



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54484

**Title:** Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn`s disease

**Reviewer`s code:** 00054993

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Emeritus Professor, Professor

**Reviewer`s Country/Territory:** Austria

**Author`s Country/Territory:** Germany

**Manuscript submission date:** 2020-02-03

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2020-02-04 10:09

**Reviewer performed review:** 2020-02-05 14:03

**Review time:** 1 Day and 3 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
<b>Conclusion</b>	[ ] Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
<b>Re-review</b>	[ ] Yes [ ] No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

Based on the observation that patients with ulcerative colitis treated with the pan-Janus kinase (JAK) inhibitor tofacitinib showed a positive healing response while patients with Crohn-Disease did not, the authors present a comprehensive review on the current knowledge of the interplay of the JAK/STAT pathway and inflammatory bowel disease (IBD). They address the JAK/STAT pathway in general, JAK/STAT signaling in T-cells, monocytes and monocyte-derived cells and genetic associations of IBD and the JAK/STAT pathway. The authors also reflect on clinical implementations and in their conclusion make several valid points as to how more specifically targeted personal treatment approaches might improve therapeutic outcomes in patients with IBD. One table and 2 figures help to comprehend the complex text. The statements on page 13, lines 260 - 262 should be referenced. A few typing errors need attention, for instance on page 5, line 77 (omit one "has"): page 11, line 225 (mechanism needs a plural "s"), etc.



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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54484

**Title:** Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn`s disease

**Reviewer`s code:** 00058695

**Position:** Peer Reviewer

**Academic degree:** DSc, MD

**Professional title:** Professor

**Reviewer`s Country/Territory:** Denmark

**Author`s Country/Territory:** Germany

**Manuscript submission date:** 2020-02-03

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2020-02-04 09:18

**Reviewer performed review:** 2020-02-07 09:09

**Review time:** 2 Days and 23 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

This review of differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn's disease summarize the latest published evidence of JAK/STAT signaling in immune cells of IBD as well as a genetic association between the JAK/STAT pathway and IBD. I have some comments. In general, the authors should provide references for key issues mentioned in the text. Thus, in the Introduction it is recommended that the authors among others give a reference for the 22 and 18 percentages, and the reference 6 seems to be placed rather awkwardly and should preferably be placed by end of the sentence. Moreover, it is preferable if the authors consequently could add reference numbers when dealing with specific publications, e.g. Soendergaard et al. on page 15 (line 309-312). Also, the statement that "previous data from our own group" as mentioned on page 8, line 148, should have a reference number affiliated. The authors should check the entire manuscript once more regarding these matters. It is recommended that the authors briefly explain for the readers the difference between canonical and non-canonical pathways, e.g. p. 6, line 106. When describing the various STATs, perhaps the authors should consider mentioning the difference between STAT5a/STAT5b. In general, the paper provides a nice summary that more selective JAK/STAT inhibitors are needed, which might increase efficacy and at the same time decrease side effects as observed with first JAK pan-inhibitor marketed for ulcerative colitis, i.e., tofacitinib. Specific comments 1. When focusing on IBD, the first sentence of the abstract should be in 2018... for the treatment of ulcerative colitis, as treatment of rheumatoid arthritis is out of scope in this context. 2. Also, in the abstract the authors should delete "human" (x 2) as IBD is a pure human disorder. In animal models you can talk about experimental colitis only, as there is absolutely no "animal IBD". 3. In keywords generic drugs should not be capitalized, including tofacitinib. 4. Add comma



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in 10,292 5. The authors should consider mentioning that the IL-23/IL-12 receptor stimulation might mimic that of ustekinumab (p. 20, line 427) 6. The authors should check all references “Epub Ahead of Print” if they have been recently published.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54484

**Title:** Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn`s disease

**Reviewer`s code:** 00503587

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Professor

**Reviewer`s Country/Territory:** New Zealand

**Author`s Country/Territory:** Germany

**Manuscript submission date:** 2020-02-03

**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2020-02-13 17:38

**Reviewer performed review:** 2020-02-15 01:54

**Review time:** 1 Day and 8 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
<b>Language quality</b>	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing [ ] Grade D: Rejection
<b>Conclusion</b>	[ ] Accept (High priority) [ ] Accept (General priority) <input checked="" type="checkbox"/> Minor revision [ ] Major revision [ ] Rejection
<b>Re-review</b>	[ ] Yes [ ] No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

This review manuscript focuses on JAK/STAT signalling and related pathways in the context of IBD. The manuscript describes the topic in great detail and is comprehensive.

**SPECIFIC COMMENTS** 1. There are many errors of grammar and/or inappropriate phraseology. As some examples line 47, line 144, line 203 and many others 2. the term "CD patients" should be rewritten to read "patients with CD" And similar other such phrases also 3. Some referencing is misplaced. When utilising the term Author et al, the relevant reference should follow immediately after e tal 4. Some of the paragraphs are very long. 5. At line 430, should this be Clinical Implications?



