also in vitro. However, OBX1-012 like other EGFR-TKIs failed to show the efficacy for exon 20 insertion mutation or C797S point mutation.

Conclusion These results identify OBX1-012 as one of highly effective, mutant-selective EGFR-TKIs for treatment of T790M-mediated resistance.

PO-404 CISPLATIN AND RUTHEONIUM(III) COMPLEXES – COMPARISON OF CELLULAR RESPONSE OF TREATED MDA-MB231 BREAST CELLS

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Introduction Since the discovery and clinical success of the platinum(II) anticancer drug, cisplatin, researchers are putting much effort to develop more efficient metal-based therapeutic compounds, with fewer side-effects and greater cytoselectivity. Ruthenium complexes arose as promising anticancer agents, due to the success of some ruthenium drug candidates in clinical trials. Here we report comparison of in vitro cytotoxic activity and mechanisms of action of cisplatin and four newly synthesised ruthenium(III) complexes with bidentate anionic Schiff base derived from 5-methylsalicylaldehyde and methylamine: (complexes 1–4).

Material and methods Cytotoxicity was tested on four human cancer cell lines (K562, A549, EA.hy926, MDA-MB231) and one human non-tumour cell line (MRC-5), by MTT assay. Being the most cytotoxic of all four tested complexes, complex 1 (C1) (Na[RuLCl₂], L=N-propyl-5-chlorosalicyldenimino) nato) is selected for further analyses of molecular mechanisms underlying its activity toward MDA-MB231 cells.

Results and discussions The average IC₅₀ values were in the low micromolar range 2–23 μM, depending on cell line. Investigated complexes displayed an apparent cytoselective profile, as they reduced the viability of tested tumour cell lines more efficiently than of the non-tumour MRC-5 cells. Cisplatin resistant MDA-MB231 cells showed to be ten times more sensitive to C1 (IC₅₀=2 μM) than to cisplatin. 24 hour treatment of MDA-MB231 cells with IC₅₀ values of C1 and cisplatin induced minor cell cycle alterations, while 48 hour treatment induced substantial accumulation of cells in Sub-G1 region, up to 22.4% (C1) and 86.4% (cisplatin), versus control 4.8%. Acridine orange/ethidium bromide dual staining confirmed the Annexin V-FITC/PI assay results of notable reduction in cell number after the treatment with C1 and cisplatin. While cisplatin-treated cells prominently die of necrosis, C1-treated cells after 24 hour treatment show apoptotic morphology, but after prolonged treatment, necrosis becomes predominant. Decrease in the intracellular levels of reactive oxygen species was comparable in the cisplatin-treated and C1-treated cells, with cisplatin displaying more conspicuous effects at higher dose. C1 entered the cells more efficiently compared to cisplatin. Intracellular C1 concentration after 4 hour treatment exceeded that of cisplatin by 7.8 times approximately.

Conclusion Present study pointed out interesting activity of this type of ruthenium(III) complex and need for further biological studies and its chemical structure optimisation.

PO-405 REPOSITIONING EXISTING DRUGS AS NOVEL THERAPEUTICS FOR HIGH-RISK PAEDIATRIC LEUKAEMIA

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Introduction Despite remarkable improvements made in the treatment of childhood acute lymphoblastic leukaemia (ALL), prognosis remains dismal for a certain subgroups of high-risk (HR) patients including infants with leukaemia harbouring rearrangement of the Mixed Lineage Leukaemia (MLL/KMT2A) gene. Development of more effective, less toxic therapeutics is therefore urgently needed. The aim of this study was to identify compounds that target HR leukaemia cells based on drug-repurposing, whereby an approved drug is applied to treat a disease other than the one for which it was originally intended.

Material and methods New AbstractSelect Abstract A phenotypic screen was performed against HR leukaemia cell lines with a tailored compound library of 3707 approved drugs and pharmacologically active compounds.

Results and discussions The screen identified that two FDA-approved drugs, auranofin and disulfiram, originally developed for treatment of rheumatoid arthritis and chronic alcoholism respectively, had preferential cytotoxicity against leukaemia cell lines compared to solid tumours and normal cells (p<0.0001). Both compounds subsequently showed potent activity in paediatric high-risk leukaemia patient-derived xenograft (PDX) cells cultured in vitro, including xenografts derived from MLL-rearranged ALL and Philadelphia-positive ALL subtypes. The compounds induced apoptosis within 12 hours of treatment through an increase in intracellular reactive oxygen species (ROS) (p<0.01), which was accompanied by induction of Nrf2, a master regulator of the antioxidant response. Incubation with ROS scavenger N-acetyl cysteine prior to treatment with either drug prevented the increase in cellular ROS levels (p<0.05) and rescued cells from apoptosis (p<0.0001). The drugs showed synergy with each other, and auranofin also potentiated the established chemotherapeutic cytarabine in resistant HR leukaemia cells (p=0.016).

