VANCOUVER PROSTATE CENTRE
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M.H. Mohseni Institute of Urologic Sciences

Department of UROLOGIC SCIENCES UBC

19TH ANNUAL LORNE D. SULLIVAN **LECTURESHIP & RESEARCH DAY**

TUESDAY, JUNE 10, 2025

Paetzold Health Education Centre, Jim Pattison Pavilion

8am to 3pm

2025 Sullivan Research Lecturer

Dr. Ganesh S. Palapattu

Department Chair, Urology
George F and Sandra G Valassis Professor of Urology
U of Michigan Urology Cancer Center

Dr. Ganesh S. Palapattu, MD, FACS is the George F. and Sandy G. Valassis Professor and Chair of Urology at the University of Michigan. Dr. Palapattu's clinical interest is in the evaluation and management of men with high-risk prostate cancer. As a surgeon-scientist, he maintains a prostate cancer translational lab and his clinical and administrative duties. Dr. Palapattu earned his undergraduate degree from the University of Texas at Austin, and medical degree from Baylor College of Medicine. He then completed his surgical internship, urologic training and chief residency in urology at the David Geffen School of Medicine at UCLA. Subsequently, Dr. Palapattu completed a 2-year laboratory research fellowship in Urologic Oncology at the Johns Hopkins Hospital/Brady Urological Institute. He joined the faculty at the University of Michigan in 2012 and was appointed chair in 2019.

Dr. Lorne D. Sullivan (1936 – 2024)

Dr. Sullivan was raised in Moss Bank, Saskatchewan, and graduated from the University of Saskatchewan, Faculty of Medicine in 1962. After an Internship at Vanderbilt University, he completed his urological training at UBC under the mentorship of Dr. John Balfour. He pursued postgraduate training in Urological Oncology as a Royal College Traveling Fellow at several US Cancer Centres before establishing his practice in British Columbia in 1971. During his years of clinical practice, he developed a highly recognized centre for the surgical management of urological cancer at UBC and was a visionary in the establishment of the Prostate Research Centre. He was a respected teacher and clinician responsible for training an entire generation of British Columbian urologists.

At the national and international level, he served as President of the Canadian Urological Association, the Northwest Urological Society, the Western Section of the AUA, Chaired the Specialty Committee in Urology and was Chief Examiner for the Royal College of Physicians and Surgeons of Canada. He was Head of the Division of Urology at UBC from 1991-1999. He retired in 1999 to spend time with his family and grandchildren.

Previous Sullivan Lectureship & Research Day Lecturers & Graduation Dinner Guest Speakers

2024 - Dr. Alberto Briganti
2023 - Dr. Scott Eggener
2022 - Dr. Anthony Atala
2021 - Dr. Christopher Barbieri
2019 - Dr. Christopher P. Evans
2018 - Dr. Robert Reiter
2017 - Dr. James E. Lingeman
2016 - Dr. Michael S. Jewett
2015 - Dr. John M. Barry
2014 - Dr. James A. Eastham
2013 - Dr. Paul Lange
2012 - Dr. Ralph V. Clayman
2011 - Dr. David A. Bloom
2010 - Dr. Gerald H. Jordan
2009 - Dr. Peter T. Scardino
2008 - Dr. Inderbir Singh Gill
2007 - Dr. Joao Pippi Salle
2006 - Dr. John Fitzpatrick

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Welcome

8:00 AM – 8:15 AM	**Dr. Martin Gleave** Distinguished Professor and Head, Department of Urologic Sciences, UBC Executive Director, Vancouver Prostate Centre British Columbia Leadership Chair in Prostate Cancer Research **Dr. Teresa S.M. Tsang** Executive Director, Vancouver Coastal Health Research Institute Professor, Cardiology; Associate Dean, Faculty of Medicine, UBC Director, VGH-UBC Echo Lab and AI Echo Core Lab, VCHRI AI Hub

Lorne D. Sullivan Lectureship

Introduction:	**Dr. Martin Gleave**
8:15 AM – 8:55 AM	**Exploring Transcriptional Diversity in Multi-focal Prostate Cancer: Implications and Impact** **Dr. Ganesh S. Palapattu** Department Chair, Urology George F. and Sandy G. Valassis Professor of Urology U of Michigan Urology Cancer Center

Session I: AI Meets Urology

8:55 AM – 9:45 AM

(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderators:	**Faraz Hach & Connor Forbes**
8:55 AM – 9:05 AM	**STIMULATED RAMAN HISTOLOGY AND ARTIFICIAL INTELLIGENCE PROVIDE NEAR REAL-TIME CLINICALLY SIGNIFICANT PROSTATE CANCER DIAGNOSIS FROM MRI TARGETED PROSTATE BIOPSIES IN PROSPECTIVELY COLLECTED 200 CASES** **Presenter:** Takeshi Namekawa
9:05 AM – 9:15 AM	**LEVERAGING MACHINE LEARNING TO IDENTIFY INTERPRETABLE HISTOPATHOLOGIC FEATURES IN MUSCLE-INVASIVE BLADDER CANCER FOR NEO-ADJUVANT TREATMENT RESPONSE PREDICTION** **Presenter:** Nikolay Alabi
9:15 AM – 9:25 AM	**PENOMETER-3D: AI-DRIVEN 3D ASSESSMENT FOR PEYRONIE'S DISEASE** **Presenter:** Ali Balapour
9:25 AM – 9:35 AM	**DEEP MODELLING OF REGULATING EFFECTS OF SMALL MOLECULES ON SPERMATOGENESIS-ASSOCIATED GENES** **Presenter:** Jiaying You

Session II: Surgical Risk, Timing and Trends

9:35 AM – 10:05 AM

(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderators	**Thomas de Los Reyes & Ryan Paterson**
9:35 AM – 9:45 AM	**ONCOLOGICAL OUTCOMES OF NON-MUSCLE INVASIVE BLADDER CANCER IN PATIENTS AGED ≤45: A RETROSPECTIVE MATCHED COHORT STUDY** **Presenter:** Marie-Pier St-Laurent
9:45 AM – 9:55 AM	**PREDICTING PERIOPERATIVE CARDIAC RISK FOR TRANSURETHRAL PROSTATE SURGERY: A COMPARATIVE ANALYSIS OF THE REVISED CARDIAC RISK INDEX (RCRI) AND NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM (NSQIP)** **Presenter:** Moe Saffarzadeh

9:55 AM – 10:05 AM	**AFTER-HOURS SURGERY IS ASSOCIATED WITH INCREASED POST-OPERATIVE COMPLICATIONS IN THE PEDIATRIC RENAL TRANSPLANT POPULATION** **Presenter:** Harshita Kour

Break and Posters 10:05 AM – 10:35 AM

State of Art Lecture I:

Introduction:	**Dr. Amina Zoubeidi**
10:35 AM – 10:50	**The Biotechnology of Liquid Biopsy and Applications to Clinical Care** **Presenter:** Dr. Alexander Wyatt

Session III: Advances in Urologic Oncology Biology I

10:50 AM – 12:00 PM
(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderators:	**Morgan Roberts & Michael Cox**
10:50 AM – 11:00 AM	**SPATIAL PROFILING OF THE TUMOR IMMUNE MICROENVIRONMENT IN MUSCLE-INVASIVE BLADDER CANCER TREATED WITH NEOADJUVANT PLATINUM CHEMOTHERAPY** **Presenter:** Nicolas Zheng
11:00 AM – 11:10 AM	**UNRAVELING THE ROLE OF FBXW7 IN MUSCLE-INVASIVE BLADDER CANCER: TARGETING MYC FOR THERAPEUTIC ADVANTAGE** **Presenter:** Alberto Contreras-Sanz
11:10 AM – 11:20 AM	**IDENTIFICATION OF A STRUCTURAL VARIANT THAT CAUSES ENHANCER HIJACKING TO OVEREXPRESS MYC IN CASTRATION-RESISTANT PROSTATE CANCER** **Presenter:** Umut Berkay Altiintas
11:20 AM – 11:30 AM	**COMPARING THE PHASE BEHAVIOUR OF THE ANGROGEN RECEPTOR (AR) AND ITS SPLICE VARIANT (AR-7) IN PROSTATE CANCER** **Presenter:** Shabnam Massah
11:30 AM – 11:40 AM	**AR ANTAGONISM-INDUCED MAP1B PROMOTES TREATMENT RESISTANCE IN PROSTATE CANCER** **Presenter:** Yusuke Shiraishi
11:40 AM – 11:50AM	**INSM1 REGULATES ARGININE METABOLISM VIA ASS1 TO MAINTAIN THE NEURONAL PHENOTYPE IN NEPC** **Presenter:** Ishana Lodhia
11:50 AM – 12:00 PM	**IDENTIFICATION OF CHD7 AS A KEY UPSTREAM CHROMATIN REGULATOR DRIVING THE DEVELOPMENT AND AGGRESSIVENESS OF NEPC** **Presenter:** Ace Mingchen Shi

Lunch and Posters 12:00 PM – 1:00 PM

Session IV: Advances in Urologic Oncology Biology II

1:00 PM – 1:50 PM
(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderators:	**Colin Collins & Miles Mannas**
1:00 PM – 1:10 PM	**LYNCH SYNDROME-ASSOCIATED UROTHELIAL CANCER: DISTINCT GENOMIC LANDSCAPE AND EARLY RESULTS FROM THE LS-URO utDNA SCREENING STUDY.** **Presenter:** Jussi Nikkola

1:10 PM – 1:20 PM	**INTRAPATIENT GENOMIC HETEROGENEITY AND EVOLUTION OF DE NOVO METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER** **Presenter:** Kamal Al Najem Azzam
1:20 PM – 1:30 PM	**WE DON'T TALK ANYMORE: DISRUPTIONS TO THE LACUNOCANALICULAR NETWORK IN PROSTATE CANCER BONE METASTASIS** **Presenter:** Naomi Jung
1:30 PM – 1:40 PM	**ORIGINS OF RELAPSE IN ADT-INDUCED PROSTATE CANCER TUMOR DORMANCY ADAM CLASSEN** **Presenter:** Adam Classen
1:40 PM – 1:50 PM	**CLONAL HEMOTOPOIESIS (CH) IN PARTICIPANTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) RECEIVING LU-PSMA-617 OR CABAZITAXEL: AN EXPLORATORY POST-HOC ANALYSIS OF A RANDOMIZED PHASE II TRIAL (THERAP ANZUP 1603)** **Presenter:** Asli Munzur

State of Art Lecture II:

Introduction:	**Dr. Peter Black**
1:50 PM – 2:15 PM	**Does the Urobiome Matter in Renal Transplantation?** **Presenter:** Dr. David Harriman

Session V: Translational Science in Urology

2:15 PM – 3:05 PM

(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderator:	**Xuesen Dong**
2:15 PM – 2:25 PM	**SPATIALXPRESS: DROPLET MICROFLUIDIC PLATFORM FOR SPATIOTEMPORAL INVESTIGATIONS INTO RARE CELL POPULATIONS IN HETEROGENOUS CANCER TISSUES** **Presenter:** Alisa Da Silva
2:25 PM – 2:35 PM	**SINGLE-CELL RNA SEQUENCING REVEALS FIBROTIC PATHWAYS IN PEYRONIE'S DISEASE. IMPLICATIONS OF ARYL HYDROCARBON RECEPTOR IN MYOFIBROBLAST ACTIVITY AND COLLAGEN DEPOSITION** **Presenter:** Soroush Mohebat
2:35 PM – 2:45 PM	**THULIUM FIBER LASER: LONG PULSE WIDTH AS AN INDEPENDENT RISK FACTOR FOR EXCESSIVE HEAT GENERATION** **Presenter:** Joel Teichman
2:45 PM – 2:55 PM	**TRANSCRIPTOMIC CHARACTERIZATION OF HUMAN HIPSC-DERIVED TESTIS CELLS AND MATURATION IN A 3D BIOPRINTED COAXIAL TESTIS MODEL-- MAHDI ASMAE** **Presenter:** Mahdi Asmae
2:55 PM – 3:05 PM	**PRESCRIBING PATTERNS AND CLINICAL IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AMONG KIDNEY TRANSPLANT POPULATION IN BRITISH COLUMBIA, CANADA -- HYUNWOONG (HARRY) CHAE** **Presenter:** Hyunwoong (Harry) Chae

ADJOURN

ABSTRACTS:

Podium Presentations

STIMULATED RAMAN HISTOLOGY AND ARTIFICIAL INTELLIGENCE PROVIDE NEAR REAL-TIME CLINICALLY SIGNIFICANT PROSTATE CANCER DIAGNOSIS FROM MRI TARGETED PROSTATE BIOPSIES IN PROSPECTIVELY COLLECTED 200 CASES

Takeshi Namekawa[1,2], Martin Gleave[1,2], Adrian Ion-Margineanu[3], Mingyu Sheng[2] , Eric Belanger[3] , Christian Freudiger[4] , Eric Belanger[5] , Samir S. Taneja[6,7,8] , Miles P. Mannas[1,2]

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8. Dept. of Biomedical Engineering, NYU Langone Health, New York, New York

Introduction

The initial core during an MRI-targeted prostate biopsy (TB) have demonstrated higher prostate cancer (PCa) diagnostic value compared to additional cores. Stimulated Raman histology (SRH) creates histologic images providing near-real time prostate biopsy pathology. This study aimed to evaluate the detection of clinically significant PCa (csPCa) detection with the first MRI TB imaged with SRH interpreted by a convolutional neural network (CNN).

Methods

200 men with a PI-RADS 3-5 finding (n=256 regions of interest (ROI)), undergoing a transperineal TB were prospectively enrolled in an IRB approved study. The TB were kept fresh before scanning with the SRH microscope using two Raman spectra, 2845cm-1 and 2930cm-1 . A published CNN, without cluster analysis, was incorporated into the SRH microscope to provide a near real-time prostate cancer risk score (CRS). Following SRH creation, the TB underwent standard pathologic processing and interpretation for ground truth diagnosis. The first TB core was separated for interpretation from other TB cores. The sensitivity and specificity of GG (ISUP Grade Group) 2 PCa detection with CNN was calculated.

Results

Time for SRH-AI for the first targeted biopsy was 2.5 minutes. Eighty-one cases demonstrated csPCa, and when a ROI contained csPCa, the first biopsy identified PCa in 81.5 % of cases. SRH-AI differentiates csPCa from Benign tissue and GG1 prostate cancer with AUC 0.92. With cutoff CRS>15, the CNN analysis of the first TB demonstrated 86% sensitivity and 80% specificity for csPCa identification. Thirty five out of 39 false positive cases showed GG1 prostate cancer

Conclusion

SRH allowed csPCa to be identified in TB within 2.5 minutes, with the CNN showing high excellent discrimination of PCa infiltrated tissue. Most false positive were GG1 PCa, however further CNN training and testing will require before clinical application. Clinical implementation may guide biopsy intensity when the ROI contains csPCa.

LEVERAGING MACHINE LEARNING TO IDENTIFY INTERPRETABLE HISTOPATHOLOGIC FEATURES IN MUSCLE-INVASIVE BLADDER CANCER FOR NEO-ADJUVANT TREATMENT RESPONSE PREDICTION

Nikolay Alabi[1], Alberto Contreras-Sanz[2], Sindhuja Patthabi[2], Htoo Z. Oo[2], Peter Black[2], Ali Bashashati[1]

1. School of Biomedical Engineering, University of British Columbia, Vancouver Canada
2. Vancouver Prostate Centre, Department of Urologic Sciences, Vancouver, Canada

Introduction

Neoadjuvant chemotherapy (NAC) improves survival in muscle-invasive bladder cancer (MIBC), yet only ~40% of patients achieve an objective pathologic response. The lack of predictive biomarkers limits therapy decision-making. While histopathological features have been explored for prognostic insights, their role in predicting NAC response remains unclear. This study aims to develop an interpretable machine-learning framework that leverages histopathology images to identify predictive biomarkers for NAC response.

Methods

Pre-treatment TURBT samples from 42 NAC-treated MIBC patients were analyzed. 122 whole slide images were encoded using histopathology foundation models. Increasingly complex models were tested in a 5-fold cross validation manner: a traditional fully connected neural network (NN), a state-of-the-art multiple-instance learning model (MIL), and a multi-magniϐication MIL model (Multi-Mag MIL). To improve interpretability, high-attention regions were further analyzed using HoverNet to extract cellular features (e.g., nuclear area, solidity, eccentricity, cell type proportions). Morphological differences between responders and non-responders were statistically assessed.

Results

Multi-Mag MIL outperformed NN and MIL at both the slide (accuracy: 0.75 vs. 0.635 and 0.62) and patient level (accuracy: 0.77 vs. 0.67 and 0.65). Morphological analyses of high-attention patches revealed that non-responders exhibit signiϐicantly smaller nuclear size ($p < 0.001$) with greater eccentricity ($p < 0.001$), while responders show increased solidity ($p < 0.0001$) and more inϐlammatory cells, including neutrophils ($p < 0.0001$). These ϐindings were consistent across multiple cellular shape metrics and suggest distinct microenvironmental features associated with treatment response.

Conclusion

We present a deep learning histopathology model that identiϐies key tissue regions linked to NAC response in MIBC. Cellular morphology within these regions reveals interpretable biomarkers that differentiate responders from non-responders. This approach offers a scalable strategy for augmenting treatment decisions using pathology slides, with the potential to support precision oncology through visual, explainable model outputs. Next steps include exploration of our model in three additional cohorts: MIBC treated without NAC (cystectomy alone), MIBC treated with pembrolizumab (PURE-01 trial), and MIBC treated with nivolumab and NAC (BLASST-1 trial).

PENOMETER-3D: AI-DRIVEN 3D ASSESSMENT FOR PEYRONIE'S DISEASE

Ali Balapour[1,2,3,4], Ryan Flannigan[1,2,3*], Faraz Hach[1,2,3*]

1. Department of Urologic Sciences, the University of British Columbia, Vancouver
2. Vancouver Prostate Centre, M.H. Mohseni Institute of Urologic Sciences, Vancouver
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4. Bioinformatics Program, the University of British Columbia, Vancouver

* Co-Corresponding

Introduction
Peyronie's Disease (PD) affects up to 15% of men and is marked by penile deformity, often causing emotional distress and relationship issues. Despite its impact, many patients hesitate to seek medical evaluation due to stigma, cost, or discomfort associated with inoffice assessments. To address this, photography-based methods have emerged as a more accessible alternative for evaluating PD. However, these tools are limited in capturing the full penile shaft anatomy, restricting their use to available views and limiting treatment outcome visualization. We aim to combine AI-based 3D reconstruction with computational assessment to improve the accuracy, accessibility, and efficiency of PD assessment.

Methods
PenoMeter-3D is an AI-powered pipeline for generating 3D models of the penile shaft from standard images. It involves 3D reconstruction using an AI-based model and anatomical assessment using the PenoMeter tool to evaluate curvature deformities.

Results
We evaluated PenoMeter-3D's ability to generate accurate 3D penile anatomy representations, which are essential for applications like PD assessment and treatment visualization. We used various 3D and 2D evaluation metrics. Synthetic PD samples were created by systematically varying deformity direction, magnitude, and location. The model achieved an F-score of 87.5%, PSNR of 21.27, and CLIP score of 96.9%, indicating strong 3D reconstruction accuracy. We also tested curvature estimation in samples with curvatures under 90 degrees, which is common among patients, and obtained a mean absolute error of 11.7 degrees. Error increased with more severe curvatures.

