

Reviewer 1 v. 1

Comments to the Author

This study investigated the possibility to make simvastatin an inhalable drug for use against pulmonary hypertension and possibly other pulmonary conditions. It is an interesting study, but I have some concerns:

Major:

1. It can't be stated in the paper that it shows that "inhaled Sim is safe and effectively and efficiently treats PH". This statement is much too strong. You have problems with cell toxicity, and you can't state that you have found efficient treatment just because you see a difference in response to Ach.
2. I couldn't understand from the text for how long the rats were treated. Was it just one dose or repeated doses? It says 10 mg/kg/day. Would it be possible to show in this model how far out in the lung the particles reached? This would strengthen the paper significantly.
3. When was that BALF taken (how long after inhalation)? How many repeats of the ELISA for each rat? What is shown in the graph, one value for each rat? Please indicate in the figure whether the differences were significant.
4. The histology needs to be described in much more detail. How many sections were analyzed for each rat lung. How was inflammation etc evaluated? Blinded observer? How long after inhalation was the tissue taken out? Enough time to see possible damage or inflammation? It is not clear to me what you would like to show in the images in Fig 12 b. Why not show high magnification images of Sim inhaled lung vs control?
5. Not enough data is shown from the lamb model. Absolute pressure and PVR values should be shown and not only relative change (for both non-treated and treated controls and non-treated and treated lambs with PH). Would also be good to show this as scatterplots for the reader to see values for individual animals. I guess you also have a lot of other parameters, like for example systemic blood pressure and saturation. Why not show this?
6. Could you please comment on the drug concentration you expect to get in the lung? How close is it to the levels when you see toxicity in cell culture? How close is it to what would be seen with systemic administration?

Minor comments:

1. Figure 1: Not so well organized. Difficult to see the what the magnification is (the text is so small) and the scale bars are too small to see clearly. Would be better to show fewer images and to clearly mark what you would like to point the readers attention to.
2. Figure 4: Why show temperatures so close to each other for a (133 and 139) and different values for b (94 and 129)? Are the images comparable when the temperatures are so different? You mention that Raw Sim showed some thermal events before the main thermal event. Can you indicate this in the images? Is it possible to see?

3. Figure 7. Would be better to have the same scale on the y-axis for a and b.