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### Format for ANSWERING REVIEWERS



December 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13999-review.doc).

**Title:** Lipoprotein based drug delivery –Potential for pediatric applications

**Author:** Nirupama Sabnis, Paul Bowman, Andras G Lacko

**Name of Journal:** *World Journal of Pharmacology*

**ESPS Manuscript NO:** 13999

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Comments to authors. The authors focused importance of lipoprotein as a vector for chemotherapy for pediatric cancer. The manuscript generally well written but there are some grammatical errors shown below. P3, final sentence; “general. utilizing” should be “general, utilizing” P8, final sentences above Table 2; “chemical constructs (including polymer based, dendrimers, flo dots, quantum dots, ceramic, metal based etc.” should be chemical constructs (including polymer based, dendrimers, flo dots, quantum dots, ceramic, metal based etc). P9, 1st sentence; “poly(lactide-co- glycolide) (PLGA)” should be “poly (lactide-co- glycolide) (PLGA)

### P3 corrected, P8 corrected, P9 corrected

(2) An interesting and well-written review discussing the potential application of lipoprotein-based nano-delivery formulations in treating childhood cancer. Interest in the manuscript depends heavily on the unique challenges of paediatric cancer. (1) The title should be amended to reflect the focus on cancer (2) While the authors make a good case for the unique challenges of paediatric cancer in pages 3 to 7, this is not reflected in the abstract. The abstract should be updated to concisely summarise the unique challenges of paediatric cancer that differ from approaches for treatment of adult cancer.

(1) The title of the paper has been modified to read: **“Lipoprotein based drug delivery –Potential for pediatric cancer applications”**

(2) A sentence is added in the abstract : “Because of the existing metabolic and physiological disparities between pediatric and adult patients, the treatment of pediatric cancer patients poses special challenges to oncologists”.

(3) This is a very useful discussion of nanotechnology and drug delivery to pediatric patients.

Thanks

(4) The manuscript by Sabnis et al aims to overview recent advances in the use of lipoprotein based drug delivery in the treatment of pediatric malignancies. While the limitations of previous treatment strategies and the advantages of the new lipoprotein based strategies are clearly highlighted in the introduction, the conclusions and novel aspects of the review are not very clear. For example, the general introduction to pediatric cancers (pages 4-5) is useful but not linked to the core topic of this review. The significance of various age groups is highlighted on page 6, but it is not clear how is this relevant to lipoprotein based drug delivery and the discussion of this topic lacks specific details. The general points raised regarding ethical etc issues are not particularly relevant to the core topic of this review and can be omitted. The structure of the review is not very clear, the text is often repetitive and the different sections are poorly connected. Each section should start with a few sentences that highlight the relevance of the topic and finished with clear conclusions. Previous studies should be discussed in greater details and more rigorously. The presented discussions are fairly superficial and represent limited advance compare to other similar publications.

The title of the paper has been modified to read: **“Lipoprotein based drug delivery –Potential for treatment of pediatric cancer applications.”** In place of **“pediatric applications”** this way the introduction will be related to the core topic.

We have considered challenges in pediatric oncology, including those faced in the preparation of formulations, appropriate for different age groups, In response, we included relevant information in the expanded “Background” section.. Lipoprotein formulation, due to their biocompatible characteristics and thus increased safety profile are considered to pose minimal ethical concerns for all age groups, unlike most conventional chemotherapy formulations.

The application of nano DDVs in general and lipoprotein DDV in particular is a novel approach in pediatric oncology. Accordingly, reports in the literature in this area are scarce,

thus limiting the opportunity for rigorous discussion on this topic. In addition, as there are no ongoing clinical trials with lipoprotein DDVs, their potential as systemic pediatric drug delivery agents can only be assessed based on their performance in pre-clinical studies.

(5) The title of the review manuscript emphasizes the potential of lipoprotein-based drug delivery for pediatric applications. However, while the authors have indeed done a good job in the first half of the review on discussing the challenges of treating pediatric malignancies, they have not explained or justified in any clear terms or arguments as to why the nanomedicine and in particular lipoprotein-based drug delivery system should be particularly applicable and advantageous to the pediatric cases. Thus, the content of second half of the review appear to be applicable equally to all cancer cases, pediatric or not. It would be a disappointment to the readers who read the review because of what the title had appeared to promise. There are also some particular concerns: 1) The literature cited to support one of the most important statements of the review manuscript – that is, “Lipoprotein-inspired DDVs possess most of these desirable these features and thus represent a promising platform for pediatric cancer therapeutics”, contains only one paper related to pediatric cases, and even this paper is a review article on advocating the application of lipoprotein-based DDV for pediatric leukemia treatments from the same team of authors as this manuscript. 2) The use of abbreviations which are either not defined when used for the first time or not at all: DDS (page 9) and rHDL (10). The term “therapeutic shielding” needs clarification. 3) Appearance of a sentence in italics on page 11. 4) Non-uniform references format, and omitted authors’ names as in reference #62.

A sentence was added to the end of the paragraph under the heading “***Why use the reconstituted/synthetic HDL (rHDL) nanoparticles for drug delivery of anti-cancer drugs in Pediatric Oncology?***” page 12 to read: Also lesser amounts of drug are likely to be required for achieving the same cytotoxic effect compared with the drug used in its free form <sup>[67]</sup>. Although these advantages of lipoprotein based nano DDV could be beneficial to all types of cancer patients, pediatric patients are anticipated to benefit the most by the



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extended safety, long drug retention time and enhanced therapeutic efficacy.

### Comments:

- (1) We agree that the supporting literature contains only one paper that has been published by our group, however, there are only a few ( if any other) groups are working on lipoprotein based drug delivery to treat pediatric cancers.
- (2) )Abbreviation DDS (page 9) is changed to DDV. rHDL abbreviation is clarified as (reconstituted high density lipoprotein on page 10
- (3) The references have been reformatted and revised as needed,

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Pharmacology*.

Sincerely yours,

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