

May/02/2016

NAME OF JOURNAL: World Journal of Gastroenterology

MANUSCRIPT NO: 25893

Manuscript Type: Topic Highlight

We would like to thank you and the reviewers of “*World Journal of Gastroenterology*” for taking the time to review our article. We made some corrections in the manuscript (Manuscript No_25893) after going over the reviewers’ comments. The corrections and revisions are listed on the following sheets.

We hope the revised manuscript will meet the requirement of the reviewers’ comments and be publishable to the “*World Journal of Gastroenterology*”.

Step 1. Please revise your manuscript according to the reviewers’ comments.

→ The manuscript has been revised according to reviewers’ comments (see below “Answers to Reviewers”).

Step 2. Please update the manuscript according to the Guidelines and requirements for Manuscript Revision-Topic Highlight.

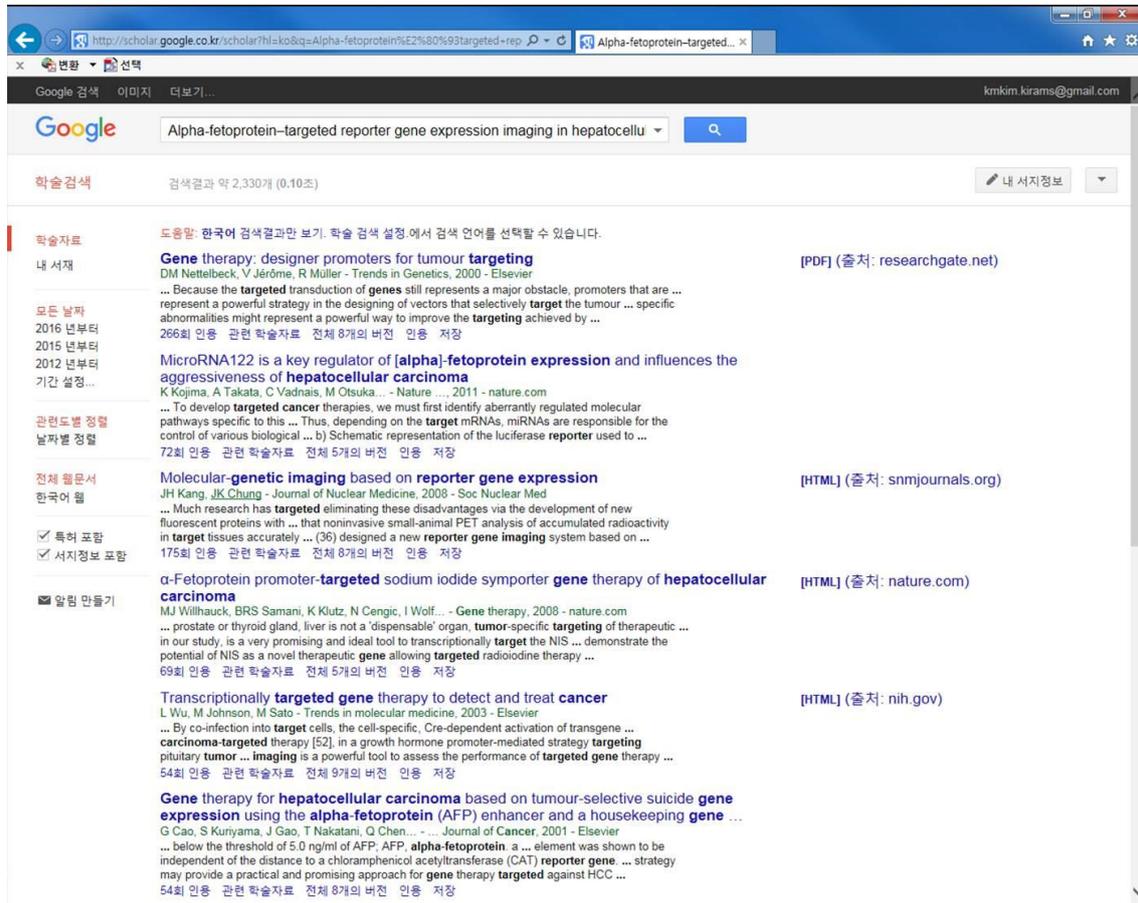
→ The manuscript has been edited including expansion of abstract section (“The current mouse ~ or drug treatment.”) according to the Guidelines and Requirements for Manuscript Revision-Topic Highlight.

Step 3. Please provide an Audio Core Tip.

→ Audio Core Tip has been performed and submitted.

Step 4. Please subject the manuscript to *CrossCheck* analysis and the final title to Google Scholar search, and store screenshot images of the results.

→ The final title has been checked using Google Scholar (attached screenshot).



→ The highest similarity is 2% with www.wjgnet.com.

The screenshot displays the iThenticate web interface. The document being analyzed is titled "Alpha-fetoprotein-targeted reporter gene expression imaging in hepatocellular" by Kwang Il Kim. The analysis shows 5205 words, 63 matches, and 37 sources, resulting in a 26% similarity score. A "Match Overview" sidebar on the right lists 11 matches, with the top match being from www.wjgnet.com (2% similarity). The main document text is partially visible, showing scientific content related to hepatocellular carcinoma models.

