

Dear Editor,

We would like to thank for your comments and we expected that modifications of our manuscript will fulfill your recommendations.

Sincerely

Dr Rachel Marion-Letellier, PhD

Reply to reviewers

Reviewer#1

Thanks for your comments

- 1- Page 11, paragraph 5, sentence "...For example, SPECT is able to chronic inflammatory diseases".

Please revise the sentence.

As suggested, the sentence was modified as following: For example, SPECT is able to monitor chronic inflammatory diseases".

- 2- Page 12, paragraph 2; "...MRI... These techniques enable to quantify and characterize inflammatory processes." On the other hand the authors indicate that SPECT is relevant imaging technique that can target specific steps early in disease progression..."

As suggested by the reviewer#1, we now clarify the paragraph to offer a better comparison among anatomical vs functional imaging techniques. The text has been modified as following:

"Anatomical imaging techniques such as MRI enable to quantify and characterize inflammatory processes. These tools provide diagnostic elements concerning intestinal lesions in IBD. However, they did not highlight the molecular mechanisms behind the inflammatory processes. By contrast, SPECT is a molecular imaging technique leading to a better understanding of *in vivo* molecular signaling events and may open doors for real functional imaging of the bowel. "

- 3- The authors was not able to show a significant difference between control and TNBS groups for pixel max. They also did not show any significant association between SPECT parameters and COX-2 expression. These points should be explained.

The reviewer#1 is right. We did not find a significant difference for pixel max among groups but only a trend (P=0.06). We hypothesized that this absence of effect is due to a small sample size (10 rats/group) and the heterogeneity of TNBS-induced colitis model including patchy lesions. We modified the text as following:

"One limitation of our study was the small sample size with 10 rats per group. We also hypothesized that this absence of effect was also the result of the heterogeneity of TNBS-induced colitis model including patchy lesions {Charpentier, 2012 #597}. The absence of association between SPECT parameters and COX-2 expression was

also observed in one of our previous study. Indeed, we previously found that some MRI parameters such as maximal wall thickness were not correlated with COX-2 expression {Charpentier, 2012 #597} in the same acute colitis model. We used COX-2 as an inflammatory marker because its lack of basal COX-2 expression in normal tissue. Nevertheless, COX-2 is involved in angiogenesis processes and chronic inflammation and be more relevant in chronic colitis assessment. Indeed, we have previously shown that MRC criteria were associated with COX-2 expression in rats with chronic TNBS-induced colitis {Melchior, 2014 #699}. Evaluation of correlation between SPECT criteria and colon COX-2 expression required further evaluation in rats with chronic colitis. “

- 4- Page 13, paragraph 1; “...In IBD patients, SPECT approach is already investigated. Endoscopy remains the gold standard for IBD screening...” The authors should indicate the originality of their study compared to the existing literature.

While endoscopy can be used to identify intestinal inflamed lesions into the bowel wall, SPECT imaging is a molecular imaging technique (Neurath, 2015). Contrary to anatomical imaging techniques such as endoscopy, SPECT provides molecular insights in order to identify potential therapeutic targets or to better understand molecular inflammatory processes leading to intestinal inflammation (Neurath, 2015). The possibility to use specific tracer enables to highlight the cellular and molecular changes that take place in vivo beyond the anatomical lesions.