

INVITED REVIEW ID 00188507

Editor in Chief, *World Journal of Gastroenterology*

Lian-Sheng Ma, President and Company Editor-in-Chief

Aug 5, 2016

Dear Editors and Reviewers,

Thank you and the reviewers for a thorough review of our manuscript entitled “**The Development of Liver-targeted Hydrodynamic Gene Therapy: Mini-review**” (Manuscript number 28546, **INVITED REVIEW ID 00188507**) by Takeshi Yokoo, Hiroyuki Abe, Yuji Kobayashi, Tsutomu Kanefuji, Takeshi Suda, Kohei Ogawa, Ryo Goto, Masafumi Oda, Shuji Terai, and myself. The thoughtful comments from the reviewers are greatly appreciated. In preparing for revision, we have carefully studied reviewers’ comments and incorporated many of their suggestions into the revised manuscript. For your convenience, we have highlighted the changes made in blue. We hope this revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*. **The provided ID for this invited review is (00188507).**

We declare that this work is original, the manuscript is not under consideration by other journals. All authors approved the contents submitted. We look forward to hearing from you at your earliest convenience.

Thank you for your consideration.

Sincerely yours,

Kenya Kamimura, M.D., Ph.D.

Division of Gastroenterology and Hepatology,

Graduate School of Medical and Dental Sciences

Niigata University

1-757 Asahimachi-dori, Chuo-ku, Niigata, Niigata, 9518510, JAPAN

Tel: +81 (25) 227-2207

Fax: +81 (25) 227-0776

E-mail: kenya-k@med.niigata-u.ac.jp

Dear Reviewers:

Thank you very much for your thoughtful comments and suggestions. In preparing the revision, we have carefully studied your comments and incorporated many of your suggestions into the revised manuscript. The following are our point-by-point responses to your comments/concerns. For your convenience, we have highlighted the changes made in blue.

Title: The Development of Liver-targeted Hydrodynamic Gene Therapy: Mini-review (Author ID 00188507)

Author: Takeshi Yokoo, Kenya Kamimura Hiroyuki Abe, Yuji Kobayashi, Tsutomu Kanefuji, Takeshi Suda, Kohei Ogawa, Ryo Goto, Masafumi Oda, Shuji Terai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 28546

Reviewer #1

There are non-viral methods of gene delivery, such as sonoporation. This manuscript discussed hydrodynamic gene delivery. As compared with sonoporation, hydrodynamic gene delivery is relatively less-popular. This manuscript is informative and well-organized. System presented in Figure 2 is interesting. Is this computer-assisted injection system innovated by a company? Is this system commercially available? Or is this system build by the authors' institute? The authors proposed congenital disease as a potential clinical application. Do the authors think hydrodynamic gene delivery to hepatocellular carcinoma (HCC) as a potential target disease? If so, how do the authors restrict delivery of therapeutic genes to HCC?

Response: We are grateful to the reviewer for the positive comments and for recognizing the significance of our work. This computer system is innovated by us and developed collaborating with the company. We are making efforts to make it to be commercially available. Thank you again for asking these points. We also consider HCC as a target for this method and have added the description (page 15, line 2).

Reviewer #2

This manuscript provides an extensive review on liver-targeted hydrodynamic gene delivery based gene therapy. Hydrodynamic delivery (HGD) is an efficient procedure to deliver numbers of nucleic acids to hepatic tissues. The successful application of hydrodynamic delivery is dependent on the rapid injection of a large volume containing nucleic acids into the liver. This review summarizes the HGD method principle, efficiency, safety, modification in large-animal models, and gene therapy in various diseases. The topic is of great interest to the field. The manuscript is very well written and easy to read. HGD method does have some effects on the immune system and activate certain immune response to some extent. The authors should address on that issue.

Response: We are grateful to the reviewer for the positive comments, high scores, and for recognizing

the significance of our work. We have added the description regarding the immune response and cytokines (page 11, line 7).

Reviewer #3

The manuscript is interesting and the authors are specialists in the topic. It is written correctly and we think it could be interesting for the readers of World Journal of Gastroenterology. However, some questions should be considered. Major question: authors did not fully focused the manuscript on describing the development of liver-targeted hydrodynamic gene therapy but payed more attention on their own system for controlled gene delivery, which is an interesting delivery system. Thus, title should be modified in order to adjust to the major content of manuscript. Minor question: the format of reference 27 is not correct, family name of authors is not complete.

Response: We are grateful to the reviewer for the positive comments, high scores, and for recognizing the significance of our work. We have modified the title and corrected the format of reference #27.

Reviewer #4 and 5 (It appears that Reviewer #4 and #5 are same.)

Good review-useful for scientists and clinicians who are interested in gene therapy. The authors may also include a section compiling the existing data on HGD, comparing the efficiency of different studies (in the literature on HGD). This may inturn be compared with the efficiency of various other gene delivery systems (lentivirus, retrovirus, AAV etc). A table would be useful.

Response: We are grateful to the reviewer for the positive comments, high scores, and for recognizing the significance of our work. As an only one clinical trial has been conducted to date using HGD, which was actually not with preferable conditions, there is no data comparable to the effect of AAVs. We have added the description regarding these points (page 15, line 4).