Conclusion In summary, we have identified two FDA-approved drugs that demonstrated potent, synergistic anti-leukaemia activity through ROS induction as well as chemosensitise cells that are resistant to current chemotherapeutics, potentially opening up new avenues for clinical treatment of HR paediatric leukaemia. We will be testing these therapies in vivo using relevant PDX models of HR paediatric ALL.

PO-406 THE OLIVE-BASED OLEOCANTHAL AS A DUAL HER2-MET INHIBITOR FOR THE CONTROL OF BREAST CANCER

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Abstracts

Introduction Dysregulation of the receptor tyrosine kinases HER2 and Met correlate with poor breast cancer prognosis and invasive aggressive profile. Met amplification proved to be the HER2-dependent tumours inevitable escape mechanism from the anticancer effects of targeted therapies including trastuzumab, and small-molecule RTK inhibitors like lapatinib, gefitinib, and erlotinib. Dual HER2-Met inhibition is expected to be effective and less likely to develop resistance. As a result, these unavoidable critical conditions now create a high demand either to design or identify a lead molecule that can inhibit Met/HER2 combinedly.

Material and methods To validate the hypothesis molecular modelling used to identify a Met/HER2 hit from a wide library of natural compounds. Identified hits via virtual screening further validated through cell free Z-LYTE and cell viability assay in a wide range of cancer cell lines. In addition, cytotoxicity tested in non-cancer cell line. Western blot and flowcytometry analysis used to validate the activity of the identified hit at molecular level. Finally, to push the hit into a lead rank used in vitro athymic nude mice in two different xenograft model such as MDA-231, BT-474 in both IP and oral administration.

Results and discussions OC showed typical type-I binding mode at Met ATP kinase domain. OC aldehydes, ester, phenol groups showed critical interactions at activation loop ASP1222/Tyr1230 and hinge region PRO1158/NET1160. OC uniquely interacting HER2 kinase domain at hinge region MET801, PHE864, THR862 and SER783. OC showed low-μM inhibitory activities against both Met and HER2 kinases in cell-free Z-LYTE assays. In vitro, OC showed inhibition of the proliferation and migration in BC cells BT-474, SK-BR-3, MDA-MB-231 at low μM IC50 dose range. OC effect on HER2 and MET were further confirmed by Western blotting, flowcytometry studies. OC potently induced autophagy in SK-BR-3 by upregulation of LCA/B, Arg-3, Arg-7, Arg-16L within 6–12 hour treatment. OC had no effect on the viability of the non-tumorigenic MCF-12A and RSC 96 cells. In vivo, 5–10 mg/kg oral/ip dose range of OC potently inhibited 65%–90% tumour growth both BT-474 and MDA-MB-231 BC cells xenograft models. This was further confirmed by significant reductions of Ki-67, CD31 in treated animal tumours by IHC.

Conclusion Collectively, these promising results suggest that OC is a unique dual Met/HER2 inhibitory lead entity with excellent therapeutic potential to control breast malignancies with aberrant Met or HER2 activity.

PO-040 METHANOL EXTRACT OF HOLOTHURIA SCABRA INHIBITS CELL GROWTH AND INDUCES APOPTOSIS IN T47D BREAST CANCER CELLS

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Introduction Breast cancer remains a major public health burden. Low efficacy, low safety and side-effects of some cancer drugs have increased the research interest for new anti-cancer drugs, particularly from natural products. Sea cucumber as one of marine organisms contains numerous bioactive compounds which have anti-oxidant, anti-inflammatory and anti-cancer properties. This study was designed to investigate the anti-cancer potential of methanol extract of sea cucumber Holothuria scabra on T47D breast cancer cell line.

Material and methods The growth inhibition of methanol extract of Holothuria scabra towards T47D cells was evaluated by the WST-1 (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolol]-1,3-benzene disulfonate) test. The extract of methanol extract of Holothuria scabra on apoptosis of T47D cells was determined by Annexin V-Propidium Iodide apoptosis