Reviewer’s report

Title: Synthetic high-density lipoprotein nanoparticles for the treatment of Niemann-Pick Diseases

Version: 0 Date: 21 Jun 2019

Reviewer: Maria Teresa Fiorenza

Reviewer's report:

This is a well conceived study that investigates the ability sHDL nanoparticles to correct the intracellular cholesterol accumulation associated to Npc1 deficiency, providing some evidence of the efficacy of this strategy/treatment. The authors perform a thorough characterization of the mechanism of action of the sHDL nanoparticle using Npc1 fibroblasts and also attempt to define their efficacy in a mouse model of NPC1 disease. The efficacy of this treatment is investigated both on NPC type C and NPC type A fibroblasts.

Studies performed using cells address the mechanisms of the sHDL nanoparticle activity and provide convincing evidence on their efficacy on cells. On the other hand, part of the studies performed using the mouse model appear preliminary and data displayed do not fully support the conclusions drawn by the authors. The rationale for using animals of a certain age, dosage and temporal schedule of treatments is not explained. Results obtained are poorly discussed with respect to other treatments performed on animal models, with particular reference to their efficacy on rescuing the neural pathology. In this regard, the proposed strategy does not seem to secure a significant improvement. These issues deserve some attention in the discussion section, at least.

Specific concerns:

- The number of animals used in each specific determination should be indicated more clearly, by also specifying whether experimental groups were made of age/sex/number matched animals.

- Fig.5e. Using score values to indicate the improvement of the body weight following treatment (y-axis) instead of "changes in weight" will help the readability of this graph. Since score values are consistently used in the field, this will allow a more immediate comparison between the efficacy of different treatments performed in various studies;

- Fig. 5g, the resolution of images displayed is poor; the dashed line tracing Purkinje cells (PCs) appears somehow arbitrary in light of accompanying images displayed by supplementary figure 3b. The latter show double - Calbindin-filipin- stained cerebellar sections that allow the detection of PCs. Based on Calbindin staining, PCs of vehicle-treated appear significantly compromised at this early stage of the disease (8 weeks). The in vitro culture of organotypic slices is tricky, with proper cell physiology depending on medium [K+] and additional critical parameters. The authors should include a panel showing specimens obtained from "sham
organotypic slices", i.e. neither vehicle- or 5A-SM-treated, obtained from wt and Npc1-I106T mice, as a control. Lacking this control, the conclusion: "Confocal imaging demonstrated that treatment of Niemann-Pick C brain slices significantly reduced cholesterol storage in Purkinje neurons", is not fully supported by data displayed.

- Also, panels of supplementary fig. 3c do not support the presence of a beneficial effect of the intraventricular administration of the treatment. Indeed, PCs appear scattered in the 5A-SM-DiD panel (some cell are lost, perhaps) and the cell body of those displayed appears shrinked.

- The efficacy of the treatment was assessed at a single time point, whereas some intermediate time points would be appropriate.

Minor points:

-pg 13: "Brama suture" is misspelled. It should be: "Bregma suture".

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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