Re: The manuscript 50197 **Pentadecapeptide BPC 157 resolves Budd Chiari syndrome in rats** now **Pentadecapeptide BPC 157 resolves suprahepatic occlusion of the inferior caval vein, Budd-Chiari syndrome model in rats**

Dear Editor,

Thank you very much for your kind letter.

The following comments were raised by the reviewer 00070537

It is a complex study involving an extended work and a professional team, worthing to be published. However, the manuscript itself seems to be not be very well written, needing an extended revision is some chapters. – The title is not correct. Multiple references in the text to Budd-Chiari syndrome are also not correct. Budd-Chiari syndrome is a complex entity involving hepatic a outflow obstructions, acute or chronic, from hepatic venules to the right atrium. The study dedicated to the suprahepatic ligation of the IVC only, so the formulation "BPC 157 resolves Budd-Chiari Syndrome" used in the title is incorrect. The phisopatological conditions in different types of Budd-Chiari syndrome are different than in the ligation / obstruction of the terminal segment of the IVC and this reflects also in the cited sourses. Reference [48] as example treated focal venous outflow obstruction, usually occurring after extended hepatectomies, in which the role of hepatic artery inflow is of particular importance, different that in the obstruction of the hepatic veins by ligation of upper part of the IVC. – The are multiple citations "in bulk", many of them including articles of the authors, part of them being repeatedly used i.e. [7-14], [18-22], [23-29], [38-43], [43-47]. – There is an abuse of qualitative terms, mostly used being the word "counteracts" (6 times in the Core tip, 14 times in "Discussion", many times in figures, including figure titles). – Chapter "Results" includes qualitative description of the results, reffering to the Figures, but the quantitative results are missing, the readers being left to find it out themselves in the Figures. – Chapter "Materials" is not showing how many rats are included in each group.- In the "Reference" chapter, the mentions "Available from htp..." are not necessary and recommended in WJG documentation.

To the comments given by the reviewer see our arguments:

Ad It is a complex study involving an extended work and a professional team, worthing to be published. We appreciate this assessment. However, the final ranking "C" given by the reviewer is inadequate for further publishing, and thereby contrasts with his/her original assessment.

Ad However, the manuscript itself seems to be not be very well written, needing an extended revision is some chapters. – The title is not correct. Multiple references in the text to Budd-Chiari syndrome are also not correct. Budd-Chiari syndrome is a complex entity involving hepatic a outflow obstructions, acute or chronic, from hepatic venules to the right atrium. The study dedicated to the suprahepatic ligation of the IVC only, so the formulation "BPC 157 resolves Budd-Chiari Syndrome" used in the title is incorrect. The phisopatological conditions in different types of Budd-Chiari syndrome are different than in the ligation / obstruction of the terminal segment of the IVC and this reflects also in the cited sourses. Reference [48] as example treated focal venous outflow obstruction, usually occurring after extended hepatectomies, in which the role of hepatic artery inflow is of particular importance, different that in the obstruction of the hepatic veins by ligation of upper part of the IVC.

From the perspective of the suprahepatic ligation of the inferior caval vein done in order to provoke Budd Chiari syndrome in rats, we strongly object this reviewer objection. Logically, this complain about inadequacy of the suprahepatic ligation of the inferior caval vein for Budd Chiari syndrome, contrasts with the general understanding (Ludwig J, Hashimoto E, McGill DB, van Heerden JA. Classification of hepatic venous outflow obstruction: ambiguous terminology of the Budd–Chiari syndrome. Mayo Clin Proc 1990; **65**: 51–5): "BCS consists of hepatic venous outflow obstruction and its manifestations, regardless of cause, the obstruction being either within the liver or in the IVC between the liver and the right atrium." Likewise, his/her complains contrast also with his/her own definition "Budd-Chiari syndrome is a complex entity involving hepatic aoutflow obstructions, acute or chronic, from hepatic venules to the right atrium." Thereby, considering reviewer's "complex entity", or general estimation expressed by Ludwig and colleagues about "regardless of cause", it is not clear why IVC suprahepatic ligation will be not included in the issue of Budd-Chiari syndrome. Likewise, it is not clear why the multiple references in the text to

