Abstract Book

Hormone Dependent Cancer Conference 2025

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Oral Communications

Symposium 1: Genomics of Hormone Dependent Cancers
Monday 17 November 2025, 10:20 – 11:20

OC1

Uncovering regulatory dependencies in neuroendocrine prostate cancer through proteomic and targeted perturb-seq (TAPseq) profiling

George Couch[1,2], Shalini Rao[1], Soleilmane Omarjee[1], Hamish McMillan[1], Abigail Edwards[1], Igor Chernukhin[1], Valar Franklin[1], James Rogan-Hill[1], Alex Deamer[1], George Gentsch[1], Paula D'Santos[1], Ania Piskorz[1], Clive D'Santos[1], Alasdair Russell[1], Jason Carroll[1]

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Prostate cancer is the UK's second most common cause of male cancer death. It typically arises as an androgen receptor (AR) pathway responsive adenocarcinoma (ARPC). Therapy involves inhibiting AR signalling, however around 20% of patients relapse with treatment-resistance, castration-resistant prostate cancer (CRPC). Treatment of CRPC can induce a phenotype switch into a highly aggressive variant, neuroendocrine prostate cancer (NEPC).

Using rapid immunoprecipitation and mass spectrometry of endogenous proteins (RIME), the interactomes of key transcription factors (TFs) in NEPC cell lines were profiled, revealing cofactors shared across TFs and NEPC models. Cofactors normally associated with the AR transcriptional complex in ARPC were instead bound to ASCL1, FOXA1, FOXA2 and POU3F2 (BRN2) in NCI-H660 (H660) NEPC cells. A CRISPR screen of 55 cofactors was performed using targeted perturb-seq (TAPseq), focusing on transcriptomic markers of prostate cancer phenotype derived from patient data.

Knockout of NEPC-associated genes ASCL1 and EZH2 downregulated the NEPC signature, while knockout of SOX2 upregulated the ARPC signature in H660 cells. Conversely, knockout of ARPC-associated genes FOXA1, HOXB13, AR and GATA2 downregulated the ARPC signature and upregulated the NEPC signature in LNCaP cells. Notably, knockout of FOXA2, an established driver of NEPC transdifferentiation, had little effect in H660 cells, possibly reflecting the relative abundance of FOXA1 in this cell line model, or suggesting FOXA2 may be required for initiation but not maintenance of the NEPC phenotype.

Several knockouts downregulated the NEPC signature while upregulating the ARPC signature in H660 cells, implying potential to reverse established NEPC towards an ARPC-like state. One candidate upregulated both AR and HOXB13, lineage-defining transcription factors of ARPC. Strikingly, FOXA1 knockout in H660 cells produced the strongest switch towards an ARPC-like transcriptional program, which may be model related or due to the binding of FOXA1 to NEPC-specific enhancers or reported interaction with SOX2 in the neuroendocrine context.

These findings highlight regulatory dependencies underlying lineage plasticity in prostate cancer. Unbiased functional genomics and proteomics approaches can uncover targets with potential to resensitise NEPC to existing AR-directed therapies, paving the way towards novel strategies in this aggressive disease.

OC2

Progestin Subtype Dictates Early Breast Carcinogenesis: Oncogenic Role of Androgenic Progestins

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Breast cancer (BC) is the most common malignancy in women, with >70% classified as estrogen receptor-positive (ER^+). ER signaling drives progression and is targeted by SERMs, SERDs, and aromatase inhibitors. Other nuclear receptors, including progesterone receptor (PR) and androgen receptor (AR), are often co-expressed in ER^+ BC and represent emerging therapeutic targets. Epidemiological data link hormonal exposures to risk: hormonal contraception modestly increases BC risk (RR 1.20–1.24), particularly with levonorgestrel (LNG)-based products (RR 1.21–1.45), and combined estrogen–progestin HRT confers higher risk than estrogen alone (RR 2.3 vs. 1.33), whereas natural progesterone does not (E3N cohort). Previous work from lab showed that androgenic progestins stimulate proliferation and induce PR target genes (Rankl, Wnt4), whereas antiandrogenic progestins do not.

We employed ex vivo assays using fresh reduction mammoplasty tissue and mammary intraductal (MIND) xenografts of patient-derived ER^+ BCs (PDXs). Tissue microstructures from five ER^+ PDXs (*ER 70–100%*, *PR 5–100%*, *Ki-67 5–50%)* and two mammoplasties in biopolymer matrices were treated with estradiol (E2) plus LNG (androgenic) or drospirenone (DSP, antiandrogenic) for 7 days. E2 alone increased proliferation in 3/5 PDXs, whereas E2+LNG induced proliferation in 4/5 PDXs ($p<0.001$), with higher Ki-67 induction (*0.73–12-fold* vs. *0.3–3-fold* with E2 alone). Conversely, E2+DSP yielded minimal proliferation and the lowest PR signaling activation, reflected by reduced WNT4 activation (*0.09–2.9-fold* vs. *0.13–5.56-fold* in E2+LNG). In mammoplasties, E2+LNG significantly increased proliferation ($p<0.001$) and Wnt4 ($p<0.01$), confirming enhanced PR target gene expression. E2+DSP was markedly less proliferative. In vivo xenografts of ER+ve PDXs corroborated these findings: E2+LNG significantly elevated IVIS growth rates ($p<0.05$) and GFP fluorescence indicating enhanced growth, while E2+DSP showed non-significant increases and even lower GFP signals. Histological analysis revealed that E2+LNG promoted poorly differentiated (high-grade) tumors with altered collagen deposits assessed by picrosirius red staining, increased nuclear/cell ratios ($p<0.0001$) and Ki-67 ($p<0.0001$). In contrast, E2+DSP yielded more differentiated (lower-grade) tumors with reduced Ki-67 ($p<0.0001$).

These findings show that androgenic progestins like LNG promote proliferation and aggressiveness, while antiandrogenic progestins like DSP are protective, highlighting progestin subtype as a key factor in HRT and contraception.

Symposium 2: Nuclear Receptor Cross-talk in Hormone-Dependent Cancers
Monday 17 November 2025, 11:45 – 12:45

OC3

Adrenal-derived factors promote tumor progression and sclerotic bone lesion formation in castration-resistant prostate cancer

Malin Hagberg Thulin[1], Lei Li[1], Sanna Abrahamsson[2], Andreas Landin[1], Karin Horkeby[1], Jianyao Wu[1], Marie. K. Lagerquist[1], Claes Ohlsson[1], Matti Poutanen[1,3,4]

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Bone metastases are the most common and serious complication of prostate cancer, affecting over 80% of patients with advanced disease and contributing significantly to cancer-related mortality. Following androgen deprivation therapy (ADT), many patients progress to castration-resistant prostate cancer (CRPC), indicating that factors beyond testicular-derived androgens drive bone metastatic progression.

In this study, we investigated the adrenal contribution to CRPC progression in bone using an intratibial prostate cancer xenograft model in mice. To mimic ADT, mice underwent orchidectomy (ORX), with a subset also receiving adrenalectomy (ORX+ADX) to eliminate adrenal-derived factors. Tumor-bearing tibiae (VCaP, 22Rv1, and LNCaP) in ORX-treated mice showed a significant increase in bone mineral density (BMD) compared to controls ($p < 0.001$), demonstrating a sclerotic response. ADX reduced tumor-induced BMD by over 80% ($p < 0.001$), and decreased serum PSA levels and tumor take rates by approximately 50% across all models. RNA sequencing, annotated separately against human (tumor) and mouse (bone) genomes, revealed that ADX downregulated key glycolytic genes (*HK2, PFK2, LDHA*) in tumors, correlating with reduced intratumoral dihydrotestosterone (DHT) levels. Notably, over 90% of tumor-induced transcriptional changes in sclerotic bone were adrenal-dependent, with significant downregulation of osteogenic and pro-angiogenic pathways (BMP, PI3K/Akt, ERK1/2) in ADX treated mice. The bone response was significantly correlated with serum progesterone levels, suggesting a direct role for progesterone in the bone remodeling process. In addition, several tumor-derived secreted proteins involved in osteogenesis and angiogenesis (including STC2 and EPDR1 and GDF15) were among the most downregulated genes following ADX, highlighting the adrenal gland's role in regulating paracrine signals that may promote bone growth.

These findings demonstrate that adrenal-derived factors, particularly progesterone, are essential for promoting both tumor growth via DHT conversion and for driving sclerotic bone lesion formation in CRPC. Importantly, the data suggest that conventional ADT, even when combined with additional androgen-targeted therapies, may be insufficient to suppress adrenal contributions to metastatic progression. A more potent blockade of adrenal signaling is likely required to effectively prevent bone metastases and improve clinical outcomes in advanced prostate cancer.

