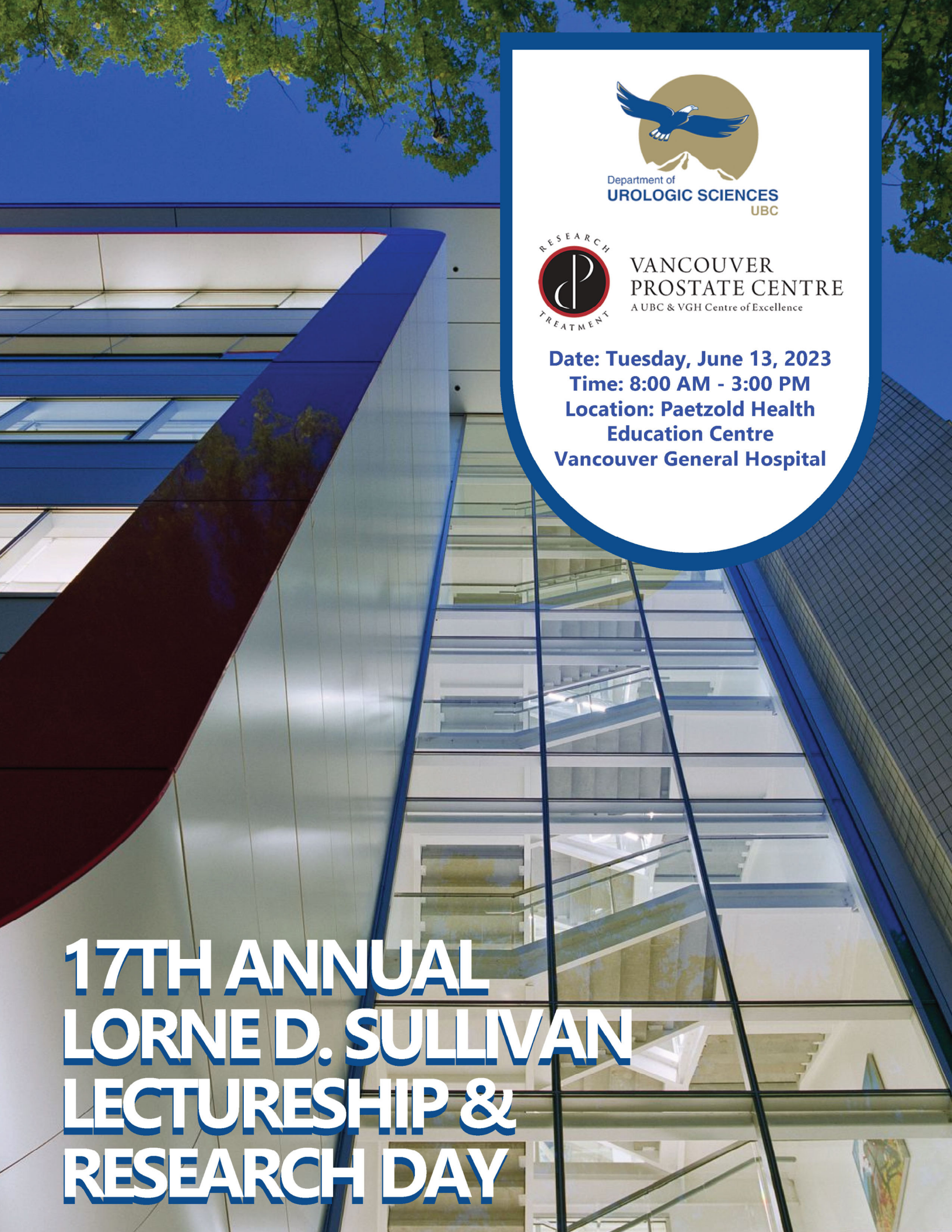

Department of
UROLOGIC SCIENCES
UBC

RESEARCH
TREATMENT

VANCOUVER
PROSTATE CENTRE
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Date: Tuesday, June 13, 2023
Time: 8:00 AM - 3:00 PM
Location: Paetzold Health Education Centre
Vancouver General Hospital

17TH ANNUAL LORNE D. SULLIVAN LECTURESHIP & RESEARCH DAY

Department of
UROLOGIC SCIENCES
UBC

VANCOUVER
PROSTATE CENTRE
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2023 Sullivan Research Lecturer

Dr. Scott Eggener, MD

Bruce and Beth White Family Professor of Surgery
Vice Chair, Section of Urology
Director, High Risk and Advanced Prostate Cancer Clinic
The University of Chicago Medicine

Dr. Scott Eggener is a urologic oncologist specializing in patient care with prostate, kidney and testicular cancers. Dr. Eggener is a Bruce and Beth White Family Professor of Surgery, Vice Chair of the Section of Urology, and Director of the High Risk and Advanced Prostate Cancer Clinic.

Dr. Eggener's research, which has resulted in over 300 publications, exclusively focuses on urologic cancers and primarily on improving the screening, diagnosis, and treatment of men with prostate cancer. He is a senior faculty scholar at the Bucksbaum Institute for Clinical Excellence, an Associate Editor at the Journal of Urology and an Executive Board Member of International Volunteers in Urology. Dr. Eggener has chaired or participated in multiple ASCO/AUA cancer guideline panels.

Dr. Lorne D. Sullivan

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 Columbia 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 but continues to grace the Department with his presence at academic and social functions.

Previous Sullivan Lectureship & Research Day Lecturers

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 A.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

Previous Division of Urology Graduation Dinner Guest Speakers

2022 – Dr. Anthony Atala
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
2005 – Dr. Laurence H. Klotz

Department of UROLOGIC SCIENCES UBC

VANCOUVER PROSTATE CENTRE
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Program

Welcome

8:00 AM – 8:15 AM	**Dr. Martin Gleave, CM, MD, FRCSC, FACS** Distinguished Professor and Head, Department of Urologic Sciences, UBC Executive Director, Vancouver Prostate Centre British Columbia Leadership Chair in Prostate Cancer Research **Dr. Robert McMaster, PhD** Vice Dean, Research, Faculty of Medicine, UBC

Lorne D. Sullivan Lectureship

8:15 AM – 8:55 AM	**PUBLIC HEALTH WOULD DRAMATICALLY IMPROVE IF GLEASON 6 (GRADE GROUP 1) WASN'T CALLED CANCER** **Dr. Scott Eggener, MD** Bruce and Beth White Family Professor of Surgery Vice Chair, Section of Urology Director, High Risk and Advanced Prostate Cancer Clinic The University of Chicago Medicine

Session I: Bladder Cancer

8:55 AM – 10:05 AM
(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderators: **Dr. Mads Daugaard & Dr. Miles Mannas**

8:55 AM – 9:05 AM	**EVALUATING THE USE OF CIRCULATING TUMOUR DNA (CTDNA) IN UROTHELIAL CANCER PATIENTS IN THE CONTEXT OF FGFR-TARGETED THERAPY** David C. Müller, Elena Schönlau, Gillian Vandekerkhove, Andrew J. Murtha, Jack V.W. Bacon, Connor Wells, Kimia Rostin, Gang Wang, Sunil Parimi, Jean-Michel Lavoie, Krista Noonan, Naveen Basappa, Jenny J. Ko, Daygen Finch, Nimira Alimohamed, Tarek A. Bismar, Lucia Nappi, Corinne Maurice Dror, Matti Annala1,11, Cecily Q. Bernales1, Christian Kollmannsberger3, Kim N Chi1,3, Alexander W Wyatt, Bernhard J. Eigl
9:05 AM – 9:15 AM	**PROTEOMIC PROFILING OF MUSCLE INVASIVE BLADDER CANCER TREATED WITH PLATINUM-BASED CHEMOTHERAPY REVEALS UNIQUE BIOLOGIC CLUSTERS WITH CLINICAL RELEVANCE** Alberto Contreras-Sanz, Gian L Negri, Moritz J Reike, Htoo Z Oo, Sandra E Spencer Miko, Karina Nielsen, Morgan E Roberts, Joshua Scurll, Kenichiro Ikeda, Chelsea L Jackson, David M Berman, Roland Seiler, Gregg B Morin, Peter C Black
9:15 AM – 9:25 AM	**A NOVEL APPROACH TO ENGINEERING THREE-DIMENSIONAL BLADDER TUMOR MODELS FOR DRUG TESTING** Monjaras-Avila, CU; Luque-Badillo, AC; Bacon, J; Chavez-Munoz, C; So, A
9:25 AM – 9:35 AM	**ROLE OF URINARY AND GUT MICROBIOTA ON BACILLUS CALMETTE-GUÉRIN-INDUCED RESPONSES IN NON-MUSCLE INVASIVE BLADDER CANCER** Dalia Othman, Tuomas Jalanko, Moritz Reike, Igor Moskalev , Breanna Nelson, Ali Hussein, Carin Tin, Mathieu Roumigué, Sheryl Munshan, Felipe Eltit, Demian Ferreira, Alberto Contreras-Sanz, Moritz Maas, Aaron Miller, Peter Black, Dirk Lange
9:35 AM – 9:45 AM	**ADVERSE EVENTS ASSOCIATED WITH ELECTROMOTIVE DRUG ADMINISTRATION OF MITOMYCIN** J Ma, LM Jonat, S Faddegon, DP Ottem, PC Black

9:45 AM – 9:55 AM	**FBXW7 LOSS-OF-FUNCTION CONTRIBUTES TO WORSE OVERALL SURVIVAL AND IS ASSOCIATED WITH ACCUMULATION OF MYC IN MUSCLE INVASIVE BLADDER CANCER** Ruiliang Wang, Takashi Matsumoto, Elaine Chen, Morgan E. Roberts, Moritz Reike, Kenichiro Ikeda, Htoo Zarni Oo, Takeshi Sano, Eric LeBlanc, Kriti Singh, Jian Gao, Igor Moskalev, Alberto Contreras-Sanz, Peter C. Black
9:55 AM – 10:05 AM	**INCIDENCE OF PELVIC SECOND MALIGNANCIES IN PROSTATE CANCER PATIENTS TREATED WITH LOW-DOSE-RATE BRACHYTHERAPY AND RADICAL PROSTATECTOMY AT EXTENDED FOLLOW-UP** Marie-Pier St-Laurent, George Acland, Scott Tyldesley, Sarah N. Hamilton, Jeremy Hamm, Martin E. Gleave

Break and Posters 10:05 AM – 10:35 AM

State of Art Lecture I

10:35 AM – 10:50 AM	**TRANSLATING BIOMARKERS INTO GENITO-URINARY ONCOLOGY CLINICAL PRACTICE: FROM DIAGNOSIS TO TREATMENT** **Dr. Lucia Nappi, MD PhD** Assistant Professor, University of British Columbia Medical Oncologist, BC Cancer - Vancouver Cancer Centre Senior Research Scientist, Vancouver Prostate Centre

Session II: Kidney

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

Moderators: **Dr. Connor Forbes & Dr. David Harriman**

10:50 AM – 11:00 AM	**MACHINE LEARNING-BASED DECISION SUPPORT SYSTEM TO DISTINGUISH URIC ACID STONES IN PATIENTS WITH KIDNEY STONES OF 'GREY ZONE' HOUNSFIELD UNITS: INTERNATIONAL MULTICENTER DEVELOPMENT AND EXTERNAL VALIDATION STUDY** Kyo Chul Koo, Abdulghafour Halawani, Victor KF. Wong, Sujin Lee, Sangyeop Baek, Hoyong Kang, Ben H. Chew
11:00 AM – 11:10 AM	**BREAK WAVETM LITHOTRIPSY FOR UROLITHIASIS: RESULTS OF THE FIRST-IN-HUMAN INTERNATIONAL MULTICENTER CLINICAL TRIAL** Ben H. Chew, Victor KF. Wong, Jonathan D. Harper, Roger L. Sur, Thomas Chi, Shubha De, Anne R. Buckley, Ryan F. Paterson, Connor M. Forbes, M. Kennedy Hall, Ross Kessler, Seth K. Bechis, Jason R. Woo, Ralph C. Wang David B. Bayne, Derek Bochinski, Trevor D. Schuler, Tim A. Wollin, Rahim Samji, Mathew D. Sorensen.
11:10 AM – 11:20 AM	**THE ROLE OF THE MICROBIOME AND SHORT CHAIN FATTY ACIDS IN KIDNEY STONE DISEASE** Sarah Hanstock, Demian Ferreira, Hans Adomat, Felipe Eltit, Qiong Wang, Dalia, Othman, Roman Herout, Breanna Nelson, Alina Reicherz, Rizhi Wang, Aaron Miller, Genelle Healey, Ben Chew, Dirk Lange
11:20 AM – 11:30 AM	**ENVIRONMENTAL PERFORMANCE OF KIDNEY REPLACEMENT THERAPIES: COMPARATIVE LIFECYCLE ASSESSMENT OF DIALYSIS AND KIDNEY TRANSPLANTATION** Saba Saleem, Tasleem Rajan, Andrea MacNeill, Caroline Stigant, Kasun Hewage, Rehan Sadiq, Christopher Nguan
11:30 AM – 11:40 AM	**FEASIBILITY OF CREATING AN UP TO DATE, TRANSPLANT FOCUSED COUNSELING AI CHATBOT** Rohit Malyala, Christopher Nguan
11:40 AM – 11:50 AM	**EVALUATING DIFFERENT METHODS FOR KIDNEY RECELLULARIZATION** Ana C. Luque-Badillo, Cesar U. Monjaras-Avila, Hans Adomat,Alan So, Claudia Chavez-Muñoz

11:50 AM – 12:00 PM	**A COMPARISON OF ACCURACY AND READABILITY FOR COMMON PATIENT QUESTIONS REGARDING SMALL RENAL MASSES BETWEEN ARTIFICIAL INTELLIGENCE AND ACCREDITED PATIENT INFORMATION MATERIALS** Jonathan Suderman, Anna Black, Connor Forbes
12:00 PM – 12:10 PM	**EVALUATING THE EFFECTIVENESS OF RENAL BIOPSY INNOVATIONS: A SYSTEMATIC REVIEW OF THE LITERATURE** Nilanga Aki Bandara, Xuan Randy Zhou, Parsa Khatami, Rochelle Gamage, Eric Belanger, Miles Mannas

Lunch and Posters 12:10 PM – 1:00 PM

Session III: Andrology & Pediatrics

1:00 PM – 1:40 PM
(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderator: **Kourosh Afshar & Dr. Dirk Lange**

1:00 PM – 1:10 PM	**PREVALENCE OF PREVIOUSLY UNDIAGNOSED PSYCHIATRIC SYMPTOM GROUPINGS IN PEDIATRIC PATIENTS WITH BLADDER AND BOWEL DYSFUNCTION (BBD)** Andrew E. MacNeily, Kourosh Afshar, Soojin Kim, Valerie Hogues, Maryam Noparast, Clara Westwell-Roper, S. Evelyn Stewart
1:10 PM – 1:20 PM	**OUTCOMES USING A NOVEL TENSION RELIEVING HITCH IN MICROSURGICAL VASECTOMY REVERSALS** Abdullah Alhamam, Ryan Flannigan
1:20 PM – 1:30 PM	**DIFFERENTIATION OF HUMAN PERITUBULAR MYOID-LIKE CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS** Meghan Robinson, Anne Haegert, Yen-Yi Li, Faraz Hach, Ryan Flannigan
1:30 PM – 1:40 PM	**FUNCTIONALIZING XENO-FREE BIOINKS TO PROMOTE TESTICULAR CELL GROWTH IN 3-D BIOPRINTED TESTICULAR MODELS** Meghan Robinson, Ryan Flannigan

State of Art Lecture II

1:40 PM – 2:05 PM	**Combining Tomography and Biochemistry Approaches to Define how Prostate Cancer Alters Bone Matrix Organization and Composition** **Dr. Michael Cox, Ph.D.** Senior Research Scientist, Vancouver Prostate Centre Associate Professor, Department of Urologic Sciences, UBC

Session IV: Prostate Cancer

2:05 PM – 2:55 PM
(10-minute presentations: 7-minute talk and 3-minute Q&A)

