general readers?**

- a) **Title**  
Yes
- b) **Summary**  
Yes
- c) **Introduction**  
Yes

**Is the length of the paper justified?**

Yes

**Should the paper be seen by a specialist statistical reviewer?**

No

**Is it clear how to make all supporting data available?**

Not Applicable

**Is the supplementary material necessary; and if so is it adequate and clear?**

Not Applicable

**Do you have any ethical concerns with this paper?**

No

### **Comments to the Author**

This is a very comprehensive and well-written review of circulating biomarkers in neuroblastoma which would benefit from some minor revision to make it suitable for a readership which might not be so familiar with the neuroblastoma field.

1. The INSS staging system is so central to the discussion of each biomarker, that it deserves more explanation in the introduction. A table would be useful.
2. ALK (and ATRX) should be defined at the first mention in section 1. For the readership of this journal it could be useful to compare and contrast the nature of ALK activation in neuroblastoma as opposed to other malignancies (lung cancer) at the first opportunity.
3. Figure 1 is very informative (although the text in the legend requires formatting), and although the authors state that liquid biopsies have been reviewed extensively elsewhere, for the Open Biology readers it would be useful to give some key examples of clinical translation for the different types of circulating biomarkers in other malignancies.
4. Section 3.3 is very long. Subtitles here would be welcome.
5. "et al" is occasionally italicised, but mostly not.
6. Section 4 is a good translational summary and discussion which could be extended to provide further "constructive discussion and/or critique of the field" (as per Open Biology guidelines). The need for a final further summary (section 5) is questionable.

## **Decision letter (RSOB-19-0056.R0)**

10-Apr-2019

Dear Dr Trigg

We are pleased to inform you that your manuscript RSOB-19-0056 entitled "Opportunities and challenges of circulating biomarkers in neuroblastoma" has been accepted by the Editor for publication in Open Biology. The reviewer has recommended publication, but also suggest some minor revisions to your manuscript. Therefore, we invite you to respond to the reviewer's comments and revise your manuscript.

Please submit the revised version of your manuscript within 7 days. If you do not think you will be able to meet this date please let us know immediately and we can extend this deadline for you.

To revise your manuscript, log into <https://mc.manuscriptcentral.com/rsob> 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.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, please revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the referee(s) and upload a file "Response to Referees" in "Section 6 - File Upload". You can use this to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the referee(s).

Please see our detailed instructions for revision requirements <https://royalsociety.org/journals/authors/author-guidelines/>.

Before uploading your revised files please make sure that you have:

- 1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".
- 2) A separate electronic file of each figure (tiff, EPS or print-quality PDF preferred). The format should be produced directly from original creation package, or original software format. Please note that PowerPoint files are not accepted.
- 3) Electronic supplementary material: this should be contained in a separate file from the main text and meet our ESM criteria (see <http://royalsocietypublishing.org/instructions-authors#question5>). All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rsob.2016[last 4 digits of e.g. 10.1098/rsob.20160049].

- 4) A media summary: a short non-technical summary (up to 100 words) of the key findings/importance of your manuscript. Please try to write in simple English, avoid jargon, explain the importance of the topic, outline the main implications and describe why this topic is newsworthy.

#### Images

We require suitable relevant images to appear alongside published articles. Do you have an image we could use? Images should have a resolution of at least 300 dpi, if possible.

#### Data-Sharing

It is a condition of publication that data supporting your paper are made available. Data should be made available either in the electronic supplementary material or through an appropriate

repository. Details of how to access data should be included in your paper. Please see <http://royalsocietypublishing.org/site/authors/policy.xhtml#question6> for more details.