OC4

How cross-over between hormonal and oncogenic signalling regulates glyco-immune checkpoints in prostate cancer

Adam Duxfield[1], Rebecca Garnham[2,1], Jamie Wills[1], Sara Luzzi[1], Emma Lishman-Walker[1], Kelly Coffey[1], Emma Scott[1]

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Prostate cancer (PCa) is governed by networks regulated by key transcription factors such as the androgen receptor (AR) and c-MYC. Previous studies described the glycosylation enzymes ST6Gal1, ST6GalNAc1 and ST3Gal1 as being androgen responsive and important for the synthesis of glyco-immune checkpoints. It currently remains unclear how the crossover between oncogenic and hormonal signalling pathways influences the regulation of these checkpoints. Here, we identify a novel coordinated role for both the AR and MYC in the regulation of ligands for Siglec immunoreceptors in PCa.

Using prostate cancer cells, mouse models and precision cut tumour slices we show that whilst ST6alNAc1 and ST3Gal1 are AR regulated. ST6Gal1 is not. Supraphysiological levels of androgens (SPA), produce distinct sialome patterns in prostate cancer cells. MYC has previously been shown to be altered by SPA, hence here we investigated the relationship between the AR and MYC in the regulation of immunosuppressive glycans. Genetic targeting of c-MYC in prostate cancer cells resulted in an increase in ST3Gal1 and its associated sialoglycans and PCa patients with high MYC activity have reduced levels of ST3Gal1. These data suggest that c-MYC represses levels of ST3Gal1-directed sialylation. Importantly, ChIP-sequencing shows that the ST3Gal1 is a direct target for both the AR and c-MYC. Knockdown of MYC with AR-antagonism (using darolutamide) resulted in significantly reduced levels of the ST3Gal1 enzyme and the glycans which it makes, showing that the two transcription factors synergise to regulate glyco-immune checkpoints.

We have previously shown that ST3Gal1 synthesises ligands for the suppressive myeloid receptor Siglec-7. Here we show that SPA and c-MYC targeting alters Siglec-7 ligand expression in an ST3Gal1-dependent manner. Using Ecotyper, we identify that the ST3Gal1-Siglec-7 immunosuppressive axis is potently repressed in patients with high AR and MYC activity and that these patients have decreased levels of suppressive neutrophils and macrophages and are predicted to have clinically favourable responses to immune checkpoint inhibitors

Our data identifies a cooperative relationship in the regulation of these critical glyco-immune checkpoints and our study highlights the importance of understanding how the tissue-specific regulatory architecture and use of standard-of-care therapies can mold the glyco-immune landscape of tumours.

Symposium 3: New Tools and Models
Tuesday 18 November 2025, 09:00 – 10:00

OC5

A defined iPSC-derived prostate organoid model as a platform to study lineage specification and primary cilia dysfunction in prostate cancer

Talia Irwin[1], Colin A Johnson[2], Rakesh Heer[1,3], Craig Robson[1], Adriana Buskin[1]

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Human models that capture the cellular complexity of the prostate are critical for understanding hormone-dependent cancer and reducing reliance on animal-derived systems. We developed a fully defined, xeno-free differentiation protocol to generate prostate organoids from induced pluripotent stem cells (iPSCs). These organoids self-organise into epithelial and stromal compartments and display hallmark features of the gland. Immunostaining and single-cell RNA sequencing confirmed basal (*TP63*, *KRT5/14*), luminal (*AR*, *NKX3.1*, *KRT8/18*, *KLK3*), stromal (*VIM*, *ACTA2*), neuroendocrine (*CHGA*, *SYP*), and club-like (*SCGB3A1*) populations. Notably, epithelial tissue formation was dependent on androgens, confirming the model reflects hormone-driven lineage specification.

The platform supports precise genetic engineering, enabling introduction of alterations commonly found in castration-resistant prostate cancer (CRPC). Organoids carrying *PTEN* and *TP53* loss with *AR* or *MYC* amplification exhibited disrupted polarity, reduced luminal space, and transcriptional programmes consistent with aggressive disease.

Primary cilia are antenna-like organelles that coordinate developmental and hormone-regulated pathways. Their loss is a frequent feature of prostate cancer and correlates with higher tumour grade and aggressiveness (Hassounah et al., 2013). Moreover, restoration of cilia formation has recently been shown to suppress androgen receptor activity and tumour progression (Fan et al., 2025), suggesting that cilia loss may represent an emerging mechanism of therapy resistance. Using our organoid platform, we found that dual- and triple-driver models displayed a marked reduction in primary cilia, with residual cilia abnormally elongated, recapitulating patterns in patient tumours. Single-cell RNA sequencing revealed downregulation of structural and trafficking genes essential for ciliogenesis, particularly in epithelial populations, with *MYC* amplification exerting the strongest effect. Several of these changes overlapped with advanced patient datasets, underscoring translational relevance.

In summary, we present a reproducible, xeno-free iPSC-derived prostate organoid model that captures hormone-dependent lineage formation and enables mechanistic dissection of tumour biology. Application to primary cilia highlights its value for uncovering resistance mechanisms and for testing pharmacological strategies to restore ciliogenesis. This platform therefore bridges developmental biology, cancer genetics, and translational therapeutics, providing a powerful human system for advancing research in hormone-dependent cancers.

Funding
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References
1: PMID: 23840776.
2: PMID: 40228678.

OC6

Tracing the evolutionary trajectory of CDK4/6 inhibitor resistance in oestrogen receptor positive breast cancer

Ioanna Mavrommatis[1], Tabitha Branston[1], Fatemeh Ahmadi Moughari[1], Shefali Thakur[1], Frederick J H Whitting[2], Yu Zhang[1], Riccardo Ferro[1], Ekaterina Izmailova[1], Andrew Tutt[1], Trevor Graham[2], Syed Haider[1], Rachael Natrajan[1]

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In oestrogen receptor-positive breast cancer, resistance to CDK4/6 inhibitors (CDK4/6i) is common and often occurs without genetic drivers. Here, we integrate expressed single-cell barcode lineage-tracing, single-cell transcriptomic and epigenomic profiling, with mathematical modelling, to dissect resistance mechanisms to Abemaciclib and Palbociclib. Our findings reveal drug- and lineage-dependent resistance trajectories driven by heritable epigenetic changes, independent of acquired mutations. These trajectories exhibit distinct phenotypic transition rates predictive of cross-resistance to other CDK4/6i. Rare pre-existing transcriptional states selectively expand under prolonged drug exposure, forming reprogrammed resistant lineages with increased enhancer accessibility despite reduced global chromatin accessibility. We further identify and validate a gene signature predictive of response to neoadjuvant endocrine together with CDK4/6i therapy. Functional genomic assessment of these genes uncovered collateral vulnerabilities in resistant cells. Overall, our study highlights how epigenetic remodelling and transcriptional plasticity fuel CDK4/6i resistance through parallel evolution.

Symposium 4: Clinical Trials and Patient-centred Research
Tuesday 18 November 2025, 10:40 – 12:10

OC7
Developing therapeutic strategies to target MCL1 and BCLXL in lethal prostate cancer

Daniel Westaby[1,2], Juan M. Jiménez-Vacas[1], Ines Figueiredo[1], Johnathan Welti[1], Bora Gurel[1], Denisa Bogdan[1], Lorenzo Buroni[1], Antje Neeb[1], Jan Rekowski[1], Ana Padilha[1], Souvik Das[1], Joe Taylor[1], Wanting Zeng[1], Nick Waldron[1,3], Thomas Goldsmith[1], Emily Hobern[1], Florian Gabel[1], Nicole Pandell[1], Susana Miranda[1], Maryou B. Lambros[1], Suzanne Carreira[1], Amanda Swain[1], Wei Yuan[1], Steven P. Balk[4], Marco Bezzi[1], Johann S. de Bono[1,3], Adam Sharp[1,3]

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Despite the approval of multiple new therapies for advanced prostate cancer (PCa) over the past two decades, the disease remains invariably fatal. The development of new treatments for lethal PCa, with novel mechanisms of action, remains an unmet clinical need. One attractive strategy is to target the anti-apoptotic BCL2 family proteins, to breach the apoptotic threshold and drive PCa cell death. Here, we show that MCL1 RNA is highly expressed in castration-resistant PCa (CRPC), associating with signalling pathways linked to PCa progression, as well as with worse clinical outcome. In addition, we demonstrate that BH3 mimetics targeting MCL1 activate the intrinsic apoptosis pathway and drive cell death in a subset of PCa cell line models. Moreover, we identify that siRNA targeting of UCHL3, a deubiquitinating enzyme, downregulates MCL1 protein expression to synergise with BCLXL/BCL2 or BCLXL blockade in PCa cell line models; however, its impact on MCL1 is driven through an off-target effect of the siRNA seed region. This raises an important methodological consideration when studying MCL1 biology. Importantly, we identify that loss of UCHL3 occurs in a significant subset of CRPC tissue biopsies and its expression associates with key signalling pathways in CRPC, warranting further investigation. Finally, we demonstrate that co-targeting MCL1 and BCLXL in patient-derived and mouse PCa models activates the intrinsic apoptosis pathway and drives PCa cell death. Taken together, targeting the intrinsic apoptosis pathway remains an attractive therapeutic strategy for lethal PCa. Future studies should focus on identifying strategies and technologies that can deliver cancer specific kill, to improve the outcome for men with this lethal disease.