Moderator: **Dr. Nada Lallous & Nathan Lack**

2:05 PM – 2:15 PM	**CHARACTERIZING AND TARGETING THE INTERPLAY BETWEEN THE BAF CHORMATIN REMODELING COMPLEX AND THE LINEAGE-DETERMINING TRANSCRIPTIOIN FACTOR ASCL1 IN PROSTATE CANCER LINEAGE PLASTICITY** Cassandra Cui, Shaghayegh Nouruzi, Dwaipayan Ganguli, Maxim Kobelev, Takeshi Namekawa, Nakisa Tabrizian, Olena Sivak, Amina Talal, Amina Zoubeidi
2:15 PM – 2:25 PM	**CHARACTERIZATION OF ANDROGEN RECEPTOR PROPERTIES IN MEDIATING TRANSCRIPTIONAL BIOMOLECULAR CONDENSATES IN PROSTATE CANCER** Nicholas Pinette, Tian Hao Huang, Shabnam Massah, Maria Guo, Sofia Kochkina, Hanadi Ibrahim, Fan Zhang, Maitree Biswas, Alex Bembridge, Jane Foo, Joseph Lee, Artem Cherkasov, Jörg Gsponer, Nada Lallous

2:25 PM – 2:35 PM	**TREATMENT-INDUCED LYSOSOME PROTEASE LEGUMAIN PROMOTES THERAPY RESISTANCE IN PROSTATE CANCER** Kotaro Suzuki, Fan Zhang, Hans Adomat, Nicholas Nikesitch, Neo Wu, Ashley Tong, Julia Dyer, Hui Xue, Syam Somasekharan, Yuzhuo Wang, Martin Gleave
2:35 PM – 2:45 PM	**SCREENING SELECTIVITY OF PSMA TARGETING APTAMERS ON MURINE XENOGRAFTS** Nicole Robinson, Atsuhiko Yoshizawa, Laetitia Ganier, Pak Lok Ivan Yu, Kun Liu, Dogancan Ozturan, Sougata Dey, Mitali Pandey, Igor Moskalev, David Perrin, Nathan Lack1, Michael E. Cox, S Larry Goldenberg
2:45 PM – 2:55 PM	**CHARACTERIZATION OF THE PHASE SEPARATION OF THE ANDROGEN RECEPTOR (AR) AND ITS SPLICE VARIANT (AR-V7) IN PROSTATE CANCER** Shabnam Massah, Maria Guo, Nicholas Pinette, Hanadi Ibrahim, Fan Zhang, Maitree Biswas, Joseph Lee1, Jane Foo, Artem Cherkasov, Jörg Gsponer, Nada Lallous

ADJOURN

Podium Presentation – Abstracts

EVALUATING THE USE OF CIRCULATING TUMOUR DNA (CTDNA) IN UROTHELIAL CANCER PATIENTS IN THE CONTEXT OF FGFR-TARGETED THERAPY

David C. Müller1,2,†, Elena Schönlau3,†, Gillian Vandekerkhove1,3, Andrew J. Murtha1, Jack V.W. Bacon1, Connor Wells3, Kimia Rostin1, Gang Wang1,4, Sunil Parimi5, Jean-Michel Lavoie6, Krista Noonan6, Naveen Basappa7, Jenny J. Ko8, Daygen Finch9, Nimira Alimohamed10, Tarek A. Bismar10, Lucia Nappi1,3, Corinne Maurice Dror1,3, Matti Annala1,11, Cecily Q. Bernales1, Christian Kollmannsberger3, Kim N Chi1,3, Alexander W Wyatt1,12,‡, and Bernhard J. Eigl1,3,‡

1. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada
2. Department of Urology, University Hospital Basel, University of Basel, Switzerland
3. 3Department of Medical Oncology, BC Cancer, Vancouver, British Columbia, Canada
4. 4Department of Pathology and Laboratory Medicine, BC Cancer, Vancouver, British Columbia, Canada;
5. Department of Medical Oncology, BC Cancer, Victoria, British Columbia, Canada
6. Department of Medical Oncology, BC Cancer, Surrey, British Columbia, Canada
7. Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada;
8. Department of Medical Oncology, BC Cancer, Abbotsford, British Columbia, Canada
9. Department of Medical Oncology, BC Cancer, Kelowna, British Columbia, Canada
10. 10Department of Medical Oncology, Tom Baker Cancer Center, Calgary, Alberta, Canada
11. 11Prostate Cancer Research Center, Faculty of Medicine and Life Sciences and BioMediTech Institute, University of Tampere, Tampere, Finland
12. 12Michael Smith Genome Sciences Centre, BC Cancer, Vancouver, British Columbia, Canada; †/‡ - equal contribution

Background

Fibroblast growth factor receptor (FGFR) inhibitors (e.g., erdafitinib) are increasingly important in the management of FGFR-mutated urothelial carcinoma. FDA-approved archival tissue testing for specific FGFR alterations was implemented as a companion diagnostic for erdafitinib. However, longitudinal sequencing studies indicate variable tumor FGFR status over time, and erdafitinib resistance mechanisms in metastatic urothelial carcinoma (mUC) are underreported. This ongoing study aims to evaluate the accuracy of cell-free DNA (cfDNA) compared to archival tissue testing in mUC for FGFR alterations detection, and to evaluate genomic mechanisms of erdafitinib resistance in cfDNA at progression.

Methods

Patients undergoing archival tissue testing for FGFR alterations were eligible. Plasma cfDNA and matched leukocyte DNA were subjected to deep targeted sequencing with a custom panel including UC-specific gene loci and all clinically approved hotspots in FGFR1+2 and all exons and introns of FGFR3.

Results

Ad interim analysis, 109 patients from 6 sites were enrolled. Tissue and cfDNA results for comparison were available for 69 patients to date. Actionable FGFR alterations were found in the tissue of 15 patients (31%). 50 of the analyzed cfDNA samples had detectable somatic circulating tumor DNA (ctDNA) variant allele fraction of 0.5% (72%). Of those, 49 had an evaluable tissue test result. Analysis of this subset revealed high concordance (92%) between the two test methods. The four discordant results comprised one cfDNA test with undetectable FGFR3-TACC3 fusion, which was detected in tissue and three positive ctDNA test results in patients with FGFR wild-type tissue tests. In one case at erdafitinib progression, ctDNA revealed multiple subclonal populations with distinct FGFR3 gatekeeper mutations suggesting polyclonal resistance.

Conclusions

This ongoing study suggests cfDNA is a valuable minimally invasive adjunct to tissue-based assays for the detection of FGFR alterations to identify patients for FGFR inhibitor therapy and to monitor for mechanisms of resistance.

PROTEOMIC PROFILING OF MUSCLE INVASIVE BLADDER CANCER TREATED WITH PLATINUM-BASED CHEMOTHERAPY REVEALS UNIQUE BIOLOGIC CLUSTERS WITH CLINICAL RELEVANCE

Alberto Contreras-Sanz1, Gian L Negri2, Moritz J Reike1, Htoo Z Oo1, Sandra E Spencer Miko2, Karina Nielsen2, Morgan E Roberts1, Joshua Scurll1, Kenichiro Ikeda1, Chelsea L Jackson3, David M Berman3, Roland Seiler4, Gregg B Morin2, Peter C Black1

1. Vancouver Prostate Centre, Department of Urologic Sciences, Vancouver, Canada
2. Canada's Michael Smith Genome Sciences Centre, BC Cancer, Vancouver, BC, Canada
3. Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada
4. Department of Urology, Inselspital, University of Bern, Bern, Switzerland

Introduction

Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is recommended for muscle invasive bladder cancer (MIBC). However, only ~40% of patients show an objective pathologic response. While DNA alterations and RNA classifiers may predict response to NAC in retrospective studies, the proteome has not been evaluated in this context. Here we profiled the proteome of a NAC-treated MIBC cohort to identify markers of response and resistance to chemotherapy.

Methods

Pre-treatment tissue was included from 107 MIBC patients who received NAC followed by RC. Residual tumor (≥ypT1N0-3M0-1) was present in the RC specimen in 66 (62%) patients post-NAC. Multiregional tumor sampling was conducted in 37/107 pre-NAC samples. Proteomics was performed on formalin-fixed paraffin-embedded tissue (FFPE). Immunohistochemistry (IHC) validation was conducted on matched tissues.

Results

Unsupervised clustering of pre-NAC tissue established 4 clusters based on biology and survival outcomes, with no difference in response by pathologic stage. Clusters consisted of: CC1, with high metabolic activity and luminal profile; CC2 with high nuclear activity; CC3 with high immune infiltration and basal profile; and CC4 with high immune and stromal signatures. CC3 showed worse survival outcomes (p<0.01). Multivariable analysis identified novel favorable and unfavorable markers of survival. Matched analysis of pre- and post-NAC tissue showed markers indicative of resistance to NAC, as well as potential new druggable targets. In post-NAC (*i.e.* resistant) tumors we identified 4 clusters, and observed cluster switch was most common in the CC1 and CC4 pre-NAC groups. Multiregional proteomic analysis of histologically-similar pre-NAC tissue revealed that highly heterogeneous tumors are enriched for non-responders and have worse outcomes.

Conclusion

Here we describe pre- and post-NAC proteomic clusters with distinct biology and survival outcomes, alongside novel prognostic biomarkers and druggable targets. Future work will include a non-NAC cohort with pre-RC tissue to confirm the prognostic vs. predictive relevance of these findings.

A NOVEL APPROACH TO ENGINEERING THREE-DIMENSIONAL BLADDER TUMOR MODELS FOR DRUG TESTING

Monjaras-Avila, CU1; Luque-Badillo, AC1; Bacon, J1; Chavez-Munoz, C2*; So, A1,3*;

1. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Canada
2. Department of Medicine, Faculty of Medicine, University of British Columbia, Canada
3. Department of Urologic Sciences, Faculty of Medicine, University of British Columbia, Canada

Introduction and objectives

Muscle-invasive BCa is currently treated with radical cystectomy and neoadjuvant chemotherapy. One clinical limitation is the inability to predict which patients would benefit from chemotherapy and which tumors are inherently chemo resistant. There are some predictive tumor models to guide individual treatment, unfortunately, they do not fulfill all the requirements. This project aims to develop a 3D in vitro patient-derived BCa tumor model as a preclinical platform for drug testing and predicting personalized patient outcomes.

Methods

To engineer the 3D cancer model, BCa samples were dissociated into single cells and seeded into decellularized bladders. For genetic validation, we used targeted sequencing in patients and their corresponding engineered 3D tumors. The 3D BCa models from patients were treated with cisplatin and gemcitabine (Cis/Gem). The results were compared to their corresponding BCa patient chemotherapy outcome.

Results

We have established a protocol for decellularizing pig bladders. Decellularization was evaluated by histology, SEM and DNA quantification. The model was first developed using UMUC3 cells for drug treatment optimization as a proof of principle. Further experiments we have done using human BCa patient cells to recreate BCa tumor in vitro. Our model demonstrated to keep genetic mutations from the parental tumor showing genetic validation. The response to treatment varies in each patient, but when we compare with the clinical outcome of each patient our model has an 83% reliability, better than 2D and 3D culture from the same patient cells.

Conclusions

This 3D patient derived BCa model will enable us to generate many in vitro avatars to accurately recreate the tumor of a patient, and simultaneously screen for suitable personalized drugs treatments.

ROLE OF URINARY AND GUT MICROBIOTA ON BACILLUS CALMETTE-GUÉRIN-INDUCED RESPONSES IN NON-MUSCLE INVASIVE BLADDER CANCER

Dalia Othman1, Tuomas Jalanko1, Moritz Reike1, Igor Moskalev 1, Breanna Nelson1, Ali Hussein1, Carin Tin1, Mathieu Roumigué1, Sheryl Munshan1, Felipe Eltit1, Demian Ferreira1, Alberto Contreras-Sanz1, Moritz Maas1, Aaron Miller2, Peter Black1 and Dirk Lange1

1. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia
2. Lerner Research Institute, Department of Cardiovascular and Metabolic Sciences, Cleveland Clinic

Introduction

Bladder cancer is the fifth most common cancer in Canada. The gold-standard treatment for non-muscle invasive bladder cancer (NMIBC) is Bacillus Calmette-Guérin (BCG). However, 40% of patients recur despite optimal therapy. Since commensal microbiota affect immune responses, we hypothesize they modulate BCG-induced anti-tumor responses. The study objective is to examine the role of urinary and gut microbiota in BCG-induced immune responses.

Methods

Urine and stool samples were collected from NMIBC patients before and after BCG treatment to identify microbiota composition through metagenomic sequencing. To assess the role of urinary microbiota on BCG-induced immune response, mice underwent BCG instillation into the bladder lumen. Mice had either a healthy or a disrupted urinary microbiota. Disruption was achieved through gentamicin instillation prior to BCG treatment. Fluorescence-activated cell sorting (FACS) and histology was conducted to examine immune cells.

Results

16s rRNA sequencing demonstrated non-responders were associated with *Pseudomonas,* which metabolize Polycyclic Aromatic Hydrocarbons (PAH). *In vivo* FACS analysis of tissue observed shifts in immune cells. Gentamicin instillation induced a pro-inflammatory environment compared to control. Subsequent BCG treatment shifted the environment towards an anti-inflammatory response, similar to mice with healthy microbiota.

Conclusions

BCG non-responders were associated with PAH metabolism, a major component of cigarettes. *In vivo* studies illustrated that disruption of the urinary microbiota alters the immune cell environment which shifts with BCG treatment, suggesting role of the microbiota in mediating BCG-induced response.

ADVERSE EVENTS ASSOCIATED WITH ELECTROMOTIVE DRUG ADMINISTRATION OF MITOMYCIN

J Ma1, LM Jonat2, S Faddegon2, DP Ottem2, PC Black1

1. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, Canada.
2. Department of Urology, Royal Inland Hospital, Kamloops, Canada.

Introduction and Objectives

The gold standard treatment of high-risk non-muscle invasive bladder cancer (NMIBC) includes induction and maintenance intravesical Bacillus Calmette-Guerin (BCG) thereapy. However, one prospective trial has demonstrated improved outcomes with electromotive drug administration of mitomycin-C (EMDA-MMC) in conjunction with BCG, compared to BCG alone. In this study, we report safety and efficacy of EMDA-MMC with BCG.

Methods

This retrospective observational study from two centers included patients who received EMDA-MMC and BCG for high risk NMIBC after Jan 1, 2011. High-risk was defined as high grade Ta, CIS, T1, or all of: multifocal, recurrent, >3cm tumors. Time to recurrence was defined as the time from diagnostic TURBT showing high risk disease preceding initiation of intravesical therapy, to pathological confirmation of recurrent high-grade bladder cancer. Adverse effects were defined as CTCAE v5.0 grade ≥3.

Results

Among 62 patients included, 37 (60%) were from Vancouver, 8(13%) were female, and the median age was 68.5 years. The median follow-up was 61 months and a high-grade recurrence was observed in 29(47%) patients. Mean time to recurrence was 26 months. Nine (15%) patients progressed to T≥2 disease and 12 (24%) underwent cystectomy. Eighteen (29%) patients experienced adverse effects following treatment, while 38 (61.3%) patients demonstrated some evidence of longstanding bladder injury on cystoscopy including erythema, necrosis, or inflammation. An additional 11 patients who received EMDA-MMC alone without BCG were assessed for adverse effects. Six of these patients experienced an adverse event, and ten had evidence of chronic bladder injury.

Conclusion

Treatment with EMDA-MMC and BCG results in outcomes comparable to historical outcomes of BCG alone. This treatment is, however, associated with a high rate of long-term local bladder toxicity resulting in chronic lower urinary tract symptoms. The incidence of bladder toxicity appears to be even higher in those that were treated with EMDA-MMC alone. Additional prospective evaluation of EMDA-MMC is required before widespread adoption.

FBXW7 LOSS-OF-FUNCTION CONTRIBUTES TO WORSE OVERALL SURVIVAL AND IS ASSOCIATED WITH ACCUMULATION OF MYC IN MUSCLE INVASIVE BLADDER CANCER

Ruiliang Wang1, Takashi Matsumoto1, Elaine Chen1, Morgan E. Roberts1, Moritz Reike1, Kenichiro Ikeda1, Htoo Zarni Oo1, Takeshi Sano1, Eric LeBlanc1, Kriti Singh1, Jian Gao1, Igor Moskalev1, Alberto Contreras-Sanz1, Peter C. Black1

1. Vancouver Prostate Centre, Department of Urologic Sciences, Vancouver, Canada

Introduction

Muscle invasive bladder cancer (MIBC) has the third highest mutation rate of any solid tumour. FBXW7, which is involved in the proteasome degradation of oncogenic proteins including MYC, is one such frequently mutated (8.5%) gene in MIBC. In other cancers, loss-of-function mutations or decreased expression have oncogenic potential and are associated with poor prognosis. Here, we investigate the role of altered *FBXW7* function and the relationship to oncogenic mechanisms in MIBC.

