



NEW RESEARCH AND CLINICAL FRONTIERS
IN BLADDER AND KIDNEY CANCER



VANCOUVER
PROSTATE CENTRE
A UBC & VGH Centre of Excellence

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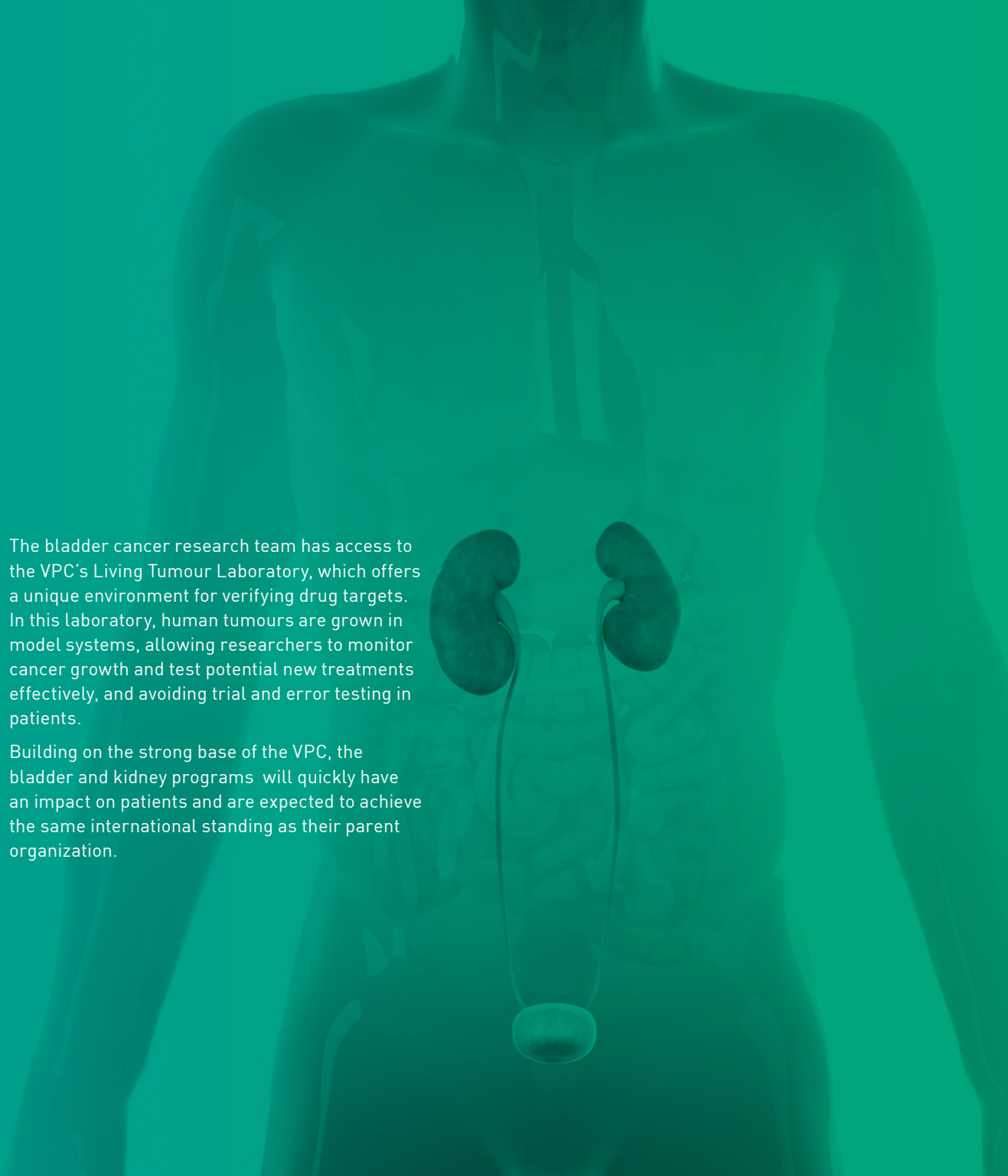
LEVERAGING EXISTING STRENGTHS