OC8

Abrogating persistent androgen receptor signalling by modulating EIF4A biology as novel therapeutic strategy in castration-resistant prostate cancer

Wanting Zeng[1], Juan Manuel Jiménez-Vacas[1], Joseph Taylor[1], Denisa Bogdan[1], Ines Figueiredo[1], Jonathan Welti[1], Daniel Westaby[1,2], Nick Waldron[1,2], Ana Prim Padilha[1], Souvik Das[1], Emily Hobern[1], Thomas Goldsmith[1], Bora Gurel[1,2], Claudia Bertan[1], Wei Yuan[1], Suzanne Carreira[1], Andrew C. Hsieh[3], Paul Clarke[1], Johann S. de Bono[1,2], Adam Sharp[1,2]

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Background: Androgen receptor (AR) pathway inhibitors (ARPIs) improve the outcomes of patients with advanced prostate cancer (PC). However, treatment resistance commonly arises, leading to lethal castration-resistant PC (CRPC). The constitutively active AR splicing variant 7 (AR-V7) emerges with castration resistance, driving persistent AR signalling and inducing ARPI resistance. Novel strategies to inhibit AR-V7 and abrogate persistent AR signalling represent an unmet clinical need. RNA helicases are ATP-dependent RNA binding proteins, commonly dysregulated in cancer, that regulate RNA metabolism and are implicated in regulating AR signalling.

Methods: An unbiased siRNA screen targeting 63 RNA helicases was conducted in CRPC cell lines, evaluating the impact on full-length AR (AR-FL) and AR-V7 protein expression by western blot, and on AR responsive genes (*KLK2*, *KLK3*, and *FKBP5*) mRNA expression by real-time quantitative PCR. Expression of candidate RNA helicases was correlated with established RNA signatures in CRPC patient samples. Cell viability, global mRNA translation, AR-FL/AR-V7 expression, and AR signalling were evaluated following EIF4A isoform knockdown (siRNAs) and EIF4A pharmacological inhibition (silvestrol and zotatifin) in CRPC cell lines.

Results: EIF4A1 and EIF4A3 knockdown reduced AR-V7 expression and AR responsive gene mRNA expression in LNCaP95, 22Rv1 and VCaP CRPC cell lines. The mRNA expression of all three EIF4A isoforms positively correlated with AR-FL and AR-V7 related mRNA signatures in CRPC patient biopsies. Genomic silencing of EIF4A1, but not EIF4A3, caused a marked reduction in global mRNA translation. Even though EIF4A1 and EIF4A3 silencing decreased viability in CRPC cells, CRISPR DepMap data and functional assays indicated that EIF4A3 depletion was possibly more toxic than EIF4A1 depletion. Importantly, EIF4A1 knockdown and its pharmacological inhibition impaired viability in both AR-positive and AR-negative PC cell lines. EIF4A inhibitor treatment led to a strong reduction in global translation, AR-FL, AR-V7, and c-MYC expression, as well as suppression of AR downstream signalling in CRPC cells.

Conclusion: EIF4A1 regulates key oncogenic pathways in CRPC, and its pharmacological inhibition represents a promising therapeutic strategy with potential applicability across different CRPC molecular subtypes.

Lightning Talks

LT1

AR-Driven Chromatin Accessibility Diverges Between Benign and Malignant Prostate Cells

Konsta Kukkonen[1], Ebrahim Afyounian[1], Hanna Rauhala[1], Matti Nykter[1,2], Alfonso Urbanucci[1,2,3], Leena Latonen[4,2], Tapio Visakorpi[1,2,5]

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Androgen receptor (AR) activation has been shown to alter chromatin structure in prostate cancer (PC) cells. However, the chromatin response to AR activation in nonmalignant prostate epithelial cells (NPEC) remains poorly characterized due to the lack of representative cell models.

To address this gap, we leveraged our previously established NPEC models (RWPE-1-AR and RWPE-1-Ctrl) alongside PC (LNCaP-pcDNA3.1 and LNCaP-ARhi) cell models to study their androgen-driven chromatin responses using ATAC-sequencing.

In the absence of androgen, we observed widespread differences in the chromatin accessibility between the NPEC and PC cells. Androgen stimulation markedly increased the number of differentially accessible peaks, suggesting a fundamental divergence in how AR influences chromatin structure in these cell types.

Separate analysis of androgen-induced changes in each cell line revealed more chromatin accessibility alterations in androgen-naïve NPEC than in the PC cells. This suggests presence of epigenetic memory in the PC cells that maintains accessibility at previously active regulatory regions.

Androgen-sensitive opening regions from both cell types were predominantly located in the distal regulatory regions enriched for nuclear receptor binding sites (AR and glucocorticoid receptor) and their respective binding motifs. Notably, AP-1 binding motifs were the second most enriched in NPEC, while FOXA1 motifs and binding sites were the second most enriched in PC cells.

To evaluate how well the chromatin accessibility patterns observed in our cell line models correspond to those in clinical disease, we compared them to profiles previously obtained from clinical samples of benign prostate hyperplasia (BPH), untreated PC, and castration-resistant PC (CRPC). We found that the chromatin accessibility of the NPEC most closely resembled that of BPH, whereas the PC cells most closely mirrored untreated PC and CRPC.

Finally, integration of ATAC-seq and mRNA-seq data identified candidate AR target genes specific to each model. We validated *CDKN1C*/p57 as a direct AR target gene in RWPE-1-AR cells, suggesting a potential mechanism for androgen-induced growth arrest in these cells.

In conclusion, our results demonstrate that AR activation reprograms chromatin accessibility in normal prostate epithelium, revealing fundamental regulatory differences compared to the tumor context.

LT2 Abstract Withdrawn

LT3

RAGE against the prostate cancer: Evaluating a novel antibody-drug conjugate

Daniel Turnham[1], Liliana Ordonez[1], Anna Richards[2], Stephen Paisey[2], Sam Mitchell[3], Deyarina Gonzalez[3], Steven Conlan[3], Helen Pearson[2]

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Globally, prostate cancer (PCa) is the second most common male malignancy and remains one of the leading causes of cancer-related deaths. Although treatment options have improved, survival remains poor (often less than 2-years) for metastatic-PCa (mPCa), emphasising the unmet clinical need for new efficacious therapies, particularly for untreatable chemo-refractory/castrate-resistant disease. Antibody-drug conjugates (ADCs) have emerged as an exciting therapeutic strategy owing to their unique ability to specifically target malignant cells for cytotoxic killing without damaging healthy normal cells. Several ADCs have now been clinically approved to treat different cancer types, including PSMA-targeted therapies for mPCa which have significantly improved survival rates. However, despite this, are large proportion of patients are ineligible for treatment, while remission is often short-lived in those who do respond well. Accordingly, the development of a broad range of ADCs, with distinct toxic payloads, is essential to offer additional treatment options and improve survival rates.

To this end, we have developed a new potent ADC targeting the receptor-for-advanced-glycation-end-products (RAGE), that delivers cytotoxic drugs specifically to PCa cells expressing RAGE. Importantly, up to 90% of mPCa cases express RAGE, thus presenting a therapeutic strategy that could benefit many patients with advanced disease. Here we demonstrate how chimeric RAGE-targeting ADCs can efficiently bind, internalize and kill RAGE-positive PCa cell lines *in vitro* and effectively target RAGE expressing PCa cells *in vivo* to inhibit tumour growth. Interestingly, our data suggests that combining RAGE-ADC treatment with docetaxel, a chemotherapy routinely used to treat patients with mPCa, can offer improved therapeutic responses *in vivo*. Finally, we highlight the potential of using Zr^{89} radiolabelled RAGE antibodies as a diagnostic tool to detect PCa's that are likely to benefit from RAGE-targeted therapy. Together this data provides evidence that RAGE could be used as a theranostic target, to diagnose and treat aggressive, hard-to-treat PCa clinically in the future.

