Reviewer’s report

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

Version: 0 Date: 15 Jun 2019

Reviewer: Frank Pfrieger

Reviewer's report:

The study explores a potentially new therapeutic approach for Niemann-Pick type C disease, a rare lysosomal storage disorder with variable neurovisceral symptoms. Currently, there is no curative therapy and new avenues are urgently needed to combat this ultimately fatal disease. Moreover, the topic is of wider interest as many other diseases lacking therapies are associated with pathologic changes of cholesterol levels. The authors' approach to use artificial HDL particles that are already in clinical use is highly pragmatic as the translation to the clinics could be straightforward. The authors used an impressive range of experimental models and methods to explore the efficacy of the HDL-like particles in reversing NPC-related changes at the cellular and systemic level. In principle, these results are of eminent interest for the NPC community, but also for other diseases that may require manipulations of brain cholesterol. However, in its present form, the ms presents several weak points that need to be addressed:

- Pg. 4, lines 88-90: This statement should be modified a bit. At present, it is not really clear how NPC1 mediates the exit of cholesterol. Its putative insertion into LE/Lys membranes mentioned by the authors is only one of at least two possible but unproven mechanisms.

- Pg. 10, lines 225-226: The authors should state the final concentration of filipin and the dilution of DMSO.

- Pg. 17, line 369; pg 23-24, Fig. 4d: Apparently, the authors studied cyclodextrin-induced cholesterol efflux. However, the results are not mentioned and no data are shown in the corresponding figure. The author should show these results, and discuss the outcome in the light of published studies showing cyclodextrin-induced release of cholesterol from cells.

- Pg. 26: The authors should show the distribution of 5A-SM-DiD in various brain regions allowing to estimate the penetrance of nanoparticles. Moreover, they should show images of sections treated with DiD alone as control.

- Pg. 26, 582 - pg. 27, line 612. The data on NPA fibroblast seem more like an add-on than an integral and indispensable part of the present ms, as none of the results provide new information about the current topic. The authors should move these data to a new ms focusing on NPA.
- Fig. 1. This figure could be fused with Fig. 2 to save space. Moreover, it is unclear whether part b requires really a logarithmic scale at the x axis, using a linear scale and well-selected max/min values should enhance the visibility of the different size distributions.

- Suppl. fig. 3: The results shown as supplementary data are very important, therefore, they should be integrated in the main figure 5.

**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.

Yes

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