April 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJOGP review.doc).

Title: MOLECULAR MECHANISMS OF ALCOHOLIC ASSOCIATED PANCREATITIS

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Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 10252

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Response to Reviewers: I would like to thank the reviewers for their input. I have made changes in response to their comments. These changes have made this a better manuscript.

Reviewer 1.

1) 1.The Review is very informative but is difficult to understand because there are no informative figures and tables. Response: I have included two tables, Table 1. Mechanisms By Which Ethanol Is Thought To Sensitize the Pancreas to Pancreatitis and Table 2. Proposed Co-factors For the Development of Alcoholic Pancreatitis. I have also included a figure entitled “Proposed Model For the Development of Alcoholic Chronic Pancreatitis “ that depicts a model for the development of chronic pancreatitis.

Reviewer 2.

1) 1. The authors stated that “It is now well accepted that chronic alcoholic pancreatitis results from repeated episodes of acute pancreatitis. This concept is supported by the observation that individuals who suffer frequent attacks of acute pancreatitis progress to

chronic pancreatitis more rapidly " The authors should add that there are another option, i.e. that chronic pancreatitis is chronic "ab initio". Response: I have changed this statement. It now reads: It has been demonstrated in a long-term prospective study that alcoholic chronic pancreatitis normally progresses from acute pancreatitis. Additionally, this study demonstrated that the progression of acute pancreatitis to chronic pancreatitis is associated with the frequency and severity of the acute attacks [4]. These finding are supported by the observation that individuals who suffer frequent attacks of acute pancreatitis progress to chronic pancreatitis more rapidly [5]. These findings led Whitcomb to propose that a sentinel acute pancreatitis event (SAPE) is required for to the development of chronic pancreatitis [6] (Figure 1).

2) They also stated that "Therefore, although acute and chronic pancreatitis have different clinical manifestations, the mechanisms by which the disease process is initiated is likely similar ". Please describe the different manifestations. In other word the clinical presentation of acute and chronic pancreatitis is the pain and the other manifestations are due to the different course of the two diseases. Response: This statement is intended to broadly provide unification between these two diseases. It is not the intention of this statement to imply that the clinical manifestations of these two diseases are similar. This statement is simply intended to propose the idea that regardless of the cause of the pancreatic injury, the initial molecular events that cause pancreatitis are likely similar in both acute and chronic pancreatitis. We had provided a description of the different manifestations of the two diseases. Acute pancreatitis is characterized by various degrees of acinar cell damage with concomitant local and systemic inflammation, mediated by inflammatory cytokines and chemokines [1]. Acute pancreatitis is usually a self-limiting condition. Unfortunately, in 10 to 20 percent of clinical cases, acute pancreatitis progresses to severe acute pancreatitis, a disease with high morbidity and mortality. In the United States alone there are approximately 210,000 new clinical cases of acute pancreatitis a year[2]. In 2009, acute pancreatitis was the most common gastrointestinal disease requiring hospitalization. Additionally, it was estimated that acute pancreatitis accounted for more than 2.5 billion dollars in direct and indirect costs [3]. Obviously, pancreatitis is a serious public health concern. Chronic pancreatitis is a progressive disease characterized by persistent pancreatic inflammation, the development of fibrotic scarring, severe pain, as well as the loss of endocrine and exocrine function.

3) "finally animal model of chronic pancreatitis failed to replicate human chronic pancreatitis. Also this point should be underlines". It is true there is no animal model of chronic pancreatitis that recapitulates all of the manifestations of chronic pancreatitis in human beings. This being

said, it has been demonstrated that alcohol administration to rats and mice enhances the onset and severity of fibrosis in animals subjected to caerulein-induced pancreatic injury {Gukovsky, et al. Am J Physiol Gastrointest Liver Physiol, 294; G68-74 and Perides et al. Gut 54:1461-1467}. Therefore, these models may be useful in elucidating the mechanisms by which ethanol alters normal pancreatic repair and predisposes the pancreas to fibrosis.

Reviewer 3. Reviewer 3 had no specific questions regarding this manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology Pathophysiology.*

Sincerely,

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