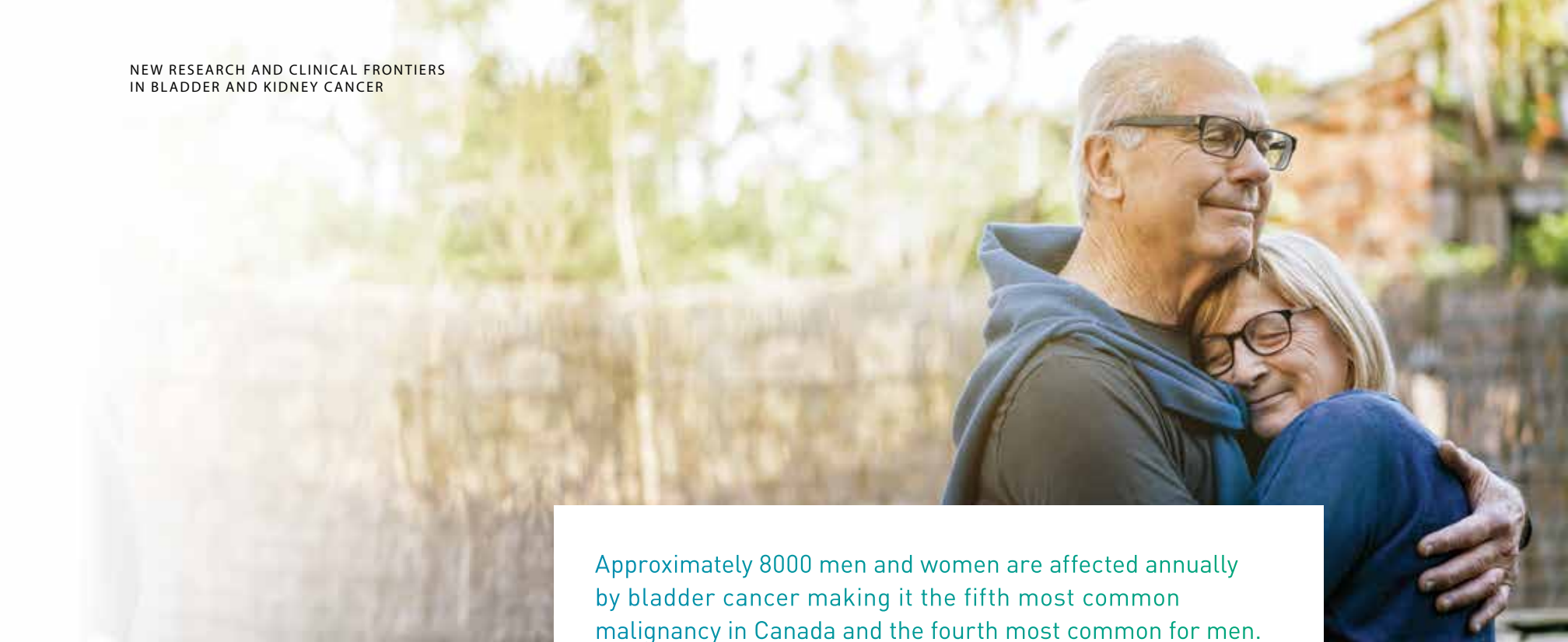
The exceptional quality of the research enterprise at the Vancouver Prostate Centre (VPC) is recognized around the world and the bladder and kidney cancer research teams' ability to move research forward quickly is supported by the infrastructure available at the VPC.

The Centre's unique team-based organization integrates many disciplines, all within close proximity to each other. The synergy created by close communication among the Centre's scientists and clinicians is foundational to the VPC's success in taking new cancer treatments from the very earliest discovery phase through to commercialization and patient benefit.

The bladder cancer research team has access to the VPC's Living Tumour Laboratory, which offers a unique environment for verifying drug targets. In this laboratory, human tumours are grown in model systems, allowing researchers to monitor cancer growth and test potential new treatments effectively, and avoiding trial and error testing in patients.

Building on the strong base of the VPC, the bladder and kidney programs will quickly have an impact on patients and are expected to achieve the same international standing as their parent organization.





Approximately 8000 men and women are affected annually by bladder cancer making it the fifth most common malignancy in Canada and the fourth most common for men.

However, therapy for bladder cancer has evolved only marginally in the past 30 years and much more laboratory and clinical research is needed to improve treatment. Frequent invasive monitoring makes it the most expensive cancer per patient lifetime and there is a 50% mortality rate if the cancer is muscle invasive. A majority of patients respond to chemotherapy, but the outcome only rarely lasts. Immunotherapy, which is a the new frontier across many cancers, holds promise in bladder cancer, but currently only 20% of patients benefit.

Today 60% of bladder cancer patients who undergo chemotherapy and suffer its negative side effects will not benefit from the treatment. In those who do respond well initially, the cancer usually becomes treatment-resistant and leaves few options for patients and their physicians.

