**Epigenetic Mechanisms**

**PO-352 HIJACKING HEPATOCellular CARCinoma (HCC) TUMOR PROGRESSION THROUGH RESTORING TP53/MIR-15A/MIR-16 TUMOR SUPPRESSOR AXIS AXBy A NOVEL QUERCETIN GLYCOSIDE**

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**Introduction** Recently, a novel arm of intrinsically embedded protection mechanism downstream the well-known tumour suppressor gene, TP53, has been revealed. Where TP53 was found to act as a pivotal regulator of the expression of several miRNAs with growth suppression properties. TP53 could indirectly affect processing machinery of several miRNAs such as miR-16, miR-15a and miR-16 forming a single cluster that is frequently deleted in cancers. However, little is known about miR-15a and miR-16 in HCC. Recently, researchers have unveiled an immense potential of several flavonoids in HCC treatment. Lately, our research group has isolated novel quercetin glycosides from Cleome droserifolia with potent anti-neoplastic effects against breast and colorectal cancers. However, their functional role in HCC has never been investigated. The aim of this study was to investigate the impact of isolated flavonoidal compounds on HCC cell lines and to further unveil its impact on TP53 and its downstream miR-15a and miR-16 as a proposed triad responsible for its anti-neoplastic actions.

**Material and methods** Huh-7 and HepG2 cells were cultured and treated with serial dilutions of isolated flavonoids. Cellular viability was assessed using MTT assay and trypan blue mediated actions were assessed using BrdU, scratch and colony forming assays respectively. Total RNA was extracted and quantified by qRT-PCR.

**Results and discussions** Isorhamnetin-3-O-β-D-glucoside, Quercetin-3′-methoxy-3-O-(4′-acetylhamnoside)-7-O-α-Rhamnoside, and Kaempferol-4′-methoxy-3,7-O-dirhamnoside were isolated from C. droserifolia showed a concentration and time dependent reduction in cellular viability and anchorage-independent growth of HCC cells. Moreover, they exhibited a reduction in the migrating capacity of HepG2 cells. Compound showed the most potent effects IC\textsubscript{50} = 36 ± 1.70 μM. Compound showed a substantial reduction in the cellular proliferation rate. In an attempt to elucidate the possible molecular mechanism of action for, a significant elevation of TP53, miR-15a and miR-16 levels were observed. Of note, attenuation of compound mediated actions was shown upon using miR-15a and miR-16 inhibitors.

**Conclusion** This study crystallises a novel role of C. droserifolia in hijacking HCC progression in-vitro. Moreover, it provides substantial evidence that acts as novel therapeutic agent through restoring TP53/miR-15a/miR-16 tumour suppressor axis in HCC.

**PO-353 TIP60-DEPENDENT ACETYLATION OF SPZ1-TWIST COMPLEX PROMOTES EPITHELIAL–MESENCHYMAL TRANSITION AND METASTASIS IN LIVER CANCER**

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**Introduction** Metastasis is the main cause of cancer mortality. However, the triggering mechanisms and regulation of epithelial–mesenchymal transition (EMT) factors in the commitment of metastasis have not been well characterised. Spermatogenic Zip 1 (SPZ1) acts as a proto-oncogene and an upstream regulator of EMT during tumorigenesis.

**Material and methods** Here we reported that acetyltransferase Tip60 (HIV-1 Tat-interacting protein 60 kDa) mediates acetylation of SPZ1 on lysine residues at positions 369 and 374 and TWIST1 on lysine residues at positions 73 and 76, which are required for of SPZ1-TWIST1 complex formation and cancer cell migration in vitro and in vivo.

**Results and discussions** Ectopic SPZ1 and TWIST1 expression, but not that of TWIST1 alone, enhanced vascular endothelial growth factor (VEGF) expression via recruitment of bromodomain-containing protein 4 (BRD4), enhancing RNA Pol II-dependent transcription for inducing metastasis. Neutralisation of VEGF by humanised monoclonal antibodies, such as avastin, effectively abrogates EMT and oncogenesis induced by acetylated SPZ1-TWIST1 complex.

**Conclusion** Our finding highlights the importance of acetylation signalling of the SPZ1-TWIST1-BRD4 axis in mediating EMT and its regulation on tumour initiation and metastasis.

**PO-354 DISRUPTING THE ACETYLATION OF ISX-BRD4 BY P300/CBP-ASSOCIATED FACTOR (PCAF) SUPPRESSES TUMOUR METASTASIS**

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**Introduction** The epithelial–mesenchymal transition (EMT) is an important process in the progression of cancer, but its occurrence and the regulatory mechanism are not fully understood.

**Material and methods** In this study, Intestine specific homeobox (ISX) acted both as a proto-oncogene and upstream regulator of EMT markers, by which modulates tumorigenic initiation and progression in lung cancer cells.

