Building a Canadian Translational Bladder Cancer Research Network

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Introduction

Bladder cancer is poised to join the precision oncology pantheon, presenting a broad array of exciting research avenues to improve current therapeutic management and patient quality of life. Emerging systemic and intravesical therapies include immune checkpoint inhibition,[1] gene therapies,[2] fibroblast growth factor receptor (FGFR)-targeted therapies,[3] and novel antibody drug conjugates.[4] As routine molecular profiling for these and other therapies becomes standard-of-care for bladder cancer, Canadian researchers have the opportunity to be world leaders in precision oncology, turning molecular insight into advanced therapeutic outcomes. Success in this complex undertaking will require coordination and cooperation across disciplines, institutions, and provinces.

With a goal of fostering collaborative translational research across Canada, the inaugural translational forum was held virtually on April 4, 2020. Organized in partnership with Bladder Cancer Canada (BCC) and the Canadian Urological Association (CUA), the meeting brought together clinicians, basic scientists, trainees, and patient advocates. Participants discussed ongoing research, identified key knowledge gaps, and formalized coalescing research themes that build on Canadian strengths and foster multicenter collaboration. Participants prioritized and built teams around four novel and interconnected themes: 1) novel biomarkers, 2) immune-oncology, 3) epigenetics, and 4) microbiome. These collective efforts have been formalized in the newly minted Canadian Bladder Cancer Research Network (CBCRN). Herein, we present meeting highlights.

Setting the stage

David Berman (Queen's University) introduced the forum by highlighting the benefits of collaborative translational team initiatives and describing the steps from the initial conceptualization of this forum to its realization.

Peter Black (University of British Columbia) presented opportunities to join forces and leverage Canadian strengths in bladder cancer translational research. He noted Canadian research capabilities, including advanced in vivo modelling,[5] genomics infrastructure,[6,7] liquid biopsy programs,[8] expertise in tumor immunology,[9-14] and epigenetics,[15] and established biospecimen repositories,[16] as well as a strong track record of linking these translational resources with investigator-initiated trials.[17,18] The growth in bladder cancer research in Canada is clearly evident from pioneering new research findings and a growing cohort of Canadian researchers with a natural inclination to collaborate. A major hurdle to further growth is the lack of funding for bladder cancer research. High-quality, collaborative research can overcome this hurdle by attracting a broader group of funders into the field. Funding agencies are aware that bladder cancer has been historically underfunded, but the responsibility rests with the bladder cancer research community to develop integrated, multicenter teams that can develop compelling and competitive research proposals. Bringing researchers with common interests together into working groups is the most direct path to achieve these goals.

As highlighted by Wassim Kassouf (McGill University), the tremendous depth and breadth of clinical trials in bladder across Canada (Table 1) represent a resource of biospecimens with clinical annotation for translational research. The present focus of clinical trials is dominated by the investigation of immune checkpoint inhibitors (ICIs) across different stages of disease and in combination with other therapies.

In the non-muscle-invasive bladder cancer (NMIBC) setting, trials in Canada and abroad primarily evaluate ICI as a monotherapy in bacillus Calmette-Guérin (BCG)-unresponsive

disease or in combination with BCG earlier in the NMIBC disease course. For muscle-invasive bladder cancer (MIBC), the focus is largely on the combination of ICIs with cisplatin-based chemotherapy or other targeted therapies, either in the neoadjuvant or adjuvant setting, or with chemoradiation. More recently developed treatments, such as targeted therapies against IDO1 (DPX-SurMAGE) or Nectin-4 (Enfortunib Vedotin) and IL-2 pathway agonists (NKTR-214), are under investigation in early-phase trials. Although most trials launch with very limited correlative science programs funded by slim budgets, researchers can leverage existing trial infrastructure in new research initiatives.

In response to a nationwide call for collaborative research ideas from across Canada, six research pitches were presented at the forum. Each pitch included research objectives, contributions that the presenter's group will bring to the project (e.g., biospecimens, technologies, expertise), and the gaps to be filled by other research groups to make the project successful.

