13th Annual Lorne D. Sullivan Lectureship & Research Day

Tuesday, June 18, 2019
Paetzold Health Education Centre
Vancouver General Hospital

Program & Abstracts Booklet
Dr. Christopher P. Evans
Professor and Chairman, Department of Urologic Surgery
University of California Davis School of Medicine
President, Society of Urologic Oncology

Dr. Evans is professor and chairman of the Department of Urologic Surgery at University of California Davis School of Medicine and a member of the UC Davis Comprehensive Cancer Center. Dr. Evans attended Dartmouth Medical School on a Health Professional Services Program scholarship and served on active duty in the United States Army, including two years as Chief of Experimental Surgery at the Walter Reed Army Institute of Research. Dr. Evans completed surgery and urology training at the University of California, San Francisco where he was also a National Kidney Foundation Scholar. He completed fellowship training in urologic oncology at the University of Texas, M.D. Anderson Cancer Center. He came to UC Davis in 1997 and he was also Director of Urology Research. In 2006, Dr. Evans became Department Chairman. Dr. Evans’ practice is dedicated to the management of patients with urologic malignancies.

Dr. Evans’ research laboratory focuses on prostate cancer; specifically, mechanisms signaling the androgen receptor to activate prostate cancer growth and progression following castration. His laboratory has developed models to study this and identified novel mechanisms that activate the androgen receptor. His laboratory work tested new agents and brought them from bench studies to animal models to clinical trials.

Dr. Evans is President of the Society of Urologic Oncology. He is an elected member of the American Association of Genitourinary Surgeons. His research laboratory has received funding from the National Institutes of Health, Department of Defense, Prostate Cancer Foundation, Stand Up To Cancer, New York Academy of Medicine, and the American Cancer Society. He has published over 170 peer-reviewed articles.
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, and 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

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
2007 – Dr. Joao Pippi Salle

Previous Division of Urology Graduation Dinner Guest Speakers

2006 – Dr. John Fitzpatrick
2005 – Dr. Laurence H. Klotz
2004 – Dr. Ralph V. Clayman
2003 – Dr. Denis H. Hosking
2002 – Dr. Anthony E. Khoury
2001 – Dr. Ian Thompson
2000 – Dr. Richard J. Finley
Program

Welcome

8:00 AM – 8:15 AM  Dr. Martin Gleave  
Distinguished Professor and Head,  
Department of Urologic Sciences, University of British Columbia  
Executive Director, Vancouver Prostate Centre  
BC Leadership Chair in Prostate Cancer Research  
Chief Executive Officer, PC-TRiADD

Dr. Robert McMaster  
Vice President Research, Vancouver Coastal Health  
Executive Director, Vancouver Coastal Health Research Institute  
Executive Associate Dean Research,  
Faculty of Medicine, University of British Columbia

Lorne D. Sullivan Lectureship

8:15 AM – 8:55 AM  Targeting the Androgen Axis in Prostate Cancer: Successes and Failures in Translational Research  
Dr. Christopher P. Evans  
Professor and Chairman, Department of Urologic Surgery  
University of California, Davis, School of Medicine  
President, Society of Urologic Oncology

Session I: PCa, Beyond the Androgen Receptor

(7-minute talk and 3-minute Q&A)

8:55 AM – 9:45 AM  Moderator: Dr. Amina Zoubeidi

8:55 AM – 9:05 AM  TREATMENT-INDUCED AR REPROGRAMMING UNDERLIES LINEAGE INFIDELITY IN ADVANCED PROSTATE CANCER  
Alastair Davies1,2, Shaghayegh Nouruzi1,2, Daksh Thaper1,2, Fatih Karaoğlanoğlu2,3, Soojin Kim1, Sahil Kumar1, Chiara Bostock1, Loredana Puca4, Jennifer Bishop1, Ladan Fazli1, Martin Gleave, Haqiee Huang5, David Goodrich6, Housheng Hansen He7, Luke Setl8, Faraz Hach1,3, Hmisha Beltran4,9, and Amina Zoubeidi1,2

9:05 AM – 9:15 AM  EVALUATION OF SYSTEMATIC ALTERATIONS ON TRANSCRIPTOME, TRANSLATOME AND PROTEOME BY ANDROGEN RECEPTOR BLOCKADE THERAPY IN PROSTATE CANCER  
Fan Zhang1, Chidi Molokwu1, Raunak Shrestha1, Robert Bell1, Syam Prakash Somasekharan1, Gian Luca Negri2, Neetu Saxena1, Anders Kristensen2, Sue Ettinger1, Anne Haegeert1, Dong Lin1, Stephane Le Bihan1, Faraz Hach1, Ladan Fazli1, YZ Wang1, Colin Collins1, Poul Sorensen2, Martin Gleave1

9:15 AM – 9:25 AM  IDENTIFYING THE GENOMIC FEATURES OF AKT1 / PIK3CA MUTANT METASTATIC PROSTATE CANCER USING CIRCULATING TUMOUR DNA  
Andrew Murtha1, Cameron Herberts1, Simon Fu1, Sinja Taavitsainen1,2, Matti Annala1,2, Gillian Vandekerkhove1, Kevin Beja1, Yulia Lektionova1, Elena Schönlau1, Kim N. Chi1,2, Alexander W. Wyatt1

9:25 AM – 9:35 AM  HETEROGENEITY AND EVOLUTION IN MISMATCH REPAIR DEFECTIVE METASTATIC PROSTATE CANCER  
Elie Ritch1, Simon Fu2, Cameron Herberts1, Evan W Warner1, Sinja Taavitsainen1,3, Andrew Murtha1, Gillian Vandekerkhove1, Kevin Beja1, Yulia Lektionova1, Daniel Khalaf2, Igal Kushnir4,5, Cristiano Ferrario6, Matti Annala1,3, Kim N Chi1,2, Alexander W Wyatt1
9:35 AM – 9:45 AM MOLI: MULTI-OmICS LATE INTEGRATION WITH DEEP NEURAL NETWORKS FOR DRUG RESPONSE PREDICTION
Hossein Sharifi-Noghabi1,3, Olga Zolotareva2, Colin C. Collins3,4, and Martin Ester1,3

State of Art Lecture I
9:45 AM – 10:00 AM Utilizing Technological Platforms for Advancing Sperm Identification and Selection
Dr. Ryan Flannigan
Assistant Professor, Department of Urologic Sciences

Break and Posters 10:00 AM – 10:30 AM

Session II: Bladder and kidney Cancers
(7-minute talk and 3-minute Q&A)
10:30 AM – 11:10 AM Moderator: Dr. Alan So
10:30 AM – 10:40 AM IDENTIFY: The Investigation and Detection of urological Neoplasia in patients referred with suspected urinary tract cancer: A multicentre analysis
Miles P. Mannas1,2, Tae Lee1, Brian Mayson3, Peter C. Black1,2, Sinan Khadhouri4, Kevin M. Gallagher5, Kenneth R. Mackenzie6, Taimur T. Shah1, Chuying Gao5, Sacha Moore5, Eleanor Zimmermann6, Eric Edison4,5, Matthew Jefferies6, Arjun Nambiar1, John S. McGrath1, Veeru Kasivisvanathan1, The IDENTIFY Study Group

10:40 AM – 10:50 AM CLINICAL CHARACTERISTICS AND OUTCOMES FOR YOUNG PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA
Cyrus Chehroudi1, Jean-Michel Lavoie2, Peter C. Black1, Bernhard Eigl1

10:50 AM – 11:00 AM THE PROGNOSTIC VALUE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY AND RADICAL CYSTECTOMY
Anna J. Black1, Homayoun Zargar1,2, Kamran Zargar-Shoshtari1,2, Adrian S Fairey3, Laura S Mertens4, Colin P Dinney2, Maria C Mi6, Laura-Maria Krabbe6,11, Michael S Cookson7, Niels-Erik Jacobsen1, Nilay Gandhi13, Joshua Griffin14, Jeffrey S Montgomery15, Nikhil Vasdev16,17, Ewan Y Yu18, Evangela Xenias19,20, Nicholas J Campain21, Wassim Kassouf22, Marc A Dal’Era23, Jo-An Seah24, Cesar E Ercole25, Simon Horenblas26, John S. McGrath27, Jonathan Aning21,25, Shahrokh F Shariat19,26, Jonathan L. Wright27, Andrew C Thorpe28, Todd M Morgan15, Jeff M Holzbeierlein16,17, Trinity J Bivalacqua13, Scott North29, Daniel A Barocas30, Yair Lotan30, Petros Grivas30,31, Andrew J Stephenson32, Jay B Shah33, Bas W van Rhijn34, Philippe E Spiess35, Siamak Daneshmand36, Srijala S Sridhar37, Peter C Black1

11:00 AM – 11:10 AM PLASMA CIRCULATING TUMOUR DNA IS SCARCE AND CONFOUNDED BY CLONAL HEMATOPOIESIS IN METASTATIC RENAL CELL CARCINOMA
Jack VW Bacon1, Matti Annala1, Maryam Soleimani2, Jean-Michel Lavoie1, Kim N Chi3, Christian Kollmannsberger3, Alexander W Wyatt1, Lucia Nappi3

Session III: Treatment Resistance and Cellular Plasticity
(7-minute talk and 3-minute Q&A)
11:10 AM – 11:50 AM Moderator: Dr. Michael Cox
11:10 AM – 11:20 AM FUNCTIONAL GENOMIC SCREEN FOR CISPLATIN RESISTANCE PATHWAYS IN MUSCLE-INVASIVE BLADDER CANCER USING A GENOME-WIDE CRISPR KNOCKOUT SCREEN
Gunjan Kumar1,2,4, Elie Ritch1,4, Timo Nykopp1,4, Davide Tortora1,3,4, Alexander Wyatt1,4, Mads Daugaard1,4, and Peter C. Black1,4
11:20 AM – 11:30 AM  DISCOVERY OF A POTENTIAL EPIGENETIC REGULATOR AS EARLY DRIVER IN NE TRANSDIFFERENTIATION
Yu Wang¹,², Xinpei Ci¹,², Dong Lin¹,², Yuzhuo Wang¹,².

11:30 AM – 11:40 AM  VALIDATING SMALL-MOLECULE N-MYC INHIBITORS AS POTENTIAL THERAPIES FOR NEUROENDOCRINE PROSTATE CANCER

11:40 AM – 11:50 AM  SELECTIVE INHIBITION OF TRANSCRIPTION FACTOR BRN2 AS A TREATMENT STRATEGY FOR NEUROENDOCRINE PROSTATE CANCER
Daksh Thaper¹, Ravi Munuganti¹, Sahil Kumar¹, Soojin Kim¹, Loredana Puca², Sepideh Vahid¹, Shaghayegh Norouzi¹, Olena Sivak, Adeleke Aguda¹, Dwaiypayan Ganguli¹, Shengyu Ku⁴, Colm Morrissey³, Himisha Beltran²,4 and Amina Zoubaidi¹

Lunch and Posters   11:50 AM – 12:45 PM

Session IV: Technology, Functional Urology & Pediatrics
(7-minute talk and 3-minute Q&A)

12:45 PM – 1:55 PM  Moderator: Dr. Ryan Paterson & Dr. Lynn Stothers

12:45 PM – 12:55 PM  CLINICAL EVALUATION OF SONouroFLOWMETRY
Louisa Ho¹, Mark Dawidek¹, Rohit Singla², Angela Cho² & Christopher Ngua1,²

12:55 PM – 1:05 PM  INDWELLING URETERAL STENT PLACEMENT INDUCES APERISTALSIS, INJURY AND FIBROSIS
Kymora B. Scotland¹, Lu Wang², Chun Seow², Ben H. Chew¹, Dirk Lange¹

1:05 PM – 1:15 PM  CORTICAL CONTROL OF BLADDER STORAGE AND EMPTYING USING FUNCTIONAL NEAR INFRARED SPECTROSCOPY (fNIRS)
Lynn Stothers¹, Jennifer A. Locke¹, Andrew Macnab¹, Adam Klausner², John Speich²

1:15 PM – 1:25 PM  GLOBAL SURGERY: SURVEYING UNMET PEDIATRIC UROLOGICAL NEEDS IN LOW AND MIDDLE INCOME COUNTRIES
Phyllis Kisa¹,², Kourosh Afshar¹, Andrew E. MacNeily¹

1:25 PM – 1:35 PM  UPDATE ON RENAL CALCULUS TARGETING USING MACHINE LEARNING FOR EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY
Rohit Singla¹, Colin Lundeen², Connor M Forbes², David Hogarth³, Christopher Ngua1,²

1:35 PM – 1:45 PM  EVALUATION OF YOUTUBE VIDEO CONTENT RELATING WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH SURGICAL STANDARD OF CARE GUIDELINES FOR SEX REASSIGNMENT SURGERY
Jacqueline Li, Lynn Stothers, Andrew Macnab, Jennifer A. Locke, Alex Kavanagh

1:45 PM – 1:55 PM  WHAT IS THE RELATIONSHIP OF STRESS TO PATIENTS' STONE-RELATED QUALITY OF LIFE?
Colin Lundeen¹, Jonathan Lim¹, Kymora Scotland¹, Reza Safae Ardekani¹, Kristina Penniston², Neecole Streep², Thomas Chi¹, Jaime Landman¹, Davis Viprakasit³, Ben H. Chew¹
State of Art Lecture II

1:55 PM – 2:10 PM  The Genome of Metastatic Prostate Cancer as a Biomarker

Dr. Alex Wyatt
Assistant Professor, Department of Urologic Sciences

Session V

(7-minute talk and 3-minute Q&A)

2:10 PM – 2:50 PM  Moderator: Dr. Mads Daugaard

2:10 PM – 2:20 PM  G3BP1-ASSISTED TRANSCRIPT COMPARTMENTALISATION SUPPORTS SELECTIVE PROTEIN SYNTHESIS IN RESPONSE TO OXIDATIVE STRESS

Syam Prakash Somasekharan1, Fan Zhang1, Neethu Saxena1, Grace Kwong1, Caitlin Low1, Robert Bell1, Nikolay Stoynov2, Leonard Foster2, Martin Gleave1, Poul H Sorensen3

2:20 PM – 2:30 PM  GLYCOSAMINOLYCYANS SERVE TO PROTECT CANCER CELLS FROM STRESS

Maj Sofie Ørum-Madsen1,2, Charlotte Spliid2,4, Morgan Roberts1, Ali Salanti2, Sarah Truong1, Poul Sorensen3, Thomas M. Clausen2,4 and Mads Daugaard1

2:30PM – 2:40 PM  A MICROFLUIDIC CELL MIGRATION ASSAY ENABLING ANTICANCER DRUG TESTING OF EX-VIVO TUMOR CELLS

Emily S. Park1, Jeong Hyun Lee2, Kerryn Matthews2, Peter C. Black1,3, and Hongshen Ma1

2:40 PM – 2:50 PM  RAPID DETECTION OF CIRCULAR RNA THROUGH PSEUDO-ALIGNMENT SCHEME

Hossein Asghari1,2, Yen-Yi Lin2, Yang Xu3, Colin C. Collins2,4, and Faraz Hach

ADJOURN
Podium Presentations
Potent targeting of the androgen receptor (AR) in castration-resistant prostate cancer has altered the archetypal course of the disease, fueling the emergence of aggressive and incurable neuroendocrine prostate cancer (NEPC). These tumors can arise from non-neuroendocrine cells in response to AR pathway inhibitors (ARPIs), such as enzalutamide (ENZ), an observation consistent with lineage plasticity. Recent evidence suggests that evolution toward a NEPC phenotype is aligned with dynamic epigenetic reprogramming, but the molecular basis underlying this phenomenon remains poorly understood.

We utilized a non-oncogene-driven model of AR-indifferent NEPC to interrogate the molecular framework that underlies treatment-induced lineage infidelity and transition to the NE lineage. Our discovery that the AR cistrome undergoes extensive redistribution to support the onset of stem cell-like and neuronal transcriptional programs due, in part, to changes in chromatin accessibility led us to identify EZH2 at the reprogrammed AR binding sites. Intriguingly, while EZH2 is most often associated with establishing transcriptional repression, we measured heightened transcriptional activity at AR:EZH2 co-bound genes. This non-canonical function of EZH2 was associated with threonine-350 phosphorylation (pEZH2-T350), which was required for cells to enter a pliable, stem-like state that underlies NE lineage conversion. Treatment of AR-indifferent/NEPC cell lines with clinically relevant EZH2 inhibitors reversed the lineage switch to an adenocarcinoma state.

