

## Thank you for your manuscript submission - Leprosy Review

Lepra-RVT Review Management System <lepra@review.rivervalleytechnologies.com>

Sel 12/10/2021 17.04

Kepada: Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Dear Dr Renni Yuniati,

The paper entitled SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction has been submitted by Renni Yuniati and will be given full consideration for publication in Leprosy Review.

Your manuscript ID is LEP-2021-094

Please quote this paper number in all correspondence with this office.

You can view the status of your paper at any time by logging in to <https://lepra-review.rivervalleytechnologies.com/> and going to My Submissions. Please also take the time to make sure your contact details are up-to-date by clicking your name on the top right of the page.

Thank you for your interest in Leprosy Review.

Regards,

Editorial Office

Leprosy Review

Leprosy Review is published by Lepra, and is a peer reviewed journal which adheres to international ethical guidelines and publishing standards. When submitting an article or reviewing for the journal, your name, email and other contact details will be captured and retained by the journal exclusively for the purposes of publication, and will not be shared or used except for this purpose. If you have any queries about Lepra's data protection policies, please contact [lepra@lepra.org.uk](mailto:lepra@lepra.org.uk)

## LEP-2021-094 - Revise and resubmit

Lepra-RVT Review Management System <lepra@review.rivervalleytechnologies.com>

Sel 30/11/2021 16.49

Kepada: Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Dear Dr Renni Yuniati,

LEP-2021-094

SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction

Thank you for submitting your paper to Leprosy Review.

The peer review process is now complete and the conclusion is that, while the paper is relevant and potentially worthy of publication, significant revisions are needed. My decision is therefore to provisionally accept your paper subject to revisions.

The comments from the reviewers and the Handling Editor are given at the foot of this email. Please make sure that you address all the comments when revising the manuscript. It will be most helpful if you also answer them point-by-point in a covering letter, including your response to any comments with which you disagree.

When you have completed your revisions please:

- Upload your revised paper in Word or other source file format. Note that figures should be uploaded separately as image files and will be used as supplied and that these should therefore be of high quality.
- Upload your covering letter, giving your response to the reviewer comments, stating what you have changed and revised.
- To upload your revised paper please log onto <https://lepra-review.rivervalleytechnologies.com/>. Enter the Author Centre, where you will find your original paper in the 'Awaiting revision' section.
- You must click "Start revision" at the head of the page.
- Please delete the original files and upload your revised article and the covering letter. You need to generate a PDF as you did with the original submission.
- Please add your comments for the editor.
- When you have finished, please click the "resubmit article" button at the foot of the page.

Please note that, in order to publish your paper as quickly as possible, we ask that you submit the revision of your paper by 05-01-2022. I look forward to receiving your revised version.

Yours sincerely,

Paul Saunderson

Editor in Chief, Leprosy Review

\*\*\*\*\*

### COMMENTS

#### Editor's Comments

##### -Comments to Author

Please make the suggested revisions. English grammar will be checked later, so don't worry too much about that.

#### Handling Editor's comments

##### -Comments to the author

In the manuscript entitled " SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction" , authors demonstrated the distribution of SUMO-1, SUMO-2/3/4, S100b and Collagen-1 distribution in the nerve lesions of leprosy cases in reversal reactions. Although this is an association study, it also presents the basic pathology around host

mediators of nerve damage and inflammation in tissue fibrosis resulting from reversal reactions. I would recommend the publication of this manuscript with minor corrections as stated below: 1. The manuscript needs to be thoroughly revised for grammatical and sentence construction errors. 2. All of the comments of the peer reviewers are addressed.

### **Reviewers' comments**

**-Please leave your comments for the authors**

#### **#1 Submitted by: Reviewer 1**

The authors have evaluated the expression levels of SUMO and other proteins involved in the the development of fibrosis in neural lesion of patients with leprosy through immunohistochemistry and immunodoublestaining methods. The study was presented in a well structured way.

Specific points:

Typo errors and english language (tense) should be corrected for example epitheloid is epithelioid. Authors should review the whole manuscript to get rid of these errors

#### **#2 Submitted by: Reviewer 2**

1. How were the expression levels for each of these markers calculated?
2. Were the expression levels mentioned by authors for each of the markers based only on the no. of cells found or something else? Expression levels measured through what?
3. Were any expression studies conducted through RT PCR?