Methods

The MSK-IMPACT and TCGA2017 MIBC cohorts were queried for *FBXW7* genomic alterations and mRNA expression levels in relation to clinical outcomes. *FBXW7* was knocked out in basal (UM-UC3) and luminal (RT112) bladder cancer cell lines. Two *FBXW7* hotspot-mutations (R479G and R505G) were introduced to explore their functional relevance. Phenotypic assays, downstream pathway analysis, and pharmacologic inhibition of the FBXW7-MYC axis were carried out on these cell lines.

Results

Low expression or genomically altered *FBXW7* was associated with shorter patient survival and enriched MYC signalling pathways. In cell lines, *FBXW7* knock-out (KO) led to increased MYC and cell cycle mRNA expression (CCNE1, CCND1, CDK2, CDK4 and CDK6). Re-transfection of a wild-type FBXW7-coding plasmid in these KO cell lines normalized MYC and cell cycle gene expression. Transfection of R479G and R505G mutants in KO-UC3 retained the KO-induced phenotype and downstream effects compared to its wild-type rescued control. We con□irmed the enhanced sensitivity of FBXW7-de□icient (mutated and KO) cell lines to MYC inhibition (MYCi) via two different compounds (in-house VPC70619, and KSI-3712).

Conclusion

Our □indings suggest that *FBXW7* plays a tumor suppressive role via MYC in MIBC. *FBXW7*-mutated tumors have high MYC activity that can be successfully abrogated pharmacologically *in vitro*, which suggests that MYCi may be a novel rational treatment strategy for selected *FBXW7*-alterated tumors. *In vivo* validation of these □indings is ongoing in orthotopic bladder cancer murine models.

INCIDENCE OF PELVIC SECOND MALIGNANCIES IN PROSTATE CANCER PATIENTS TREATED WITH LOW-DOSE-RATE BRACHYTHERAPY AND RADICAL PROSTATECTOMY AT EXTENDED FOLLOW-UP

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Introduction and Objectives

Second malignancy (SM) from radiotherapy (RT) is a rare but concerning risk. Data remains scarce on the risk associated with prostate brachytherapy (BT) monotherapy. Our study aims to analyse long term risk of SM following BT compared to radical prostatectomy (RP).

Methods

This study represents a long-term follow-up of a previously published cohort of patients treated with LDR 125I prostate BT monotherapy at BCCA from 1999 to 2010. The population-based cohort includes patients treated with either BT or RP, (the RP patients include RP who received adjuvant/salvage external bean RT (EBRT)). SM and mortality data was obtained from the BC population cancer registry and linked via the patient's identification number. Cox multivariate analysis for initial treatment type, age, smoking status (smoking status was imputed when unknown) were performed.

Results

Between 1999 to 2010, a total of 2378 patients treated with BT and 9089 patients with RP were included. Median age was 66 years old (IQR 61-71) in the BT group and 63 years old (IQR 58-67) in the RP group. Follow-up was obtained until censor date (12/31/2020), making the potential follow-up 10 to 22 years. Median time from initial treatment to next malignancy was 13 years. Smoking status at diagnosis was known for 94.6% of BT and 37.6% of RP patients. Of those with known status, 59.3% of BT, and 54.6% of RP were previous/current smokers. In Cox-multivariate analysis, there was a significant increase in pelvic SM in the BT group compared to RP (HR 1.81 [95% CI 1.45-2.26], p <.0001), and invasive pelvic SM (HR 2.13 [95% CI 1.61-2.83], p<.0001). Age and smoking status were also associated with increased risk ($p<0.05$). Time to any type of SM and time to death from any SM were not significantly different ($p>0.05$). The absolute risk of first invasive pelvic SM at 15 and 20 years were 4.3% and 6.5 % in the BT group, and 1.9% and 2.2% in the RP group.

Conclusion

After adjusting for age and smoking status, long-term risk of pelvic and invasive SM is increased for patients treated with BT compared to RP, even with inclusion of patients who had post-RP EBRT.

MACHINE LEARNING-BASED DECISION SUPPORT SYSTEM TO DISTINGUISH URIC ACID STONES IN PATIENTS WITH KIDNEY STONES OF 'GREY ZONE' HOUNSFIELD UNITS: INTERNATIONAL MULTICENTER DEVELOPMENT AND EXTERNAL VALIDATION STUDY

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Purpose

Correct differential diagnosis of uric acid (UA) stones has important clinical implications since patients with a high risk of perioperative morbidity may be spared with surgical intervention and be offered alkalization therapy. We developed and validated a machine learning-based autonomic decision support system (DSS) to distinguish UA stones in patients with kidney stones of Hounsfield units (HU) <800.

Methods

An international, multicenter, cross-sectional study was performed on 176 patients who received percutaneous nephrolithotomy for kidney stones with HU <800. Data from 136 (77.3%) patients were used for model training, validation, and testing (ratio 8:1:1), while data from 40 (22.7%) patients from a transnational institution with distinct ethnic backgrounds were used for external validation. Demographic and clinical data consisted of 30 features that were potentially associated with stone components. A total of 14,843 kidney and stone contour-annotated computed tomography (CT) images were trained with the ResNet-18 Detectron2 Mask R-convolutional neural network algorithm to delineate renal anatomy and kidney stones and to measure stone features. Finally, the model was interpreted using the SHAP algorithm to enable visual interpretation of the association between the variables and model output.

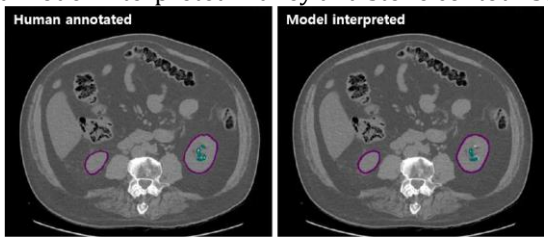
Results

There were no significant differences in demographic and clinical features between the development and external validation cohorts. Our model was 100% sensitive in detecting kidney stones in each patient. The delineation of kidney and stone contours was precise within clinically acceptable ranges (Figure 1). The development model provided an excellent predictive performance of 95.9% with 92.9% sensitivity and 97.1% specificity. On external validation, the model's prediction accuracy remained within a clinically acceptable range of 87.9% with 66.7% sensitivity and 92.6% specificity. SHAP plots revealed stone density, diabetes mellitus, and urinary pH to be the important features for distinguishing UA stones.

Conclusions

Our development and external validation study show that an automated DSS can conveniently identify and delineate kidney stones and distinguish UA stones from other component stones within the 'grey zone' Hounsfield units. Our DSS can be reliably used to select candidates for an earlier-directed alkalization therapy.

Figure 1. Human-annotated and model-interpreted kidney and stone contour segment of a sample patient



BREAK WAVETM LITHOTRIPSY FOR UROLITHIASIS: RESULTS OF THE FIRST-IN-HUMAN INTERNATIONAL MULTICENTER CLINICAL TRIAL

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Introduction

Break Wave lithotripsy is a new non-invasive technology for the treatment of urolithiasis that can be performed with little to no anesthesia, potentially allowing stone treatment in non-operative settings. This study reports safety, efficacy, and anesthesia requirements from a first-in-human, prospective, multicenter, open-label single-arm clinical trial (NCT03811171) utilizing the SonoMotion (San Mateo, CA) Break Wave device.

Methods

Forty-four (44) patients with ureteral or renal stones were treated across five North American centers (US/Canada) between 08/2019 – 02/2022. Patients were recruited and treated in the operating room, office/clinic, or emergency department (ED). Thirty minutes of Break Wave therapy was delivered under continuous ultrasonography targeting. Varying therapy dose levels up to 8MPa of acoustic pressure were administered and safety, effectiveness and anesthesia requirements were assessed to establish optimal dose settings. The efficacy objective was stone free rate or fragments ≤ 4 mm assessed via non-contrast CT at 8-12 weeks by an independent radiologist. Patients were followed for 90 days with all adverse events (AEs) recorded.

Results

Target stones were in typical locations and sizes (Table 1) with 59% renal (n=26) and 41% in the distal ureter (DU) (n=18). No serious AEs, hematomas, cardiac arrythmia or sepsis occurred at any dose level. Overall, 86% of subjects received either no medication (50%) or minor analgesia (36%) (e.g., ketorolac 15-30mg). All patients completed the procedure. Stone fragmentation occurred in 88% of cases, with 70% of subjects being either completely stone free or with fragments ≤ 4 mm on CT. The retreatment rate was 7% within 90 days with either SWL or URS. The optimal dose setting was identified and delivered to 36 of 44 patients. Of these 36 patients, 75% had fragments ≤ 4mm and 58% were completely stone free, 71% of lower pole patients (n=14) had fragments ≤ 4mm with 29% stone free, and 89% of DU patients (n=18) were completely stone free.

Conclusion

Break Wave Lithotripsy appears to be a safe and effective non-invasive stone therapy requiring little to no anesthesia. It is potentially suitable for non-operative environments such as the office or ED and is being evaluated in ongoing trials.

THE ROLE OF THE MICROBIOME AND SHORT CHAIN FATTY ACIDS IN KIDNEY STONE DISEASE

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Introduction and Objectives

Microbiome dysbiosis is suggested as a risk factor for kidney stone disease (KSD). As such, a few studies have reported that individuals with KSD tend to have a lower abundance of intestinal butyrate-producing bacteria. Our study aims to examine the role of microbederived short chain fatty acids (SCFAs), such as butyrate, in calcium oxalate (CaOx) kidney stone formation. We hypothesize that SCFAs modulate oxalate homeostasis to reduce hyperoxaluria, and thus is preventative for kidney stone formation.

Methods

To test our hypothesis, we used a novel diet-induced *in vivo* murine model of hyperoxaluria to assess the effect of supplementing inulin (prebiotic) and tributyrin (butyrate precursor) in combination with oxalate on CaOx crystal formation. Urine, blood, and stool samples were collected for oxalate measurements, and microbiome analyses. Renal and intestinal tissues were collected to measure expression of oxalate transporters, expression of inWlammatory markers, and histology.

Results

Histology results indicate efWicacy of our *in vivo* model, speciWically showing renal calcium oxalate crystal formation in mice on the high oxalate diet. Supplementation of tributyrin in animals fed a high oxalate diet resulted in a signiWicant decrease in CaOx crystal formation versus animals on the oxalate diet alone ($p<0.0001$). Urinary oxalate levels were signiWicantly higher in animals fed the combination tributyrin + oxalate diet, versus that of animals on the oxalate diet alone ($p<0.05$).

Conclusions

Tributyrin appears to attenuate crystal formation in mice that are on a high oxalate diet and may do this by modulating oxalate transport. Findings from this study may provide insight into the etiology of KSD, and inform the development of novel diet-based strategies to prevent KSD.

ENVIRONMENTAL PERFORMANCE OF KIDNEY REPLACEMENT THERAPIES: COMPARATIVE LIFECYCLE ASSESSMENT OF DIALYSIS AND KIDNEY TRANSPLANTATION

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Introduction and Objectives

Healthcare delivery associated with a considerable amount of greenhouse gas (GHG) and other pollutant emissions. End-stage kidney disease (ESKD) is often treated with resource-intensive kidney replacement therapies (KRTs). Although various KRT's relative health and economic impacts have been examined, their environmental impacts have received little attention. This study aims to assess the environmental performance of primary modes of KRTs in British Columbia, Canada.

Methods

A process-based life cycle assessment study was performed on 3 KRTs: (i) deceased donor kidney transplantation (DDKT), (ii) incentre hemodialysis (HD), (iii) and automated peritoneal dialysis (PD). Environmental impact related to energy and material consumption per therapy/ patient/ year was quantitatively evaluated by lifecycle assessment tool, SimaPro (version 8.3.0.0).

Results

The results declared that out of 18 environmental impact categories, 14 are highly impacted by the HD, followed by PD and DDKT. HD and PD had considerably higher climate impact (3960 and 1370 kgCO2eq/person/year respectively) than DDKT. Patient and staff commute in HD, waste management in PD, and energy consumption in DDKT were the highest contributors to these environmental impacts.

Conclusion

The study demonstrates a considerable disparity in environmental impacts across different modes of KRT, with DDKT associated with the least environmental impact. When comparing dialysis modalities, PD is more environmentally preferable than HD and could be considered for more prevalent use. In combination with existing clinical and economic data, these results could enlighten policy and decision-makers to optimize the delivery of chronic kidney care.

FEASIBILITYOFCREATINGANUP-TO-DATE, TRANSPLANT FOCUSED COUNSELING AI CHATBOT

Rohit Malyala, Christopher Nguan
Department of f Urologic Sciences, University of British Columbia

Transplantcounsellingisanessentialcomponentofthecareforpatientsinneedoftransplantservices.However,providingtimelyandaccurateinformationtopatientscanbechallenging,particularlygiventheconstantlyevolvingdomain-specificdata.Toaddressthisissue,wehavedevelopedanopen-source,self-hostableChatGPT-basedchatbotaimedatprovidingaccurate,timely,andregion-specificchatanswersfromtheChatGPTlargelanguagemodel.OurapplicationusestheOpenAIAPIwiththegpt-3.5-turbomodel,enablingittoprovidepatientswithasmoothandconsistentlarge-languagemodelchatinterface.Ourchatbotworksbyfirstuploadingavastconcourseofdiscretefacts,inquestionandanswerform,tothewebsite.Whenauserentersaquery(e.g.whatarethewaittimesforatransplantinBC?),thechatclientcomparesthequestiontoeachofthefactsintheconcourseandranksthembasedontheirsimilaritytothequestion.Thetopthreemostrelevantfactsarethenfedtothemodelasasystempromptinadvanceoftheactualquery.TheChatGPTmodelthenprovidesananswertothepatientbasedontheselectedrelevantfacts,ensuringthatpatientsreceiveaccurate,locallyrelevant,andup-to-dateinformation.Ourdeploymentisopen-sourceundertheGPL-3license.ItcanbehostedforfreefromGitHubpages.ProspectiveuserscanbringtheirownAPIkey,whichcanbeobtainedbymakinganaccountwithOpenAI.Furthermore,themodeliscost-effective,witheachpromptcostinganaverageoflessthan$0.0010perexchange.Nextstepsincludevalidationandreliabilityassessmentoftheappthroughpatientandclinicianfeedback,andextendingtheprojecttowardsotherdomainsinurology.

EVALUATING DIFFERENT METHODS FOR KIDNEY RECELLULARIZATION

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Introduction and Objective

In Canada, end-stage renal disease (ESRD) has been increasing by 31% over the last 10 years and representing a healthcare burden. Kidney transplant is the gold-standard treatment for ESRD. Unfortunately, the number of available organs for transplantation is not enough. Tissue engineering has emerged as an alternative solution for organ shortage; the extracellular matrix (ECM) obtained from decellularized organs maintain the organ's microarchitecture and bioactive molecules that aid in the recellularization process. However, complete organ repopulation has not been accomplished. Therefore, current study aims to evaluate different methods for kidney recellularization that can potentially be functional for transplantation.

Methods

Pig kidneys were decellularized using our established protocol. The ECM and the primary kidney cells (WKPC) were characterized. A whole pig kidney was recellularized by perfusion with WKPC for 12 days using an in vitro bioreactor and applying negative pressure. Human erythrocytes were perfused along with media to increase the oxygenation inside the organ.

Results and Conclusions

I have successfully decellularized a pig kidney in 46 hours. A complete cell removal was obtained, preserving the organ's ECM while retaining growth factors and structural proteins. In the histological evaluation of the recellularized kidney, a higher density of cells can be observed compared to previous publications. The media analysis did not reveal signs of cell death. Furthermore, we could show cell colonies expressing kidney cell markers in almost all areas of the kidney. This research will enable us to perform proof of principle of this technology that could be translated into reseeding human kidneys.

A COMPARISON OF ACCURACY AND READABILITY FOR COMMON PATIENT QUESTIONS REGARDING SMALL RENAL MASSES BETWEEN ARTIFICIAL INTELLIGENCE AND ACCREDITED PATIENT INFORMATION MATERIALS

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Introduction

Artificial intelligence (AI) has provided an alternate platform for patients to ask health-related questions which may influence patient care decisions. Patient Information Materials (PIMs) from accredited bodies such as the CUA, AUA, and EAU are often provided to patients for independent reading. ChatGPT has recently emerged as an open-access AI platform which provides outputs in plain language. We compared the accuracy and readability of ChatGPT's outputs compared to PIMs published by accredited bodies regarding a diagnosis of a small renal mass (SRM).