Conclusion
By integrating AI-driven 3D reconstruction into PD assessment, PenoMeter-3D aims to offer a non-invasive, cost-effective, and comprehensive assistive diagnostic tool. This approach has the potential to significantly reduce barriers to medical evaluation, offering patients a more accessible alternative to traditional clinical assessments. Our proposed method could revolutionize PD diagnosis, improve patient outcomes, and enhance the overall quality of care in men's health.

DEEP MODELLING OF REGULATING EFFECTS OF SMALL MOLECULES ON SPERMATOGENESIS-ASSOCIATED GENES

Jiaying You[1,2], Meghan Robinson[1,3], Mahdi Asmae[1,3], Faraz Hach[1,2,3], Ryan Flannigan[1,3], Artem Cherkasov[1,2,3]

1. Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada
2. Vancouver Prostate Centre, Vancouver, British Columbia,
3. Reproductive & Sexual Medicine Centre, M.H. Mohseni Institute of Urologic Sciences

Introduction:
The most severe form of male infertility is characterized by the absence of sperm in the ejaculate due to a sperm production problem. This occurs among 1% of the general population. Treatments are limited. Therefore, regenerative treatments, such as in vitro spermatogenesis (IVS), are required; however, a major limitation is understanding molecules to support somatic cell maturation or germ cell differentiation.
Objective:
To identify drugs that will mature induced pluripotent stem cell (iPSC)-derived testis somatic cells and guide stage-wise-specific differentiation of human germ cells.

Methodology:
To identify potential therapeutic candidates that could facilitate this process, we developed a machine learning pipeline for large-scale screening across chemical spaces. This pipeline integrates single-cell transcriptomic data (scRNAseq) with high-throughput drug perturbation profiles. Marker genes corresponding to distinct stages of germ cell development were identified from healthy human testis scRNAseq. Deep learning models incorporating molecular fingerprints and gene ontology features were constructed for human cell lines using the Library of Integrated Network-Based Cellular Signatures (LINCS) Level 5 perturbation dataset that provides gene expression signatures under compound treatments. The trained models were screened against differentially expressed spermatogenesis genes from approved DrugBank compounds. Compounds predicted to regulate spermatogenesis-associated genes in desired direction were ranked as therapeutic Candidates.

Results:
Using statistical threshold of 0.9, we selected drugs that interact with the most differentially expressed genes and cell lines, we identified 23 drugs that may support maturation of iPSC-Sertoli cells, 13 drugs for iPSC-Leydig cell maturation, 3 drugs for iPSCMyoid cell maturation. Finally, drugs for stage-wise-specific germ cell differentiation were also identified. Upon validating these potential drug targets, many have been cited to have implications in spermatogenesis, supporting our hypothesis.

Conclusions:

We have developed a novel machine learning drug discovery pipeline to support functionalization and maturation of human testis cells in efforts to support in vitro spermatogenesis.

Oncological Outcomes of Non-Muscle Invasive Bladder Cancer in Patients Aged ≤45: A Retrospective Matched Cohort Study

Marie-Pier St-Laurent[1], Shayan Din[2], Joseph Moryousef[3], Katherine Lajkosz[2], Jethro C.C Kwong[2], Amy Chan[2], Jaehoon Kim[2], Afton Taborek[4], Iman Sadri[3], Gabrielle Reznik[1], Caris Tin[1], Neil E. Fleshner[2], Girish S. Kulkarni[4], Peter C. Black[1], Wassim Kassouf[3], Alexandre R. Zlotta[2,4]

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3. Department of Urology, McGill University Health Centre, Montreal, Canada
4. Division of Urology, Department of Surgery, Mount Sinai Hospital, Sinai Health System, University of Toronto, Toronto, Canada

Introduction

Bladder cancer (BC), most frequently diagnosed as non-muscle invasive (NMIBC), primarily affects older adults. While several cancer are on the rise in younger adults and exhibit aggressive behavior, our knowledge on BC remains limited. We aim to assess oncological outcome of NMIBC in ≤45 years patient and compared to matched cohort of older patients.

Methods

Retrospective study of NMIBC patients diagnosed at age ≤45 (1988-2022) conducted at four Canadian academic centers. Endpoints included cancer-specific mortality (CSM), recurrence, stage progression (Ta to T1), grade progression, and progression to muscle invasion or metastases. Competing risk analysis and Kaplan-Meier survival estimates were used. Hazard ratios were calculated using Fine and Gray regression models. Propensity score matching (3:1) was used with patients aged >45 to compare outcomes, with logistic regression model incorporating sex, carcinoma in situ (CIS), stage, grade, number of tumors, and tumor diameter as predictors.

Results

Among 162 patients, median age was 39 years (IQR 31-42) and median follow-up 7.8 years (IQR 3.5-12.1). Majority were male (66%), non-smokers (64%), with solitary (78%) and low-grade (65%) tumors. Stage distribution included 82% Ta, 16% T1, and 3% CIS-only. After matching, 122 younger patients were compared to 359 older patients (median age 71 years, IQR 63-79). Recurrence rates were higher in older patients (HR 1.75, 95% CI 1.28- 2.41, $p<0.001$). CSM, grade progression, and progression to muscle invasion or metastases were not significantly different (all $p>0.05$) between groups.

Conclusion

NMIBC does not exhibit more aggressive behavior in younger patients compared to older patients.

PREDICTING PERIOPERATIVE CARDIAC RISK FOR TRANSURETHRAL PROSTATE SURGERY: A COMPARATIVE ANALYSIS OF THE REVISED CARDIAC RISK INDEX (RCRI) AND NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM (NSQIP)

Saffarzadeh M[1], Moussaoui G[1], Dorner A[1], Paterson R[1], Chew BH[1], Forbes CM[1]

1. Department of Urologic Sciences, University of British Columbia

Introduction

The Revised Cardiac Risk Index (RCRI) and the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) are both validated tools to predict 30-day postoperative cardiac events in non-cardiac surgeries. This study compared RCRI- and NSQIP-predicted cardiac outcomes with the actual incidence of cardiac events following transurethral prostate surgery.

Methods

We conducted a retrospective review of patients who received Transurethral prostate surgery over a 6-month timeframe (July to December 2022). We assessed for post-operative cardiac events within 30 days, as defined by the seminal cardiac VISION study used in the RCRI prediction index. RCRI and NSQIP cardiac event predictions were calculated. Fisher's exact test was used to determine statistical significance.

Results

We included 185 patients with an average age of 73 ± 8.4 (SD) years, 86 of whom (46%) had Transurethral Resection of the Prostate (TURP), and 99 underwent Holmium Laser Enucleation of the Prostate (HoLEP) (54%). Myocardial Injury After Noncardiac Surgery (MINS) surveillance was needed for 34 patients (18.4%) per standard practice. No patient had any intra-operative cardiac events. One patient experienced a nonfatal post-operative cardiac event (asystole) within hours of surgery. The 30-day cardiac event prediction by RCRI was 4.8% of the patient cohort ($n \approx 9$), significantly higher than the observed incidence of 0.5% ($p = 0.0198$). NSQIP predicted 0.54% of the patient cohort ($n = 1$) will have a cardiac complication within 30 days, which is not significantly different from the observed cardiac event incidence ($p = 1$).

Conclusion

In this study, RCRI significantly overestimated the 30-day cardiac risk following transurethral prostate surgery while NSQIP had a similar prediction rate of cardiac events to the observed incidence. Utilizing more representative predictive tools helps improve risk stratification and will allow patients and surgeons to make better informed decisions about transurethral surgery.

AFTER-HOURS SURGERY IS ASSOCIATED WITH INCREASED POST-OPERATIVE COMPLICATIONS IN THE PEDIATRIC RENAL TRANSPLANT POPULATION

Harshita Kour [1], Julie Wong[1], Maryam Noparast[1] , Kourosh Afshar[1]

1. Division of Pediatric Urology, Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia.

Introduction
The unpredictable availability of donor organs creates unique scheduling challenges for solid organ transplants. Performing kidney transplants in after-hours requires mobilizing extra hospital resources and risks surgical team fatigue, with the presumed benefit of decreased cold ischemic time. While research in adult kidney transplantation has shown mixed evidence regarding outcomes during nighttime surgeries, no prior studies have focused on pediatric kidney transplants, which are technically challenging due to intraabdominal implantation into major vessels.

Objective
This study examines whether pediatric renal transplant surgeries performed afterhours are associated with increased post-operative complications. Methods: A retrospective single-center chart review was conducted at a large quaternary children's hospital in Canada for pediatric renal transplants performed between 2000 and 2019. Post-operative complications were analyzed using univariate and multivariate analyses, adjusting for covariates such as vascular anastomotic time and obstructive causes of end-stage renal disease (ESRD).

Results
Of the 158 kidney transplants, 48 (30.3%) started after-hours (17:00–07:00). Postoperative complications occurred in 31 patients (19.6%). Multivariate analysis revealed that after-hours transplants were significantly associated with increased post-operative complications (OR 3.3, 95% CI 1.4–7.5), even after adjusting for covariates such as anastomotic and type of ESRD.

Conclusion
These findings highlight the need to balance the benefits of reduced cold ischemic time against the risks of nighttime surgery.

SPATIAL PROFILING OF THE TUMOR IMMUNE MICROENVIRONMENT IN MUSCLE-INVASIVE BLADDER CANCER TREATED WITH NEOADJUVANT PLATINUM CHEMOTHERAPY

Nicolas Zheng[1], Nikolay Alabi[2], Joshua Scurll[1], Nemat Haroon[1], Jussi Nikola[1], Htoo Z Oo[1], Katy Milne[3], Brad Nelson[3], Ali Bashashati[2], Morgan Roberts[1], Alberto Contreras-Sanz[1], Shilpa Gupta[4], Peter Black[1]

1. Vancouver Prostate Centre, Department of Urologic Sciences, Vancouver, Canada
2. School of Biomedical Engineering, University of British Columbia, Vancouver, Canada
3. Deelay Research Centre, BC Cancer, Victoria, Canada
4. Department of Oncology, The Cleveland Clinic, Cleveland, OH, USA

Introduction
Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is standard of care for muscle-invasive bladder cancer (MIBC), yet only ~40% of patients respond. The tumor immune microenvironment (TIME) influences therapy response, but prior studies lack RC-alone cohorts, limiting differentiation between prognostic and predictive biomarkers. Here, we analyze TIME spatial relationships to identify immune features linked to NAC response and clinical outcomes.

Methods
Pre-treatment transurethral resection (TUR) specimens from 42 NAC+RC and 61 RC-alone patients were analyzed, along with residual tumors (≥ypT1N0-3M0-1) from 13 and 32 patients, respectively. Tumor regions were assembled into tissue microarrays and assessed using three multiplex immunofluorescence panels (B&T cell, adaptive resistance, and myeloid panels). Digital image analysis and spatial modeling of first nearest-neighbor (1NN) distances and frequency of cellular triads captured higher-order insights into immune-tumor dynamics patterns.

Results
The spatial organization of immune populations and the prevalence of specific cellular triads in TUR specimens were associated with NAC response. Increased triads of B cells, CD4+ T cells, and Tregs correlated with NAC resistance (OR=0.77, 95% CI [0.55, 0.94], p=0.04). Statistical modelling of the distance relationship between CD4+ T cells and Tregs showed longer distances were linked to resistance to NAC (OR=0.22, 95% CI [0.05, 0.67], p=0.02). Additionally, NAC-resistant tumors exhibited distinct immune architecture, including decreased proximity between CD8+ T cells and tumor cells. Posttreatment RC samples showed significant immune reorganization, including the increased mean distance between NK cells and tumor cells (p=0.04).

Conclusion
Spatial immune metrics correlate with NAC response and clinical outcomes in MIBC. Further refinement of the models, and comparison with RC-alone cohorts, is ongoing. This analysis will enhance biomarker development aimed at personalized treatment strategies.
Funding: Department of Defense (US) Innovation award (W81XWH2010877)

UNRAVELING THE ROLE OF FBXW7 IN MUSCLE-INVASIVE BLADDER CANCER: TARGETING MYC FOR THERAPEUTIC ADVANTAGE

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Introduction

Loss-of-function mutations in FBXW7 occur in up to 10% of muscle invasive bladder cancer (MIBC). Although FBXW7 is known to play a critical role in the proteasome degradation of oncogenic proteins including NOTCH, mTOR, and MYC, suggesting that loss of its function could be oncogenic, its significance in MIBC has not been studied. Here, we investigate the oncogenic role of altered FBXW7 function and explore strategies for targeting FBXW7-deficient tumours.

Methods

The MSK-IMPACT and TCGA (2017) MIBC cohorts were analyzed for FBXW7 genomic alterations and mRNA expression levels in relation to clinical outcomes. FBXW7 was knocked out (KO) in basal (UM-UC3) and luminal (RT112) MIBC cell lines. Two hotspot-mutations in FBXW7 (R479G and R505G) were introduced to assess their functional impact. Phenotypic assays, downstream pathway analysis, and pharmacologic inhibition of the FBXW7-MYC axis were carried out on these cell lines, as well as in an in vivo orthotopic MIBC model.

Results

In patients, low expression or genomic alteration of FBXW7 was associated with increased MYC signalling and shorter survival. In cell lines, FBXW7 KO resulted in elevated expression of MYC and cell cycle genes (CCNE1, CCND1, CDK2, CDK4 and CDK6). Re-transfection of a wild-type FBXW7-coding plasmid in these KO cell lines normalized the expression of MYC and cell cycle genes. FBXW7-KO cells transfected with R479G and R505G mutants retained the KO-induced phenotype and downstream signaling. We confirmed that FBXW7-deficient (mutated and KO) cell lines displayed enhanced sensitivity to MYC inhibition (MYCi) using two different compounds (VPC70619, and KSI-3716). Furthermore, we demonstrated the increased efficacy of KSI-3716 in an orthotopic mouse MIBC model harboring the R479G and R505G mutants compared to the wild-type FBXW7-rescued control.

Conclusion

Our findings suggest that FBXW7 functions as a tumor suppressor through its regulation of MYC signalling in MIBC. Tumours with FBXW7 mutations have high MYC activity, which can be effectively abrogated pharmacologically, both in vitro and in vivo. This suggests that MYCi may represent a promising treatment strategy for select FBXW7-altered tumors.

IDENTIFICATION OF A STRUCTURAL VARIANT THAT CAUSES ENHANCER HIJACKING TO OVEREXPRESS MYC IN CASTRATION-RESISTANT PROSTATE CANCER

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Introduction

Castration-resistant prostate cancer (CRPC) evades androgen-deprivation therapy through transcriptional reprogramming. Emerging evidence suggests these changes are driven, in part, by the rewiring of the three-dimensional genome, enabling enhancers to interact with new promoters. However, the underlying mechanism in CRPC is poorly understood. Therefore, we mapped chromatin architecture and developed a statistical framework to identify the structural changes that enable oncogenic gene expression in the resistant state.

Methods

We mapped chromatin architecture using H3K27ac HiChIP in both castration-sensitive LNCaP and CRPC LuCaP35CR cells. With this data, we quantified the cumulative contact frequencies of cis-regulatory elements (CREs) and identified high-contact regulatory hubs. Super-enhancers were mapped using H3K27ac ChIP-seq, and structural variants (SVs) were detected from HiChIP contact maps using a deep-learning framework. We validated key findings using low-pass whole-genome sequencing and cfDNA from CRPC patients, as well as CRISPRi of target enhancers.

Results

We identified a subset of gained high-contact interactions in our CRPC model (LuCaP35CR) compared to castrate-sensitive PCa (LNCaP). These CREs frequently overlapped with super-enhancers (61.7%), suggesting a functional relevance. We identified CRPC-specific changes at the AR, GRHL2, and HOXB genes (HOXB13, 7, and 8), indicating a shift toward developmental and oncogenic programs. A ~1.7 Mb deletion upstream of the MYC locus increased interactions with an upstream super-enhancer and may drive higher MYC expression. Low-pass whole-genome

sequencing confirmed the deletion, and extrachromosomal DNA analysis revealed co-amplification of MYC and the hijacked enhancer. Further, cfDNA profiling detected this SV in a low frequency of CRPC patients. CRISPRi silencing of the enhancer reduced viability in LuCaP35CR, indicating that SV-mediated enhancer hijacking contributes to therapy resistance.

Conclusion
Our findings show that CRPC reshapes genome architecture to amplify regulatory hubs and hijack enhancers through SVs. This rewiring supports oncogenic transcription and uncovers therapeutic vulnerabilities, including SVs detectable in patient cfDNA.

COMPARING THE PHASE BEHAVIOR OF THE ANDROGEN RECEPTOR (AR) AND ITS SPLICE VARIANT (AR-V7) IN PROSTATE CANCER

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The androgen receptor (AR) is the primary target for prostate cancer (PCa) therapies. Resistance can develop through AR ampliOication or the expression of splice variants like ARV7. We recently reported that full-length AR (AR-FL) forms nuclear condensates in response to androgens, driving its oncogenic functions. AR-V7, however, behaves differently in androgen-sensitive models. We investigated AR-V7 condensate formation in PCa models and in vitro, compared its phase behavior with AR-FL and identiOied its condensate-dependent transcriptome. We used confocal Oluorescence microscopy to study condensates formed by exogenous AR-FL and AR-V7 tagged with non-dimerizing EGFP. We used PROTAC AU15330 to degrade the chromatin remodeler SMARCA2/4 and assess its role in AR-V7 condensate formation. AR-FL was degraded with ARV-110 to evaluate the interdependency between ARFL and AR-V7 condensates in PCa cells. We examined the role of AR-V7 condensates in transcription by checking their colocalization with RNA Pol II and MED1 using immunoOluorescence and proximity ligation assays (PLA), and assessing target gene expression via qPCR. We identiOied an AR-V7 mutant disrupting condensate formation without affecting nuclear translocation or DNA binding and used it for RNA-seq to study the condensate-dependent transcriptome. Finally, we analyzed AR-V7-mEGFP droplet formation in vitro and their colocalization with red-labeled MED1 using confocal microscopy. AR-V7-mEGFP forms condensates more prominently in PCa models expressing splice variants, regardless of the presence of androgens or AR-FL. AR-V7 condensates show dynamic behavior and require chromatin accessibility. In PCa cells and in vitro, AR-V7 needs 3 to 5 times higher concentrations than AR-FL to form condensates. AR-V7 condensates colocalize with MED1 and RNA Pol II, and their formation correlates with transcriptional activity. The AR-V7-5YS mutant altered phase behavior and revealed that KRAS signaling depends on AR-V7 condensates.

AR ANTAGONISM-INDUCED MAP1B PROMOTES TREATMENT RESISTANCE IN PROSTATE CANCER

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Introduction

Despite significant advances in prostate cancer (PCa) therapy, treatment-induced resistance to androgen receptor pathway inhibition continues to pose a major clinical challenge. Our proteomic profiling in ARPI-treated PCa cells revealed upregulation of the microtubule-associated protein 1B (MAP1B), a protein recognized for its role in neuronal development. Elucidating the role of MAP1B in the context of AR antagonism may provide insights into the mechanisms underlying treatment-induced resistance.

Methods

The regulation of MAP1B by AR antagonism and agonism was validated in both PCa cell lines and patient-derived tumor samples. To assess the regulation mechanism, MAP1B protein synthesis and degradation rates were inspected with cycloheximide pulse chase assay and quantitative PCR. The function of MAP1B in PCa progression was investigated using loss-of-function models employing siRNA or shRNA approaches.

