

RESPONSE TO REVIEWERS

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a very interesting manuscript with original findings based on extensive literature search and analysis. The hypothesis of treatment repurposing and repositioning is scientifically valid and previously proved effective. The authors present a potent treatment repurposing engine applicable to IBD as well as virtually any other disease with overlapping pathogenesis. As such, the presented results could serve as a basis of future animal experiments and clinical studies in IBD, with the advantage of having been previously proved for safety in the literature. This concept is original and the work meets high methodological standards. The literature search mechanism includes extensive and comprehensive queries to retrieve the desired information. The results are appropriately summarized and the conclusion is clear. The study contributes to the problem of novel drug discovery, which is often obstructed by commercial interest of the companies. It also helps to search for novel candidate drugs without the need of time and resources-consuming research. The limitations include the fact that no further experimental work has been conducted based on the results of literature search, although it is clear that this was not the aim of the work. The authors have properly stated what are the next future directions and how the results can be exploited. The impact on basic and clinical science is unclear, but the potential is high.

RESPONSE: We agree with these comments.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It is an interesting and well written manuscript

RESPONSE: We agree with these comments.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a relatively cutting-edge paper. How can this paper ensure the comprehensiveness and feasibility of retrieval? And science and rationality? What do you think of the application prospect of probiotics / engineering bacteria / fecal bacteria transplantation technology in the field of IBD in the future?

RESPONSE: The goal of this study was a proof-of-principle demonstration of the improved concept, with application to IBD. The comprehensiveness and feasibility of the approach used allowed the goal to be met. A more comprehensive study would require far more resources, in terms of people and time.

The number of query terms possible for n biomarkers used and all combinations of r terms can be approximated by $n^r/r!$ (the Binomial Theorem for $r/n \ll 1$). For example, we identified many hundreds of biomarkers (and could have identified hundreds more), and selected ~twenty to be used in the discovery retrieval query. We examined all combinations of two biomarkers within the twenty that were used. Based on the approximate formula above, the query contained about 200 terms. The number of records retrieved was about 9500, of which the most recent 350 were evaluated for potential discovery. Even examining ~4% of the retrieval allowed us to generate over fifty potential novel treatments!

For more comprehensiveness, we could have examined the remainder of the retrieval. Further, we could have selected forty biomarkers for the query instead of twenty, and examined all combinations of two (or three or four, etc). Because the numbers of permutations are combinatorial, the numbers of query terms increase significantly with larger numbers of combinations and larger numbers of biomarkers used. For the case of forty biomarkers in the query, and all combinations of two, the number of query terms would now be about 800. This would result in larger numbers of records retrieved, and significantly more time required for analysis.

To address the reviewer's question, is it feasible? Given adequate resources, using forty terms, or even eighty terms, would certainly be feasible. Examining thousands of records for potential discovery would be feasible, although time-consuming. Would it be cost-effective? Assume forty terms were used in the query, and the most recent 5,000 records retrieved were evaluated for discovery. If an evaluator could examine ~ten records per hour, this means ~500 person-hours of effort would be required. Assume a rate of ~\$50/hour. The evaluation cost would be about \$25,000. Considering the total cost of bringing a drug to market, even a repurposed drug, the benefit-cost ration for the effort described above would be extremely high!

We are not clear on the question about science and rationality. We believe the scientific basis for our approach is sound, as evidenced by the validation of predictability that we demonstrated. We believe the fundamental approach of matching biomarker change signatures is rational, coupled with the judgment of credible mechanisms identified. We also believe the potential impact on basic and clinical science could be large. The technique has the capability of opening new areas of research of potential benefit to IBD. It would include both applied research, with laboratory and clinical demonstrations confirming the science predictions, as well as basic research focused on examining and understanding the basic mechanisms responsible for effecting the desired biomarker changes.

The final question requests we estimate the application prospect of probiotics / engineering bacteria / fecal bacteria transplantation technology in the field of IBD in the future. Probiotics and fecal transplant are already active areas of research in inflammatory bowel disease, and the promise of these two

technologies is being researched vigorously. More laboratory and clinical data are required to allow better estimations of their eventual success, as well as to demonstrate both interim and long-term safety of the techniques.

Science Editor: 1 Scientific quality: The manuscript describes the inflammatory bowel disease. Manuscript type is "Frontier". The topic is within the scope of the WJG. (1) Classification: Grade B, Grade B and Grade B; (2) Summary of the Peer-Review Report: Reviewer# 02519674 thinks this is a very interesting literature search study of high methodological significance. The authors present a potent treatment repurposing engine applicable to IBD as well as virtually any other disease with overlapping pathogenesis. However, there are some points need to be addressed. The impact on basic and clinical science is unclear. Reviewer# 04046744 thinks this is a relatively cutting-edge paper. The authors need to comment the application prospect of probiotics / engineering bacteria / fecal bacteria transplantation technology in the field of IBD in the future. The questions raised by the reviewers should be answered;

RESPONSE: We have addressed these comments in detail, above.

(3) Format: There are 5 tables and 1 figure. A total of 103 references are cited, including 58 references published in the 2020. There are 7 self-citations. 2 Language evaluation: Classification: Grade A, Grade B and Grade B. The manuscript is from the United States. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form, and Copyright License Agreement signed by all authors.

RESPONSE: We have the required forms completed, and will mail them by surface mail to the Editorial Office when the manuscript submission has been completed.

No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The study is without financial support. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions;

RESPONSE: The manuscript has been modified to include the author contributions

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

RESPONSE: The figure has been prepared using PowerPoint

(3) I found the PMID numbers in the reference list were wrong, the authors need to add the correct PMID numbers; and

RESPONSE: We have generated the PMID numbers in the reference list by two different methods, independently, and have obtained the same numbers. The first author used EndNote Online to format the Bibliography in the provided WJG format. The second author did the following:

"I also completed a complete review/search for every PMID in PubMed and checked verified, PMID, DOI, Title, 1st Authors name in PubMed. I made the edits in the Draft 4 version you emailed me today using track changes. I also went thru this version with spell check, essentially ignore once for all the items.

There were a few reference titles with a space btwn a word and colon which I removed that the spell checker underlined in blue.

The original had added an "MEDLINE:" to the line [PMID: MEDLINE:32036038]. I deleted all these first with find & and replace.

There were no mistakes in the PMID or DOI numbers;

A couple refs had only a PMID or DOI and I deleted the "PMID" or "DOI" accordingly;

Had to add a couple DOIs that were not originally included with the PMID;"

(4) the authors need to complete the Conflict-of-Interest Disclosure Form, and provide the Copyright License Agreement signed by all authors. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

RESPONSE: Have submitted revised version.