Match Number	Source	Words	Similarity
1	Internet (www.wjgnet.com)	64 words	2%
2	Internet (www.ncbi.nlm.nih.gov)	64 words	2%
3	Internet (spandidos-publications.com)	57 words	2%
4	CrossCheck ("Proceedings of the World Molecular Imaging Congress 2013, Savannah, Georgia, September 18-21, 2013", Molecula)	53 words	2%
5	CrossCheck (Park, J.H. "Non-invasive monitoring of hepatocellular carcinoma in transgenic mouse with bioluminescent imaging", C)	46 words	2%
6	Internet (office.wjgnet.com)	41 words	2%
7	Internet (jnm.snmjournals.org)	36 words	1%
8	Internet (www.spandidos-publications.com)	29 words	1%
9	CrossCheck (Nelson Fausto. "Mouse Models of Hepatocellular Carcinoma", Seminars in Liver Disease, 02/2010)	21 words	1%
10	CrossCheck (Kim, Kwang Il, Yong Jin Lee, Tae Sup Lee, Inho Song, Gi Jong Cheon, Sang Moo Lim, June-Key Chung, and Joo Hy)	18 words	1%
11	Internet (edoc.lib.uni-muenchen.de)	17 words	1%

Step 5. Please provide the files related to academic rules and norms.

→ Conflict-of-interest statement is included in this article.

Step 6. Please provide the approved grant application form(s) or funding agency copy of any approval document(s)/letter(s).

→ Detailed grant numbers from Korea government are included in this article.

Step 7. Please revise the language of your manuscript.

→ The manuscript has been revised and submitted after language editing service.

Step 8. Please sign the Copyright Assignment form.

→ The Copyright Assignment form has been signed and submitted.

Step 9. Submit the revised manuscript and all related documents.

→ The authors submit the revised manuscript with related documents.

Responses to reviewers' comments

Reviewer 1

This manuscript was generally well written, however, I think the authors should consider to combine the sections of EXPERIMENTAL HCC MOUSE MODEL and AFP-TARGETED REPORTER GENE EXPRESSION-IMAGING IN HCC MODEL together. By classifying HCC models into three categories, they can be first described and then the studies based on them were stated.

→ Because AFP-targeted reporter gene expression imaging has been reported for two categories (xenograft and carcinogen-induced HCC) of three HCC model categories, sections of experimental HCC model and AFP-targeted reporter gene imaging is separated in this article.

Reviewer 2

This article title with "Alpha-fetoprotein-targeted reporter gene expression imaging in hepatocellular carcinoma" should be published at WJGO. It is well documented and there is new new informations for us.

→ The authors thank reviewer's comment.

Reviewer 3

The authors reviewed several HCC animal models, focusing on AFP-targeted reporter gene expression imaging. The authors think AFP-targeted reporter gene expression imaging can provide the information about hepatocarcinogenesis. The AFP-targeted reporter gene expression imaging has the potential to be applied for the detection of AFP-expressing HCC tumors and screening of increased/decreased AFP levels due to disease or drug treatment. The authors review a lot of publication. However, they should provide more information to support their conclusion.

1. The bioluminescent signal was detected during the early stage of DEN-induced HCC prior to neoplastic transformation. Thus, how do we know the timing of malignant

transformation? The ideal model is that no gene expression before the malignant transformation and gene expression is detected only after malignant transformation. Please comment.

→ The authors agree with reviewer's comment. In this article, we described the molecular imaging system in which reporter gene expression is turned on only followed by AFP expression. If we want to evaluate the timing of malignant transformation, we first have to secure the specific biomarkers for malignant transformation.

2. The whole review does not touch upon the clinical application. Please provide some information to support or speculate the idea that such molecular imaging can be applied clinically.

→ According to reviewer's suggestion, we added the some clinical application data in "Introduction" section ("Because HSV1-tk ~ has been reported") and 2 references(8, 9).

8 Jacobs A, Voges J, Reszka R, Lercher M, Gossmann A, Kracht L, Kaestle C, Wagner R, Wienhard K, Heiss WD. Positron-emission tomography of vector-mediated gene expression in gene therapy for gliomas. *Lancet* 2001; **358**(9283): 727-729 [PMID: 11551583 DOI: 10.1016/S0140-6736(01)05904-9]

9 Penuelas I, Mazzolini G, Boan JF, Sangro B, Marti-Climent J, Ruiz M, Ruiz J, Satyamurthy N, Qian C, Barrio JR, Phelps ME, Richter JA, Gambhir SS, Prieto J. Positron emission tomography imaging of adenoviral-mediated transgene expression in liver cancer patients. *Gastroenterology* 2005; **128**(7): 1787-1795 [PMID: 15940613 DOI: 10.1053/j.gastro.2005.03.024]

3. Sensitivity is an issue that should be discussed on molecular imaging. Do these papers discuss about the sensitivity? Any data of comparing molecular imaging to current standard imaging modality, such as CT/ MRI?

→ Sensitivity of molecular imaging methods is described in "Introduction" section. We added one reference (6) for comparison of molecular imaging methods including sensitivity.

6 Massoud TF, Gambhir SS. Molecular imaging in living subjects: seeing fundamental biological processes in a new light. *Genes Dev* 2003; **17**(5): 545-580 [PMID: 12629038 DOI: 10.1101/gad.1047403]