

OPEN PEER REVIEW REPORT 2

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Title: Soluble Alpha-synuclein Post-translational Modifications: Unexpected Regulators of Alpha-synuclein Amplification

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COMMENTS TO AUTHORS

The authors summarize and contextualize their own work published recently, regarding the differential impact that post-translational modifications (PTMs) of alpha-synuclein can have on seeding and amplification of pathological species of this protein.

The article is well written and provides a concise yet sufficiently comprehensive overview over this highly interesting field of research.

I have only two comments:

- 1) In the title and at some occasions in the text the phrase "alpha-synuclein amplification" is used. This should be corrected to "amplification of pathological forms of alpha-synuclein", as there is no general amplification of this protein in any kind of situation.
- 2) Discussing individual PTMs and their influence on seeding and generation of pathologically relevant conformations of alpha-synuclein is certainly warranted, but it should be mentioned that several of these PTMs can occur simultaneously in a non-predictable manner, so that one PTM that may accelerate formation of toxic conformers may be attenuated by another PTM that acts differently. Thus, rather than considering single PTMs as putative therapeutic target sites, it might as well be important to take into the interplay of several PTMs of the same molecule.