14th Annual Lorne D. Sullivan Lectureship & Research Day

Date: Tuesday, June 16, 2020
Zoom Meeting: https://ubc.zoom.us/j/99326943759

Program & Abstracts Booklet
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

2019 – Dr. Christopher P. Evans  
2018 – Dr. Robert Reiter  
2017 – Dr. James E. Lingeman  
2016 – Dr. Michael A.S. Jewett  
2015 – Dr. John M. Barry  
2014 – Dr. James A. Eastham  
2013 – Dr. Paul Lange  
2012 – Dr. Ralph V. Clayman  
2011 – Dr. David A. Bloom  
2010 – Dr. Gerald H. Jordan  
2009 – Dr. Peter T. Scardino  
2008 – Dr. Inderbir Singh Gill  
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
9:30 AM – 9:35 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

State of Art Lecture I
9:35 AM – 9:50 AM

The Future of Endourology: Kidney Stone Fragmentation in the 21st Century

Dr. Ben H. Chew
Associate Professor, Department of Urologic Sciences

Session I:
(7-minute talk and 3-minute Q&A)
9:50 AM – 10:30 AM

Moderator: Dr. Ryan Flannigan

9:50 AM – 10:00 AM

DIAGNOSTIC PERFORMANCE OF ULTRASOUND AND CYTOLOGY IN UPPER TRACT CANCER: RESULTS FROM A GLOBAL MULTICENTRE ANALYSIS
Taeweon Lee1,2, Miles Mannas1,2, Peter Black1,2, Mark Assmus1, Tim Wollin1,2, Sian Khadhour1,2, Kevin M. Gallagher2, Kenneth R. MacKenzie1, Taimur T. Shah3, Chuanyu Gao4, Sacha Moore5,6, Eleanor Zimmermann1, Eric Edison1,2, Matthew Jeffries1,2, Arjun Namblar1, Matthew E. Nielsen1,2, John S. McGrath1,2, Veeru Kasivisvanathan1,2, The IDENTIFY Study Group

10:00 AM – 10:10 AM

PREDICTORS OF PERIOPERATIVE COMPLICATIONS IN PEDIATRIC RENAL TRANSPLANTATION: A LONG-TERM RETROSPECTIVE STUDY
Cyrus Chehroudi1, Alexander Danechi1, Andrew MacNeily1, Kourosh Afshar1
1Department of Urologic Sciences, University of British Columbia

10:10 AM – 10:20 AM

IDENTIFICATION OF A COMPREHENSIVE GENE SIGNATURE TO DETERMINE TREATMENT RESPONSE AND GUIDE PRECISION ONCOLOGY IN CLEAR-CELL RENAL CELL CARCINOMA
Ninadh M. D’Costa1,2, Davide Cina1, Raunak Shrestha1,2, Robert H. Bell2, Yen-Yi Lin2, Hossein Asghari2,3, Cesar U. Monjaras-Avila1,2, Christian Kollmannsberger3, Faraz Hach2,4, Claudia I. Chavez-Munoz1,2, and Alan I. So1,2

10:20 AM – 10:30 AM

BIOMARKER POTENTIAL OF ACTIVATING AKT1 AND PIK3CA MUTATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER
Cameron Herberts1†, Andrew J Murtha1†, Simon Fu1, Gang Wang1, Elena Schönlaub, Hui Xue5, Dong Lin1,2, Anna Gleave1, Steven Yip1, Argham Angeles1, Sebastien Hotte6, Ben Tran7, Scott North8, Sinja Taavitsainen9, Kevin Beja1, Gillian Vandekerkhove1, Elie Ritch1, Evan Warner1, Fred Saad10, Nayer Iqbal11, Matti Nykter1, Martin E Gleave1, Yuzhuo Wang1, Matti Annala12, Kim N Chi12, and Alan I. So1,2†, †co-first; †co-corresponding