Collectively, our studies establish a cooperative role for AR and EZH2 in driving the insurgence of a NE phenotype in response to ARPIs, and posits that drugging the epigenome via EZH2 inhibition may reverse or delay lineage transformation to extend the durability of clinically beneficial therapies.
EVALUATION OF SYSTEMATIC ALTERATIONS ON TRANSCRIPTOME, TRANSLATOME AND PROTEOME BY ANDROGEN RECEPTOR BLOCKADE THERAPY IN PROSTATE CANCER

Fan Zhang1, Chidi Molokwu1, Raunak Shrestha1, Robert Bell1, Syam Prakash Somasekharan1, Gian Luca Negri2, Neetu Saxena1, Anders Kristensen2, Sue Ettinger1, Anne Haegert1, Dong Lin1, Stephane Le Bihan1, Faraz Hach1, Ladan Fazli1, YZ Wang1, Colin Collins1, Poul Sorensen2, Martin Gleave1

1The Vancouver Prostate Centre, Department of Urological Sciences, University of British Columbia, 2775 Laurel Street, Vancouver, British Columbia, Canada V6H 3Z6
2Department of Pathology and Laboratory Medicine, BC Cancer Research Centre, University of British Columbia, Vancouver, British Columbia, Canada V5Z 1L3

Introduction: Advances in technologies and data analytics in large-scale omics promote comprehensive understanding of biological and pathological phenomena. While genomics and transcriptomics have led efforts defining biomarkers and pathways related to responses to androgen receptor pathway inhibition (ARPI) and progression to castrate resistant prostate cancer (PCa), alterations in the global proteome after ARPI remain poorly understood. We hypothesize that defining the landscape of the ARPI-associated proteome will provide systematic and novel information at the functional molecular level that will facilitate identifying new biomarkers and therapeutic targets.

Methods: Tandem Mass Tag (TMT)-labelled quantitative proteome analysis was conducted along with the gene microarray analysis in LNCaP cells treated with Dihydrotestosterone and enzalutamide (ENZA). Translatome analysis was performed using Stable Isotope Labelling by Amino acid in Cell culture (SILAC)-labelling assay. The abundance of proteins and genes were overlapped among multi-omics datasets and the pathway enrichment were analysed.

Results: ENZA induced distinct alterations among the transcriptome, translatome and proteome datasets. Systematic functional pathway analysis from the proteome dataset unveiled numerous pathways that are modulated by AR blockade, such as cellular signaling, immune system, protein synthesis, bioenergetics, amino acid metabolism, transmembrane transport and RNA splicing. Unique alterations of proteome dataset were validated and the associated biological procedures were investigated.

Conclusions: This systematic study enabled generation of a high-resolution map on how PCa cells respond to androgen stimulation and AR antagonist treatment at mRNA and protein levels. This integrated multi-omics approach will provide new insights into complex mechanisms of stress response and progression of PCa.
IDENTIFYING THE GENOMIC FEATURES OF AKT1 / PIK3CA MUTANT METASTATIC PROSTATE CANCER USING CIRCULATING TUMOUR DNA

Andrew Murtha1, Cameron Herberts1, Simon Fu2, Sinja Taavitsainen1,3, Matti Annala1,3, Gillian Vandekerkhove1, Kevin Beja1, Yulia Loktionova1, Elena Schönlaub1, Kim N. Chi2, Alexander W. Wyatt1

1Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, British Columbia, Canada; 2Department of Medical Oncology, BC Cancer, British Columbia, Canada; 3Prostate Cancer Research Center, Faculty of Medicine and Life Sciences and BioMediTech Institute, University of Tampere, Tampere, Finland

Background: Hotspot activating mutations in AKT1 and PIK3CA represent a rare but potentially unique subset of metastatic prostate cancers (mPCa). The genomic and clinical features of these patients is currently unknown. Preclinical evidence suggests that unconstrained PI3K signalling via PTEN loss may render Androgen Receptor (AR) targeted therapy less effective. Given the availability of agents that target nodes within the PI3K pathway, elucidating the genomic properties of AKT1/PIK3CA mutant patients and their response to AR-targeted therapy is critical for therapeutic selection.

Methods: We performed deep targeted sequencing on 1381 cell-free DNA samples from 774 patients with mPCa. 552 patients had sufficient circulating tumour DNA (ctDNA) for detection of somatic alterations. Analysis was restricted to patients with hotspot AKT1/PI3KCA mutations of presumed clonal origin.

Results: 5.6% (31/552) of patients harboured ≥1 clonal hotspot mutation in either AKT1/PI3KCA, of which p.E17K and p.E545* were most common. This population was enriched for TP53 defects compared to a control cohort of AKT1/PIK3CA wild-type mPCa patients (23/31 vs. 70/135, p=0.027 Fisher’s Exact Test). Although AR aberrations were observed at similar frequencies, patients harbouring AKT1/PI3KCA mutations had fewer additional copies of AR (median 4.71 vs. 10.33, p=0.011, Mann-Whitney U test).

Conclusions: AKT1/PIK3CA mutant mPCa is defined by an aggressive genomic landscape, characterized by frequent disruption to TP53 and lower levels of AR amplification. These findings may nominate patients unlikely to respond to androgen-pathway inhibition who may instead benefit from PI3K targeted therapeutics. Work is ongoing to correlate genomic features with clinical variables to clarify this hypothesis.
HETEROGENEITY AND EVOLUTION IN MISMATCH REPAIR DEFECTIVE METASTATIC PROSTATE CANCER

Elie Ritch1, Simon Fu2, Cameron Herberts1, Evan W Warner1, Sinja Taavitsainen1,3, Andrew Murtha1, Gillian Vandekerkhove1, Kevin Beja1, Yulia Loktionova1, Daniel Khalaf2, Igal Kushnir4,5, Cristiano Ferrario6, Matti Annala1,3, Kim N Chi1,2*, Alexander W Wyatt1*

1Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, British Columbia, Canada; 2Department of Medical Oncology, BC Cancer, British Columbia, Canada; 3Prostate Cancer Research Center, Faculty of Medicine and Life Sciences and BioMediTech Institute, University of Tampere, Tampere, Finland; 4The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada; 5Sackler faculty of medicine, Tel Aviv University, Tel Aviv, Israel; 6Jewish General Hospital, McGill University, Montreal, QC, Canada. *co-corresponding authors.

Purpose: DNA mismatch repair defects (MMRd) and tumor hypermutation are rare in metastatic prostate cancer. As such, the salient genomic and clinical features of this distinct disease subtype remain poorly characterized. Furthermore, since MMRd prostate cancers can respond to immune checkpoint inhibitors, there is an urgent need for practical MMRd detection tools.

Experimental design: We performed targeted sequencing of 1047 plasma cell-free DNA samples from patients with clinically-progressing metastatic prostate cancer. Suitable MMRd samples and available archival tissue were also subjected to whole exome sequencing.

Results: 665 samples from 434 patients had circulating tumor DNA (ctDNA) purity above 2% and were evaluable. 15 patients (3.5%) had MMRd etiology, evidenced by pathogenic alterations in MSH2 or MSH6, and/or a combination of somatic hypermutation, microsatellite instability, and characteristic trinucleotide signatures. Tumor suppressors such as PTEN, RB1, and TP53 were typically inactivated by mutation rather than copy number loss. Unlike mismatch repair intact prostate cancer, hotspot mutations in oncogenes such as AKT1, PIK3CA and CTNNB1 were common, and the AR ligand binding domain was mutated in 9/15 patients. We observed high intra-patient clonal diversity, evidenced by subclonal driver mutations and dynamic shifts in clonal populations over time. MMRd patients had a worse clinical prognosis, including a poor response to AR targeted therapy, than mismatch repair intact prostate cancer.

Conclusions: MMRd metastatic prostate cancer is associated with oncogene activation and subclonal diversity, which may contribute to a clinically aggressive disposition. In patients with detectable ctDNA, panel-based cell-free DNA sequencing is a practical tool to prioritize this subtype for immunotherapy.
MOLI: MULTI-OMICS LATE INTEGRATION WITH DEEP NEURAL NETWORKS FOR DRUG RESPONSE PREDICTION

Hossein Sharifi-Noghabi¹,², Olga Zolotareva², Colin C. Collins³,⁴ and Martin Ester¹,³

¹School of Computing Science, Simon Fraser University, Burnaby, BC, Canada.
²Faculty of Technology and Center for Biotechnology, Bielefeld University, Germany.
³Vancouver Prostate Centre, Vancouver, BC, Canada.
⁴Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada.

Introduction: Historically, gene expression has been shown to be the most informative data for drug response prediction. Recent evidence suggests that integrating additional omics can improve the prediction accuracy which raises the question of how to integrate the additional omics. Regardless of the integration strategy, clinical utility and translatability are crucial. Thus, we reasoned a multi-omics approach combined with clinical datasets would improve drug response prediction and clinical relevance.

Method: We propose MOLI, a Multi-Omics Late Integration method based on deep neural networks. MOLI takes somatic mutation, copy number aberration, and gene expression data as input, and integrates them for drug response prediction. MOLI uses type-specific encoding subnetworks to learn features for each omics type, concatenates them into one representation and optimizes this representation via a combined cost function consisting of a triplet loss and a binary cross-entropy loss. The former makes the representations of responder samples more similar to each other and different from the non-responders, and the latter makes this representation predictive of the response values.

Results: We validate MOLI on in vitro and in vivo datasets for five chemotherapy agents and two targeted therapeutics. Compared to state-of-the-art single-omics and early integration multi-omics methods, MOLI achieves higher prediction accuracy in external validations. Moreover, a significant improvement in MOLI’s performance is observed for targeted drugs when training on a pan-drug input, i.e. using all the drugs with the same target compared to training only on drug-specific inputs. MOLI’s high predictive power suggests it may have utility in precision oncology.
IDENTIFY: The Investigation and DETection of urological Neoplasia in patients referred with suspected urinary tract cancer: A multicentre analysis

Miles P. Mannas1,2, Tae Lee1, Brian Mayson3, Peter C. Black1,2, Sinan Khadhouri4, Kevin M. Gallagher5, Kenneth R. MacKenzie6, Taimur T. Shah7, Chuanya Ga8, Sacha Moore9, Eleanor Zimmermann10, Eric Edison11, Matthew Jefferies12, Arjun Nambiar13, John S. McGrath14, Veeru Kasivisvanathan15, The IDENTIFY Study Group

1. The Department of Urologic Sciences, UBC, Vancouver, BC, Canada
2. Vancouver Prostate Centre, Vancouver, BC, Canada
3. St. Paul’s Hospital, Vancouver, BC, Canada
4. Aberdeen Royal Infirmary, Dept. of Urology, Aberdeen, United Kingdom
5. Western General Hospital, Dept. of Urology, Edinburgh, United Kingdom
6. Freeman Hospital, Dept. of Urology, Newcastle, United Kingdom
7. Charing Cross Hospital, Imperial College Healthcare NHS Trust, Dept. of Surgery and Cancer, London, United Kingdom
8. Peterborough City Hospital, Dept. of Urology, Peterborough, United Kingdom
9. Wrexham Maelor Hospital, Dept. of Urology, Wrexham, United Kingdom
10. Weston General Hospital, Dept. of Urology, Weston-super-Mare, United Kingdom
11. North Middlesex Hospital, Dept. of Urology, London, United Kingdom
12. Morriston Hospital, Dept. of Urology, Swansea, United Kingdom
13. Freeman Hospital, Dept. of Urology, Newcastle, United Kingdom
14. University of Exeter Medical School, Dept. of Urology, Exeter, United Kingdom
15. West Hertfordshire NHS Trust, Dept. of Urology, London, United Kingdom

Introduction & Objectives

The IDENTIFY study aims to determine contemporary urinary tract cancer prevalence and diagnostic test performance in patients referred to secondary care with suspected urothelial cancer.

Materials & Methods

An international, multi-centre, prospective study of patients referred to Urology, with or without haematuria, for the investigation of suspected urinary tract cancer. Patient demographics, presenting features and diagnostic test results were recorded. Prevalence rates were calculated for each subtype of urological cancer and diagnostic test accuracies were calculated.

Results

Over 11,000 patient records were collected from 111 hospitals in 27 countries (Dec 2017 - Dec 2018). 65.5% had visible haematuria [VH], 28.9% non-visible haematuria [NVH] and 5.6% no haematuria [NH]. The prevalence of bladder cancer [BC] overall was 17.9%; (VH: 22.4%, NVH: 5.2%, NH: 30.6%). The prevalence of upper tract urothelial cancer [UTUC] was 1.17% (VH: 1.60%, NVH: 0.28%), renal cell carcinoma [RCC] 0.98% (VH:1.26% NVH:0.41%) and prostate cancer 1.14% (VH:1.37% NVH:0.54%). The diagnostic performance of ultrasound [US] and computed tomography [CT] is given in Table 1.
Conclusions

IDENTIFY provides contemporary cancer detection rates and patient variables in a global population alongside diagnostic test performance for each cancer type.

Table 1: Test characteristics of US and CT in diagnosis of BC and UTUC for tests that were deemed adequately conducted.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
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<tbody>
<tr>
<td><strong>Bladder cancer</strong></td>
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<tr>
<td>US</td>
<td>77.8% (95% CI 74.4%-81.0%)</td>
<td>93.5% (95% CI 92.7%-94.3%)</td>
<td>67.8% (95% CI 64.9%-70.5%)</td>
<td>96.0% (95% CI 95.5%-96.6%)</td>
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<tr>
<td>Contrast CT</td>
<td>80.5% (95% CI 77.3%-83.4%)</td>
<td>92.3% (95% CI 91.3%-93.3%)</td>
<td>71.5% (95% CI 68.7%-74.1%)</td>
<td>95.2% (95% CI 94.4%-95.9%)</td>
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<tr>
<td><strong>UTUC</strong></td>
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<td>US</td>
<td>42.5% (95% CI 27.0%-59.1%)</td>
<td>97.7% (95% CI 97.3%-98.1%)</td>
<td>12.7% (95% CI 12.4%-27.7%)</td>
<td>99.5% (95% CI 99.4%-99.7%)</td>
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<td>CT Urogram</td>
<td>95.7% (95% CI 88.0%-99.1%)</td>
<td>94.4% (95% CI 93.5%-95.2%)</td>
<td>26.8% (95% CI 24.0%-29.8%)</td>
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CLINICAL CHARACTERISTICS AND OUTCOMES FOR YOUNG PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA

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Introduction: The outcomes of patients with advanced urothelial carcinoma (UC) remain poor. While UC is predominantly a disease of the elderly, there is a cohort of relatively young patients whose natural history is incompletely studied. We present a multi-center series of young patients diagnosed with metastatic UC.

Methods: We identified patients from the BC Cancer Registry who had a diagnosis of metastatic UC at age ≤55 and received first-line cisplatin-gemcitabine (Cis-Gem) from 2000-2017. Individual patient records were reviewed for baseline characteristics, treatment and outcomes. Kaplan-Meier analysis was conducted with Log-Rank tests for statistical significance.

Results: 94 cases were identified, of which the majority were male (78%) and smoking-related (68%). Median ECOG was 1 and 40% had visceral metastases at diagnosis. 42 patients (45%) had previous cystectomy and 17% received peri-operative Cis-Gem. Nearly half of patients were unable to complete first-line Cis-Gem due to progression (26%) and adverse events (18%). Median overall and progression-free survival were 9.7 and 7.1 months, respectively, for all patients. 33 patients received subsequent systemic therapies, mostly taxanes (n=19) or another platinum doublet (n=9). 4 patients went on to clinical trial and 5 received immunotherapy. Univariate factors associated with poor survival include anemia (median 15 vs. 8.8 months; p=0.02), visceral metastases (median 12.9 vs. 8.7 months; p=0.01), and having received only 1 line of systemic therapy (17.5 vs. 8.5 months; p<0.0001). There was a trend towards worse survival in patients diagnosed with de novo metastatic disease (median 11.7 vs. 10.5 months; p=0.06) and ECOG ≥2 (median 10.8 vs. 6.3 months; p=0.19).

Conclusions: Metastatic UC in young patients is an aggressive entity with poor survival that appears worse than expected for the general population. Known risk factors for mortality were validated in this cohort. Further studies are warranted to directly analyze the impact of age on outcomes.
THE PROGNOSTIC VALUE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY AND RADICAL CYSTECTOMY

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**INTRODUCTION:** The neutrophil-to-lymphocyte ratio (NLR) has shown promise as a prognostic factor in muscle invasive bladder cancer (MIBC), but its value in patients receiving neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) is not yet established. Since NLR is related to an oncogenic environment and poor anti-tumor host response, we hypothesized that a high NLR would be associated with a poor response to NAC and would remain a poor prognostic indicator in patients receiving NAC.

**METHODS:** A retrospective analysis was performed on patients with non-metastatic MIBC who received NAC prior to RC between 2000-2013 at one of 19 centres across Europe and North America. The pre-NAC NLR was used to split patients into a low (NLR≤3) and high (NLR>3) group. Demographic and clinical parameters were compared between the groups. Putative risk factors for disease-specific and overall survival, as well as predictors of response to NAC were investigated using multivariable analyses.

**RESULTS:** Data was available for 340 patients (199 NLR≤3, 141 NLR>3). NLR was the only significant risk factor in the logistic regression for predictors of response (OR: 0.36, \( p = 0.003 \)). NLR was also a significant risk factor for both disease-specific and overall survival (HR:2.4, \( p = 0.006 \) and HR:1.8, \( p = 0.02 \)).

**CONCLUSION:** NLR>3 is associated with a decreased response to NAC and worse patient outcomes, including reduced disease-specific and overall survival. This suggests that NLR is a simple tool that can aid in MIBC risk stratification in clinical practice.
PLASMA CIRCULATING TUMOUR DNA IS SCARCE AND CONFOUNDED BY CLONAL HEMATOPOIESIS IN METASTATIC RENAL CELL CARCINOMA

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Background: Clear cell renal cell carcinoma (ccRCC) accounts for 75-80% of all kidney cancer. Over the past decade, the diversity of treatments available for this indication has increased dramatically. However, access to somatic information will be critical for improving patient outcomes. In other genitourinary malignancies, circulating tumour DNA (ctDNA) has been an effective, minimally-invasive technique for profiling the tumour genome.

