

PEER-REVIEW REPORT 1

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Title: Drug repurposing for neuroregeneration in multiple sclerosis

Reviewer's Name: Tetsuya Akaishi

Reviewer's country: Japan

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Yes

COMMENTS TO AUTHORS

In this manuscript, the authors are vigorously discussing on the difficult but very important topic about the neuro-regenerative process in MS lesions, which has not been fully investigated yet. Their aim and perspective are pertinent to the current trend of research and this report offers us new insights into the next step of therapeutic approach in MS. Several minor comments are listed below.

[Minor comments]

> affecting at least 2.5 million people worldwide

Is there an appropriate reference about this knowledge?

> ...is characterized by episodes of autoimmune attacks (relapse) followed by spontaneous partial functional recovery (remission) most patients eventually develop a...

I think that a comma (,) is needed just before "most patients".

> progressive disease course featuring reduced or absent immune cell infiltration but ongoing neurodegeneration.

The sentence after "featuring" looks unnatural English and hard to understand.

> axonal sheaths

I noticed the above-shown words in several locations. Is the "axonal sheath" countable? I am not sure on this matter; so, if I am wrong, please ignore this comment.

> none of the currently available disease-modifying therapies (DMT) can effectively enhance lesion repair.

This sentence sounds a little bit radical and aggressive; "can" may be better to be replaced by "has been shown to" or something like that.

> For this purpose different strategies for enhancing remyelination are conceivable...

A comma (,) should be placed just after "For this purpose".

Also, "different" seems to be better to be replaced by "multiple" or "several".

> To this end, either the development of new drugs, acting on inhibitory or stimulatory glial pathways or the repurposing of existing drugs represent two possible approaches

This sentence looks grammatically incorrect. "Either A or B" is usually regarded as a singular

noun. What are the phrases fitting to "A" and "B" in this sentence?

> To this end, To this end, ...

The same phrase of "To this end" is repeatedly used in the manuscript. Can the second one be replaced by some other phrases?

> To this end, high-throughput drug-screenings as well as computational drug-repurposing approaches are being used.

Most readers, including me, would not be so familiar with "high-throughput drug-screenings" or "computational drug-repurposing approaches". Please roughly describe the outlines of these methods or simply cite some pertinent references utilizing these methods.

> ... ocrelizumab, a monoclonal antibody directed against CD20 on B cells and initially designed for treatment of rheumatoid arthritis (RA) demonstrated efficacy on...

A comma will be needed after "(RA)".

> Investigating its effects in secondary progressive MS a clinical study found that...

A comma will be needed after "MS".

> ...their ability to differentiate and wrap around CNS axons.

"CNS" is better to be spelled out in its first appearance in the main text.

> However and in general, given the heterogeneity of clinical MS subtypes and the dynamics of lesion development in time and space it will be challenging to find the appropriate window of opportunity for therapy - no matter if using newly designed drugs or repurposed ones.

This whole sentence is better to be radically revised. Comma (,) is lacking in some locations. Also, the sentence gives quite pessimistic impression as a conclusion to the readers. Can this sentence be replaced by more positive and constructive conclusion?

> Figure 1: Teriflunomide's mode of action: Whereas it has been well accepted that Teriflunomide reduces the number of activated peripheral T and B lymphocytes, which could potentially infiltrate the CNS our new study provides evidence that local parenchymal Teriflunomide concentrations could also positively affect oligodendroglial precursor cells and promote their differentiation, maturation and generation of myelin sheaths around previously demyelinated axons.

This is too long for a single sentence. Please separate this sentence appropriately for the readability. Also, this sentence seems to be grammatically incorrect: "their" differentiation, "their" maturation and "their" generation of myelin sheaths? "Their generation of myelin sheaths" does not seem to make sense. Also, a comma (,) will be needed after "infiltrate the CNS".

The green arrow in the Figure 1 means a positive promotion (positive feedback)?