**Author Response Letter to Reviewer Comments:**

**Name of Journal:** World Journal of Gastrointestinal Surgery

**Manuscript NO.:** 21748

**Column:** Review

**Title:** Intestinal Inflammation and the Diet: Is Food Friend or Foe?

**Authors:** Bryant W Megna, Patrick R Carney and Gregory D Kennedy

**Correspondence to:** Gregory D. Kennedy, Associate Professor, Vice Chairman of Quality, Associate Chief, Section of Colorectal Surgery, University of Wisconsin School of Medicine and Public Health - Department of Surgery, 600 Highland Avenue, K4/736 CSC Madison, WI 53792 U.S.A. (608) 263-2521 kennedyg@surgery.wisc.edu

**Reviewer codes:** 00037324, 00036023 and 02441672

**First decision:** 2015-11-06 11:08

**Scientific editor:** Jin-Lei Wang

---

November 13th, 2015

Dear Editor:

Enclosed, please find our revised manuscript entitled ***"Intestinal Inflammation and the Diet: Is Food Friend or Foe?"***. This manuscript is being submitted for consideration as a review article in *World Journal of Gastrointestinal Surgery*.

You will find a final manuscript with all revisions highlighted as well as two figures corresponding to this revised manuscript (in PowerPoint format). In this letter you will find a point-by-point response to each of the reviewer's concerns. We have completely followed the comments made by the reviewers and have carefully revised the manuscript.

We appreciate the thoughtful and positive reviews from the reviewers. We hope that the revised manuscript will now be suitable for publication, and thank you to the reviewers for their effort and time.

Sincerely yours,

Gregory D. Kennnedy, MD, PhD

University of Wisconsin Department of Surgery
Section of Colon and Rectal Surgery
600 Highland Avenue, K4/736 CSC
Madison, WI 53792
Tel: 608-263-2521
Fax: 608-265-8810
E-mail: kennedyg@surgery.wisc.edu

---

**Authors' Rebuttal to Reviewers' Comments:**
In the following we discuss the points raised by the reviewers and the changes in the manuscript to address these points. We appreciate these thoughtful comments, and hope that our responses and in particular our revisions have allowed this paper to achieve priority sufficient for publication in *World Journal of Gastrointestinal Surgery*.

**Reviewer Code: 00036023**
**Reviewer's Comments:** This paper focuses on interaction between certain dietary elements and the aryl hydrocarbon receptor (AHR). This is amongst many lines of inquiry into pathogenesis and therapy of IBD. While I cannot see any problems in the paper, their conclusions may be rather on-sided. Saying "Future directions of study must center on the isolated function of the aryl hydrocarbon receptor " is somewhat overstating the case.

**Authors' Response:** Thank you for your comments. We agree that the sentence in question was indeed overstating the current importance of the AHR as the primary avenue of study in the treatment of IBD. Also, we understand that it is imperative to explain the many potential mechanisms of IBD aside from the AHR. We have rewritten and softened portions of the conclusion to be more inclusive of other research directions as well as highlighting that the AHR is only one of many lines of inquiry.

**Revised Conclusion Section (with revisions highlighted):**

**CONCLUSION AND FUTURE DIRECTIONS**

The complex and often dangerous treatment of inflammatory bowel disease is a dilemma faced by gastroenterologists and colorectal surgeons alike. The intricate

inflammatory milieu of IBD presents many avenues for potential targets to attenuate the inherent autoimmunity of the condition. In order to better understand the role that dietary ligands of the AHR play in attenuating IBD, potential avenues of study should focus on the aryl hydrocarbon receptor as it pertains to intestinal barrier function, immune regulation, and inflammation. To achieve this, portions of the IBD phenotype would be isolated and measured under AHR stimulation by a dietary agonist such as I3C or DIM. Also, the binding affinities of these compounds to the AHR in an array of gastrointestinal tissues must be established in order to localize the cell and tissue types where these agents will achieve the most robust response. Another important line of inquiry is to delineate the molecular cross-talk between AHR stimulation and the numerous other pathways previously identified as those that drive IBD. More globally, tissue-specific AHR activity should be investigated in order to ascertain off target effects of treatment with a dietary AHR agonist. Finally, the most rigorous examination of these agents would be a randomized controlled trial of I3C or DIM for the treatment of IBD within the Phases set by the FDA. However, incorporation of dietary AHR ligands into human clinical studies demands a crystal clear picture put forth by exhaustive *in vitro* and *in vivo* murine models as to how these compounds exert their effects. Throughout these various investigations, it would remain important to delineate additional molecular pathways engaged by these dietary ligands in addition to the AHR in order to better understand their complete mechanisms of action.

Further investigation of how IBD-related cascades can be manipulated exogenously, perhaps via the AHR, could one day lead to diet-derived and well-tolerated regimens for those with ulcerative colitis and Crohn's disease. That being said, it must be appreciated that the AHR is only one of many potential signaling cascades that may influence the IBD phenotype in humans. The characterization of a diet-derived agent, AHR agonist or not, that targets the hallmark imbalances in inflammatory bowel disease without compromising host

immune function would revolutionize current medical treatment modalities and save many from radical surgical intervention.

**Reviewer Code: 02441672**
**Reviewer's Comments:** The manuscript contains a good review about the the relationship between intestinal inflammation and diet. However , I agree with the other reviewer. The future studies should not be focused only on the aryl hydrocarbons receptors. The remaining text is good.

**Author's Response:** Thank you for your comments. We now recognize that portions of our conclusion paragraphs may have overstated the importance of the AHR as a sole driver of IBD. We have addressed your comments and the comments of your fellow reviewer in a revised version of our "conclusion and future directions" section, which can be found above. We hope that our revisions have served to highlight the potential of the AHR as a therapeutic target in IBD without overstating the case. Thank you again.

**Reviewer Code: 00037324**
**Reviewer's Comments:** Congratulation to the authors for writing this excellent review.

**Authors' Response:** Thank you for your comments. We have incorporated revisions addressing the comments of your fellow reviewers above.