Methods

The most common clinical questions asked by patients were identified regarding SRMs. ChatGPT was used to identify which questions were asked most frequently. Questions were cross-referenced against PIMs to ensure the validity, and were input directly into ChatGPT. Two independent reviewers assessed the accuracy of each response using accredited PIMs as ground truth (1=inaccurate, 5=accurate). Readability scores were assessed for each ChatGPT response along with the CUA PIM for comparison, using standardized SMOG and Gunning Fog readability assessments.

Results

Readability scores ranged from 11.58 – 18.46, and 8.81 – 19.78 on the SMOG and Gunning Fog scales, respectively. Accuracy assessment for ChatGPT answers regarding general information, treatment options, and long-term care scored 4.5, 4.72, 4.42, respectively, indicating accurate information with minor detail omitted. On average, the CUA PIM was more "readable" compared to the ChatGPT outputs. All categories were found to have a statistically significant difference in readability, favoring the CUA PIM.

Conclusions

Overall, ChatGPT provided accurate answers that omitted minor detail to common patient questions regarding SRMs. ChatGPT answers did not compare favorably to the CUA PIM regarding readability. ChatGPT provides a novel way to access information from a patient perspective, but it should not replace PIMs from accredited institutions such as the CUA. Limitations to the information provided by ChatGPT are important to understand by clinicians to appropriately counsel patients.

…/continued on page 22

ChatGPT	Mean Accuracy	SMOG	Gunning Fog	Mean Grade
General information	4.50	14.60	15.17	14.89 [14.50 - 15.28]
Treatment options	4.72	16.09	17.01	16.55 [15.9 - 17.2]
Long-term care	4.42	13.30	14.10	13.70 [13.13 - 14.27]

Table 1: Accuracy and Readability for ChatGPT answers for common patient questions regarding small renal masses

CUA PIM	SMOG	Gunning Fog	Mean Grade
General information	12.5	13.595	13.60 [12.83 - 14.37]
Treatment options	14.8	15.28	15.28 [14.94 - 15.62]
Long-term care	12.88	12.885	12.89 [12.88 - 12.90]

Table 2: Readability for the CUA PIM regarding small renal masses

EVALUATING THE EFFECTIVENESS OF RENAL BIOPSY INNOVATIONS: A SYSTEMATIC REVIEW OF THE LITERATURE

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Introduction and objectives

Percutaneous core renal biopsy (PCRB) plays an important role assessing intrinsic renal disease and renal masses. The safety profile of PCRB is well-studied. However, the documented diagnostic effectiveness of PCRB is variable; PCRB has a non-diagnostic rate ranging from 10-40%. PCRBs may be improved by assessing PCRB innovations. This systematic review aims to present PCRB innovations.

Methods

A systematic search was conducted on Medline, Embase, and Web of Science, while additional articles were identified through PubMed searching. No exclusions were made on age, gender or biopsy indications. Review articles, non-English written articles, animal studies, or articles discussing one PCRB modality were excluded. The Joanna Briggs Institute critical appraisal tools were used for quality assessment. The primary outcome was diagnostic accuracy associated with PCRBs. Secondary outcomes included the safety and efficiency of PCRBs

Results

A total of 1,553 articles were found, 24 were included in this review. Papers were thematically analyzed into four themes including needle size, imaging innovations, technique comparison, and ultrasound-guided versus blind biopsy. Eight studies were included under the needle size theme. Our results highlight the 16G needle optimizes diagnostic yield and complications. In the imaging innovation section, three articles were included. Our search demonstrates that cone beam CT navigation may increase diagnostic efficiency, while reducing ionizing radiation exposure. Eight articles were included in the technique comparison theme. The coaxial technique appears to optimize diagnostic yield, complications, and efficiency. Five studies were included in the ultrasound-guided versus blind biopsy theme. Ultrasound guidance is superior to blind biopsies in optimizing diagnosis and complications. Following quality assessment, all studies were assessed to be eligible for inclusion in this review.

Conclusions

In summary, these studies described various innovations in PCRBs. Imaging modalities have provided the majority of innovations in PCRBs, while pathologic advances are limited to date.

PREVALENCE OF PREVIOUSLY UNDIAGNOSED PSYCHIATRIC SYMPTOM GROUPINGS IN PEDIATRIC PATIENTS WITH BLADDER AND BOWEL DYSFUNCTION (BBD)

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Introduction and Objective

The incidence of concomitant psychiatric disorders in conjunction with BBD is thought to be higher than the general population. The identification of these disorders with validated tools followed by management may improve urological outcomes. The objective of this study was to determine the prevalence of psychiatric symptom groupings in patients presenting with BBD.

Methods

Consecutive patients 6-18 y.o. with a clinical diagnosis of BBD (score ≥11 on the Vancouver Symptom Score (VSS)) and no prior psychiatric diagnosis were recruited. Two validated questionnaires (Child Behavior Checklist for Ages 6-18 (CBCL) and Autism Spectrum Quotient 10 items (AQ-10)) were used to screen for psychiatric comorbidities. Distribution of VSS for normal & abnormal categories (borderline/clinical) of CBCL scores were compared, and the relationship between VSS domain scores and CBCL was examined.

Results

From Sept 2017-May 2022, 50 (17 male) of 110 eligible patients completed the study. Median VSS was 18 (11-33), indicating significant BBD. In 36 patients (72%), at least one of the CBCL subscales scored as borderline/clinical. Thirty-two patients (64%) scored in the abnormal range for Internalizing symptoms, 21(42%) for Externalizing symptoms, and 31(62%) for Total problem scores. Four patients of 48(8%) scored > 6 on the AQ-10. The only significant correlation found between CBCL and VSS sub scores was with the Bowel Habit Domain of VSS and Internalizing CBCL T-scores (P=0.02).

Conclusion

This study shows a high prevalence of previously undiagnosed psychiatric symptom groupings in patients presenting with BBD, with a higher prevalence internalizing and externalizing symptoms and autism traits than reported in the general population. These findings should encourage urologists to use validated tools to screen for psychiatric comorbidities with referral for further assessment as appropriate. This may prevent unnecessary testing, save valuable health resources and potentially improve treatment outcomes of BBD in this population.

OUTCOMES USING A NOVEL TENSION RELIEVING HITCH IN MICROSURGICAL VASECTOMY REVERSALS

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Introduction

Vasectomy reversals (VR) are commonly performed microsurgical procedures Tension on the anastomosis is believed to be a contributing fa ctor to failure. This study reports VR outcome s using a novel technique introducing a tension reliving hitch in the multi-layer microdot vasovasostom y (VV) procedure, Longitudinal Intussuscepted Vasoepididymostomy (VE) and mixed VV+V E procedures.

Methods

All vasectomy reversal patients since 2018 were reviewed Inclusion criteria included d patients who underwent a VR with at least one semen analysis within 6 months of surgery and a minimum of 6 months of follow-up after the surgery to deem a failure. Primary outcome was patency defined classically as any sperm in the ejaculate, and functionally as at least 2 million motile sperm. Late failure is defined as the disappearance of sperm in the semen after previously documented presence

Results

A total of 1 41 patients underwent a vasectomy reversal between May 2019 and March 2023 1 1 0 patients met inclusion criteria. The patency rate among all VRs VV, VE s and mixed VV VE s) was s 9 7.2 %%. The overall functional patency rate was 91.1 % 80 patients underwent bilateral VV s with a 98. 7 % patency rate and 93.9% functional patency rate. The mean time to achieve patency was 81 4 days. Only 4 patients had a late failure. 20 patients underwent a mixed VV+VE procedure. Patency rates were 100%, while functional patency rates were 88 The mean time to patency was 76.8 days respectively. 10 patients underwent bilateral VE s. Patency was 80% while functional patency was 77.7% The mean time to patency was 8 3.6 days. No late failures were identified. The time to either patency definition based upon microscopic fluid evaluation were comparable.

Conclusion

We report the novel use of a tension relieving hitch for both VV s and VE s. Patency results are among the highest reported in the literature.

DIFFERENTIATION OF HUMAN PERITUBULAR MYOID-LIKE CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS

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Introduction and Objectives

Peritubular myoid cells are a type of contractile muscle cell critical to the production of sperm in the testis. During testis morphogenesis they arise from the intermediate mesenchyme and surround the seminiferous tubules where spermatogenesis takes place. Their dysfunction is associated with infertility but not well understood. In vitro models to study myoid cells are limited due to access to human testicular tissue. To address this need we set out to define a method for generating peritubular myoid cells in vitro using human induced pluripotent stem cells (hiPSCs).

Methods

Two hiPSC lines were subjected to in vitro culture with a program of growth factors and hormones mimicking in vivo testicular morphogenic signaling for 4 weeks. They were evaluated by whole transcriptome profiling and immunocytochemistry. Testicular myoid cells were isolated from a healthy patient as a positive control. The derived myoid cells were incorporated into an hiPSC-derived multi-cellular testicular organoid model to determine their effect on tissue-like organization.

Results

During differentiation the derived myoids upregulated gene expression necessary for gonadal tissue development and hallmark peritubular myoid functionality including specific secreted growth and matrix factors, smooth muscle function, and integrin and receptor expression. Hierarchical clustering showed acquisition of transcriptomes similar to primary control myoids, and immunostaining for alpha actin smooth muscle further confirmed the acquisition of a smooth muscle phenotype. Organoid modeling showed that the presence of hiPSC-myoids was required for organization into cystic tissues.

Conclusions

These hiPSC-derived peritubular myoid cells can be used for in vitro study of testicular tissue development and function. Future personalized-medicine approaches could be employed to model patient-specific in vitro testis avatars through derivation of these cell lines from a simple blood sample.

FUNCTIONALIZING XENO-FREE BIOINKS TO PROMOTE TESTICULAR CELL GROWTH IN 3-D BIOPRINTED TESTICULAR MODELS

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Introduction and Objectives

The differentiation of sperm, termed spermatogenesis, is coordinated by somatic cells within the seminiferous tubules of the testis niche. Human in vitro models of spermatogenesis are needed as experimental tools to develop novel therapeutic platforms to treat infertility. However, in vitro microenvironments supportive of testicular tissue regeneration have yet to be established. In this study we targeted one aspect of optimizing a supportive in vitro microenvironment using 3-D bioprinting. We explored the use of xeno-free bioink components incorporating either natural extracellular matrix proteins or recombinant matrix motif peptides for their ability to support human testicular cells in terms of viability and tissue-like growth.

Methods

Human testicular cells were bioprinted into microfibers using the Cellink BioX6 extrusion printer fitted with a 26-gauge stainless steel needle (254 μm inner diameter). Bioprints were cultured for 7 days and assessed for viability by live dead staining, as well as cell-matrix interactions by immunostaining for cytoskeletal components F-actin and beta-tubulin.

Results

Cell viability and attachment was significantly improved in the bioinks with recombinant matrix motif peptides over the natural matrix proteins. Bioinks which incorporated metalloproteinase degradable peptides or laminin motif peptides were the most mechanically stable and consistent bioinks to print. Incorporation of the fibronectin motif peptide proved to be the best for cell-matrix interactions within the bioinks.

Conclusions

Our results illustrate the promise of synthetic xeno-free bioinks to improve printability and cell growth in human testicular cells. These results will contribute to customizing the bioink required for optimizing in vitro testicular cell function, organization and communication within the spermatogenic niche.

CHARACTERIZING AND TARGETING THE INTERPLAY BETWEEN THE BAF CHORMATIN REMODELING COMPLEX AND THE LINEAGE-DETERMINING TRANSCRIPTIOIN FACTOR ASCL1 IN PROSTATE CANCER LINEAGE PLASTICITY

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Introduction and Objectives

Prostate cancer (PCa) cells can become independent of AR signaling and resist androgen deprivation by acquiring an alternative lineage, activating stem and neuronal programs. This lineage plasticity leads to neuroendocrine PCa (NEPC). Chromatin accessibility data from our lab indicates an epigenetic basis of NEPC with widespread chromatin rearrangements. Interesting, increasing evidence has pointed to the deregulation of the Brg/Brahma-associated factor (BAF) complex, an ATP-dependent chromatin remodeler, to correlate with NEPC development and progression.

Methods

A PROTAC degrader of BAF ATPases (BRM and BRG1) was tested and used in NEPC models to investigate the role of BAF in PCa lineage plasticity. RNA-seq was performed for matched control and treated NEPC cells to evaluate changes in the expression of major stemness and neuroendocrine markers. Functional analyses on ALDH activity and cell surface marker expression were carried out as further validations. ATAC-seq, ChIP-seq, and RIME were conducted on BRG1 to explore chromatin dynamics and interrogate BRG1 interactome during lineage plasticity.

Results

RNA-seq indicates that BRG1, as opposed to its mutually exclusive counterpart BRM, is enriched in NEPC cell lines and patients, and correlates with high expressions of ASCL1, a master neuronal lineage-determining transcription factor that we have previously shown to drive PCa lineage plasticity. Targeting BAF ATPases prevents neurite development in castration resistant PCa cell lines and depletes ASCL1 expression within 24 hours. ATAC-seq and ChIP-seq revealed that BRG1 and ASCL1 co-occupy accessible regions of chromatin flanked by H3K27ac histone marks, with 2,685 co-bound genes regulating stemness and neuronal programs.

Conclusions

BAF subunits are deregulated during PCa progression, with a higher expression of BRG1 correlating with NEPC. Targeting BAF reverts the ENZ-induced phenotypic changes and activation of neuronal programs observed in NEPC. BAF inhibition also diminishes the expression and activity of ASCL1, pointing to a potential co-operation between these two factors at the epigenetic level. Continuing work will aim to elucidate the molecular mechanism by which BAF and ASCL1 co-operate to drive PCa lineage plasticity.

CHARACTERIZATION OF ANDROGEN RECEPTOR PROPERTIES IN MEDIATING TRANSCRIPTIONAL BIOMOLECULAR CONDENSATES IN PROSTATE CANCER

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Introduction & Background

Prostate cancer (PCa) is the leading diagnosed cancer among Canadian men. The main driver of PCa is the androgen receptor (AR), a ligand activated transcription factor that contains three domains: N-terminal domain (NTD), DNA-binding domain (DBD), and the ligand-binding domain (LBD). The NTD of AR is intrinsically disordered and plays an essential role in mediating the formation of condensates. These condensates contain players of the transcriptional machinery and enhances transcription of key oncogenes in various cancers, including PCa. Recently we demonstrated that full-length AR is more prone to form nuclear condensates upon androgen stimulation in PCa models than in benign epithelial prostate models. However, the details of this mechanism are still unknown.

Methods

We used bioinformatics tools to predict AR residues/regions with high propensity for condensate formation and created the corresponding mutants/truncations and evaluated them in LNCaP cells. Starved cells were transfected with wild-type or mutated/truncated AR tagged with mEGFP. After 48h, cells were treated with 1 nM DHT for 2h, fixed and visualized by confocal microscopy. We used recombinant full-length AR-mEGFP-MBP-His, OFPSpark-WT-MED1-IDR, and OFPSpark-T1457D-MED1-IDR to evaluate the role of MED1 and its phosphomimic on AR's ability to form droplets *in vitro* in the presence of 10% PEG 8K. We also evaluate the effect of various treatments targeting different domains of the AR for their ability to disrupt these droplets *in vitro*.

Results

We found that mutants Del 361-559, R596A, and E898A reduced foci compared to wild-type. Drugs that target the NTD domain of AR had a significant reduction of foci/droplets *in vivo* and *in vitro*. MED1 phosphomimic had an increased number of droplets compared to MED1 wild-type, indicating the importance of this phosphorylation site for AR droplet formation.

Conclusion

We hope by better understanding what drive AR condensates formation in PCa, to elucidate this new mechanism of transcriptional regulation and to identify new therapeutic avenues for patients with advanced forms of the disease.

TREATMENT-INDUCED LYSOSOME PROTEASE LEGUMAIN PROMOTES THERAPY RESISTANCE IN PROSTATE CANCER

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Background

Defining the mechanisms of treatment resistance to AR pathway inhibition (ARPI) and co-targeting strategies remains a key goal to improve prostate cancer (PCa) outcomes. Our previous work on profiling the global alterations in the proteome after ARPI revealed induction of the lysosome protease Legumain (LGMN), a cysteine protease specifically cleaving its substrates at the Asparagine residue. We set out to define mechanisms of LGMN induction and its role in ARPI resistance.

Methods:

Induction of LGMN protein levels by ARPI was quantified in both *in vitro* and *in vivo* PCa models. Enzymic activity of LGMN in PCa cells was measured with a fluorescent-based assay. Effects of LGMN silencing with siRNA or shRNA on cell growth and migration was investigated with Incucyte and transwell assays, respectively.