As surgeon-scientists who see patients and families regularly and must often deliver unwelcome news, Drs. Peter Black and Alan So are dedicated to addressing the challenges of bladder cancer.

With the support of senior leadership at the VPC, they are quietly building the critical mass to emerge as the leading bladder cancer program in Canada.



At the Vancouver Prostate Centre (VPC) a strong team is focused on precision oncology in bladder cancer, with particular interest in understanding resistance to chemotherapy and immunotherapy. New therapies are being developed to overcome bladder cancer, improve cancer outcomes and promote regional growth of biotechnology.



AREAS OF RESEARCH

Precision Oncology & Immunotherapy

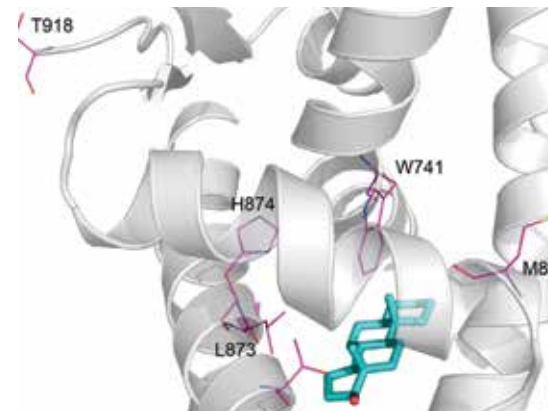
The bladder cancer team is building on their previous work to investigate molecular pathways of resistance to cisplatin-based chemotherapy in patients with muscle invasive bladder cancer (MIBC), and are working to develop a strategy for translating this information into patient-specific targeted therapy.

Chemotherapy is administered to patients with MIBC prior to radical cystectomy, or to patients with metastatic disease as primary therapy. While response rates are high, subsequent recurrences are common, and nearly all patients with recurrent or metastatic bladder cancer will succumb to their disease. Immunotherapy, which has been recently introduced into the clinic, is the only second-line therapy with proven benefit but only ~20% of patients respond. Targeted therapies, which involve drugs that affect specific molecular changes in an individual tumour, have yet to impact patients with MIBC, but that will

change with ongoing advances in evidence-based precision oncology. Often the molecular change is a single alteration in the genetic code of the cancer, and the validity of such targets is usually uncertain.

The critical advancement in this strategy is the integration of RNA, DNA and protein information from patient samples to identify presumed drug targets, and test the effectiveness of the selected drugs in models of bladder cancer derived directly from patient tumours. This type of integrative analysis has never been conducted in bladder cancer with a focus on a specific clinical question. With innovative computational tools to identify molecular signatures of chemoresistance, the team can test candidate drugs optimally for pre-clinical proof of principle of this precision oncology paradigm.

There is a current unmet clinical need for the development of novel treatments for muscle-invasive bladder cancer (MIBC). To this end, the recent emergence of immunotherapy for treatment of metastatic bladder cancer has provided a much-needed step forward, however only a minority of patients experience an objective response. The success in a subset of patients highlights the potential for immunotherapy to induce potent anti-cancer immune responses, but the lack of response in most patients is indicative of a need to better understand the underlying mechanisms of treatment resistance. The full clinical utility of immunotherapy for treatment of MIBC will therefore require a comprehensive understanding of the mechanisms of immune evasion and their relationship to specific aspects of tumour biology.



Another complementary stream of research focuses on non-muscle invasive bladder cancer (NMIBC), which is normally the initial diagnosis (~70%) of all new bladder cancer cases. With a recurrence rate of 50-80%, NMIBC is associated with enormous costs to the health care system and significant morbidity to patients. About 25% of patients with non-muscle invasive bladder cancer will progress to the lethal muscle invasive form. Current treatments are trial and error, thus valuable time is lost and cancer can become lethal. Ongoing work at Dr. So's lab includes the identification of novel gene therapies as novel approaches in bladder cancer chemotherapy.

Genetic Analysis

A method for real-time genetic analysis of tumours is urgently needed, especially one that can identify patients with tumours that have high mutation rates. Current approaches are based mostly upon tissue obtained at the time of bladder tumour biopsy (TURBT) or bladder removal (radical cystectomy), which may have reduced applicability in the setting of second and subsequent lines of systemic/targeted therapies.

