glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. GLP-1 binds to a specific GLP-1 receptor (GLP-1R), which is expressed in many tissues including; pancreatic beta cells, gastric mucosa, kidney, lung, heart, skin, immune cells, and the hypothalamus. In addition, those receptors are expressed in some types of cancers; including medullary thyroid, ovarian and colorectal cancers. The aim of our study is to explore the effect of GLP-1R agonist (exendin-4) and GLP-1 antagonist (exendin 9–39) on human pheochromocytoma (hPheo1) and colorectal cancer (HT29) cell proliferation and migration.

Material and methods GLP-1 receptor expression was detected by Western Blotting and real time PCR in 4 different cell lines; colorectal HT29, HCT116, [m1] pheochromocytoma (hPheo1) and neuroblastoma (SH-SY-5Y). Different concentrations (0.1–100 μM) of exendin-4 and exendin 9–39 (5 and 10 μM) were applied on hPheo1 and HT29 cell lines. The effect on proliferation was detected after 48 and 72 hours by cell viability assay (MTT). Cell migration assay was detected by wound healing experiment through measuring migration distance rate. Statistical significance was assessed using ANOVA, followed by post hoc Tukey Kramer test when groups were significantly different.

Results and discussions The GLP1R gene is expressed in all 4 cell lines cell lines. Exendin-4 increased proliferation of hPheo1 and HT29 cell lines at 0.1μM and 1μM concentrations, as compared to control group (p<0.001). No proliferative effect was observed of exendin-4 at 10 μM, or exendin 9–39 in both hPheo1 and HT29 cell. Combination of exendin 4 and exendin 9–39 significantly decreased cell proliferation in both cell lines (p<0.001). There was no significant difference on cell migration distance rate after 24 hour-treatment of cells with either exendin-4 or exendin 9–39 or combination of both.

Conclusion The GLP-1R agonists may increase the proliferation of cancer cells initially and at low doses, whereas higher doses decreases the proliferation rate. They are likely to have no effect, or potentially favourable suppressing effect on cancer cell proliferation and migration in pheochromocytoma and colorectal cancer.

PO-454 BIOLOGICAL ACTIVITIES OF NOVEL BRASSINOSTEROID ANALOGUES IN BREAST CANCER CELLS

1O Andreeva, 2O Savochka, 1D Scherbinin, 2V Zhabinskii, 2V Khripach, 3A Scherbakov*. 1N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Laboratory of Molecular Endocrinology, Moscow, Russia; 2Institute of Bioorganic Chemistry- National Academy of Sciences of Belarus, Laboratory of Steroids, Minsk, Belarus; 3Skolkovo Institute of Science and Technology, Center for Data-Intensive Biomedicine and Biotechnology, Moscow, Russia; 2Institute of Biomedical Chemistry, Laboratory of Structure Bioinformatics, Moscow, Russia; 3N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Laboratory of OncoProteomics, Moscow, Russia

Introduction Brassinosteroids (BS) are plant steroid hormones playing an important roles in various physiological processes and being of particular interest because of their antiproliferative activities towards human cancer cells. The study was dedicated to the synthesis of novel BS analogues and to the analysis of their effects on breast cancer (BC) cells and normal epithelium.

Material and methods We developed an approach for the synthesis of novel secasterol derivatives with variations in the B cycle and side chain. Six new compounds, BS2-BS7, were obtained. Biological experiments were performed on the MCF-7 BC and MCF-10A normal breast epithelium cell cultures. The cytotoxicity was assessed by MTT test. Dock6 and Autodock Vina were used for molecular docking. Binding energies were evaluated using MM_PBSA approach on the 15 ns trajectories of MD simulation (Gromacs 5.1). Reporter assays were performed in steroid-free conditions. The MCF-7 BC cells were transfected with plasmids containing sequences for ERα- and AP-1-driven luciferase expression together with β-galactosidase plasmid to control the transfection efficacy. After transfection cells were treated with BS or vehicle control; then in 9–24 hour the cells were collected for subsequent analysis of luciferase and β-galactosidase activities. ERα expression was measured by immunoblotting.