Biomarkers working group

Bernie Eigl (BC Cancer) and Paul Toren (Université Laval) presented an overview of ongoing research on circulating tumour (ct)DNA and extracellular vesicles (EV), respectively. Dr. Eigl proposed to grow a research network to establish the clinical value of ctDNA in selecting patients for molecularly targeted therapy. A non-invasive testing modality, ctDNA can be drawn in real-time and may, therefore, better reflect the current tumor mutational landscape than an archived tissue sample. As a first priority, Dr. Eigl aims to compare FGFR alteration status measured from ctDNA to routine tissue testing in patients being considered for FGFR-targeted therapy. Prior work by the same group demonstrated compelling proof of principle for the utility of ctDNA analysis in this clinical context.[8] He stressed that this effort requires a national collaboration to enroll an adequate sample size, and suggested the already established multicenter biobanking at the six sites of BC Cancer could be mirrored across Canada and invited interested investigators to join this growing network. This study will yield important specimens, techniques, and insights that Canadian researchers can apply to develop a variety of new precision diagnostics.

Expanding on the theme of circulating biomarkers, Dr. Toren described ongoing research at Laval and the Atlantic Canada Research Institute (Rodney Ouellette) using multiomic (i.e., protein, RNA, and DNA) profiling and artificial intelligence to discover new EV-derived circulating biomarker signatures of response to immunotherapy. This is an excellent example of broadening the bladder cancer research footprint in Canada through collaboration with established research groups that have not previously studied bladder cancer. The leveraging of collected samples from similar target patient populations across Canada permits more rapid and cost-efficient biomarker studies.

Epigenetics working group

Dr. Berman highlighted epigenetic-directed therapies as a new frontier in bladder cancer translational research. Among all common adult cancers, bladder cancer is one of the most enriched for mutations in genes encoding epigenetic regulators, including ARID1A and KDM6A.[18] Their high frequency suggests that such mutations impart important selective advantages, the nature of which remains unclear. They have been hypothesized to block cellular differentiation and apoptosis, to modulate epithelial differentiation, and to promote immune evasion.[19-25] Defining the functional significance of these mutations could reveal new avenues for treating bladder cancer, including synthetic lethal strategies. The group has access to large, well-annotated cohorts of tissue samples from bladder cancer patients, as well as expertise in genomics and bioinformatics. The group sought collaborators with expertise in epigenetic biology and therapeutics, tumor immunity, and experimental models for bladder cancer therapeutics (e.g., organoids).

Microbiome working group

Under the microbiome theme, Dirk Lange (University of British Columbia), Dr. Kassouf, Jose Mansure (McGill University), and Yves Fradet (Université Laval) highlighted the development of strategies that exploit the host microbiome as a modulator of response to therapy. The UBC group is focusing on the impact of the urine microbiome on response to BCG, while the McGill group is investigating the role of the gut microbiome in response to chemoradiation immunotherapy and the Laval group is focusing on improving response to intravesical and systemic immunotherapies by modulating the gut microbiome with prebiotics. The group proposed to comprehensively characterize microbiome signatures associated with treatment response and use the results to develop interventional strategies to improve host anti-tumor immunity.

Immuno-oncology working group

Building on four decades of intravesical BCG immunotherapy for NMIBC,[26] systemic ICI with PD(L)1 inhibitors has recently revolutionized management of locally advanced and metastatic urothelial carcinoma,[2] and has even been approved for BCG-unresponsive NMIBC.[27] Moreover, additional immune modulatory agents, such as stimulator of interferon genes (STING) agonists (e.g., NCT04109092) and oncolytic viruses[28] (e.g. NCT04387461), are currently being evaluated in patients with NMIBC or MIBC.

