

Format for ANSWERING REVIEWERS



July 11, 2014

Dear Editor,

Please find enclosed our revised manuscript in Word format (file name: 11989-review.doc).

Title: Searching for a treatment for Alport syndrome using mouse models

Author: Kan Katayama, Shinsuke Nomura, Karl Tryggvason, Masaaki Ito

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 11989

The manuscript has been improved based on the suggestions from the reviewers, including the following changes:

1. The format has been updated, and the revised file is named "11989-review".
2. Revisions have been made based on the reviewers' comments and suggestions. All modifications are indicated in red in the revised manuscript.

(1) Responses to reviewer 00503252:

The following sentence was added based on the reviewer's comments:

Treatment with an ACE inhibitor reduced the levels of transforming growth factor-beta 1 (TGF- β 1) and connective tissue growth factor (CTGF) more effectively than did treatment with an ARB, which might explain the different effects between ACE inhibitors and ARBs, because TGF- β 1 was associated with the renal disease progression in Col4a3 -/- mice.

The following sentence was removed:

This was because the ACE inhibitor could block both the AT1 and AT2 receptors, while the ARB blocked only the AT1 receptor.

“Distal tubular membranes” was corrected to “distal tubular basement membranes”.

(2) Responses to reviewer 00503255:

1. The following sentences were added based on the reviewer's comments:

“...which was associated with increased interstitial fibrosis. This dual effect might explain why MMPs played a pathogenic role in the early stage, although they played a protective role in the late stage in the Col4a3 -/- mice [32].

2. The following sentence was added in response to the reviewer's comments:

The mechanism by which irradiation improved the survival remains to be clarified, since radiation itself is associated with numerous effects.

3. The reference style was corrected to fit the Instructions for Authors.

(3) Responses to reviewer 00503179

1. The abstract was modified according to the reviewer's comments.

The following sentence was deleted from the Abstract because it described human patients:

"and a randomized prospective clinical trial is ongoing based on the results of an observational study in Alport patients."

2. In the Introduction section, the following sentence was added based on the reviewer's comments:

The purpose of this review is to summarize the current knowledge that has been found by using mouse models of Alport syndrome.

3. The Conclusion section was rewritten, and the description about human patients, which was not relevant to the present review, was removed according to the reviewer's comments. The revised conclusion is as follows:

At present, there is no treatment available that can cure AS, and symptomatic renal protective therapies are the mainstay of treatment for AS. In connection with the search for

a treatment using Alport mice, ACE inhibitors were found to be the most promising therapeutic drugs as first-line therapy. This is a good example of the use of these mice, which has led to a double-blind, randomized, placebo-controlled, multicenter EARLY PRO-TECT Alport trial [52]. BMT therapy is also promising, but is still controversial, given the fact that BMT itself is invasive [53]. Other therapeutic agents that have been proven effective in AS mouse models should be considered as the next options for clinical trials in patients with Alport syndrome.

3. The references and typesetting were corrected according to the Instructions for Authors.

Thank you again for considering our manuscript for publication in the *World Journal of Nephrology*.

Respectfully yours,

A handwritten signature in cursive script that reads "Kan Katayama".

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