Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Re: Revision of ESPS Manuscript 4742

Title: IDENTIFICATION AND CHARACTERIZATION OF A NOVEL BIPARTITE NLS IN THE HBV POLYMERASE
Authors: Joachim Lupberger, Stephanie Schaedler , Alexander Peiran and Eberhard Hildt

Name of the Journal: World Journal of Gastroenerology
ESPS Manuscript: 4742

Dear Editor
Thank you for your mail from august, 3rd. The positive feedback of the reviewer encouraged us to perform a careful revision of our manuscript. All alterations are marked in red in the revised version of the manuscript. We thoroughly addressed all points raised by the reviewers. Please find below our detailed reply to the comments of the reviewer. We hope that with these alterations our manuscript will be suitable for publication in the World Journal of Gastroenterology

Yours sincerely

Eberhard Hildt

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Paul-Ehrlich-Straße 51-59
63225 Langen
Deutschland / Germany

Telefon / Phone +49 (0) 6103 77 0
Fax +49 (0) 6103 77 1234
>> www.pei.de

Point to point reply to the reviewer:

1. "Inconsistence of hepatoma cell line nomenclature in different places, please follow the original designation shown in ref.22. "

As requested by the reviewer we corrected the spelling of this cell line to HuH-7.

2. "In consistence of using P and Pol in various places."

In the revised version of the manuscript we consistently use P instead of Pol.

3. "In the introduction, the statement of "100-fold increased risk of developing primary HCC' should double check many other epidemiological studies. Suggest to add a reference showing a thrombin cutting site located in the TP domain".

As suggested by the reviewer we changed this statement to "infected individuals have an increased risk of developing primary hepatocellular carcinoma (HCC)" (page 2, bottom of the revised ms) and included additional references.

In the revised version we include as requested by the reviewer a reference describing the thrombin cleavage site in the spacer domain. ….."The spacer domain, however, harbors at aa position 320 a thrombin cleavage site. This generates the possibility that not a full length protein but a truncated polymerase is linked to the HBV genome to intracellular proteolytic processing ….. "(page 3, top of the revised ms).

4. "It is better to provide a scheme of HBV domains above the fig. 1a and to indicate the location of novel finding sites of NLS and CKII and label the amino acid sequence number for the stretch of sequence in the original fib 1a for clarity. "

In the revised version of the manuscript we include this additional figure as new figure 1a as suggested by the reviewer (figure 1a and corresponding figure legend of the revised manuscript)