LT4

Illuminating the future of Breast Cancer Therapeutics: Applying Synthetic Biology's UV Crosslinking Amino Acids for Drug Target Discovery.

Thomas Grimes, Andrew Holding, Lianne Willems

University of York, York, United Kingdom

Breast cancer is the second most common malignancy worldwide, with over 2 million new diagnoses annually. Approximately 75% of cases are driven by the activity of the Estrogen Receptor (ER), classifying them as ER+ tumours. Although endocrine therapies (e.g. anastrozole, tamoxifen) have significantly improved outcomes, nearly one third of patients will relapse with highly resistant disease that often proves fatal. Consequently, there is a pressing need for novel treatments that specifically target resistant ER+ breast cancers.

Developing such therapies requires a detailed understanding of the ER interactome, and how it changes between cellular states – from normal physiology, to first-line malignancies, and ultimately treatment-resistant tumours. The current gold standard for mapping steroid hormone receptor (SHR) interacting partner proteins is RIME[1,2], which has previously been used to characterise the ER interactome following various ligand treatments. However, present forms of RIME have two key limitations: {i} they capture large protein complexes, making it tedious to distinguish direct from indirect interactions, and {ii} they provide limited structural insights about any protein-protein interactions.

In this project, we aim to combine two cutting edge molecular biology techniques – amber stop codon suppression (AKA genetic code expansion) and metabolic glycan labelling – with existing RIME workflows to insert photoactivatable probes directly into ER within breast cancer cell lines (**Fig. 1**). Upon exposure to an external activation signal (e.g. UV), these probes will drive covalent crosslinking between ER and close proximity (<20nm) interacting partners, enabling high-resolution structural mapping of the ER interactome across diverse cellular states (e.g. therapy-naive vs therapy-resistant).

This novel approach could identify new therapeutic targets, and aid the development of innovative therapies against ER+ breast cancer in highly resistant settings.

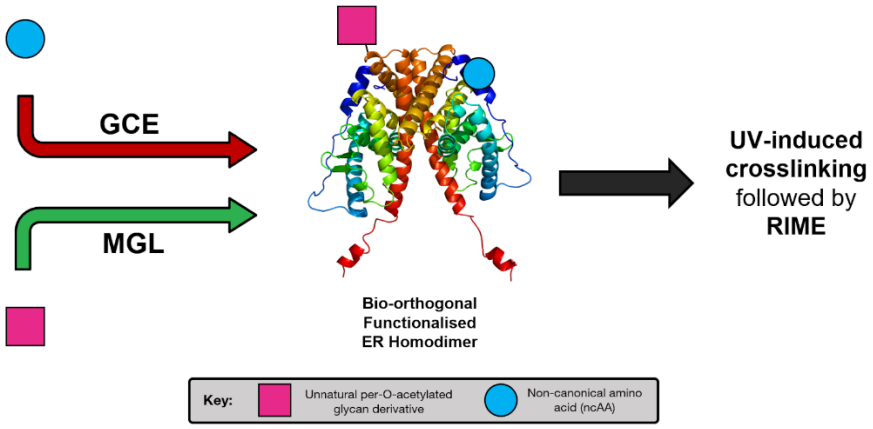

Figure 1 - Schematic representation of the unnatural functionalisation of ER within breast cancer cell lines using genetic code expansion (GCE) and metabolic glycan labelling (MGL) approaches.

References:

1. Mohammed, H. et al. (2016) 'Rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) for analysis of chromatin complexes' *Nat. Protoc.*, 11; 316–326.
2. Papachristou, E. K. *et al.* (2018) 'A quantitative mass spectrometry-based approach to monitor the dynamics of endogenous chromatin-associated protein complexes' *Nat. Commun.,* 9; 2311.

LT5
Prostate Cancer: Are Male Testosterone Assays Fit For Purpose?

Jonathan Atkins[1], Megan Dolan[1], Alice Stephenson[1], Laura Owen[2], Phillip Monaghan[3,4], Andrew Hudson[3], Rachel Marrington[5], Carol Evans[6], Mark Saunders[6], Thomas Morris[7], Brian Keevil[1], James Hawley[1,8]

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Introduction: Prostate cancer is the most common cancer affecting males in the UK. Androgen-deprivation therapy (ADT) is recommended for the treatment of advanced prostate cancer to slow tumour progression and improve patient outcomes. Historically, an ADT testosterone target of <1.7 nmol/L has been applied. However, improvements in routine testosterone analysis resulted in the 2025 Prostate Cancer Guideline from the European Association of Urology recommending a lower target of <0.7 nmol/L as this is associated with improved patient outcomes. To date, limited work has been undertaken to assess the performance of routine testosterone assays in this concentration range.

Methods: Surplus serum was obtained from a tertiary centre from males taking ADT (n = 50), alongside normal female samples (n = 40). These were pseudoanonymised, aliquoted and frozen at -80°C before being sent to participating laboratories. Testosterone was analysed using the Abbott Alinity, Beckman DxI 9000, Roche Cobas 801 and Siemens Atellica immunoassays. An in-house LC-MS/MS method was used as a reference method, the performance of which was verified by analysis of CDC certified reference materials. Platforms were compared through Bland-Altman and Passing-Bablok analyses.

Results: In samples from males taking ADT, mean biases for the Abbott, Beckman, Roche and Siemens immunoassays were 0.37 nmol/L (102.4%), 0.75 nmol/L (153.0%), 0.19 nmol/L (40.5%) and 0.12 nmol/L (38.1%), respectively. If applied to our cohort, this may have resulted in 12 (24%), 13 (26%), 1 (2%) and 2 (4%) patients being incorrectly identified as having testosterone >0.7 nmol/L, respectively. In female samples, mean biases were 0.20 nmol/L, 1.00 nmol/L, 0.23 nmol/L and 0.01 nmol/L, respectively.

Conclusions: We have identified variable degrees of positive bias in testosterone immunoassays when applied to samples taken from patients on ADT. This may currently be putting patients at risk of overtreatment, depending on the assay employed by their local laboratory. Clinicians should be aware of the bias exhibited by their local assay when monitoring ADT efficacy in their patients.

LT6

Therapeutic potential of targeting the BCL-2 family in prostate and breast cancer tumour initiation, growth and metastasis.

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Evasion of apoptosis is a hallmark of cancer that is required for cancer cells to 1) survive the oncogenic or environmental insults that drive tumour initiation, 2) sustain tumour growth, 3) facilitate cellular viability during the process of metastasis. Disruption in cell death pathways is most frequently evidenced in cancer through altered expression/activity of the BCL-2 protein family. This not only promotes these tumorigenic steps but also creates a barrier to effective tumour cell elimination in response to anti-cancer therapies, enabling treatment resistance and disease recurrence. Therapeutic approaches to reinstate cancer cell death are therefore an attractive clinical prospect that has shown practice-changing efficacy in the treatment of some blood cancers, where mitochondrial apoptosis can be effectively restored with drugs targeting the BCL-2 protein family.

Analysis of prostate and breast cancer tissue shows elevation in pro-survival members of the BCL-2 family of apoptotic regulators. We have demonstrated that targeting these BCL-2 family proteins can inhibit both breast and prostate cancer growth *in vitro and in vivo*. We hypothesise this can have further application in prevention of tumour initiation and inhibition of metastatic spread and outgrowth. To investigate this, we are utilising genetic and pharmacological approaches to reinstate apoptosis in mouse models of prostate and breast cancer. This reveals that distinct members of the BCL-2 family are essential at discrete stages of the oncogenic process, and we have found that these dependencies create vulnerabilities that can be differentially targeted to have anti-cancer impact on multiple stages of tumour progression.

LT7

AKT and MCL1 co-inhibition triggers intrinsic apoptosis in PTEN-loss/PI3K-activated castration resistant prostate cancer

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Introduction: Castration resistant prostate cancer (CRPC) remains a lethal disease, highlighting the need for new therapeutic strategies. The anti-apoptotic BCL2 family protein MCL1 promotes cancer cell survival across tumour types, including prostate cancer. However, single agent MCL1 inhibitors have shown limited activity in CRPC models. Here, we investigated combination strategies to enhance MCL1 inhibition effects and drive tumour-selective apoptosis in CRPC.