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54484

**Title:** Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn`s disease

**Reviewer`s code:** 03478404

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer`s Country/Territory:** Romania

**Author`s Country/Territory:** Germany

**Manuscript submission date:** 2020-02-03

**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2020-02-15 10:53

**Reviewer performed review:** 2020-02-15 14:12

**Review time:** 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

In this manuscript, the authors analysed available data on differential JAK/STAT-signaling in ulcerative colitis and Crohn's disease and it resulted in a very comprehensive and detailed review. Up-to-date references regarding JAK/STAT signaling were used, others are old. Obviously, there was a lot of work involved in collecting the data and writing the manuscript. Comments/suggestions: 1. English language should be revised and corrected all over the manuscript. Even the abbreviations contain errors - e.g. CD, Crohn`disease; RA, rheumatoid arthirits 2. Core tip: Please rewrite the sentence "Clinical implications include more specific JAK/STAT targeting as well a cell-subset-specific JAK/STAT inhibition.", in order to be clearer. 3. Introduction: a. lines 59-62: Authors should mention that IBD comprise also IBD-U (unclassified). Please also correct - strictures and fistulas appear only in CD. There are more recent references than 1-4. b. line 63 "medical treatment " is repeated twice. c. References 5 and 6 should be replaced by more recent ones. (i.e. instead of reference 5 - use "Wong DJ, et al. Surgery in the age of biologics. Gastroenterology Report 2019; 7(2): 77-90. d. Authors should carefully revise all references in the manuscript and use the correct ones. As an example, they wrote - lines 65-66 "Population based studies reported that 44% and 34% of patients with CD and UC..." and inserted reference 4. In fact, reference 4 is only a review of the data known in 2007 (OLD!). The population-based study the authors referred to is Faubion WJ, Loftus EJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001; 121: 255-60. This is just one example. And there are many instances. The original article should be referenced and not the review. E. Lines 69-72 "maintenance of remission is still challenging: While approximately 22% of CD and one third of UC patients were classified as primary



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non-responder or had to stop treatment due to severe side effects, up to 18% of IBD patients revealed a secondary loss of response to biological therapy.” This long sentence is not clear and has no reference. Where are these data taken from? According to a very recent review (Papamichael K, et al. Clinical Gastroenterology and Hepatology 2019), up to one-third of patients with Crohn’s disease (CD) and ulcerative colitis (UC) show primary non-response (PNR) to biologic therapies, and up to 50% of patients after an initial clinical response stop therapy for either secondary loss of response (SLR) or a serious adverse event. Correct references of these studies are are “Ben-Horin S, Chowers Y. Loss of response to anti-TNF treatments in Crohn’s disease. Aliment Pharmacol Ther 2011;33:987-995”. AND “Papamichael K, et al. Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: defining a therapeutic drug window. Inflamm Bowel Dis 2017;23:1510-1515”. These references are not cited in this manuscript. f. Paragraph “The JAK/STAT-pathway” contains pertinent data; however, it should be shortened and made clearer. A figure showing the mechanisms would be very useful. g. Paragraph “Clinical efficacy of JAK inhibition in RA and IBD”: g1. Please define DMARDs before the abbreviation (for readers). g2. When referring to a study, the reference should be inserted there (e.g. lines 128-129 - In a recently published phase III RCT, tofacitinib demonstrated efficacy for induction and maintenance of remission in patients with UC - reference 55). g3. REFERENCE 60 HAS ALREADY BEEN PUBLISHED. It should show all coordinates: Inflamm Bowel Dis. 2020;26(3):391-406. This remark is valid for other references not having all complete data. 4. Paragraph “JAK/STAT SIGNALING IN IBD: T-CELLS” Fig.1 is explanatory and contains most important data. 5. Paragraph STATs - lines 200-201 - “Mudter et al. found increased IFN $\gamma$ -induced STAT1 but not phospho-STAT1 in lamina propria T-cells of CD compared to UC patients.” Reference should be inserted here. 6. Paragraph “JAK/STAT”: Lines 312-313 “Oppositely to that, Soendergaard et al. found SOCS1 and



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additionally SOCS3 mucosal RNA level..." please insert reference 26. Figure 2 shows most important data and connections between pathways. 7. Paragraph "GENETIC ASSOCIATION OF IBD AND THE JAKS/STAT PATHWAY". Table 1 - reference 142 is missing from "Prager 2014" 8. Paragraph "JAKs" - references 130-133 should be after those used in Table 1, as they are referred later in the manuscript, after Table 1. 9. Conclusion is too long and too detailed. Please shorten it and make it crispier. Conclusion should not contain redundant data.