Re: Manuscript 54700 – revision

Dear Editor,

Thank you very much for your kind letter and reminding. We are now sending our revised manuscript with all changes that you requested.

The following comments were given by the reviewers:
Rev. 03031029
Conclusion: Accept
(General priority)
Scientific Quality:
Grade B (Very good)
Language Quality:
Grade A (Priority
publishing)
This is a well designed and well written experimental study about abdominal adhesions. Thanks for your valuable efforts.

Rev. 00052899
Conclusion: Rejection
Scientific Quality:
Grade E (Do not publish)
Language Quality:
Grade B (Minor language
polishing)
This study focused on the bowel adhesion and the therapy with the BPC 157, its most and application of NO-agents. The authors concluded that BPC 157 therapy was suited for the realization of the peritoneal
defect healing with minimal or no adhesion formation. Overall, this manuscript is not well written. However, there are still several problems that should be considered. Comments: 1. The underline mechanism for BPC 157 in the treatment of bowel adhesion should be studied intensively. 2. More high-impact articles in the latest five years should be cited as references. 3.There are several typographical
errors.

To the comments of the reviewers see our arguments:

Ad Rev. 03031029
We appreciate the reviewer’s comments.

Ad Rev. 00052899
We strongly object this reviewer’s attitude. In our view, the comments are vague, and without real argumentation.
To counteract general argumentation that paper is not well written, the large part of the manuscript is completely rewritten (Introduction and Discussion, Article Highlights clearly added). Considering the comments that the mechanism for BPC 157 should be studied intensively, we should emphasize that this study provide a clear demonstration about the mechanism behind the treatment of bowel adhesions. Initial vascular recruitment was precisely documented. It was also challenged with the prototypic agents, NOS-blocker and NOS-substrate L-arginine, and the combinations. Thereby, the establishing the BPC 157-NO-system relations was in this terms quite clearly established. In addition, we assessed also NO- and MDA-levels in the injured tissue. Therefore, in our view, providing demonstration of a new phenomenon – that may have also practical importance – vessels-adhesion relation – is well covered, and the possible mechanism behind clearly demonstrated, or at least convincingly indicated. To additionally counteract this complain, and to

support our contention, we added the most recent data (**Gojkovic et al.**. Pentadecapeptide BPC 157 resolves suprahepatic occlusion of the inferior caval vein, Budd-Chiari syndrome model in rats. *World J Gastrointest Pathophysiol* 2020;**11**:1-19 [PMID:32226643doi: 10.4291/wjgp.v11.i1.1.], **Kolovrat et al.** Pentadecapeptide BPC 157 resolves Pringle maneuver in rats, both ischemia and reperfusion. *World J Hepatol* 2020. Likewise, the most recent data were added to concluding section: "BPC 157 may act as stabilizer of cellular junction, leading to significantly mitigated indomethacin-induced leaky gut syndrome, via increasing tight junction protein ZO-1 expression, transepithelial resistance. Likewise, there are inhibited the mRNA of inflammatory mediators (iNOS, IL-6, IFNγ and TNF-α), increased expression of HSP 70 and 90, and antioxidant proteins, such as HO-1, NQO-1, glutathion reductase, glutathione peroxidase 2 and GST-pi.", and the paper *Curr Pharm Des* 2020; (in press) included in the references list. Considerint the citation of the most recent data, two very recent studies are included (see ref. 71 and ref. 72).

We hope that you will find that we adequately responded to the comments given by the reviewer, and that you will find this manuscript to be suited for final presentation. Also, you will see that the figures are adequately modified.

Looking forward to hearing from you very soon

Sincerely

Predrag Sikiric, MD, PhD
Professor