Methods: A high-throughput screen using the NCI NIH FDA-approved Oncology Set (166 compounds) was performed at 5 µM in the absence or presence of the MCL1 inhibitor AZD5991 (1 µM), measuring viability (CellTiter-Glo) and apoptosis induction (Caspase-Glo 3/7). Selected agents including MCL1, PI3K, AKT and CDK9 inhibitors were tested individually and in combination in CRPC cell lines and patient-derived xenograft organoids (PDX-Os). Protein expression of PI3K/AKT pathway activity markers, apoptosis markers and BCL2 family members was assessed by western blotting. Resistant cell lines were generated by prolonged exposure to increasing concentrations of capivasertib. *In vivo* efficacy of ipatasertib (50 mg/kg), S63845 (25 mg/kg) and fadraciclib (40 mg/kg), alone or in combination, was evaluated in the CP253c PDX model.

Results: The FDA drug screen identified synergy between MCL1 and PI3K inhibition in CRPC cells. AKT inhibition exerted an even stronger synergy with MCL1 blockade. Knockdown of the pro-apoptotic BH3-only proteins BIM, BAD and BAK abrogated this synergy. AKT inhibition reduced BAD

phosphorylation and increased BAD-BCLXL and BIM-MCL1 interactions. Synergy was restricted to PTEN-loss/PI3K-activated CRPC cell lines and PDXOs, and PTEN knockout sensitised mouse prostate organoids to AKT and MCL1 co-inhibition. Phospho-BAD levels correlated with response to the combination. *In vivo*, AKT and MCL1 co-inhibition significantly suppressed tumour growth. CRPC cells with acquired resistance to capivasertib remained sensitive to the combination. CDK9-mediated MCL1 downregulation, combined with AKT inhibition, recapitulated these findings *in vitro* and *in vivo*.

Conclusion: Our findings demonstrate that co-targeting MCL1 and AKT induces potent and selective antitumor effects in PTEN-loss/PI3K-activated CRPC. These results support early-phase clinical trials targeting MCL1, either directly or through CDK9 inhibition, in combination with AKT inhibition as a therapeutic strategy in this molecularly defined subgroup.

LT8

Baseline Sex Steroid Profiles Predict Biochemical Recurrence in High-Risk Prostate Cancer patients with N0 Disease

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High-risk prostate cancer (HrPC) represents a clinically heterogeneous subgroup with limited prognostic accuracy. Current risk stratification methods often fail to reliably predict biochemical recurrence (BCR) and inadequately account for the independent prognostic impact of nodal (N) stage. We evaluated whether baseline sex steroid profiles could enhance risk stratification in HrPC.

A prospective cohort of 80 patients diagnosed with HrPC between 2007-2010 was analyzed. MRI was used as staging modality, including nodal status. All patients received androgen deprivation therapy (ADT), followed by intensity-modulated radiotherapy (IMRT) with continued ADT for a total of 2.5 years. Baseline serum concentrations of eight steroids: testosterone (T), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione, estrone (E1), estradiol (E2), progesterone, and 17α-hydroxyprogesterone (17αOH-P4) were measured using liquid chromatography-tandem mass spectrometry. Median follow-up time was 9 years (range 7–13).

A cross-sectional ANOVA between measured steroid concentrations and clinical risk factors revealed significant differences in T, DHT, and DHEA across N-stage (n=80). However, after age adjustment using ANCOVA, only T remained significant. When separating N-stage, a univariate Cox regression model revealed that among N0 patients (n=52), elevated DHEA levels were associated with increased risk of BCR (HR 2.48, 95% CI 1.09–5.64, *p*=0.030), while an elevated T/DHEA ratios were associated with a lower risk of BCR (HR 0.34, 95% CI 0.13–0.87, *p*=0.024). The Multivariate Cox analysis in N0 patients showed that elevated DHEA and reduced T together were associated with BCR when adjusted for age. No significant associations were found when analyzing T, DHEA or T/DHEA independently with age adjustment. Notably, no significance was observed in N1 patients (n=28) in the Cox regression models. Additionally, the prognostic value of the T/DHEA ratio in N0 patients was further supported by Kaplan-Meier survival analysis (p=0.02), whereas T and DHEA independently did not show significant separation.

Our data indicates that elevated baseline DHEA and reduced T levels are associated with an increased risk of BCR in HrPC with N0 disease. These findings suggest that increased adrenal activity at the time of diagnosis may be linked to a more aggressive tumor behavior and could improve risk stratification within this subgroup.

LT9

Crosstalk Between ERα and Hypoxia Drives a Novel Transcriptional Programme and Therapeutic Vulnerability in Breast Cancer

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Estrogen receptor alpha (ERα) is a key driver of tumour proliferation in hormone receptor-positive breast cancer. However, as tumours progress, the microenvironment becomes increasingly hypoxic, activating hypoxia-inducible factors (HIF-1 and HIF-2) and initiating widespread transcriptional changes.

Combining ChIP-seq and RNA-seq, we demonstrate that hypoxic activation markedly redistributes ERα binding across the genome, resulting in a distinct transcriptional programme not observed under normoxia. Novel ERα binding sites were identified in the promoters of several genes with established roles in epithelial-to-mesenchymal transition (EMT), consistent with a more aggressive tumour phenotype. Further, expression of these ERα-hypoxia target genes is associated with reduced relapse-free survival in TCGA cohorts.

In parallel, we showed that depletion of ERα significantly attenuates the transcriptional hypoxic response, suggesting a reciprocal relationship in which ERα and HIF transcription factors regulate each other's transcriptional activity.

Amongst the ERα-dependent hypoxia-induced genes, we identified multiple regulatory subunits of the epithelial sodium channel (ENaC), which have not previously been linked to ERα or hypoxia signalling in breast cancer. Targeting the ENaC using the inhibitor amiloride demonstrated that we were able to prevent the formation of MCF7 spheroids at the point of developing a hypoxic core.

In summary, we have identified a novel transcriptional programme driven by the crosstalk between ERα and the hypoxic response and revealed a potential opportunity to target this axis as a therapeutic strategy in ERα-positive breast cancers.

LT10

MiR-16-5p and MiR-424-5p: Cell Cycle Regulation and Therapeutic Potential in Prostate Cancer

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Prostate cancer (PCa) is one of the most prevalent malignancies among men in the UK, with a lifetime diagnosis risk of 1 in 8 and approximately 12,000 associated deaths annually. Despite good response to initial androgen deprivation therapies, castration-resistant prostate cancer (CRPC) remains a significant therapeutic challenge, necessitating novel treatment strategies. MicroRNAs (miRs) are small, non-coding RNAs that regulate gene expression through mRNA degradation or translational repression. MiRs may act as oncogenes or tumour suppressors depending on their targets, thus representing attractive candidates for cancer therapy. This study investigates miR-16-5p and miR-424-5p, members of the miR-16 family previously identified as tumour suppressors in various cancers, but not extensively characterised in PCa.

Initial analysis demonstrated that both miR-16-5p and miR-424-5p significantly suppressed PCa cell growth, supporting their tumour-suppressive roles. Enrichment analysis of predicted target genes, based on prior transcriptome-wide mapping of miR:RNA interactions across five PCa cell lines, revealed that these miRs modulate a network of cell cycle-related genes, including cyclins and cyclin-dependent kinases (CDKs). Functional assays confirmed that they downregulate key cell cycle regulators, resulting in G0/G1 cell cycle arrest.

Notably, the anti-proliferative effects of both miRs depend on the functional status of the tumour suppressors retinoblastoma (*RB*) and *TP53*. In PCa cells expressing wild-type Rb and p53, both miRs inhibited proliferation, whereas cells harbouring mutant or deleted Rb/p53 showed limited response. This hypothesis was validated using CRISPR-engineered LNCaP cells with single or double knockouts of *RB* and *TP53*, which showed increased resistance to miR-mediated growth inhibition compared to wild-type cells.

Furthermore, both miRs target multiple cell cycle checkpoint regulators, thereby sensitising PCa cells to DNA damage response (DDR)-targeting agents. Synergistic anti-proliferative effects were observed when miR mimics were combined with inhibitors of ATM/ATR, WEE1, and PARP1. In addition, both miRs downregulated the anti-apoptotic protein BCL2, promoting apoptosis. The therapeutic potential of these miRs is currently being investigated in *ex vivo* patient-derived prostate explants, in which successful transfection has been validated.

These findings highlight the therapeutic potential of miR-16-5p and miR-424-5p in CRPC and support their potential application in combination with DDR-targeted therapies in clinically relevant models.