State of Art Lecture II
10:30 AM – 10:45 AM

Targeting SEMA3C for treatment of advanced prostate cancer

Dr. Christopher Ong
Associate Professor, Department of Urologic Sciences
Session II:
(7-minute talk and 3-minute Q&A)

10:45 AM – 11:45 AM  Moderator: Dr. Alex Wyatt

10:45 AM – 10:55 AM  FREDDIE: ANNOTATION-FREE ISOFORM DISCOVERY USING LONG-READ SEQUENCING
Baraa Orabi1, Brian McConeghy2, Cedric Chauve3, Faraz Hach2,4

10:55 AM – 11:05 AM  GENOME-WIDE CRISPR SCREEN REVEALS SLFN11 AS A POTENT MEDIATOR OF CISPLATIN-SENSITIVITY IN MUSCLE-INVASIVE BLADDER CANCER
Gunjan Kumar1,2, Elie Ritch1, Davide Tortora1, Igor Moskalev1, Htoo Zarni Oo1, Daksh Thaper1
Alexander Wyatt1, Peter Black1*, and Mads Daugaard1*

11:05 AM – 11:15 AM  FUNCTIONAL MAPPING OF ANDROGEN RECEPTOR ENHANCERS
Shreyas Lingadahalli1, Flora Huang1, Tunc Morova1, Dogancan Ozturan2, Ivan Yu1, Eugene Hu1, Colin
Collins1, Eldon Emberly1, Wilbert Zwart4, Nathan A. Lack1,2

11:15 AM – 11:25 AM  DISCOVERY AND CHARACTERIZATION OF A NOVEL CATALYTIC TOPOISOMERASE II INHIBITOR FOR ANTICANCER THERAPEUTICS
Victor M. M. Barrios1,2, Maria Radaeva1,2, Yi Song1,2, Zaccary Alperstein1,2, Ahn R. Lee1, Veronika
Schmitt1, Mary Bowden1, Joseph Lee1, Fuqiang Ben1, Ning Xie1, Nada Nallous1, Martin E. Gleave1,
Artem Cherkasov1,2, Xuesen Dong1,2

ADJOURN
Abstract
Presentations
DIAGNOSTIC PERFORMANCE OF ULTRASOUND AND CYTOLOGY IN UPPER TRACT CANCER: RESULTS FROM A GLOBAL MULTICENTRE ANALYSIS

Taeweon Lee1,2, Miles Mannas1,2, Peter Black1,2, Mark Assmus3, Tim Wollin3,4, Sinan Khadhouri5, Kevin M. Gallagher6, Kenneth R. MacKenzie7, Taimur T. Shah8, Chuanyu Gao9, Sacha Moore10, Eleanor Zimmermann11, Eric Edison12, Matthew Jefferies13, Arjun Nambiar7, Matthew E. Nielsen14, John S. McGrath15, Veeru Kasivisvanathan16, The IDENTIFY Study Group

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2. Vancouver Prostate Centre, Vancouver, BC, CA
3. The Division of Urology, University of Alberta, Edmonton, AB, CA
4. Alberta Urology Institute, Edmonton, AB, CA
5. Aberdeen Royal Infirmary, Dept. of Urology, Aberdeen, United Kingdom
6. Western General Hospital, Dept. of Urology, Edinburgh, United Kingdom
7. Freeman Hospital, Dept. of Urology, Newcastle, United Kingdom
8. Charing Cross Hospital, Imperial College Healthcare NHS Trust, Dept. of Surgery and Cancer, London, United Kingdom
9. Peterborough City Hospital, Dept. of Urology, Peterborough, United Kingdom
10. Wrexham Maelor Hospital, Dept. of Urology, Wrexham, United Kingdom
11. Weston General Hospital, Dept. of Urology, Weston-super-Mare, United Kingdom
12. North Middlesex Hospital, Dept. of Urology, London, United Kingdom
13. Morriston Hospital, Dept. of Urology, Swansea, United Kingdom
14. University of North Carolina, Dept. of Urology, Chapel Hill, North Carolina, USA
15. University of Exeter Medical School, Dept. of Urology, Exeter, United Kingdom
16. University College London, Dept. of Urology, London, United Kingdom

Introduction
We examined the performance of diagnostic tests used in the detection of upper tract urothelial carcinoma (UTUC) and renal cell carcinoma (RCC) in patients referred to secondary care for suspected urinary tract cancer.