Results

LGMN protein level and enzymic activity are induced by enzalutamide (ENZA) and charcoal-stripped serum treatment and repressed by androgen stimulation with DHT or R1881 in AR+ PCa cells. Upon ENZA treatment, *LGMN* mRNA is enriched in polysomes but depleted in stress granules (SG), indicating selective translation of *LGMN* under ARPI stress. An important regulator of mRNA homeostasis involves RNA epitranscriptomic methylation at the N6-position of adenosine (m6A), a process coordinately regulated by writers, readers and erasers. ENZA treatment led to increased m6A modified *LGMN* mRNA transcripts to support polysome enrichment and translation, while knockdown of the readers YTHDF1/3 attenuated induction of *LGMN* by ENZA. LGMN levels increased in LNCaP xenograft and PDX models after castration. Knockdown of LGMN promoted apoptosis in LNCaP cells and further sensitized cells to ENZA. LGMN presents in the lysosomes at the leading edge of LNCaP cells and silencing of LGMN supressed cell migration.

Conclusions

LGMN as an ARPI-induced lysosome protease is selectively translated to promote cell survival and treatment resistance.

SCREENING SELECTIVITY OF PSMA TARGETING APTAMERS ON MURINE XENOGRAFTS

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Introduction and Objectives

Prostate Specific Membrane Antigen (PSMA) is a transmembrane carboxypeptidase that is highly expressed in prostate cancer with expression increasing with disease progression. PSMA targeting has enabled great improvements in diagnostic imaging, and ligand-guided therapies for advanced metastatic prostate cancer. PSMA expression by other tissues, including the salivary glands, hinders the use of PSMA-targeted radiotherapies due to dose limiting off-target damage. More selective PSMA targeting strategies are therefore needed. To address this, we are evaluating the PSMA binding activity of 23 slow off-rate, chemically modified DNA aptamers (SOMAmers).

Methods

Binding affinities were established in vitro using bio-layer interferometry with recombinant PSMA. On-cell affinities were determined using flow cytometry to compare binding to PSMA expressing LNCaP cells and CRISPR modified PSMA negative LNCaP cells (PSMA KO LNCaP). Binding characteristics were further determined through competition assays with an active site-targeted small molecule PSMA-617 variant, and an apical domain-targeted minibody based on the J591 antibody. In vivo imaging analysis was performed with parental LNCaP, PSMA KO LNCaP, 22Rv1 (PSMA positive), and PC3 (PSMA negative) xenografts in athymic nu/j mice. IVIS fluorescence imaging was performed after injection of a fluorescently conjugated SOMAmer or PSMA-617 variant.

Results

We have established a relative rank order of the SOMAmers based on binding saturation and affinity kinetics, and identified those whose binding is competed with either, or both, the PSMA-617 variant and J591 minibody allowing for prioritization moving forward. In vivo, the majority of tissue accumulation after 24 hours was in the liver, kidney, and salivary glands, but accumulation was preferentially detected in the PSMA-expressing xenografts by whole body and excised imaging.

Conclusions

This study provides initial evidence that modified DNA aptamers may provide a uniquely flexible molecular targeting agent that may be able to overcome limitations of current small molecule and antibody-based PSMA targeting agents.

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

Shabnam Massah1, Maria Guo1, Nicholas Pinette1, Hanadi Ibrahim1, Fan Zhang1, Maitree Biswas1, Joseph Lee1, Jane Foo1, Artem Cherkasov1, Jörg Gsponer2 and Nada Lallous1.

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Background

The androgen receptor (AR) is an androgen-activated transcription factor that plays an essential role in prostate cancer (PCa) progression and is the main target for PCa therapies. However, treatment resistance occurs and leads to advanced forms of PCa with ligand independent AR activity due to other mechanisms including expression of splice variants such as AR-V7. We recently showed that full-length AR forms nuclear condensates in LNCaP cells to execute its oncogenic program. In this study, we will investigate the ability of AR and AR-V7 to form such condensates across a panel of PCa cell models and identify their corresponding binding partners.

Methods

We assessed the ability of endogenous and transiently transfected AR and AR-V7 to form nuclear condensates in benign (RWPEI, PNT1B cells) and cancerous (LNCaP, LN95, 22RV1, VCaP, PC3) prostate models using fluorescent confocal microscopy. We also evaluated the impact of AR inhibitors on these condensates. We used AU-15330 (PMID: 34937944), a SWI/SNF degrader that inhibit chromatin accessibility to evaluate the role of DNA binding on AR and AR-V7 condensates. Additionally, we optimized a pelleting assay to isolate AR and AR-V7 condensates in the presence of nuclear extract to identify their corresponding binding partners using mass spectrometry.

Results:

AR tagged with a non-dimerizing EGFP (AR-mEGFP) forms condensates in PCa cell models but not in benign prostate epithelial cells. AR-V7-mEGFP forms such condensates only PCa models that express splice variants such LN95, 22Rv1 and VCaP cells. These data were also confirmed with endogenous AR and AR-V7. AR antagonists EPI-001 and 14449 that target the N-terminal and DNA-binding domain respectively, reduced AR-V7 condensates, however, enzalutamide that targets the ligand-binding domain, did not affect their formation. When we induced chromatin compaction through AU-15330 treatment, PCa cells did not form AR and AR-V7 condensates, validating the importance of chromatin binding in this mechanism. Furthermore, we developed a pelleting assay where recombinant full-length AR formed droplets in the presence of nuclear proteins extracted from AR-negative PCa cells (PC3). We are currently optimizing the recovery of the droplets to identify the proteins partitioning within AR condensates by mass spectrometry. In parallel, we are developing the same assay to characterize AR-V7 interactome.

Conclusions

Our study focused on analyzing the nuclear condensates of AR and AR-V7 in various PCa models representing different disease stages. We aim to identify the corresponding interactome within AR and AR-V7 condensates, which could open new avenues for treatment development for patients with lethal PCa.

Poster Presentation – Abstracts

Department of UROLOGIC SCIENCES UBC

VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence

2023 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 13, 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.

Poster Number	Presenter	Abstract Title
1	Abdulghafour Halawani	CUMULATIVE THULIUM FIBER LASER ENERGY AND STONE-FREE RATES: OUTCOMES FROM THE TEAM OF WORLDWIDE ENDOUROLOGICAL RESEARCHERS' (T.O.W.E.R.) THULIUM FIBER LASER REGISTRY
2	Abdulghafour Halawani	INITIAL REAL-WORLD EXPERIENCE OF URETEROSCOPIC LITHOTRIPSY USING THE LITHOVUE™ ELITE SYSTEM WITH INTRARENAL PRESSURE MONITORING CAPACITY
3	Abdulghafour Halawani	FIRST-IN-SEAL – KIDNEY STONE TREATMENT IN THE HARBOUR SEAL: RESULTS FROM COMBINED NOVEL BREAK WAVE LITHOTRIPSY AND URETEROSCOPY
4	Nilanga Aki Bandara	THE GENITOURINARY IMPACTS OF ELECTRONIC CIGARETTE USE: A SYSTEMATIC REVIEW OF THE LITERATURE
5	Alec Mitchell	READABILITY OF PATIENT RESOURCES ON NEPHROLITHIASIS FROM AUA, CUA, AND EAU
6	Cedric Kamani	ADIPOSE DERIVES STEM CELL TRANSDIFFERENTIATION INTO RENAL EPITHELIAL CELLS.
7	Dennis Xie	VERTEBRAL OSTEOSCLEROTIC BONE METASTASIS LESIONS OF PROSTATE CANCER ACQUIRE ALTERED EXTRACELLULAR MATRIX CHARACTERISTICS
8	Ivan Yu	HARNESSING PROXIMITY LIGATION TO PROBE THE ANDROGEN RECEPTOR VARIANT 7 INTERACTOME
9	James Ryeburn	EFFICACY OF NEGATIVE PRESSURE BIOREACTOR IN RECELLULARIZATION OF DECELLULARIZED KIDNEY
10	Jane Foo	CHARACTERIZATION OF ER-AF2 INHIBITORS IN BREAST CANCER
11	Jian Gao	GENERATION OF HUMAN KIDNEY ORGANOIDS AS A NOVEL MODEL FOR KIDNEY RESEARCH

12	Joshua Scurll	CASE STUDY OF A HIGHLY MUTATED PROSTATE CANCER TREATED WITH A COMBINATION OF ANDROGEN RECEPTOR PATHWAY INHIBITION AND IMMUNE CHECKPOINT BLOCKADE IN THE GENOMIC UMBRELLA NEOADJUVANT STUDY
13	Julie Wong	METHODS TO INCREASE EQUITY, INCLUSION, AND DIVERSITY IN UROLOGY PROGRAMS: A REVIEW
14	Julie Wong	ONE-YEAR RENAL RECOVERY POST DONOR NEPHRECTOMY FOLLOWING POSTOPERATIVE INTRAVENOUS KETOROLAC PAIN MANAGEMENT
15	Kerim Yavuz	CHARACTERIZING THE EFFECT OF INSERT SIZE ON ENHANCER REPORTER ACTIVITY
16	Kimia Rostin	GENOMIC DISSECTION OF ERBB2 AS A PREDICTIVE BIOMARKER IN METASTATIC UROTHELIAL CARCINOMA
17	Margaret Javier	NUCLEOLAR PROMINENCE IN PROSTATE CANCER: STUDIES ON THE BIOPHYSICAL PROPERTIES AND FUNCTIONS OF RNA BINDING MOTIF PROTEIN X-LINKED 2
18	Mohammadali Saffarzadeh	TRACKING THE HIDDEN CULPRITS: OCCUPATIONAL RISK FACTORS BEHIND KIDNEY STONES IN CANADA
19	Monica Bronowski	EVOLUTION OF STANDARDIZED CANNABIDIOL EXTRACTS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE
20	Moritz Maas	DEVELOPMENT OF INFIGRATINIB-ELUTING SEEDS FOR LOCALIZED TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC)
21	Reid Vassallo	IMPLEMENTATION OF STRAIN AND SHEAR WAVE ELASTOGRAPHY WITH MICRO-ULTRASOUND
22	Ryan Flannigan	DETECTION AND TRANSCRIPTIONAL PROFILING OF MESENCHYMAL STEM CELLS IN PEYONIE'S PLAQUE EXPLANTS
23	Anna Hudon-Kaide	IMPLEMENTING VIRTUAL PELVIC FLOOR PHYSIOTHERAPY TRAINING IN THE PROSTATE CANCER SUPPORTIVE CARE (PCSC) PROGRAM
24	Sheryl Munshan	ABNORMAL STRUCTURE OF IRREGULAR PROSTATE CANCER ASSOCIATED BONE IS A RISK FACTOR FOR BONE FRACTURES
25	Herman Kazakov	LIPOTEICHOIC ACID AND LIPOPOLYSACCHARIDE ARE ANTAGONISTIC BACTERIAL CONSTITUENTS WHICH STIMULATE DIFFERENTIAL IMMUNE RESPONSES BETWEEN RENAL PROXIMAL TUBULAR AND MESANGIAL CELLS
26	Ugur Dikbas	EXPRESSION AND CHARACTERIZATION OF HOXB13 A CRITICAL PROSTATE-SPECIFIC TRANSCRIPTION FACTOR
27	Xinglan Li	CLUSTERIN KNOCKOUT MICE: A MURINE MODEL OF GLOMERULAR FIBRILLOGENESIS

CUMULATIVE THULIUM FIBER LASER ENERGY AND STONE-FREE RATES: OUTCOMES FROM THE TEAM OF WORLDWIDE ENDOUROLOGICAL RESEARCHERS' (T.O.W.E.R.) THULIUM FIBER LASER REGISTRY

Abdulghafour Halawani, Kyochul Koo, Mitchell R. Humphreys, Wilson Molina, Bodo Knudsen, Mantu Gupta, Victor KF. Wong, Peter Kronenberg, Palle Osther, Olivier Traxer, Ben H. Chew.

Purpose

The Thulium fiber laser (TFL) is an effective tool for ureteroscopic lithotripsy. The Endourological Society's T.O.W.E.R. registry sought to evaluate the stone-free rate (SFR) at 1 month following ureteroscopy. This subset of the study sought to determine the association between cumulative TFL energy and SFRs.

Methods

A retrospective analysis was performed on 323 patients from nine international sites who received ureteroscopic lithotripsy with TFL (SOLTIVETM, Olympus, Southborough, MA) between December 2021 and September 2022. Baseline clinical characteristics and SFR data for kidney and ureter stones were separately analyzed according to quartile cumulative TFL energy ranges.

Results

Median patient age was 57.0 (IQR 44.0–67.0) years and maximal stone diameters were 10.0 (IQR 7.0–13.0) mm and 7.8 (IQR 6.2–10.5) mm for kidney and ureter stones, respectively. Lithotripsy was performed by dusting, fragmentation, and by combination in 69.9%, 5.5%, and 24.6% of all cases. The overall SFR for kidney stones was 70.5% and 86.6% for ureteral stones at 1 month. We divided the cumulative energy levels into quartiles and lower SFRs were observed with the highest quartile in both kidney and ureter (Figure 1. $p<0.001$). This correlated with stone size as larger stones required more energy. Renal stones >9.5 mm and ureteral stones >12.6 mm resulted in lower SFR (Figures 2&3). Energy levels >21.1kJ in the kidney and >7.22kJ in the ureter resulted in lower SFR ($p<0.001$).

Conclusions

Higher stone burdens had lower stone free rates and required more cumulative energy delivery. The TFL laser is effective in ureteroscopic laser lithotripsy with what appear to be equivalent results to holmium:YAG. Longer term follow-up would be helpful to evaluate clearance of the dust created by this laser technology.

INITIAL REAL-WORLD EXPERIENCE OF URETEROSCOPIC LITHOTRIPSY USING THE LITHOVUE™ ELITE SYSTEM WITH INTRARENAL PRESSURE MONITORING CAPACITY

Kyochul Koo, Abdulghafour Halawani, Victor KF. Wong, Naeem Bhojani, Ben H. Chew

Purpose

The increment of intrarenal pressure (IRP) during ureteroscopic lithotripsy is considered to deteriorate surgical outcomes. Nevertheless, factors associated with increments in IRP and its acceptable thresholds are not well understood. We report our initial experience with the LithoVue™ Elite system with IRP monitoring capacity.

Methods

A single-arm retrospective observational analysis was performed on 46 patients who received ureteroscopic lithotripsy using the LithoVue™ Elite system between April and October 2022. Ureteral access sheath (UAS) was placed at the physician's discretion. Spiking pressures that exceeded threefold ratios from previous values that persisted for less than 3 seconds were considered artifacts and were removed from the analysis. Median and maximum IRPs, and relative cumulative time exceeding 20, 40, 60, 80, 100, 120, 140, 160, and 200 mmHg per total procedure time were analyzed. The two-sample Mann-Whitney U-test was used with a statistical significance set at $p<0.005$.

Results

Median patient age and body mass index (BMI) were 62.5 (IQR 47.8–72.0) years and 29.4 (23.3–32.8) kg/m2, respectively (Table 1). During the median total procedure time of 31.9 (IQR 17.4–44.9) minutes, median and maximum IRPs of 30.0 (IQR 21.0–51.5) mmHg and 177.0 (IQR 129.0–266.0) were observed, respectively. IRP sustained below 60 mmHg during 91.3% of the total procedure time (Figure 1). Patients with Asian ethnicity and hypertension exhibited longer relative cumulative time ≥20 mmHg than their counterparts, while patients with tight ureters and no UAS use exhibited longer relative cumulative time ≥60 mmHg than their counterparts. The use of 11/13 Fr and 12/14 Fr UAS conferred shorter relative cumulative time ≥40 mmHg compared to the use of 10/12 Fr UAS. Age, pre-stenting, preoperative α-blockade, and BMI did not show any associations with IRPs.

Conclusions

Preemptive measures such as UAS placement can be considered for patients with tight ureters, hypertension, and Asian ethnicity since these patients are prone to increments in IRP.

Table 1. Clinical characteristics of patients.