\*\*\*\*\*

Leprosy Review

## Extension of deadline

Lepra-RVT Review Management System <lepra@review.rivervalleytechnologies.com>

Sen 17/01/2022 16.23

Kepada: Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Dear Dr Renni Yuniati,

Thank you for contacting us and requesting an extension to your deadline. It has now been extended to 31-01-2022.

Follow the below URL to perform your task:

<https://lepra-review.rivervalleytechnologies.com/journal/lpr/view-article?JmFydGJjbGVfaWQ9NDlwJnN0YXR1c19pZD0xNzM3>

Yours sincerely,

Paul Saunderson

Editorial Office

Leprosy Review

Leprosy Review is published by Lepra, and is a peer reviewed journal which adheres to international ethical guidelines and publishing standards. When submitting an article or reviewing for the journal, your name, email and other contact details will be captured and retained by the journal exclusively for the purposes of publication, and will not be shared or used except for this purpose. If you have any queries about Lepra's data protection policies, please contact [lepra@lepra.org.uk](mailto:lepra@lepra.org.uk)

## Leprosy Review: Article Accepted

Lepra-RVT Review Management System <lepra@review.rivervalleytechnologies.com>

Sen 11/04/2022 15.56

Kepada: Rennu Yuniati <renniyuniati@lecturer.undip.ac.id>

Dear Dr Rennu Yuniati,

LEP-2021-094.R1

SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction

Thank you for submitting your paper to Leprosy Review. I am pleased to say that I found your paper interesting and worthy of publication. My decision is therefore to accept your paper as it stands.

Your article will now enter production, so you can expect a proof to check in a few weeks. Please look out for the email notification so there are no delays at this stage.

Thank you again for an interesting article, and I hope you will consider submitting future research to the journal

Yours sincerely,  
Paul Saunderson

Editor in Chief

Leprosy Review

**BIs: BIs: Revised proof - Ir2021094**

Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Rab 01/06/2022 11.45

Kepada: Uday <uday@rivervalleytechnologies.com>;psaunderson@leprosy.org <psaunderson@leprosy.org>

Cc: lepra@rivervalleytechnologies.in <lepra@rivervalleytechnologies.in>;lepra@lepra.org.uk <lepra@lepra.org.uk>

Dear Mr. Paul,

Thank you so much for your confirmation.

Regards,

Renni Yuniati

---

**Dari:** Paul Saunderson <psaunderson@gmail.com> atas nama Paul Saunderson <psaunderson@leprosy.org>

**Dikirim:** Minggu, 29 Mei 2022 19.00

**Kepada:** Renni Yuniati <renniyuniati@lecturer.undip.ac.id>; Uday <uday@rivervalleytechnologies.com>

**Cc:** lepra@rivervalleytechnologies.in <lepra@rivervalleytechnologies.in>; lepra@lepra.org.uk <lepra@lepra.org.uk>

**Subjek:** Re: BIs: Revised proof - Ir2021094

Dear Dr Yuniati,

It will appear in the June issue, in a few days time!

Best wishes,

Paul

**Paul Saunderson, MD**

Senior Technical Adviser, The AIM Initiative

Editor, Leprosy Review | <https://leprosyreview.org/>

**American Leprosy Missions | The AIM Initiative**

Østremvegen 49, 6013 Ålesund, Norway

[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org) | [www.leprosy.org](http://www.leprosy.org)

Phone: +47 4807 8869 | [psaunderson@gmail.com](mailto:psaunderson@gmail.com)

On 5/29/2022 1:03 PM, Renni Yuniati wrote:

Dear Mr. Paul Sanderson and Mr. Uday,

First of all, thank you for accepting our article and confirming the proof of our article. The submission process was straightforward and flawless, we really appreciated it.

We would like to confirm when will our article be online? And when we checked the DOI, the DOI web site says that it is not registered -- is that normal?

Thank you very much for your attention.

Regards,

Renni Yuniati

---

**Dari:** Uday <[uday@rivervalleytechnologies.com](mailto:uday@rivervalleytechnologies.com)>

**Dikirim:** Senin, 09 Mei 2022 11.59

**Kepada:** Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)>

**Cc:** [renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com) <[renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)>; Paul Saunderson <[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org)>; [lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in) <[lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)>

**Subjek:** Re: Revised proof - Ir2021094

Dear Dr. Renni

Thanks for the confirmation.