Recent advances in DNA and RNA sequencing have made possible the study of tumour DNA that is circulating freely in the blood of patients with cancer (ctDNA). The team and others have shown that this "liquid biopsy" provides a non-invasive tool for sampling. The concept is particularly attractive for bladder cancer, given the high mutation rate and the known release of abundant ctDNA into the blood. The team is studying the presence of clinically informative genetic changes in ctDNA from patients with advanced bladder cancer, focusing on patients with very high mutation rates, as a first step towards developing a novel biomarker with clinical utility.

Computer Aided Drug Discovery (CADD)

A number of recent studies, including especially those from the team at the VPC, have identified an association between the activity of peroxisome proliferator activator receptor gamma (PPARγ), a particularly important gene in bladder cancer, and decreased expression of immune related genes in MIBC. The VPC team determined that PPARγ expression in MIBC shuts off any immune response to bladder cancer, which suggests that targeting this pathway could overcome resistance to current immunotherapies. The bladder cancer team at VPC is working with Dr. Art Cherkasov, an expert in computer-aided drug design at the VPC, to develop an inhibitor of PPARγ, which has otherwise remained elusive to other research groups.



Tissue Engineering

The development of 3D bladder cancer tissues offers a new platform for drug testing, discovery and personalized medicine. These 3D lab-grown tissues replicate the bladder cancer tumour growing in patients. The goal is to test these 3D lab grown tissues with several currently available drugs and identify the most efficacious one to combat that patient's particular cancer. Creating personalized 3D bladder cancer tissues for quick accurate personalized drug testing will revolutionize patient care and outcomes. This will help to answer the question about which drug is most efficacious for each individual patient.

Muscle-invasive bladder cancer patients are currently treated with radical cystectomy with neoadjuvant chemotherapy (cisplatin-centred chemotherapy) or a combination of radiation and cisplatin chemotherapy. The great clinical limitation is the inability of predicting which patients would benefit from neoadjuvant chemotherapy, and moreover, which tumours are inherently chemo-resistant. Furthermore, current research is showing great promise for novel targeted therapies as the future for locally advanced and metastatic bladder cancer treatment, increasing treatment options. Thus, current and future management of bladder cancer will centre on choosing the optimal treatment for each patient from a potentially vast array of options.

Clinical Trials

Activity in clinical trials for bladder cancer has increased dramatically in recent years, and the team at VPC has been actively involved in this area. OGX-427 (an antisense oligonucleotide) was developed at VPC and the first-in-man trial was conducted there. Another Phase I trial, STK-01, is a collaboration between UBC, the VPC and Sitka Biopharma. In addition the team at VPC actively participates in cooperative and industry trials in bladder and kidney cancer.

The VPC has created a large tissue bank of bladder and kidney cancer samples – a biorepository. These precious tissues are carefully categorized to aid in the discovery of novel findings.

KIDNEY CANCER

Closely tied with bladder and prostate cancer is kidney cancer. Dr. Alan So and his team are additionally focused on the study of renal cell carcinoma, in particular the clear cell type and more specifically in mechanisms involved in drug-resistance in metastatic clear cell renal cell carcinoma (mRCC). This groundbreaking work is primarily around the identification of novel therapies. They have recognized new pathways of resistance which has led to the identification of novel therapies to overcome this resistance. The team is currently extensively testing these new drugs before taking them into clinical trials.



Renal cell carcinoma (RCC) is the sixth most common malignancy in Canada with an annual increase of 4.1% in men and 2.3% in women. Patients with localized tumour may be “cured” with partial or radical nephrectomy but about 30% of the patients present with *de novo* mRCC. These metastatic cases are treated with tyrosine kinase inhibitors, which target the tumour’s vasculature depriving the cancer cells of oxygen and nutrients leading to cell death. However, 100% of patients who initially responded to the medication will develop resistance to the medication in 10 - 14 months, leading to progression of their mRCC. Therefore, there is a great need to understand the mechanisms of drug resistance and to develop novel therapies targeting the effectors of resistance to improve survival in mRCC patients.

OUR PEOPLE



Dr. Peter Black, the Khosrowshahi Chair in Bladder Cancer at Vancouver Hospital, is targeting Notch2, a key oncogene in bladder cancer. This year he developed a transgenic model of specific overexpression of Notch2 that caused bladder tumours to grow. He is also working on signaling pathways to discover how Notch1 (tumour suppressor) differs from Notch2 (oncogene). He is also working with **Dr. Artem Cherkasov**, an expert in computer aided drug design, to develop a specific Notch2 inhibitor.