Table 1. Bladder cancer trials in Canada*

Trial	NCT	Setting	Disease state	Experimental intervention
A Randomized Control Trial of a Modified Cystoscopy Method to Reduce Pain Perception [Power]	03257293	Hematuria	First detection	Conventional cystoscopy vs. non-pharmacological modifications in procedure
A Clinical, Non-intervention Study of the Cxbladder Urine Test for the Detection of Recurrent Urinary Tract Urothelial Carcinoma	03673202	NMIBC	Detection of recurrence	Performance (sensitivity/ specificity) of CxBladder compared to cystoscopy/ cytology
The Efficacy of the Bladder EpiCheck for Detection of Recurrent Urothelial Cell Carcinoma: A Multicenter, Prospective Blinded Pivotal Study	02700464	NMIBC	Detection of recurrence	Performance (sensitivity/ specificity) of EpiCheck compared to cystoscopy/ cytology
A Pilot, Single-center, Randomized, 5-year, Parallel-group, Superiority Trial to Compare Re-resection of High-grade T1 Bladder Urothelial Carcinoma to no Re-resection for Improving Progression-Free Survival (RESECT) [Kulkarni]	03266900	NMIBC	High-grade T1	Randomization to re-resection vs. no re-resection before intravesical BCG therapy
A Phase 3, Randomized, Open-Label, Multicenter, Global Study of Durvalumab and Bacillus Calmette-Guérin Administered as Combination Therapy vs. BCG Alone in High-Risk, BCG-Naive Non-muscle-invasive Bladder Cancer Patients (Potomac)	03528694	NMIBC	BCG-naive, high-risk	1. BCG induction/ maintenance 2. BCG induction/ maintenance + durvalumab 3. BCG induction only + durvalumab
A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab in Combination with Bacillus Calmette-Guérin in Participants with High-risk Non-muscle-invasive Bladder Cancer That is Persistent or Recurrent Following BCG Induction (Keynote-676)	03711032	NMIBC	BCG-naive, High-risk	BCG ± pembrolizumab
A Phase 3, Randomized, Double-blind Trial of Nivolumab in Combination with Intravesical BCG vs. Standard of Care BCG Alone in Participants with High-risk Non-muscle-invasive Bladder Cancer that is Persistent or Recurrent After Treatment with BCG (CheckMate 7G8)	04149574	NMIBC	BCG-exposed	BCG ± nivolumab
Phase 2 Trial of Atezolizumab in BCG-unresponsive Non-muscle-invasive Bladder Cancer (S1605/BLC4) [Black]	02844816	NMIBC	BCG-unresponsive	Single arm: atezolizumab
A Phase 2 Clinical Trial to Study the Efficacy and Safety of Pembrolizumab in Subjects with High -risk Non-muscle-invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin Therapy (Keynote-057)	02625961	NMIBC	BCG-unresponsive	Single arm: pembrolizumab
Phase 1/2 Trial of Local Cystoscopic Injection of Tremelimumab plus Systemic Durvalumab for High-risk Non-muscle-invasive Bladder Cancer (Rideau) [Black]	pending	NMIBC	BCG-unresponsive	Single arm: intramural tremelimumab + systemic durvalumab
A Phase 2 Clinical Study of Intravesical Photodynamic Therapy in Patients With BCG-Unresponsive Non-muscle-invasive Bladder Cancer or Patients Who Are Intolerant to BCG Therapy [Kulkarni]	03945162	NMIBC	BCG-unresponsive	Single arm: intravesical photodynamic treatment with TLD1433 (photosensitizer)
Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Oportuzumab Monatox in Subjects with Non-muscle-invasive Carcinoma in Situ and/or High-Grade Papillary Disease of the Bladder Treated With BCG (Vista)	02449239	NMIBC	BCG unresponsive	Single arm: oportuzumab monatox (anti-EpCAM antibody drug conjugate)
A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants With BCG-Unresponsive, High-risk, Non-muscle-invasive Bladder Cancer (CheckMate 9UT)	03519256	NMIBC	BCG unresponsive	1. Nivolumab 2. Nivolumab + BCG 3. Nivolumab + BMS-986205 4. Nivolumab + BCG + BMS-986205 (IDO-1 inhibitor)
Impact of Positron Emission Tomography (PET) Imaging in Muscle-invasive Urothelial Carcinoma of the Bladder Staging (PET MUSE) [Sridhar]	02462239	MIBC	Radiation/ radical cystectomy	PET CT vs. CT for pre-treatment staging

*Trials identified in ClinicalTrials.gov with condition/disease term "bladder cancer" and country "Canada" (recruiting; not yet recruiting; active; not recruiting; enrolling by invitation) accessed July 24, 2020. Eight phase 1 trials for multiple solid tumors were excluded. [Canadian trial chairs] are listed when applicable. BCG: bacille Calmette-Guérin; CT: computed tomography; NMIBC: non-muscle-invasive bladder cancer; PARP: poly (ADP-ribose) polymerase; PET: positron emission tomography; pre/post: neoadjuvant and adjuvant; VEGF2: vascular endothelial growth factor-2

