Format for ANSWERING REVIEWERS

Dear Editor,

Please find attached files of revised manuscript in word format (file name: 14014-Review.doc).

Title: Disease control by treatment targeting P-glycoprotein on lymphocytes in patients with rheumatoid arthritis

Author: Shizuyo Tsujimura and Yoshiya Tanaka

Name of Journal: *World Journal of Experimental Medicine*

ESPS Manuscript NO: 14014

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:

Reviewer 00505881

We appreciate the concern of the reviewer and recommendations for improving our presentation by adding new descriptions to confirm our findings.

This is a very well written report about the P-glycoprotein (P-gp) on lymphocytes which is a promising marker of drug resistance and a suitable target to prevent drug resistance in patients with active rheumatoid arthritis (RA). Because drug therapy is still the main form of RA treatment, and lymphocyte-based drug resistance is an important clinical problem, this report suggest that P-gp overexpression is a good marker for the use of P-gp competitors, and for application of biological agents in RA patients. This review would be a good addition to the journal.

Thank you for your estimation.

Minor comments: 1. A structure diagram of P-gp on lymphocyte under healthy and RA conditions will be helpful.

As recommended by the reviewer, we added a figure (newly created Figure 3) in which we assessed the expression of P-gp on lymphocytes in RA patients and healthy subjects and the relationship between clinical responsiveness to treatments and the expression levels of P-gp on lymphocytes. The levels of P-gp expression on lymphocytes were significantly high in patients with inadequate response to at least two DMARDs or one DMARD and corticosteroids for at least 2 years. The above information appears on page 6, line 7-15 and the new Figure 3 of the revised manuscript.

Minor comments: 2. Because there is no a Material and Method section, the authors may add

sources where the reagents came from, e.g., Abs of anti-P-gp and anti-CD19.

According to reviewer's suggestion, we have added reagent sources in Figure legends of Figure 1 and 3.

Reviewer 00458932

We appreciate the concern of the reviewer and recommendations for improving our presentation by adding new descriptions to confirm our findings.

It is a well-written manuscript. Few points to consider: In the Table: colchicines.Change to colchicine salphasalazine. Change to sulfasalazine azathioprine. Change to: azathioprine

We thank the reviewer for bringing these errors to our attention. We corrected these errors in the revised manuscript (Table).

Line 210: Overexpression of P-gp on pathogenic lymphocytes is induced by activation of lymphocytes by various stimuli. Change to: Overexpression of P-gp is observed on activated lymphocytes leading...

According to the suggestion, we changed the relevant description.

Editor-in-Chief

We appreciate the concern of the reviewer and recommendations for improving our presentation by adding new descriptions to confirm our findings.

The authors revised the manuscript after referring to the reviewers' comments. However, the following problems still remained:
(1) The authors cited 30 references. In these references, only 2 references were published in 2010. Other references were mainly published before 2000. Is it possible to cover new information? It is difficult to update information based on these old manuscripts.

As pointed out by the reviewer, we reviewed considerably before-published references and carefully updated it in appropriate references. The updated references are reference 1, 2, 8-10, 12, 18, 21-23, 28 and 29.

(2) Figure 2 is useful to understand the relationship of P-glycoprotein and drug resistance in rheumatoid arthritis. Is it the original figure for this manuscript? If it is not, an appropriate reference should be cited. Even if the authors developed it by themselves for previous manuscripts, it should be cited.

Figure 2 is the original figure for this manuscript.

(3) Although there was not mistaken grammatically, several sentences may be revised more fluently.

According to reviewer's suggestion, our revised manuscript has received the proofreading by the native speaker.

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

Sincerely Yours,

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