Reviewer’s report

Title: NTP42, a novel antagonist of the thromboxane receptor, attenuates experimentally induced pulmonary arterial hypertension

Version: 0 Date: 21 Jan 2020

Reviewer: Fabrice Antigny

Reviewer's report:

Mulvaney and colleagues have studied the consequences of thromboxane receptor pharmacological inhibition (NTP42) in Monocrotaline-induced pulmonary hypertension. Authors found that preventive NTP42 treatment reduced the MCT-induced PH similarly to Sildenafil treatment. Although the results are very interesting, however this manuscript requires additional experiments or precisions.

Major comments:

1-As demonstrated by the low increase of mPAP, RVSP as well as Fulton index, in these Wistar-Kyoto rats, MCT induce not severe PH but very moderate PH.

Authors should discuss this point or insert a limitation part in their study. Or perform this pharmacological approach (NTP42 treatment) in more severe animal PH (may be another strain of rats or younger Wistar-kyoto rats).

I'm not familiar with Wistar-kyoto rats. Wistar-kyoto developed less severe than Wistar or Spragues Dawley?

2-Regarding the immunostaining presented in figure 1, it is very difficult to see the staining. Author should add more convincing staining!

Immunostaining is not quantifiable approach, and it could be very interesting to quantify the expression of TPa, TPb and IP by Western blot or Quantitative PCR at least.

3-Authors should also measure (thermo-dilution) or evaluated (echocardiography) the cardiac output. These experiments will determine if RV hypertrophy is adaptive or maladaptive?

4-Why NTP42 treatment had no consequence on RV remodeling while mPAP is reduced?
Thromboxane receptor are expressed in RV? TP expression are modified in RV from MCT animals? TP inhibition on RV cardiomyocytes could have pro-hypertrophic consequence?

5-NTP42 results are similar to the results obtain with sildenafil. I could be very interesting to combine NTP42+sildenafil treatment or use NTP42 in curative treatment.

6-How authors explain the Selexipag results (Fulton index)?
6-The introduction is too long! However, authors should add the actual new definition of PAH, and add additional paper to support their rational

7-The discussion is too too long. Please reduce.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
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