Methods
The IDENTIFY study group prospectively assessed 10,896 patients (27 countries). Patients with previous urological malignancy were excluded. Index diagnostic tests (e.g. cytology, imaging) were evaluated against the predetermined reference diagnostic tests for UTUC and RCC including histopathology and computed tomography urography (CTU). Equivocal outcomes were considered positive as they prompted further workup.

Results
UTUC prevalence was 1.17% (n=128). It was diagnosed in 114 patients with visible hematuria (VH) (1.60%). It was found in nine patients (0.29%) with non-visible hematuria (NVH). No patient with NVH below the age of 60 (n=1,313) had UTUC. RCC prevalence was 0.98% (n=107). It was more prevalent in VH (1.26%, n=90) vs. NVH (0.41%, n=13). USS was poor at detecting UTUC alone, however improved in sensitivity when combined with cytology (Table 1).
### Table 1: The diagnostic test performance of USS and cytology in RCC and UTUC

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6,913</td>
<td>81.6%</td>
<td>98.0%</td>
<td>22.6%</td>
<td>99.9%</td>
</tr>
<tr>
<td>in VH **</td>
<td>4,165</td>
<td>82.1%</td>
<td>97.8%</td>
<td>26.0%</td>
<td>99.8%</td>
</tr>
<tr>
<td>in NVH</td>
<td>2,380</td>
<td>87.5%</td>
<td>98.3%</td>
<td>14.6%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Upper tract urothelial cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USS</strong></td>
<td>**</td>
<td>50.0%</td>
<td>97.9%</td>
<td>16.9%</td>
<td>99.6%</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>**</td>
<td>58.8%</td>
<td>89.4%</td>
<td>8.4%</td>
<td>99.2%</td>
</tr>
<tr>
<td><strong>USS + Cytology</strong></td>
<td>5,798</td>
<td>78.7%</td>
<td>92.3%</td>
<td>9.8%</td>
<td>99.8%</td>
</tr>
<tr>
<td><strong>USS + Cytology + Cystoscopy</strong></td>
<td>Overall</td>
<td>**</td>
<td>80.0%</td>
<td>92.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>in VH</td>
<td>3,265</td>
<td>79.2%</td>
<td>91.2%</td>
<td>13.0%</td>
</tr>
<tr>
<td></td>
<td>in NVH</td>
<td>2,282</td>
<td>100%</td>
<td>94.2%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

*Cystoscopy findings suspicious for tumour (e.g. hematuric jet from ureteric orifice, bulge in the transmural ureter)

**Final numbers pending distribution from the IDENTIFY study group

### Conclusion
UTUC and RCC are rare in patients presenting with hematuria, especially in patients <60 years with NVH. USS misses 18.4% of RCC. Urine cytology significantly improves the diagnostic accuracy of USS in detecting UTUC, but together these still miss 21.3% of cases. Nonetheless, given the rarity of upper tract findings in patients with NVH (0.29%), USS and cytology should be considered in place of CTU in a risk stratified model.
PREDICTORS OF PERIOPERATIVE COMPLICATIONS IN PEDIATRIC RENAL TRANSPLANTATION: A LONG-TERM RETROSPECTIVE STUDY

Cyrus Chehroudi¹, Alexander Danechi¹, Andrew MacNeily¹, Kourosh Afshar¹
¹ Department of Urologic Sciences, University of British Columbia

Introduction and Objective:
Renal transplantation is the treatment of choice for pediatric end-stage renal disease (ESRD). However, the fragility of children, size discrepancy between adult kidneys and pediatric recipients, and greater prevalence of urinary tract anomalies make pediatric renal transplantation more prone to surgical complications. Small sample sizes also make it difficult to study pediatric renal transplantation and factors associated with perioperative morbidity. Here, we report our perioperative outcomes for pediatric renal transplant over 12 years.