Methods: Blood samples were collected from stage IV ccRCC patients for next-generation sequencing of ctDNA and germline DNA. Targeted sequencing was performed using Roche Human Oncology Design panel (981 genes) to a median depth of 937x.

Results: We accrued a cohort of 55 ccRCC patients not receiving systemic therapy. Somatic mutations were detected in 28/51. No alterations were detected in canonical RCC-associated genes for 13/28. These likely represent an independent somatic expansion of the leukocyte population, rather than ccRCC. For 15 patients with RCC-associated gene alterations, the median ctDNA fraction was 4.9%. This is significantly lower than both prostate (67% lower) and bladder (80% lower). Consistent with tissue-based reports, VHL, BAP1, PBRM1, and TP53 were the most frequently altered.

Conclusions: The rate of ctDNA detection in metastatic ccRCC appears to be lower than in prostate and bladder cancer. Furthermore, many alterations may reflect an independent somatic expansion and not ctDNA. Nevertheless, ~30% of patients exhibited clinically-informative alterations in their liquid biopsy. Overall, our findings suggest that ctDNA, as a tool to survey the somatic genome, may not be suitable for all metastatic ccRCC patients.
FUNCTIONAL GENOMIC SCREEN FOR CISPLATIN RESISTANCE PATHWAYS IN MUSCLE-INVASIVE BLADDER CANCER USING A GENOME-WIDE CRISPR KNOCKOUT SCREEN

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Introduction: Neoadjuvant chemotherapy (NAC) followed by radical cystectomy in patients with bladder cancer has been shown in multiple trials and meta-analyses to improve five-year survival, and is therefore currently the first-line standard of care in patients. However, 60% of patients are inherently resistant to NAC at the time of cystectomy. While several mechanisms of cellular resistance to cisplatin have been proposed, the complete landscape of genetic modification remains largely unknown.

Our central hypothesis is that using a genome-wide CRISPR knockout library, we can identify specific gene targets that confer cisplatin resistance in bladder cancer cell lines.

Methods: To test this hypothesis, we take advantage of a pooled genome-wide pooled CRISPR knockout library (Brunello) targeting 19,114 protein coding genes with 76,441 synthetic guide RNAs (sgRNAs). Transduced cells were subject to treatment with 1μM of cisplatin for 5, 7 and 10 days. Surviving cells were harvested and the integrated sgRNAs are sequenced to determine sgRNA enrichment scores. Gene hits were validated individually using CRISPR knockout and shRNA knockdown experiments.

Results: Overall, knockdown of genes involved in the cellular apoptosis (e.g. CASP8) regulation pathways lead to a resistance phenotype. Furthermore, we have also identified a novel gene (SLFN11) in a bladder cancer context which also plays an important role in the modulation of resistance to cisplatin.

Conclusion: The results from the screen and subsequent validation suggests that there are multiple different modes of regulation of cisplatin resistance and studying pathways as a whole, could potentially give us novel targets for future therapeutic application.
DISCOVERY OF A POTENTIAL EPIGENETIC REGULATOR AS EARLY DRIVER IN NE TRANSDIFFERENTIATION

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Introduction: Neuroendocrine prostate cancer (NEPC) is a lethal subtype of prostate cancer (PCa) generally developed from adenocarcinoma after long-term androgen deprivation therapy (ADT) via a NE transdifferentiation process. The high conservation of genome characteristics suggests that NEPC development is an adaptive transdifferentiation process in which epigenetic regulators may play important roles. In this study, we have identified PRDM16 as an epigenetic regulator potentially drives the NE transdifferentiation process and promote NEPC development.

Results: PRDM16 has been screened as our candidate by RNA-seq data of PDX models using bioinformatics technique. In both PDX model and clinical cohorts, upregulated expression level of PRDM16 in NEPC was observed compared with adenocarcinoma. The in vitro study was consistent with the clinical observation, upregulation of PRDM16 is significantly high in NEPC cell line compared with other PCa cell lines. In the functional study, overexpression PRDM16 in PC3 induced NE markers expression, and knockdown PRDM16 in NEPC cell line suppress the expression of NE markers.

Conclusions: we have identified PRDM16 as a potential driver of NEPC development in this study. Expression of PRDM16 starts to be upregulated at the time point of castration, keeping increase during the NE transdifferentiation process, which suggests PRDM16 is an early regulator. The in vitro study revealed that PRDM16 is associate with NE phenotype, suggests that PRDM16 might be a driver of NE transdifferentiation. Taken together, we identify that the epigenetic regulator PRDM16 is an early driver of NE transdifferentiation during NEPC development.
VALIDATING SMALL-MOLECULE N-MYC INHIBITORS AS POTENTIAL THERAPIES FOR NEUROENDOCRINE PROSTATE CANCER


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Introduction: N-Myc is a proto-oncogene implicated in various neuroendocrine tumours. It is an important driver of transition from castration resistant prostate cancer (CRPC) to neuroendocrine prostate cancer (NEPC). N-Myc overexpression is observed in many NEPC cases and is associated with poor prognosis and aggressive phenotype, making it a compelling target for therapeutic intervention. Nevertheless, no drugs directly targeting N-Myc-Max complex/its binding to DNA have yet been approved for clinical use.

Methods: An in silico drug discovery approach was used to identify potential small molecule N-Myc inhibitors targeting a pocket on the interface of the N-Myc-Max complex and DNA. Compounds were evaluated in cell-based assays for their effects on the viability of N-Myc driven neuroblastoma cells and models of NEPC. In addition, their capability to induce apoptosis and to regulate the expression of N-Myc target genes were studied.

Results: The lead compound, VPC-70551 has excellent stability (half-life: 140 minutes) in microsomes (compared to literature compound, 10074-G5: 3 minutes). VPC-70551 shows low (10%) toxicity at 10 µM in Myc-negative HO15.19 cells and an IC50 of 4 µM in transcriptional assay. Importantly, this compound effectively stopped the growth of N-Myc driven IMR32 cells in a dose dependent manner, with no effect on non-N-Myc driven neuroblastoma cell lines, SK-N-AS and NB-16. The compound effectively induced apoptosis and downregulated N-Myc target genes in these cells.

Conclusions: These results position us to investigate key structure activity relationships (SAR) to further develop more potent and selective N-Myc-Max inhibitors for in vitro and in vivo validation.
SELECTIVE INHIBITION OF TRANSCRIPTION FACTOR BRN2 AS A TREATMENT STRATEGY FOR NEUROENDOCRINE PROSTATE CANCER

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Introduction: Resistance to newly developed androgen receptor pathway inhibitors (ARPIs), such as Enzalutamide (ENZ), rapidly emerges. In particular, a subset of patients who relapse following ARPI therapy their dependence on AR signaling and emerge with neuroendocrine features. These tumors, termed treatment induced neuroendocrine prostate cancer (t-NEPC), carry an extremely poor prognosis and, to date, treatment remains decades old cytotoxic chemotherapies. Recently our group identified the neural transcription factor BRN2 as a major clinically relevant driver of NEPC and targeting BRN2 is a promising strategy to prevent neuroendocrine differentiation or treat NEPC.

Methods/Results: In silico screening of small molecules was conducted on a model of BRN2 which was validated with the first-in-field crystal structure of BRN2 DNA binding domain. On the basis of the model, several small molecules were identified that showed direct binding to BRN2 and inhibited its reporter activity. Pharmacokinetic studies measured stability and bioavailability of medchem optimized lead compound (BRN2i) that significantly reduced tumor growth in multiple xenograft models with no measurable side effects.

In silico modeling showed a 7Å shift in the DBD once it was bound to BRN2i, this shift translated to reduced interaction with DNA by chromatin fractionation and ChIP-seq, thus confirming the mode of action for BRN2i is through loss of DNA binding. Loss of BRN2 binding drastically reduced cell proliferation in NEPC cell lines 42D\textsuperscript{ENZ}, NCI-H660 and NEPC organoids as well as downregulated several known targets in NEPC like \textit{EZH2}, \textit{ASCL1}, \textit{SOX2} and \textit{PEG10}. These results were validated with CRISPR/Cas9 mediated knockout of BRN2, demonstrating on-target specificity for the BRN2i.

Conclusion: The described work aims to lay the pre-clinical foundation for the integration of BRN2 targeted therapies into the treatment landscape to improve survival for patients suffering from small-cell neuroendocrine prostate cancer.
CLINICAL EVALUATION OF SONOUROFLOWMETRY

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Introduction: Uroflowmetry is a widely used diagnostic test for evaluating lower urinary tract symptoms. Sonouroflowmetry is a novel approach to uroflowmetry based entirely on acoustic measurement. The purpose of this study was to evaluate sonouroflowmetry in a clinical setting, using the publicly available “Uroflow Trace” application, against the gold standard Laborie device. Due to its simplicity, low-cost, and portability, sonouroflowmetry has implications for screening and monitoring pathologies such as benign prostatic hyperplasia and urethral stricture disease.

Methods: Adult men (n =20) visiting the urology clinic for various pathologies performed uroflowmetry simultaneously using the “Uroflow Trace” application and a Laborie device. MATLAB script was written to extract volume, time, and flow data, which were compared using Bland-Altman analysis.

Results: The correlation coefficient for measurements of peak urine flow was 0.43. This improved to 0.91 when normalized by the voided volume, however, Bland-Altman analysis revealed limits of agreement (LoA) of -13.2 and -0.3 cc/s. Correlation for time to max flow was 0.74 with LoA -8.5 and 12.5 s, while correlation for total voiding time was 0.96 with LoA -7.2 and 7.1 s.

Conclusions: This study suggests that the acoustic based “Uroflow Trace” application is in poor agreement with the gold standard Laborie device. “Uroflow Trace” performed particularly poorly in evaluating peak urine flow, typically the most clinically relevant measurement. This is likely attributable to inherently high variability and difficulty standardizing acoustic signals. Future work might evaluate acoustic uroflowmetry for specific pathologies as well as intra-patient reliability.
INDWELLING URETERAL STENT PLACEMENT INDUCES APERISTALSIS, INJURY AND FIBROSIS

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Introduction and Objectives:

Ureteral stenting can cause symptoms including pain and discomfort in more than 80% of patients. Previous work suggested a role for the Gli family proteins and erythropoietin in regulating proper function of ureteral smooth muscle. We sought to investigate the effects of cellular signaling by Gli proteins and erythropoietin on stented porcine ureters.

Methods:

Pigs were stented for set time periods. They were evaluated for extent and timing of hydronephrosis, ureteral dilation, and rate of peristalsis. Tissues were examined for evidence of urinary system inflammation by a blinded pathologist. RNA and protein level experiments were used to evaluate expression of potential biomarkers. Ureteral contractile force was evaluated.

Results:

Stent placement triggers massive ureteral dilation, aperistalsis and moderate hydronephrosis within 48 hours of placement. Gli1 expression was increased in stented ureters as compared to contralateral unstented ureters. Similarly, increased expression of markers of kidney injury and fibrosis was noted. Erythropoietin did not improve peristalsis or contraction force but was noted to decrease non-purposeful spasming in stented ureters. Tamsulosin administration affects force of contraction but not rate of peristalsis in stented ureters.

Conclusions:

Regulation of peristalsis in stented ureters is multifactorial. Tamsulosin increases contractile force, consistent with previous theories on alpha blocker function in ureteral obstruction. Prophylactic erythropoietin may regulate ureteral stabilization in stretch induced spasming following stent placement. Stent placement causes kidney injury, potentially leading to Gli family activation and efforts at repair. Continuing work will elucidate the role of these agents in coordinating ureteral contractions and combatting stent-induced injury.
CORTICAL CONTROL OF BLADDER STORAGE AND EMPTYING USING FUNCTIONAL NEAR INFRARED SPECTROSCOPY (fNIRS)

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Introduction: Control of micturition is complex. Cortical activity related to pelvic floor muscle (PFM) contractions has been demonstrated using fMRI but is limited due to imaging solely in the supine position. Functional near infra-red spectroscopy (fNIRS) which detects changes in oxyhemoglobin (O2Hb) and deoxy-hemoglobin (hHb) concentrations is non-invasive, maps cortical activity in real time and allows upright posture.

Methods: Fifteen subjects were included. A protocol proving PFM control by fMRI was replicated then extended to include spontaneous voiding, uroflow and post void residual urine. fNIRS was performed using a 4x4 optode grid over the frontal cortex, at 10 Hz. Storage parameters were conducted using a wireless 23 channel fNIRS instrument during natural filling. At capacity, subjects imitated voiding by releasing or imitated interruption of voiding by contracting PFMs for 10 sec over 10 repetitions followed by voluntary voiding. O2Hb and hHb patterns were captured, then linked to uroflow in video format. A distractor was introduced at the time of urgency to examine for the ability to ablate cortical signals.

Results: In subjects PFM contraction and relaxation induced a repetitive activation pattern in the frontal cortex with increases in O2Hb evident. There was an increase in O2Hb detectable in the lateral prefrontal area following permission to void at capacity with urge*. Distraction is able to ablate cortical responses during urgency**.

Conclusion: A fNIRS protocol to detect activation of the frontal cortical micturition region during voluntary uroflow and during PFM is presented for future studies.

* Distraction is able to ablate cortical responses during urgency.
** Distraction is able to ablate cortical responses during urgency.
Introduction: The World Health Organization estimates that over 90% of congenital malformations occur in Low and Middle Income Countries (LMICs). Surgical collaborations and short-term missions help address unmet needs in LMICs. Most literature describes programs addressing several pediatric surgical specialties but little pediatric urology. Although pediatric urologic conditions compose a substantial burden in LMICs with a paucity of providers to meet these needs, little is known about global engagement in pediatric urology.

Objective: To describe the scope, challenges and recommendations for advancing pediatric urology in global health.

Methods: We reviewed databases (PUBMED, EMBASE and MEDLINE Ovid), reports and websites, and surveys by Global Initiative for Children Surgery (GICS) and American Pediatric Surgical Association (APSA).

Results: 41 responses were reviewed from the GICS survey. 30% cited complex pediatric urologic patients as most neglected, 10% reported main challenge as lack of specialist surgeons. Local specialist training was universally recommended as the most effective way to meet pediatric surgical needs. APSA members provided a 10% response rate. 46% were involved in LMICs, 80% for less than 10 days. 12% cared for pediatric urologic patients. Main challenges were lack of specialist training, no commitment to training and infrastructure. Over 50% of respondents could not host and train LMIC surgeon. KidsOR® had only 1 of 8 centres request for urologic equipment.

Conclusion: Despite complex pediatric urology being perceived as most neglected, there isn’t much activity in this sphere of global surgery. There is a great need to train local pediatric urology expertise.
UPDATE ON RENAL CALCULUS TARGETING USING MACHINE LEARNING FOR EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY

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Introduction: Extracorporeal Shockwave Lithotripsy (ESWL) requires the focused delivery of energy. A urinary stone is initially targeted, but its movement during the procedure reduces the time that the stone remains at the focal point. This reduces ESWL efficacy and potentially increases damage to surrounding tissues. Automated identification of the stone would increase efficiency in initial targeting and energy delivery. We propose a computer vision algorithm to locate stones during ESWL.

Methods: 15367 fluoroscopic images from 5586 patients that underwent ESWL were manually annotated by drawing a bounding box around any stone present. The RetinaNet algorithm was trained via supervised learning on a training set of images. After optimization, it was tested on a separate set of testing images. The mean Average Precision (AP) and stone detection time were obtained.

Results: The mean (± stdev) AP was 0.81 ± 0.15, indicating that in 1 of every 1.23 images the algorithm was able to locate the stone to within ≥ 50% of the annotation. Images that were challenging included those with a small target size (< 5% of image) or technically inadequate images. The average (± stdev) detection time was 63 ± 1ms.

Conclusions: An algorithm to automatically detect urinary stones during ESWL is presented, achieving ample precision to further develop an active targeting system.

Source of funding: None
EVALUATION OF YOUTUBE VIDEO CONTENT RELATING WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH SURGICAL STANDARD OF CARE GUIDELINES FOR SEX REASSIGNMENT SURGERY

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INTRODUCTION: World Professional Association for Transgender Health (WPATH) promotes evidence-based care and education to support practices including surgery for transsexual, transgender and gender non-conforming people. WPATH indicates the Internet is often used by patients to share information on their experience with surgeons and can be used for education. Herein, we analyze the quality and comprehensiveness of Youtube videos matched against surgical care standards recommended in WPATH.

METHODS: Youtube videos were identified using search terms including gender affirmation surgery, sex reassignment surgery (SRS) and vaginoplasty. Each was independently evaluated by 4 investigators using a standardized questionnaire based on WPATH criteria.

RESULTS: Of 352 videos identified, 177 were topically related, 31 met inclusion criteria. 20 were narrated by patients, 6 by surgeons, 1 by an institute and 4 news anchors. The most common surgery described was vaginoplasty. Only 1 covered all common complications set out by WPATH. Patients reported pain, bleeding and urologic complications.

Of 8 indications for SRS, 26% mentioned cosmesis. Of 3 conditions related to ethics of surgery, 19% mentioned altering normal structures. Regarding consent, only 2 mentioned the term “informed consent.” No video met all surgical competency requirements or discussed the surgeons role. 29% discussed costs; 2 patients openly monetizing their video and showed their genital reconstruction to raise funds to support their care.

