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RE: Revised manuscript field-of-vision entitled "Tryptophan: a gut microbiota-derived metabolite regulating inflammation"

Dear editor,

We would like to thank the reviewers for their careful and thoughtful review of our commentary entitled "Tryptophan: a gut microbiota-derived metabolite regulating inflammation" (World Journal of Gastrointestinal Pharmacology and Therapeutics ID 29407). Our manuscript has been modified following reviewers' advices and please find below a point-by-point reply to the reviewers' comments. We trust your reviewers will be pleased with our revised manuscript and thank you for re-evaluating it.

Thank you for considering our manuscript further,

Best Regards,

A handwritten signature in black ink, appearing to read "Lucie Etienne-Mesmin". The signature is stylized and includes a large flourish at the end.

Lucie Etienne-Mesmin, Ph.D.

## Point by point to reviewers' comments

- **Reviewer's code:** 03519163

This is a "Field of Vision" article written by Etienne-Mesmin et al., introducing a key recent publication just appeared in Nature Medicine regarding the role of tryptophan in regulation of intestinal inflammation. Overall, this is well written article that reviews key finding of the publication by Lamas et al, Nature Medicine 2016. The writing and structure of the manuscript are lucid and appropriate. The references cited are adequate.

*We thank the reviewer for his supportive comments.*

I have some minor concerns that listed below:

1. In the abstract, sentences starting from line 8, the authors described Card9 as "a gene encoding an adaptor protein involved in innate immune responses to intracellular pathogens through the activation of IL-22signaling pathway". However, Card9 is rather known as an adaptor molecule of Dectin-1, and therefore involved in recognition of fungi. I would recommend to rephrase this sentence.

*We thank the reviewer for his comment and this sentence has been modified accordingly in the revised version of the manuscript.*

2. The authors described functional impairment of the gut bacterial community in Card9<sup>-/-</sup> mice, and blunted IL-22 production by ILCs as a consequence of the bacterial dysbiosis. However, the role Card9 plays in regulation of the gut bacterial communities was not discussed. The authors should explain a potential mechanism of how Card9 controls the gut bacterial communities (presumably through regulation of fungal communities).

*We thank the reviewer for his comment and this sentence has been modified.*

- **Reviewer's code:** 03648086

Minor revisions:

1. Title: "microbiota-derived metabolites" should be "microbiota-catabolizing substrate"

*We think the term metabolite is more appropriate than substrate when referring to microbial products (see <sup>[1]</sup> Rooks and Garret, 2016 Nature Reviews Immunology).*

2. Accordingly in the Core tip: "a microbiota-derived metabolite" should be "a microbiota-catabolizing substrate."

*As addressed in the previous point, we think the termed metabolite is more appropriate (see <sup>[1]</sup> for review).*

3. Abstract: “Genetic wide association studies” should be “Genome-wide association studies”, which involves large-scale genome-wide screening of potential polymorphisms.

*We thank the reviewer for his comment and this term has been modified in the manuscript*

4. The last sentence in the first paragraph of Main text: consider re-phrase, it's sort of lengthy.

*We thank the reviewer for his comment and this sentence has been edited to make it clear for the reader.*

5. A new sentence would be necessary for the phrase on Page 5: “with such defects also correlating with CARD9 polymorphism.” For example: “These reductions also correlate with CARD9 polymorphism.” (although the significance is sort of borderline.)

*This sentence has been edited to make it clear for the reader.*

6. Following this phrase, the “seric” should be “serum” or “serumal”.

*We thank the reviewer for his comment. This sentence has been edited accordingly.*

#### **Reference cited**

1 Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nature reviews Immunology* 2016; **16**(6): 341-352 [PMID: 27231050 DOI: 10.1038/nri.2016.42]