Results

AR antagonism induces MAP1B expression in PCa cells in a time-dependent manner. Upon treatment, MAP1B mRNA becomes enriched in polysomes, leading to accelerated translation. The induction is also observed in radical prostatectomy tissues of PCa patients compared to their paired biopsy samples. Androgens, on the other hand, repress MAP1B expression in PCa cells. Knockdown of MAP1B reduces the levels of proteins involved in cell migration and impairs wound closure in the scratch assay. Additionally, MAP1B is found highly expressed in NEPC cells, and repression of MAP1B modulates the biological activities of these cells.

Conclusions

Our study suggests that MAP1B, a neuron-enriched protein involved in neural differentiation, is upregulated in response to AR antagonism and may contribute to the development of treatment-induced resistance in PCa.

INSM1 REGULATES ARGININE METABOLISM VIA ASS1 TO MAINTAIN THE NEURONAL PHENOTYPE IN NEPC

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Introduction

Neuroendocrine prostate cancer (NEPC) is distinguished from prostate adenocarcinoma by marked epigenetic and transcriptional rewiring, driven in part by the expression and activation of lineage-defining transcription factors (TFs). Among these, we identified Insulinoma-associated 1 (INSM1) as one of the top upregulated TFs in NEPC. INSM1 is known to regulate normal neuroendocrine development and pancreatic metabolic function. It is a well-established biomarker for neuroendocrine tumors. However, whether INSM1 serves solely as a biomarker or also plays a role in promoting NEPC remains to be elucidated.

Methods

To understand the role of INSM1, we generated an INSM1 knockout NEPC cell model using a CRISPR/Cas9 system, followed by an unbiased multi-omics approach using RNA-seq, ATAC-seq, and metabolomics. Mitochondrial function was evaluated via Seahorse assay, flow cytometry, and immunofluorescence.

Results

INSM1 is highly expressed in NEPC. Upon targeting INSM1, we observed decreased chromatin accessibility at key TF motifs associated with neuroendocrine and epithelialmesenchymal transition lineages. Accessibility concomitantly increased at FOX and RUNX motifs, suggesting that loss of INSM1 may promote a shift towards a luminal phenotype. Notably, INSM1 knockout disrupted cellular energy metabolism and mitochondrial respiration, leading to increased oxidative stress. This was validated by a metabolomic shift toward oxidized glutathione, accumulation of γ-H2AX, G1 cell cycle arrest, and reduced cell proliferation. To further investigate these effects, we performed an unbiased metabolomic analysis encompassing a panel of 400 metabolites. Arginine metabolism emerged as the most significantly downregulated pathway following INSM1 loss. Mechanistically, we identified the silencing of ASS1, a key enzyme in arginine biosynthesis, with the absence of INSM1. Consistent with this, pharmacological inhibition of ASS1 led to a marked reduction in cell proliferation.

Conclusion

Our findings establish that INSM1 functions not only as a biomarker but also as a key regulator of the neuronal phenotype in NEPC. Specifically, given that arginine metabolism plays a critical role in supporting respiration, our findings suggest a potential metabolic vulnerability in NEPC.

IDENTIFICATION of CHD7 AS A KEY UPSTREAM CHROMATIN REGULATOR DRIVING THE DEVELOPMENT AND AGGRESSIVENESS OF NEPC

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Neuroendocrine prostate cancer (NEPC) is a lethal subtype of prostate carcinoma that arises through neuroendocrine (NE) transdifferentiation in response to androgen receptor pathway inhibitors (ARPIs). Extensive research, including pivotal studies from our group and others, has highlighted the critical role of aberrant epigenetic reprogramming in driving this transition and contributing to the aggressiveness of terminal NEPC. However, the upstream chromatin regulators orchestrating this process remain largely undefined.

Through integrated analysis of longitudinal RNA-seq data from our clinically relevant LTL331/331R PDX model, which captures the complete temporal progression from adenocarcinoma to castration-induced NEPC, we identified CHD7 as a master chromatin remodeler that is upregulated early during NEPC development, with its expression preceding NE marker acquisition, and further elevated in terminal NEPC.

Functional studies demonstrated that CHD7 overexpression promotes NE transdifferentiation of adenocarcinoma cells under androgen deprivation, while knockdown (KD) in NEPC cells impairs viability, reduces DNA synthesis, increases apoptosis, and suppresses NE markers and key lineage-specific transcriptional factors (TFs) such as ASCL1, SOX2, and PROX1. RNA-seq analysis of CHD7-KD cells revealed downregulation of pathways governing NE differentiation, cell cycle progression, and DNA damage response (DDR), further implicating CHD7 in regulating the NE-lineage commitment and replication stress of NEPC cells. Additionally, CHD7 ChIP-seq analysis revealed direct binding to regulatory elements of those NE-specific TFs, supporting its role as an upstream epigenetic regulator of NEPC development and progression.

Notably, we uncovered that CHD7 maintains genomic stability through regulation of the ATR-CHK1 axis. CHD7-KD impairs CHK1 phosphorylation at key activation sites (Ser317/Ser345), leading to DNA damage accumulation and heightened sensitivity to genotoxic stress. Therapeutically, CHD7-KD cells show increased cisplatin susceptibility and pharmacological inhibition of CHEK1 synergistically enhances cisplatin-induced cell death, suggesting that targeting the CHD7-CHK1 axis could potentiate DNAdamaging/cisplatin combinatorial therapeutic strategy in NEPC.

Collectively, our findings position CHD7 as a critical epigenetic driver coordinating both NE phenotype and aggressiveness in NEPC. This work not only provides novel insights into CHD7 in NEPC development and progression but also reveals the CHD7-CHK1 axis as a promising therapeutic vulnerability for the disease.

LYNCH SYNDROME-ASSOCIATED UROTHELIAL CANCER: DISTINCT GENOMIC LANDSCAPE AND EARLY RESULTS FROM THE LS-URO utDNA SCREENING STUDY

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Introduction

Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by germline mutations in DNA mismatch repair (MMR) genes. It confers a 10–25% lifetime risk of urothelial cancer (UC), particularly in the upper urinary tract. We investigated the somatic mutational landscape of LS-associated urothelial cancer (LS-UC) and concurrently initiated a multicenter screening effort using urine tumor DNA (utDNA) in British Columbia and Finland (LS-URO study).

Methods

We analyzed 44 tumors from 34 patients with LS-UC. Tumors were profiled using the UroScout assay, a high-sensitivity targeted panel covering 25 UC-relevant genes. Immunohistochemistry confirmed MMR protein loss in all cases. Whole-exome sequencing (WES) was performed in selected tumors. Additionally, the LS-URO study utilizes in-mail collection of urine for utDNA analysis to screen LS carriers, with 153 patients recruited to date.

Results

TERT promoter mutations, found in ~83% of sporadic UC, were nearly absent (5%) in LS-UC ($p<0.00001$). LS-UC exhibited a hypermutated landscape dominated by 5- methylcytosine deamination (CG>TG) and microsatellite instability. Mutations were enriched in ARID1A (82%), FGFR3 (80%), and KMT2D (78%), and showed preferential use of CG>TG hotspots. We propose that the scarcity of TERT promoter mutations in LS-UC arises from mutational constraint: the GABP-binding motif (5'-GGAA) required for TERT activation cannot be generated by CG>TG transitions or microsatellite instability. This constrained mutagenesis also appears to affect other canonical UC driver hotspots, which were absent or altered in LS-UC.

Conclusions

Our findings define LS-UC as a genomically distinct disease characterized by constrained hypermutation and a near-universal absence of TERT promoter mutations. These insights refine our understanding of LS-UC pathogenesis and have implications for biomarker design and molecular diagnostics. Preliminary results from the LS-URO screening study using non-invasive utDNA analysis demonstrate feasibility and high patient uptake, supporting broader implementation in LS surveillance programs.

INTRAPATIENT GENOMIC HETEROGENEITY AND EVOLUTION OF DE NOVO METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

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Androgen blocking hormonal therapies underpin systemic prostate cancer (PCa) treatments. PCa is initially diagnosed “castration sensitive” (CS) and is responsive to androgen blockade, but over the course of therapy, some evolve into castration-resistant PCa (CRPC). At initial diagnosis, 5-10% of PCa has already spread to other organs, known as de novo metastatic castration-sensitive PCa (dnCSPC). These cancers are aggressive, inevitably progress to CRPC, and represent ~50% of PCa-related deaths. Extensive genomic heterogeneity is often present within and between the prostate and metastases, but its impact on outcome is unclear. We used patient-matched CS and CRPC samples and comprehensive clinical data to identify genomic changes associated with progression from dnCS to CRPC and patient outcomes.

Patients retrospectively identified from a BC Cancer biobank had DNA extracted from banked tissue and blood samples and subjected to targeted sequencing. Custom bioinformatic tools were used to identify somatic alterations.

114 patients provided tumor-positive blood (n=112) or tissue (n=194) samples from CS and CRPC. 47 patients had at least 1 CSPC and CRPC sample and 78 had synchronous CS biopsy samples. In synchronous biopsies, we detected 54 heterogeneous mutations, most commonly within PTEN (n=9). Whole genome duplication (WGD) heterogeneity was low (5/78). 27 and 72 mutations were identified exclusive to either patient-matched CS or CRPC samples, respectively. CRPC-emergent mutations were frequent in AR (n=18), RB1 (n=8), and TP53 (n=8). Common copy number alterations during the CS-CRPC transition included AR gains (n=15), NKX3-1 loss (n=10), PTEN loss (n=8) and WGD (n=5). Clinical outcome analysis is ongoing.

Genomic alterations detected during the CS-CR transition emphasize the role of intrapatient heterogeneity in disease progression and resistance, providing potential biomarkers for detecting aggressive subclones and guiding treatment strategies.

WE DON'T TALK ANYMORE: DISRUPTIONS TO THE LACUNOCANALICULAR NETWORK IN PROSTATE CANCER BONE METASTASIS

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Introduction

Prostate cancer is the most diagnosed male cancer in Canada, affecting 1 in 8 men. Approximately 15% progress to metastatic disease, and over 90% develop incurable bone metastases, leading to pain, increased fracture risk, and decreased quality of life. Bone homeostasis is dysregulated in PCBM, with predominantly osteosclerotic lesions characterized by increased bone deposition on residual trabeculae (RT). Osteocytes are mechanosensitive cells embedded within small cavities called lacunae and connected by fine channels known as canaliculi, forming the lacunocanalicular network (LCN). Osteocyte communication through the LCN enables bone homeostatic control in response to mechanical stimulation. We hypothesize that disruption of the LCN contributes to the loss of homeostasis, excess and disorganized matrix deposition, and increased fracture risk.

Methods

We performed synchrotron holotomography imaging at the European Synchrotron Radiation Facility on seven resin-embedded vertebral trabecular bone samples (2 cancerfree, 5 PCBM) at 50–120 nm isotropic voxel size (18 image volumes, field of view 160×160×102 to 385×385×245 µm). A U-Net-based segmentation model was developed to identify lacunae, canaliculi, and bone structures. Model performance was evaluated using accuracy, precision, and Dice score, and applied to the dataset to extract quantitative descriptors of LCN shape, volume, and density.

Results

The model achieved high performance across all resolutions (mean accuracy: 99%, precision: 90%, Dice score: 90%). In osteosclerotic bone, the LCN showed loss of anisotropic organization compared to RT and control bone. Lacunae exhibited higher density, lacked common alignment, and showed fewer canalicular connections between lacunae within osteosclerotic regions and with adjacent RT. Lacunae in RT also showed irregular mineralization patterns.

Conclusions

Disruption of the LCN in PCBM leads to increased void formation and suggests impaired osteocyte mechanosensitivity, abnormal fluid flow, and a reduced ability to resist crack propagation, potentially contributing to increased fracture risk in osteosclerotic metastatic bone.

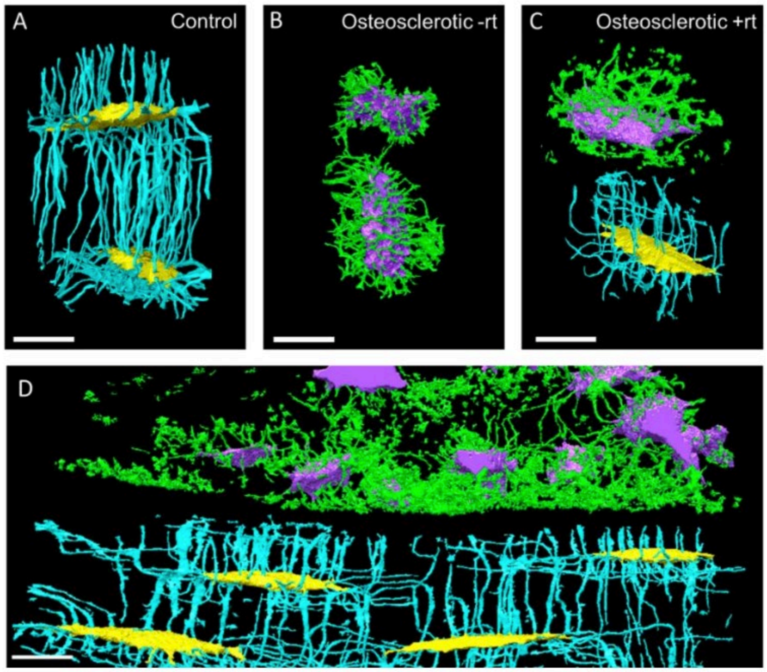

Figure 1. Segmentations of the LCN from synchrotron holotomography scans of cadaveric vertebral trabecular bone. Two lacunae and their canaliculi from A) Control, B) osteosclerotic PCBM, and C) across the boundary of PCBM residual trabecular (rt) and osteosclerotic bone. D) Osteosclerotic with residual trabeculae lesion with two bone regions: residual trabeculae (bottom) and osteosclerotic (top). Render (thickness 30 μm) generated by superimposition of 50 nm sections. Lacunae shown in yellow and canaliculi in blue in control and residual trabecular bone. Lacunae shown in purple and canaliculi in green in osteosclerotic PCBM bone. Scale bars = 10 μm

ORIGINS OF RELAPSE IN ADT-INDUCED PROSTATE CANCER TUMOR DORMANCY

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High-risk localized prostate cancer (PCa) remains a significant challenge in the clinic, with standard treatments such as androgen-deprivation therapy (ADT) achieving only ~50% disease-free survival. While ADT can effectively eliminate the majority of androgen receptor (AR)-dependent PCa cells, it induces a small subset into a dormant state. These dormant PCa cells can evade treatment and eventually relapse. Identifying dormant cell populations and understanding the adaptive mechanisms that trigger relapse is an essential but often neglected area of PCa research, especially given that most therapies for castration-resistant prostate cancer (CRPC) are only marginally effective. In order to biologically characterize dormant tumours, we utilized single-cell RNA sequencing (scRNAseq) on the hormone-naï ve LTL-607 patient-derived xenograft (PDX) model. We mapped the progression of PCa cells under ADT from the hormone-naï ve state to dormancy to relapse. Clustering and trajectory analysis revealed two major dormant cell populations with different relapse potentials. Importantly, we identified a subset, which we termed dormancy capable cells (DCCs), that are predisposed to entering a relapse-prone dormant state. These DCCs exhibit greater plasticity before treatment initiation and undergo significant metabolic and translational reprogramming after ADT. DCCs play a crucial role in driving dormancy and relapse, prompting us to develop a predictive DCC-based gene signature and apply it to clinical cohorts to assess ADT response and relapse risk. The gene signature showed promise as it could predict ADT response in high-risk patients prior to treatment supporting its potential clinical relevance. Significantly, DCCs have never been previously identified or characterized in PCa. Their essential role in surviving ADT and entering a relapse-prone dormancy highlights a missed but critical opportunity for therapeutic intervention and improving patient outcomes.

CLONAL HEMATOPOIESIS (CH) IN PARTICIPANTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) RECEIVING 177LU-PSMA-617 OR CABAZITAXEL: AN EXPLORATORY POST-HOC ANALYSIS OF A RANDOMIZED PHASE II TRIAL (THERAP ANZUP 1603)

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On behalf of the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

Introduction

The prostate-specific membrane antigen (PSMA)-targeted radioligand [^{177}Lu]Lu-PSMA-617 (177Lu-PSMA-617) is an effective new standard-of-care for mCRPC. Since radiation may cause CH, an age-related preleukemic condition, we hypothesized that 177Lu-PSMA-617 drives an increase in CH compared to other mCRPC treatments. Here, we explored CH in the TheraP trial randomizing participants (pts) with docetaxel-refractory mCRPC to cabazitaxel or 177Lu-PSMA-617 (NCT03392428).

Methods

We performed targeted DNA sequencing with a CH gene panel on blood samples from trial baseline (n=176) and disease progression (n=103; 56 post-177Lu-PSMA-617, 47 post-cabazitaxel). Baseline CH mutations were detected in both cell-free DNA (cfDNA) and leukocyte DNA with variant allele frequency (VAF) ≥0.25%. Progression leukocyte DNA was unavailable at analysis, so progression CH mutations were identified via cfDNA only. We used Fisher's exact test to compare proportions, and the Mann-Whitney U test for changes in VAF.

Results

Data was evaluable in 174/176 pts with baseline samples, and 103/103 with progression samples. Median time between baseline and progression blood draws was 28 and 27 weeks for 177Lu-PSMA-617 and cabazitaxel arms, respectively. CH was detected in 77% (135/174) of pts at baseline (median age: 72). 71 (41%) pts had baseline CH mutations with VAF≥2%. The most commonly mutated genes at baseline were DNMT3A (n=67 pts, 38%), TET2 (n=44, 25%), PPM1D (n=26, 15%) and ASXL1 (n=19, 11%), with no difference in gene mutation frequency between arms. At progression, new mutations of presumed CH origin were detected in 83% and 46% of 177Lu-PSMA-617 and cabazitaxel pts, respectively (47 vs 22 pts, p=0.0001). The most frequently mutated gene at 177Lu-PSMA-617 progression was the DNA damage repair gene PPM1D; and new PPM1D CH mutations were 8 times more common after 177Lu-PSMA-617 than cabazitaxel (p=0.00032). Progression mutations in ATM or CHEK2 were also 5 times more commonly observed after 177Lu-PSMA-617 (p=0.01). Among CH variants concordantly detected at baseline and progression on 177Lu-PSMA-617, the median VAF change for mutations in DNA damage repair genes was higher than in canonical CH genes DNMT3A, TET2 and ASXL1 (1.53% vs. 0.15%, p=0.01).

Conclusions

177Lu-PSMA-617 was associated with a greater number of new CH mutations, especially in DNA damage repair genes, compared to cabazitaxel. Whilst the clinical relevance of this finding in a population of patients with heavily-treated mCRPC is unclear, CH emergence and expansion may have implications as radioligand therapy is used as an earlier line of therapy.

SPATIALXPRESS: DROPLET MICROFLUIDIC PLATFORM FOR SPATIOTEMPORAL INVESTIGATIONS INTO RARE CELL POPULATIONS IN HETEROGENOUS CANCER TISSUES

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Introduction
Capturing rare cells is essential for understanding tumor heterogeneity, as they drive therapeutic resistance and cancer progression. High-throughput single-cell sequencing characterizes global cellular heterogeneity and identifies rare populations but loses spatial context. Spatial sequencing can localize these rare populations, but its low sensitivity often leads to ambiguous reads. To enhance rare cell capture in spatial single-cell analysis, I propose SpatialXpress: a platform combining high-resolution sampling with droplet microfluidics to compartmentalize lysates into miniature reactors, enabling concentration of genomic content and spatial barcoding to preserve spatial origin.