Table 1 (cont'd). Bladder cancer trials in Canada*

Trial	NCT	Setting	Disease state	Experimental intervention
A Phase 3 Surgical Trial to Evaluate the Benefit of a Standard vs. an Extended Pelvic Lymphadenectomy Performed at Time of Radical Cystectomy for Muscle-invasive Urothelial Cancer (S1011)	01224665	MIBC	Radical cystectomy	Standard vs extended pelvic lymph node dissection
Tranexamic Acid During Cystectomy Trial (TACT) [Breau]	01869413	MIBC	Radical cystectomy	± Intraoperative tranexamic acid for hemostasis
Measuring the Analgesic Effect of Adding Preoperative Single-Shot Rectus Sheath Blocks to Postoperative Rectus Sheath Continuous Blocks for Major Urologic Surgery: A Randomized Controlled Trial [Dillane]	03458598	NMIBC/ MIBC	Radical cystectomy	Epidural vs. rectus sheath catheter for perioperative analgesia
A Phase 3, Randomized, Study of Neoadjuvant Chemotherapy Alone vs. Neoadjuvant Chemotherapy Plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Post-Surgery Therapy with Nivolumab or Nivolumab and BMS-986205 in Participants with Muscle-invasive Bladder Cancer (Energize)	03661320	MIBC	Neoadjuvant/ adjuvant, cisplatin-eligible, radical cystectomy	1. Neoadjuvant chemotherapy 2. Neoadjuvant chemotherapy + nivolumab (pre/post) 3. Neoadjuvant chemotherapy + nivolumab (pre/post) + BMS-986205 (pre/post)
A Phase 3, Randomized, Open-Label, Multicenter, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine + Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-invasive Bladder Cancer (Niagara)	03732677	MIBC	Neoadjuvant/ adjuvant, cisplatin-eligible, radical cystectomy	Neoadjuvant chemotherapy ± durvalumab (pre/post)
A Phase 3, Randomized, Double-blind Study to Evaluate Perioperative Pembrolizumab + Neoadjuvant Chemotherapy vs. Perioperative Placebo + Neoadjuvant Chemotherapy in Cisplatin-eligible Participants with Muscle-invasive Bladder Cancer (Keynote-866)	03924856	MIBC	Neoadjuvant/ adjuvant, cisplatin-eligible, radical cystectomy	Neoadjuvant chemotherapy ± pembrolizumab (pre/post)
Dual Target T cell therapy in Muscle-invasive Bladder Cancer [Fradet]	pending	MIBC	Neoadjuvant/ adjuvant, cisplatin-ineligible, radical cystectomy	DPX-SurMAGE + pembrolizumab + low dose cyclophosphamide
A Randomized, Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab vs. Cystectomy Alone in Cisplatin-Ineligible Participants with Muscle-invasive Bladder Cancer (KEYNOTE-905/EV-303)	03924895	MIBC	Neoadjuvant/ adjuvant, cisplatin-ineligible, radical cystectomy	Neoadjuvant/adjuvant pembrolizumab ± neoadjuvant/adjuvant enfortumab
A Phase 3, Randomized Study of Neoadjuvant and Adjuvant Nivolumab Plus NKTR-214 vs. Nivolumab Alone vs. Standard of Care in Participants with Muscle-invasive Bladder Cancer Who Are Cisplatin-ineligible	04209114	MIBC	Neoadjuvant/ adjuvant, cisplatin-ineligible, radical cystectomy	Neoadjuvant/adjuvant nivolumab ± neoadjuvant/ adjuvant NKTR-214 (IL-2 agonist)
Exercise-based Pre-habilitation in Bladder Cancer Patients Prior to Radical Cystectomy: A Feasibility Study [Mason]	04223063	MIBC	Neoadjuvant/ radical cystectomy	12-week exercise program in patients receiving neoadjuvant chemotherapy
A Phase 1/2 Trial of a Combination of Paclitaxel and Trastuzumab With Daily Irradiation or Paclitaxel Alone with Daily Irradiation Following Transurethral Surgery for Non-cystectomy Candidates with Muscle-invasive Bladder Cancer	00238420	MIBC	Concurrent with radiation	Paclitaxel ± trastuzumab (non-randomized phase 1/2)
A Phase 2 Trial of Transurethral Surgery Followed by a Combination of Atezolizumab an Anti-PDL-1 with Trimodal Therapy in Patients with Muscle-invasive Bladder Cancer [Kassouf]	03620435	MIBC	Concurrent with radiation	Trimodal therapy + atezolizumab
A Randomized Phase 2 Trial Assessing Trimodality Therapy with or without Adjuvant Durvalumab to Treat Patients with Muscle-invasive Bladder Cancer (BL13) [Kassouf]	03768570	MIBC	Adjuvant, radiation	Trimodal therapy ± durvalumab