Poster Presentations

P1

Genome-Wide CRISPR-Cas9 Knock Out Screening to Investigate Therapeutic Resistance in Prostate Cancer

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Prostate cancer is the most commonly diagnosed cancer in men and remains a leading cause of cancer-related mortality. Androgen receptor (AR) signaling is central to disease progression, and enzalutamide, a potent AR antagonist, has improved clinical outcomes in advanced disease. However, acquired resistance to enzalutamide is inevitable, limiting long-term therapeutic benefit. Although several mechanisms of resistance have been proposed, including AR splice variants, lineage plasticity, and activation of alternative survival pathways,, the full spectrum of vulnerabilities that emerge in resistant cells remains poorly defined.

To address this, we are performing a genome-wide CRISPR-Cas9 loss-of-function screen in enzalutamide-sensitive and enzalutamide-resistant prostate cancer cell lines. By systematically comparing genetic dependencies between these models, we aim to identify genes and pathways that are selectively essential in resistant cells. These resistance-specific vulnerabilities could represent novel therapeutic targets that may be exploited to overcome treatment failure. Candidate genes emerging from the screen will undergo validation through secondary CRISPR knockout studies and pharmacological inhibition, followed by functional assays to determine their mechanistic role in resistance biology.

Importantly, to extend the translational relevance of our findings, we will integrate results from the CRISPR screen with transcriptomic datasets derived from prostate cancer patients and additional in vitro models. This integrative approach will allow us to prioritize candidate vulnerabilities that are not only essential in resistant cell lines, but also clinically relevant in patient tumors. Cross-comparison with independent models will further help to distinguish core resistance mechanisms from context-specific adaptations.

We anticipate that this work will generate a comprehensive map of genetic dependencies in enzalutamide resistance, reveal novel therapeutic vulnerabilities, and highlight druggable pathways for clinical development. Ultimately, by bridging unbiased functional genomics with patient-derived data, our study seeks to provide insights that could inform more effective precision treatment strategies for patients with advanced, treatment-resistant prostate cancer.

P2

Pre-clinical and patient-derived cancer models to identify novel biomarkers and treatment targets in *SPOP*-mutant prostate cancer.

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Prostate cancer (PC) is the most common cancer in men, with 10-15% of patients harbouring *SPOP* mutations. These loss-of-function mutations lead to abnormal SPOP protein function, disrupting normal protein regulation and contributing to cancer growth and progression. *SPOP*-mutant PC represents a distinct molecular phenotype characterised by high androgen receptor signalling, high genomic instability due to an altered DNA damage response (DDR), and altered epigenome with DNA hypermethylation. Despite being identified over a decade ago, targeted treatments for *SPOP*-mutant PC have not yet reached the clinic. This is largely due to the lack of suitable models for studying *SPOP*-mutant PC. To address this, the project aims to develop and utilise models of *SPOP*-mutant PC to further understand this PC subtype better and identify novel therapeutic vulnerabilities for improved personalised treatments for this patient cohort.

Here, a CRISPR/Cas9-mediated *SPOP* knock-out (KO) cell line has been successfully developed in our androgen-dependent LNCaP-iCas9 PC cell line. In addition, to the already developed androgen-independent CWR22Rv1-AR-EK-iCas9 *SPOP* KO model, these lines have been used to reflect the loss-of-function mutations seen within patients. Downstream analysis of these cell lines revealed alterations within the DDR, including reduced expression of homologous recombination (HR)-associated genes consistent with the defective HR repair pathway observed within patients. Moreover, within the androgen-dependent LNCaP model, KO cells observed higher levels of androgen-signalling through increased expression of downstream AR target genes. Furthermore, we performed a candidate-based drug screen to identify potential vulnerabilities across a range of DDR and epigenetic inhibitors. The *SPOP*-KO cells showed increased sensitivity to DDR agents such as DNA-PK inhibitors and increased sensitivity to epigenetic inhibitors such as CBP/P300 bromodomain inhibitors compared to wild-type *SPOP* cells. These findings suggest a novel therapeutic strategy targeting the altered DDR and epigenome in *SPOP*-mutant tumours. Further validation of these results is required to confirm their clinical relevance and potential for targeted treatments for *SPOP*-mutant PC patients.

P3

Investigating long non-coding RNAs as drivers of therapy resistance in prostate cancer

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Therapy resistance in prostate cancer (PCa) is primarily associated with alterations to the androgen receptor signalling pathway but can also be driven by other factors. One mechanism by which PCa progresses and acquires resistance is through altered expression of non-protein coding RNA transcripts called long non-coding RNAs (lncRNAs). LncRNAs regulate gene expression at the transcriptional and post-transcriptional levels via their ability to interact with and modulate activity of cellular proteins, RNA or DNA. Several lncRNAs can be transcribed from cis-regulatory regions (CREs) such as enhancers or promoters and play important roles in oncogenic pathways through regulating host CRE. In this project, we aim to identify candidate lncRNAs and the mechanisms by which they drive therapy resistance in prostate cancer. To this end, we have analysed ten published prostate cancer datasets, comprising of cell lines and patient samples, to identify ~600 lncRNAs whose expression is altered in treatment resistance. These results were integrated with ChIP-seq datasets for H3K27Ac, a mark of active CREs, to identify ~200 CRE associated lncRNAs. Candidate lncRNAs identified by these analyses were then computationally validated in additional independent PCa patient datasets. Currently, in-vitro validation work is being undertaken in therapy-sensitive and -resistant cell lines to determine effects of modulating expression of lncRNAs on resistance and their mechanisms of action. Further validation will then be performed in near patient models (patient-derived explants and organoids). This work will ultimately identify lncRNA associated pathways with potential for therapeutic targeting, laying the groundwork for more treatment options at advanced stages of PCa.

P4

Assessing the temporal dynamics of ASCL1 control of lineage plasticity in neuroendocrine prostate cancer (NEPC)

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Neuroendocrine prostate cancer (NEPC) is a highly aggressive form of advanced prostate cancer that emerges as the tumour develops resistance to potent anti-androgen therapies. It is associated with the loss of androgen signalling and acquisition of small cell neuroendocrine histology and is a major clinical challenge.

Evidence suggests powerful transcription factors, such as ASCL1, may drive these dynamic changes by initiating proneural transcriptional programs; though the molecular details of ASCL1 control of lineage switching remain poorly understood. Our previous work shows ASCL1 expression correlates with acquisition of the NE phenotype and expression of NE markers in response to androgen deprivation. Furthermore, ASCL1 expression is retained even when androgen signalling is reactivated, and prostate cancer reverts to a more luminal-like morphology.

We investigated the temporal dynamics of ASCL1 control of lineage plasticity in LNCaP cells in response to cycles of androgen deprivation and androgen rich conditions. Androgen deprivation triggered a robust increase in ASCL1 expression that preceded the increase in expression of ASCL1 target genes, DLL1 and Hes1. ASCL1 signalling is therefore an early event initiating NE switching of prostate cancer cells.

ASCL1 signalling is intricately linked with the NOTCH cell fate pathways and is a potent regulator of the Wnt pathways. ASCL1 induction following androgen deprivation was mirrored by robust induction of NOTCH expression, particularly NOTCH 3, and the non-canonical Wnt planar cellular polarity pathway ligand, Wnt5, and ROR receptors. Importantly, ASCL1, NOTCH and Wnt expression were blunted by the reintroduction of androgens, indicating the molecular changes associated with lineage switching are not fixed. However, ASCL1 and NOTCH expression in cells previously exposed to androgen deprivation remained elevated above control cell levels, suggesting these cells could be primed for more robust reactivation of lineage switching programs when exposed to further androgen deprivation. This data shows ASCL1 controls powerful transcriptional reprogrammes in response to androgen deprivation therapy and provides much needed insights into ASCL1's role in driving NEPC development and therapeutic resistance via lineage plasticity.

P5

Taking the PROTAC-tical approach against the progesterone receptor in ER+ breast cancer

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Introduction

Resistance to endocrine therapy remains a major clinical challenge in hormone receptor-positive (HR+) breast cancer (BC), contributing to persistent risk of recurrence and limiting the long-term efficacy of these therapies. While the estrogen receptor (ER) is the primary therapeutic target, increasing evidence suggests significant roles for other hormone receptors, including the progesterone receptor (PR) due to extensive crosstalk within steroid hormone signalling pathways. However, the lack of selective tools has made it difficult to distinguish ER- from PR-driven effects, limiting our ability to fully understand PR's role and therapeutic potential.