Methods:
Retrospective chart review of renal transplants from 2007-2019 at BC Children’s Hospital. Perioperative outcomes were assessed within 8 weeks of transplantation, including delayed graft function (DGF) as well as vascular, urinary, or wound complications requiring intervention.

Results:
Ninety-two renal transplants were performed with median age 13 and 66% in male patients. Twenty-two patients had ESRD due to obstruction/reflux and 10 had previous transplants. Mean warm ischemia and surgical times were 29min (SD 9.4) and 210min (SD 59.8), respectively. DGF occurred in 4 cases and 10 patients developed surgical complications, most commonly allograft thrombosis (n=4) and urine leak (n=2). Seven patients required allograft nephrectomy. Patients with ESRD due to obstruction/reflux and transplants performed overnight were more likely to experience a complication (27% vs. 7%, p=0.02; 31% vs. 8%, p=0.022 respectively). Patients with prior transplants trended towards worse complication rates (30% vs. 10%, p=0.096). There was no association between complication rates and living vs. cadaveric donors (8% vs. 16%). Mean warm and cold ischemic times were similar for patients who experienced complications compared to those who did not (33 vs. 29min; 389 vs. 397min, respectively). There was also no difference in warm ischemic times for transplants performed overnight compared to daytime hours.

Conclusions:
Perioperative complications post-pediatric renal transplant are infrequent, but cause significant morbidity. We identify cause of ESRD and time of surgery as predictors for surgical complications. Strategies to mitigate surgeon fatigue may optimize outcomes in this patient population.
IDENTIFICATION OF A COMPREHENSIVE GENE SIGNATURE TO DETERMINE TREATMENT RESPONSE AND GUIDE PRECISION ONCOLOGY IN CLEAR-CELL RENAL CELL CARCINOMA

Ninadh M. D’Costa¹,², Davide Cina¹, Raunak Shrestha¹,², Robert H. Bell², Yen-Yi Lin², Hossein Asghari²,⁴, Cesar U. Monjaras-Avila¹,², Christian Kollmannsberger³, Faraz Hach²,⁴, Claudia I. Chavez-Munoz¹,², and Alan I. So¹,².

¹Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
²Vancouver Prostate Centre, Vancouver, BC, Canada
³BC Cancer Agency, Vancouver, BC, Canada
⁴School of Computing Science, Simon Fraser University, Burnaby, BC, Canada

Introduction and Objective:
Clear-cell renal cell carcinoma (ccRCC) tumors have aberrant angiogenic and immunosuppressive features. According to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, favorable-risk patients are treated with antiangiogenic (TKIs) and intermediate/poor-risk patients with immune therapies (ICI). However, resistance to TKI usually develops and only a small subset of patients respond to ICI. Therefore, we aimed to identify a gene signature to guide treatment decision-making and improve response in ccRCC patients.

Methods:
We have analyzed RNA-sequencing data of 469 ccRCC patients from The Cancer Genome Atlas (TCGA, Nature 2013). Using featured selection technique, we have analyzed the expression profiles of 20,483 genes and discovered 500 ranked genes. Ingenuity Pathway Analysis and unsupervised clustering methods were then used to determine a comprehensive 66-gene signature that can sub-classify ccRCC patients. Overall survival (OS) was analyzed for each sub-group of ccRCC patients.

Results:
Our empirical analysis of the expression patterns and unsupervised clustering method enabled the sub-classification of ccRCC patients into distinct groups: Angiogenic, Immunogenic and Mixed. The 66-gene signature can identify ccRCC patients who will potentially benefit from TKI treatment (Angiogenic) and ICI therapy (Immunogenic). We found that the Angiogenic patients have longer OS compared to Immunogenic group. This could be due to the use of TKI as the first-line of treatment before 2013. Moreover, we have identified a novel comprehensive expression profile to distinguish between migratory stromal and immune cells. Furthermore, the proposed 66-gene signature was validated using a different cohort of 64 ccRCC patients.

