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Detection of misfolded protein aggregates from a clinical perspective

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Detection of Mis-folded Protein Aggregates from a Scientific and a Clinical Perspective
Journal of Clinical and Translational Research

Dear authors,

A reviewer specialized in the field has evaluated your work and was cautiously enthusiastic about the paper. I have also carefully read your work and share some of the reviewer's points of view. However, I certainly want to give the paper another chance because, like the reviewer, I think the paper is potentially interesting and useful. I therefore want to help you in improving the work if you choose to pursue a resubmission. Please let me know whether you are willing to resubmit a revised version.

Your revision is due by Feb 09, 2016.

To submit a revision, go to http://jctres.edmgr.com/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Thank you for submitting your work to JCTR and good luck with your studies.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1:

Although the topic, title and the abstract call for an interesting read, this review is a little bit all over the place and does not provide enough details and cohesiveness.
This review contains quite a few grammatical errors and typographical errors. Also a lot of the English language used is more 'colloquial language'. Overall this makes it unpleasant to read, however this could be improved.
I found that many sentences used do not contain much information at all and other sentences contain important conclusions, but often this is not further explained/backed up by data or examples. The structure of the manuscript, the different subchapters and the content of them lack cohesiveness. It is unclear why some examples are chosen when I think a lot more information is known, for example on abeta oligomers. This should be summarised better. Perhaps separating the different example proteins/diseases would make it easier to read, but each would need to be elaborated. I feel that the topic and idea of this review is an interesting one, but the execution is insufficient. Since it is a broad topic and much more literature is available, the review should be either much longer or should be separated into specific subcategories.

I would reject this review as it is, although I can see potential in the topic as an interesting read, also for this journal.

Editor-in-chief:

In addition to addressing the concerns raised by the reviewer I kindly ask you to follow my instructions (or rebut where you feel this is warranted):

1. The text does indeed contain grammar and spelling errors. Please eliminate these to the maximum possible extent. There will be other occasions where this will be done (e.g., proofs).
2. You may disregard the statement regarding “colloquial language.” The most important aspect of the review is that it is linguistically accessible to a broader audience, including physicians, who are not per se familiar with field-specific jargon. That is the case now.
3. This point is critical. In order to increase the value of your work in a clinical and translational framework, I would like you to include the following tables:

A. A table (Table 1) in the section “Introduction” summarizing all the proteopathies (column A), the clinical manifestation/main symptoms of the condition (column B), and key points related to the pathogenic mechanism (column C). Please organize the table according to the classification

of the disorder (e.g., induced or congenital) and insert references for every bit of information provided. An example is provided on the Wikipedia page (http://en.wikipedia.org/wiki/Proteopathy)

B. A table (Table 2) in the section "Clinical detection of protein aggregates" that describes the proteopathy (column A), the type of protein fibrils/aggregates responsible for the proteopathy (column B), and the contemporary clinical detection method(s) (column C). This table should focus primarily on the detection methods available for the protein fibrils. Please be specific in terms of column C (e.g., polarization microscopy of tissue sections is not enough; also state which polarizing dyes are used for these purposes, etc.). If there are no clinical chemistry assays available for the respective protein fibril analysis, please state so because this underscores the potential medical need. Again, please use thorough referencing. Finally, attune the text of this section to the table. That having said, at this point the text is quite complementary to the table in that it describes the general techniques rather than describing the specifics, which will be listed in the table.

C. A table (Table 3) in the section "Concluding remarks and future perspectives" to delineate: part 1) the antibodies that have been used to date to detect protein aggregates, including information, where available, on the antigen specificity (what part of the protein do they react with), the species in which these were derived, their cross-reacting species, and the detection technique (e.g., Western blot, ELISA, etc.). Part 2) Specific examples of improperly glycosylated proteins with a similar level of detail as addressed for the antibodies. Part 3) Specific examples that have been found by MS, again focusing on details such as the type of sample used (plasma, tissue homogenates, histological sections, etc.). The table does not have to be exhaustive, but I want the readers to get a good overview of what is out there and what can be done. Proper referencing is again requested.