Using clinically relevant mammary intraductal (MIND) models, we showed that some HR+ patient-derived xenografts (PDXs) require PR for growth. Moreover, ectopic PR expression can independently drive tumour growth in MCF-7 MIND xenografts, even in the absence of ER signalling and ovarian hormones. These findings raise the question of whether personalising endocrine therapy by incorporating PR blockade could offer a more effective therapeutic approach.

The clinical use of PR antagonists has been limited by glucocorticoid receptor (GR) cross reactivity and off-target effects. This study aims to use novel PR-targeting PROTAC degraders to investigate the role of PR in HR+ BC and evaluate their potential as a therapeutic strategy.

Results

A panel of first-in-class PR PROTAC degraders were developed in collaboration with the Centre for Protein Degradation (ICR). Mifepristone and Vilaprisan were used as progesterone receptor ligands, with different linkers connecting them to either von Hippel–Lindau (VHL) or cereblon (CRBN) E3 ligase recruiters. PROTAC compounds were tested in T47D human breast cancer cell line *in vitro*. Four out of nine VHL-based compounds and seven out of twenty-four CRBN-based compounds showed strong PR degradation.

One lead compound showed minimal cross-reactivity with the GR while maintaining robust PR degradation. This was further validated in *ex vivo* cell line and patient derived MIND xenograft assays to assess tumour response in a physiologically relevant microenvironment. This tool compound will be taken forward in these models to identify responders and non-responders and interrogate mechanisms of PR dependency.

P6

The tumour suppressor PDCD4 regulates the androgen receptor signalling pathway and correlates with androgen receptor expression in advanced prostate cancer.

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Background: The androgen receptor (AR) plays a central role in prostate cancer development and progression. Despite advancements in therapies targeting the AR, treatment resistance commonly emerges, and castration-resistant prostate cancer (CRPC) remains a fatal disease. An improved understanding of prostate cancer biology is therefore required to deliver new therapeutic strategies for patients. PDCD4 is a tumour suppressor protein implicated in prostate cancer progression, however its relationship with the AR pathway remains poorly understood. Herein we investigated the interplay between PDCD4 and the AR in advanced prostate cancer.

Methods: We investigated PDCD4 mRNA and protein expression by RNA sequencing and immunohistochemistry (IHC) in multiple metastatic CRPC patient cohorts to determine association with molecular subtypes, correlation with the AR pathway and overall survival. We next analysed PDCD4 protein expression by IHC in 15 matched, same-patient samples to investigate how expression changed as patients progressed from localised castration sensitive to metastatic castration resistant disease. shRNA-induced *PDCD4* knockdown was employed in the AR-driven prostate cancer cell lines LNCaP and C4-2 and the effect on the AR signalling pathway was determined by quantitative real-time PCR and by western blotting. Lastly, we investigated androgen-dependence and response to the AR antagonist enzalutamide by cell viability analysis following *PDCD4* knockdown.

Results: *PDCD4* mRNA was highly expressed in multiple metastatic CRPC patient cohorts and correlated with AR-positive subtypes and improved overall survival. PDCD4 and AR protein expression positively correlated in two independent IHC CRPC cohorts. In a focused analysis of a subset of patients PDCD4 expression increased as disease progressed from castration sensitive to metastatic CRPC. *In vitro* PDCD4 knockdown decreased AR activity in AR-dependent prostate cancer, increased androgen independent growth and conferred resistance to the AR antagonist, enzalutamide.

Conclusions: Our findings reveal PDCD4 as an important node regulating prostate cancer progression, AR activity and response to AR-targeted therapy. Further investigations probing PDCD4 biology may deliver new therapeutic strategies for patients with advanced prostate cancer.

P7

Genomic loss of the splicing factor SRSF12 drives prostate cancer growth and resistance to apoptosis.

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Background: Despite the development of androgen receptor (AR) pathway inhibitors and taxane-based chemotherapies, the outcome for men with castration-resistant prostate cancer (CRPC) remains poor (1). This highlights the need for improved therapies and biomarkers to guide treatment selection. Although aberrant RNA splicing is increasingly recognised as a driver of CRPC, pharmacological inhibition of splicing is likely to be toxic (2). However, the impact of genomic loss of individual splicing factors on CRPC biology remains poorly understood. We hypothesise that these alterations in RNA splicing machinery may confer survival advantages while exposing therapeutic vulnerabilities.

Methods: The incidence of splicing factor genomic aberrations was assessed in publicly available CRPC biopsy cohort (Stand Up To Cancer/Prostate Cancer Foundation). The association of SRSF12 mRNA levels with hallmark gene sets was examined. SRSF12 protein expression across multiple prostate cancer cell lines was analysed by western blot, and SRSF12 CRISPR-Cas9 knockout 22Rv1 cells were generated. Cell viability (CellTiter-Glo) was evaluated in SRSF12 knockout and control 22Rv1 cells following treatment with BH3-mimetics.

Results: SRSF12 was found to be deleted in 7% of CRPC biopsies. SRSF12 mRNA expression negatively correlated with signatures related to apoptosis and immune modulation. Next, we demonstrated that 22Rv1 cells express SRSF12 at the protein level. SRSF12 knockout led to an increase in cell growth and conferred resistance to MCL1-targeting BH3-mimetics. Interestingly, transient SRSF12 knockdown with siRNAs did not phenocopy the stable knockout model, suggesting that long-term abrogation is required.

Conclusions: Our preliminary data show that SRSF12 is lost in CRPC, and that these tumours might represent a more aggressive subset due to increased proliferation and resistance to apoptosis. Further work will focus on elucidating the molecular consequences of SRSF12 loss to identify exploitable therapeutic vulnerabilities in this patient population.

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P8

Threshold-dependent androgen receptor activation induces morphological reprogramming in prostate cancer cells

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The androgen receptor (AR) is a transcription factor activated by androgens and expressed in most prostate cancers (PCa), where it regulates growth, differentiation, and survival. Current PCa therapies target and disrupt AR signaling, but many patients develop resistance within a few years, and AR is frequently overexpressed in castration-resistant prostate cancer (CRPC). We investigated how different androgen levels influence cell morphology and cell growth in prostate cancer cells overexpressing AR. We utilized an LNCaP cell subline (LNCaP-ARhi) stably expressing 4-6x higher AR than its parental cell line expressing an empty vector (LNCaP-pcDNA3.1). The cells were treated with increasing concentrations (0.001nM-10nM) of a synthetic androgen R1881 and the cell morphology and growth were monitored with phase-contrast imaging. AR dependency was tested by co-treatment with apalutamide or enzalutamide. Expression of AR target genes FKBP5 and KLK3 was measured by qPCR. LNCaP-ARhi cells showed a distinct morphological change after 48h of treatment with >0.06 nM R1881, transitioning from elongated, spindle-shaped cells to a flattened, polygonal morphology. Growth of LNCaP-ARhi was stimulated at 0.003–0.03 nM but inhibited at 0.06–10 nM R1881. Morphological alterations and growth induction were blocked by apalutamide or enzalutamide, suggesting AR dependency. In contrast, parental LNCaP-pcDNA3.1 cells displayed no morphological changes, with growth induced at 0.01–0.1 nM and inhibited by co-treatment with antiandrogens as expected. At the transcriptional level, FKBP5 and KLK3 expression were significantly induced at 0.1 nM R1881 for both cell lines but showed minimal induction at 0.01 nM. Small changes in androgen concentration can reprogram prostate cancer cell state when AR is overexpressed, producing threshold-dependent effects on morphology and growth. These findings highlight the sensitivity of AR-driven biology and may provide insights into therapy resistance and treatment strategies. Future work will utilize this data as a basis to study the molecular mechanisms of treatment-resistance in prostate cancer, specifically, for AR mutations.

P9

Development of a Novel MicroRNA-based DNA-Damaging Therapeutic for the Treatment of Advanced Prostate Cancer

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Prostate Cancer (PC) is the 2nd most common cancer in men, affecting 1 in 8 in the UK. Even in advanced stages of metastatic castration-resistant PC, tumour growth remains highly dependent on Androgen Receptor (AR) signalling. Androgen Deprivation Therapy (ADT), which targets AR, is the current standard of care. While initially effective, resistance to ADT inevitably develops, leading to poor survival rates, demonstrating need for new treatments. Advanced PC accumulates multiple DNA damage-response (DDR) defects, creating vulnerabilities exploitable for therapeutic benefit. For example, Homologous Repair-deficient tumours are sensitive to PARP inhibitors, while Miss Match Repair-deficient tumours are responsive to immunotherapy.