Methods
The SpatialXpress platform uses Microfluidic Probe (MFP) technology to precisely lyse small cell populations (~10 cells) from an open biological surface via hydrodynamic confinement. To achieve single-cell throughput, the MFP integrates droplet microfluidics for compartmentalized, sequential lysis, using oil spacers to minimize cross-contamination and capture rare cells from defined regions. Lysed droplets are transferred to DNA processing chips where one combines the lysates with DNA binding beads, and the second spatially barcodes the DNA. The DNA processing chips are fabricated using soft lithography and the droplet MFP is created using digital light processing 3D printing.

Results
The MFP geometry was adapted to sequentially insert oil into the collection line, generating water-in-oil droplet microreactors at 1.25 droplets/second with a volume of 0.001 µL. This enables rapid transfer of concentrated lysates at low volumes, improving enzymatic reaction efficiency and coupling with the chip's incubation, mixing, merging, and splitting functions. Given the low DNA content per lysate, in situ droplet measurements of unconcentrated lysates were performed using SYBR Green binding, and DNA was quantified and qualified using qPCR and post-isolation electrophoretic evaluation.

Conclusions
This platform integrates spatial DNA barcoding with single-cell sequencing to identify rare, resistant cell populations while preserving spatial context. Using this method we aim to study heterogeneity in TMPRSS2-ERG fusions in low and high-risk prostate cancers.

SINGLE-CELL RNA SEQUENCING REVEALS FIBROTIC PATHWAYS IN PEYRONIE'S DISEASE. IMPLICATIONS OF ARYL HYDROCARBON RECEPTOR IN MYOFIBROBLAST ACTIVITY AND COLLAGEN DEPOSITION.

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Background

Peyronie's disease (PD) is characterized by fibrotic plaque formation in the tunica albuginea, leading to penile deformation, discomfort and distress. While the precise mechanisms of PD pathogenesis remain unclear, single-cell RNA sequencing (scRNA-seq) offers insights into cell-type-specific gene expression within PD plaques.

Aim

This study aimed to investigate transcriptional pathways related to the microenvironment in explanted PD cells and to identify key regulators of fibrosis and inflammation.

Methods

Cells were explanted from PD plaque tissue, cultured, and collected for scRNA-seq analysis. Principal Component Analysis (PCA) and Unifold Manifold Approximation and Projection (UMAP) visualizations were used for dimensional reduction, clustering, and celltype identification. The top 100 expressed genes by cell types were analyzed. Ingenuity Pathway Analysis (IPA) generated networks were utilized to pinpoint upstream regulators linked to fibrosis, extracellular matrix (ECM), and collagen production. The transcription factor gene AHR was derived from IPA analysis as a potential fibrosis regulator. Stimulation of AhR was performed to assess its effects on collagen production at RNA and protein levels and on myofibroblast activation, assessed by immunostaining for αSMA.

Results

ScRNA-seq revealed distinct fibroblast subtypes among the explanted PD plaque cells including mesenchymal and secretory fibroblasts in addition to myofibroblasts. Among myofibroblasts, AHR emerged as a suppressed upstream regulator in fibrotic conditions in IPA analysis. In vitro, the expression of AHR and its downstream gene, CYP1A1, was notably reduced upon fibrosis induction with TGF-β1. Activating AhR with its ligand 6-Formylindolo(3,2-b) carbazole (FICZ) restored CYP1A1 levels and reduced the expression of αSMA. ELISA assays demonstrated reduced COL1A1 secretion in vitro upon AhR activation with FICZ, further supporting its anti-fibrotic role.

Conclusion

AhR acts as a crucial regulator in PD, influencing pathways related to inflammation and collagen synthesis. Activation of AhR reduced fibrosis markers and may provide therapeutic potential for acute phase PD management

THULIUM FIBER LASER: LONG PULSE WIDTH AS AN INDEPENDENT RISK FACTOR FOR EXCESSIVE HEAT GENERATION

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INTRODUCTION

Laser dosimetry selection is utilized to enhance fragmentation and reduce stone retropulsion. Diode-pumped thulium fiber lasers (TFL) allow for increased pulse energy by lengthening the pulse width. As pulse width lengthens, thermal diffusion has the potential to increase temperature generation outside of an irradiated target. We test the hypothesis that extending the TFL pulse duration longer than the thermal relaxation time poses an independent risk for increased non-specific heat generation.

METHODS

A two-dimensional numerical simulation of TFL thermal confinement was performed. Energy output and pulse duration of the SOLTIVE Premium-SuperPulsed TFL was measured. Pulse energies (1.5 J) were selected for pulse durations shorter and longer than thermal relaxation time. We compared temperature increases in vitro for identical dosimetries (1.5 J at 20 Hz for 300 seconds) for short (3.1 ms) versus long (11.8 ms) pulse durations.

RESULTS

TFL thermal confinement time was calculated at 11.4 ms. For any given pre-set (short or long pulse), as pulse energy increased, pulse width was longer. For both short and long pulse settings, temperature increased as total energy increased. The maximum temperature achieved for the long pulse width was 79.6C vs. 71.8C for the short-width arm ($p=0.002$).

CONCLUSION

TFL pulse duration longer than the thermal relaxation time poses an independent risk for increased non-specific heat generation. Diode laser lithotripsy may pose an unrecognized risk for thermal injury.

TRANSCRIPTOMIC CHARACTERIZATION OF HUMAN HIPSC-DERIVED TESTIS CELLS AND MATURATION IN A 3D BIOPRINTED COAXIAL TESTIS MODEL

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Introduction
Fertility preservation following pediatric cancer therapy programs has become a major avenue of infertility research. In vitro spermatogenesis (IVS) aims to generate sperm from banked prepubertal testicular tissues in a lab setting. While successful using rodent tissues, progress with human tissues is limited by the scarcity of human prepubertal testicular tissues for research.

Objective
To utilize, characterize and mature human induced pluripotent stem cells (hiPSCs) to model human prepubertal testicular cells in vitro.

Methods
PIPseq was used for single cell sequencing (scRNAseq) of the hiPSC-derived testicular cells. Human scRNAseq datasets were publicly accessed from a range of pre- and post-pubertal sources and used to compare the HiPSC-derived testicular cells. Testicular cells derived from hiPSCs were characterized for phenotype markers and subsequently bioprinted into core–shell constructs representative of testis cytoarchitecture. Retinoic Acid microspheres were used to further functionalize these 3D constructs.

Results
Single-cell RNA sequencing (scRNA-seq) subclustering within each lineage revealed distinct cellular heterogeneity, including both immature and maturing subpopulations. Integration with a public human testis atlas spanning infant, pubertal, and adult stages, along with pseudotime analysis, demonstrated progressive maturation trajectories in Sertoli, Leydig, and spermatogonial stem cells. The transcriptomic profiles of hiPSC-derived cells are most closely aligned with prepubertal testis states, whereas hiPSC-derived peritubular myoid cells were mapped prior to infant samples. The utility of the model is tested by comparing 2 methods of supplementing retinoic acid (RA), the

vitamin responsible for inducing spermatogenesis. The model reveals improved activity under microsphere-released RA compared to RA medium supplementation.

Conclusions

While hiPSC derived testicular cells are transcriptomically different from primary human testis cells, their transcriptomic maturity corresponds to peripubertal primary testicular cells. In vitro validation supports expression of canonical markers and coaxial 3D bioprinted constructs facilitates Sertoli cell maturation with the addition to RA releasing microspheres.

PRESCRIBING PATTERNS AND CLINICAL IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AMONG KIDNEY TRANSPLANT POPULATION IN BRITISH COLUMBIA, CANADA

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Introduction

To characterize the current pattern of Glucagon-like Peptide-1 Receptor Agonists (GLP1RA) usage and its impact on kidney transplant (KT) populations in in British Columbia (BC).

Methods

This is a retrospective cohort study of patients assessed for potential KT and received a KT at Vancouver General Hospital between January 2014 – August 2024. We analyzed medication prescription patterns, changes in patient weights, and post-transplant outcomes.

Results

At time of pre-KT assessment, 63/2789 (2.3%) patients were on GLP1RA. The proportion of GLP1RA users significantly increased in the last decade, from 0 during 2014- 2018, to 1(0.3%), 2(0.9%), 9(4.4%), 8(4.3%), 23(6.2%), and 20(8.7%) patients from 2019 to 2024 (OR 1.65, 95% CI 1.39–2.00, p<0.001). Among users, 88.7% (55/62) had type 2 diabetes, 4.8% (3/62) had type 1 diabetes, and 6.2% (4/62) had neither. There was a mean weight loss of 1.82 kg (1.93%) at 6 months (p=0.031; n=26) and 2.50 kg (2.62%) at 12 months (p=0.016; n=25) of use.

Among these, 25 patients received a KT and were followed up for a median of 1.14 (IQR 0.19-1.79) years. There were no significant differences in graft failure (0% vs. 4.6%, p=1) and mortality (0% vs. 3.0%, p=1) between GLP1RA users vs. non-users at 1-year postKT. Estimated Glomerular Filtration Rate (eGFR) at 1-year (median 67.00 (IQR 65.5-78) vs. 59 (IQR 45-75) mL/min, p=0.18) post-KT was not significantly different between the two groups

Conclusion

GLP1RA use among the KT population in BC has significantly increased over the last decade. This medication was prescribed primarily for type 2 diabetics, rather than nondiabetic obese patients solely for weight-loss purposes. GLP1RA use was associated with moderate weight loss at 6 and 12 months of use, but was not associated with differences in post-transplant outcomes such as mortality, graft failure, and eGFR at 1 year post-KT.

ABSTRACTS:

Poster Presentations

2025 LORNE D. SULLIVAN LECTURESHIP AND RESEARCH DAY POSTER PRESENTATIONS.

INSTRUCTIONS:

1. Print or re-use a poster you already have. Your poster must measure **3.75 feet width x 3.5 feet height (landscape orientation)**. **NOTE:** Your poster can be smaller but **NOT** bigger as there is not enough space to accommodate it.
2. Each poster is assigned a poster number. Please see below for your poster number.
3. There are 4 posters per board, 2 on each side. On June 18, 2024, please set up your poster on the poster board with your poster number from **7:30am to 9:30am** in the Paetzold Education Centre in the Jim Pattison Pavilion, Vancouver General Hospital.

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2	VEDANTH DESAIGOUDAR	MULTIPARAMETRIC MICRO-ULTRASOUND FOR PROSTATE CANCER DETECTION: AN EX VIVO IMAGING SYSTEM FOR PROSTATE TISSUE SPECIMENS
3	UGUR MERIC DIKBAS	BIOCHEMICAL AND STRUCTURAL CHARACTERIZATION OF PROSTATE CANCER ASSOCIATED HOXB13 GERMLINE VARIANTS
4	JIAN GAO	EPITHELIAL-TO-MESENCHYMAL TRANSITION DRIVES RESISTANCE TO IMMUNE-MEDIATED CYTOTOXICITY IN BLADDER CANCER
5	WITHDRAWN	
6	GRACE HARMS	VISUALIZING LACUNOCANALICULAR NETWORK ALTERATIONS IN PROSTATE CANCER BONE METASTASES USING CONFOCAL MICROSCOPY
7	ALI HOSSEINZADEH	RESEARCH PRIORITIES COMPARED TO PUBLICATIONS IN BENIGN PROSTATIC HYPERPLASIA (BPH) FROM 2010-2025: ARE WE HITTING OUR TARGETS?
8	HASTI JALALI	REAL-TIME PROSTATE CANCER GLAND GLEASON PATTERN SCORING USING AI-ASSISTED RAMAN MICROSCOPY
9	SUDHA S KOTAPALLI	EPIGENETIC CONTROL OF LUMINAL MIBC BY DOT1L
10	YUE LI	CPSF1-MEDIATED ALTERNATIVE POLYADENYLATION CONTROLS EMT AND METASTASIS IN BLADDER CANCER
11	YI JOU (RUBY) LIAO	PREVALENCE AND CLINICOGENOMIC DISSECTION OF TUMOR SUPPRESSOR LOSS IN LETHAL METASTATIC PROSTATE CANCER
12	BRIAN MA	SKETCH & ETCH: MICROFLUIDIC TECHNOLOGY FOR SPATIAL INVESTIGATION INTO RARE TUMOUR CELL POPULATIONS

13	ZOE MAYLIN	THE ROLE IN NFIX IN PROSTATE CANCER DORMANCY AND PROGRESSION TO CASTRATION-RESISTANT PROSTATE CANCER
14	OLKA MISSAGHI	MAPPING ENHANCER DYNAMICS AND TRANSCRIPTION FACTOR NETWORKS DRIVING LINEAGE PLASTICITY IN TREATMENT-EMERGENT NEPC
15	BITA MOJTAHEDZADEH	PROSTATE CANCER BONE METASTASIS: SPATIAL PROFILING OF CANCER, BONE AND IMMUNE CELLS
16	ANDREW I MURTHA	ERBB2/HER2 ALTERATIONS IN CTDNA AND METACHRONOUS TISSUES OF PATIENTS WITH METASTATIC UROTHELIAL CANCER
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DEEP LEARNING INTEGRATION OF INTRONIC SEQUENCE AND SECONDARY-STRUCTURE FEATURES IMPROVES BACK-SPLICING PREDICTION

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Introduction and Objectives

Circular RNAs (circRNAs) are a class of regulatory RNAs with diverse cellular functions and growing relevance in cancer biology. Their closed structure confers exceptional stability in comparison to linear RNAs, making them promising candidates for diagnostic and prognostic biomarkers. However, their typically low abundance in RNA sequencing (RNA-seq) data presents challenges for reliable detection and validation using RNA-seq data alone.

Methods

To improve circRNA validation, we developed a deep learning model that integrates intronic sequences and secondary-structure information. The model takes as input the one-hot encoded (a binary matrix representation of the nucleotides at each position) sequences of introns from acceptor and donor splicing sites and a secondary-structure representation of the corresponding pre-mRNAs. A multi-branch convolutional neural network (CNN) processes splice acceptor and donor sequences separately and then merges them with the compressed folding representation.

Results

Our model achieved high predictive performance across multiple evaluation metrics, including accuracy (97%), and AUC score (99%). Interpretability analysis further revealed that both sequence and structural branches contribute to model predictions and its ability to discriminate between true and false back-splicing events.

Conclusions

This work demonstrates that integrating structural features with sequence information provides a more biologically informed confidence score for circRNAs. Our approach enables more accurate scoring of back-splicing sites and holds promise for accurate discovery of circRNAs from RNA-seq data.

MULTIPARAMETRIC MICRO-ULTRASOUND FOR PROSTATE CANCER DETECTION: AN EX VIVO IMAGING SYSTEM FOR PROSTATE TISSUE SPECIMENS

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Introduction and Objectives

Biopsy acquisition for prostate cancer (PCa) diagnosis is guided by conventional ultrasound (US). While US effectively delineates the external border of the prostate, they have low sensitivity and specificity for detecting PCa. The ExactVu (Exact Imaging, Markham, ON, Canada) microUS system offers increased spatial resolution down to 70 μm and is non-inferior to the gold standard of PCa imaging. We plan to increase the ExactVu PCa detection accuracy by multiparametric microUS (mpMUS). Shear wave elastography (SWE) and transfer function (TF) imaging—a type of automated relative elastography—have been implemented in an ex-vivo study of prostate specimens with a confirmed PCa diagnosis.

Methods

First, a phantom validation was carried out to evaluate the design and implementation of the hardware components of the ex-vivo mpMUS system. Next, to hold the prostate specimen, a custom 3D-printed holder with an ellipsoidal imprint was designed. For SWE, a modified transperineal shaker with a 2 cm diameter contacts the inferolateral surface of the prostate, generating mechanical shear waves at 230 and 250 Hz. TF imaging is carried out with a linear voice coil mounted to the probe in an orientation that is perpendicular to the transducer elements. The mechanical excitation is a sum of sinusoids from 1 to 10 Hz. B-mode images are also acquired. Volumetric images are acquired at each of the four settings, sweeping at 1° increments from -45° to +45°. Imaging depth is set to 3 cm, to sufficiently cover the peripheral zone of the prostate.

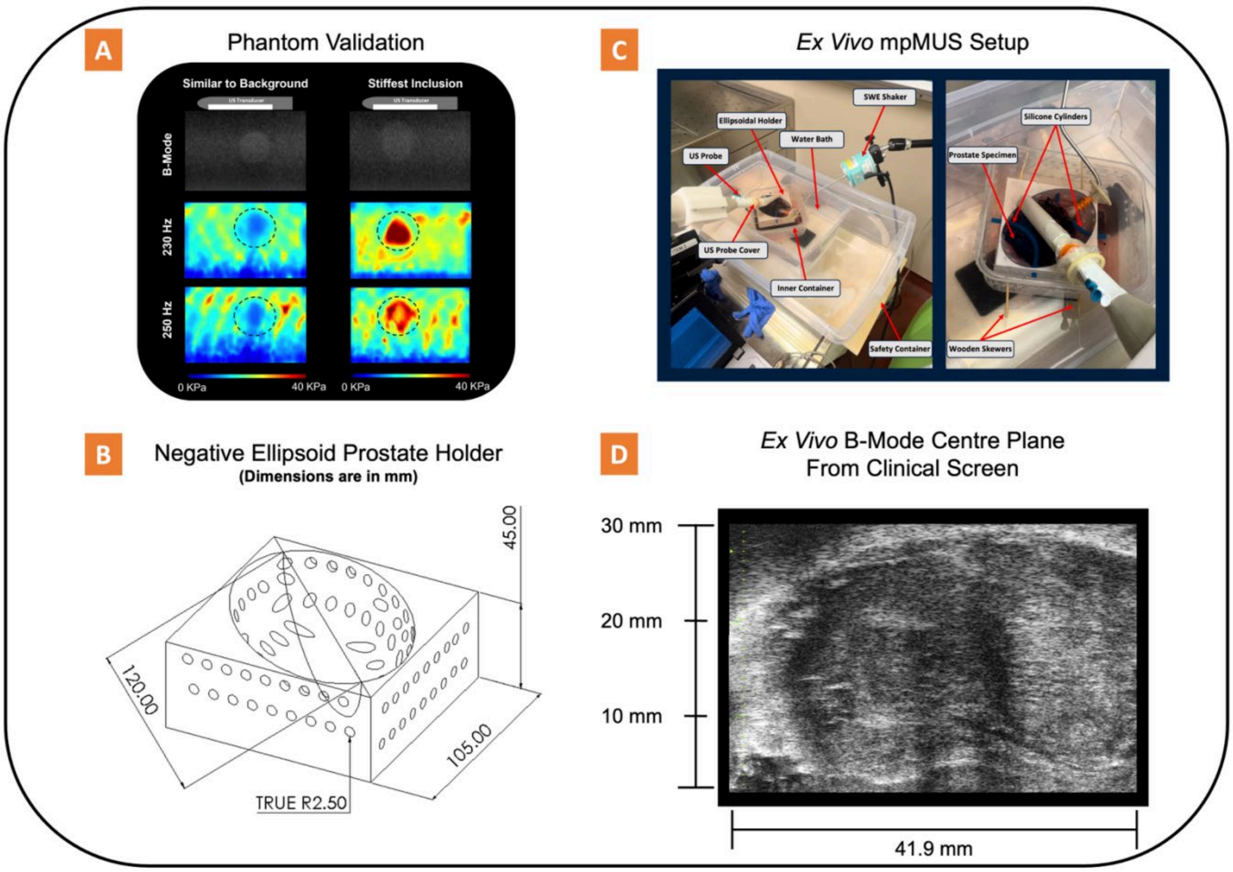
Results

Figure 1 illustrates the phantom validation results, the 3D model of the specimen holder, its implementation in our ex-vivo mpMUS system, and a B-mode image at the centre plane for one prostate.

