Reviewer's report

Title: Y-27632 is associated with corticosteroid-potentiated control of pulmonary remodeling and inflammation in guinea pigs with chronic allergic inflammation

Version: 1 Date: 30 December 2014

Reviewer: William Gerthoffer

Reviewer's report:

General comments

The study provides some novel information on remodeling of the airway parenchyma and the airways of OVA sensitized guinea-pigs. Extending studies of Rho kinase inhibition to parenchymal structures and airways is a novel approach that has yielded useful new information on the cellular targets of rho kinase inhibition. The use of inhaled rho kinase inhibitor is a strength of the study. The efficacy of this dosing method as a single therapy and in combination with corticosteroids is encouraging. The data provides further proof of principle that rho kinase is a valid target for therapy of allergic asthma and that its mechanisms of action will include anti-remodeling effects via multiple downstream pathways. One of the weaknesses of the study is use of that guinea-pig model rather than a more state of the art mouse model (eg. HDM sensitized Balb/c).

Major

1. Some rationale should be provided for the sensitization protocol, and references cited that validate the approach. Since there are many allergen sensitization methods used in experimental asthma it is important to explain why this one was used, what the strengths are and what the limitations are.

2. Page 6, 1st paragraph. The last sentence needs to be revised. It seems the authors meant to suggest ROK inhibition would relax airway smooth muscle and REDUCE muscle tone, not elevate it.

3. Explain the rationale for treating with rho kinase inhibitor after the fifth inhalation exposure.

4. Were the investigators who conducted point count stereology blinded to the treatment groups?

5. Methods, provide manufacturer (or distributor) and catalog number for all antibodies used.

6. Add the number of animals/treatment group to the tables.

7. Discussion, page 29. The following sentence is inaccurate: “The isoprostanes contribute to smooth muscle contraction by acting through the tyrosine kinases Rho and Rho-kinase....”

Neither protein is a tyrosine kinase. Rho is a small G-protein and Rho kinase is a
Ser/threonine protein kinase.

8. Discussion, last 3 paragraphs. All that is said about NFkB is true but may or may not figure into this study. Only a simple correlation of NFkB signaling was observed along with numerous other inflammation markers. This section could be eliminated or reduced a single sentence hypothesizing that some effects of ROK inhibition may be mediated by changes in NFkB signaling.

Minor

1. It does not seem necessary to abbreviate “guinea pig”. The paper would be easier to read with fewer nonstandard abbreviations.

2. Page 3, last sentence is a run-on sentence. Divide the sentence into at least two different sentences. Are these results from refs 20 and 21?

3. Page 6, second paragraph, last sentence is a run-on sentence. Divide the sentence into at least two different sentences. The results of the previous are identical to those in the abstract.

4. How were the lungs fixed for morphometric analysis? The method states that they were pressurized (5 cm H2O) but what was the fixative and how was it delivered – via the airway or by immersion of the lungs?

5. En bloc is misspelled on page 10.

6. Discussion, pg. last sentence of first full paragraph – actin is missing.

7. There are numerous misspelled words in the References that should be corrected.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.