Conclusion:
Our proposed strategy will enable the design of a panel of genes to better identify patients of appropriate genotype and to improve treatment decision-making. These findings are foundational for the development of reliable biomarkers that may facilitate precision oncology and improve therapy response in ccRCC patients.
BIOMARKER POTENTIAL OF ACTIVATING AKT1 AND PIK3CA MUTATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Cameron Herberts1†, Andrew J Murtha1†, Simon Fu2, Gang Wang3, Elena Schönlaub1, Hui Xue4, Dong Lin1,4, Anna Gleave1, Steven Yip5, Arkhjamil Angeles2, Sebastien Hotte6, Ben Tran7, Scott North8, Sinja Taavitsainen9, Kevin Beja1, Gillian Vandekerkhove1, Elie Ritch1, Evan Warner1, Fred Saad10, Nayyer Iqbal11, Martin E Gleave1, Yuzhuo Wang1,4, Matti Annala1,9, Kim N Chi1,2*, and Alexander W Wyatt1†; †co-first; *co-corresponding

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Background:
Hotspot activating mutations in AKT1 and PIK3CA represent a potentially unique subset of metastatic prostate cancers (mPCa), and in other cancers are linked to PI3K signaling activation and sensitivity to pathway inhibitors. However, the accompanying genomic and clinical features of these mPCa patients is currently unknown. Elucidating the genomic properties of AKT1/PIK3CA mutant patients and their response to androgen-receptor (AR)-targeted therapy will be critical for therapeutic selection.

Methods:
We performed targeted sequencing on 1554 cell-free DNA samples from 847 mPCa patients (599 harbouring detectable ctDNA). Analysis was restricted to patients with hotspot AKT1/PIK3CA mutations of presumed clonal origin. Patient records were reviewed for baseline clinical characteristics, as well as time to castration-resistance and overall survival (OS).

Results:
6.0% (36/599) of patients harboured at least 1 clonal hotspot mutation in either AKT1 or PIK3CA, of which p.E17K and p.E545K/Q/A were most common. This population had a significantly higher ctDNA fraction compared to a control cohort of AKT1/PIK3CA wild-type mPCa patients (Mann-Whitney U test, 0.48 vs 0.21, p < 0.001).

Although AR mutations and copy number amplifications were observed at similar frequencies, patients harbouring AKT1 or PIK3CA mutations had fewer additional copies of AR (median 4.71 vs. 10.33, p=0.011, Mann-Whitney U Test). 31 patients with activating AKT1/PIK3CA mutations had clinical outcomes available. Interestingly, there were no significant differences in time to castration resistance or OS compared to ctDNA-positive patients without activating PI3K defects. A heavily-pretreated mCRPC patient with an AKT1 mutation experienced a 50% PSA decline to Akt inhibitor (ipatasertib) monotherapy. Ipatasertib also had a marked anti-tumour effect in a patient-derived xenograft harbouring an AKT1 mutation.

Conclusions:
AKT1/PIK3CA activating mutations are relatively common and delineate a distinct mPCa molecular subtype with low-level AR copy gain. CtDNA screening enables prospective clinical trials to test PI3K pathway inhibitors in this population.
Background
Recent studies show that novel alternative splicing (AS) events are essential to understanding the development of cancer and may play a role as an independent onco-driver. Moreover, cancer-specific AS is potentially an effective target of personalized cancer therapeutics. However, detecting novel AS events remains a challenging task: existing reference transcriptome annotation databases are far from universal comprehensiveness, especially for tumor-specific AS, and traditional sequencing technologies are severely limited by their short-read lengths that rarely span more than a single splice junction. Given these challenges, transcriptomic long-read sequencing (LRS), from both Oxford Nanopore Technologies and Pacific Biosciences, presents a promising potential for novel AS discovery given their noisy yet orders-of-magnitude longer reads.