CONCLUSIONS: There is a lack of WPATH criteria in current Youtube video content. Discussions regarding urologic surgery, indications and complications is scant and additional detail could further patient education.
WHAT IS THE RELATIONSHIP OF STRESS TO PATIENTS’ STONE-RELATED QUALITY OF LIFE?

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Introduction

Patients with kidney stones have lower health-related quality of life (HRQOL) not only when they have a stone but also between stone events and even when their stone(s) are asymptomatic. Higher stress has been reported as a potential factor in HRQOL, yet there have been few investigations into the effect of stress on stone-related quality of life (QOL). In this study, we evaluated the relationship of stress to stone-related QOL.

Methods

Patients enrolled in the Wisconsin Stone Quality of Life (WISQOL) Research Consortium who contemporaneously completed both the WISQOL and the Perceived Stress Scale (PSS-10), a validated general stress questionnaire, were included. Patients were stratified into those with stones at the time of the questionnaires (further subdivided into those with and without symptoms) and those without stones. Statistical comparisons were made between groups and correlations between responses on the 2 instruments.

Results

Patients (n=704) from 6 centers were included. There was no overall correlation (R=-0.05; Pearson correlation coefficient) between the questionnaires. Moreover, while the WISQOL identified patients who currently had a stone, the PSS-10 did not (p<0.0001). These factors suggest that stress is not a significant driver of stone-related QOL.

Conclusions

General stress does not appear to drive overall stone-related QOL, including in patients with a current kidney stone. The lack of correlation between QOL and stress indicates that patients with stone disease have factors other than stress that affect QOL. The WISQOL is a highly sensitive tool capable of measuring patients’ stone-related QOL.
G3BP1-ASSISTED TRANSCRIPT COMPARTMENTALISATION SUPPORTS SELECTIVE PROTEIN SYNTHESIS IN RESPONSE TO OXIDATIVE STRESS

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Introduction: In response to stress, organisms limit energy-consuming mRNA translation and protein synthesis to maintain metabolic and protein homeostasis. One mechanism involves binding and sequestration of mRNAs by RNA binding proteins (RBPs) in large ribonucleoprotein complexes called stress granules (SGs). While SG formation is accompanied by reduced translation, it remains unclear whether SGs also influence partition of specific transcripts to polysomes (PSs) for selective translation.

Methods: To study stress-induced selective translation and possible transcript partitioning between PSs and SGs, we profiled the transcripts that are differentially present in the PSs by sucrose gradient fractionation in arsenite stressed cells, and then compared those transcripts with transcripts that are complexed with G3BP1, a key component and nucleator of SGs, using APEX method in unstressed and arsenite stressed cells.

Results: Our results suggest that short-term oxidative stress profoundly effects translation by promoting selective enrichment or depletion of transcripts in PSs, without effecting rates of global transcription. G3BP1 participates in the compartmentalisation of transcripts in this selective translation. In unstressed cells, G3BP1 in complex with other RBPs keeps transcripts for translation in stressed cells, and in the stressed cells, G3BP1 recruits transcripts away from polysomes, sequestering them in the stress granules.

Conclusion: By partitioning transcripts in different compartments to guide selective translation, G3BP1 plays an essential role in cell survival and adaptation in response to stress.
GLYCOSAMINOGLYCANS SERVE TO PROTECT CANCER CELLS FROM STRESS

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Background: Malignant cells utilize various strategies to adapt to oxidative and endoplasmic reticulum (ER) stress, imposed on them by the local tumor microenvironmental. During brain trauma, chondroitin sulfate (CS), a sulfated class of glycosaminoglycans, is promptly upregulated. Despite plenty of research describing the numerous roles and abnormal expression of CS in cancer, little is known about its regulation during carcinogenesis. Here, we investigated the regulation and functional impact of GAGs, particularly CS, during cancer-associated stress.

Results: Quantitative and qualitative analyses of total CS levels and sulfation pattern was performed on stress challenged cells compared to untreated controls. Total and 4-O-sulfated CS (CSA) levels were increased upon ER and oxidative stress as shown by reverse phase HPLC. Confocal microscopy using labelled rVAR2 to detect the cancer-specific CSA epitope, showed increased Golgi signal and surface staining consistent with increased CS biosynthesis during stress. Only minor changes in CS enzyme mRNA expression were observed, suggesting that mechanisms other than enzyme expression are at play. Importantly, cell lines modified to not express GAGs were significantly more susceptible to ER stress, committing the cells to apoptosis as compared to wildtype cells with intact GAG expression. This implies a protective role of GAGs during stress.

Conclusions: We report that perturbations in the ER and oxidative homeostasis trigger CS biosynthesis in the Golgi, suggesting that these pathways are linked. GAG synthesis is likely a part of the mechanisms allowing cancer cell to adapt to stress by antagonising the detrimental effects during oxidative/ER stress and preventing apoptosis.
A MICROFLUIDIC CELL MIGRATION ASSAY ENABLING ANTICANCER DRUG TESTING OF EX-VIVO TUMOR CELLS

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Introduction: The migration of cancer cells via chemotaxis is a fundamentally important capability during metastasis. While existing in vitro migration assays have improved our understanding of cell migration, these approaches are primarily useful for testing homogenous cells, and cannot be used to test ex vivo samples that are heterogeneous. Furthermore, these assays require a substantial number of cells, making them incompatible with fine-needle biopsies. In order to overcome these challenges, we developed a microfluidics cell migration assay to assess anticancer drug efficacy on ex vivo samples from patient tumors.

Methods: We developed a microfluidic device to generate uniform and stable chemical gradients. Additionally, we developed in situ staining methods after chemotaxis in order to phenotype the heterogenous cell samples. We tested this device with chemotaxis assays on LNCaP and PC3 under drug and hormone treatments.

Results: Using this microfluidic-based cell migration assay, we observed LNCaP and PC3 migratory behavior during drug treatment after 4 h serum starvation. The velocity of LNCaP towards chemoattractant (FBS) was reduced with enzalutamide or docetaxel while r1881 stimulated migration. Only docetaxel affected the velocity of PC3. In situ staining after chemotaxis enabled the subtyping of heterogenous cells by identifying intra/extracellular proteins.

Conclusion: We developed a microfluidic device that provides uniform and stable chemical gradients to perform cell migration assays. Using this assay, we showed the migration of prostate cancer cells under drug and hormone treatment, demonstrating its potential for evaluation of the migratory capacity of patient-derived tumor cells in response to therapy.
RAPID DETECTION OF CIRCULAR RNA THROUGH PSEUDO-ALIGNMENT SCHEME

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Recent advances in high-throughput sequencing data reveal ubiquitous expressions of circular RNAs (circRNAs) in a variety of eukaryotes with back-splice junctions between a downstream 3’ splice site and an upstream 5’ splice site. Since their expression patterns are often disease-specific, circRNAs are believed to have great potentials as cancer biomarkers. Most available circRNA detection pipelines only analyze breakpoints of chimeric mappings from RNA-Seq mappers which are time and memory intensive, and lightweight pseudo-alignment tools cannot be applied here since they require complete transcript and circRNA sequences in the databases. Therefore accurate and fast detection of circRNAs remains computationally challenging.

We present circMiner that rapidly identifies the back splice junctions with single nucleotide resolution from RNA-Seq datasets with smaller memory footprint. Using its internal pseudo-aligner, circMiner quickly detects non-canonical junctions including circRNAs by filtering reads mappable to genome and transcriptome.

First we simulate multiple datasets of linear transcripts. Pseudo-alignments from circMiner are fast and highly consistent with state of the art RNA-Seq mappers. We then simulate two different sets of circRNAs based on CIRCpedia, showing that circMiner provides best back-splice junction detection in terms of combined accuracy and sensitivity compared to other popular pipelines. Finally we test circMiner and other pipelines on HeLa and Hs68 ribosomal RNA depleted RNA-seq data which were further treated with RNase R enzyme and supposed to keep only circRNAs. For both cell-lines, circMiner outperforms all tools by recovering top 100 high support events in the enriched experiments where the second-best competitor only recovers 79 calls.
Poster Presentation Display
**2019 Lorne D. Sullivan Lectureship and Research Day**

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LIN28B/LET-7 PATHWAY REGULATES THE EXPRESSION OF SOX2 IN THE DEVELOPMENT OF TREATMENT-INDUCED NEUROENDOCRINE PROSTATE CANCER

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Background: Lin-28 Homolog B (LIN28B) is a highly conserved protein coding gene that is expressed in embryonic stem cells (ESCs) and is a key factor involved in self-renewal and the development of pluripotency networks. Studies have shown that an increase in LIN28B expression and the subsequent suppression of let-7 is correlated with poor prognosis and advanced malignancies. However, it is unclear whether there is a relationship between ESC/stemness reprogramming and tumor transformation into treatment-induced neuroendocrine prostate cancer (t-NEPC).

Methods: LIN28B expression was determined by qPCR, immunoblotting, luciferase assays, and immunohistochemistry. LIN28B expression in clinical cohorts and the DuNE cell model was profiled by AmpliSeq and analyzed by gene enrichment studies. Colony formation rates, viability, and the ability to gain an EMT phenotype was also studied. Tumor take and growth rates were measured in mice using a LIN28B CRISPR cell line. Downstream targets of LIN28B were determined by qPCR, immunoblotting, and luciferase assays.

Findings: By comparing the whole transcriptomes of AdPC and t-NEPC, we found a subset of t-NEPC tumors that highly express LIN28B. We demonstrated a positive correlation between LIN28B and SOX2 in clinical data and our DuNE cell model. LIN28B expression was sufficient to enhance both SOX2 expression in CRPC-TMAs and xenografts, as well as stem cell properties in DuNE cells. HMGA2 was identified as a downstream effector of LIN28B/let-7d signaling that regulated SOX2 expression.

Interpretation: Taken together, our data shows how LIN28B/let-7d along with SOX2 regulates key cancer stem–like properties in a subset of t-NEPC tumors.
**INTRODUCTION:** Systemic immune checkpoint blockade represents a major breakthrough in the treatment of patients with advanced bladder cancer. Response to checkpoint inhibition correlates with molecular subtypes of bladder cancer. Tumors of the claudin-low subtype respond poorly even though they are highly immune infiltrated. These tumors are also mesenchymal. We therefore hypothesized that induction of epithelial-to-mesenchymal transition (EMT) induces intrinsic immune evasion in bladder cancer.

**Method:** The bladder cancer cell line UC1 was selected as an in vitro model to test our hypothesis because they are epithelial and highly sensitive to immune cell (T cell and NK cell) killing. SNAI1, a well studied transcription factor that promotes EMT, was overexpressed in UC1. Wildtype and SNAI1-overexpressing UC1 cells were co-cultured with T cell and NK92 cells to determine the impact of EMT on immune resistance. We further dissected the immune components into death ligand (FasL/TRAIL) or granzyme-mediated tumor apoptosis to evaluate the specific pathway involved in inducing resistance.

**Results:** Overexpression of SNAI1 induced partial EMT as demonstrated by down-regulation of E-cadherin. This did not alter the sensitivity to T cell or NK cell-induced cytotoxicity. However, SNAI1-overexpressing UC1 cells were more resistant against TRAIL but not in FASL. In the bladder cancer cohort of The Cancer Genome Atlas, TRAIL RNA expression was elevated in the claudin-low subtype. Studies of granzyme-mediated killing are ongoing.

**Conclusion:** EMT appears to desensitize bladder cancer cells to TRAIL-induced apoptosis. Since FAS ligand remains cytotoxic even after EMT, soluble FasL may be a potential therapeutic for claudin-low patients.
PROGRESSIVE DOCKING - A DEEP LEARNING BASED APPROACH FOR ACCELERATED VIRTUAL SCREENING

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ABSTRACT

Drug discovery is an expensive process that takes an average of $3 billion dollars and at least 10 years to bring a drug from laboratories to patients. Two of the main challenges are 1) low hit discovery rate (< 1%) from conventional compound screening based on in vitro experiments, and 2) unwanted side-effects and bioactivities arisen from hit compounds cross-reacting with other protein targets. Computer-aided drug discovery can significantly speed up this process with improved hit rate (> 10%) through virtual screening of millions of drug-like small molecules against a specific site on a target protein structure, followed by experimental validations on the best candidates. Small molecule databases such as ZINC contains more than 1 billion purchasable compounds, a 100X fold increase from 10 million molecules just a couple of years ago. This sudden surge of synthesisable chemicals not only presents great opportunities for discovering novel classes of small molecule drugs, but also demands faster computational methods to screen against such a large chemical library efficiently. While in silico screening via molecular docking methods are already much faster than in vitro screening, it would still take years to screen them all. We demonstrate that ‘progressive docking’ can speed up the process of virtual screening by training QSAR models (deep learning model), based on docking scores generated by the slower but more accurate docking methods on a small subset of molecules. We are able to virtually screen 360 million molecules within 2-3 weeks, achieving 50X speed-up and 90X fold enrichment while retaining 90% of good compounds.
GENOMIC CHARACTERIZATION OF METASTATIC BLADDER CANCER VIA CIRCULATING TUMOR DNA

Gillian Vandekerkhove1, Matti Annala1,2, Jean-Michel Lavoie3, Nora Sundahl4, Simon Walz5, Takeshi Sano1, Andrew Murtha1, Tilman Todenhöfer5, Piet Ost4, Kim N Chi3, Peter C Black1, Bernhard Eigl3 and Alexander W Wyatt1

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Predictive biomarkers are urgently needed to enable optimal therapy selection in metastatic bladder cancer (mBCa). Putative biomarkers described from primary tissue require validation in metastatic tumours, however, metastatic tissue is infrequently available. Thus, we aimed to describe the somatic landscape of mBCa via analysis of circulating tumour DNA (ctDNA).

Blood samples from 90 mBCa patients (162 in total) were collected for targeted next-generation sequencing of plasma cell-free DNA (median depth of 986x) and matched leukocyte DNA. Gene alteration frequencies were compared between our metastatic cohort and primary muscle-invasive bladder cancer (MIBC; TCGA Cell 2017, n=412).

81% of patients (73/90) had ctDNA fractions above 2% in at least one blood collection. The landscape of somatic mutations was similar to primary MIBC, with frequent alteration of chromatin modifiers (ARID1A 27%, KDM6A and KMT2D 25%) and PI3K pathway components (PIK3CA 22%, PTEN 5.5%). Mutations in ERBB2 and FGFR3 were detected in 12.3% and 8.2% of patients, respectively. Comparison to TCGA MIBC revealed enrichment for mutations in TP53 and FGFR1 in mBCa (TP53 63.0% vs 48.1%, p = 0.022; FGFR1 5.5% vs 1.5%, p = 0.049; two-sided Fisher’s Exact Test). Applying a threshold of 30 mutations per Mb, 14% of mBCa patients exhibited a high tumour mutation burden.

We identified driver gene alterations in ctDNA from mBCa patients, highlighting that ctDNA offers a powerful alternative to metastatic tissue biopsy. Profiling of ctDNA suggests that the primary and metastatic mutational landscapes are similar; however, key alterations with prognostic implications may differ in mBCa.
GLI3 BINDING, GLI3 STABILIZATION AND GLI ACTIVATION BY STEROID RECEPTORS IN PROSTATE AND BREAST CANCER CELLS

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The nuclear steroid receptor superfamily are well understood to function as conditionally-active transcription factors. Previously we showed that androgen receptor (AR) binds to and activates Gli transcription in prostate cancer (PCa) cells by increasing the stability of high molecular weight (active) Gli3. Here, we show that other members of this protein family (estrogen receptor [ER-α], progesterone receptor [PR], and glucocorticoid receptor [GR]) share Gli-activating and Gli3 stabilizing properties with AR.

When ER, PR or GR were co-transfected into 293FT cells with a Gli-luciferase reporter (Gli-Luc), treatment with their respective ligands (estradiol, lovenorgestrel or dexamethasone) significantly upregulated reporter activity. Treatment of MCF7 breast cancer cells which endogenously express each of these receptors with the respective ligands (including an androgen) also significantly upregulated Gli reporter activity. AR-Gli3, ER-Gli3, PR-Gli3 and GR-Gli3 complexes can be visualized, in situ, in cancer cells by proximity ligation. Estradiol-induced upregulation of Gli activity in MCF7 cells was accompanied by increased expression of full-length (active) Gli3 and reduced expression of truncated Gli3 repressor. Co-treatment with fulvestrant, an ER degrader, or ER knockdown by siRNA suppressed estradiol-induced Gli activity and significantly increased the levels of truncated Gli3 repressor. Treatment of GR-expressing PCa cells with dexamethasone also stabilized Gli3.