*Trials identified in ClinicalTrials.gov with condition/disease term "bladder cancer" and country "Canada" (recruiting; not yet recruiting; active; not recruiting; enrolling by invitation) accessed July 24, 2020. Eight phase 1 trials for multiple solid tumors were excluded. [Canadian trial chairs] are listed when applicable. BCG: bacille Calmette-Guérin; CT: computed tomography; NMIBC: non-muscle-invasive bladder cancer; PARP: poly (ADP-ribose) polymerase; PET: positron emission tomography; pre/post: neoadjuvant and adjuvant; VEGF2: vascular endothelial growth factor-2

Table 1 (cont'd). Bladder cancer trials in Canada*

Trial	NCT	Setting	Disease state	Experimental intervention
A Study of Adaptive Radiation Therapy for Pelvic Genitourinary Cancer (ARTGU) [Chung]	03909893	MIBC	Radiation	Single arm: modification of radiation treatment plan during treatment using pelvic imaging
A Phase 2 Randomized Study for Patients with Muscle-invasive Bladder Cancer Evaluating Transurethral Surgery and Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil and Cisplatin or QD Irradiation Plus Gemcitabine Followed by Selective Bladder Preservation and Gemcitabine/Cisplatin Adjuvant Chemotherapy	00777491	MIBC	Radiation	Radiation once vs. twice daily
A Multicenter Randomized Double-blind Study Examining the Efficacy and Safety of Denosumab in Combination with First-line Platinum-based Chemotherapy for Patients With Bone Metastasis Secondary to Metastatic Urothelial Cancer [Sridhar]	03520231	Metastatic & locally advanced	Treatment-naive	Platinum chemotherapy ± denosumab
A Phase 3, Randomized, Open-Label, Controlled, Multicenter, Global Study of First-line Durvalumab in Combination with Standard of Care Chemotherapy and Durvalumab in Combination with Tremelimumab and Standard of Care Chemotherapy vs. Standard of Care Chemotherapy Alone in Patients with Unresectable Locally Advanced or Metastatic Urothelial Cancer (Nile)	03682068	Metastatic & locally advanced	Treatment-naïve	1. Platinum chemotherapy 2. Platinum chemotherapy + durvalumab 3. Platinum chemotherapy + durvalumab + tremelimumab
A Phase 3, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti–PD-L1 Antibody) as Monotherapy and in Combination with Platinum-based Chemotherapy in Patients with Untreated Locally Advanced or Metastatic Urothelial Carcinoma (IMvigor 130)	02807636	Metastatic & locally advanced	Treatment-naive	1. Platinum chemotherapy 2. Atezolizumab 3. Platinum chemotherapy + atezolizumab
A Phase 2, Single-arm Study of Bempegaldesleukin (NKTR-214) in Combination with Nivolumab in Cisplatin-ineligible, Locally Advanced, or Metastatic Urothelial Cancer Patients	03785925	Metastatic & locally advanced	Treatment-naive, cisplatin-ineligible	Single arm: nivolumab + NKTR-214 (IL-2 agonist)
A Phase 2, Randomized, Multicenter, Double-blind, Comparative Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Olaparib for First-line Treatment in Platinum-ineligible Patients with Unresectable Stage IV Urothelial Cancer (Bayou)	03459846	Metastatic & locally advanced	Treatment-naive, platinum-ineligible	Durvalumab ± olaparib (PARP inhibitor)
A Phase 3, Multicenter, Multinational, Randomized, Open-label, Parallel-arm Study of Avelumab Plus Best Supportive Care vs. Best Supportive Care Alone as a Maintenance Treatment in Patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress after Completion of First-line Platinum-Containing Chemotherapy	02603432	Metastatic & locally advanced	Post-platinum switch maintenance	Avelumab vs. best supportive care
A Phase 2, Multicenter, Single-Arm Study of Atezolizumab in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer (IMvigor 210)	02951767/ 02108652	Metastatic & locally advanced	Cisplatin-ineligible or platinum refractory	Single arm: atezolizumab
An Open-Label, Randomized, Multidrug, Biomarker-Directed, Multicentre, Multi-arm, Phase 1b Study in Patients with Muscle-invasive Bladder Cancer Who Have Progressed on Prior Treatment (Biscay)	02546661	Metastatic & locally advanced	Platinum refractory	Multidrug, multi-arm, biomarker-directed,
A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Ramucirumab Plus Docetaxel vs. Placebo Plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-based Therapy (Range)	02426125	Metastatic & locally advanced	Platinum refractory	Docetaxel ± ramucirumab (VEGF2 receptor antagonist)
An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs. Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)	03474107	Metastatic & locally advanced	Platinum refractory, post-immunotherapy	Enfortumab vs. 2nd-line chemotherapy