He has initiated a research program in immunotherapy, which is becoming very important in bladder cancer. Molecular subtypes of bladder cancer correlate with response to chemotherapy and immunotherapy, and immune gene expression signatures make up a big component of the molecular subtypes. He and his team are dissecting out different immune cell populations by mass cytometry and flow cytometry in fresh patient tumours to determine what makes the different subtypes respond differently; this will reveal new targets that will facilitate rational combination therapies moving forward.

Dr. Alan So focuses on the development of novel therapeutics for bladder cancer and determination of the functional role of GLI1/2 in the progression of prostate cancer to its lethal stage of androgen independence. He has characterized the functional role of different survival genes (including clusterin and Hsp27) in different tumour models (prostate, breast, lung, and bladder) in cancer progression. His current research focuses on discovery and development of novel agents to treat bladder cancer as well as development of the mechanisms of treatment resistance in renal cell carcinoma.



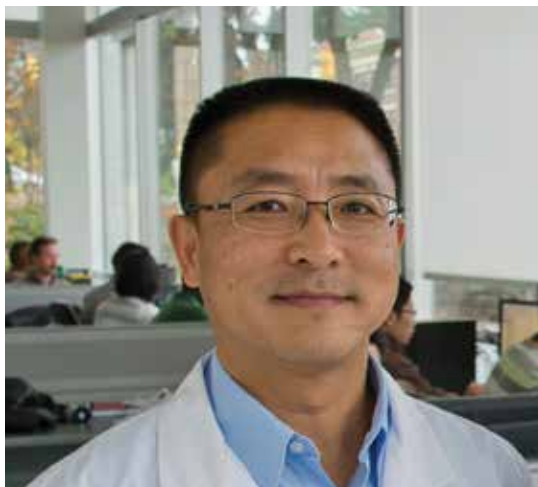
Dr. Martin Gleave supports a research program in bladder cancer primarily through drug development around the compound apatosen which has had positive results in Phase II clinical trials. He is also developing a polymer paste formulation of existing chemotherapy drugs for the treatment of upper urinary tract cancers.



Dr. Colin Collins is collaborating with Dr. Black to perform whole exome sequencing on bladder cancer samples in patients receiving neoadjuvant chemotherapy. This project aims to identify which patients are most likely to respond to chemotherapy, and also to determine why some patients do not respond.



Dr. Alex Wyatt is working on the analysis of circulating tumour DNA in patients with metastatic bladder cancer. This allows for molecular analysis that can identify changes that occur for patients while on therapy and can identify potential targets for therapy. Up until now this type of analysis has required biopsy of patient's tumour or metastatic sites.



Dr. YZ Wang leads a program of patient derived primary xenografts (PDX) for all cancers and within this program there is a growing catalogue of bladder cancer PDX. For this he takes fragments of patient tumour and grows them in the lab, where they act as a model of the patient's original tumour to test how effective drugs are.



Dr. Mads Dugaard is using a VAR2-drug conjugate as a new therapeutic to target bladder cancer. VAR2 is a recombinant protein derived from the Malaria parasite that binds to specific chondroitin sulfates on the surface of cancer cells. VAR2 is also being used to detect chondroitin sulfate in urine, which will serve as a new test to identify the presence or absence of bladder cancer. Together with Dr. Black he is investigating the role of PPARgamma signaling on the regulation of immune infiltration in bladder cancer with the intention to develop a specific PPARgamma inhibitor.

WHERE WE ARE AT

Already, the Vancouver Prostate Centre is bringing first access to new treatments to British Columbians. One of the few new targeted therapies for bladder cancer is OGX-427, a treatment discovered and developed by VPC scientists is now in Phase II trials. Dr. Black is also leading a large North American trial to introduce a novel immune therapy for patients with non-invasive bladder cancer who are resistant to current treatment options.

Dr. Black is internationally recognized for his study of the mechanisms of chemotherapy resistance in bladder cancer is working with Dr. Alex Wyatt who is himself an internationally recognized authority in the study of circulating cell free DNA. They are leading research to find a “liquid biopsy” – an innovative way of predicting a patient’s response to treatment and monitoring their response by analyzing circulating tumour cells and cell free DNA in the blood.

GRANTS:

Close to \$3.5 million since 2016 in competitively earned research dollars.

HOW TO GIVE:

The goal of the bladder and kidney cancer teams at the VPC is to fill the unmet needs of bladder and kidney cancer patients by being the top centre in Canada for patient care, clinical trials and translational research. With your help they will reach that goal.