Collectively our results established a unique secondary function of Gli activation shared by an important evolutionary spectrum of human steroid receptors. As Gli regulates the expression of a large number of genes that regulate cell growth, our observations may explain the pro-growth effects of steroid receptors in steroid-dependent tumour systems.
ANDROGEN RECEPTOR (AR) STABILIZES GLI2 AS WELL AS GLI3 IN PROSTATE CANCER CELLS; PURIFICATION OF THE AR-GLI3 COMPLEX

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Gli is an oncogenic family of transcription factors (Gli1/Gli2/Gli3) causative of brain and skin cancers. Previously we showed that androgen receptor (AR) binds Gli3 in prostate cancer (PCa) cells and stabilizes it in a high molecular weight, active form. Although Gli2 expression is much lower than Gli3 in PCa, here we show that AR binds to and stabilizes Gli2 as well. Androgen increased the expression of high molecular weight (active) Gli2 protein in several AR+ PCa cell lines. Full length- and truncated AR (AR-V7) intranuclear complexes with Gli2 can be visualized by proximity ligation in various PCa cells. Selective knockdown (by siRNA) of Gli2 or Gli3 in androgen-treated PCa cells decreased the expression of a Gli luciferase reporter in PCa cells to near-similar extent. As Gli2 is expressed hundreds of fold lower than Gli3, this indicates that Gli2 is a more potent transcriptional activator than Gli3 in agreement with current belief. Immunohistochemical staining for Gli2 and Gli3 in human prostate tissue microarrays showed that both are significantly upregulated in castration resistant disease (CRPC). Finally, we will describe here our efforts leading to purification of the AR-Gli3 complex in anticipation of structural determination.

Our work continues to show that AR has the unexpected activity of Gli activation in PCa cells and that this activity is increased in CRPC. Interference with AR activation of Gli may provide a novel therapeutic approach for advanced disease and our efforts towards purification of the AR-Gli3 complex will accelerate discovery of small molecules for this purpose.
NOVEL CROSS-TALK BETWEEN ANDROGEN RECEPTOR (AR) AND RESPIRATORY COMPLEX II (CII) IN PROSTATE CANCER

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Introduction: Prostate cancer cells reprogram their metabolic pathways as adaptive mechanisms after AR pathway inhibition (ARPI). A key player in energy metabolism, CII is comprised of succinate dehydrogenase (SDH) and succinate:ubiquinone oxidoreductase (SQR) with tumor-suppressor and -promoter activities, respectively. Considering its relevance to cancer, we aim to evaluate if ARPI modulates CII, whether this functions as an adaptive survival response, and if CII could be targeted to overcome this response.

Experimental Procedure: Castration-sensitive LNCaP cells were treated with Enzalutamide (ENZA), followed by proteomic analysis using Tandem mass tagging assay. SDH activity was inhibited by silencing catalytic subunits of CII whereas SQR activity by Atpenin A5 (AA5) and Theonyl trifluoracetone (TTFA). EMSA (electrophoretic mobility shift assay) was performed with AR-DNA binding domain.

Results: Proteomic analysis of LNCaP cells after acute treatment with ENZA showed decreased expression of CII catalytic subunits: SDHA and SDHB leading to reduced SDH activity. These subunits also carried AREs in their promoters as confirmed by ChIP and EMSA assays. Interestingly, inhibition of SDH activity significantly increased AR protein levels; however, this effect was abrogated on targeting p-Hsp27. In contrast, combination of ENZA with SQR activity inhibitors synergistically reduced AR expression and cell viability.

Conclusions: Our study defines novel cross-talk between energy metabolism and AR pathway activity after ARPI. Reduced SDH activity of CII post ARPI may adaptively support AR pathway activity via Hsp27 phosphorylation. Inhibition of SQR activity of CII or Hsp27 post ARPI could potentially block this adaptive response and sensitize prostate cancer cells to ARPI treatments.
COMMON AND DISTINCT BIOLOGICAL ACTIVITIES OF GLI2 OR GLI3 IN PROSTATE CANCER CELLS

Na Li, Jane Foo, Shabnam Massah, Mannan Nouri, Ralph Buttyan

Abstract

Gli transcription factors (Gli1/Gli2/Gli3) are oncogenic and are causative of skin and brain cancers. Gli activity in a cell is regulated by a site-specific proteolysis of Gli3 and, to a lesser extent, Gli2, which removes their C-terminal transactivation domains rendering them into transcriptional repressors. Hedgehog signaling suppresses this proteolysis and was thought to be needed for Gli activity. We have found, however, that androgen receptor (AR) binding to Gli3 and Gli2 suppresses their proteolysis and provides a non-canonical (non-Hedgehog) means of activating Gli transcription in prostate cancer (PCa) cells. Here we show that Gli2 and Gli3 activity is necessary for PCa cell growth and describe a unique biological activity of Gli3 that protects AR from degradation. Specific knockdown of Gli2 or Gli3 by siRNA strongly suppressed the growth of a wide variety of PCa cell lines and dual knockdown showed additive effects. Complete Gli suppression by Gli antagonists totally blocks PCa cell growth. Knockdown of Gli3, but not Gli2, however, had an additional effect of decreasing the stability of the AR protein. Exogenous overexpression of Gli2 did not further stabilize AR when Gli3 was knocked down (with an N-terminal siRNA), however exogenous overexpression of the Gli3 C-terminal domain alone was sufficient to stabilize AR. Our results continue to support the idea that AR-regulated Gli activity (Gli2 and Gli3) is necessary for PCa cell growth but the distinct activity of Gli3 as an AR stabilizer suggests that Gli3 plays a unique role in PCa that is not replaced by Gli2.
PATIENT REPORTED OUTCOMES FROM RENAL TRANSPLANT DONORS AND RECIPIENTS: INITIAL RESULTS FROM A SINGLE CENTRE STUDY

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INTRODUCTION: Patient reported outcomes (PROs) are gaining popularity in various medical disciplines as a mechanism to improve accountability and overall quality of health care services. PROs can be useful and effective tools for characterizing symptom burden and health-related quality of life. While medical guidelines for many treatments do not account for diversity in symptom presentation and recovery among patients, using PROs in post-operative patients can help to obtain useful clinical findings and establish a more accurate estimation of expected symptoms.

METHODS: Patients undergoing a kidney transplant at Vancouver General Hospital were recruited (n=50) to complete a post-operative recovery survey at a gradually reduced frequency over a 6-month period. The survey followed the symptom occurrence and progress of the patient to identify whether the patient was recovering as expected.

RESULTS: Initial results have documented common causes of concern among patients, including graft rejection, sleep, pain, fluid overload, and bowel movements. Trends in the data give insight into symptoms of recipients, including but not limited to: 15% (n=42) will continue to have an elevated temperature after postoperative day three, 27% (n=42) have a bowel movement by postoperative day two, and 78% (n=42) are able to do short walks by day two.

CONCLUSION: PROs are gaining an increasing role in patient-centered care and in supporting important research. Longer term analysis is needed to evaluate the usability and applicability of this PRO tool into clinical practice. Next steps are to increase recruitment, reduce variance through increased compliance, and compare results with clinical guidelines.
CIRCLUATING TUMOR DNA PROFILING SUGGESTS TAXANE-CHEMOTHERAPY RESPONSE IS INDEPENDENT OF TUMOR MOLECULAR SUBTYPE IN ADVANCED PROSTATE CANCER

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\textbf{Introduction}: Taxane chemotherapeutic agents such as docetaxel are a standard treatment for men with metastatic castration-resistant prostate cancer (mCPRC). However, half of all patients treated with taxanes will exhibit primary resistance, and unfortunately even those who respond will inevitably progress. There are currently no biomarkers to predict docetaxel response. Our objective was to assess whether tumor genomic alterations that are predictive for response to other mCRPC therapies have a relationship with patient outcomes on docetaxel.

\textbf{Methods}: We collected plasma from 58 patients prior to commencing docetaxel and performed deep targeted sequencing on cell-free DNA and matched leukocyte DNA (as a germline control).

\textbf{Results}: Consistent with the known somatic landscape in mCRPC, we identified frequent disruption to \textit{TP53} (20/58, 35\%), \textit{PTEN} (14/58, 24\%), and \textit{RB1} (11/58, 19\%), as well as recurrent \textit{AR} copy number amplification (24/58, 41\%). Of the 52 patients for which clinical outcomes were assessed, the median time to PSA progression (TTPP) was 3.93 months, and 38.4\% (20/52) experienced a PSA response. No significant relationships with either PSA response or TTPP were identified among these genomic factors, although both \textit{TP53} status and circulating tumor DNA fraction correlated with overall survival.

\textbf{Conclusions}: These findings point to lack of relationship between common prostate cancer molecular subtypes and taxane therapy response in mCRPC. However, this analysis does not address the role of regulatory or epigenetic mechanisms, nor rarer somatic alterations not covered by our gene panel.
TARGETING N-MYC IN NEUROENDOCRINE PROSTATE CANCER THROUGH COMPUTER-AIDED DRUG DESIGN

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Introduction: Resistance against androgen-deprivation therapies (ADT) is accentuated in neuroendocrine prostate cancer (NEPC), an advanced setting of prostate cancer (Pca). ADT or inhibitors targeting the androgen-receptor (AR) signaling pathways are rendered ineffective due to Pca clones escaping AR addiction. AR expression levels are diminished in androgen-dependent cell line due to N-Myc. MYCN gene amplification and overexpression during Pca evolution allow escape from AR dependence and promote the emergence of NEPC. We propose N-Myc as a novel target to regulate NEPC.

Methods: The N-Myc protein, bound to the Max transcription factor, was modeled as the target for consensus docking simulations. SAR (structure-activity relationships) were constructed based on active compounds identified from a previous virtual screen of 9 million compounds on C-Myc. Hit compounds were tested to determine microsomal stability, effects on transcriptional activity, potency, and cell viability.

Results: Optimized compounds, based on SAR analysis, successfully dock to the newly designed N-Myc/Max target. Molecular dynamics simulations show key interaction residues involved in keeping the lead compounds bound to the pocket site. Hit compounds tested experimentally, decreased transcriptional activity of N-Myc without incurring apoptosis.

Conclusions: The results suggest that the proposed in-silico pipeline can target an IDP (intrinsically disordered protein) when bound to its co-transcription factor. The optimized compounds inhibit DNA E-box binding to the N-Myc/Max complex, and exhibit good microsomal stability and potency. An enhanced scaffold of successive hits was constructed for lead optimization. Targeting N-Myc is possible and opens the possibility for subsequent advanced drug design approaches against resistance in cancer.
INVESTIGATING THE ROLE OF ENDOTHELIN-1 AS A VEGFA-INDEPENDENT ANGIOGENIC FACTOR IN SUNITINIB-RESISTANT METASTATIC CLEAR-CELL RENAL CELL CARCINOMA

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Background: Patients with metastatic clear-cell renal cell carcinoma (mccRCC) are treated with either an anti-angiogenic or immunotherapy, but treatment resistance develops in 1-2 years. Our preliminary data has identified increased endothelin-1, an endogenous and vasoactive peptides, secretion by sunitinib-resistant metastatic ccRCC (mccRCC) in vitro model. The aim of the current objective is to understand the role of ET-1 on drug-resistant mccRCC angiogenesis and to determine a suitable therapeutic regimen to revert resistance.

Methods: Caki-1WT (Sunitinib-sensitive) and Caki-1DC (Sunitinib-resistant) were co-cultured with HUVEC and rat aorta to investigate endothelial cell (EC) sprouting. Angiogenic secretory factors were determined using Luminex. Chick chorioallantoic membrane (CAM) was used to investigate tumor vascularization. Publicly available data on ccRCC patient was used to determine the expression. Western blot and RT-PCR techniques were used to determine the expression pattern of EDN1.

Results: Increased HUVEC and EC migration was also observed when co-cultured with Caki-1DC. Luminex 17-plex analysis showed increase angiogenic factors secreted, ET-1, by Caki-1DC vs WT. CAM assay showed increased tumor vascularity following Caki-1WT and DC inoculation. Publicly available patient data established significant upregulation of EDN1 gene in ccRCC patients treated with sunitinib compared to treatment naïve patients. Results from Western blots confirmed increased secretion of ET-1 protein in the media but decreased intracellular ET-1 in Caki-1DC vs WT.

Conclusion: The preliminary results strongly suggests the association of increased ET-1 and tumor neovascularization in the resistant mccRCC phenotype. We hypothesize that sunitinib-resistance development leads to VEGF-independent and ET-1-dependent angiogenic switch in advance mccRCC. In further steps, we will elucidate the mechanistic role of ET-1 in mccRCC.
THE IMPACT OF URINARY TRACT INFECTIONS IN SPINAL CORD INJURED POPULATION: INSIGHTS FROM THE SPINAL CORD INJURY COMMUNITY SURVEY

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Introduction: Urinary tract infections (UTIs) are one of the most frequent types of infections following spinal cord injury (SCI). Here we assess the impact of UTI on activity and overall quality of life (QOL), determine the frequency of secondary consequences of UTI and identify factors associated with frequent UTIs.

Methods: The Spinal Cord Injury Community Survey is a Canadian national dataset from an online survey developed to assess major dimensions of community living and health outcomes in persons with chronic SCI. Participants were stratified by UTI frequency. The impact of UTI on QOL, activity, and health resource utilization and secondary consequences were assessed. Results were analysed with cross tabulations, chi square tests, and ordinal logistic regression.

Results: 1124 of 1529 (73.5%) participants experienced at least 1 symptomatic UTI since the time of injury (mean 18.5 years). Overall QOL was worse with increasing frequency of UTI. Those with frequent UTIs had twice as many hospitalizations and doctors' visits and were limited in financial, vocational and leisure situations, physical health and ability to manage self-care as compared to those with no UTIs. UTIs were associated with higher incidence of secondary consequences including bowel incontinence, constipation, spasticity and autonomic dysreflexia. Individuals who were younger and female were more likely to have frequent UTIs and those with constipation and autonomic dysreflexia had worse QOL.

Conclusions: UTIs have a profound impact on the QOL of individuals with long-term SCI. These findings will be incorporated into SCI UTI surveillance and management guidelines.
COLD PRESERVATION WITH A HYPERBRANCHED POLYGLYCEROL-BASED SOLUTION IMPROVES FUNCTIONAL RECOVERY OF KIDNEY TRANSPLANTS IN A PIG MODEL

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Abstract

Background: Organ preservation solutions are used to limit donor organ injury during cold preservation (perfusion and storage), and the hyperbranched polyglycerol (HPG)-based solution shows promise in rodent experiments for improving donor organ protection. This study was to evaluate the outcomes of kidney transplants after cold preservation with a HPG-based solution in a pig model.

Materials and Methods: The orthotopic kidney autotransplantation was performed in farm pigs (Sus scrofa domesticus, weighing 35–45 kg). The left kidney was perfused with and statically stored in either cold HPG-based solution or UW solution, followed by autologous transplantation to the right side after right nephrectomy. The outcomes of transplanted kidneys was determined by urine output and levels of serum creatinine, BUN and serum potassium, and histological analysis of grafts at day 7 post-transplantation.

Results: There was no significant difference of donor kidney weight after 24 h of cold storage between UW and HPG groups, but less remaining red blood cells were observed in the kidneys after perfusion with HPG solution. With no difference in CIT, the urine output from the first day post-transplantation in HPG group was 1593.33 ± 887.39 mL, which was significantly higher than 310.83 ± 419.48 mL in UW group (P = 0.0095, t-test, n = 6), and this difference was consistent during the entire period of 7 days (P = 0.0002, two-way ANOVA, n = 6). In consistent with more urine output, both lower levels of serum creatinine, BUN and serum potassium and less graft injury were seen in HPG group as compared to those in UW groups.

Conclusion: As compared to the standard UW solution, the HPG solution has less negative impact on the immediate functional recovery of kidney transplants after transplantation in the pig model, which may suggest that the HPG solution is a promising organ preservation solution for better outcomes of kidney transplants.
CORRELATION OF SURFACE-ENHANCED RAMAN SPECTROSCOPIC FINGERPRINTS OF RECIPIENT’S URINE WITH KIDNEY TRANSPLANT FUNCTION PARAMETERS

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Background: The stability and the function of kidney transplants are determined mostly by monitoring recipients’ serum creatinine levels and in some cases additionally by transplant biopsies, which however have problems with time lag, sensitivity and specificity. Raman spectroscopy (RS) is a vibrational spectroscopic technique for chemical fingerprinting of both organic and inorganic substances in seconds. The objective was to evaluate the feasibility of chemical fingerprint analysis of recipients’ urine by using surface-enhanced RS (SERS) to determine transplant function.

Materials and Methods: Urine samples were collected from both rats (n = 20) and humans (n = 29) with kidney transplants. Blood test and urinalysis were performed by using standard methods in clinical biochemical laboratories. SERS spectra of urine samples were analyzed with partial least squire (PLS) analysis.

Results: The PLS regression of rat urine SERS spectra was $R^2=0.8371$ for urine protein, $R^2=0.7936$ for urine creatinine, $R^2=0.6285$ for urine protein to creatinine ratio (PCR), $R^2=0.8762$ for blood urea nitrogen (BUN) and $R^2=0.9375$ for serum creatinine. Similarly, the regression analysis of human urine SERS spectra indicated $R^2=0.8361$ for urine protein, $R^2=0.8260$ for urine creatinine, $R^2=0.8778$ for PCR, $R^2=0.6131$ for BUN and $R^2=0.5496$ for serum creatinine.

Conclusion: The data from this pilot study may suggest that SERS spectral analysis of recipient’s urinary chemical fingerprints could provide a rapid, convenient and non-invasive method to monitor kidney transplant function in the post-kidney transplant management.
Bladder cancer is the fifth most common cancer in North America with high rates of morbidity and mortality. Muscle-invasive bladder cancer (MIBC) is an aggressive form of the disease with limited therapeutic options. Most patients do not respond to immunotherapies targeting PD-1/PD-L1 treatment, suggesting the existence of complementary immune evasion mechanisms. Therefore, to exploit the full potential of immunotherapy, the mechanisms by which tumours suppress anti-tumour immunity must be elucidated.