Wishign you a nice day!

Regards

--

Uday

**River Valley Technologies**

On Fri, May 6, 2022 at 10:48 PM Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)> wrote:

Dear Mr. Uday, Mr. Paul Sanderson and Editorial Board of Leprosy Review,

Thank you for the article proof. I think the proof is already correct and there are no further amendments to the Proof.

Regards,  
Renni Yuniati

---

**Dari:** Uday <[uday@rivervalleytechnologies.com](mailto:uday@rivervalleytechnologies.com)>

**Dikirim:** Jumat, 06 Mei 2022 16.39

**Kepada:** Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)>; [renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)  
<[renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)>

**Cc:** Paul Saunderson <[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org)>; [lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)  
<[lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)>

**Subjek:** Revised proof - Ir2021094

Dear Dr. Renni Yuniati

Please find revised proof of your article attached herewith the email. Please mark any further changes on the attached PDF, so that we shall make the amendments in the source file and finalize the article for publication.

Thanks and regards

--

Uday

**River Valley Technologies**

*Accelerating the Communication of Research*

**BIs: BIs: Revised proof - Ir2021094**

Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Rab 01/06/2022 11.45

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Editor, Leprosy Review | <https://leprosyreview.org/>

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Phone: +47 4807 8869 | [psaunderson@gmail.com](mailto:psaunderson@gmail.com)

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Regards,

Renni Yuniati

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**Dikirim:** Senin, 09 Mei 2022 11.59

**Kepada:** Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)>

**Cc:** [renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com) <[renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)>; Paul Saunderson <[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org)>; [lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in) <[lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)>

**Subjek:** Re: Revised proof - Ir2021094

Dear Dr. Renni

Thanks for the confirmation.

Wishign you a nice day!

Regards

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Uday

**River Valley Technologies**



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Dear Mr. Uday, Mr. Paul Sanderson and Editorial Board of Leprosy Review,

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Renni Yuniati

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**Dari:** Uday <[uday@rivervalleytechnologies.com](mailto:uday@rivervalleytechnologies.com)>

**Dikirim:** Jumat, 06 Mei 2022 16.39

**Kepada:** Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)>; [renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)  
<[renniyuniati@yahoo.com](mailto:renniyuniati@yahoo.com)>

**Cc:** Paul Saunderson <[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org)>; [lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)  
<[lepra@rivervalleytechnologies.in](mailto:lepra@rivervalleytechnologies.in)>

**Subjek:** Revised proof - Ir2021094

Dear Dr. Renni Yuniati

Please find revised proof of your article attached herewith the email. Please mark any further changes on the attached PDF, so that we shall make the amendments in the source file and finalize the article for publication.

Thanks and regards

--

Uday

**River Valley Technologies**

*Accelerating the Communication of Research*

## BIs: Leprosy Review 2021-094.R1

Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

Sab 16/04/2022 12.25

Kepada: psauderson@leprosy.org <psauderson@leprosy.org>

📎 1 lampiran (4 MB)

LR-2021-094.R1 Histopathology of nerve damage - Yuniati\_PS.docx;

Dear Mr. Paul,

Thank you for the notification. We would like to amend the paper according to what you've found, as follows:

1. The "Figure 6" was mistyped; it should be Figure 5.
2. The citation 12-16 has been added to the Reference List.

Thank you for your cooperation.

Regards,  
Renni Yuniati

---

**Dari:** Paul Saunderson <psauderson@gmail.com> atas nama Paul Saunderson <psauderson@leprosy.org>

**Dikirim:** Selasa, 12 April 2022 13.48

**Kepada:** Renni Yuniati <renniyuniati@lecturer.undip.ac.id>

**Subjek:** Leprosy Review 2021-094.R1

Dear Renni,

Our production team has noted missing references and a Figure in your paper:

References 12--16 and Figure 6 are cited on page 11 of the manuscript, but these are not provided.

I don't know why this was not noted before, as I see that even in earlier versions of the paper, these are also missing.

Can you please send these missing items by email, and I can insert them.

