

## Format for ANSWERING REVIEWERS

October 10, 2014

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.

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

Sincerely Yours,

Yoshiya Tanaka, MD, PhD,  
Professor and Chairman  
The First Department of Internal Medicine, School of Medicine  
University of Occupational and Environmental Health, Japan  
1-1, Iseigaoka, Yahata-nishi Kitakyushu 807-8555 Japan