In a subset of MIBC, we and others have recently identified a correlation between the activity of the nuclear peroxisome proliferator activated receptor gamma (PPARγ), and decreased expression of immune related genes. Based on this observation, we hypothesized that aberrant activation of PPARγ in tumour cells might be a major mechanism of immune evasion. The overall goal of this project is to 1) gain a deeper understanding of the function of PPARγ in MIBC, 2) validate the impact of PPARγ signaling on PDL1/PD-1 immunotherapy in pre-clinical models, and 3) investigate the mechanisms responsible for regulating PPARγ signalling in MIBC.

We show that overexpression of PPARG in bladder cancer cell lines leads to activation of PPARγ regulated pathways and decreased expression of inflammatory chemokines and cytokines. In a murine orthotopic model of bladder cancer, high Pparg expression correlates with impaired tumor initiation and T cell-mediated clearance. Finally, a high throughput genome-wide CRISPR knock-out screen of endogenous regulators of PPARG expression has been designed to identify novel cellular components that could potentially be exploited clinically to sensitize luminal MIBC to immunotherapy.
NOVEL 3D KIDNEY CANCER MODEL FOR PERSONALIZED MEDICINE

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Introduction: Renal cell carcinoma (RCC) is the 6th most common cancer in Canada, however, approximately 30% of patients present with de novo metastatic disease (mccRCC). In the absence of a predictive biomarkers, treatment selection continues to be based on clinical evidence and expert opinion. There are some predictive tumor models to guide individual treatment, unfortunately, they do not fulfill all requirements. Therefore, there is a need to develop a model that mimics the complex biology and can be used as a high throughput method for drug testing.

Methods: Kidneys will be collected from animals undergoing euthanasia. Kidneys will be decellularized and after kidneys will be reseeded with different kidney cell lines. After model establishment, the decellularized kidneys will be reseeded with ccRCC patient’s tumor cells. To validate genetically our model, we will use targeted sequencing in patients and their corresponding engineered 3D tumors. Finally, engineered 3D tumors will be treated with the same therapy as its matching patient. The response to therapy will be compared between the engineered tumor and its corresponding mccRCC patient’s therapy outcome.

Results: We have successfully developed a process of tissue decellularization by whole kidney perfusion. We have established the reseeding of different kidney cell lines into the decellularized kidney, however we are still working in the optimization of these protocols.

Conclusions: This 3D patient-derived mccRCC model will enable us to generate many in vitro avatars to accurately recreate the tumor of a patient, and simultaneously screen for suitable drugs for the patient. Personalized medicine results as an effective therapy that will improve patient’s overall survival.
LANDSCAPE OF NON-CODING VARIANTS IN PRIMARY PROSTATE CANCER FROM DIFFERENT ETHNIC COHORTS

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Prostate cancer (PCa) is one of the most common causes of cancer-related death in North American men. However, the mortality rates in different ethnic groups vary significantly. Several factors can impact this including access to healthcare and diet. However there is increasing evidence that the patient's underlying genetics can also play a significant role. This is clearly observed with a TMPRSS2:ERG gene fusion which is seen at vastly different rates within Chinese, Caucasian and African populations. While this work suggests that somatic mutations are impacted by genetic variants, almost all studies considering ethnicity have focused on specific protein-coding genes. Yet, there is increasing evidence that non-coding mutations also play a critical role in PCa development and growth. Therefore, in this work we investigated the difference in non-coding somatic mutations in large African-American, Chinese and European primary prostate cancer cohorts. Preliminary studies have demonstrated that there is a marked difference in the frequency and type of SNV observed at androgen receptor binding sites in these ethnic groups. Work is ongoing to identify and characterize other non-coding mutations to understand how they impact PCa development.

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PATHOGENESIS OF *PROTEUS MIRABILIS* IN URINARY INFECTION STONES

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**Introduction**

Urinary infection stones are painful stones that form in the urinary system post-urinary tract infection and are often reoccurring. These complicated stones are initiated by the urease activity of *Proteus mirabilis*. This Gram-negative microbe utilizes the urease enzyme to break down the urea in urine into carbon dioxide and ammonia, increasing urinary pH to form a pro-crystallization environment. The rise in pH affects the solubility of ions in urine, causing them to precipitate out and form struvite stones. These stones lead to numerous health complications and painful symptoms, all triggered by *Proteus mirabilis* infection. Thus far, the hypothesis has been that *Proteus mirabilis* attaches onto uroepithelial cell and initiates crystal attachment to exopolymeric substances. We believe that *Proteus mirabilis* is internalized into vacuoles in these cells and begins its pathogenic processes intracellularly, aiding to explain the reoccurrence of urinary infection stones, even after they are extracellularly removed.

**Methods**

Adhesion and invasion assays are employed for these observations. A498 kidney cells are exposed to urease-positive and negative strains of *Proteus mirabilis*. These cells are incubated for 2 hours and 24 hours, and then lysed for CFU counts of bacterial adhesion. Some cells are treated with antibiotics to eliminate extracellular bacteria, and then lysed for invasion CFU counts.

**Results**

There are observable differences between the adhesion and invasion patterns of *Proteus mirabilis* between the urease-positive and negative strains. Overall, urease-positive strains exhibit greater adhesion, and the invasion CFU counts increase over time and are higher after 24 hours.

**Conclusions**

Urinary infection stones are painful and debilitating, with high rates of recurrence. Targeting *Proteus mirabilis*, the culprit of these infection stones, can give us greater insight into them, and how their high recurrence can be diminished.
Cancer is a complex disease that involves rapidly evolving cells, often forming multiple distinct clones. In order to effectively understand progression of a patient-specific tumor, one needs to comprehensively sample tumor DNA at multiple time points, ideally obtained through inexpensive and minimally invasive techniques. Current sequencing technologies make the ‘liquid biopsy’ possible, which involves sampling a patient’s blood or urine and sequencing the circulating cell free DNA (cfDNA). A certain percentage of this DNA originates from the tumor, known as circulating tumor DNA (ctDNA). The ratio of ctDNA may be extremely low in the sample, and the ctDNA may originate from multiple tumors or clones. These factors present unique challenges for applying existing to the analysis of ctDNA, especially in the detection of structural variations which rely on sufficient read coverage. We introduce SViCT, a structural variation (SV) detection tool designed to handle the above challenges. SViCT can detect breakpoints and sequences of various structural variations including deletions, insertions, inversions, duplications and translocations. We assessed the performance of SViCT and compared it to state-of-the-art tools using simulated cfDNA datasets with properties matching those of real cfDNA samples. The positive predictive value and sensitivity of our tool was superior to all the tested tools and reasonable performance was maintained down to the lowest dilution of 0.01% tumor DNA in simulated datasets. Additionally, SViCT was able to detect all known SVs in two real cfDNA reference datasets (at 0.6–5% ctDNA) and predict a novel structural variant in a prostate cancer cohort.
RB1 LOSS ACCELERATES ASCL1 INDUCED REPROGRAMMING OF PROSTATE ADENOCARCINOMA TO SMALL CELL

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Introduction: Continued dependence on AR signaling drives castrated-resistant prostate cancer (CRPC) progression and is the basis for the efficacy of enzalutamide (ENZ), a potent AR inhibitor. However, there has been a dramatic increase in drug resistance and the prevalence of treatment-induced neuroendocrine prostate cancer (t-NEPC). RB1 loss is a hallmark of NEPC and it has been associated with poor clinical outcome. We have identified that the transcription factor ASCL1 is slightly upregulated at the basal level of RB1 knockdown (shRB1) cells and its expression accelerates with ENZ treatment. ASCL1 expression and activity is significantly higher in NEPC patient compare to CRPC.

Methods: Study the affects of ASCL1 inhibition on transdifferentiation and maintenance of NEPC phenotype using siRNA and shRNA using CRPC and ENZ resistant (ENZR) cell model.

Results: Inhibition of ASCL1 (siASCL1 and shASCL1) reduced cell proliferation in ENZR and NCI-H660 NEPC cell lines accompanied by downregulation of NE markers such as synaptophysin and neuron specific enolase. Furthermore, inhibition of ASCL1 reduces the pace of transdifferentiation in CRPC cell model under the pressure of ENZ.

Conclusion: Downstream of RB1 loss, several molecular events such as differential activation of ASCL1 play a major role in the NE differentiation. Our preliminary data suggested that ASCL1 is a major player in NEPC progression. Toward this end we aim to investigate the mechanism behind ASCL1 induced NEPC and establish whether ASCL1 inhibition can prevent and/or reverse NEPC progression.
THE EFFECT OF CISPLATIN-BASED NEOADJUVANT CHEMOTHERAPY ON THE RENAL FUNCTION OF PATIENTS UNDERGOING RADICAL CYSTECTOMY

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ABSTRACT

Introduction: Platinum-based neoadjuvant chemotherapy (NAC) is standard of care for patients with muscle invasive bladder cancer undergoing radical cystectomy (RC). Cisplatin, the favoured platinum agent, is known to cause renal injury. Furthermore, RC is an independent risk factor for renal injury, with GFR decreases of 2-6 points reported at one year post-op. Our objective was to evaluate the effect of cisplatin-based NAC on the renal function of patients undergoing RC.

Methods: We analysed a multicentre database of bladder cancer patients, all of whom received neoadjuvant chemotherapy. We included patients who received cisplatin-based chemotherapy. We found or calculated GFR values based on available data at the following time points: pre-NAC, post-NAC but pre-RC, and 1 year post-RC. GFR and proportion of patients with GFR < 60 was compared between these time points.

Results: We identified 578 patients with renal function data pre-NAC (baseline), 403 at the pre-RC time point, and 234 at 1 year post-RC. There was progressive decline in mean GFR from baseline to pre-RC (74.1 vs. 69.9, p < 0.01), to 1 year post-RC (69.9 vs. 61.8, p < 0.001). The proportion of patients with GFR < 60 increased from 27% at baseline to 34% pre-RC (p < 0.05) and to 50% at 1 year post-RC (p < 0.001).

Conclusions: There was a significant and progressive decline in GFR from baseline when NAC was administered. Similarly, the percentage of patients with GFR < 60 increased over time. The magnitude of GFR decrease appears to be greater than the effect of RC alone reported in the literature.
**COMPREHENSIVE INTEGRATED MULTI-OMICS CHARACTERIZATION OF THERAPEUTIC VULNERABILITIES IN THE LOW-GRADE SEROUS OVARIAN CANCER**

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**Introduction**: Low-grade serous ovarian cancer (LGSC) accounts for only 5% of all epithelial ovarian cancers. About 80% of the LGSC patients will present at advanced stage, recur, and die. In the last decade, LGSC has been recognized as a distinct disease with unique clinical, pathological and molecular characteristics. However effective therapeutic strategies have not yet been identified due to the lack of disease-specific research.

**Methods**: A total of 15 LGSC cell cultures recently established from 11 advanced/recurrent patients were analyzed at molecular level using whole exome sequencing, RNA sequencing, and mass spectrometry platforms. We assessed and integrated the somatic mutation, copy-number aberration, gene expression, and protein quantification of the cell lines using different bioinformatics tools. LGSC cell line data was also compared to publicly available LGSC tumors data. Response phenotype to MEK inhibitor (MEKi) treatment was used for cell line comparison.

**Results**: Our analysis revealed distinct patterns of nucleotide substitution mutations and COSMIC mutational signatures in MEKi-sensitive and MEKi-resistant LGSC. KRAS mutations were exclusively found in MEKi-sensitive LGSC and NRAS mutations mostly in MEKi-resistant LGSC. Interestingly, we identified deletions of CDKN2A/B in almost all LGSC cell lines. Furthermore, we identified differentially expressed genes/proteins between the MEK inhibitor response phenotypes. Notably, we found differential activity of MAPK pathway as well as many other signaling pathways characterizing MEK inhibitor response phenotypes.

**Conclusions**: Patient-derived LGSC cell cultures contain similar mutational profiles as previously identified in LGSC tumors. These findings confirm their value as research models for drug discovery/testing in a rare and lethal disease setting. Deletion of CDKN2A/B was identified as a potential disease driver gene mutation. Drugs that target this molecular alteration are available and should be further investigated for the treatment of this disease.
WELL-DIFFERENTIATED PAPILLARY MESOTHELIOMA OF THE PERITONEUM IS GENETICALLY DISTINCT FROM MALIGNANT MESOTHELIOMA

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Abstract:

Well-differentiated papillary mesothelioma (WDPM) is an uncommon mesothelial proliferation that is most commonly encountered as an incidental finding in the peritoneal cavity. There is controversy in the literature about whether WDPM is a neoplasm or a reactive process, and if neoplastic, whether it is a variant or precursor of epithelial malignant mesothelioma or is a different entity. Using whole exome sequencing of five WDPM of the peritoneum, we have identified distinct mutations in \textit{ATM}, \textit{FBXO10}, \textit{SH2D2A}, \textit{CDH5}, \textit{MAGED1} and \textit{TP73} shared by WDPM cases but not reported in malignant mesotheliomas. Furthermore, we show that WDPM is strongly enriched with C>A transversion substitution mutations, a pattern that is also not found in malignant mesotheliomas. The WDPMs lacked alterations involving \textit{BAP1}, \textit{SEDT2}, \textit{NF2}, \textit{CDKN2A/B}, \textit{LASTS1/2}, \textit{PBRM1} and \textit{SMARCC1} that are frequently altered in malignant mesotheliomas. We conclude that WDPMs are genetically distinct from malignant mesotheliomas, and based on observed mutations do not appear to be precursors of malignant mesotheliomas.
IDENTIFICATION OF POTENTIAL NON-CODING DRIVER MUTATIONS IN PROSTATE CANCER

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Androgen receptor (AR) mediated-transcription is critical at almost all stages of prostate carcinogenesis. Recent studies have shown that non-coding mutations of AR enhancers can act as drivers in prostate cancer (PCa) progression and that AR binding sites (ARBS) themselves are heavily mutated in a tissue specific manner. We propose that these ARBS mutations can impact AR activation and alter the transcriptional landscape of PCa. To identify the genetic elements crucial to AR signaling, we systematically tested every clinical ARBS using a massively multi-parallel enhancer assay (STARRseq). Combining these results with large-scale genomic data including whole genome sequencing from primary and metastatic PCa, long-range chromatin interaction data and CRISPR screens we ranked somatic mutations for validation. When we phenocopy several of these potentially important clinical mutations, we observed a significant alteration in AR-enhancer activity. These results are being validated in situ with genome editing. This approach provides a road map to identify novel hormone regulated enhancers and characterize the mechanism of PCa-associated GWAS SNPs and somatic non-coding driver mutations.
ROLE OF GRB10 IN THE DEVELOPMENT OF CASTRATION-RESISTANT PROSTATE CANCER

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ABSTRACT

Androgen deprivation therapy (ADT) is the mainstay treatment of advanced and metastatic prostate cancers in the clinic. While the initial response to ADT is effective and almost universal in hormone-naïve prostate cancer (HNPC), incurable castration-resistant prostate cancer (CRPC) inevitably develops. In our previous study, we reported that Growth Factor Receptor Bound Protein 10 (\textit{GRB10}), an adaptor protein, was a novel driver gene upregulated and functionally critical during CRPC development. In this study, we utilized transcriptomic analysis and found that GRB10 knockdown in LNCaP cells significantly inhibited glycolysis pathway, which is upregulated in CRPC compared to HNPC in clinical cohorts. Glucose consumption and lactate acid production assays also showed that GRB10 knockdown inhibited glycolysis activity. Combined with mitochondria respiration inhibitor, metformin, GRB10 depletion dramatically impeded cell growth. To further analyze molecular mechanisms mediated by GRB10, we performed interactome analyses in LNCaP and C4-2 cells using co-immunoprecipitation coupled to liquid chromatography-mass spectrometry. Serine/threonine-protein phosphatase 2A (PP2A) which is a well-established tumor suppressor was identified as a novel and top-ranking binding partner of GRB10. We showed that the direct interaction between GRB10 and PP2A facilitated PP2A degradation, while GRB10 knockdown stabilized PP2A. These findings further established the crucial role of GRB10 during CRPC development and elucidated a novel mechanism mediated by GRB10-PP2A axis. Our data also suggest that GRB10 is a promising therapeutic target, particularly combined with metformin, in the management of CRPC patients.
Dianhydrogalactitol induces cell cycle arrest in S/G2 phase and shows synergy with topoisomerase inhibitors in prostate cancer cells.

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Introduction: 1, 2:5, 6-dianhydrogalactitol (VAL-083) is a small water soluble DNA damaging agent that has been shown to have anti-neoplastic effects in a range of malignancies, including brain tumour, lung and ovarian cancers. Recently, the mechanism of action of VAL-083 was elucidated in our study using lung cancer cells as a model system. VAL-083 causes cell cycle arrest in S/G2 phase and activates homologous recombination (HR) DNA repair pathway by inducing interstrand DNA crosslinks. Here we validated the mechanism of action of VAL-083 in prostate cancer cells and investigated potential DNA-targeting agents for combination therapies, such as topoisomerase inhibitors.