Many thanks,

Paul

**Paul Saunderson, MD**  
Senior Technical Adviser, The AIM Initiative  
Editor, Leprosy Review | <https://leprosyreview.org/>

**American Leprosy Missions | The AIM Initiative**  
Østremesvegen 49, 6013 Ålesund, Norway  
[psauderson@leprosy.org](mailto:psauderson@leprosy.org) | [www.leprosy.org](http://www.leprosy.org)  
Phone: +47 4807 8869 | [prsaunderson@gmail.com](mailto:prsaunderson@gmail.com)

On 4/4/2022 10:27 AM, Renni Yuniati wrote:

Dear Paul,

Thank you for the kind response and clarification. We would like to thank you for the revision list too. We will reply the revision soon.

Regards,  
Renni Yuniati

---

**Dari:** Paul Saunderson <[prsaunderson@gmail.com](mailto:prsaunderson@gmail.com)> atas nama Paul Saunderson <[psauderson@leprosy.org](mailto:psauderson@leprosy.org)>

**Dikirim:** Senin, 28 Maret 2022 15.33

**Kepada:** Renni Yuniati <[renniyuniati@lecturer.undip.ac.id](mailto:renniyuniati@lecturer.undip.ac.id)>

**Subjek:** Re: Trs: Thank you for your manuscript submission - Leprosy Review

Dear Renni,

Thank you for letting me know about the poster. I sent you a response a month ago (see below), but I have not heard back from you about this. If you want to go ahead with publication in Leprosy Review, please send a revised paper directly to me by email. If it goes forward for publication, we can make a footnote to say that the poster is online.

Many thanks,

Paul

**Paul Saunderson, MD**  
Senior Technical Adviser, The AIM Initiative  
Editor, Leprosy Review | <https://leprosyreview.org/>

**American Leprosy Missions | The AIM Initiative**  
Østremnsvegen 49, 6013 Ålesund, Norway  
[psaunderson@leprosy.org](mailto:psaunderson@leprosy.org) | [www.leprosy.org](http://www.leprosy.org)  
Phone: +47 4807 8869 | [prsaunderson@gmail.com](mailto:prsaunderson@gmail.com)

On Feb 23rd, 2022, Paul Saunderson, Editor, wrote to you:

I'm writing about your paper "SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction."

Revision was previously advised and the revised paper has been submitted. It should go forward for acceptance soon.

However, there are four remaining problems, which I think should be fairly easy for you to correct:

1. The current title is a bit overwhelming for the general reader. I would prefer a more general title, such as "The histopathology of nerve damage in leprosy."
2. The Methods section is far too long - currently 4 pages! I would have thought this could be reasonably summarized in half a page, with references for the specific steps in the laboratory work.
3. One point that seems inconsistent to me is that you say that S100b is raised in the RR patients (Table 2), but the penultimate paragraph of the Discussion says that S100b is a sign of neural integrity and is higher when the nerve structure is more 'normal'. This needs to be clarified.
4. The last sentence of the Conclusion "These results show that the nerve damage in patients with reversal reaction is more severe than the leprosy patients without reversal reaction." is very weak - pretty obvious to clinicians! I suggest something like "This study identifies a number of different histological indicators of nerve involvement during episodes of reversal reaction, which should be studied in more detail."

If you are happy to make these changes, please send the revised paper to me by email and I will put it into the system, after a final copy edit

On 3/27/2022 12:06 PM, Renni Yuniati wrote:

Dear Editorial Office of Leprosy Review,

We would like to contact you regarding our article entitled "SUMO May be Involved in TGF- $\beta$ 1 Signaling in Neural Lesion of Leprosy Reversal Reaction" (manuscript ID: LEP-2021-094.R1).

We would like to let you know that our article has been previously submitted as an E-poster in 2019 World Dermatology Congress, albeit in a reduced and incomplete version compared to the current version that we submitted in your esteemed Journal.

The aforementioned E-poster has also been published in the WCD 2019 Website (Google indexed) as an abstract. The screenshot of the Google index page and the result are as follows:



Google

M

sumo may be involved in tgf

Semua

Gambar

Berita

Belanja

Video

Maps

E

<https://www.wcd2019milan-dl.org> > ... PDF

## SUMO May be Involved in TGF- $\beta$ 1 Signalling in Neural Lesion of Leprosy ...

SUMO MAY BE INVOLVED IN TGF- $\beta$ 1. SIGNALLING IN NEURAL LESION OF ... Background: Neural lesion in leprosy is characterized by chronic inflammation which can.

<https://www.ncbi.nlm.nih.gov> > ...

