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 of 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 tumourigenesis 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

therapies. The relationship between acquisition of drug resistance and invasive potential is poorly understood. Currently, invasive behaviour is thought to be driven mainly by epithelial to mesenchymal transition.

Material and methods MCF7 cell line and derived resistant clones were used for this study. MCF7 Tamoxifen Resistant (MCF7TR) and LTED (Long Term Oestrogen Deprivation) were derived from MCF7 upon one-year Tamoxifen or oestrogen deprivation, respectively. LTED combination treatments were also used (LTEDT and LTEDF). Additionally, we used T47D and T47D-LTED. Stable cell lines were generated for both KRT80 over-expression and knockdown. 3D organoids invasion assay, immunofluorescence, confocal microscopy, RNA-seq, ChIP-seq, RT-qPCR and Western blot were performed. Seventy-five human breast specimens and ten metastatic lymph nodes were selected with the approval of Imperial College Healthcare NHS Trust Tissue Bank. Twenty women with suspected breast cancer were prospectively recruited and radiological exam using shear wave ultrasound was used to determine tissue stiffness in the normal and peritumoral stroma, and suspected lesion.

Results and discussions In this study, we show that cells that acquire resistance to aromatase inhibitors (AI) undergo active cytoskeleton re-organisation via Keratin 80 (KRT80) and F-Actin remodelling. These features directly drive the invasive phenotype. Mechanistically, we show that this process is driven by epigenetic reprogramming at the type II keratin locus (chromosome 12) leading to Keratin 80 (KRT80) up-regulation. Reprogramming is dependent on *de novo* SREBP1 binding to a single enhancer that is activated upon chronic AI treatment. AI-treated patients show KRT80 cytoskeletal re-organisation and an increased number of KRT80 positive cells at relapse. We find that KRT80 activation and redeployment leads to increased F-actin deposition and focal adhesion. Additionally, we show that KRT80 manipulation directly contributes to changes in cellular stiffness and invasive potential. In agreement, shear-wave elasticity imaging of prospective patients show that KRT80 levels correlate with stiffer tumours *in vivo*.

Conclusion Collectively, our data uncover an unexpected and potentially targetable link between epigenetic reprogramming and cytoskeletal changes promoting cell invasion.

PO-358 ABSTRACT WITHDRAWN

PO-359 OVEREXPRESSION OF HISTONE H3K4 DEMETHYLASES IN CLEAR CELL RENAL CELL CARCINOMA WITH LSD2 AS PLAUSIBLE THERAPEUTIC TARGET

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Introduction Clear cell renal cell carcinoma (ccRCC) is the leading cause of cancer related deaths among urological malignancies. ccRCC arises through the acquisition of genetic and epigenetic alterations, of which histone modifications are emerging filed of interest. Histone methylation has been implemented in renal cancer but its clinical value and underlying pathology is still unexplored. Hence, the goal of present study was to elucidate the expression profile of histone 3 lysine 4 (H3K4) modifiers in ccRCC and to evaluate their role in tumour biology.

Material and methods The expression profile of 20 H3K4 modifiers, including 13 methylases (HMTs) and 7 demethylases (HDMs), was estimated in 50 cases of ccRCC and adjacent normal tissues using RT-PCR. For functional analysis, siRNAs mediated gene silencing was used in A498 and ACHN cell lines followed by evaluation of tumour characteristics by FACS and MTT assay. The study was approved by Institute Ethics Committee (ref. no- NK/1597/Ph.D/10916).

Results and discussions The data showed the differential expression of histone modifiers in ccRCC. Among 13 HMTs, 4 genes viz, MLL1 ($p=0.012$), MLL2 ($p=0.024$), SMYD2 ($p=0.016$) and NSD2 ($p=0.004$) was significantly up regulated in ccRCC in comparison to normal tissue. Similarly, out of 7 HDMs, the mRNA levels of 4 genes, KDM5A ($p=0.001$), KDM5B ($p=0.047$), LSD2 ($p=0.002$) and FBXL10 ($p=0.000$) was significantly augmented in ccRCC. Interestingly, when HMTs and HDMs were compared with one another, it was found that higher percentage of histone demethylases was significantly over-expressed with cumulative expression of 1.31 times elevated compared to methylases. This over-expression of HDMs might be engaged in the reduction of H3K4me code in ccRCC. Further, two demethylases LSD2 and KDM5A were selected for functional characterisation. Cell viability of A498 and ACHN cells was reduced after 48 hours of inhibition of LSD2 and KDM5A genes. This decreased in cell viability was due to induction of early apoptosis as revealed by annexin-V/PI staining using FACS. Further, cell cycle analysis showed the arrest of A498 and ACHN cells at S and sub-G1 phase after LSD2 and KDM5A knockdown. Taken together, these data suggest that LSD2 and KDM5A inhibition impaired cell proliferation with the induction of apoptosis and corresponding cell cycle arrest.

Conclusion Our findings provide the novel insights behind the pathology involved in H3K4 methylation code alteration in ccRCC and further provide the drugable targets with therapeutic potential.

PO-360 EPIGENETIC CHANGES IN TESTICULAR CANCER SURVIVORS TREATED WITH CISPLATIN

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Introduction Testicular germ cell cancer, hereafter called testicular cancer (TC), is the most common malignancy in young men in lagre parts of the world. Cisplatin-based chemotherapy (CBCT) has contributed to an increase in TC survival rates over the last decades. However, cisplatin exposure has been shown to result in drug-induced DNA hypermethylation. The aim of the present study is to study the effects of CBCT on DNA methylation in cisplatin-treated vs untreated TC survivors.

Material and methods We included 279 Norwegian TC survivors, where 103 underwent orchiectomy, and 176 orchiectomy and additional CBCT. The two groups were matched on age at blood sampling. The TC survivors were re-examined on