Methods: The activation of HR pathway by VAL-083-induced DNA double strand breaks (DSBs) was demonstrated by the biochemical and microscopic analyses in PC-3 cells. We tested the combination effects of VAL-083 with docetaxel, etoposide (Top2), camptothecin (Top1), or irinotecan (Top1) in PC-3 cells. The cells were treated with the drugs at fixed molar ratios based on their individual IC50 values. The combination effects were assessed using Chou-Talalay Method.

Results: We report VAL-083 is a DNA targeting agent that induced DNA DSBs, S/G2-cell cycle arrest, and activation of the HR repair pathway in prostate cancer cells. The combination treatment demonstrated synergy between VAL-083 and topoisomerase inhibitors. There is no synergistic effect between VAL-083 and docetaxel, further demonstrating VAL-083 causes S/G2 arrest.

Conclusion: Our results will guide a potential treatment strategy of VAL-083 in combination with topoisomerase inhibitors in prostate cancer treatment.
SMALL MOLECULE ERG AND ILK ANTAGONISTS INCREASE SENSITIVITY OF TMPRSS2-ERG PROSTATE CANCER CELLS TO ENZALUTAMIDE

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While the introduction of second-generation androgen receptor (AR) pathway inhibitors (ARPIs), including enzalutamide, has dramatically improved survival of patients with advanced prostate cancer (PC), nearly all men treated with these ARPIs go on to develop resistance. Approximately half of PCs harbour the transmembrane protease, serine 2-erythroblast transformation-specific-related gene (TMPRSS2-ERG) fusion. TMPRSS2 allows the transcription factor ERG to be regulated and expressed by the AR, with ERG driving transcriptional reprogramming that promotes transformation and enhances the metastatic potential of these tumours. It may be possible to increase sensitivity of ERG-expressing PCs to ARPIs through co-targeting ERG transcriptional function and proteins like integrin-linked kinase (ILK) which are involved in pathways that ERG upregulates. We have developed small molecule ERG antagonists, including VPC-18005 and the superior analog VPC-18156, which can inhibit ERG binding to DNA, transcriptional activity, and metastatic properties of ERG-expressing PC cells. We have shown that a small molecule antagonist of ILK, QLT-0267, phenocopies aspects of ERG antagonism. We hypothesize that VPC-18156 and QLT-0267 can increase the sensitivity of ERG-expressing PC cells to enzalutamide-mediated cytotoxicity by further suppressing activity of ERG and ILK that is incompletely eradicated by ARPIs. Proliferation and viability assays, performed through live-cell imaging and fluorescent-activated cell sorting, show that VPC-18156 and QLT-0267 increase sensitivity of VCaP cells to enzalutamide, causing increased cell death. RNA Seq assays indicate selective efficacy of antagonizing ERG and ILK in conjunction with enzalutamide that offer insights into possible new treatment strategies to improve the effect of ARPIs in ERG-expressing metastatic castration-resistant PCs.
Efficacy of androgen receptor (AR) inhibitor, Enzalutamide’s (ENZ) in prolonging survival of castrated-resistant (CRPC) patients is short lived as resistance rapidly occurs. Beyond re-activation of AR, drug resistance has been hypothesized to occur via enrichment of cancer stem-like cells (CSC) and immune evasion, phenotypes associated with poor survival in patients. We have previously shown that PD-L1 is highly expressed in Enzalutamide resistant prostate cancer.

To define molecular mechanisms contributing to treatment resistance, Transcriptomic profiling of LNCaP, CRPC and ENZ-Resistant (ENZR) cell lines identified WNT5A/ROR2 as a major signaling pathway up-regulated in 42D\textsubscript{ENZR} and 42F\textsubscript{ENZR} cells compared to 16D\textsubscript{CRPC}. Targeting this pathway affects large number of signaling pathways as shown by set enrichment analysis that were involved in immune response. Specifically, we found that downregulation ROR2 induces a decrease of NF-kB transcriptional activity as measured by luciferase activity an IkB phosphorylation leading to a drastic decrease pf NF-kB target gene PDL1 and a decrease of stem cell features.

Our data suggests that ROR2 can regulate PD-L1 in ENZR cell lines possibly through re-activation of NFkB signaling pathway. Taken together, our study proposes WNT5A/ROR2 pathway as a potential target in ENZ-resistant tumors.
Structural variations (SVs) are genomic alterations, larger than 50 base-pairs, which affect the human genome the most among all types of genetic variations. Furthermore, these types of variations are known to be more responsible for resistance and susceptibility to many of the common and rare genetic diseases such as different types of cancer (e.g. breast and prostate cancers), Autism, and Diabetes. Therefore, the identification of SVs is crucial in developing personalized treatments.

While short reads cannot detect SVs in all size ranges due to their short template length, the more recent long read sequencing technologies have overcome that limitation as they resolve many of the repetitive regions. However, SV detection methods based on long reads do not perform well for events with high zygosity in diploid or polyploid cases.

Our proposed approach is based on de novo assembly using both short and long read technologies. We use long reads that align to short read contigs to stitch them and generate contiguous paths of short read contigs. The gaps between consecutive contigs are filled by consensus sequence of long reads. Our preliminary results on simulated and real datasets demonstrated that this method generates assemblies comparable to off-the-shelf methods. Next, in order to detect heterozygous events, we cluster long reads into two (or more) groups that represent two (or more) copies of the chromosome. Our experiments on simulated data shows the effectiveness of this clustering approach in correctly separating reads originating from two different haplotypes in presence of heterozygous SVs.
IDENTIFICATION OF ZRSR2 IN MEDIATING THE DEVELOPMENT OF CASTRATION-RESISTANT PROSTATE CANCER

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Introduction: Androgen deprivation therapy (ADT) remains the leading systemic therapy for locally advanced and metastatic prostate cancers in the clinic, while the initial response to ADT is effective and almost universal in hormone-naïve prostate cancer (HNPC), the durability of response is variable. Unfortunately incurable castration-resistant prostate cancer (CRPC) inevitably develops. Our research objective is to identify critical driver genes responsible for CRPC development.

Method: We have developed a unique panel of HNPC Patient-derived xenograft (PDX) models in the Living Tumor Lab. Such HNPC PDX models mimic the development of CRPC following host castration. Thus the models were used for driver gene discovery by examining gene expression at various time points after castration using transcriptome profiling analysis; particular attention was given to pre-CRPC changes in expression indicative of genes acting as potential CRPC drivers which were further validated in terms of their clinical relevance using data from prostate cancer patient databases. Then a top gene candidate was selected for functional studies.

Results: 1. We identified ZRSR2 as a potential candidate gene. 2. ZRSR2 was significantly and consistently upregulated in CRPC PDX models. 3. ZRSR2 was significantly upregulated in CRPC samples in three independence prostate cancer clinical cohorts. 4. ZRSR2 expression upregulated after ADT or ENZ in LNCaP and C4-2. 5. Knocking down of ZRSR2 inhibited cell proliferation in 22RV1 CRPC cells. 6. Overexpression of ZRSR2 mildly promoted cell proliferation in C4-2.

Conclusion: ZRSR2 is a potential driver gene of CRPC. Targeting ZRSR2 might improve the sensitive of AR pathway inhibitors for treatment of CRPC.
DESIGN AND DEVELOPMENT OF A NOVEL PHOTOSENSITIVE URINARY CATHETER SYSTEM WITH ANTIMICROBIAL PROPERTIES

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Background: Catheter Associated Urinary Tract Infections (CAUTI) resulting from indwelling devices such as Foley Catheters account for 80% of hospital acquired urologic infections. Bacterial adhesion and biofilm formation on the surface of indwelling urinary devices result in post-treatment infections to be common problems for both patients and the healthcare system. The conventional method to battle against urinary pathogens is the administration of antibiotics, the efficacy of which is significantly hindered by the fact that many pathogens develop resistance to antibiotics. As a result, there exists a significant need for the development of alternative antimicrobial modalities. To address this, our group is developing a novel antimicrobial urethral catheter system based on Photodynamic Therapy (PDT). Specifically, the exposure of a novel photosensitizing material to light at a specific wavelength results in the generation of Reactive Oxygen Species (ROS) which results in the killing of adherent bacteria.

Methods: The photosensitizer(PS) is synthesized and purified from a transition metal complex with no toxicity to human body. The PS is then loaded into the urinary catheter and is illuminated by means of fiber optic LED light source to produce the photokilling effect against adherent bacteria.

Results: So far, In-vitro studies have been performed to identify the optimum experimental parameters. Nearly 2 Logs of photokilling effect has been observed with the experimental groups.

Conclusions: The incorporation of antimicrobial PDT into urologic practices can provide an alternative to the conventional treatment methods to battle against urinary infections.
THE LNCRNA HOTAIR PROMOTES INVASION BY STABILIZING AP1 IN PROSTATE CANCER

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Introduction: Long non-coding RNA (lncRNA) are a class of non-coding RNA that have many diverse functions. We have identified the lncRNA HOTAIR as being highly overexpressed in metastatic tumors and androgen indifferent tumors and cell lines. HOTAIR interacts with various proteins such as EZH2 and AR to promote aggressiveness. However it is unclear what role it plays in AR indifferent prostate cancer. Computational analysis has identified various transcription factor (TF) binding sites along the HOTAIR transcript which we aimed to validate.

Methods: We performed RNA associated transcription factor array (RATA) to investigate HOTAIR-TF interactions and validated them with RNA-IP. RNA-seq and gene set enrichment analysis was used (GSEA) to determine transcriptomic consequences of HOTAIR expression. qPCR and western blot were used to determine HOTAIR impact on AP1 expression. Zymography and in vitro invasion were employed to determine if HOTAIR promotes invasion.

Results: HOTAIR showed significant interaction with several TFs in particular AP1 as measured by RATA and RNA-IP (FOS and JUN). GSEA reveals that AP1 and FOS activity is promoted by HOTAIR expression. Western blot and qPCR has shown that HOTAIR promoted FOS protein expression and expression of downstream invasion markers.

Conclusions: HOTAIR interaction with AR has previously been established but here we show that HOTAIR can bind AP1 and promote its transcriptional activity as well. HOTAIR seems to be promoting AP1 activity through stabilizing FOS protein. Increased AP1 signalling results in increased expression of invasion markers and in vitro invasion.
NOVEL ONE-STEP APPROACH TO A UNIVERSAL ANTI-ADHESION COATING TO PREVENT CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

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Introduction: Catheters associated urinary tract infection (CAUTIs), being the main factor for hospital-acquired infections. In USA and Canada more than 33 million catheters are inserted each year. Urinary catheters provide ideal surfaces for bacterial biofilm formation. Several attempts to change catheters biomaterial design to prevent urinary tract infection have met with poor success. The universal PDA-PDMA coating will be biocompatible and effective in preventing CAUTI. Here, we present the efficacy of the coating against one of the common uropathogens Proteus mirabilis in vitro and the development of relevant in vivo models.

Materials and Methods: A novel coating was developed, highly efficacious and safe universal coating based on a binary coating composed of polydopamine (PDA) and high molecular weight poly(N,N-dimethylacrylamide)(PDMA). Antimicrobial activity of our novel coating was determined in vitro via Proteus mirabilis colony counts after periods 4, 8, 12, and 24 hrs post-exposure to uropathogens.

Results: In this study our novel coating prevented the bacterial adhesion uropathogens to coated polyurethane (PU) surfaces by >95% compared to uncoated surfaces in vitro, the effective was (up to10² fold decrease).

Conclusions: Based on in vitro data, coating provides a non-fouling hydrated layer to prevent bacterial adhered onto the surface and effectively prevents CAUTI. Further testing of this novel coating using more environmentally-relevant in vivo CAUTI models will be important.
SYNTHETIC IMMUNOTHERAPY FOR CANCER TREATMENT

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In cancer immunotherapy, immune cells are modified to attack cancer cells. One popular strategy is to exploit presentation of cancer-specific neoantigens on major histocompatibility complex (MHC) class-I molecules able to engage a cytotoxic CD8 T-cell response. However, this strategy is challenged by inherent tumor heterogeneity, potential on-target cross-reactivity with normal tissues, as well as low neoantigen abundance in tumors with low mutation burden. To overcome these challenges, we propose a strategy where synthetic CD8 T-cell epitopes are specifically delivered into tumor cells for MHC-I presentation via the recombinant pan-cancer-binding lectin VAR2CSA (rVAR2), derived from the malaria parasite Plasmodium falciparum.

We have engineered a triple-repeat CD8 epitopes separated by cathepsin-S cleavage sites that can be conjugated to rVAR2. When internalized into endosomes of tumor cells via rVAR2, the sequences are processed by cathepsin-S to release endosome-permeable MHC-I compatible CD8 epitopes. We will interrogate the entire process of internalization, processing, and MHC-I presentation using the established OVA257-264 SIINFEKL CD8 epitope as proof-of-concept model. The approach will be functionally validated using the OT-1 animal model with endogenous CD8 T cells reactive against SIINFEKL.

Our data showed that tumor cells pulsed with our VAR2-conjugated SIINFEKL-based construct can prime the cytotoxicity of OT-1 mice T-Cells.

In this project we combine a malaria-based cancer-specific delivery system with engineered CD8 T cell epitopes. This work will be a powerful addition to current neo-antigen-based cancer immunotherapy approaches. We will expand the CD8 epitope repertoire to include components of vaccines currently in population-wide use.
THE USE OF 2D PRIMARY BLADDER CULTURES AS A PREDICTIVE TOOL FOR IN VIVO DRUG RESPONSE

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Introduction: Patient-derived xenograft (PDX) models are the gold standard for pre-clinical drug testing in bladder cancer (BCa), despite being low throughput and costly. 2D primary cultures can remedy both these issues. Here, we set out to establish and characterize 2D BCa cultures from primary human tumors and existing PDXs, and to assess their sensitivity to cisplatin and gemcitabine (CDDP/GEM).

Methods: BCa tissue was obtained from radical cystectomies, and established pre and post-neoadjuvant chemotherapy (NAC)-derived PDXs. Tissues were homogenized to single cell suspensions and plated in organoid-specific media. Cultures were characterized by growth curves and immunofluorescence (IF). PDX-derived cultures were also treated with CDDP/GEM and their responses compared to those seen in PDXs.

Results: Fifteen primary cultures, and two 2D cultures from existing PDXs, have been successfully established, frozen, and passaged 15 times. Primary and PDX-derived cultures vary both in cell morphology and growth rate. IF shows a skew towards a basal phenotype, and the presence of fibroblasts in some cultures. Finally, the response to CDDP/GEM of PDX cultures was shown to mimic those found in vivo in one model, with the second still ongoing.

Discussion/Future Aims: 2D BCa cultures have been successfully established from human primary and mouse PDX tissues. Preliminary data indicate that the response of the in vitro cultures to chemotherapy are similar to that of the in vivo models, suggesting that 2D primary cultures may be used as a predictive tool for in vivo drug response. Further characterization of cultures and establishment of 3D organoids are ongoing.
THE ATP-BINDING CASSETTE GENE ABCF1 FUNCTIONS AS AN E2 UBIQUITIN-CONJUGATING ENZYME CONTROLLING MACROPHAGE POLARIZATION TO DAMPEN LETHAL SEPTIC SHOCK

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Sepsis is a bi-phasic inflammatory disease that threatens approximately 30 million lives and claims over 14 million annually, yet little is known regarding the molecular switches and pathways that regulate this disease. Here, we have described ABCF1, an ATP-Binding Cassette (ABC) family member protein, which possesses an E2 ubiquitin enzyme activity, through which it controls the Lipopolysaccharide (LPS)- Toll-like Receptor-4 (TLR4) mediated gram negative insult by targeting key proteins for K63-polyubiquitination. Ubiquitination by ABCF1 shifts the inflammatory profile from an early phase MyD88-dependent to a late phase TRIF-dependent signaling pathway, thereby regulating TLR4 endocytosis and modulating macrophage polarization from M1 to M2 phase. Physiologically, ABCF1 regulates the shift from the inflammatory phase of sepsis to the endotoxin tolerance phase, and modulates cytokine storm and interferon-b (IFN-b)-dependent production by the immunotherapeutic mediator, SIRT1. Consequently, ABCF1 controls sepsis induced mortality by repressing hypotension-induced renal circulatory dysfunction.
DEEP NEURAL MAPS FOR UNSUPERVISED VISUALIZATION OF HIGH GRADE PROSTATE CANCER

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Introduction: Analysis of core biopsies taken under transrectal ultrasound guidance (TRUS-guided) and MR TRUS-guided fusion biopsy are current approaches for Prostate Cancer (PCa) diagnosis. Both of these methods are limited in accurately identifying PCa. Visualizing highly probable areas of PCa before taking the biopsy, can significantly improve the accuracy of these procedures. Prior studies have used machine learning techniques to show that Temporal Enhanced Ultrasound (TeUS), is a promising modality to successfully extract features of cancerous tissue. These studies focused on supervised classification of PCa verified by pathology results. A major challenge in ultrasound-based cancer detection is noisy labeling. Data from an entire core has a single label. Additionally, supervised methods are limited by data from cores with known pathology, and a significant portion of unlabeled data is discarded.

