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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 42023

Title: Current therapies and novel approaches for biliary diseases

Reviewer's code: 02566971

Reviewer's country: China

Science editor: Ying Dou

Date sent for review: 2018-09-12

Date reviewed: 2018-09-17

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[Y] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a timely and well written review of chronic liver fibrosis and cirrhosis with special emphasis on biliary fibrosis. Also the authors discussed the advantages and disadvantages about the clinically or preclinically available therapeutic options for biliary fibrosis. Interestingly, the authors showed that ACE2 over-expression produced a

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large reduction in biliary fibrosis in BDL mouse models that display either short-term or long-term biliary disease, suggesting ACE2 gene therapy has potential to treat patients with chronic biliary fibrosis. Importantly, this manuscript suggests that novel methods of gene therapy research by using liver-specific AAV vectors would lead to provide therapeutic gene therapy applications for human biliary fibrosis in future.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 42023

Title: Current therapies and novel approaches for biliary diseases

Reviewer's code: 02444978

Reviewer's country: Italy

Science editor: Ying Dou

Date sent for review: 2018-09-25

Date reviewed: 2018-10-01

Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[Y] Yes
			[ ] No

SPECIFIC COMMENTS TO AUTHORS

This is a very good review which describes general epidemiologic and pathogenetic aspects of liver injuries, focusing in particular on cholestasis and biliary diseases. Moreover it approaches the most modern option for the treatment, also reporting future perspectives. The text is synthetic and clear, appropriated for a mini-review. I have only

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to indicate few minor revisions: - In the description of cirrhosis (section Cirrhosis), the sentence "intrahepatic vascular shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver", although reported in ref.10, is uncertain. In general, the hepatic artery supplies the peribiliary capillary plexus and in developing fibrosis can supply the fibrous tissue by means of a newly formed capillary network. So, direct connection with the central vein are not ascertained. Other studies on experimental cirrhosis (Gaudio et al, Hepatology 1993, 17(3):477-485; Onori et al, J Hepatol 2000;33:555–63) does not report the presence of shunts between the branches of the hepatic artery and the central vein. I suggest to delete "portal vein and hepatic artery" inside the bracket. - The presence of some typos and very little linguistic revisions.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 42023

Title: Current therapies and novel approaches for biliary diseases

Reviewer's code: 02444931

Reviewer's country: China

Science editor: Ying Dou

Date sent for review: 2018-09-25

Date reviewed: 2018-10-05

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1.More attention needed to be payed to the languageexpression andword spelling. For example, the word "focused" was misspelled in the "Abstract", and the word "myofibroblasts" was misspelled in the "Liverinjuryandfibrosis". 2.References were a bit outdated. There were62 references in the text, of which 19 references were published in

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the last 5 years, and only 5 references were published in the past 3 years. 3.The focus of the article was not prominent. The title of the article was "Current therapeutic advances in biliary diseases"; in the abstract, the article mainly described the pathophysiology of liver fibrosis and its progression to cirrhosis with special emphasis on biliary fibrosis and current therapeutic options; in the main body of the article, it devoted much space to discuss the epidemiology and etiology of chronic liver disease, the process of liver fibrosis andbasic characteristics of cirrhosis. The focus of this review was not prominent enough, and the background introduction needed to be more concise and clearer. 4.The article structure was unreasonable. The article consisted of seven parts: Introduction, Liver injure and fibrosis, Cirrhosis, Biliary disease, Pathogenesis of cholestasis and biliary fibrosis, Current treatment options for cholangiopathies and ACE2 overexpression in the liver. The content inthe "Introduction" was too simple to elaborate on the disease background, and contents of "Liver injure and fibrosis" and "Cirrhosis" actually belonged to the "Introduction". In addition, there was a lack of summary at the end. 5.The contents of the review were a bit vacuous and lacked logic. For example, in the "Liver injure and fibrosis", the article introduced different classifications of liver injure, the process of liver fibrosis and cellular crosstalk. The mechanism of hepatic stellate cells, Kupffer cells, myofibroblasts and mast cells was listed separately, which lacked logic and depth.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 42023

Title: Current therapies and novel approaches for biliary diseases

Reviewer's code: 01221925

Reviewer's country: Greece

Science editor: Ying Dou

Date sent for review: 2018-09-25

Date reviewed: 2018-10-12

Review time: 17 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting minireview paper discussing the issue of hepatic fibrosis and how this relates to diseases of biliary origin or etiology. The authors provide a nice review of several of the relevant mechanisms with special emphasis on the work done in their own laboratory having to do with the role of the ACE-2 overexpression in liver disease and

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how this could be a therapeutic target. Although this is of significant interest, the title "Current therapeutic advances in biliary diseases" creates an expectation for a more well-rounded presentation, rather than placing too much emphasis on the specific mechanism. Potentially, this paper may be presented as a research paper, other than a mini-review.

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