The Vancouver Prostate Centre receives directed donations through the VGH & UBC Hospital Foundation, the UBC Faculty of Medicine and the Sullivan Urology Foundation.

www.prostatecentre.com/donate

INSTITUTIONAL PARTNERS

As with any successful research enterprise the key to success is establishing and maintaining strong networks and partnerships with local, national, and international collaborators, as well as funders, patients and benefactors.



EXECUTIVE TEAM

Dr. Martin Gleave

Executive Director, Vancouver Prostate Centre
Chief Executive Officer, PC-TRIADD
Distinguished Professor and Head, Department of Urologic Sciences,
University of British Columbia
BC Leadership Chair in Prostate Cancer Research

Dr. Gleave (MD, FRCSC, FACS) is a clinician-scientist and urologic surgeon. His major research focus involves the study of cellular and molecular mechanisms mediating progression of prostate cancer to its lethal stage of androgen independence, and use of this information to develop integrated multimodality therapies that specifically target these mechanisms.

Dr. Larry Goldenberg

Director of Development and Supportive Care,
Vancouver Prostate Centre
Professor, Department of Urologic Sciences,
University of British Columbia
Stephen A. Jarislowski Chair in Urologic Sciences at VGH

Dr. Goldenberg (CM, OBC, MD, FRCSC, FACS, FCAHS) is a urologic surgeon and clinical scientist with an international reputation for excellence in prostate cancer research and treatment. His current research involves the evaluation of the role of multiparametric MRI in prostate cancer, the potential use of focal therapy, patient education, daVinci robotic prostatectomy and novel treatments for benign prostatic hyperplasia. He has been recognized for his contributions to health care by being inducted into the Order of British Columbia and the Order of Canada.

Dr. Paul Rennie

Director, Laboratory Research, Vancouver Prostate Centre
Professor, Department of Urologic Sciences,
University of British Columbia

Dr. Rennie is a PhD research scientist. His current research is aimed at determining how androgens regulate gene transcription and how to use this knowledge to prevent progression to androgen independence in prostate cancers. He is also studying prostate-specific elements of gene promoters and working to develop lenti and herpes virus-based vectors as a targeting vehicle for delivery and prostate-specific expression of genes that can control or kill prostate tumour cells.

Dr. Graeme Boniface

Chief Operating Officer, Vancouver Prostate Centre
Chief Operating Officer, PC-TRIADD

Dr. Boniface joined the Prostate Centre in 2008 as COO, after more than 20 years in drug development in both the academic and private industry sectors. Prior to joining the Centre, he was Senior Director of Clinical Research at QLT Inc. where he oversaw the clinical development of the company's drug platform in Oncology, Urology, Dermatology, and Endocrinology indications. Trials conducted by his team have led to successful regulatory marketing approvals by the US FDA, Canadian, and European agencies.

Mr. Brian Shankaruk

Chief Financial Officer, Vancouver Prostate Centre
Chief Financial Officer, PC-TRIADD

Brian Shankaruk has over 25 years experience in the financial field. For 20 years prior to joining the Centre, Brian worked in the insurance and financial services industry, focusing on Canadian and US statutory government reporting. Brian studied accounting at UBC and received his Certified General Accountant designation in

1990 from the Certified General Accountants Association of BC. He was admitted to the Chartered Professional Accountants Association of BC in June 2015.

Dr. Kim Chi

Associate Director, Clinical Research, Vancouver Prostate Centre
Senior Research Scientist, Vancouver Prostate Centre
Regional Medical Director, BC Cancer Agency – Vancouver Centre
Medical Oncologist, BC Cancer Agency – Vancouver Centre
Director, Clinical Research, BC Cancer Agency
Professor, Department of Medicine, University of British Columbia

Dr. Chi is a medical oncologist with the BC Cancer Agency who, at a relatively early stage in his career, has received national and international recognition for his contributions to prostate cancer research.

Dr. Colin Collins

Senior Research Scientist, Vancouver Prostate Centre
Director, Laboratory for Advanced Genome Analysis,
Vancouver Prostate Centre
Professor, Department of Urologic Sciences,
University of British Columbia

Dr. Collins is a PhD research scientist and Director of the Laboratory for Advanced Genome Analysis (LAGA). In addition, he is an associate adjunct professor at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center and a visiting scientist at Lawrence Berkeley National Laboratory. He has held positions at Lawrence Livermore National Laboratory, Lawrence Berkeley National Laboratory, and UCSF.



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