Number	46
Age (years)	62.5 (47.8 – 72.0)
Gender (male)	27 (58.7%)
Race (caucasian)	37 (90.2%)
Body mass index (kg/m2)	29.4 (23.3 – 32.8)
Stone diameter (mm)	10.0 (7.0 – 12.0)
Stone number	2 (1.0 – 2.3)
Hypertension	18 (39.1%)
Diabetes mellitus	6 (13.3%)
Preoperative pain	16 (34.8%)
Prior ESWL	22 (47.8%)
Ureteral access sheath placement	32 (69.6%)
Preoperative α-blocker use	11 (23.9%)
Pre-stenting	7 (15.2%)
Prior endourological intervention	34 (73.9%)
Tight ureter	11 (23.9%)

FIRST-IN-SEAL – KIDNEY STONE TREATMENT IN THE HARBOUR SEAL: RESULTS FROM COMBINED NOVEL BREAK WAVE LITHOTRIPSY AND URETEROSCOPY

Ben H. Chew, Jean Buckley, Victor K.F. Wong, Abdulghafour Halawani, Kyo Chul Koo, Doug Corl, Paul Fasolo, Martin Haulena, Oren Levy

Introduction

Harbour seals (*Phoca vitulina*) are marine mammals that obtain a majority of their hydration by metabolism of fat stores and directly from prey. Renal calculi have been reported in both free-ranging harbour seals as well as those living under human care. Chronic dehydration and diet may lead to development of kidney stones. Harbour seals have a unique multilobed reniculated kidney anatomy consisting of numerous collection systems that funnel into a common renal pelvis and ureter. Four harbour seals currently reside at the Vancouver Aquarium. One animal died from renal failure approximately 10 years ago. Post-mortem revealed extensive renal calculi resulting in renal damage. An additional seal, named Hermes, was recently diagnosed with extensive renal calculi via sonography and computed tomography (CT)(Figure 1). We describe a multi-team approach to dealing with stones in the harbour seal.

Methods

The 71 kg male seal was given a general anesthetic and placed in the right lateral decubitus position to allow simultaneous access to the flank and penile urethra. Break Wave lithotripsy (Sonomotion Inc, San Mateo, CA) was performed. Ureteroscopy was carried out using a single use digital ureteroscope (LithoVue, Boston Scientific, Marlborough, MA) through an 11/13Fr 46 cm ureteral access sheath. A degradable ureteral stent (URIPRENE, ADVA-Tec, South Carolina) was prepared for post-operative drainage and would not require subsequent removal.

Results

Break Wave Lithotripsy was performed non-invasively on several stones in the left kidney at pressure levels of 8 MPa, the pressure dose level typically used in humans. Real time ultrasound image guidance from the SonoMotion Break Wave system showed complete fragmentation of the primary targeted 1 cm stone which was confirmed on postoperative CT scan. In addition, numerous stones in the vicinity of the main stone targeted were also reduced substantially or were not observed in the postoperative CT scan. The seal had gross hematuria and an uneventful recovery. Simultaneously, retrograde ureteral access took a prolonged time due to the tortuous urethra and ureter. After 90 minutes the ureteroscope finally reached the renal pelvis but the seal became unstable under anesthesia so the ureteroscopic procedure was abandoned.

Conclusion:

Non-invasive Break Wave Therapy is an effective tool to treat nephrolithiasis in sea mammals under general anesthesia. The tortuosity of the urethra and ureter make endoscopic access difficult (but not impossible).

THE GENITOURINARY IMPACTS OF ELECTRONIC CIGARETTE USE: A SYSTEMATIC REVIEW OF THE LITERATURE

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Introduction and objectives

Electronic cigarette (e-cig) use is prevalent. The potential harm these products can cause the genitourinary (GU) system is uncertain. A better understanding of their overall risks and benefits is necessary before any recommendation can be made on their use for smoking cessation, or more generally to advise against their use at all. The aim of this systematic review is to evaluate the impact of e-cigs on the GU system.

Methods

A systematic search was conducted in PubMed, Embase and Ovid and citation searching using terms specific to e-cigs and the GU system. Review articles, articles not written in English, animal models studies, cell line studies or articles only on combustible cigarettes were excluded. Quality assessment was undertaken using the Joanna Briggs Institute critical appraisal checklists. The primary endpoint was to assess the impact of chronic e-cig use on bladder cancer incidence. Secondary outcomes included urine carcinogen levels, chronic kidney disease (CKD), infertility, and other GU diseases.

Results

Our search strategy yielded a total of 244 articles, of which 28 met inclusion criteria and were included in this systematic review. One study assessed risk of bladder cancer and 21 articles measured potential urinary carcinogens associated with bladder cancer. Two and three articles evaluated the association of e-cig use with CKD and reproductive disorders, respectively. One study reported on other GU diseases. All studies were appraised to be of acceptable quality for inclusion. These studies described the diverse effects that e-cigs have on GU health through unintended acute and chronic exposures and provide suggestions for future research.

Conclusions

In light of the potential increase of carcinogenic toxins found in urine and the increased risk of bladder cancer, as well as other functional impacts, further studies are needed to study the long-term effects of e-cig use on the GU system.

READABILITY OF PATIENT RESOURCES ON NEPHROLITHIASIS FROM AUA, CUA, AND EAU

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Introduction

Patient engagement is essential in nephrolithiasis to navigate complex choices among interventions and preventative measures.

Many urologists rely upon patient information materials (PIMs) published by major urologic organizations such as the CUA, AUA and EAU to improve patient health literacy. The readability of CUA PIMs has been previously assessed for general urologic conditions. However, a comparative assessment of major urology association PIMs for different facets of kidney stone disease has not been performed. We undertook this comparative readability analysis to provide a resource for clinicians and patients.

Methods

We located CUA, AUA, EAU PIMs on 4 topics related to nephrolithiasis; general information, dietary, surgical and medical. We then performed a readability analysis of each PIM using three major scoring systems: SMOG, Gunning Fog and FKGL. Average readability levels for each topic PIM were then calculated for each organization and compared.

Results

Readability for CUA PIMs ranged 9.5-11.6 (grade 10-12). This compared similarly to EAU PIMs at 9.2-11.2 (grade 9-grade 11). Comparatively, AUA resources were had lower readability scores with averages scores 7.5-10.1, corresponding to grade 8-10. For the topic 'medical' AUA PIM did have a higher readability score at 10.1 compared to both CUA 9.5 and EAU 9.2.

Conclusion

The CUA resources on nephrolithiasis compare favourably to the EAU but poorly to the AUA in terms of readability. Both, CUA and EAU do not meet the standard of 6-8th grade reading level for patients recommended by NIH and AMA. However, AUA only meets this recommendation on some of their PIMs. As all of these resources are freely available online, we invite physicians to assess available PIMs from our analysis and curate the resources that they provide for patients accordingly.

ADIPOSE DERIVES STEM CELL TRANSDIFFERENTIATION INTO RENAL EPITHELIAL CELLS

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Introduction and Objectives

More than 48,000 Canadians live with end-stage kidney disease (ESKD). This crisis places a significant strain on the healthcare system. The most effective therapy for ESKD is transplantation; however, even after transplantation, patients present with alloimmune tissue injury. We propose a new solution to an old problem: using tissue engineering to generate a new kidney using the patient's stem cell. The patient's stem cells will be derived from adipose tissue and transdifferentiated into kidney epithelial cells. This could circumvent the risk of alloimmune rejection and shorten the wait time for kidney transplantation.

Methods

The first step is to obtain human adipose tissue from liposuction or tissue reductions. Next, we will isolate adipose-derived stem cells (ASC) from human adipose tissue and characterize ASC using a fluorescence-activated cell sorting (FACS) machine. After that, we will transdifferentiate our ASC into renal epithelial cells using two techniques. The first will be a co-culture system, and the second will use renal epithelial cell-conditioned media. Our final step will be to characterize the transdifferentiated cells' protein profile and genetic profile. The final step will be to test cell functionality, which should be similar to that presented in renal epithelial cells.

Anticipated result

Our lab preliminary results have demonstrated the capacity of adipose-derived stem cells to transdifferentiate into renal epithelial cells, at least by morphological changes and the protein expression of AQP1. However, more experiments need to be done in order to confirm our preliminary results.

Conclusion

From our work, we expect to trans-differentiate ASC to renal epithelial cells. ASCs are easy to obtain and culture; we hope that following ASC trans-differentiation, the renal epithelial-like cells produced will repopulate decellularized kidney scaffolds as an alternative cell source for kidney transplantation lessening a critical problem in our healthcare system.

VERTEBRAL OSTEOSCLEROTIC BONE METASTASIS LESIONS OF PROSTATE CANCER ACQUIRE ALTERED EXTRACELLULAR MATRIX CHARACTERISTICS

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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 osteoblastic/osteolytic lesions with increased, irregular, bone density and deposition, loss of collagen alignment and increased porosity. Under pathological conditions or repair, bone matrix composition is altered and can include cartilage-associated proteins. We hypothesize that PCBMs induce dysregulated repair-like bone remodeling activity resulting in differential deposition and organization of extracellular matrix factors relative to residual trabecular bone.

Methods

We analyzed lumbar vertebrae specimens from 13 cadaveric PCBMs, 6 biopsies from patients undergoing decompression surgery, and 4 age-matched cancer-free donors. We used mass spectrometry (MS) to compare the protein content of sclerotic and lytic vertebral PCBMs vs. cancer-free controls. We performed Goldner's trichrome staining to compare bone matrix organization among specimens. We performed immunohistochemistry to evaluate the composition of irregular and residual trabecular PC-associated bone matrix.

Results

MS analysis differentially segregated sclerotic and lytic PCBMs from control specimens. Differential Goldner's staining of irregular PC-associated bone and lamellar bone under brightfield, and loss of collagen alignment under polarized light in the PCBM specimens confirmed irregular bone interspersed with lamellar (residual trabeculae) bone. Stronger COL-III, OSC, OSP, ALP, and BMP2 staining in sclerotic regions of PCBMs validated noted MS findings from the sclerotic PCBM specimens. Aggrecan and COL-I levels were indistinguishable between specimen groups, and COL-II was not detected in sclerotic, PC-associated bone. We did not observe evidence of a collagenous matrix switch based on the absence of COL-II and aggrecan.

Conclusions

High COL-III content suggests that a process akin to bone repair occurs in the PCBM, while elevated levels of polyanionic proteins, such as OSP, suggest an accelerated process of mineralization. Our observations demonstrate structural and biochemical alterations in irregular PC-associated bone consistent with a hyperblastic dysregulation of matrix deposition that results in a disorganized sclerotic matrix distinct from healing physiology.

HARNESSING PROXIMITY LIGATION TO PROBE THE ANDROGEN RECEPTOR VARIANT 7 INTERACTOME

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Introduction

Inhibiting androgen receptor (AR) signalling is the standard of care for recurrent or metastatic prostate cancer (PCa). While treatment is initially effective, 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 patients. Several resistance mechanisms have been shown to maintain AR signalling, including the expression of constitutively active AR splice variants. Yet how these variants drive resistance remains poorly understood. Recent work has demonstrated that the most clinically abundant variant (AR-V7) and full length protein (flAR) largely share similar binding sites but have very different transcriptional activity. Taken together, 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 global interactomes of flAR and AR-V7, we utilized TurboID, a promiscuous biotin ligase that biotinylates all nearby proteins . After expressing flAR or AR-V7 fused to TurboID, we isolated and identified the putative flAR/AR-V7 interactors by affinity purification-mass spectrometry (AP-MS). Next, to elucidate the proteins uniquely associated with AR-V7 homodimers and flAR/AR-V7 heterodimers, we developed and optimized a split version of TurboID that only biotinylates proteins following dimerization.

Results and conclusions

Characterization of the global interactomes for flAR and AR-V7 yielded several hundred high confidence interactors, which included well-characterized AR-interacting proteins, such as HOXB13 and FOXA1, as well as proteins specific to each isoform. Further, based on publicly available CRISPR screen data, we have identified and validated a subset of the AR-V7 preferential interactors as selectively essential in AR-V7 expressing CRPC cells. Currently, we are working to characterize how these AR-V7 specific interacting proteins alter CRPC and AR mechanism of action. Overall, this work will further our understanding of AR-V7 mediated therapeutic resistance and suggest novel therapeutic approaches.

EFFICACY OF NEGATIVE PRESSURE BIOREACTOR IN RECELLULARIZATION OF DECELLULARIZED KIDNEY

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Introduction and Objectives

End-stage kidney disease is a significant cause of morbidity and mortality. Transplantation is the most effective treatment, however, donor organs are scarce, and immunosuppression carries risks. Consequently, the authors propose a new solution: recellularizing decellularized donor kidneys with renal epithelium transdifferentiated from the patient's adipose-derived stem cells to create isograft kidneys. However, there are still several limitations, including repopulating the organ periphery. Therefore, this research aims to investigate different kidney recellularization protocols.

Methods

Three strategies for kidney recellularization were compared using previously decellularized pig kidneys. In each case, 500*106 whole kidney pig cells; mixed cell media; perfusion through the renal artery, vein, and ureter via a peristaltic pump; and 42 hours duration of culture inside a gastight-sealed bioreactor were standard:

A) Decellularized kidney was perfused with cells plus cell mixed media and growth factors.
B) Decellularized kidney was perfused with cells and submerged in nutrients and growth factors.
C) Decellularized kidney was perfused with cells under different negative pressures (-10, -14, and -17 inHg) for 10 minute intervals.

Results

H&E showed a high percentage of recellularization, uniform distribution, and migration of cells into the periphery of the kidney. H&E showed cells within structures resembling glomeruli and lining tubular structures, resembling a native kidney. Immunofluorescence confirmed the presence of podocin in circular structures resembling glomeruli, CD31in the endothelium, and AQP-1/4 in the epithelium.

Conclusions

Negative pressure (-17 inHg) demonstrated the highest percentage of recellularization, with migration of cells into the periphery of the kidney, and uniform distribution. This research aims to provide a proof-of-principle for reducing transplant wait times and complications by effectively turning each patient into their own organ donor. Organ decellularization is a promising option for regenerating organs for transplantation, and this research offers new insights into kidney recellularization protocols.

CHARACTERIZATION OF ER-AF2 INHIBITORS IN BREAST CANCER

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Majority of breast cancers (BCa) express the estrogen receptor (ER) and rely on these proteins for the growth and progression of the disease. This dependence on ER has led to the development of many hormonal therapies that target this receptor. However, up to 40% of these cancers will acquire resistance over the course of the treatment period. One potential cause of resistance is due to mutations in the estrogen binding site (EBS) of ER. As such, there is an increasing need for novel inhibitors that targets ER at a site separate from the EBS. Here, we propose targeting the activation-function (AF2) pocket of ER that is important for cofactor binding and transcription activation.

Billions of compounds were screened through an *in-silico* deep docking method, and potential AF2 inhibitors were then validated in cell-based and biophysical assays. We tested the effect of potential AF2 inhibitors on ER transcriptional activity using luciferase reporter assay in ER+ T47D-kbluc cells, as well as on cell viability of ER+ T47D and ER- MDA-MB-231 cells using PrestoBlue assays to exclude off-target effects. From these cell-based assays, we identified several inhibitors that effectively reduced transcriptional activity and viability in ER-positive T47D cells at low micromolar concentrations. We conducted PGC-1α peptide displacement assay to confirm their AF2 binding and estradiol displacement assays to exclude any binding to the EBS. Proximity ligation assay (PLA) showed disruption of the interaction between ER and coactivator SRC-3 upon treatment with ER-AF2 inhibitors in T47D cells. Current work focuses on confirming the direct binding between the compounds and recombinant ER-ligand binding domain by various biophysical assays (MST, BLI, and ITC). Future work aims to solve the structure of ER-LBD in a complex with our lead compound by X-ray crystallography. We predict that the use of potent ER-AF2 inhibitors along with current treatments, will provide a novel tactic that can act as a complementary therapeutic to target treatment resistance in ER+ BCa.

GENERATION OF HUMAN KIDNEY ORGANOIDS AS A NOVEL MODEL FOR KIDNEY RESEARCH

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Introduction and Objectives

Recently there has been a great interest in the directed differentiation of human induced pluripotent stem cells (iPSCs) to generate kidney organoids that resemble the human kidney *in vitro*. The successful generation of human kidney organoids will fundamentally change our biomedical research in the laboratory. Because of the differences of biology or genomics between humans and animals, the pathogenetic pathways for kidney disease in patients may not be accurately replicated in animal models. Furthermore, as compared with human kidney cell line cultures, kidney organoids contain more than one cell type and more closely represent the pathophysiological modeling of a human kidney when the pathogenesis involves interactions between different cell type.

Methods

Here, we generated kidney organoids from Episomal iPSC line. The iPSC cells were then undergone various induction methods for kidney organoid differentiation. The formed organoid is then immune-labelled with renal specific markers to identify the structural components of the organoid. Functional assay testing selective permeability was also performed with different sizes of filtration solutes.

Results

The organoid exhibited to encompass podocyte, proximal tubule and distal tubule characteristics. Functionality wise, the organoids were selectively permeable only for small size solutes (3 kDa) but not large one (150 kDa), which resembled kidney function.