Conclusions

We present a new ex-vivo mpMUS imaging system along with preliminary results. As this project develops further, SWE and TF imaging results will be shown.

Figure 1.



BIOCHEMICAL AND STRUCTURAL CHARACTERIZATION OF PROSTATE CANCER ASSOCIATED HOXB13 GERMLINE VARIANTS

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Introduction and Objectives

It is estimated that 5–10% of prostate cancer (PCa) is hereditary with specific germline variants increasing the risk of PCa initiation and metastasis. HOXB13 is a tissue-specific transcription factor that is essential for prostate organogenesis and cellular identity. It has been linked to PCa progression through both androgen receptor (AR)-dependent and - independent pathways. Several clinical studies have identified specific HOXB13 germline variants in the homeobox domain that are associated with increased PCa risk, early-onset and hereditary disease. Yet we do not know how these variants impact HOXB13 mechanism of action. To understand their role in PCa initiation we have biochemically, structurally and functionally characterized the impact of HOXB13 germline variants on DNA binding.

Methods

In this study, four homeobox (HBX) HOXB13 variants that are clinically associated with hereditary PCa (R229G, F240L, T253P and X285K) were biochemically characterized. Utilizing a bacterial expression system, we expressed and purified WT and mutated HBX proteins. With Isothermal Titration Calorimetry we quantified the binding affinity of HBX mutants to HOXB13 motifs (CAA, uTCG and mTCG). R229G and X285K proteins showed similar binding affinity to all HOXB13 DNA motif compared to WT HBX. In contrast, the F240L variant showed significantly lowered binding affinity to all DNA sequences. Changes to DNA binding were validated with Electrophoretic Mobility Shift Assay (EMSA). To understand the mechanism of action, the structures of both WT and F240L HBX were solved by X-Ray crystallography up to 1.95 Å resolution. We observed that the F240L variant found on turn region of the helix-turn-helix had possibly altered binding to the DNA backbone. To understand the impact of this variant on function activity, we have designed a luciferasebased HOXB13/AR transcription assay. We found that the F240L variant had significantly altered enhancer activity. To investigate the effect of mutant HOXB13 activity in PCa, we generated inducible stable cell lines that simultaneously knock down endogenous HOXB13 and also overexpress exogenous F240L mutant, allowing us to functionally study the effect of the F240L variant on cellular processes. We observed that the F240L mutation had limited impact on cellular proliferation but caused significant changes in gene transcription. In addition to, AR-dependent pathways being significantly reduced we observed that the F240L variant activated Myc and mTORC1 oncogenic pathways. Work is currently ongoing to characterize how this variant impact the genome wide HOXB13 binding by ChIP-seq.

Conclusions

Through a combination of protein biochemistry, structural biology and functional genomics, we have demonstrated that the HOXB13 F240L germline mutation lowers DNA affinity by impacting the mechanism of binding. This in turn likely contributes to PCa progression by altering enhancer activity. Overall, this study describes the first mechanism of action for a disease associated HOXB13 variant.

EPITHELIAL-TO-MESENCHYMAL TRANSITION DRIVES RESISTANCE TO IMMUNE-MEDIATED CYTOTOXICITY IN BLADDER CANCER

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Introduction and Objectives

Immune checkpoint blockade targeting PD-(L)1, represents a significant advancement in the management of advanced bladder cancer (BC). However, most patients do not respond to therapy, despite having tumours with high immune infiltration. This resistance suggests the presence of underlying mechanisms that allow cancer cells to evade immune-mediated cytotoxicity. The objective of this study is to investigate the mechanisms by which BC cells resist immune-mediated destruction.

Methods

A panel of BC cell lines was evaluated for sensitivity to T cell-mediated cytotoxicity, and to death receptor signaling via FasL and TRAIL. A TRAIL resistant cell line was also generated by long-term exposure of a UM-UC1 cells to TRAIL. Gene set enrichment analysis was used to identify differences between resistant and sensitive cell lines at the transcriptomic level. To assess the role of epithelial-to-mesenchymal transition (EMT), the EMT master regulator SNAI1 was overexpressed in UM-UC1 cells, a BC cell line with an epithelial phenotype that is highly sensitive to immune cell-mediated cytotoxicity and death ligands. The resulting changes in sensitivity to TRAIL were assessed.

Results

EMT was the most upregulated pathway common to T cell-, FasL-, and TRAIL-resistant cell lines. In contrast, oxidative phosphorylation emerged as the most consistently downregulated pathway. Overexpression of SNAI1 effectively induced a mesenchymal/stromal phenotype in UM-UC1 cells at the transcriptomic level, which significantly increased their resistance to TRAIL-mediated apoptosis. Furthermore, the EMT-related gene signature was significantly enriched in TRAIL-resistant cells compared to controls, further suggesting that EMT contributes directly to TRAIL resistance.

Conclusions

These findings highlight EMT as a key mechanism of resistance to immune-mediated cytotoxicity in BC. By promoting an apoptosis-resistant phenotype, EMT may enable tumour cells to evade immune clearance, even in the presence of activated cytotoxic immune cells. Targeting EMT-associated pathways could therefore potentially enhance the efficacy of immunotherapies and improve patient outcomes.

VISUALIZING LACUNOCANALICULAR NETWORK ALTERATIONS IN PROSTATE CANCER BONE METASTASES USING CONFOCAL MICROSCOPY

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Introduction and Objectives

Prostate cancer bone metastases (PCBMs) occur in over 90% of advanced prostate cancer (PC) cases, increasing fracture risk, causing severe pain, reducing quality of life, and strongly indicating mortality. PCBMs disrupt bone remodeling, producing regions of both decreased (osteolytic) and increased (osteosclerotic) bone density. Although underlying mechanisms remain unclear, in-vivo models implicate the lacunocanalicular network (LCN), a system of osteocyte containing lacunae and dendrite-like filled canaliculi, critical for bone homeostasis. While LCN alterations have been observed in select PCBM lesions, comprehensive morphometric analysis across PCBM phenotypes is limited by the high cost or poor resolution of current imaging techniques. To address this, we aim to develop a high-resolution, cost-effective method to visualize the LCN in human PCBM samples using rhodamine staining and laser scanning confocal microscopy (LSCM).

Methods

Trabecular bone cores were obtained from the thoracic or lumbar vertebrae of three cadaveric PC donors (one osteolytic, two osteosclerotic) and one age-matched control. Samples were formalin-fixed, resin-embedded, and sectioned into 0.5 × 0.5 × 5 mm bone sticks. To optimize staining, sticks were treated with rhodamine for 1, 2, or 3 days (n=2/timepoint) and imaged with LSCM (1–2 ROIs/sample, FOV: 1024×1024 pixels, voxel size: 0.31 × 0.31 × 0.24 µm). To refine imaging, we compared constant vs. depth-dependent acquisition settings, adjusting detector voltage.

Results

Three-day staining enhanced LCN visualization to depths of 25 µm (vs 8 µm at 1 day) using LSCM. Analysis of mean fluorescence intensity vs. depth showed that modifying detector voltage every 5 µm preserved consistent signal up to 25 µm. Optimal z-stacks were achieved with 3-day staining and depth-specific imaging settings modified every 5 µm.

Conclusions

This study establishes an optimized, cost-effective protocol for high-resolution LCN imaging in rhodamine-stained PCBM samples, supporting future analyses of LCN alterations in disease.

RESEARCH PRIORITIES COMPARED TO PUBLICATIONS IN BENIGN PROSTATIC HYPERPLASIA (BPH) FROM 2010-2025: ARE WE HITTING OUR TARGETS?

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Introduction and Objectives

Expert opinion shapes research priorities in urology, guiding efforts to address key knowledge gaps that impact patient care. In Benign Prostatic Hyperplasia (BPH), these priorities are unclear and not readily accessible. It is also unknown how well ongoing publications align with them. This study identifies established BPH research priorities and evaluates the degree to which publications from 2010–2025 reflect these targets.

Methods

Two scoping reviews were conducted following PRISMA guidelines using MEDLINE and Web of Science. The first reviewed consensus papers from urological societies and medical literature to identify BPH research gaps. The second review examined BPH-related studies published between 2010 and 2025, cited at least 10 times as of February 13, 2025. Screening and data extraction were conducted by three independent reviewers (AH, AE, HJ). Research priorities were weighted by frequency of mention and compared with the number of published studies using a chi-square test (χ^2) to evaluate alignment between research output and established BPH priorities.

Results

Thirteen priorities were identified. A total of 3527 BPH-related studies met the inclusion criteria for analysis. There was a significant misalignment ($\chi^2 = 4006.4$, $p < 0.001$) between published research and stated priorities. Pathophysiology was the most represented priority topic by number of studies (19.5%) and weight (standard residual (SR) +44.5). β3-agonists and anticholinergics were the most under-represented topics based on weight (SR -20.6 each). Minimally invasive surgical therapies were the next lowest-represented priority topic (SR -19.5), despite having the highest growth based on linear regression (+0.4 studies/year). Other under-represented priority topics included PDE5 inhibitors (SR -12.0), equity/diversity/inclusion (SR -11.9), and diode laser (SR - 11.3).

Conclusions

This study compared consensus BPH research priorities with the existing literature. While pathophysiology was over-represented, several priority topics, particularly minimally invasive surgical therapies, β3-agonists and anticholinergics, were underrepresented and require more research focus.

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REAL-TIME PROSTATE CANCER GLAND GLEASON PATTERN SCORING USING AI-ASSISTED RAMAN MICROSCOPY

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Introduction

Prostate cancer (PCa) is the most common cancer worldwide and treatment relies on accurate grading. Gleason pattern identification, essential in PCa grading, has a high degree of pathologist interobserver variation. Raman microscopy, which uses inelastic light scattering to reveal molecular structure, enables label-free tissue imaging. Stimulated Raman scattering (SRS) improves signal quality, and stimulated Raman histology (SRH) produces virtual H&E-like images by capturing lipid and protein content. These advances provide a foundation for near real-time, intraprocedural diagnostics.

Methods

We propose an AI-powered platform for real-time Gleason pattern identification and grade group identification using SRH images of prostate tissue. Our initial approach uses an InceptionResNetV2-based convolutional neural network to classify Gleason patterns 3 and 4 by learning molecular features. We selected a subset of Raman slides (out of 700) with grade groups 1 and 4, where patterns 3 and 4 are present. We pre-processed these images for dual-shift imaging, pixelwise subtraction to enhance contrast, image channel registration, and dense sliding window patch extraction. Using Raman machine masks that identify benign, no tissue, and tumor regions, we manually extracted 400 patches for each class.

Results

Our preliminary results based on the deep-learning model, trained on SRH-based Raman microscopy images, are achieving a high validation accuracy of 90% in distinguishing between Gleason patterns. We use accuracy as the primary evaluation metric for both validation and test sets. Preliminary results indicate reliable classification performance across common prostate cancer subtypes, including distinctions between patterns 3 and 4.

Conclusion

Integrating AI with Raman microscopy offers a promising approach to enhance intraprocedural cancer diagnosis, improving personalized medicine by enhancing the diagnostic paradigm. This platform has the potential to increase diagnostic objectivity in pathology, minimize interobserver variability, and expand access to expert-level cancer grading, especially in low-resource settings.

EPIGENETIC CONTROL OF LUMINAL MIBC BY DOT1L

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Urothelial carcinomas are classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). While NMIBCs are low grade tumors, MIBCs are high grade tumors that tend to metastasize. MIBC is further grouped into molecular subtypes and can broadly be defined as either luminal or basal. While basal MIBC appears to be more aggressive, luminal MIBC is associated with poor responses to therapy. Luminal MIBC is characterized by high PPARγ, GATA3, and FOXA1 expression, and knowledge of how these luminal genes are regulated is critical for understanding lineage commitment and tailor therapeutic strategies. In this study, we sought to identify the molecular mechanisms regulating lineage commitment in luminal MIBC subtypes.

We find that DOT1L (disruptor of telomeric silencing 1-like) is a direct upstream regulator of FOXA1, GATA3 and PPARγ. Mechanistically, DOT1L activates transcription by catalyzing H3K79 methylation of the luminal genes and this epigenetic event is required for maintaining the luminal phenotype. Consequently, inhibition of DOT1L activity shifts the transcriptomic signature of luminal MIBC cells towards a more basal signature.

In summary, our data suggest that DOT1L is a key upstream regulator of luminal MIBC that can be targeted by small molecule inhibitors.

CPSF1-MEDIATED ALTERNATIVE POLYADENYLATION CONTROLS EMT AND METASTASIS IN BLADDER CANCER

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Introduction and Objectives

Metastasis, the leading cause of cancer-related death, remains a major challenge in bladder cancer treatment. EMT is a well-known driver in metastasis, endowing cancer cells with enhanced migration and invasion properties. While EMT is often triggered by transcriptional reprogramming of gene expression, the contribution of post-transcriptional regulations, such as alternative polyadenylation (APA), remains largely uncharted. In this study, we investigate the effects of CPSF1- mediated APA on EMT and metastasis in bladder cancer.

Methods

CRISPR/CAS9 was used to generate CPSF1 knockout stable cell lines. Quantification of APA (QAPA) was performed to systematically analyze alternative polyadenylation alteration after CPSF1 knockout. Ultrasound guided Sub-renal capsule xenograft model was utilized to investigate bladder cancer invasion and metastasis.

Results

Through unbiased bioinformatics interrogation, we identified elevated CPSF1 expression across multiple distinct cancer types, which correlated with metastasis and unfavorable clinical outcomes. Functionally, CPSF1 gain-of-function studies revealed enhanced bladder cancer cell proliferation and motility, while genetic abrogation of CPSF1 impaired bladder cancer cell migration, invasion and EMT. CPSF1-knockout cancer cells exhibited a biased shift towards lengthened 3'UTRs in many gene transcripts through QAPA analysis, including the key EMT regulators such as TGFBR1 and SOX9. Using ultrasound-guided sub-renal capsule xenograft models and orthotopic bladder xenograft models, we demonstrated that CPSF1-deficiency impaired tumor growth, invasion, and metastasis. Additionally, we found that CPSF1 was required to maintain CPSF complex stability by preventing ubiquitin-mediated degradation of the complex components.

Conclusions

Collectively, our research uncovers the pro-invasion/metastasis role of CPSF1 by maintaining mesenchymal features. These insights position CPSF1 as a potential therapeutic target in bladder cancer treatment.

PREVALENCE AND CLINICOGENOMIC DISSECTION OF TUMOR SUPPRESSOR LOSS IN LETHAL METASTATIC PROSTATE CANCER

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Introduction and Objectives

Metastatic prostate cancer (mPCa) is a lethal disease and is associated with an accumulation of genomic defects impacting key tumor suppressor genes (TSGs; TP53, PTEN, RB1). TSG inactivation is traditionally understood to require biallelic loss for tumor development, but studies have shown that oncogenesis can occur without biallelic loss. Despite this, the relevance of multi-gene allelic complexities to mPCa disease trajectories is largely unknown. We sought to define the frequency of TP53, PTEN, and RB1 alterations at allelic resolution in a large mPCa cohort and determine the association between TSG inactivation and mPCa clinical metrics.

Methods

We analyzed circulating tumor DNA (ctDNA) and matched white blood cell (WBC) DNA from 2,874 Canadian mPCa patients. Sequencing was performed with a targeted panel covering exons of 73 mPCa genes and introns of TP53, PTEN, and RB1. Using a computational pipeline, genomic alterations were identified and ctDNA fraction estimated using orthogonal approaches leveraging mutation allele frequencies and copy number profiles. We developed a computational tool to integrate intragenic alterations to predict allelic functional status for each TSG. Combined TSG status was summarized per patient to determine frequencies and co-occurrence.

Results

Among 1,560 patients with detected ctDNA, we identified somatic TSG mutations in 783 (50%) patients, SVs in 380 (24%), and biallelic copy losses in 120 (8%). TP53 alterations were predominantly missense mutations; PTEN and RB1 alterations were often translocations and deletions. Co-occurring alterations in three TSGs were observed in 114 (7%) patients, two TSGs in 361 (23%), and one TSG in 536 (34%). Pathogenic germline mutations were detected in five patients (4 TP53, 1 RB1).

Conclusions

Our findings reveal distinct inactivation patterns, frequent co-alterations of TSGs, and potential insights into the biology of aggressive mPCa. Ongoing clinical data analysis will clarify prognostic implications of these TSG inactivation patterns

SKETCH & ETCH: MICROFLUIDIC TECHNOLOGY FOR SPATIAL INVESTIGATION INTO RARE TUMOUR CELL POPULATIONS

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Introduction

Collective epithelial migration is ubiquitous in biology: in wound healing, tissue regeneration, embryogenesis, and cancer progression. While standard in vitro wound assays have provided significant insights, they oversimplify both heterogeneity and microenvironmental complexity due to bulk treatment and analysis. This limits our ability to address key questions on the dynamics of cells that initiate these processes. Here, we present a high-resolution method for spatiotemporal analysis of collective cancer migration.

Methods

Using a microfluidic probe (MFP), we achieved contact-free reagent localization on an immersed substrate at micrometer scale. This enabled 2 key applications: (1) Sketch: Rapid, localized lysis of cell monolayers to generate complex wound geometries in real time, and (2) Etch: Selective extraction of migrating and non-migrating cells for downstream gene expression analysis. We applied this approach to CFPAC-1 pancreatic adenocarcinoma cells, stratified into high and low expressers of podocalyxin (PODXL), a marker associated with poor prognosis in several cancers. Additionally, we used velocimetric analysis to quantify wound closure dynamics and migration rates across different wound geometries, and immunofluorescent staining to validate spatial patterns of expression.

Results

In standard scratch wounds, PODXL-high cells at the wound edges showed elevated expression of genes linked to hybrid epithelial-mesenchymal states and leader phenotypes compared to parental cells. In triangular wound models, which introduced concave and convex geometries, we observed position-dependent variations in both migration dynamics and gene expression profiles

Conclusions

Our technology enables spatiotemporal investigations, uncovering intratumoral heterogeneity in collective cancer migration missed by bulk sampling, and aiding in biomarker discovery for transformed cells in tumors. With adenocarcinomas as our first model, we will expand the study to metastable states of prostate adenocarcinomas during neuroendocrine transformation.

THE ROLE IN NFIX IN PROSTATE CANCER DORMANCY AND PROGRESSION TO CASTRATION-RESISTANT PROSTATE CANCER

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Prostate cancer (PCa) remains a major clinical challenge, particularly in its advanced stages. PCa often progresses from treatment-sensitive disease to a dormant stage (remission) then eventually to castration-resistant prostate cancer (CRPC), a condition with limited treatment options and poor survival rates. Treatment for prostate cancer frequently involves androgen deprivation therapy (ADT), either alone or in combination with second-generation anti-androgen medications. This approach targets the testosterone (or androgen receptor) signalling pathway, which is the primary driver of prostate cancer growth and progression. After a certain duration of time in a dormant phase however, treatment efficacy fails and resistance mechanisms occur, leading to a treatment-resistant disease.

