Conclusion Our data support the advantage of targeting HBP for therapeutic purpose and encourage further investigation about the use of this small-molecule as promising compound for breast cancer therapy.

PO-260 ANTI-LYMPHOMA ACTIVITY OF NOVEL SELECTIVE GLUCOCORTICOID RECEPTOR AGONISTS (SEGRAS) IN VITRO AND IN VIVO

E Lesovaya 1, L Tllova, A Savinkova, E Zhidkova, K Kuzin, F Tetisov, K Kiryanov, A Shirinian, M Yakubovskaya 1. Institute of Carcinogenesis- Bl收款 Cancer Research Center, Chemical Carcinogenesis, Moscow, Russia; 2. P. Pavlov Ryazan Medical State University, Oncology, Ryazan, Russia; 3. N.D. Zelinsky Institute of Organic Chemistry, Organic Chemistry, Moscow, Russia

10.1136/esmoopen-2018-EACR25.292

Introduction Glucocorticoids (GCs) are widely used in blood cancer treatment; although, they cause metabolic disorders. Biological response to GCs is mediated by glucocorticoid receptor (GR) regulating gene expression via transactivation (TA), which requires GR binding to GC-responsive elements in gene promoters, and transrepression (TR), negative interaction between GR and transcription factors. TR mediates anticancer effects of GR, while side effects are associated with GR TA. Selective GR agonists (SEGRAs) that preferentially activate GR TR could be a better option for cancer treatment. One of well characterised SEGRAs is 2-(4-acetoxyphenyl)-2-chloro-N-methyl ethylammonium-chloride, or CpdA, isolated from Namibian shrub Salsola tuberculatiformis. CpdA demonstrated anticancer activity in vitro and in vivo. We extended SEGRA list by synthesis of CpdA enantiomers and its chemical derivatives.

Material and methods Synthesis of (S) and (R)-CpdA was based on Sharpless asymmetric dihydroxylation. Chemical analogues of CpdA, CpdA01-08, were designed by appending of bulky substituent into benzene ring and to nitrogen atom or alkylation of carbon atom adjacent to chlorine atom. All experiments in vitro were carried out on Granta (lymphoma) and CEM (leukaemia) cells. Cells were treated with Dex, CpdA, (R) and (S)-CpdA, CpdA01-08. Effects on cell growth were evaluated by cell counting and flow cytometry. Affinity to GR was measured by competitive binding assay. Gene expression was measured by qPCR and Western blotting. GR and NF-kB activity was assessed using Luciferase reporter analysis. Anti-cancer effect in vitro was determined using the model of murine lymphoma P388.

Results and discussions The most cytotoxic compounds among 10 newly synthesised, CpdA03 and CpdA05, demonstrated the highest affinity to GR. They induced GR TR but not TA and proved their SEGRA properties. Effect of CpdA enantiomers on cell growth and survival was not significantly different from Dex and CpdA. CpdA03, cytotoxic SEGRA with the highest affinity to GR, comparable with DEX and CpdA, was tested in vivo for evaluation its anti-lymphoma activity, and demonstrated 3-fold decrease of tumour size in comparison with 2-2.5-fold decrease after Dex or CpdA treatment.

Conclusion The design of synthesis and evaluation of anti-cancer properties of new SEGRA are provided. According to our data one novel SEGRA, CpdA03, is perspective for further investigation as anti-lymphoma drug with reduced side effects.

Study is funded by Russian Science Foundation No. 17-75-20124.