Budd-Chiari syndrome can be incorrect, since all of them are dealing with ligation of the suprahepatic inferior caval vein as the rat model of Budd Chiari syndrome. Even if reviewer's "different types of Budd-Chiari syndrome are different than in the ligation / obstruction of the terminal segment of the IVC" was correct, the acknowledged reviewer's "complex entity" and Ludwig and colleagues generalization "regardless of cause" would done suprahepatic ligation of inferior caval vein as a suited experimental approach. Thus, in these terms, the resolving of the issue of the occlusion of the suprahepatic inferior caval, which is permanent by ligation, is thereby tightly related to the resolving of the issue of the Budd-Chiari syndrome. Furthermore, considering that general understanding expressed by Ludwig and colleagues involves also the manifestations, it should be noted that this study evidences also multiple consequences (i.e., vascular recruitment (activated shunts), portal/caval hypertension, aortal hypotension, thrombosis in veins and arteries, organs lesions, oxidative stress, arrhythmias, etc). Thereby, there is fulfilling of "hepatic venous outflow obstruction and its manifestations" emphasized by Ludwig and colleagues. Concluding, it is clear that his/her statement about "study dedicated to the suprahepatic ligation of the IVC only" is not well done. Anyway, in the revised version, we made an additional effort to establish, even more clearly than before, the strict connection between suprahepatic ligation of the inferior caval vein and Budd-Chiari syndrome, in both experimental and general terms (to this point see the revised Introduction and revised Discussion). In this point, the title **Pentadecapeptide BPC 157 resolves Budd Chiari syndrome in rats** is changed to **Pentadecapeptide BPC 157 resolves suprahepatic occlusion of the inferior caval vein, Budd-Chiari syndrome model in rats.**

Ad The phisopatological conditions in different types of Budd-Chiari syndrome are different than in the ligation / obstruction of the terminal segment of the IVC and this reflects also in the cited sourses. Reference [48] as example treated focal venous outflow obstruction, usually occurring after extended hepatectomies, in which the role of hepatic artery inflow is of particular importance, different that in the obstruction of the hepatic veins by ligation of upper part of the IVC.

To counteract this complain the original text In particular, hepatic artery patency might be essential, as hepatic artery perfusion could be essential for recovery from hepatic venous outflow obstruction in rats[48] and indicative for the thrombosis counteraction in all of the investigated veins and arteries, which were investigated[18,37]. is modified as follows: In particular, hepatic artery patency might be essential, and indicative for the thrombosis counteraction in all of the investigated veins and arteries, which were investigated[21,40]. Note, hepatic artery perfusion could be essential for recovery from hepatic venous outflow obstruction in rats, pointed out when usually occurring after 70% hepatectomy and right median hepatic vein ligation, in which the role of hepatic artery inflow is of particular importance, in the condition likely even more severe than the obstruction of the hepatic veins by ligation of the upper part of inferior caval vein[51].

Ad The are multiple citations "in bulk", many of them including articles of the authors, part of them being repeatedly used i.e. [7-14], [18-22], [23-29], [38-43], [43-47]. – There is an abuse of qualitative terms, mostly used being the word "counteracts" (6 times in the Core tip, 14 times in "Discussion", many times in figures, including figure titles). – Chapter "Results" includes qualitative description of the results, reffering to the Figures, but the quantitative results are missing, the readers being left to find it out themselves in the Figures. – Chapter "Materials" is not showing how many rats are included in each group.- In the "Reference" chapter, the mentions "Available from htp..." are not necessary and recommended in WJG documentation.

The "bulk" citations are used to substantiate that the extent of the support is considerable, and consistent, and not related to the only one single report. However, they are now more separated to specify the support. The objected point that many of them include articles of the authors is, on the other hand, quite understandable considering that a large majority of the papers belong to pioneer work of our group in this issue while supportive manuscripts from other groups were also accordingly cited. Therefore, in our believe, this should be not a concern for the reviewer (thus, the reply would be "responsible, but not guilty"). To emphasize, the number of the animals per

groups had been already mentioned in the previous text (see Materials and Methods, Animals, line 2). Some terms criticized by the reviewer ("counteracts", "counteraction") accordingly modified. Considering the Results section, the extent of the data that had to be presented, mandates the concise and precise description, related to close connection between the text and supportive Figures. In the "Reference" chapter, the mentions "Available from htp..." are removed.

In conclusion, I hope that we adequately counteracted all complaints given by the reviewer, and we raised arguments for a better manuscript ranking and final acceptance.

Sincerely
Predrag Sikiric, MD, PhD
Professor