Results and discussions Evaluation of BS toxicity against MCF-7 revealed that compounds with cholestane/ergostane based side chain inhibited cell growth with IC50 values of 12.7–23.6 μmol. (22R,23R,24R)–22,23-Dihydroxy-24-methyl-B-homo-7-oxa-5α-cholesten-2-ene-6-one (BS4) was chosen as the lead compound with low toxicity in MCF-10A normal epithelium and high activity against BC. ERα was found to be a presumable target of BS. BS/ERα complex structures were obtained using molecular docking software. The best BS4 conformation was found to match 17β-oestradiol conformation in ERα ligand-binding domain and had the best binding energy values during MD simulation compared with BS2 analogue. Reporter assays showed that compound BS4 decreased (up to 47%) 17β-oestradiol-mediated activation of ERα transcription; moreover it also reduced ERα expression. BS4 was found to downregulate ERα–related transcription factor, AP-1.

Conclusion Anticancer activities of novel compound BS4 look promising and require further studies to investigate their complex effects on breast cancer cells. The study was carried out with financial support by RFBR (project No. 17-54-04054 Bel_mol_a) and BRFFR (project No. X17PM-040).

PO-455 EPIGENETIC INSIGHTS: RESMINOSTAT REGULATES TARGETS ASSOCIATED WITH THE PATHOGENESIS OF CUTANEOUS T CELL LYMPHOMA (CTCL)

AC Bretz*, T Wulf, U Parnitzke, S Schreper, K Kronthaler, M Borgmann. 4SC, Translational Pharmacology, Planegg-Martinsried, Germany

Introduction Cutaneous T cell lymphoma (CTCL) is a heterogeneous group of extra-nodal non-Hodgkin lymphomas arising from transformation and clonal expansion of skin-homing T cells. Epigenetics alterations have been described for the molecular pathogenesis of CTCL. Resminostat is a potent, orally bioavailable histone deacetylase (HDAC) inhibitor targeting class I, IIb and IV and is currently in phase II of clinical development. Resminostat showed anti-tumoral in vitro efficacy by inhibiting proliferation of CTCL cell lines. The aim of this study was to elucidate resminostat’s molecular mechanism of action in CTCL using a genome-wide approach.

Material and methods Resminostat’s mechanism of action was analysed using a set of established CTCL cell lines representing different types of CTCL. Global lysine acetylation was evaluated by flow cytometry and specific histone H3 acetylation at lysine residue 27 (H3K27ac) was mapped genomewidely by chromatin immunoprecipitation followed by
sequencing (ChIP-seq). Resminostat’s effect on global gene expression was analysed by RNA-seq focusing on CTCL-relevant pathways and genes.

**Results and discussions** Resminostat increased total lysine acetylation in CTCL cell lines. The active epigenetic mark H3K27ac dose-dependently accumulated on a genome-wide level as detected by ChIP-seq analysis. Global gene expression profiling revealed both gene induction and repression by resminostat. First data showed a regulation of T helper (Th) 1 and 2 specific genes implying that resminostat normalises the Th1/Th2 imbalance in CTCL which is discussed to be associated with disease progression. Moreover, expression of skin-homing receptor genes was reduced by resminostat indicating a potential effect of resminostat on the cutaneous tropism of malignant T cells. Furthermore, the pruritus mediator IL-31 was downregulated by resminostat suggesting an attenuation of itching and thus indicating an important benefit for CTCL patients regarding their health-related quality of life.

**Conclusion** First results from a genome-wide study suggest a promising impact of resminostat on different targets relevant for the pathogenesis of CTCL. These data broaden our understanding of resminostat’s molecular mechanism of action in CTCL and support our current clinical phase II trial evaluating resminostat for maintenance treatment of patients with advanced stage CTCL (RESMAIN, NCT02953301).