#### Data accessibility section

To ensure archived data are available to readers, authors should include a 'data accessibility' section immediately after the acknowledgements section. This should list the database and accession number for all data from the article that has been made publicly available, for instance:

- DNA sequences: Genbank accessions F234391-F234402
- Phylogenetic data: TreeBASE accession number S9123
- Final DNA sequence assembly uploaded as online supplemental material
- Climate data and MaxEnt input files: Dryad doi:10.5521/dryad.12311

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

Sincerely,

The Open Biology Team  
<mailto:openbiology@royalsociety.org>

#### Reviewer's Comments to Author:

Referee:

#### Comments to the Author(s)

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## Author's Response to Decision Letter for (RSOB-19-0056.R0)

See Appendix A.

## Decision letter (RSOB-19-0056.R1)

23-Apr-2019

Dear Dr Trigg

We are pleased to inform you that your manuscript entitled "Opportunities and challenges of circulating biomarkers in neuroblastoma" has been accepted by the Editor for publication in Open Biology.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it within the next 10 working days. Please let us know if you are likely to be away from e-mail contact during this time.

Thank you for your fine contribution. On behalf of the Editors of Open Biology, we look forward to your continued contributions to the journal.

Sincerely,

The Open Biology Team  
mailto: [openbiology@royalsociety.org](mailto:openbiology@royalsociety.org)

# Appendix A



UNIVERSITY OF CAMBRIDGE  
DEPARTMENT OF PATHOLOGY  
DIVISION OF CELLULAR AND MOLECULAR PATHOLOGY

Level 3 Lab Block, Box 231,  
Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ  
Tel: 01223 336911 – Email: [rt473@cam.ac.uk](mailto:rt473@cam.ac.uk)

Dr Ricky M. Trigg, PhD  
*Postdoctoral Research Associate*

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April 16, 2019

Dear Buchi,

We are delighted that our manuscript has been accepted for publication in *Open Biology* and would like to sincerely thank the reviewer for their time and very helpful feedback.

Please see below a point-by-point response to the reviewer's comments. Changes in the manuscript are shown in red.

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1. The INSS staging system is so central to the discussion of each biomarker, that it deserves more explanation in the introduction. A table would be useful.

We have now provided Table 1 – a description of the INSS stages, and have also stated that the INSS system is post-surgical.

2. ALK (and ATRX) should be defined at the first mention in section 1.

We have now defined the biological roles of ALK and ATRX at the first mention.

For the readership of this journal it could be useful to compare and contrast the nature of ALK activation in neuroblastoma as opposed to other malignancies (lung cancer) at the first opportunity.

We have now contrasted the activation of full-length ALK in ALK+ NB with the fusion of ALK to other oncogenes in ALK+ ALCL and NSCLC.

3. Figure 1 is very informative (although the text in the legend requires formatting), and although the authors state that liquid biopsies have been reviewed extensively elsewhere, for the Open Biology readers it would be useful to give some key examples of clinical translation for the different types of circulating biomarkers in other malignancies.

We have now formatted the text in the figure legend. We have now introduced two examples of clinically translated liquid biopsy tests: the Cobas test for EGFR mutation testing in NSCLC and the CELLSEARCH test for enumeration of CTCs in several cancer types.

4. Section 3.3 is very long. Subtitles here would be welcome.

We have now split this section into three further sections: the first is an introduction to CTCs, the second is methodology of CTC detection and the third is association of CTCs with clinical features.

5. "et al" is occasionally italicised, but mostly not.

We have now italicised every instance of *et al*.

6. Section 4 is a good translational summary and discussion which could be extended to provide further "constructive discussion and/or critique of the field" (as per Open Biology guidelines). The need for a final further summary (section 5) is questionable.

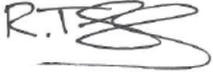
We have added some more narrative to the discussion on clinical implementation of circulating biomarkers in NB. We feel that the Summary is concise and brings the review to an end; however, we will leave the decision of whether to include or exclude the Summary with the Editorial team.

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We have also designed a graphical abstract to appear alongside our published article and feel it would also serve as a more informative Figure 1, so have substituted it.

Thank you for your time and we look forward to reading the proofs of our manuscript in due course.

Kind regards,

A handwritten signature in black ink, appearing to read 'R. Trigg' with a stylized flourish underneath.

Ricky Trigg