We identified miR-346, which induces extensive, genome-wide, transcription-dependent DNA damage via transcription-hyper initiation and R-loop formation, causing replication fork collapse and induction of cell cycle arrest. MiR-346 binds chromatin remodelling and repair factors to prevent repair of transient DSBs formed during active transcription and DNA replication to relieve torsional stress. MiR-346 DSBs are enriched at gene promoters bound by key PC transcription factors. Importantly, miR-346 does not induce DNA damage in non-malignant prostate cells, but induces tumour regression as a monotherapy in vivo.

To validate miR-346 as a novel PC therapy, we are investigating:

1. Synthetic lethality: Generating PC cell lines with CRISPR-mediated knockouts of key DNA repair proteins to test whether their loss enhances sensitivity to miR-346–induced DNA damage.

2. Additive/Synergistic drug combinations: Combining miR-346 with inhibitors of PARP, ATR, ATM, DNA-PK, and Wee1 to assess whether co-targeting DNA repair and cell cycle checkpoints amplifies therapeutic efficacy.

3. Optimising therapeutic miR-346 delivery: Evaluating efficacy of LNP- and nanogel-encapsulated miR-346 formulations.

4. Ex vivo studies: Confirming miR-346 therapeutic efficacy in Patient-Derived Explants (PDEs).

Our preliminary data shows that miR-346 is particularly effective when combined with DNA-damaging agents, such as the PARP inhibitor (Olaparib), highlighting its promising therapeutic potential. By integrating studies of synthetic lethality, drug combinations, delivery optimisation and PDE models, we aim to establish the mechanism and translational potential of miR-346. Collectively, these findings will provide a foundation for pre-clinical development and support the advancement of miR-346 as a novel therapeutic strategy for prostate cancer.

P10

Synergistic targeting of AR, SRF, and shared co-regulators to overcome resistance to androgen deprivation therapy in prostate cancer.

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Background: Prostate cancer (PCa) is the most common invasive cancer in men worldwide. Current treatments target the Androgen Receptor (AR) through androgen deprivation therapies (ADT), such as enzalutamide. While initially effective, resistance to these therapies inevitably develops. This highlights the need for alternative strategies that disrupt AR signalling without directly targeting AR, such as inhibiting AR co-regulators. One such candidate is the Serum Response Factor (SRF), previously implicated in PCa progression. Previous studies in our laboratory identified shared interactors between AR and SRF, including HSP70, HSP90, and members of the PI3K/Akt pathway. This study investigates AR-SRF signalling crosstalk and explores whether targeting common co-regulators offers novel therapeutic strategies in advanced PCa.

Methods: Cell proliferation and viability were assessed via MTT assays and IncuCyte analysis using inhibitors targeting SRF (CCG1423, Lestaurtinib), AR (Enzalutamide, EPI7170), HSP70/90 (VER-15508, JG-98, Ganetespib), and the PI3K/Akt pathway (Ipatasertib, Alpelesib) singly and in combination in LNCaP, C4 and 22rv1 cell lines. Whole proteomics and phosphoproteomics were analysed via mass spectrometry.

Results: Inhibiting AR, SRF, and shared co-factors, both individually and in combination, reduced PCa cell viability and proliferation. Notably, several drug combinations demonstrated synergy at IC_{30} and IC_{10} concentrations, including Lestaurtinib + Ipatasertib, CCG1423 + EPI7170, EPI7170 + Ipatasertib, and EPI7170 + Lestaurtinib. Proteomics and phospho-proteomics analysis following treatment with Lestaurtinib and Ipatasertib, singly and in combination is ongoing.

Conclusion: These findings suggest that targeting the AR-SRF signalling network is a promising strategy for overcoming ADT resistance in PCa. Ongoing proteomic analyses aim to uncover deeper insights into resistance mechanisms and identify additional therapeutic targets.

P11

Comparing imaging modalities for identifying parathyroid adenomas with a focus on effective resource usage

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Introduction:

At Frimley Park Hospital, patients being investigated for primary hyperparathyroidism secondary to a parathyroid adenoma usually undergo an ultrasound parathyroid scan along with a NM Parathyroid MIBI SPECT CT. A CT 4D Parathyroid with contrast is requested when concordance is not seen on both Ultrasound and MIBI scans. The purpose of our study was to identify potential cost savings by proving the superiority of CT 4D scans and potentially offering this as a single investigation instead.

Methods:

We reviewed data for all patients who had undergone a CT 4D parathyroid scan between January 2021 and February 2024 at Frimley Park Hospital. We looked at whether these patients had undergone an ultrasound or MIBI scan prior to undergoing a CT 4D parathyroid, and what the respective success rates were of the various imaging modalities at identifying parathyroid adenomas. We also looked at what proportion of adenomas identified via the various imaging modalities were later confirmed to be present during explorative surgery.

Results:

A total of 91 patients underwent a CT 4D Parathyroid between January 2021 and February 2024. Of these patients, 65 patients underwent an ultrasound and a MIBI scan, followed by a CT 4D; 14 patients underwent a MIBI and CT 4D scan, but not an ultrasound; 10 patients underwent an ultrasound and CT 4D scan, but not a MIBI scan. Only 2 patients underwent a CT 4D scan only.

Successful identification of an adenoma using the various imaging modalities taken in isolation was as follows: 62% with CT 4D, 44% with MIBI, and 34% with ultrasound.

Of the proportion of patients with positive adenoma identification on CT 4D, 89.8% underwent surgery. An adenoma was identified on surgical exploration in 54% of these cases.

Conclusion:

Our results revealed that the CT 4D scan is by far the most accurate imaging modality of the three included in our study. Whilst this is certainly not groundbreaking information, we are using these results locally to change previous trust policy and help drive savings by avoiding unnecessary preliminary imaging requests and proceeding to CT 4D directly.

P12

Exploring KMT2D as a disease driver and susceptibility biomarker in advanced prostate cancer

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Prostate cancer (PC) is the second most common male cancer, with 1 in 6 men in the UK expected to be diagnosed with the disease in their lifetime. The epigenome is dysregulated in PC, and as such is an emerging therapeutic target for management of the disease. Approximately 6% of all PCs harbour either truncating or missense mutations of KMT2D – a histone 3 lysine 4 (H3K4) methyltransferase which plays roles in several biological processes, including transcription. Previous studies have highlighted context-specific oncogenic roles for KMT2D loss-of-function mutations, putting forward KMT2D as a potential therapeutic target. Despite this, the functional interplay between KMT2D and the androgen receptor (AR) signalling axis, upon which most PC is dependent, is yet to be comprehensively investigated. Here, our preliminary data shows reduction of both AR transcript and AR target gene expression in response to siRNA-mediated depletion of KMT2D. Furthermore, ChIP-qPCR assays demonstrate recruitment of KMT2D to AR-regulated genes implicating a coregulatory role for KMT2D in the AR signalling cascade.

Although KMT2D presents as an interesting therapeutic target, there are currently no available inhibitors of the protein. Given the propensity for KMT2D mutations in advanced PC, we hypothesise that this genetic defect will drive novel synthetic-lethality susceptibilities in this patient cohort. Here, we investigate if KMT2D mutation is a driver of synthetic lethality in PC by developing novel CRISPR-derived models for wide-scale drug testing. Although very much preliminary, we have evidence of altered drug sensitivities in wild-type and KMT2D mutant PC backgrounds which we will fully validate in future studies.

P13

Association Between Anti-TPO Antibody Levels and FNA Cytology in Thyroid Nodules: A Meta-Analysis and systematic review

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Background:

Anti-thyroid peroxidase (anti-TPO) antibodies are commonly elevated in autoimmune thyroiditis, especially Hashimoto's thyroiditis. Their relationship to fine-needle aspiration (FNA) cytology findings is of growing clinical interest, particularly in the context of malignancy risk.

Objective:

To evaluate whether anti-TPO antibody positivity is associated with specific FNA cytological outcomes, with a focus on the likelihood of malignancy.

Methods:

This meta-analysis included six observational studies encompassing 12,634 patients who underwent both anti-TPO antibody testing and thyroid nodule FNA. All studies used the Bethesda System for Reporting Thyroid Cytopathology. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between anti-TPO positivity and malignancy risk.

Results:

Anti-TPO-positive patients were more likely to have benign cytology and Hashimoto's thyroiditis. The pooled OR for malignancy in anti-TPO-positive individuals was 0.72 (95% CI: 0.58–0.90), indicating a significantly reduced risk. This trend remained consistent across studies.

Conclusion:

Anti-TPO antibody elevation is associated with a decreased risk of malignancy on FNA and is indicative of autoimmune, rather than neoplastic, thyroid pathology. While not a substitute for cytology or imaging, anti-TPO status may serve as an adjunctive marker in nodule risk stratification.