**PO-456**

**CELL LINE PANEL PROFILING OF ALL CLINICALLY APPROVED KINASE INHIBITORS FOR CANCER TREATMENT**

JJ Kooijman*, JCM Uitdehaag, IAOMDe Roos, JRF De Vetter, MBW Prinsen, J Dylus, J De Man, SIC Van Gerwen, RC Buljiman, GR Zaman. Netherlands Translational Research Center B.V., n/a, Oss, The Netherlands

10.1136/esmoopen-2018-EACR25.477

**Introduction** Profiling of drugs on cancer cell line panels can uncover new insights into the mechanisms of drug response. We have established a panel of 102 genetically well-characterised cell lines from distinct tumour origins, called Oncolines. Earlier work on kinase inhibitor profiling showed that our workflow generates highly reproducible data. Here we present the profiling of seventeen kinase inhibitors which have been approved since November 2014 in the Oncolines panel.

**Material and methods** The profiled agents include the ALK inhibitors ceritinib, brigatinib, and alectinib, the CDK4/6 inhibitors palbociclib, abemaciclib, and ribociclib, the BTK inhibitors ibrutinib, and acalabrutinib, and nine other novel marketed inhibitors that were not profiled earlier. The cell lines were screened in parallel in a high-throughput proliferation assay based on ATP-lite read-out, at 9 duplicate concentrations of each inhibitor. Drug response was expressed as IC50 and GR50 values.

Drug response metrics were associated with genomic alterations in the cell lines. These were retrieved from the Catalogue of Somatic Mutations in Cancer database and filtered for relevance in primary patient tumours.

**Results and discussions** Of the ALK inhibitors, alectinib was more selective than ceritinib and brigatinib. Cell lines harbouring the NPM-ALK translocation were potently inhibited by all three inhibitors. There was a strong correlation between drug sensitivity and high ALK expression levels. Furthermore, elevated expression of JAK3 and other JAK-STAT signalling genes correlated with drug sensitivity, indicating a potential role of JAK-STAT signalling in response to ALK inhibitors. Elevated expression of the transcription factor MYCN was indicative of the sensitivity of NPM-ALK negative cell lines for ceritinib and brigatinib.

**Conclusion** By profiling all clinically approved kinase inhibitors, we were able to compare their selectivity and identify novel response biomarkers. These data will be important in guiding novel applications of these inhibitors as well as future drug development in the kinase field.

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**PO-457**

**IS 8-AZAGUANINE SELECTIVELY ACTIVE AGAINST ANEUPLOID ACUTE MYELOID LEUKAEMIA?**

A Cazzola*, I Jansen, A Kraemer. German Cancer Research Center DKFZ, Clinical Cooperation Unit Molecular Hematology/Oncology and Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany

10.1136/esmoopen-2018-EACR25.478

**Introduction** Aneuploidy, the presence of an abnormal number of chromosomes within a cell, is a recurrent characteristic of both solid and haematological tumours. A substantial number of patients with acute myeloid leukaemia (AML) harbour a complex karyotype, which consists in three or more aberrations, including numerical chromosome abnormalities in the absence of prognostically favourable rearrangements. The prognosis of these patients is dismal due to the poor response to the conventional therapy, a combination of the nucleoside analogue cytarabine and the anthracycline daunorubicin. For this reason compounds that specifically cause lethality in karyotypically abnormal cells with numerical chromosome aberrations could provide a novel treatment approach.

**Material and methods** With the aim to identify compounds that are more cytotoxic against aneuploid versus diploid AML cells, we tested a group of chemicals on 36 primary human AML samples (18 with a euploid karyotype, 18 with an aneuploid karyotype) derived from either bone marrow or peripheral blood. We further established an isogenic AML cell line model to confirm the observations made on primary cells and to gain insight into the aneuploidy-specific mechanisms of action of the drugs.

**Results and discussions** We identified 8-azaguanine as a compound that causes lethality in aneuploid primary cells more efficiently than in euploid cells. In the cell line model, both viability and apoptosis assays suggest that the aneuploid clones at earlier differentiation levels respond better to 8-azaguanine than the euploid cells, with the tetraploid clone responding the best.

**Conclusion** Our results provide an initial clue to proceed with further investigations on the therapeutic application of 8-azaguanine against aneuploid AML.