Methods
We present Freddie, an annotation-free isoform discovery and detection computational tool. Freddie uses transcriptomic LRS reads as input and generates isoform clusters of these reads for a specified gene of interest. Freddie starts by mapping the reads to the reference genome using a splice-aware mapper and extracting the reads aligning to the gene interval. Freddie then segments the gene interval using the read alignments into canonical exon segments. Finally, Freddie clusters the reads into isoform clusters that satisfy a set of expected transcriptomic LRS constraints. We formulate this clustering as an optimization problem that we name Minimum Error Clustering into Isoforms (MErCi) problem and solve it by modelling it as an Integer Linear Program.

Results
We evaluate the performance of Freddie on both simulated and real datasets and show that both its segmentation and clustering steps are highly accurate and computationally efficient. We also run Freddie on a transcriptomic LRS dataset that we generated from a prostate cancer cell line, 22Rv1, and observe a potentially novel Androgen Receptor splicing event. This event exhibits a potentially novel intron retention and will require further validation using orthogonal laboratory methods.
Genome-wide CRISPR screen reveals SLFN11 as a potent mediator of cisplatin-sensitivity in Muscle-Invasive Bladder Cancer

Gunjan Kumar1,2, Elie Ritch1, Davide Tortora1, Igor Moskalev1, Htoo Zarni Oo1, Daksh Thaper1 Alexander Wyatt1, Peter Black1*, and Mads Daugaard1*

1Department of Urologic Sciences, University of British Columbia, Vancouver, BC
2Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC

*Authors contributed equally

Cisplatin-based Neoadjuvant chemotherapy (NAC) followed by radical cystectomy in patients with muscle-invasive bladder cancer (MIBC) improves the five-year survival rate of patients. While currently used as first-line treatment of MIBC, 60% of patients are inherently resistant to NAC at the time of cystectomy. Several mechanisms of cellular resistance to cisplatin have been proposed, however, the mechanisms and related biomarkers presented thus far still do not offer an effective patient response prediction in the context of MIBC. We performed a genome-wide CRISPR knock-out screen to identify novel components involved in MIBC cisplatin resistance. We found that SLFN11, a member of the Schlafen family of proteins, is required for sensitivity to cisplatin in MIBC cells. Loss of SLFN11, renders MIBC cells resistant to cisplatin in vitro and in vivo. Mechanistically, SLFN11 is required for proper activation of G1/S phase cell cycle checkpoint that would normally redirect cisplatin-treated cells towards apoptosis. Consequently, when SLFN11 activity is lost, MIBC cells are allowed to progress through the cell cycle and avoid apoptosis. Overall, we have identified SLFN11 as an essential component in the MIBC cisplatin response-pathway. As such, targeting SLFN11 associated pathways could be an attractive strategy for breaking resistance to cisplatin.
Functional mapping of androgen receptor enhancers

Shreyas Lingadahalli1, Flora Huang1, Tunc Morova1, Dogancan Ozturan2, Ivan Yu1, Eugene Hu3, Colin Collins1, Eldon Emberly3, Wilbert Zwart4, Nathan A. Lack1,2

1Vancouver Prostate Centre, Vancouver, Canada
2Koc University, Turkey, Turkey
3Department of Physics, Simon Fraser University, Canada
4Netherlands Cancer Institute, Amsterdam, Netherlands

Androgen receptor (AR) mediated transcription is the primary driver of prostate cancer (PCa) growth and progression. AR activates the expression of critical PCa genes by binding to distal regulatory elements and enhancing transcription. Yet there are vastly more AR binding sites (ARBS) (tens of thousands) than AR regulated genes (hundreds). It remains unknown if multiple ARBS enhancers interact in an additive, synergistic or dominant mechanism to induce gene transcription.