By analysing data from patient samples and our in-house patient-derived xenograft models, our preliminary studies have identified a protein, Nuclear Factor I X (NFIX) that is significantly upregulated post-treatment during the dormancy phase and persists in CRPC. NFIX is a transcription factor (TF), a type of protein that regulates gene expression. NFIX's increased activity during these disease phases suggest it has a potential role in driving tumour survival, dormancy, and progression. We hypothesise that a subset of PCa cells upregulate NFIX to initiate and maintain dormancy, ultimately leading to CRPC progression. These cells are capable of surviving androgen deprivation therapy (ADT), entering dormancy, and eventually giving rise to CRPC.\

This innovative approach focuses not only on CRPC but also on PCa dormancy, a critical phase that precedes the onset of lethal CRPC. It utilises cutting-edge techniques such as single-cell RNA sequencing, unique patient-derived xenografts (PDX), and advanced bioinformatics to uncover the pivotal role of NFIX, a TF not previously recognised in this context. By investigating the mechanisms and activity of NFIX in both dormancy and CRPC, the project aims to enable the development of earlier, more effective interventions that can delay or prevent progression to CRPC, ultimately improving patient survival and quality of life.

MAPPING ENHANCER DYNAMICS AND TRANSCRIPTION FACTOR NETWORKS DRIVING LINEAGE PLASTICITY IN TREATMENT-EMERGENT NEPC

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Introduction and Objectives

While androgen receptor pathway inhibitors (ARPIs) are the standard treatment for castration-resistant prostate cancer, resistance frequently develops, leading to the emergence of treatment-induced neuroendocrine prostate cancer (t-NEPC). The development of t-NEPC involves widespread changes in gene expression that enable lineage plasticity. Prior studies have shown that NEPC-associated transcription factors can activate gene expression networks to support this transition. However, it remains unclear how these transcription factors coordinate reprogramming and how the profile of cis-regulatory elements (CREs) changes during this process. Understanding the enhancer "grammar" of these shifts in CRE and TF activity is critical for identifying early markers of lineage plasticity and uncovering actionable targets to prevent or delay NEPC onset.

Methods

To identify the t-NEPC specific enhancers we conducted self-transcribing active regulatory region sequencing (STARR-seq), a high-throughput reporter assay that quantifies genome-wide enhancer activity, in models of both adenocarcinoma (LNCaP) and t-NEPC (DUNE). Candidate sequences will be compared with NEPC-specific active CREs identified in clinical H3K27ac ChIP-seq. Shared CREs are selected, and GIGGLE analysis are used to identify transcription factors enriched in NEPC-specific enhancer regions which later be used to study how each of those TFs contribute to lineage plasticity.

Results and Conclusion

Our findings reveal a shift in the enhancer landscape during the transition from adenocarcinoma to NEPC. Notably, many H3K27ac-marked regions do not function as active enhancers in DuNE cells. This shift occurs independently of global changes in chromatin accessibility, suggesting that enhancer activation is regulated through additional mechanisms beyond open chromatin status. GIGGLE analysis highlights transcription factors with motifs enriched in both active CREs and H3K27ac regions. These results improve our understanding of t-NEPC lineage plasticity and identify transcription factors that could serve as potential targets for new therapeutic strategies in prostate cancer patients.

PROSTATE CANCER BONE METASTASIS: SPATIAL PROFILING OF CANCER, BONE, AND IMMUNE CELLS

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Background

The most prevalent complication of advanced prostate cancer (PC) is bone metastases (BM) occurring in >80% of advanced PC patients, causing pain, fractures, and spinal cord compression. We have previously established that PCBMs present as a spectrum of pathologic skeletal morphologies. However, it is not clear exactly what specific PC phenotypes reside in PCBMs. Further, immunosuppression is a feature of the bone tumor microenvironment but the distribution of immune cells in PCBMs is unknown. It is crucial to study PC and immune phenotypes present in PCBMs to understand their interactions and develop novel therapeutics.

Hypothesis

PCBM tumors will be heterogenous and present multiple PC phenotypes within one sample, a differing distribution of bone resident cells and proteins according to BM subtype. Immune landscape will differ according to PC phenotype and/or BM subtype.

Methods

Our specimens are biopsies of PCBMs, collected through collaboration with the Vancouver Spine Oncology Program. Histology and immunohistochemistry were performed to analyze tissue morphology, collagen alignment, and protein distribution. Immunofluorescence (IF) was used to analyze cellular composition. Multiplex IF (mIF) is being established for visualization of multiple cell/markers in PCBMs, so that spatial distribution, proximity, and density of bone tumor microenvironment cells can be analyzed. Bone tissue presents challenges with adherence, decalcification, and antigenicity. Thus, protocols were adapted for PCBM analysis using formic-acid decalcified femoral head tissue, with formic-acid treated tonsil as a control for impacts of decalcification process on antigenicity.

Results and Conclusion

Preliminary results show a heterogenous PC population within BMs, with varying tumor morphology and marker presentation (PSMA, androgen receptor) in cancer cells. We see co-localization of PC cells near osteoblasts, and a low degree of CD45+ immune cell infiltration in the osteosclerotic (bone forming) subtypes of PCBMs. Future mIF efforts will allow more in-depth analysis of immune cell subtypes in PCBMs.

ERBB2/HER2 ALTERATIONS IN CTDNA AND METACHRONOUS TISSUES OF PATIENTS WITH METASTATIC UROTHELIAL CANCER

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Purpose

HER2 targeting is increasingly relevant in metastatic urothelial cancer (mUC) due to emerging antibody drug conjugates, where assessment of tumor HER2/ERBB2 status could aid interpretation of ongoing trials. We evaluated whether precise ERBB2 genotype can be determined from mUC ctDNA, and the relationship with archival tissue status.

Experimental design

Custom sequencing was performed on 402 cell-free DNA samples from 226 mUC patients to determine ERBB2 genotype. ctDNA genotype was compared with clinical outcomes and metachronous tumor tissue ERBB2 genotype, HER2 immunohistochemistry (IHC) or fluorescence in-situ hybridization (FISH) status.

Results

ERBB2 status was assessed in patients with ctDNA detected (178/226). Activating ERBB2 mutation and/or amplification was identified in 16% (28/178). In a subset of cases, ctDNA whole-genome sequencing and tissue FISH suggested extrachromosomal ERBB2 amplification. ERBB2 alterations were associated with coactivation of other oncogenes (suggesting redundancy), increased tumor mutational burden, and genomic instability. Nevertheless, patients with ERBB2 alterations showed no difference in outcomes after standard-of-care therapy compared to patients with wildtype ERBB2. Activating ERBB2 mutations were rarely clonal, and imbalance favoring the mutant allele was uncommon. ERBB2 ctDNA status strongly correlated with IHC 3+. However, serial ctDNA genotyping and tissue IHC scoring revealed marked intra-patient heterogeneity, and HER2 IHC negative versus positive switch occurred in 34% of patients.

Conclusions

We report variability in ERBB2 alteration characteristics and spatiotemporal heterogeneity in mUC. Our data endorse ctDNA for HER2/ERBB2 biomarker development in mUC and provide a framework for assessing nuanced genomic indicators of HER2 pathway reliance.

ARTIFICIAL INTELLIGENCE ANALYSIS OF PROSTATE BIOPSY STIMULATED RAMAN HISTOLOGY EVALUATES PERI-TUMORAL TISSUE TO PREDICT BIOLOGICALLY AGGRESSIVE PROSTATE CANCER

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Introduction
Local invasion of prostate cancer (PCa) at time of radical prostatectomy (pT3) is common and associated with recurrence, metastasis, and death. Stimulated Raman histology (SRH) is a novel technique allowing near real-time, label-free, highresolution images of unprocessed, un-sectioned tissue providing both morphologic and biochemical information. Prediction of locally aggressive PCa based on nomograms have a receiver operating curve area under the curve (AUC) of 0.72-0.8. We hypothesized that artificial intelligence (AI) applied to prostate biopsy SRH from MRI-identified PCa could predict pT3.

Methods
Prospectively, prostate biopsies cognitively targeted MRI-visible PCa from ex-vivo radical prostatectomy specimens were utilized for training (NYU), internal testing (NYU), and external testing (UBC). Biopsies were scanned using SRH at two Raman shifts. A total of 97 ex-vivo biopsies (NYU) were used to train an attention-based multiple instance learning deep learning neural network (DLNN) for PCa identification and prediction of pT3. Internal testing was performed on 33 consecutive ex-vivo biopsies from NYU, and external testing on 33 ex-vivo biopsies from UBC. No training or testing biopsies exhibited pT3.

Results
The DLNN demonstrated an AUC of 0.959 for PCa identification at the SRH image level. Internal testing for pT3 prediction using SRH plus clinical variables (grade group, clinical stage, PI-RADS)

showed an AUC of 0.908 (Figure 1A), compared to 0.79 using SRH alone. External testing (UBC) yielded an AUC of 0.715 with clinical variables and 0.694 with SRH alone. Comparing the DLNNs for PCa identification and pT3 prediction, the model focused on apparently benign stroma to predict EPE while avoiding PCa in its analysis, Figure 1B-E.

Conclusion

AI prediction of locally aggressive PCa using SRH performs comparable to current tools, but requires further improvement. AI-assisted prediction may help uncover novel variables not previously identified as significant, such as benign stroma and/or benign glands, relevant for biologically aggressive PCa prediction.

INVESTIGATING THE ROLE OF URINARY AND GUT MICROBIOMES IN MODULATING RESPONSE TO BACILLUS CALMETTE-GUERIN THERAPY IN NON-MUSCLE INVASIVE BLADDER CANCER

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Introduction
Intravesical administration of Bacillus Calmette-Guérin (BCG) remains the gold- standard therapy for high-risk non-muscle invasive bladder cancer (NMIBC); however, approximately 40% of patients experience disease recurrence despite receiving optimal treatment. In light of the established role of the commensal microbiome in regulating inflammatory and immune responses, we hypothesized that the urinary and gut microbiomes may influence BCG-mediated anti-tumor activity in NMIBC. This study aimed to investigate whether these microbiomes can serve as biomarkers for BCG responsiveness and to evaluate the effects of BCG therapy on microbiome composition and gene expression profiles.

Methods
Urine samples (n=62 pre-BCG, n=44 post-BCG) and stool samples (n=23 pre-BCG, n=16 post-BCG) were collected from a multi-center cohort comprising 74 patients with high- risk NMIBC. The urinary microbiome was characterized using shotgun metagenomic sequencing, whereas the gut microbiome was profiled through 16S rRNA gene sequencing. Bacterial metabolic pathways were inferred by mapping sequencing reads to a reference gene database, followed by functional pathway annotation. Non-response to BCG therapy was defined according to the U.S. Food and Drug Administration (FDA) criteria for BCG- unresponsive NMIBC.

Results
Pre-treatment urinary shotgun sequencing revealed a higher relative abundance of Actinomycetota in BCG responders. Following treatment, regardless of clinical response, Actinomycetota taxa were largely supplanted by Pseudomonadota. BCG therapy induced enrichment of 315 bacterial genes out of approximately 62,000 analyzed, with significant increases observed in butyrate synthesis pathways among non-essential genes. Analysis of stool samples demonstrated a significant

reduction in overall bacterial load post-BCG treatment. Furthermore, Blautia was enriched in pre-treatment stool samples from non- responders.

Conclusions

Our Windings reveal BCG-associated alterations in the urinary and gut microbiomes of patients with high-risk NMIBC, including notable enrichment of Actinomycetota among responders. Future studies are warranted to explore strategies for microbiome modulation, such as antibiotic or dietary interventions, to potentially enhance BCG therapeutic efficacy.

MAPPING THE DIFFERENTIATION LINEAGE OF HUMAN PROSTATIC EPITHELIAL CELLS THROUGH SINGLE-CELL TRANSCRIPTOMICS

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Prostate cancer is one of the leading causes of cancer-related deaths among men, highlighting the critical need for a deeper understanding of its biological mechanisms. Given that prostatic carcinogenesis often recapitulates embryonic developmental processes, understanding cell differentiation in the fetal prostate is critical.

Using single-cell RNA sequencing (scRNA-seq), we generated a high-resolution molecular atlas of human fetal prostatic cells. We identified distinct prostatic cell clusters with unique transcriptional profiles and lineage-specific markers. Notably, we identified prostatic progenitor cells with highly embryonic stem-like and proliferative properties. Our findings indicate that the earliest fetal prostatic cells co-express both luminal and basal markers, suggesting they serve as bipotent progenitors for both lineages. Trajectory analysis further supports this model by revealing a clear developmental progression from progenitor cells to more differentiated cell types. This comprehensive molecular characterization not only elucidates the developmental dynamics and lineage relationships of human fetal prostatic cells but also offers valuable insights into prostatic development and its implications for prostate-related diseases. Overall, our study advances the understanding of prostatic stem/progenitor cells and may offer potential avenues for therapeutic strategies targeting prostate cancer.

CHARACTERIZATING ANDROGEN RECEPTOR CONDENSATES IN PROSTATE CANCER

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Introduction & Background

Prostate Cancer (PCa) is the leading cancer in Canadian men, accounting 22% of new diagnoses in 2024. PCa is driven by a ligand induced transcription factor, the androgen receptor (AR) containing three distinct domains: N-terminal domain (NTD), DNA-binding domain (DBD), and the ligand-binding domain (LBD). The AR's NTD is intrinsically disordered, playing a vital role in mediating the formation of nuclear condensates. Composed of transcriptional machinery that enhances the transcription of important oncogenes in various cancers, including PCa. We have shown that full-length AR is more prone to form nuclear condensates in PCa cell models compared to benign epithelial prostate models. The underlying details of this mechanism are still unknown.

Methods

We used bioinformatic prediction tools to identify AR regions and residues with high potential for driving condensate formation. Based on these predictions, we generated AR mutants and truncations to test their effects in LNCaP cells. Cells were serum-starved and transfected with mEGFP-tagged wild-type or modified AR constructs. After 48 hours, cells were treated with 1 nM DHT for 2 hours, then fixed and imaged via confocal microscopy. This allowed visualization of nuclear condensates and assessment of how specific alterations in AR influence its capacity to form phase-separated foci.

Results

The point mutations P133I and P135I, along with the truncation Δ412–535, significantly reduced nuclear foci formation compared to wild-type AR. These findings suggest that residues within Tau-1 and the Δ412–535 region are critical for condensate formation and may play a key role in AR-driven transcriptional regulation.

Conclusion

By better understanding the governing factors driving AR condensate formation in PCa that can open new therapeutic options for patients with advanced stages of PCa disease.

MODELLING TREATMENT OF BONE CANCER IN A PHYSIOLOGICALLY RELEVANT 3D PRINTED BONE MATRIX

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Bone is a complex organ that consists of a heterogeneous cellular component that remodels the surrounding extracellular matrix through breakdown and deposition of bone matrix elements. Primary bone cancers like Ewing Sarcoma (ES), have 5-year survival rate of ~20% and often result in osteolytic (bone degrading) lesions that are painful for patients. For bone metastasis, prostate cancer accounts for the highest proportion of these cases. ~90% of prostate cancer patients who die with metastasis are diagnosed with bone lesions that can be either osteolytic or osteoblastic (bone forming). The microenvironment plays a crucial role in development and treatment of both primary and bone metastasized prostate cancer. Here, we describe the design and functional performance of artificial 3D bone constructs, bioprinted with fluorescent ES or bone-derived metastatic prostate cancer cells in a hydroxyapitate/collagen-mimicking bioink. The constructs were treated with both traditional and novel DNA damage inhibitors as a model for drug screening. Bone cell populations were differentiated from progenitor cell types and the 3D bioprinted bone model was capable of growing both primary and bone metastasized tumor-like cancer clusters. The model showed decreased ES tumor cluster formation with inhibitor treatment. Osteoblasts and osteoclasts were created in 2D and validated via functional assays and expression of appropriate protein markers. This model offers a complex in vitro bone environment that can be utilized for drug screening with optional integration of bone cell populations to improve physiological relevance and clinical translation.

PSMA TARGETING SOMAMERS FOR ADVANCED METASTATIC PROSTATE CANCER THERANOSTICS

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Purpose
This project seeks to develop an aptamer to target Prostate Specific Membrane Antigen (PSMA) in the treatment of advanced prostate cancer (PCa). Small molecule based, PSMA targeting therapy has been seen to modestly extend patient survival, but with dose-limiting offtarget damage to the salivary glands, kidneys and other organs which also produce PSMA[1]. We have evaluated modified aptamers produced by our industry partner Somalogic as an alternative targeting approach with many potential benefits of modification capacity, conjugation and selectivity.

Methods
Bio-layer interferometry and flow cytometry competition and binding assays using PSMA expressing cells and CRISPR modified PSMA negative cells were employed to evaluate and characterize the binding of these aptamers in vitro. Lead candidates were evaluated through in vivo imaging of PSMA-expressing and PSMA-negative xenografts which were grown in the same mouse at separate sites. Imaging methods employed include IVIS fluorescence imaging and PET imaging.

Results
We have established a relative rank order of the SOMAmers based on binding saturation and affinity kinetics, and characterized which aptamers competed with PSMA probes on known binding sites. Our model of growing different modifications of tumours within the same mouse has proven effective and resource efficient. In vivo, aptamer biodistribution resembled that of the clinically approved small molecule ligand. This included preferential accumulation in PSMAexpressing xenografts over PSMA-negative xenografts.

Conclusions

This study provides initial evidence that modified DNA aptamers have the potential to target PSMA with a similar quality of a clinically approved small molecule. They also suggest salivary accumulation of aptamers independent of targeting. If this PSMA independent salivary accumulation can be evaluated and overcome, aptamers may offer a novel targeting approach to PCa theranostics.

STIMULATED RAMAN HISTOLOGY AND ARTIFICIAL INTELLIGENCE IDENTIFY PROSTATE CANCER AFTER NEOADJUVANT THERAPY AND SHOW PROMISE TO IMPROVE PROSTATE CANCER BIOBANKING

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Introduction and Objectives

The GUNS trial is a precision oncology trial assessing the use of biomarker-driven neoadjuvant therapies prostate cancer (PCa) prior to radical prostatectomy. Biobanking of post-treatment PCa is essential in this translational trial, yet current methods have limited success resulting in minimal PCa biobanking of fresh frozen tissue. Stimulated Raman histology (SRH), a label-free optical imaging technique, combined with artificial intelligence (AI), offers a novel near real-time approach for direct identification and evaluation of residual PCa. This study assesses the feasibility of using SRH-AI analysis to detect residual PCa and assess burden in post-prostatectomy specimen from patients treated in the GUNS trial.

Methods

Patients enrolled in the GUNS trial at Vancouver General Hospital (Nov 2023-March 2025) who subsequently underwent prostatectomy were included. Fresh or frozen postprostatectomy tissue targeting regions with prior PCa were imaged using SRH in 4-8 minutes per sample. SRH-AI quantified the proportion of cancerous tissue present within each sample. Corresponding specimens underwent standard H&E staining and were independently reviewed by pathologists for ground truth assessment.

