Dubova *et al.: Intrinsic Activity*, 2017; **5**(Suppl.2):A2.14
doi:10.25006/IA.5.S2-A2.14
published online: 16 October 2017

INTRINSIC ACTIVITY

2nd International Conference in Pharmacology: From Cellular Processes to Drug Targets

Rīga, Latvia, 19–20 October 2017

MEETING ABSTRACT

A2.14

Evaluation of small-molecule effectors of hepatitis B virus capsid assembly

Unda Nelda DUBOVA[1,*] , Karīna SPUNDE[1], Irēna TIMOFEJEVA[1], Anda SĪPOLA[2], Brigita VĪGANTE[2], Gunārs DUBURS[2] and Tatjana KOZLOVSKA[1]

[1]*Latvian Biomedical Research and Study Centre , Riga, Latvia;*
[2]*Latvian Institute of Organic Synthesis, Riga, Latvia*

Background: Estimated 240 million persons worldwide are chronically infected with hepatitis B virus (HBV). Chronic hepatitis B (CHB) in up to 40% of cases progresses to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), a leading cause of cancer-related morbidity and mortality worldwide [1]. In spite of therapy with efficient inhibitors of HBV reverse transcriptase, a complete cure of CHB can rarely be achieved by this approach [2]. There is an urgent need for development of novel molecular targeted antiviral strategies to improve therapeutic outcomes for HCC. We are focused on antiviral strategy intended to suppress the self-assembly process of HBV core (HBc) protein as one of the promising ways to cure CHB without induction of drug resistance.

Objectives: The objective of the study is the discovery of new, small-molecule, antiviral drug candidates targeted on disruption of HBV capsid assembly.

Methods: The cytoplasmic expression of HBc gene driven by exogenously delivered recombinant self-replicating alphavirus RNA replicons were used for high level production of HBc and HBV capsids in eukaryotic cells. Drug candidates—heterylarylpyrimidines (HAPs) comprising a 1,4-dihydropyrimidine moiety—were obtained according to methods of synthesis of 1,4-dihydropyrimidine derivatives. The evidence of the HBc assembly was assessed by native agarose gel electrophoresis following by western blot analysis. Cytotoxicity of the compounds was estimated by phase-contrast microscopy and MTT viability assay.

Results: The method for direct assessment of HBV capsid assembly in cell culture was established and optimized. Dose-dependent effects on the level of cytoplasmic capsid release were assessed for 8 new HAPs—analogues of Bay-41-4109 [3]. Two compounds (V-4-84s, AS-M-I) showed promising effects by inducing a dose-dependent decrement of the relative quantity of assembled capsids in concentrations less than those needed to affect cell viability. Two other compounds (V4-93, AS-M-III) showed dose-dependent effects on HBc aggregation, possibly inducing disruption in capsid assembly.

Conclusions: Eight newly synthesized small-molecule effectors of HBV capsid assembly were evaluated for their ability to disrupt the capsid assembly in cell culture, promising candidates were selected for further evaluation of antiviral activity and discovery of mechanisms of action.

Acknowledgements: This study was supported by the National Research Programme „Biomedicine for Public Health" (BIOMEDICINE), project no. 3: „Development of novel anticancer drugs and immunotherapeutic approaches", provided by the Latvian Ministry of Education.

Keywords: heterylarylpyrimidines (HAPs) – hepatitis B virus – capsid assembly – Bay-41-4109

**Corresponding author: Unda Nelda Dubova, Biomedical Research and Study Centre, 1 Ratsupites Str., Riga LV-1067, Latvia.*
E-mail: undadubova@inbox.lv

References

1. Gish RG, Given BD, Lai CL, Locarnini SA, Lau JY, Lewis DL, Schluep T: **Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities.** *Antiviral Res,* 2015; 121: 47–58. doi:10.1016/j.antiviral.2015.06.008
2. Phyo WW, Soh AY, Lim SG, Lee GH: **Search for a cure for chronic hepatitis B infection: How close are we?** *World J Hepatol,* 2015; 7(9):1272–1281. doi:10.4254/wjh.v7.i9.1272
3. Stray SJ, Zlotnick A: **BAY 41-4109 has multiple effects on Hepatitis B virus capsid assembly.** *J Mol Recognit,* 2006; 19(6):542–548. doi:10.1002/jmr.801