**Results and discussions** Mechanistically, ISX acetylated by p300/ CBP-associated factor (PCAF) recruits chromatin reader, bromodomain- containing protein 4 (BRD4), to initiate chromatin remodelling, and upregulated EMT downstream regulators in tumours cells. Ectopic expression of ISX were shown to enhance TWIST1, Snail1, vascular endothelial growth factor (VEGF) expression by recruiting BRD4 to enhance Pol II-dependent transcription, leading to remodelling of the tumour
microenvironment. Neutralising VEGF by avastin effectively abrogates metastasis induced by the ISX-BRD4 complex. In NSCLC carcinoma samples, significantly increased ISX expression was noted, correlating with distinct clinical metastatic features and poor prognosis.

**Conclusion** These results suggest that the ISX-BRD4 axis mediates EMT signalling and exerts significant regulatory effects on tumour initiation and metastasis.

**PO-355** ENHANCERS MAPPING UNCOVERS PHENOTYPIC HETEROGENEITY AND EVOLUTION IN PATIENTS WITH LUMINAL BREAST CANCER

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**Introduction** Breast cancer (BC) is the most common cancer type and the second most frequent cause of cancer related death in women. 70% of all BC cases contain variable amounts of oestrogen receptor-alpha (ERα) positive cells. ERα is central to BC pathogenesis and serves as the target of endocrine therapies (ET). ERα-positive BC is typically subdivided in two ‘intrinsic’ molecular subtypes (luminal A and luminal B) characterised by distinct prognosis, highlighting functional inter-patient heterogeneity. Recent analyses demonstrate that patient-to-patient heterogeneity is more pervasive (reflected by histological, genetic architecture and transcriptional differences) ultimately influencing long-term response to endocrine treatment. Additionally, the presence of genetic intra-tumour heterogeneity has also now been extensively documented in several cancer types, demonstrating the role of clonal evolution in cancer. Parallel to genetic evolution, phenotypic/functional changes driven by epigenetic mechanisms can also contribute to breast cancer progression and ET resistance in cell lines. Nevertheless, little is known about the epigenome of BC patients, its influence on intra-tumour phenotypic heterogeneity and its role in breast cancer progression.

**Material and methods** Here we show the results of a systematic investigation of the epigenetic landscape ERα positive primary and metastatic breast cancer from 47 individuals. Our results represent the first large scale topographic mapping of the active regulatory landscape of longitudinal ERα-positive BC. Using H3K27ac we mapped active promoters and enhancers across treatment naïve primary and endocrine treated metastatic patients. We used bioinformatic approaches to deconvolute the complex regulatory landscape and identified inter- and intra-patient epigenetic heterogeneity.

**Results and discussions** We mined promoters and enhancers from clinically relevant breast cancer samples for potential regulatory drivers identifying YY1 as a novel key player in ERα-positive BC. Finally, we demonstrate that epigenetic mapping can efficiently estimate phenotypic heterogeneity changes throughout BC progression.

**Conclusion** Collectively, our data show that epigenetic mechanisms significantly contribute to phenotypic heterogeneity and evolution in systemically treated breast cancer patients.

**PO-356** WHITE BLOOD CELLS FROM PROSTATE CANCER PATIENTS CARRY DISTINCT CHROMOSOME CONFORMATIONS

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**Introduction** Current diagnostic blood tests for prostate cancer are unreliable for the early stage disease, resulting in numerous unnecessary prostate biopsies in men with benign disease and false reassurance of negative biopsies in men with prostate cancer. Three-dimensional genome architecture and chromosome structures undergo early changes during tumorigenesis both in tumour and in circulating cells and can be potentially used for cancer diagnosis.

**Material and methods** In this report, we have performed chromosome conformation screening for 14,240 chromosomal loops in the loci of 425 cancer related genes in peripheral blood mononuclear cells (PBMCs) of prostate cancer patients (n=107) and non-cancer controls (n=105).

**Results and discussions** Our data show that PBMCs from prostate cancer patients acquire specific chromosome conformation changes in the loci of cancer-related genes. New chromosomal loops in the loci of CASP2, ETS1, SLC22A3, MAP3K14 genes were unique to the prostate cancer cohort. In prostate cancer patients, chromosome conformations identified in PBMCs had high similarity to those in primary prostate tumours. Blind testing on an independent validation cohort of prostate cancer patients yielded prostate cancer detection with 80% sensitivity and 80% specificity.

**Conclusion** Our results indicate that there are specific chromosome conformations in the blood of prostate cancer patients that are not present in control group. These conformations are shared between PBMCs and primary tumours, but exact mechanism of their appearance is not yet identified. It is possible that these epigenetic signatures may potentially lead to development of a blood-based prostate cancer diagnostic tests. Similar approaches could be used to investigate the prognostic significance of these signatures to determine the risk of tumour progression.

**PO-357** SREBP1 DRIVES CELL-AUTONOMOUS CYTOSKELETAL CHANGES BY KRT80 REMODELLING DURING ERα BREAST CANCER PROGRESSION

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**Introduction** Approximately 30% of oestrogen receptor α positive (ERα) breast cancer patients progress to invasive metastatic disease despite adjuvant treatment with targeted endocrine