Authors' rebuttal:

Date: 22-Mar-2016

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Dr Michal Heger
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22nd March 2016

Dear Dr Heger, Ms. Liu,

Re: Submission of the revised versions of the review manuscript entitled "Detection of Mis-folded Protein Aggregates from a Clinical Perspective", manuscript id JCTRes-D-15-00017

Please find enclosed a heavily revised version of the above manuscript. We would like to apologize for the long delay in delivery of the manuscript. This time has been used to perform a thorough implementation of the comments received, with a view to making this article accessible and useful to both medics and researchers. We adopted a narrower focus and believe that the reworking has led to significant improvement. We have tabulated:

1. Neurodegenerative protein mis-folding diseases (*Table 1*) in order to provide useful references for original research in this area and to orientate the reader;
2. The clinical detection of protein aggregates (*Table 2*) to orientate the reader;
3. The recent advances in the three approaches with the strongest promise for producing a diagnostic clinical test for PMDs. This comes in three parts. *Table 3a*: Oligomeric protein states detected by antibodies; *Table 3b*: Identification of prion protein glycosylation states; *Table 3c*: Identification of oligomeric states by mass spectrometry.

We respond to the comments received in turn.

Reviewer:

Although the topic, title and the abstract call for an interesting read, this review is a little bit all over the place and does not provide enough details and cohesiveness. This review contains quite a few grammatical errors and typographical errors. Also a lot of the English language used is more 'colloquial language'. Overall this makes it unpleasant to read, however this could be improved. I found that many sentences used do not contain much information at all and other sentences contain important conclusions, but often this is not further explained/backed up by data or examples. The structure of the manuscript, the different subchapters and the content of them lack cohesiveness. It is unclear why some examples are chosen when I think a lot more information is known, for example on abeta oligomers. This should be summarised better.

We fully appreciate this comment, and have taken the following steps to improve the manuscript: We have tried to narrow the focus of the text from the outset, and limit the

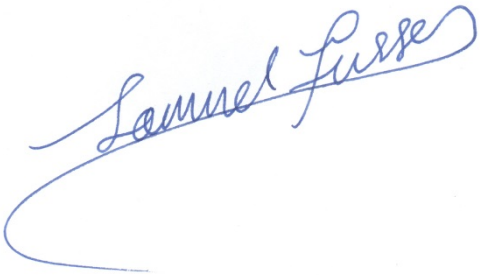
discussion to neurodegenerative protein misfolding diseases (PMDs) only. The manuscript has received a complete rewrite and copy-edit, as well as more advise on clinical practice and terminology from an MD (Dr. Viste, acknowledgements). We have also merged two paragraphs, reducing the number of topics discussed. As for the amount of information available on especially the abeta oligomers, we've been forced to limit ourselves for two reasons. First, this is a mini-review, and second it focuses on detection rather than, for instance, the large variety of oligomer and fibril morphologies reported. We have chosen to focus on the toxic mechanism of the oligomers as these are implicated in the disease mechanisms. Our description of their properties has to be brief, given the format of the requested submission.

Perhaps separating the different example proteins/diseases would make it easier to read, but each would need to be elaborated. I feel that the topic and idea of this review is an interesting one, but the execution is insufficient. Since it is a broad topic and much more literature is available, the review should be either much longer or should be separated into specific subcategories.

We agree that there is a definite need to help the reader orient and increase the reader value of the manuscript. We have added, at the editor's suggestion, three tables to provide some help to the reader as s/he orients in a large and complex field. The tables provide examples of protein/disease pairs, lists of antibodies used in translational research, and a summary of combinatorial detection methods currently being researched. Table 1 indicates that the number of protein misfolding diseases related to neurodegeneration alone is very large, and this makes a full review of each case outside the scope of a mini-review. The main text thus has to focus on the proteopathies that has the largest medical impact and where research has advanced furthest.

We believe that the modifications made increase readability and usefulness of this manuscript to both clinicians and research scientists, look forward to your response.

Yours sincerely,



Prof. Øyvind Halskau Dr Samuel Furse (invited author)

Signed on behalf of all authors

2nd editorial decision:

Date: 22-Mar-2016

Ref.: Ms. No. JCTRes-D-15-00017R1
Recent advances in the detection of mis-folded protein aggregates for clinical diagnosis
Journal of Clinical and Translational Research

Dear Dr Furse,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

Comments from the editor and reviewers can be found below.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Dear authors,

Thank you for resubmitting a revised version of your paper. I have read the paper and considered your modifications in light of the reviewer comments. Based on your extensive effort in modifying the draft, consulting with a medical doctor for relevant feedback, and your forthcoming revisions in line with the reviewer's and editor's critical appraisal I am pleased to accept the manuscript for publication.

We are grateful that you have chosen to submit your work to JCTR.

Kindest regards,

Michal.