*Trials identified in ClinicalTrials.gov with condition/disease term "bladder cancer" and country "Canada" (recruiting; not yet recruiting; active; not recruiting; enrolling by invitation) accessed July 24, 2020. Eight phase 1 trials for multiple solid tumors were excluded. [Canadian trial chairs] are listed when applicable. BCG: bacille Calmette-Guérin; CT: computed tomography; NMIBC: non-muscle-invasive bladder cancer; PARP: poly (ADP-ribose) polymerase; PET: positron emission tomography; pre/post: neoadjuvant and adjuvant; VEGF2: vascular endothelial growth factor-2

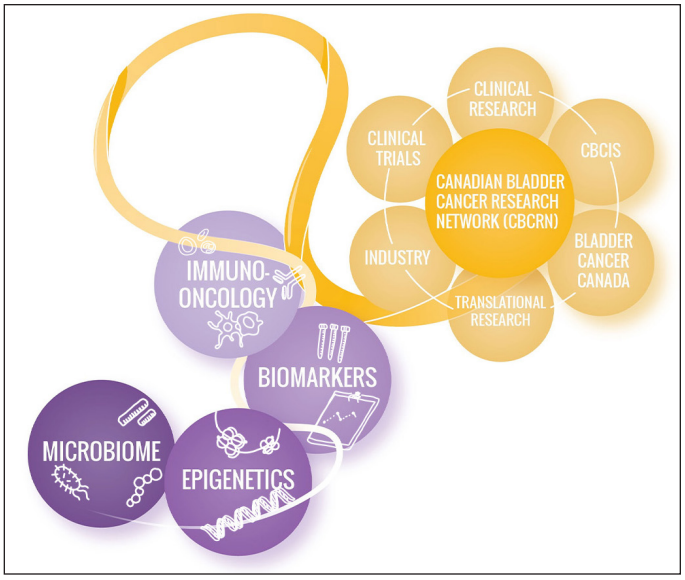

Fig. 1. Canadian Bladder Cancer Research Network (CBCRN). Diagram highlights the four founding research themes established at the inaugural translational research forum (left), and integral role of the forum as part of the network (right).

Edwin Wang (University of Calgary) and Madhuri Koti (Queen's University) highlighted ongoing research in this field. Dr. Wang described a testing pipeline to identify genes that block immune cell infiltration into tumors, suggesting that inhibition of these genes could convert "cold" tumors to "hot" tumors that could be more responsive to immunotherapy. Dr. Koti proposed research to monitor and enhance anti-tumor innate immunity by activating the STING pathway through a variety of means, including pharmacological (Dr. Koti), radiation (Dr. Kassouf), oncolytic viruses (David Evans, University of Alberta), and inhibitors of kinases involved in DNA damage repair (Dr. Koti).[9] Overall, the immuno-oncology group aims to develop immune sensitization approaches to monitor and improve response to conventional and novel immune-based therapies. This work will also integrate the importance of poorly understood host factors, such as sex and age.

Canadian Bladder Cancer Research Network

Participants endorsed the four major research themes as the main areas of focus for collaboration, each with a working group tasked with formulating more specific research objectives (Table 2). While initially, the working groups are likely to work in parallel on established projects, the longer-term goal is to build inter- and intra-group collaborative projects, along with team grant applications. With this manuscript, we are extending an open invitation to researchers in Canada and elsewhere to collaborate within the context of the four working groups.