Results

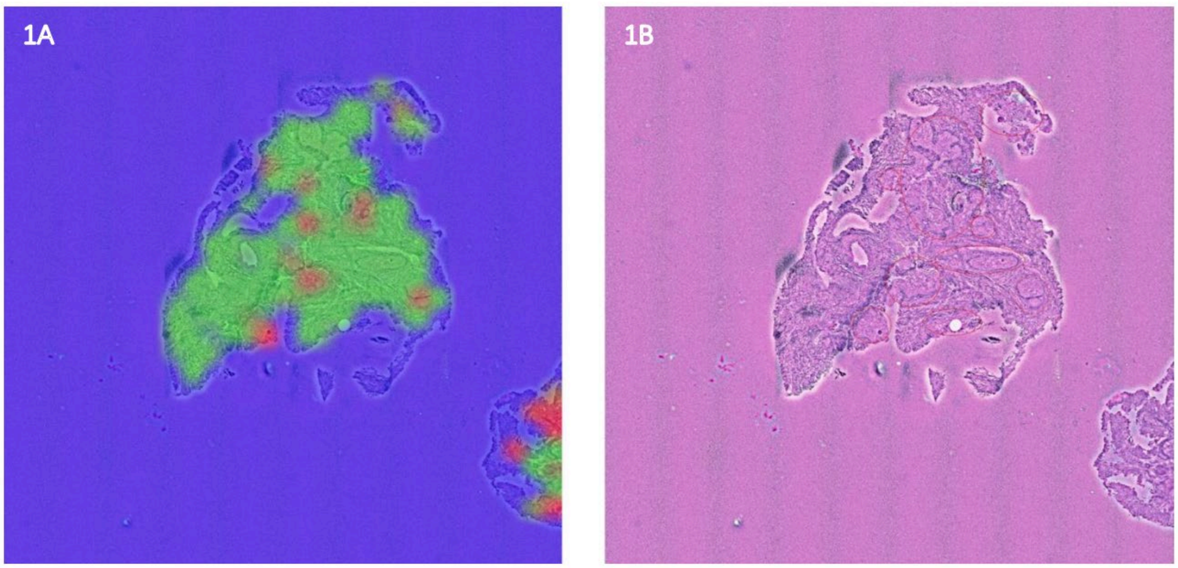
43 samples from 31 patients were analyzed with pathologist review of H&E slides confirming 27 patients' samples had no residual. However, 4 patients exhibited residual PCa ranging from 4%-70% infiltration of sampled tissue. In benign prostatectomy tissue, the SRH-AI cancer risk score median was 3% (IQR 1%-5%). In PCa infiltrated tissues, the SRH-AI cancer risk score median was 9% (IQR 5.8%-14.5%). SRH-AI closely mirrored the pathologist findings though underestimated PCa volume, Figure 1.

Conclusions

SRH-AI demonstrates strong potential for near real-time identification of PCa after 6 months of neoadjuvant therapy, showing good concordance with the standard histopathology. SRH-AI routine integration during sampling may improve PCa yield for biobanking after neoadjuvant therapy.

Figure 1

SRH-AI analysis shows identification of PCa after 6 months of neoadjuvant therapy in the GUNS trial. 1A shows SRH-AI identification of PCa: red = predicted PCa, green = predicted benign and purple = non-diagnostic/non-tissue. 1B shows SRH with pathologist annotations showing concordance with SRH-AI, though underestimation of PCa tumor volume.



A MULTIOMIC ATLAS OF ADVANCED UROTHELIAL CANCER

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Urothelial cancer (UC) is one of the most common cancers in Canada, with ~12,000 yearly diagnoses. In advanced disease (muscle-invasive and metastatic) the 5-year survival rate drops below 50%. Prognostic and predictive biomarker development has been impeded by both the scarcity of relevant tumour tissue and disease heterogeneity. Recent studies have demonstrated that plasma cell-free circulating tumor DNA (ctDNA) is a minimally-invasive biomarker representative of the genomic landscape of cancer. Thus, to allow for comprehensive characterization of advanced UC, we have collected 1082 plasma samples from 632 UC patients (66% of samples taken in the metastatic setting, 34% muscle-invasive), along with 543 FFPE tumor tissue samples from 250 patients. To date, 662 plasma samples have undergone deep targeted cell-free DNA sequencing, using a custom panel containing key UC-associated genes. ctDNA was detected in 59% (n=392) of samples, with a detection limit of 2% (measured as fraction of total cell-free DNA). Frequently mutated genes were consistent with the known landscape of somatic alterations in advanced UC, and included TERT (54% metastatic patients, 39% muscle-invasive), TP53 (49% metastatic patients; 61% muscle-invasive), KMT2D (29% metastatic patients; 26% muscle-invasive) and ARID1A (22% metastatic patients; 26% muscle-invasive). Regarding tumor tissue, to date RNA-sequencing has been performed on 105 samples with 438 pending. Samples that passed quality control (n=67) were found to belong to a variety of distinct transcriptomic subtypes, including luminal papillary (33%), luminal nonspecified (15%), luminal unstable (15%), stroma-rich (15%), basal/squamous (19%), and neuroendocrine-like (3%). Future work includes correlating genomic and transcriptomic features with clinical outcomes, and performing enzymatic methylation sequencing, ChIP sequencing and whole genome sequencing on samples to characterize the epigenome of advanced UC.

COMPARITIVE ANALYSIS OF APIXABAN VERSUS ENOXAPARIN FOR THROMBOPROPHYLAXIS AFTER RADICAL CYSECTOMY: A SINGLE CENTER OBSERVATIONAL BEFORE-AFTER STUDY

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Introduction and Objectives

Radical cystectomy (RC) is the standard treatment for muscle invasive bladder cancer and select high-risk non-muscle invasive bladder cancer (BCa). Venous thromboembolism (VTE) is a common and preventable postoperative complication. Extended thromboprophylaxis with low-molecular-weight heparin such as enoxaparin is recommended, but direct-acting oral anticoagulants like apixaban are a possible alternative. This study evaluates the safety and efficacy of apixaban compared to enoxaparin for extended postoperative thromboprophylaxis following RC.

Methods

A single-center observational before-after study of RCs performed between October 2021, and August 2024, was conducted. Patients receiving 28-days of post-discharge thromboprophylaxis with either enoxaparin or apixaban were included. The primary outcome was postoperative VTE within 30 days. Secondary outcomes included 90-day postoperative VTE, 30-day post-discharge emergency room (ER) visits, readmissions, complications such as bleeding, and 90-day mortality.

Results

A total of 102 patients who received enoxaparin and 83 patients who received apixaban for VTE thromboprophylaxis were included. No significant differences were found in 30-day postoperative VTE rates [0 (0%) apixaban vs. 2 (2%) enoxaparin; P=0.5], 90-day postoperative VTE rates, or 30-day post-discharge ER visits, readmissions, or hemorrhagic complications ($p>0.05$). There were no deaths by 90 days postoperatively.

Conclusions

Apixaban demonstrated a safety and efficacy profile comparable to enoxaparin for extended VTE prophylaxis following RC for BCa, with no VTE event in 83 patients. These findings support the potential use of apixaban as an alternative to enoxaparin.

NEO-BLAST: NEOADJUVANT THERAPY FOR BLADDER CANCER FOLLOWED BY ACTIVE SURVEILLANCE VS TREATMENT

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Background

Neoadjuvant therapy (NAT) followed by radical cystectomy (RC) is the standard of care for muscle-invasive bladder cancer (MIBC). Despite this, approximately 35–40% of patients have no residual cancer (pathological complete response, pCR) at the time of surgery, raising questions about whether definitive bladder treatment (DBT) is necessary for this subset of patients. Existing clinical tools for identifying patients with a clinical complete response (cCR) following NAT remain inadequate. The NEO-BLAST trial aims to address this gap by evaluating whether MRI, circulating tumor DNA (ctDNA) and transurethral resection of bladder tumor (TURBT) can reliably identify cCR, and whether active surveillance (AS) can provide comparable outcomes to DBT in patients achieving cCR

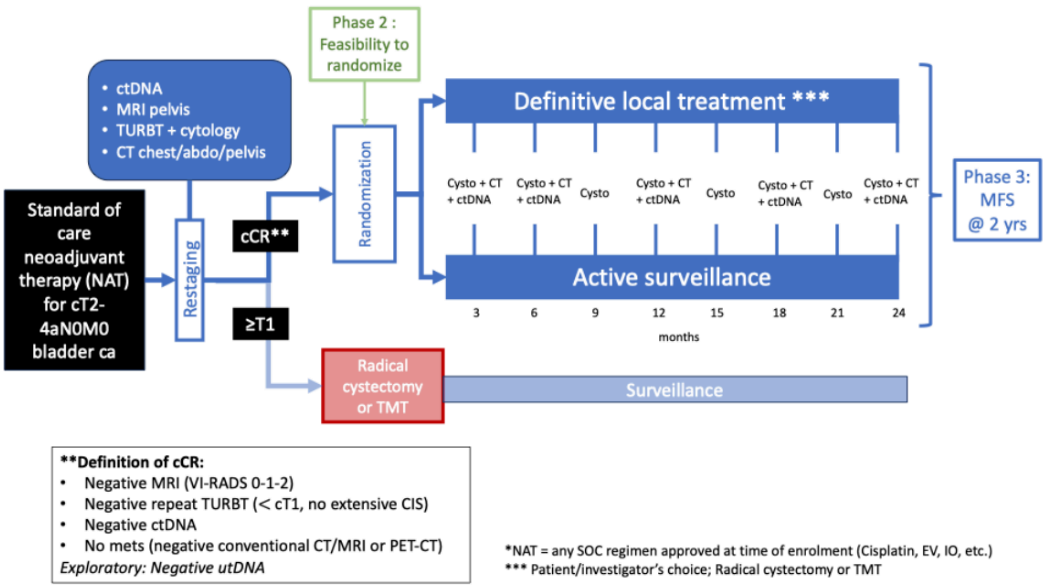
Methods

NEO-BLAST is a multi-center, open-label, phase II/III, non-inferiority trial (NCT06537154). Adult patients with non-metastatic MIBC (≥T2N0M0) who are eligible for NAT and DBT (RC or trimodal therapy (TMT)) will be eligible for enrollment. Subjects will undergo clinical restaging using pre- and post-NAT ctDNA, bladder MRI, urine cytology, and TURBT with template biopsies to rule out residual invasive cancer as well as conventional imaging to rule out metastasis. Participants with cCR—defined as negative ctDNA, MRI, and TURBT—are randomized to AS vs DBT. Patients without cCR proceed to DBT.

The first stage of the trial is a phase II feasibility RCT targeting enrollment of 72 patients in two years. Feasibility is defined as 25% of enrolled subjects achieving cCR and agreeing to be randomization. The phase III component will evaluate metastasis-free survival (MFS) at two years, with a planned sample size of 172 randomized patients with cCR, accounting for 10% loss to follow-up. Patients will be monitored every three months for two years with cystoscopy, urine cytology (for AS participants), and imaging, including ctDNA assessments at prespecified intervals.

Results

This is a clinical protocol; no results are available.



Definitions: cCR (clinical complete response, as defined in protocol), CT (computerized tomography), ctDNA (cell-free tumor DNA), MIBC (muscle invasive bladder cancer), MRI (magnetic resonance imaging), NAT (neoadjuvant chemotherapy), RC (radical cystectomy), SOC (standard of care), TMT (trimodal therapy including TURBT, chemotherapy and radiation), TURBT (transurethral resection of bladder tumor), utDNA (urine tumor DNA)

SURVIVAL AND PREDICTORS OF OUTCOME IN RADIATION-ASSOCIATED BLADDER CANCER: A SINGLE-CENTRE RETROSPECTIVE STUDY WITH IPTW-BASED ANALYSIS

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Introduction and Objectives

Radiation-associated bladder cancer (RABCA) following pelvic radiotherapy (RT) remains a challenging entity to treat with poor clinical outcome albeit from limited data available. We aimed to evaluated the clinicopathologic and oncologic outcomes of patients with RABCA and to compare survival of RABCA to bladder cancer without prior pelvic radiation (non-RABCA).

Method

Single institution retrospective study of patients diagnosed with bladder cancer following ≥2 years post pelvic RT between 2005 to 2024. Comparison with non-RABCA from 3 datasets looking at event-free survival (EFS), cancer specific survival (CSS) and overall survival (OS). Comparison using cox proportional hazards models including age, sex, RABCA, neoadjuvant (NAC), smoking, stage, histology and node status and Inverse Probability of Treatment Weighting (IPTW) analysis for NAC, age, sex, histology and stage.

Results

64 RABCA and 182 non-RABCA had RC with outcome available for weighted analysis were included. In RABCA only, Cox regression analyses, higher pT stage (EFS HR 10.07, p=0.002; CSS HR 40.34, p=0.0015) and RT with EBRT were associated with worse outcomes (EFS HR 0.36; p=0.018; CSS HR 0.36; p=0.016). In comparative analysis with Cox model, only pT was associated with risk of recurrence (HR 1.71, p<0.001) and OS (HR 1.71, p<0.001). RABCA not significant (HR 1.37, p=0.2). In the IPTW analysis RABCA not significantly associated with RFS (HR 1.58 [95% CI 0.96-2.60], p=0.07), but was associated with a worse OS (HR 1.70 [95% CI 1.17-2.45], p=0.005).

Conclusion

RABCA is associated with aggressive histology and poor oncologic outcomes. Higher tumor stage and EBRT were associated with worse outcomes (compared to brachytherapy). On weighted model, RABCA had worst OS (RFS not significant). We are conducting molecular analyses to better understand tumor biology, especially in comparison to bladder cancer that is not associated with RT.

THE ROLE OF METHYLNALTREXONE IN THE LENGHT OF HOSPITAL STAY AND BOWEL RECOVERY AFTER RADICAL CYSTECTOMY: A RETROSPECTIVE STUDY

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Introduction and Objectives

Post-operative ileus (POI) is a frequent complication after radical cystectomy (RC) and contributes to extended hospitalization. Alvimopan, a peripherally acting opioid antagonist (PAMORA), reduces length of hospital stay (LOS) and improves bowel recovery after RC, but is unavailable in Canada. We investigated the impact of methylnaltrexone (MNTX), a PAMORA available in Canada, to the enhanced recovery after surgery (ERAS) protocol on LOS and POI.

Methods

Single-center retrospective review including patients undergoing RC for bladder cancer from 2021 to 2024. MNTX (12 mg SC pre-incision, then daily for up to 6 days post-surgery) was added to the ERAS protocol in May 2023. Patients undergoing additional surgeries (e.g., bowel resection) or taking preoperative narcotics were excluded. The primary outcome was LOS, with secondary outcomes including time to flatus, time to bowel movement, POI (inability to tolerate oral diet by day 7 and/or nasogastric tube placement), and 30-day emergency visits. Pearson's Chi-squared and Mann-Whitney U tests were applied.

Results

Among 294 cases, 191 patients were included (82 MNTX, 109 controls). Median age was 71 [IQR 66–77], 79% were male, and 89% had an epidural. LOS was significantly shorter in the MNTX group (median 6 days [6, 8]) compared to controls (median 7 days [7, 8]; $p < 0.001$). There was no difference in POI rate (16.0% vs. 18.3%; $p = 0.8$) or other secondary outcomes ($p > 0.05$). Univariate analysis showed no significant association between MNTX and POI ($p=0.8$), but MNTX was significantly associated with reduced LOS ($W = 5782$, $p < 0.001$).

Conclusion

MNTX as part of the ERAS protocol for RC was associated with a shorter LOS, but no significant difference in bowel recovery. Given the potential healthcare cost savings, MNTX appears beneficial, although randomized trial are needed to confirm these findings.

THE ROLE OF THE CHONDROTIN SULFATE GLYCOCALYX IN TUMOR VASCULARIZATION

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Tumor growth and progression depend on the capacity to form new blood vessels through angiogenesis, allowing tumors to access essential nutrients and oxygen. Unlike normal vasculature, tumor blood vessels typically exhibit abnormal permeability, structural disorganization, and chaotic arrangement. Within the tumor microenvironment (TME), the glycocalyx, primarily composed of glycoproteins and glycosaminoglycans (GAGs), plays a role in regulating tumor vascularization. Our research investigates the role of chondroitin sulfate (CS), a sulfated GAG subtype, in tumor vascularization using a prostate cancer (PC) model. Employing the LNCaP xenograft model, we demonstrated that degradation of CS resulted in alterations to tumor vasculature, notably reversing tumor-associated erythrocyte leakiness. Removal of CS improved vascularization by increasing pericyte coverage, thereby enhancing the structural integrity of endothelial cells around PC tumors. CS-depleted tumors exhibited morphological changes characterized by more organized and diffuse vascular patterns. These vascular alterations correlated with increased infiltration of host stromal cells. Furthermore, molecular analyses, including RNA sequencing and mass spectrometry, provided additional insights into the mechanisms underlying these structural and functional vascular improvements following CS removal. Restoring abnormal tumor vascularization has therapeutic implications, such as improving drug delivery.

CDK12 AS A PROSTATE CANCER PREDISPOSITION GENE

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Introduction
Germline variants in DNA damage response genes are associated with increased risk of prostate cancer development and aggressive disease, but the full spectrum of relevant genes is unknown. CDK12 mutations are found in 5-7% of metastatic prostate cancers (mPCa) and were previously thought to be exclusively somatic. Here, we tested whether CDK12 pathogenic variants are present in the germline of patients with aggressive prostate cancer.

Methods
This study applied targeted sequencing across coding exons of CDK12 to white blood cell and tumour DNA from patients with aggressive PCa in a discovery cohort (n=2869, 100% mPCa) and independent validation cohort (n=1621, ~80% mPCa). CDK12 variants were classified on their potential to truncate the gene or alter kinase activity. Tumours were evaluated for second somatic allele inactivation and the characteristic CDK12- associated tandem duplication phenotype (TDP).

Results
In the discovery cohort we identified two patients with germline CDK12 truncating variants. Both were diagnosed with de novo mPCa at a young age (44 and 61) and had multiple independent CDK12-driven tumours characterised by unique secondary somatic CDK12 mutations and associated TDP in tumour tissue. Germline CDK12 truncating mutations were enriched in mPCa compared to Gnomad non-cancer controls (odds ratio 18.7, 95%CI 1.8-114.7). In the validation cohort, we identified two further patients with truncating CDK12 germline mutations, each diagnosed at a young age with de novo mPCa and had tumour confirmed secondary somatic CDK12 mutations and TDP. Family histories included multi-generation PCa diagnoses in two patients and a younger sister with ovarian cancer (the other solid cancer associated with somatic CDK12 mutations) in another patient.

Conclusion

Germline variants predicted to truncate CDK12 are present in ~0.1% of mPCa and associated with CDK12-driven disease in affected patients. Therefore, CDK12 is a rare mPCa predisposition gene and should be incorporated into clinical genetic testing workflows.

HIGH EPHA2 EXPRESSION IS ASSOCIATED WITH IMMUNE SUPPRESSION IN BASAL-SQUAMOUS SUBTYPE OF BLADDER CANCER

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Introduction and Objectives

Bladder cancer (BCa) is widely regarded as immunogenic; however, only approximately 20% of patients respond to immune checkpoint inhibitors (ICIs), highlighting the need to clarify tumor immune–evasion mechanisms. We previously identified Eph receptor tyrosine kinase A2 (EphA2) as a novel BCa biomarker, with elevated expression in both tumor tissues and urinary extracellular vesicles that correlates with aggressive disease. Recent studies in pancreatic cancer indicate that EphA2 promotes immune escape, suggesting a similar modulatory role within the BCa tumor microenvironment. This study investigates whether EphA2 mediates immunosuppression in BCa, potentially influencing the response to ICIs.

Methods

We analyzed RNA-seq data from 192 metastatic urothelial carcinoma patients treated with atezolizumab in the IMvigor210 trial, stratifying tumors by consensus molecular subtype (luminal-papillary vs. basal-squamous). To validate our observations, we established syngeneic orthotopic tumors in immunocompetent C57BL/6 mice by ultrasound-guided injection of EphA2-overexpressing or vectorcontrol BBN963 cells (basal-squamous subtype, n = 14 mice in total). Tumor growth was measured serially, and Kaplan–Meier analysis assessed time to humane endpoint. Endpoint tumors underwent bulk RNA-seq, and human and murine datasets were analyzed in parallel.