Method: We provide an end-to-end unsupervised solution to map PCa distribution from TeUS data to a 2D lattice. Deep Neural Maps (DNM) is used as representation learning method that transformed TeUS data to a topologically arranged hyper-lattice. This new map is a manifold of data where similar samples are closer together. Therefore, similar regions of malignant and benign tissue in the prostate are clustered together.

Result: Our proposed method increases the number of training samples by several orders of magnitude by effectively using unlabeled data from all prostate region. Data from biopsy cores with known labels are used to associate the clusters with PCa. Cancer probability maps generated using the unsupervised clustering of TeUS data helps intuitively visualize the distribution of abnormal tissue for augmenting TRUS-guided biopsies.

Conclusions: we proposed a new approach for identifying and visualizing benign and various grades of cancer in the prostate tissue from TeUS data. We utilized an unsupervised representation learning model, namely DNM, to obtain a topology-preserving mapping from the data space to a 2D lattice space from unlabeled data.
UNDERSTANDING THE ROLE OF CALCIUM CHANNELS IN THE REGULATION OF URETERAL PERISTALSIS

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**Background:** Ureteral peristalsis is the movement of the ureter (wavelike contractions) that transports urine from the kidney to the bladder. Obstruction of the ureter disrupts ureteral peristalsis resulting in cessation of urine flow and kidney drainage, and the development of hydronephrosis as a result of the increasing pressure. Similarly, the placement of a ureteral stent to alleviate the negative effects of obstruction results in cessation of ureteral peristalsis resulting in residual hydronephrosis. Currently, the molecular mechanisms driving obstruction-induced ureteral aperistalsis are unknown and warrant further investigation. Calcium (Ca2+) is one of the most important secondary messengers that plays a crucial role in muscle contractions. Transient receptor potential (TRPs) channels are a family of cation-permeable channels that play a role in homeostasis and signaling pathways by regulating mainly Ca2+ ion influx into cells. TRPs were previously shown to regulate intestinal peristalsis. Given that both intestinal and ureteral peristalsis share numerous physiological characteristics, we investigated a role for TRPs in regulating ureteral peristalsis with the specific hypothesis that ureteral aperistalsis due to obstruction is driven by dysfunctional TRPs.

**Methods:** We developed an experimental model of unilateral ureteral obstruction in mice where one side is obstructed for 24, 48 or 72 hours using an atraumatic vascular clamp. Kidney and ureter tissue samples were obtained from these obstructed mice and RNA was extracted from these tissues. Candidate TRP expression levels were quantified using RT-PCR and qPCR analysis.

**Results:** In the 24 hours obstructed mice, TRPC4, TRPC6 and TRPV4 are significantly downregulated in the kidney only. However; in the 48 and 72 hours obstructed mice, all candidate TRPs are significantly downregulated in both kidney and ureter suggesting that in 24 hours, the disruption of urine outflow by obstruction increases the pressure starting in the kidney and continues building up in the ureter after 24 hours (in 48 and 72 hours) resulting in downregulation of TRPs and inhibition of ureteral peristalsis.

**Conclusions:** The significant downregulation of candidate TRPs in obstructed kidney and ureter suggest that these TRPs are required for ureteral peristalsis. Our next approach is to utilize the use of TRPs agonists and antagonists to confirm if the downregulation of these TRPs results in ureteral aperistalsis.
CONDITIONALLY REPROGRAMMED CELLS FROM PATIENT-DERIVED XENOGRAFT TO MODEL NEUROENDOCRINE PROSTATE CANCER DEVELOPMENT

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Treatment-emergent neuroendocrine prostate cancer (t-NEPC) is a lethal subtype of advanced prostate cancer that occurs via NE transdifferentiation of prostate adenocarcinomas in response to androgen receptor (AR)-inhibition therapy. Study of t-NEPC has been hampered by a lack of clinically relevant models. We previously established a unique and first-in-field patient-derived xenograft (PDX) model of adenocarcinoma (LTL331)-to-NEPC (LTL331R) transdifferentiation. In this study, we established conditionally reprogrammed (CR) cells from the adenocarcinoma PDX tumor line LTL331. These LTL331-derived CR cells retained the same genomic mutations of the parental tumor and, can be genetically manipulated and continuously propagated in vitro. Further androgen deprivation treatment on LTL331-CR cells showed no effect on cell proliferation. Transcriptomic analyses of the LTL331-CR cells revealed profound downregulation of androgen response pathway, and enrichment of stem/progenitor-like marker genes, compared with the parental tumor LTL331. Notably, when grafted back into the subrenal capsule of male NOD/SCID mice, these LTL331-CR cells gave rise to NEPC tumors directly as manifested by histological expression of NE markers. Transcriptomic analyses of the newly developed NEPC tumors also demonstrated marked enrichment of NEPC signature genes and loss of AR signaling genes. This study provides a novel strategy to investigate the mechanisms underlying t-NEPC development with a unique PDX by enabling gene manipulation ex vivo and subsequent functional evaluation in vivo.
DE NOVO IDENTIFICATION OF SPLICE ISOFORMS USING LONG READ SEQUENCING AND SEQUENCE TO DAG ALIGNMENT

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The identification of splice variants has an important role in cancer diagnostics and identification of potential drug targets. Recently, it has been shown that long reads can identify isoforms that are not reported previously. Current methods for novel isoform detection that use short reads has theoretical and empirical limitations as the short reads hardly cross more than one or two junctions. Long mRNA reads provide an excellent opportunity to identify novel isoforms as they span more than one junction and sometimes the full length of the transcript. However, the level of noise present in these long reads as well as the fact that not all long reads span the full length of transcripts means that such task of isoform discovery is not trivial. To successfully utilize long reads, a computational method that clusters reads into isoforms and aggregate evidence from all reads in an isoform cluster to identify splice events is needed. In this work, we propose an alignment method that performs de novo isoform detection from long read mRNA-seq data. The method aligns reads to a directed acyclic graph (DAG) representation of the gene of interest. The proposed alignment is an extension of sequence to DAG alignment with local alignment scoring matrix. The reads alignment paths are then clustered into isoforms that are post processed for identification of splice junctions.
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Background: VPC implemented an ePRO system in April 2017 to collect data on a research protocol in collaboration with University Health Network of Toronto, funded by Prostate Cancer Canada. Responses to ePRO questionnaires collected on iPads were entered into the national PC360 registry. Herein we describe our experience implementing the ePRO system over the last two years.

Methods: All new cases of PC and those being booked for prostate surgery/biopsy at VPC were asked to complete ePROs on iPads at clinic appointments. REB required in person consent by the coordinator rather than electronically on the iPad. ePROs included EPIC-26, EQ-5D-5L, WHODAS 2.0, and Distress Thermometer.

Results: 878 eligible pts completed at least one ePRO. Completion rates were 77% vs 75% for years 1 and 2 respectively. Data was missing for 16% in both years, often due to logistical problems finding the patient to give him the iPad before he left the clinic. In a small percentage of cases, ePRO reports were incomplete due to fluctuating WiFi connectivity, inadequate time to complete the questions prior to being called for appointment, refusal, or no show.

Conclusions: Incorporation of ePROs as a research tool was accomplished with high completion and low refusal rates but required significant manpower. The next step is to incorporate ePROs into clinical practice, in which case consent will not be required. WiFi reliability will remain challenging but can be overcome. It is anticipated that real-time ePRO data will facilitate and enhance clinical care.
OVERVIEW OF ENROLLMENT AND PARTICIPATION IN RESEARCH STUDIES CONDUCTED AT THE PROSTATE CANCER SUPPORTIVE CARE (PCSC) PROGRAM

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Background: The mission of PCSC is to provide clinical care focused on the needs of prostate cancer patients and partners. Incorporation of research into daily care provides evidence for these practices, identifies areas for improvement, and tests new approaches. We review the metrics of the PCSC Research program to date.

Methods: Studies were grouped by type and enrollment logs provided accrual as well as reasons for non-participation information.

Results: The PCSC research team participated in 22 studies. Of these, we referred patients to 6 studies but were not certain how many actually enrolled. For the remaining 16 studies, we recruited 1080 participants, not including those who consented for the PCSC SPIRIT databank. 2 studies were Canadian registry studies, 9 involved therapeutic or lifestyle changes, 2 were prospective observational studies, 1 survey, and one was for germline testing of active surveillance patients. Eight studies recruited dyads (patient and partner or caregiver). Of the 1080 participants, 760 (70.4%) enrolled in 1 study, 210 (19.4%) in 2 studies, and 110 (10.2%) in ≥ 3 studies. Reasons for 583 patients not consenting included lack of interest (43.7%), patient out of town (21.1%), time constraints (10.3%), travel distance (6.7%).

Conclusions: Our data show that a subspecialty supportive care program can provide a rich environment in which to conduct clinical research. We believe that the integration of the research program and personnel into the clinical setting is key to our success. Current on-going studies are evaluating the impact of and patient satisfaction with all PCSC modules.
FEASIBILITY OF USING A HOME SLEEP MONITORING DEVICE TO MEASURE SLEEP PARAMETERS IN MEN BEFORE AND 3 AND 6 MONTHS AFTER STARTING ANDROGEN DEPRIVATION THERAPY (ADT)

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Background: We hypothesized that hot flashes due to ADT might impact sleep. Since the effects of ADT on sleep have not been well characterized, a pilot study to assess the feasibility of using a home sleep monitoring device (ARESTM) and to obtain preliminary data on sleep parameters before and after starting ADT was initiated.

Methods: Men with no symptomatic distant metastases who were about to start ADT were eligible. Participants were instructed in use of the ARESTM and wore the device for 2 consecutive nights at baseline before starting ADT and at 3 and 6 months after starting ADT. Hot Flash Related Daily Interference Scale (HFRDIS), Pittsburgh Sleep Quality Index (PSQI), Modified EPIC, and Health and Lifestyle questionnaires were obtained at all time points.

Results: Between 12-2015 and 2-2018 we enrolled 12 patients, median age 65.5 years (range 61-86). One patient was unable to complete any sleep studies and one other patient did not complete month 6 sleep study. Of 11 baseline assessments, 6 had mild, 2 moderate, 1 moderate-severe, 2 severe measures of obstructive sleep apnea (OSA). After 6 months: OSA measures were worse in 4 men, 58% reported one or more daily hot flashes, 6 reported that hot flashes interfered with sleep mildly to moderately, and 7 patients gained a median of 5.5 lbs (2.2-7.6 lbs).

Conclusions: The home sleep monitor was reasonably tolerated by 10 of 12 men. More than half the patients experience hot flashes that disturb sleep and experience weight gain. Further analysis is on-going.
The Long Noncoding RNA Landscape of Neuroendocrine Prostate Cancer and Its Clinical Implications


Neuroendocrine prostate cancer (NEPC) is a lethal subtype of castration-resistant prostate cancer (CRPC). It can develop de novo from prostate neuroendocrine cells, yet primarily is a treatment-induced phenotype arising from transdifferentiated prostate adenocarcinoma (AD) cells (NEtD). Currently there is an unmet clinical need for predictive biomarkers, therapeutic targets, and more reliable diagnostics. Our research interrogates the first-in-field patient-derived xenograft model of NEtD, six in vitro CRPC/NEPC models, and ~30,000 PCa patient samples, including 344 NEPC or molecular analogous NEPC samples. We implement a state-of-the-art next-generation sequence analysis pipeline, capable of detecting transcripts at low expression levels to build a comprehensive lncRNA catalog (~N=40,000). Our xenograft model enabled identification of transcriptional changes during NEtD. Our in vitro models were used for functionalization and our patient samples were used to determine clinical relevancy and/or to test for patient survival. We first review lncRNA research in PCa over the last 30 years. We include known genomic structures, mechanisms of actions, roles in PCa progression, and their use in disease management. Second, we identify a 122-lncRNA signature capable of robustly classifying NEPC from AD, 25 with predictive ability to classify metastatic patients, and 2 (SSTR5-AS1 and LINC00514) capable of stratifying patients more probable to develop metastasis following androgen deprivation therapy (ADT). Third, we identify two NEPC molecular subtypes driven by lncRNAs FENDRR and GAS5. They also have a predictive ability to stratify ADT patients by clinical outcome. Last, we investigate our top candidate NEPC lncRNA H19. We identify the active isoform, determine it is conserved, a dozen associated PCa risk single nucleotide polymorphisms (SNPs) nearby, and NEPC-related TFBS (MYC/MAX) embedded within. H19 was highly sensitive and relatively specific for NEPC. Functionally, we identified associations to invasion, proliferation, the NEPC phenotype, and physical interactions with EZH2. Most importantly H19 is predictive for ADT-patient outcome. Collectively, this thesis constitutes a step forward in understanding the complexity of the transcriptome for NEPC and the NEtD process. The results here will advance our knowledge of clinically relevant lncRNAs involved in cancer progression and treatment resistance.
THE ROLE OF URINARY TRACT MICROBIOTA IN DIAGNOSE AND THERAPEUTICS ON NON-MUSCLE INVASIVE BLADDER CANCER TREATED WITH BCG (BACILLE CALMETTE GUERIN)

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Introduction: For more than 30 years BCG has worked as an immunotherapy to treat superficial bladder cancer, and although any other treatment surpassed its efficacy, around 30 to 40% of patients don’t respond to it. For those reasons, we are investigating potential roles of naturally occurring bacteria from the urinary tract regarding its ability to work as an adjuvant to modulate BCG’s immune response.

Methods: Microorganisms were isolated from the urine of healthy individuals. Urine was plated on media dishes until pure isolates obtained. Bacterial DNA extracted, 16S rRNA primers utilized to run PCR, amplified product checked on an agarose gel, the product sequenced by Sanger method. The nucleotide sequence was submitted to an NCBI’s blast search database sequences to be analyzed.

Results: Twenty-eight bacterial isolates were sequenced, two genera identified Enterococcus with two species and Staphylococcus with three species.

Conclusions: Bacterial strains were successfully isolated from individuals who didn't present bacteriuria or infection. These results enable us to research the roles of the urinary microbiome (UM) in immune surveillance and the dynamic of intravesical immune responses with an emphasis on bladder cancer patients submitted to BCG therapy. This also has the potential to assess the UM as a biomarker for a positive outcome of BCG therapy.
SURVEYING SOURCES OF ANXIETY IN FAMILY AND FRIENDS OF PATIENTS UNDERGOING SURGICAL OPERATIONS

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**Introduction:** The perioperative process proves to be an anxiety- and stress-inducing ordeal for not only the patient, but their family and friends as well. In order to improve this process and reduce undue stress, this work investigates the causes of worry in the perioperative process as well as supporter-staff dynamics.

**Methods:** After REB approval (H18-03229), a survey was administered to family and friends in the Surgical Family Waiting Room at Vancouver General Hospital (n=40). The survey consisted of questions regarding the respondents’ relation to the patient, the surgical procedure taking place, and anxiety levels. Causes of such anxiety were explored, as were communication with the health care team.

**Results:** Majority of participants were waiting during a major surgery (78%, n=31). Common causes of worry as identified by participants included poor outcomes (53%, n=21), death (13%, n=5), and logistics regarding the patient’s location, status, and surgical timeline (15%, n=6). The majority of respondents reported less than 3 visits to the nursing station (73%, n=29), while 40% (n=16) reported hesitancy in approaching staff for updates. Types of questions participants had were centered around logistics, procedural status, and timeline. When prompted on how communication could be improved, responses indicated more frequent updates during surgery (73%, n=11 of 15 responses).

**Conclusions:** The results of this survey indicate a need for improved communication between the health care team and the family and friends of patients in order to properly address the anxiety experienced as surgical procedures are taking place.
EVALUATION OF A SINGLE USE FLEXIBLE CYSTOSCOPE: A MULTI-INSTITUTIONAL INTERNATIONAL STUDY

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Introduction:
Acquisition costs and prohibitively expensive technical support for endoscope maintenance, repair and reprocessing have deterred adoption of flexible cystoscopes by many international urologists. This study evaluated the performance of novel single use digital cystoscopes in which an engineering modification allowed for direct connection of each endoscope cord to a laptop or computer monitor for visualization.

Methods:
The performance characteristics of flexible single use cystoscopes (Neoscope) were prospectively evaluated versus a reusable flexible cystoscope (Olympus) in three clinical cases and two independent benchtop testing episodes in Canada. Cystoscope maneuverability, imaging, deflection, irrigation and ease of use of instrumentation were investigated. Additional investigations were performed during clinical use in Zimbabwe (7 patients), Egypt (10 patients) and Dominica (5 patients).

Results:
Bench testing revealed average smaller tip diameter and shorter single use cystoscopes (4.05mm and 35.35cm) versus reusable cystoscopes (6.09mm and 38cm). Deflection of the single use scope was superior with an empty working channel (230 up/220 down) versus the reusable (195 up/95 down) but was inferior on placement of instruments including a 365um laser fibre (85 up/85 down versus 175 up/85 down). Clinical use revealed satisfactory maneuverability, ease of use of instruments, deflection and visualization.

Conclusions:
Benchtop testing performance of the single use digital flexible cystoscopes was inferior compared to reusable digital cystoscopes. However, these single use endoscopes offer adequate illumination, imaging and maneuverability. Direct connection to any computer monitor allowed truly portable use, allowing for treatment of patients in a variety of clinical settings without the need for equipment maintenance.
Organizing Committee

- Dr. Amina Zoubeidi
- Dr. Ben H. Chew
- Dr. Koroush Afshar
- Dr. Peter C. Black

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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