Conclusions

The iPSC induced kidney organoids have the potential to replace the current 2D culture as a more accurate culturing model for biological studies.

CASE STUDY OF A HIGHLY MUTATED PROSTATE CANCER TREATED WITH A COMBINATION OF ANDROGEN RECEPTOR PATHWAY INHIBITION AND IMMUNE CHECKPOINT BLOCKADE IN THE GENOMIC UMBRELLA NEOADJUVANT STUDY

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Background

The Genomic Umbrella Neoadjuvant Study (GUNS) is a window-of-opportunity phase-II clinical trial (NCT04812366) of combination therapies targeting genomic biomarkers in prostate cancer (PCa). GUNS sub-protocol (SP) 4 combines an androgen receptor (AR) pathway inhibitor (ARPI) with the anti-PD-L1 immunotherapy agent atezolizumab for neoadjuvant treatment (Tx) of prostate tumours that exhibit mismatch repair (MMR) deficiency (MMRd) or functional loss of *CDK12*, as these tumours may be immunogenic. We report analysis of an SP-4 GUNS case (01-001) that presented with MMRd, tumour mutational burden = 87.4 mut/Mb (~100th percentile), and an *RB1* loss-of-function (LOF) mutation.

Methods

Pre-Tx biopsy and post-Tx radical prostatectomy (RP) specimens from GUNS Patient 01-001 underwent bulk whole-transcriptome RNA-seq and 648-gene panel DNA sequencing (both performed by Tempus), whole-transcriptome Digital Spatial Profiling (DSP, NanoString GeoMx), and immunohistochemistry (IHC).

Results

Tempus detected 664 and 1,430 somatic mutations in the pre- and post-Tx specimens, respectively, of which 166 were shared. Retained alterations included LOF mutations of *RB1* and the MMR gene *MLH3*, as well as copy number loss of another MMR gene, *MSH2*. Lost alterations included a LOF mutation of the MMR gene *MLH1* and a splice-region mutation of *EZH2*, which had a pre-Tx variant allele fraction of 75.3%. LOF mutations of *TP53* and *SUZ12* were gained. In bulk RNA-seq analysis, gene signatures of embryonic stem cells, RB loss, PTEN loss, p53 loss, and proliferation scored highly both before and after Tx. In contrast, signatures of neuroendocrine PCa (NEPC) swung from very low before Tx to very high after Tx. DSP and IHC revealed striking post-Tx heterogeneity in terms of expression of AR and of NEPC marker genes. Nevertheless, unbiased whole-transcriptome DSP analysis indicated post-Tx enrichment of neuronal and endocrine genes across all tumour regions analysed. Furthermore, DSP showed an abundance of immune cells in both the pre-Tx and post-Tx specimens. Importantly, gene signatures of CD8+ T cells were evident in the post-Tx RP specimen.

Conclusions

A highly mutated, MMR-deficient, *RB1*-deficient prostate tumour displayed evidence of being “immune-hot” on presentation and following Tx with an ARPI and immunotherapy. Despite great genetic diversity and evolution and an embryonic mRNA signature, post-Tx enrichment of neuronal/NEPC genes was surprisingly homogeneous throughout the tumour.

METHODS TO INCREASE EQUITY, INCLUSION, AND DIVERSITY IN UROLOGY PROGRAMS: A REVIEW

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Introduction and Objectives

Women and ethnic minorities are underrepresented at all levels of training and practice in urology residency programs. Equity, diversity, and inclusion (EDI) is a growing field of interest in medical research and business literature, especially regarding recruitment. The objective of this review was to evaluate evidence-based strategies to increase EDI to improve urology residency recruitment.

Methods

A review was conducted using Ovid Medline to identify publications reporting strategies to increase women and underrepresented minorities (URM) in healthcare fields. An evaluation of business models was incorporated. Identified strategies were sorted and ranked based on how many papers reported an increased proportion of women or URM in their program following implementation.

Results

We assessed 234 publications from 1972 to 2022. Eleven underwent full review. Six additional pieces of business literature were reviewed and incorporated. The following methods were most often identified to increase diversity: mentorship and holistic application review (6 publications), funded internship programs and diverse selection committees (4 publications). Diversity statements and application blinding were highlighted by multiple business sources but were each only reviewed in 1 medical publication.

Conclusions

Recommendations identified include mentorship, holistic application review by diverse selection committees with bias training, and developing funded internship programs. Standardized questions and rubrics were also well-studied. Business strategies such as publishing diversity statements and application blinding were rarely studied in medical education literature. This study is unique in its inclusion of both medical and business literature and provides concrete strategies for urology residency programs to increase EDI during recruitment.

ONE-YEAR RENAL RECOVERY POST DONOR NEPHRECTOMY FOLLOWING POSTOPERATIVE INTRAVENOUS KETOROLAC PAIN MANAGEMENT

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Introduction and Objectives

Intravenous (IV) ketorolac is a safe, effective alternative to opioids in pain management after donor nephrectomy. However, previous literature has not accounted for continuous ketorolac infusions, and the effect on post-donation renal function is not fully established.

Methods

Retrospective study of minimally invasive donor nephrectomy operations by a dedicated two surgeon team at a high-volume transplant centre in Canada. Comparative analysis between patients that received either 24h continuous IV ketorolac, or opioid pain management postoperatively occurred, with the primary outcome being renal function after 1-year.

Results

93 patients underwent donor nephrectomy between May 2019 and September 2021, with 52 (55.9%) receiving continuous IV ketorolac and 41 (44.1%) managed with opioids postoperatively. Median age was 52 years with 40 (43.0%) male patients. There was no significant difference between the two cohorts' renal function in short-term follow-up or 1-year postoperatively (Table 1). A gender-segregated analysis and age-segregated analysis (donors ≥ 55 years only) revealed similar results. Hemoglobin drop on post-operative day 1 was more significant in the ketorolac group (mean 83.4% from pre-operative levels, compared to 87% in the opioid cohort; p=0.016), but this effect was not seen on gender-segregated analysis and at 1-year postoperatively there was no difference between groups.

Conclusions

This study adds to the growing body of literature that IV ketorolac is safe in kidney donors during their postoperative hospitalization, with no demonstrated impact on 1-year renal recovery and hemoglobin level post donation.

CHARACTERIZING THE EFFECT OF INSERT SIZE ON ENHANCER REPORTER ACTIVITY

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Introduction and Objectives

Self-Transcribing Active Regulatory Region sequencing (STARR-seq) is a powerful experimental methodology that provides functional measurements of enhancer activity at speciTic genetic loci. In this approach, DNA fragments are cloned downstream of a minimal promoter allowing their enhancer activity to drive self-transcription. However, despite the increasing number of applications, many fundamental questions remain about this method. Most importantly, how does DNA insert size affect enhancer activity in this plasmid-based assay? This is particularly critical as there is increasing evidence that enhancers are driven by multiple transcription factors that work together with cell-speciTic “grammar”.

Methods

To determine the impact of insert size on STARR-seq activity, we have generated varying whole-genome libraries. Human genomic DNA (gDNA) was fragmented using sonication and size selected to generate four different STARR-seq libraries with overlapping size ranges to cover published insert sizes (50-1000bp). These plasmid libraries were transfected into LNCaP, an androgen sensitive human prostate adenocarcinoma cells, in the presence and absence of dihydrotestosterone (DHT). We will carry out RNA-seq to measure the transcriptional activity from enhancers.

Results and Conclusion

Four different STARR-seq libraries with insert sizes of 50-250bp, 150-400bp, 400- 650bp, and 650-900bp were generated with fragmented and size-selected Human Male gDNA. These libraries have approximately 930 million, 94 million, 108 million, and 40 million unique clones respectively, which account for 46-, 9-, 18-, and 10-times respective genome coverages. STARR-seq experiments are currently ongoing to determine any potential affects in enhancer activity with changing insert size. The results will help us to identify the importance of size and surrounding sequences of transcription factor binding sites in enhancer activity.

GENOMIC DISSECTION OF *ERBB2* AS A PREDICTIVE BIOMARKER IN METASTATIC UROTHELIAL CARCINOMA

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Introduction and Objectives

ERBB2 (HER2) alterations are common in urothelial cancer (UC) and increase in frequency with disease state; ~20% of metastatic tissue samples harbour *ERBB2* mutation or amplification. While clinical trials of HER2-targeted therapies in UC have historically been negative, recently HER2 antibody-drug conjugates have shown promise. This renewal of interest, combined with past challenges, underlines the importance of accurate biomarker-driven patient selection to optimize the clinical benefit of HER2-targeted therapy. Previously, we demonstrated that *ERBB2* alterations in circulating tumour DNA (ctDNA) can reflect clinically relevant tumour characteristics, including high HER2 protein expression. Here, we set out to evaluate the genomics of *ERBB2*-altered tumours via ctDNA, and the nuances of *ERBB2* as a predictive biomarker for patients with metastatic UC.

Methods

In this retrospective analysis, we used a custom targeted sequencing panel covering >50 bladder cancer relevant genes to profile 411 plasma cell-free DNA samples from 236 metastatic UC patients. Patient-matched leukocyte DNA was profiled for all patients as a germline control.

Results

76% of patients had evidence of ctDNA in at least one blood collection. Protein-altering *ERBB2* mutations were identified in 14% of patients, with two thirds of the mutations falling in known oncogenic hotspot loci. *ERBB2* copy gain (*i.e.,* amplification) was detected in 8% of patients. Leveraging genome-wide probes, we resolved ploidy and *ERBB2* loci structure, revealing amplification genomic breakpoints on chromosome 17, and cases of inset tandem duplications resulting in >50 copies of *ERBB2*.

Conclusions

We demonstrate the feasibility of a ctDNA-based approach for determination of *ERBB2* biomarker status in metastatic UC. We will obtain formalin-fixed paraffin-embedded samples for comparison of ctDNA results to fluorescence *in situ* hybridization, mRNA, and immunohistochemistry results from tissue. Moving forward, it will be imperative to prospectively test the utility of ctDNA in clinical trials of HER2-targeted agents.

NUCLEOLAR PROMINENCE IN PROSTATE CANCER: STUDIES ON THE BIOPHYSICAL PROPERTIES AND FUNCTIONS OF RNA BINDING MOTIF PROTEIN X-LINKED 2

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Introduction and Objectives

Biophysical studies of the nucleolus have revolutionized the understanding of its assembly and organization – notably, the discovery of soluble macromolecules condensing to form nucleoli through liquid-liquid phase separation. As the nucleolus regulates many aspects of cell physiology, maintaining nucleolar functions is essential to homeostasis and preventing the development of pathologies like cancer. Investigating this further, the RNA Binding Motif Protein X-Linked 2 (RBMX2) was studied.

Methods

Polysome RNA sequencing was used to screen for RBMX2 against castration-resistant and treatment-naïve prostate cancer. Immunofluorescence staining was performed to confirm the localization of the protein and a variety of siRNA experiments to investigate possible functions. A prokaryotic expression system was used to purify recombinant RBMX2 and study its biophysical properties.

Results

There is enhanced mRNA translation of RBMX2 in castration-resistant prostate cancer compared to treatment-naïve prostate cancer. RBMX2 is located in small nuclear condensates partially distributed in the nucleolus and its knockdown was observed to significantly alter nucleoli morphology and reduce the proliferation of castration-resistant prostate cancer cells. RBMX2 undergoes liquid-liquid phase separation, which was notably enhanced under heat stress and determined by the protein's C-terminus intrinsically-disordered region.

Conclusions

There is a connection between the enhanced translation of nucleolar proteins and prostate cancer tumour resistance. Specifically, RBMX2 confers a vital role in regulating nucleolar functions and proposes this mechanism's significance in cell survival in treatment-resistant prostate cancer. Future studies will provide further insights into the proteomic analysis of RBMX2 and other nucleolar proteins, and its potential as a cancer therapeutic agent.

TRACKING THE HIDDEN CULPRITS: OCCUPATIONAL RISK FACTORS BEHIND KIDNEY STONES IN CANADA

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Introduction and Objectives

Development of nephrolithiasis has been linked to environmental heat exposures, as well as direct contact with lead, cadmium, and arsenic. The objective of this study is to assess the geographical prevalence of the following environmental risk factors for nephrolithiasis across Canada: ambient temperature, occupational heat, and occupational exposure to lead, cadmium, or arsenic. Our findings can guide future resource planning and allocation strategies to develop targeted preventative measures.

Methods

To identify Canadian regions with the hottest summers, we calculated the average ambient temperature of the three warmest months in each region. Statistics Canada data was utilized to quantify the number of Canadians who are exposed to occupational heat or those who work in the top 5 industries with lead, cadmium, or arsenic exposures. Easily interpretable risk maps were generated, and statistical significance was calculated based on 95% confidence interval difference from the null hypothesis.

Results

Regions at lower latitudes, particularly Ontario, had the warmest climates in summer months. Comparable occupational heat exposure risk was noted across the country, ranging from 619-865 per 10,000 Canadians, except for Nunavut (375 per 10,000). Working Canadians in Yukon, Northwest Territories, and Nunavut had significantly higher rates of occupational lead, cadmium, and arsenic exposures than other Canadian provinces/territories, except for Nunavut and Prince Edward Island, which were not statistically different from one another.

Conclusions

Occupational heat exposures did not significantly defer between regions. Canadians living in Northern regions were found to have higher rates of occupational exposure to lead, cadmium, and arsenic; however, a direct association between these exposures and stone formation cannot be made due to existing confounding factors. Nonetheless, these findings highlight the need for resource planning in Northern Canada given the underserved nature of these areas and challenges in receiving urological care.

EVOLUTION OF STANDARDIZED CANNABIDIOL EXTRACTS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

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Introduction and Objectives

Inflammatory Bowel Disease (IBD) consists of two primary forms, Crohn's disease (CD) and Ulcerative Colitis (CD). Symptoms consist of diarrhea, rectal bleeding, unintentional weight loss, and abdominal pain. Although treatment options are improving, these therapies are often not sustainable long term and can be associated with undesirable side effects. Our goal is to develop a more effective alternative therapy to help manage the disease.

Methods

For this pilot study, mice were induced with colitis by combining dextran sulphate sodium (DSS) with their drinking water. Once they showed clinical signs and symptoms of chronic IBD, the DSS was removed from their cages, and they were randomized to treatment. They received either 100mg/kg of CBD oil, or 100mg/kg of control treatment. Each group was given treatment intrarectally for seven days.

Results

The mice being treated with CBD returned to baseline and showed a reduction in symptoms quicker than the control group. During dissection, physical differences were noted between the thickness and length of the distal colon, proximal colon, and cecum. The spleen was also examined. Those treated with CBD, physically showed healthier spleens compared to those in the control group. Results suggest that CBD may attenuate the intestinal inflammation by promoting the development of anti-inflammatory macrophages.

Conclusions

CBD has the potential to act as a very powerful anti-inflammatory drug. The delivery of CBD alone showed significant improvements in reducing signs and symptoms of chronic IBD, resulting in a localized response. Further investigation will include a histological examination of the distal colon, proximal colon, cecum, and spleen. Additionally, the serum levels will be analysed to examine the effects of treatment on the systemic inflammation.

DEVELOPMENT OF INFIGRATINIB-ELUTING SEEDS FOR LOCALIZED TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC)

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Introduction

Repeated resections make non-muscle invasive bladder cancer (NMIBC) a challenge for patients and healthcare systems. Intravesical therapy has been limited to chemotherapeutic agents and BCG, ignoring the high rate of activating *FGFR3* mutations in NMIBC. The use of systemic FGFR inhibitors (FGFRi) in NMIBC is limited due to the high rate of adverse effects. Therefore, our aim was to develop a novel approach for sustained intravesical delivery using titanium seeds coated with the FGFRi infigratinib (Infb).

Methods

Titanium seeds were coated with Infb using a standardized coating template (PMID 34328312). Liquid chromatography was used to evaluate the seeds' ability to release Infb in cell-culture media over time. The antiproliferative efficacy of seed-released Infb was compared with freshly prepared Infb solution *in vitro* in FGFRi-sensitive (RT112) and FGFRi-resistant (UM-UC13) bladder cancer cell lines. *In vivo* efficacy and release tests in mouse models including 4 treatment arms (negative control without treatment, positive control with oral gavage of Infb, seeds without Infb coating and Infb-coated seeds) are currently ongoing.

Results

Seeds with an adhesive Infb-containing coating were successfully developed after testing multiple coating solutions. Continuous release of Infb over a period of 15 days was observed, resulting in cumulative doses of up to 12 μM. Seed-released Infb showed inhibition of RT112 growth comparable to 10 μM freshly prepared solution. Incubation with media from coated seeds without integrated Infb-coating showed no growth reduction. Results of *in vivo* experiments are pending.