To characterize AR activity in PCa, we functionally tested all high-confidence clinical ARBS (n=4139) with a massively multi-parallel enhancer assay. Surprisingly we found that only 7% of ARBS showed androgen-dependent enhancer activity (induced), while the vast majority of binding sites were inactive (82%). Further, many ARBS (11%) were constitutively active enhancers that were not influenced by androgen treatment. These in vitro classifications were remarkably preserved in clinical PCa tissue. In tumour samples, only AR-induced enhancers showed decreased H3K27ac when treated with enzalutamide. Next, we computationally and experimentally demonstrated that inducible enhancers act as ‘hubs’ for long-range chromatin interactions and are critical for AR-mediated gene transcription. To understand the characteristics of these different ARBS we developed a deep neural network that identified critical features for each enhancer class. Finally, combining these results with clinical whole genome sequencing data, we identified and validated several non-coding SNVs that significantly alter enhancer activity. Of particular interest we found a somatic mutation that reduces the expression of \( ZBTB16 \), a well-known tumour suppressor of PCa that is frequently mutated in castrate resistant PCa. In conclusion, by functionally testing all ARBS we provide the first comprehensive ‘map’ of AR enhancer activity. This novel resource suggest that a small subset of ARBS in a dominant mechanism drive the androgen-mediated transcription and PCa development.
Discovery and Characterization of a Novel Catalytic Topoisomerase II Inhibitor for Anticancer Therapeutics

Victor M.M. Barrios\textsuperscript{1, 2}, Mariia Radaeva\textsuperscript{1, 2}, Yi Song\textsuperscript{1, 2}, Zaccary Alperstein\textsuperscript{1, 2}, Ahn R. Lee\textsuperscript{1}, Veronika Schmitt\textsuperscript{1}, Mary Bowden\textsuperscript{1}, Joseph Lee\textsuperscript{1}, Fuqiang Ben\textsuperscript{1}, Ning Xie\textsuperscript{1}, Nada Nallous\textsuperscript{1}, Martin E. Gleave\textsuperscript{1}, Artem Cherkasov\textsuperscript{1,3}, Xuesen Dong\textsuperscript{1,3}

1. The Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, 2660 Oak Street, Vancouver, British Columbia, Canada V6H 3Z6
2. Authors who equally contribute to this work
3. Corresponding authors

ABSTRACT
DNA topoisomerase II (TOP2) is a well-validated drug target for anticancer therapies. Clinically successful TOP2 poison inhibitors induce DNA damages to cause cell cycling arrest and subsequently cell death. Unfortunately, this mode of action is associated with severe adverse effects to patients. In contrast, TOP2 catalytic inhibitors induce limited DNA damages, have low cytotoxicity, and thus have been sought after to be applied independently or in combination with TOP2 poisons to control tumor growth. Herein the discovery and characterization of novel TOP2 catalytic inhibitors are described. A novel drug-able pocket at the interface between TOP2 protein and its DNA substrate was identified and validated by in silico experiments. It was used as a docking site to virtually screen \textasciitilde6 million molecules from the ZINC15 virtual library. This led to the discovery of the lead compound T60 and its derivatives as catalytic TOP2 inhibitors. T60 binds TOP2 protein and interrupts TOP2 from interacting with DNA. T60 shows limited cytotoxicity, but strongly inhibits cell cycling, cell proliferation, and xenograft growth. T60 is synergistic to etoposide, camptothecin, and paclitaxel in suppressing cancer cell growth. Since the transcriptional activity of the androgen receptor (AR) requires TOP2, T60 inhibits AR activity and suppresses cell proliferation of AR-positive prostate cancer cells including enzalutamide-resistant prostate cancer cells. In summary, T60 is a promising candidate compound that warrants further development into anticancer drugs in clinics.
Organizing Committee

- Dr. Amina Zoubeidi
- Dr. Ben H. Chew
- Dr. Kourosh 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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