Lian-Sheng Ma, Science Editor,

Company Editor-in-Chief, Editorial Office

Baishideng Publishing Group Inc

12/30/2020

Dear Prof. Ma:

Thank you for your letter regarding our manuscript, **Artificial Intelligence in Gastroenterology Manuscript NO: 60114,** dated on 12/18/2020.

We have revised our manuscript according to the suggestions of the referees. The following are our responses and changes according to the referees' comments and criticisms. We also made a few simple revisions in terminology and for grammatical reasons, and they were also shown using red color font in the revised manuscript.

We hope these changes meet with your approval, and we would appreciate your kind consideration of our paper, entitled "**Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites**" to *Artificial Intelligence in Gastroenterology as a Minireview.*

We certify that the submission of this article implies that the work described has not been previously published; it is not under consideration for publication elsewhere; its publication is tacitly or explicitly approved by all authors, and if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder. All the authors have seen and agreed to the submitted version of the paper.

We look forward to hearing from you soon.

Sincerely yours,

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Response to the comments of reviewer #1: *"This is an interesting review about the artificial intelligence and machine learning for anti-HAV drug development. I am very grateful for been chosen as a reviewer for this article. I have learned a lot. This review from Kanda T et al seems to be well summarized and be nicely written for the current topic AI for supporting drug development for anti-HAV internal ribosomal entry site."*

Thank you for your encouraging comments.

Response to the comments of reviewer #2: Thank you for your valuable comments.

Response to your comment: *"The authors in this manuscript pretend to write a mini review focusing on AI and machine learning in the area of drug development for hepatitis A virus internal ribosomal entry-site. However, a very short paragraph dedicates to the AI and only to disclose that it be will very useful in this matter. The mini review has no examples or citations from others using AI, no explanation and examples of which are the tools and the sources of information and no details for the development of AI in this area."*

Thank you for your valuable comments. We agree with you. According to your suggestions, we made a new Figure 1 and revised our manuscript as follows.

In page 5, lines 7-12,

Structure-based drug design is becoming an essential tool for faster, more cost-efficient drug discovery, compared to traditional methods[13]. The combination of AI and deep learning, which is a family of machine learning models that use artificial neural networks, may be a more powerful tool for drug discovery. The

associations of machine learning, deep learning and AI are shown in Figure 1.

Moreover, network-based *in silico* drug efficacy screening allows us….

In page 11, line 2-page 14, line 5,

MACHINE LEARNING AND DRUG DEVELOPMENT FOR HEPATITIS VIRUSES AND GLUCOSE-REGULATED PROTEIN 78 (GRP78)

Hepatitis B virus (HBV)

Qureshi et al. developed virus-specific as well as general quantitative structure–activity relationship (QSAR) models and computed approximately 18000 chemical descriptors (1D, 2D and 3D), including geometric, constitutional, electrostatic, topological, hydrophobic and binary fingerprints, using PaDEL, an open-source software to calculate molecular descriptors and fingerprints[55]. They also employed SVMlight software (freely available at http://svmlight.joachims.org) for machine learning[55]. After attribute selection, there were 15 relevant descriptors for HBV. Arora et al. performed a QSAR study based on a series of anti-hepatitis B virus (HBV) agents, namely, a series of novel bis(L-amino acid) ester prodrugs of 9-[2--(phosphonomethoxy)ethyl]adenine, a

similar series of compounds comprising 2-amino-6-arylthio-9-[2-(phosphonoethoxy)ethyl] purine bis(2,2,2-trifluoroethyl) esters, and a series of 1-isopropylsulfonyl-2-amine benzimidazoles[56]. These systems may also be useful for the development of anti-HAV drugs.

Deep learning has been applied for the diagnosis and treatment of chronic hepatitis B. Compared with two-dimensional shared wave elastography and fibrosis biomarkers, deep learning radiomics of elastography (DLRE) is valuable and practical as a noninvasive accurate diagnosis of liver fibrosis in HBV-infected patients[57]. Analysis of the quasispecies pattern of HBV genomes by the combination of deep sequencing and machine learning is also useful for the prediction of HCC and direct therapeutic strategies[58,59]. A valid systematic approach based on big data mining and genome-wide RNA-seq data may be imperative to further investigate the pathogenic mechanism and identify biomarkers for drug design[60].

Hepatitis C virus (HCV)

Weidlich et al. developed SAR with advanced machine learning methods and

performed in vitro antiviral assays, resulting in the identification of the candesartan cilexetil, which is used to treat hypertension, as an HCV NS5B inhibitor[61]. Using a support vector machine (SVM), three classification models were built in HCV NS3 protease inhibitors[62] or HCV NS5B polymerase inhibitors[63]. Qin et al. reported that the combination of the best sub- and whole dataset SVM models can be used as reliable lead design tools for new NS3/4A protease inhibitors[64].

Wei et al. reported that the multiple QSAR method is useful in predicting chemical-protein interactions for the discovery of multitarget inhibitors for the treatment of HIV/HCV coinfection[65]. This strategy may be useful for the treatment of the cooccurrence of HAV infection and chronic liver disease[66].

Combination information from yeast-based library screening, next-generation sequencing, and structure-based modeling in a supervised machine learning approach is useful for the comprehensive sequence-energetics-function mapping of the specificity landscape of the HCV NS3/4A protease, whose function-site-specific cleavages of the viral polyprotein are a key determinant of viral fitness[67]. Deep learning recurrent neural network (RNN) models could be used to identify patients with HCV-related cirrhosis with a high risk of

developing HCC for risk-based HCC outreach and surveillance strategies[68]. Deep learning should also be helpful for the development of antivirals.

GRP78

We previously found that GRP78 is an antiviral target for HAV (Table 1)[51-53]. Computational drug discovery using the structure of HAV and GRP78 may lead to the discovery of new anti-HAV drugs or drug repositioning and drug repurposing for anti-HAV drugs [69-71].

Response to your comment: *"Additionally, there are spelling errors and the paper needs English editing."*

Thank you for your valuable comments. We agree with you. According to your suggestions, we asked to edit our manuscript and extensively revised our manuscript.

Response to your comment: *"The keywords are not reflecting the focus of the manuscript."*

"For example: GRP78 is not related to the manuscript at all. The manuscript need to be rewrote."

Thank you for your valuable comments. We agree with you. According to your suggestions, we added new references, “description about GRP78” and extensively revised our manuscript.

In page 14, lines 1-5,

GRP78

We previously found that GRP78 is an antiviral target for HAV (Table 1)[51-53]. Computational drug discovery using the structure of HAV and GRP78 may lead to the discovery of new anti-HAV drugs or drug repositioning and drug repurposing for anti-HAV drugs [69-71].