## The SUMO System and TGF $\beta$ Signaling Interplay in Regulation of Epithelial ...

oleh A Chanda · 2018 · Dirujuk 18 kali — The secreted protein Transforming Growth Factor beta (TGF $\beta$ ) is a potent inducer ... Under certain conditions, several SUMO molecules may get ...

<https://pubmed.ncbi.nlm.nih.gov> > ...

## The type I TGF-beta receptor is covalently modified and regulated by sumoylation

oleh JS Kang · 2008 · Dirujuk 160 kali — Often associated with nuclear and perinuclear proteins, such as transcription factor...

<https://www.researchgate.net> > ...

## (PDF) SUMO Proteins are not Involved in TGF- $\beta$ 1-induced, Smad3/4-mediated ...

12 Des 2021 — SUMO Proteins are not Involved in TGF- $\beta$ 1-induced, Smad3/4-mediated Coreline  $\alpha$  Transcription, but

The abstract has been attached to this email and can also be downloaded at the original site using this URL: <https://www.wcd2019milan-dl.org/abstract-book/documents/late-breaking-abstracts/22-infectious-diseases/sumo-may-be-involved-in-123.pdf>, or can be seen in the screenshot below:

**ABSTRACT BOOK**  
LATE-BREAKING ABSTRACTS



24<sup>TH</sup> WORLD CONGRESS  
OF DERMATOLOGY  
MILAN 2019

A new ERA for global Dermatology  
10 - 15 JUNE 2019  
MILAN, ITALY

INFECTIOUS DISEASES (BACTERIAL, FUNGAL, VIRAL, PARASITIC, INFESTATIONS)

## **SUMO MAY BE INVOLVED IN TGF- $\beta$ 1 SIGNALLING IN NEURAL LESION OF LEPROSY REVERSAL REACTION**

Renni Yuniati<sup>(1)</sup> - Wibi Riawan<sup>(2)</sup> - Aris Widayati<sup>(3)</sup>

Diponegoro University, Dermatology And Venereology, Semarang, Indonesia<sup>(1)</sup> - Brawijaya University, Biochemistry And Biomolecular, Malang, Indonesia<sup>(2)</sup> - Brawijaya University, Neurology, Malang, Indonesia<sup>(3)</sup>

**Background:** Neural lesion in leprosy is characterized by chronic inflammation which can develop into fibrosis causing neural damage which remains to be a burden in leprosy because of its ability to cause deformity and permanent disability. Transforming growth factor  $\beta$  is a key growth factor in the development of tissue fibrosis. SUMOylation is a post-translational modification and as a result, regulate TGF- $\beta$  response.

**Objective:** The aim of this study was to evaluate the in vivo expression of Schwann cell TGF- $\beta$ 1, SUMO 1, and SUMO 2/3/4 in the nerve biopsy of leprosy patients.

**Materials and Methods:** This study comprised 50 people consisted of 28 leprosy patients with reversal reactions (RR) and 22 leprosy patients without RR as control, conducted in Dermatovenereology outpatient clinic of Donorojo Hospital, Jepara, Indonesia and Health Department of Jepara District, Indonesia from June to August 2014. The patients were 20-60 years old and have signed informed consent according to the standard from Airlangga University Ethics Committee. A punch biopsy was done in the lesion area or forearm extensor.

**Results:** Immunohistochemistry staining showed an increasing distribution of mononuclear cells in the perineurium area of RR patients. The distribution of TGF- $\beta$ 1 was increased in the perineurium area s100b positive in RR patients. There was an increased distribution of collagen-1, SUMO-1, and SUMO 2/3/4 in the positive TGF- $\beta$ 1 perineurium area in RR patients compared to those without reversal reaction.

**Conclusion:** The increased expression of SUMO-1 and SUMO 2/3/4 in the neuritis area of leprosy patients indicated there was a transcription process regulation mediated by TGF- $\beta$ 1 signaling by SUMO-1 and or SUMO 2/3/4. SUMO may be involved in TGF- $\beta$ 1 signaling in the neural lesion of leprosy reversal reaction.



24<sup>TH</sup> WORLD CONGRESS  
OF DERMATOLOGY  
MILAN 2019



International League  
of Dermatological Societies  
Skin Health for the World



Società Italiana di Dermatologia  
(SIDeMAT)

Should there any issues regarding the publication of our article, feel free to contact us again.

Regards,  
Renni Yuniati