Reviewer Assessment

Florian Obermayr* and Guido Seitz

Recent developments in cell-based ENS regeneration – a short review

https://doi.org/10.1515/iss-2018-0005
Received January 24, 2018; accepted February 15, 2018

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Reviewers’ Comments to Original Submission

Reviewer 1: anonymous
Feb 11, 2018

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: 85

Custom Review Questions Response
Is the subject area appropriate for you? 5 - High/Yes
Does the title clearly reflect the paper’s content? 5 - High/Yes
Does the abstract clearly reflect the paper’s content? 5 - High/Yes
Do the keywords clearly reflect the paper’s content? 5 - High/Yes
Does the introduction present the problem clearly? 5 - High/Yes
Are the results/conclusions justified? 5 - High/Yes
How comprehensive and up-to-date is the subject matter presented? 4
How adequate is the data presentation? 4
Are units and terminology used correctly? 5 - High/Yes
Is the number of cases adequate? N/A
Are the experimental methods/clinical studies adequate? N/A
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 4
Please rate the practical significance. 1 - Low/No
Please rate the accuracy of methods. N/A
Please rate the statistical evaluation and quality control. N/A
Please rate the appropriateness of the figures and tables. 4
Please rate the appropriateness of the references. 4
Please evaluate the writing style and use of language. 4
Please judge the overall scientific quality of the manuscript. 4
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
This is an invited review on recent developments in cell-based ENS regeneration. Under these circumstances, the review is perfectly appropriate. The authors describe the current methods and results in lab-based ENS regeneration. Naturally, these approaches lack a clear clinical significance. As an invited review, this manuscript perfectly meets the requirements.

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Reviewer 2: anonymous

Feb 07, 2018

Reviewer Recommendation Term: Accept with Minor Revision
Overall Reviewer Manuscript Rating: 85

Custom Review Questions Response
Is the subject area appropriate for you? 5 - High/Yes
Does the title clearly reflect the paper’s content? 4
Does the abstract clearly reflect the paper’s content? 4
Do the keywords clearly reflect the paper’s content? 5 - High/Yes
Does the introduction present the problem clearly? 3
Are the results/conclusions justified? 4
How comprehensive and up-to-date is the subject matter presented? 5 - High/Yes
How adequate is the data presentation? N/A
Are units and terminology used correctly? 5 - High/Yes
Is the number of cases adequate? N/A
Are the experimental methods/clinical studies adequate? N/A
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 4
Please rate the practical significance. N/A
Please rate the statistical evaluation and quality control. N/A
Please rate the appropriateness of the figures and tables. N/A
Please rate the appropriateness of the references. 4
Please evaluate the writing style and use of language. 4
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
Recent developments in cell-based ENS regeneration - a short review.
The author described all cell sources to generate ENS progenitor cells and their application in different animal or human in vitro models. A separate paragraph is focused on delivery techniques of the ENS progenitor cells into the colon.
He discussed specific details of each model and their implication for ENS regeneration in humans.

Some comments:
1. Within the introduction the author mentioned that the field of application for ENS regeneration comprises developmental diseases such as Hirschsprung disease (HSCR) on the one hand and acquired degenerative disorders on the other. But the following exposition are considered on the potentially HSCR treatment by ENS regeneration only. Are there any studies investigating ENS regeneration in degenerative disorders?
2. More the 80% of the Hirschsprung disease patient are suffering from short segment aganglionosis causing a recto-sigmoid resection - no complete colectomy - which results in a really good outcome in most cases. Therefore, I cannot share the disastrous picture of the HSCR treatment in the manuscript.
3. The paragraph about iPSC cells should include a few sentences that discuss safety problems of iPSC cells and how to circumvent them.
4. There are several typing errors.

Authors’ Response to Reviewer Comments

Feb 15, 2018

Dear Professor Jaehne,
thank you for sending the reviewers’ comments. We’ve revised the manuscript accordingly:

Reviewer I: no changes.
Reviewer II:
1. Are there any studies investigating ENS regeneration in degenerative disorders?
   There are some studies investigating cell-based regeneration in animal models different to a Morbus Hirschsprung pheno- or genotype. However Hirschsprungs disease represents the model disease for this research, thus most of the research on this topic was done on Hirschprung animals. Therefore we introduced a sentence that clarifies this in the introduction section:
   “Since HSCR is well defined from a genetic and clinical point of view, and numerous small animal models for HSCR exist, most of the research was performed focusing on regeneration the ENS of HSCR animal models in the past.”
2. Most of the patients treated for HSCR suffer from short-segment disease and have a good surgical outcome!
   We agree with the reviewer, that surgical outcome in a proportion of patients is good after surgical intervention. However literature is contradictory, mainly concerning functional outcome. Detailed review of surgical outcome of surgery for Hirschprung disease is beyond the scope of the manuscript. Accordingly we changed the paragraph dealing with HSCR outcome:
   “Therapeutic options are limited for both, developmental and acquired ENS disorders. In HSCR surgical resection of the affected gut segment and colo-anal anastomosis leads to cure in many patients with short-segment disease, but is associated with numerous long-term complications in those suffering from syndromic or long-segment disease (10,11).
   Since therapeutic options are limited and quality of life appears to be impaired in a relevant proportion of patients suffering from neurogenic motility disorders of the gut, a regenerative therapeutic approach was proposed many years ago (12-14).”
3. iPS cell safety issues:
   We agree that safety issues are important, teratoma formation in particular. This was mentioned already in the ES cell section, to which we referenced in the iPS cell section already. To underline the importance of this problem we added:
   “Therefore, reliable cell selection strategies need to be established in order to prevent transplantation of immature cells.”
   and
   “…avoiding tumor formation within the recipient.”
4. The manuscript was checked for typing errors.

We hope the manuscript will be appropriate now for publication.

With best regards

Reviewers’ Comments to Revision

Reviewer 2: anonymous

Feb 15, 2018

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: N/A

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Please rate the practical significance. 3
Please rate the accuracy of methods. N/A
Please rate the statistical evaluation and quality control. N/A
Please rate the appropriateness of the figures and tables. N/A
Please rate the appropriateness of the references. 4
Please evaluate the writing style and use of language. 4
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
I have no further comments. I suggest accepting the manuscript for publication ISS.