Conclusion

Current results demonstrate the successful release of biologically active Infb from coated seeds in antiproliferative doses *in vitro*. The transferability of these results regarding growth inhibition and Infb release into blood and locally in tissue is currently under evaluation. Assuming positive results, this could broaden the therapeutic landscape of NMIBC by providing local applicability of FGFRi.

IMPLEMENTATION OF STRAIN AND SHEAR WAVE ELASTOGRAPHY WITH MICRO-ULTRASOUND

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Background, Motivation and Objective

Conventional ultrasound is used for many prostate cancer (PCa) interventions, but it cannot accurately delineate PCa tumors. In contrast, the ExactVu (Exact Imaging, Markham, ON, Canada) micro-ultrasound (microUS) system uses a higher frequency transducer (29 MHz), and was shown to guide targeted biopsies for PCa as well as multi-parametric MRI. To improve PCa detection further, we propose the augmentation of microUS with both strain elastography (SE) and shear wave absolute vibro-elastography (S-WAVE). This is the first report of elastography imaging on the ExactVu microUS, enabling studies that combine microUS parameters with tissue stiffness and viscosity.

Methods

Both SE and S-WAVE were integrated into a commercial ExactVu microUS system with an EV29L transducer. Time-series radio-frequency data were captured while applying manual compression for SE and using an external mechanical exciter with two frequencies (138 and 160 Hz) for S-WAVE. A speckle tracking algorithm was used to measure axial tissue displacements, band-pass sampled at 43 Hz. Tissue strain was computed by taking the low-pass filtered spatial derivative of the tissue displacement map. Tissue motion phasors were computed by fitting a sum of sinusoids to the displacement time series. The S-WAVE elasticity map was generated from the phasor maps using local frequency estimation. Performance was validated by imaging 1 cm inclusions in a CIRS 049 quality assurance elastography phantom.

Results/Discussion

Results from SE and S-WAVE using the ExactVu microUS system are presented below. Both methods show the inclusions having varying levels of stiffness. This work will allow for combining elasticity maps with microUS to improve PCa diagnosis. Volumetric microUS elastography imaging will be implemented next.

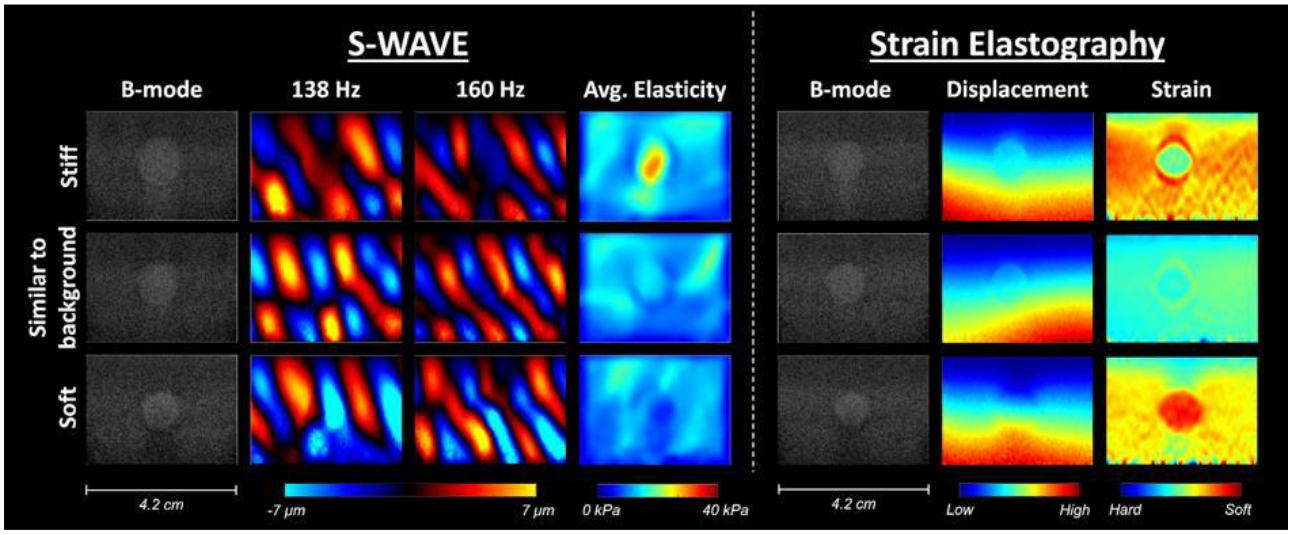

Figure 1: Results of microUS elastography imaging.

DETECTION AND TRANSCRIPTIONAL PROFILING OF MESENCHYMAL STEM CELLS IN PEYONIE'S PLAQUE EXPLANTS

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Introduction and Objective

The mechanisms behind the pathogenesis of Peyronie's disease largely remain a mystery. Plaques have largely been thought to be derived from epithelial to mesenchymal transformation of fibroblasts to myofibroblasts. We sought to transcriptomically profile explanted cells from Peyronie's plaques and evaluate their profiles with transforming growth factor (TGF-) stimulation.

Methods

Peyronie's plaque were excised from 3 patients undergoing penile incision and grafting surgery. Cells were explanted from biopsy tissue and propagated. Cells were profiled using single cell RNA sequencing (scRNAseq). These cells were then exposed to TGF- to simulate the active phase of Peyronie's disease, and profiled with scRNAseq at baseline and 24 hours following TGF- stimulation. We used principle component analysis (PCA) to reduce the dimension of data and built the nearest-neighbors graph using PCA weights. We performed clustering over the nearest-neighbor graph and visualized the clusters using UMAP algorithm. Differential gene expression and pathway analyses were performed using the top 50 genes with increased expression between 0- and 24-hour time points. Multi-channel flow cytometry and immunofluorescence were used for mesenchymal stem cell (MSC) phenotypic validation.

Results

Assessment of cell clustering identified profiles of fibroblasts, myofibroblasts, smooth muscle, and mesenchymal stem-like cells. We further confirmed rare presence of mesenchymal stem cells using multi-channel flow cytometry in our cultured cells and plaque biopsies. Differential gene expression of the 50 genes showing the greatest induction showed that genes involved in cellular binding and catalytic activity were most commonly upregulated following introduction of TGF-.

Conclusions

This analysis provides unique insight into the expression profiles of Peyronie's plaque cell populations explanted in culture and stimulated via TGF- to activate myofibroblasts akin to the active phase of Peyronie's disease. Using the information gained from this single-cell RNA sequencing analysis ongoing efforts can be performed to identify therapeutic targets for active phase Peyronie's disease.

IMPLEMENTING VIRTUAL PELVIC FLOOR PHYSIOTHERAPY TRAINING IN THE PROSTATE CANCER SUPPORTIVE CARE (PCSC) PROGRAM

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Background

The PCSC Program is a comprehensive prostate cancer (PC) survivorship program that offers eight educational modules addressing issues from initial diagnosis onwards. The pelvic floor physiotherapy (PFP) module provides three complimentary appointments to help patients manage urinary incontinence (UI) post-PC treatment. In 2020, PFP was offered virtually in response to COVID-19 safety measures. We compared the change in patient-reported outcomes (PROs) of PFP virtual patients from baseline to discharge to assess the effectiveness of virtual PFP.

Methods

The ICIQ-LUTSqol is a PRO for evaluating the quality of life (QoL) affected by UI. All virtual patients received the ICIQ-LUTSqol before the first and after the third/discharge appointments. Part (a) of each question evaluates the impact of UI on activites of daily living. Part (b) rates level of bother for part (a). ICIQ-LUTSqol score is the sum of part (a), whereas part (b) informs the bother score.

Results

From APR 30, 2020 to NOV 30, 2022, 76 virtual patients were seen. 13/76 virtual patients completed the ICIQ-LUTSqol at baseline and discharge. A pair-wise comparison was performed to compare the differences in ICIQ-LUTSqol score and bother score at baseline and discharge. There was a significant decrease in ICIQ-LUTSqol score between the baseline and discharge ($p= 0.0112$), with a mean difference of -6.615 (Figure 1). Similarly, the overall bother score demonstrated a significant decrease in bother from baseline to discharge ($p= 0.0124$), with a mean difference of -32.46 (Figure 2).

Conclusions

Although the sample size is small, the data provide preliminary evidence that virtual PFP significantly decreases the impact of UI on QoL and the bother experienced post-PC treatment. We are analyzing pad use and frequency of leakage to further evaluate the effectiveness of virtual PFP and will compare the results to matched patients who had in-person PFP.

ABNORMAL STRUCTURE OF IRREGULAR PROSTATE CANCER ASSOCIATED BONE IS A RISK FACTOR FOR BONE FRACTURES

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Introduction

Prostate cancer (PC) affects more than 1.5 million men worldwide. Bone metastasis is a frequent complication of PC and is associated with bone weakness, intractable pain, and increased risk of fracture. More than 70% of PC patients with advanced disease develop bone metastasis, which is associated with a poor prognosis. In this study, we aimed to investigate the hypothesis that irregular PC-associated bone is responsible for the increased fracture risk in PC patients.

Methods

We obtained 13 cadaveric bone samples and performed micro-CT imaging with 6 micrometer isometric voxel size, back scattered electron scanning electron microscopy to analyze differences in matrix composition in normal and PC-associated bone, and nanoindentation to evaluate calcium content, point hardness, and elastic modulus. SEM was performed to compare the collagen alignment and lacunae shape between sclerotic and
normal trabecular bone. We also compared lacunae density and orientation in sclerotic and trabecular regions of PC-associated bone.

Results

Qualitatively we have identified 3 types of PC-associated bone as osteolytic, osteoblastic with residual trabeculae and osteoblastic without residual trabeculae. Sclerotic bone is observed in osteoblastic samples. No significant difference was found in calcium content, elastic modulus, or point hardness between normal and PCassociated bone. However, lacunae were larger in the minor axis causing them to be more circular than eccentric in the sclerotic regions. Moreover, lacunae density was higher in the sclerotic regions relative to the normal trabecular regions, leading to crack initiation and fracture propagation. This resulted in higher porosity suggesting increased stress accumulation points.

Conclusions

Our findings suggest that abnormal structure of irregular PC-associated bone is a risk factor for bone fractures in PC patients. The irregular trabeculae, sclerotic bone, and altered extracellular matrix composition corresponds to higher lacunae density and size. Irregular lacunae orientation and absence of trabecular structures in osteoblastic PC bone metastases may also increase the chances of crack initiation and fracture propagation under tensile and compressive forces. Further studies are needed to validate these findings and develop strategies to reduce the risk of fracture in PC patients.

LIPOTEICHOIC ACID AND LIPOPOLYSACCHARIDE ARE ANTAGONISTIC BACTERIAL CONSTITUENTS WHICH STIMULATE DIFFERENTIAL IMMUNE RESPONSES BETWEEN RENAL PROXIMAL TUBULAR AND MESANGIAL CELLS

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Department of Urologic Sciences, University of British Columbia.

Introduction and Objectives

While bacteria presence was previously thought to be entirely virulent, acknowledgement is growing for the microbiome's potential in immune modulation and protection. Lipoteichoic acid (LTA) and lipopolysaccharide (LPS) are key bacteria call wall polymers which contribute to strong immune system activation. This study comparatively assessed their effects from a genomic level, looking at the changes in human inflammatory gene expression in vivo.

Methods

Human Mesangial Cells (T-HMC) and Human Kidney Proximal Tubular Cells (HKC-8) were cultured in varying treatments of LTA (Staphylococcus aureus) and LPS (Escherichia coli) for 48 hours followed by PCR. Results were normalized and relative fold change to the control was assessed.

Results

Individual LTA and LPS treatments both resulted in an overexpression of human inflammatory genes as compared to control. When assessing expression strength, mesangial cells showed lower sensitivity to treatment in comparison to tubular cell. When LTA and LPS are combined, a competitive interference is observed which leads to declined gene expression for both cell lines. This effect is prominent in the genes CD14, IL10, IL1A, CXCL8 and MYD88.

Conclusions

Though limited literature exists for this novel topic, tubular cells were found to possess higher energy demand and are more sensitive to changes in metabolism. Whereas mesangial cells exhibit fibroblast characteristics and lead to more robust resistance. Our findings support past studies' argument for LTA and LPS's antagonist relationship as they possess overlapping pathways and highlights the proposed dose dependency observed for bacteria pathogenicity. Below threshold amounts, a lowered immune reaction is observed which supports the importance of a diverse microbiome for good renal health. These results coincide with our previous study of LTA and LPS's effect on kidney cell's metabolic changes and further support the inflammatory effects of LTA and LPS on kidney cell viability.

EXPRESSION AND CHARACTERIZATION OF HOXB13 A CRITICAL PROSTATE-SPECIFIC TRANSCRIPTION FACTOR

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Introduction and Objectives

HOX family of proteins are master regulators of embryonic development that shares a highly conserved DNA binding domain. One of the members of this family, HOXB13 is a tissue-specific transcription factor that is essential for prostate organogenesis. Mutations, aberrant expression or interactome of HOXB13 are linked to prostate cancer (PCa). Even though HOXB13 is essential for the growth and proliferation of almost all prostate cancer models, there is little known about its unique co-regulator binding domain. While DNA-binding domain is highly conserved, the co-regulator domain of HOXB13 offers a promising pharmacological target potentially treat late stage PCa. In this study, we aim to exogenously express and characterize HOXB13 to support the design of small-molecule compounds for the treatment of CRPC.

Method and Results

Utilizing a bacterial expression system, we optimized the exogenous expression of HOXB13 with different purification tags and truncations. From this, we found that both the presence of a maltose binding protein (MBP) tag and DNA greatly improved the solubility and stability of exogenously expressed truncated co-activator domains. Using these findings, I was able to successfully purify both the HOXB13 DNA binding domain (HBX) and full length (FL) protein with good yields and purity. To our knowledge, this is the first time that FL HOXB13 has been purified.

Conclusions

In this study, we, for the first time, were able to purify FL HOXB13 with high yield and purity. This will help guide development of small molecule inhibitors that target HOXB13 and potentially treat late stage PCa. Moreover, this study will help us understand how homeobox proteins function within the cell.

CLUSTERIN KNOCKOUT MICE: A MURINE MODEL OF GLOMERULAR FIBRILLOGENESIS

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Background

Both fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (ITG) are characterized by deposits of fibril proteins in the glomeruli in humans, but the pathogenesis of these diseases is poorly understood. Clusterin (CLU) is a multifunctional chaperone-like glycoprotein, and CLU knockout (KO) mice develop age-dependent glomerulopathy. Interestedly, the glomerulopathy in these CLU KO mice is also characterized by glomerular fibril protein deposit, but the clinical relevance of this disease is not investigated. We hypothesize that CLU-KO mice represent a murine model of FGN or ITG in humans. This study was designed to further characterize the pathology of the glomerulopathy in CLU KO mice.

Methods

Wild type (WT) C57BL/6 (B6) and CLU-KO mice in B6 background (both female and male, 10-24 months old) were used. The kidney specimens were sectioned for staining with hematoxylin and eosin (HE), Masson-Trichrome and Congo red. Immunohistochemistry (IHC) was used to detect the special antigens (such as DNAJB9) in the glomerulus. Immunofluorescence (IF) was used to character the immune components in the mesangial deposits. Electron microscopy (EM) was used to characterize the fibril formation of the electron-dense mesangial deposits.

Results

Mice deficient in clusterin developed a progressive glomerulopathy characterized by the deposition of immune complexes in the mesangium. Up to 75% of glomeruli in CLU-KO mice exhibited moderate to severe mesangial lesions by 22 months in males and 12 months in females. WT mice exhibited little or no glomerular pathology at the same age. Masson-Trichrome revealed that fibrosis and immunocomplex were present in the mesangial lesion, but the amyloid was not detected. IHC staining showed that the glomeruli were negative for DNAJB9. Immune complexes of immunoglobulin were detectable in CLU-KO mice. EM revealed the accumulation of electron-dense material in the mesangial matrix were tubulo-fibrillary structures.

Conclusions

Data show that histopathological changes in the kidney of CLU KO mice were similar to ITG, implying that the CLU-KO mice may represent a murine model of glomerular fibrillogenesis in humans especially for ITG.

Organizing Committee

- Dr. Amina Zoubeidi
- Dr. Ben H. Chew
- Dr. Kourosh Afshar
- Dr. Peter C. Black
- Dr. Xuesen Dong

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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