Results

In basal-squamous tumors with high EphA2 expression exhibited significantly lower transcripts of CD4, CXCL9, and CD274 (PD-L1), suggesting an immunosuppressive microenvironment. In orthotopic models, EphA2 overexpression accelerated tumor growth and shortened time to humane endpoint, with intratumoral CD4 expression also decreased. In both human and murine samples, EphA2-high tumors showed Wnt/β-catenin and KRAS/MAPK activation with concurrent suppression of multiple immune-related pathways.

Conclusions

High EphA2 expression in basal-squamous BCa is associated with an immunosuppressive microenvironment, marked by reduced $CD4^+$ T-cell infiltration and coordinated suppression of immune pathways. These findings nominate EphA2 as a potential modulator of ICI efficacy and warrant further studies to define its precise role in ICI responsiveness in BCa.

3D ORGANOID CULTURE FOR BENIGN PROSTATE HYPERPLASIA SHOWS GLUCOCORTICOID SPECIFIC BRANCHING

Liliana Vega, Xuesen Dong, Connor M Forbes

Introduction

Glucocorticoids are elevated in patient tissue with Benign Prostatic Hyperplasia (BPH). We previously developed a 3D organoid model which can bud and branch with glucocorticoid exposure. Herein, we evaluate for the specificity of the phenotypic changes with glucocorticoid exposure in our 3D organoid model compared to other key steroid hormones.

Methods

BPH cell lines NHPRE-1, BHPRE-1 and PZ-HPV-7 were maintained and grown in 3D organoid culture in Matrigel. They were treated with control, dexamethasone, dihydrotestosterone (DHT), estradiol (E) or the dexamethasone antagonist RU-486. Budding and branching was quantified by automated segmentation with quantification of circularity (Incucyte).

Results

Dexamethasone induced phenotypic budding and branching for NHPRE-1, BHPRE-1 and PZ-HPV7 (Figure 1), showing a statistically significant decrease in circularity. With the addition of RU-486, this phenotypic change was inhibited. E (Figure 1) and DHT (Figure 2) did not induce budding and branching in 3D culture.

Conclusions

Dexamethasone induces a statistically significant phenotypic change in BPH in 3D culture. This budding/branching change is inhibited by glucocorticoid antagonist RU-486. Budding and branching is specific to Dex, and is not induced by E or DHT. Glucocorticoids are implicated as a phenotypic driver in BPH cells in vitro, mimicking the budding/branching seen in patients with BPH. Further characterization is required.

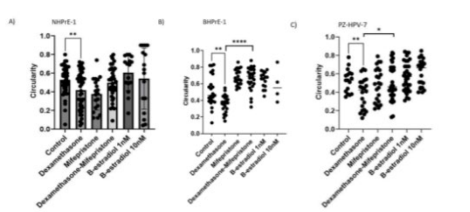

Figure 1. Dexamethasone-induced circularity changes are inhibited by RU486 (mifepristone) in a) NHPrE1 b) BHPrE-1 and c) PZ-HPV-7. Estradiol does not induce budding and branching changes.

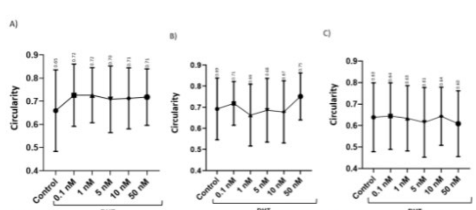

Figure 2. DHT does not increase budding and branching for A) NHPRE-1 (less budding/branching vs control, all p <0.001); B) BHPRE-1 (same or LESS branching, only p<0.01 at 50nM); and C) PZ-HPV-7 (no sig diff).

DECIPHERING THE TRANSCRIPTION FACTOR LANDSCAPE IN NEUROENDOCRINE PROSTATE CANCER PROGRESSION: A NOVEL APPROACH TO UNDERSTAND NE TRANS DIFFERENTIATION

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Introduction and Objectives
Prostate cancer (PCa) is a leading cause of cancer mortality in men, with neuroendocrine prostate cancer (NEPC) representing a particularly resistant subtype. The role of transcription factors (TFs) in the progression from prostatic adenocarcinoma (PRAD) to NEPC is poorly understood. This study aims to identify and analyze lineage-specific TF profiles in PRAD and NEPC and illustrate their dynamic shifts during NE transdifferentiation.

Methods
A novel algorithmic approach was developed to evaluate the weighted expression of TFs within patient samples, enabling a nuanced understanding of TF landscapes in PCa progression and TF dynamic shifts during NE transdifferentiation.

Results
Unveiled TF profiles for PRAD and NEPC, identifying 126 shared TFs, 46 adenocarcinomaTFs, and 56 NEPC-TFs. Enrichment analysis across multiple clinical cohorts confirmed the lineage specificity and clinical relevance of these lineage-TFs signatures. Functional analysis revealed that lineage-TFs are implicated in pathways critical to cell development, differentiation, and lineage determination. Novel lineage-TF candidates were identified, offering potential targets for therapeutic intervention. Furthermore, our longitudinal study on NE transdifferentiation highlighted dynamic TF expression shifts and delineated a threephase hypothesis for the process comprised of de-differentiation, dormancy, and redifferentiation, proposing novel insights into the mechanisms of PCa progression.

Conclusion
This study reveals lineage-related transcription factors in prostate cancer, highlighting their roles in cell development and providing novel potential therapeutic targets. It proposes a "three-phase hypothesis" for neuroendocrine transdifferentiation, offering insights into neuroendocrine prostate cancer progression.

ULTRASOUND IMAGING BIOFEEDBACK ENHANCES PELVIC FLOOR MUSCLE TRAINING AND INCONTINENCE OUTCOMES AFTER PROSTATECTOMY

Calvin Wong, MPT, MRSc[2]; Anna Hudon-Kaide, BSc, MHScPT[2]; Sean Lee BSc, MPT[2]; Rosalie Ho MSc, CCRP; Monita Sundar, MA[2]; Celestia Higano, MD, FACP[1]

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Introduction and Objectives

Pelvic floor muscle training (PFMT) significantly improves quality of life for patients with post-prostatectomy incontinence (PPI)1,2. Outcomes are enhanced when PFMT targets the striated urethral sphincter (SUS) using real-time ultrasound (RTUS) for biofeedback3. In 2024, the Prostate Cancer Supportive Care (PCSC) Program integrated RTUS into physiotherapist-led PFMT to support motor learning. This report describes our clinical approach and early experience integrating RTUS and surface electromyography (sEMG) for individualized PFMT to manage PPI.

Methods

Since July 2024, physiotherapists have used RTUS to observe displacement of key pelvic floor structures during contraction (Figure 1b) and relaxation3 (Figure 1a). sEMG detects motor unit action potentials during pelvic floor muscle (PFM) contractions, offering biofeedback on levator ani activation. Increases in sEMG amplitude indicate muscle activation and reductions reflect local muscle fatigue4. RTUS and sEMG biofeedback are used to teach effective motor recruitment strategies and monitor muscle performance. Incontinence outcomes are assessed using ICIQ-UI scores and pad usage.

Results

RTUS has proven valuable in allowing patients and physiotherapists to observe optimal PFM recruitment patterns and confirm effective exercise practice. sEMG provides complementary insights into levator ani recruitment and fatigue. Patients showed increased engagement and comprehension with RTUS-guided biofeedback5. The sustained endurance test (SET) and rapid response test (RRT) are validated, reliable measures collected using US to assess key aspects of PFM function5. The SET evaluates the ability to sustain PFM contraction, while the RRT measures coordination of rapid contractions. This data may support comparison of sEMG and US biofeedback in improving PPI and PFM function.

Conclusion

RTUS and sEMG provide distinct, yet complementary biofeedback for PFMT. RTUS supports learning PFM coordination; sEMG reflects levator ani recruitment and fatigue. These tools improve patient engagement and motor learning, potentially optimizing PPI outcomes. Further trials should evaluate long-term effectiveness and device-specific contributions to PFMT.

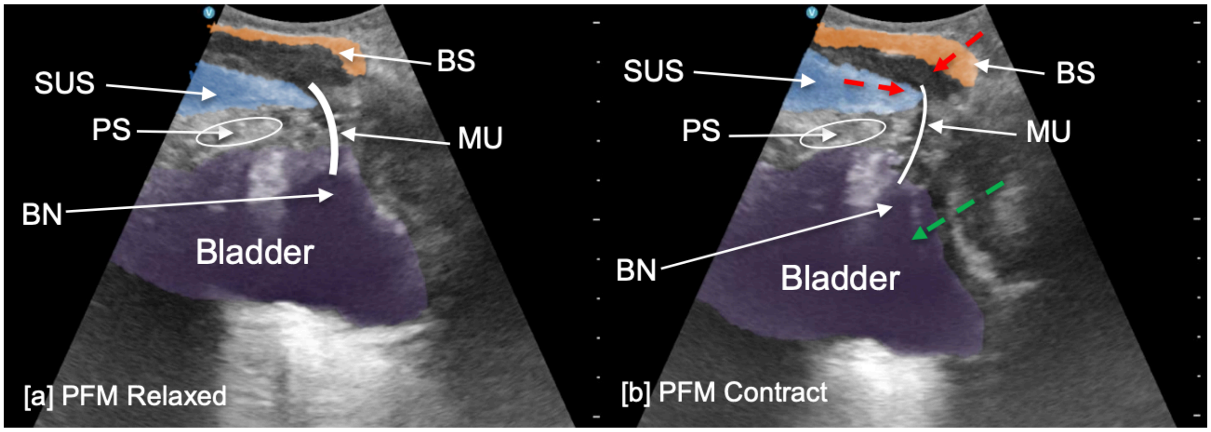

Figure 1. Mid-sagittal transperineal ultrasound (US) capture showing key structures used to assess pelvic floor muscle recruitment: striated urethral sphincter (SUS, blue highlight), bulbospongiosus (BS, orange highlight), bladder neck (BN), membranous urethra (MU), and pubic symphysis (PS). [a] Pelvic floor muscles at rest. [b] Pelvic floor muscles during concentric contraction. Red arrows indicate SUS and BS movement compressing the MU (white line); green arrow indicates BN movement due to puborectalis and pubococcygeus contraction.

CHARACTERIZATION OF STRUCTURAL VARIANTS IN KEY METASTATIC PROSTATE CANCER DRIVER GENES

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Background

Structural variants (SVs) can modulate key metastatic prostate cancer (mPCa) driver genes. However, they remain poorly characterized, as the majority fall in noncoding regions not typically captured by contemporary targeted sequencing methods. Here, we aim to characterize the frequency and distribution of SVs within key mPCa genes, including DNA damage repair (DDR) and tumour suppressor genes, in a large cell-free DNA (cfDNA) mPCa cohort.

Methods

We analyzed 3971 plasma cfDNA samples from a unique meta-cohort of 2279 mPCa patients. To facilitate SV detection, samples were sequenced on a targeted panel with full intragenic and sparse intergenic coverage around key mPCa genes. Somatic mutations, copy number alterations, and SVs, including inversions, tandem duplications, translocations, and deletions, were identified and circulating tumour DNA (ctDNA) fraction was estimated using an established bioinformatics pipeline. For patients with multiple samples, the sample with the highest ctDNA fraction was chosen for SV profiling.

Results

Within 1689 patients with detected ctDNA, 444 (26.3%) had a putative pathogenic SV in at least one DDR or tumour suppressor gene. PTEN, TP53, RB1, and BRCA2 were the most frequently impacted genes with SVs detected in 197 (11.7%), 124 (7.3%), 74 (4.4%), and 48 (2.8%) patients respectively. Within these genes, 79.8% (473/593) of SVs had breakpoints exclusively in intronic or intergenic regions. Analysis of SV distributions further revealed potential breakpoint hotspot regions.

Conclusions

SVs impacting tumour suppressor and DDR genes are commonly detected in mPCa patient ctDNA. Positions of recurrent SV breakpoints may guide the design of targeted panels to improve SV detection. Future work analyzing the association between SVs and patient outcomes will provide insight into the clinical relevance of these alterations.

PROTEOMICS CHARACTERIZE PROSTATE CANCER BONE METASTASES SUBTYPES

Dennis Xie[1], Bita Mojtahedzadeh[1], Hans Adomat[1], Felipe Eltit[1,2,] Raphaele Charest-Morin[3,4], Colm Morrissey[5], Eva Corey[5], Michael E. Cox[1,2.]

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Introduction and Objectives
Prostate cancer (PC) bone metastases (BM) is a debilitating disease morbidity that primarily affects the axial skeleton. PCBMs form mixed osteosclerotic/osteolytic lesions with increased, irregular, bone density and deposition, loss of collagen alignment and increased porosity that mimic features of woven bone that forms during development and repair. We hypothesize that PCBMs induce dysregulated repair-like bone remodeling activity leading to distinct protein signatures that correlate with the extent of osteosclerotic and osteolytic characteristics in different PCBM subtypes.

Methods
We performed tandem mass spectrometry (MS) to measure the protein composition in lumbar vertebrae specimens from 3 age-matched controls and 32 cadaveric PCBM specimens: 17 defined as osteosclerotic and 15 as osteolytic based on microcomputed tomography bone volume vs total volume (BV/TV) measurements. We employed unsupervised hierarchical clustering and dimension reduction techniques to identify clusters with distinct protein composition profiles and performed differential expression analysis.

Results
We identified proteins differentially enriched in osteosclerotic and osteolytic specimens. High BV/TV specimens were uniquely enriched in bone sialoprotein 2, osteopontin, osteonectin. Low BV/TV specimens had elevated levels of cathepsin G, myeloblastin, and neutrophil elastase compared to the osteosclerotic specimens. Unsupervised clustering segregated the 3 control samples and 17 osteosclerotic samples into distinct groups. The 15 osteolytic samples separated into three subgroups: one clustering with controls, one exhibiting features overlapping with osteosclerotic lesions, and one unique osteolytic group.

Conclusion
Proteomic profiling revealed distinct differences between predominantly osteosclerotic and osteolytic PCBM highlighting altered process of mineralization, suggesting potential biomarkers, and provide mechanistic insights. The osteosclerotic samples are distinctly characterized by proteins that promote bone production and mineralization. The osteolytic lesions displayed signatures of immune cell activity. The proteomic segregation of three molecular subtypes of osteolytic lesions was unexpected and demonstrates the sensitivity of MS-based analysis, highlighting its promise for further characterizing PCBM subtypes.

CHARACTERIZATION OF A NOVEL AR ENHANCER AS POTENTIAL DRIVER OF CASTRATION-RESISTANT PROSTATE CANCER

Kerim Yavuz[1, 2], Roselyn Ma[1], Umut Berkay Altıntaş [1, 2], Uğur Meriç Dikbaş [1, 2], Emma Minnee[3], Ji-Heui Seo[4], Matthew Freedman[4], Wilbert Zwart[3], Nathan A. Lack[1, 2, 5]

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Introduction and Objectives

Androgen receptor (AR) pathway inhibitors (ARPI) is the standard-of-care for recurrent or metastatic prostate cancer (PCa) While initially effective, nearly all patients eventually progress to lethal castration-resistant prostate cancer (CRPC). Most resistant tumors (70–85%) remain AR-dependent, often through AR overexpression. Recently, we identified a novel cis-regulatory element (CRE) downstream of the AR gene, amplified in 40–50% of CRPC tumors during ARPI treatment, potentially causing AR overexpression and contributing to progression to CRPC. This study aimed to functionally characterize this CRE and investigate its role in treatment resistance

Methods

We assessed the enhancer activity of this CRE using luciferase assays in CRPC (LuCaP-35CR) and castrate-sensitive PCa cells (LNCaP, LuCaP-35CS). AR-driven enhancer function was tested via luciferase assay with AR inhibition and knockdown. Functional genomics approaches characterized genomic and epigenomic features of this CRE in primary PCa and CRPC. Luciferase assay with ectopic AR overexpression in castrate-sensitive models evaluated the role of increased AR levels in enhancer activation during CRPC.

Results

This CRE exhibited selective enhancer activity in LuCaP-35CR but not in LNCaP or LuCaP-35CS. AR inhibition and knockdown reduced luciferase expression, indicating AR-dependent activity. While accessible in all tumors, this CRE had enhancer associated histone modifications (H3K27Ac) exclusively in clinical CRPC but not primary prostate cancer samples. Chromatin conformation analyses in LuCaP-35CR revealed interaction of this enhancer with the AR promoter. Ectopic AR overexpression alone did not activate this enhancer in castrate-sensitive cells.

Conclusions

The accessibility of this CRE across all stages of PCa, combined with its selective AR-driven activity in CRPC and lack of activation by AR overexpression alone, suggests that other transcription factors play a role in the activation of this enhancer. Ongoing studies will identify and characterize these factors as drivers of treatment resistance to identify therapeutic vulnerabilities in lethal CRPC.

HARNESSING PROXIMITY LIGATION TO PROBE THE ANDROGEN RECEPTOR VARIANT 7 INTERACTOME

Ivan Yu[1,2], Shreyas Lingadahalli[1], Hans Adomat[1], Sila Akdogan[3], Daniel Robinson[1], Bengul Gokbayrak[1], Ugur Meric Dikbas[1], Adam Sharp[4], Colin Collins[1], Nathan Lack[1,2,3]

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Introduction

Inhibiting androgen receptor (AR) signalling is a common treatment for recurrent or metastatic prostate cancer (PCa). Yet the cancer almost inevitably develops resistance, resulting in the more aggressive castration resistant prostate cancer (CRPC). Interestingly, AR signalling is still critical in the majority of CRPC. Several resistance mechanisms can maintain AR signalling, including the expression of constitutively active AR splice variants. However, numerous studies have demonstrated that the AR variants (AR-V7) and fulllength protein (flAR) share similar DNA binding sites but have very different transcriptional activity. This suggests that there may be differential co-regulatory proteins recruited by the two isoforms that potentiate their divergent transcriptional activity.

Methods

To characterize the interactomes of flAR and AR-V7, we utilized TurboID, a biotin ligase that tags nearby proteins with biotin. Following fusion protein expression, we isolated putative flAR/AR-V7 interacting partners by streptavidin pulldown and identified them via mass spectrometry (MS). From analyzing publicly available essentiality data, Polybromo-1 (PBRM1) emerged as a novel co-regulator selectively essential in AR-V7 expressing cells. We validated its interaction with AR-V7 through numerous orthogonal biochemical methods and mapped the interaction site of the two proteins through coimmunoprecipitation (Co-IP). To further characterize the validated interactor PBRM1, we developed inducible knockdown models for PBRM1 and AR-V7 and performed chromatin binding and transcriptomic profiling.

Results and conclusions

Probing the interactomes for flAR and AR-V7 yielded several hundred high confidence hits, including well-characterized AR-interacting proteins, including HOXB13 and FOXA1. Moreover, among proteins associated with AR-V7 specifically, we identified PBRM1 as a novel co-regulator critical for AR-V7 expressing cells, and defined their interaction interface. Currently, we are analyzing the genomic and transcriptomic data to understand the signaling and epigenomic changes that occur upon depletion of these proteins. Overall, this work will further our understanding of AR-V7 mediated therapeutic resistance and suggest novel therapeutic approaches.

Organizing Committee

- Dr. Kourosh Afshar
- Dr. Ben H. Chew
- Dr. Xuesen Dong
- Dr. Miles Mannas
- Dr. Amina Zoubeidi

Learning Objectives

- To inform members of the types of clinical and basic science research being conducted in the Department of Urologic Sciences.
- To familiarize members with new innovative research techniques.
- To foster an atmosphere of collaborative research within the Department of Urologic Sciences.

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