This translational research forum begins to formalize the CBCRN (Fig. 1), which will serve as a platform for team science across multiple Canadian research institutions. Research will be promoted along two balanced arms, one translational and one clinical. Other established projects, such as the National Bladder Cancer Quality of Care Initiative[29-32] and the Canadian Bladder Cancer Information System (CBCis) will be complementary to the CBCRN. In addition, the CBCRN will work alongside Canadian clinical trials groups (eg., Canadian Urologic Oncology Group [CUOG], Canadian Clinical Trials Group [CCTG]) and industry, particularly in the areas of correlative studies and research advocacy. Finally, the CBCRN will support BCC in developing patient-centerd research priorities and raising funds for bladder cancer research.

United in an effort to improve outcomes for Canadians with bladder cancer, the CBCRN aims to advance translational and clinical science by uniting research stakeholders from across the country.

Table 2. Translational research working groups

Working group	Lead	Initial focus	First steps
Biomarkers	Dr. Eigl Dr. Toren	– FGFR alterations in ctDNA – Multi-omic analysis of EVs (in blood from patients with unresectable/ metastatic urothelial carcinoma)	– Standardized blood collection and clinical annotation – Research ethics protocols for banking and sample sharing
Microbiome	Dr. Lange Dr. Fradet	– Urine and gut microbiome in patients receiving BCG – Gut microbiome in patients receiving radiation (± immune checkpoint blockade) – Functional studies with pre-biotics and fecal transplant	– SOPs for collection and processing of samples – SOPs for metagenomic analysis of patient samples – Uniform collection of patient nutritional survey data
Epigenetics	Dr. Berman	– Define functional significance of genomic alterations in key chromatin modifying genes (CMGs) in bladder cancer	– Assembly of multidisciplinary team. – In-depth investigation of potential CMG roles in silico
Immuno-Oncology	Dr. Koti	– Develop immune sensitization approaches through direct and indirect activation of STING pathway – Understand sexual dimorphism of tumor immunology in bladder cancer	– Assembly of researchers with expertise in the field of cancer immunology across institutions in Canada – Initiation of project on characterization of sex associated immune responses to bladder tumors

BCG: bacille Calmette-Guérin; CMG: chromatin-modifying gene; ctDNA: circulating tumor DNA; EV: extracellular vesicles; FGFR: fibroblast growth factor receptor; SOP: standard operating procedures.

This paper has been peer-reviewed

Competing interests: Dr. Berman has received honoraria and travel support from Bayer and Janssen. Dr. Siemens has participated in clinical trials supported by Astellas, Merck, and Pfizer. Dr. Lange has received grants/honoraria from AdvaTec, BD/Bard, Boston Scientific, and Cook. Dr. Toren has been an advisor for AbbVie, Astellas, and Janssen; has received honoraria from Tersera; has received research grants from BMS and Janssen; and has participated in clinical trials supported by Janssen, Merck, and Roche. Dr. Eigl has received honoraria and travel support from Astellas, AstraZeneca, Bayer, Janssen, Merck, and Roche. Dr. V. Fradet has received travel support from Ferring; and has received research grants from Astellas and Sanofi. Mr. Purves is Chair of the Board and receives a salary from Purves Redmond Limited Insurance Brokers. Dr. Y. Fradet has been an advisory board member for AstraZeneca, Merck, Sanofi, and Tersera; has received travel support from Sanofi and Tersera; and has received research grants from Astellas, IMV Inc., Janssen, Merck, and Tersera. Dr. Kassouf has received grants/honoraria from Amgen, Astellas, and Janssen. Dr. Black is an advisory board member for AbbVie, Asieris, AstraZeneca, Astellas, Bayer, Biosyent, BMS, EMD-Serono, Ferring, Fergene,H3-Biomedicine, Janssen, Merck, Roche, Sanofi, and Urogen; a speakers' bureau member for AbbVie, Biosyent, Janssen, Ferring, Tersera, and Pfizer; has received honoraria from Bayer, GSK, iProgen, and Sanofi; and has participated in a clinical trials supported by Astellas, AstraZeneca, BMS, Genentech, Janssen, MDx Health, Pacific Edge, Sitka, and Therelase; and shares a patent with Decipher Biosciences. The remaining authors report no competing personal or financial interests related to this work.

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