Early Prostate Cancer Translational Research Initiative Planning Workshop Report

Wednesday, January 20, 2016
8:30 am – 3:30 pm
Location: OICR | West Tower Boardroom 5-20/21

Participants	
Rima Al-awar	Ontario Institute for Cancer Research
Bharati Bapat	Lunenfeld-Tanenbaum Research Institute
John Bartlett	Ontario Institute for Cancer Research
Glenn Bauman	London Health Sciences Centre/London Regional Cancer Program
David Berman	Queen's University
Paul Boutros	Ontario Institute for Cancer Research
Stuart Edmonds	Prostate Cancer Canada
Urban Emmenegger	Sunnybrook Health Sciences Centre
Aaron Fenster	Robarts Research Institute
Michael Fraser	University Health Network
Masoom Haider	Sunnybrook Health Sciences Centre
David Jaffray	University Health Network
Thomas Kislinger	University Health Network
Hon Leong	London Health Sciences Centre
Andrew Loblaw	Sunnybrook Health Sciences Centre
Mathieu Lupien	University Health Network
Nicole Mittmann	Cancer Care Ontario
Linda Penn	University Health Network
Melania Pintilie	University Health Network
Greg Pond	McMaster University
George Rodrigues	London Health Sciences Centre
Cynthia Stewart	GE Healthcare
John Valliant	Centre for Probe Development & Commercialization
Aaron Ward	Western University
Theodorus van der Kwast	University Health Network
Martin Yaffe	Sunnybrook Health Sciences Centre
Katherine Zukotynski	McMaster University

OICR & FACIT	
Rob Campos	Head, Research Operations
Jeff Courtney	Chief Commercial Officer, FACIT
Elliann Fairbairn	Project Manager, Ontario Molecular Pathology Research Network
Laura Fung	Program Coordinator, Transformative Pathology
Tom Hudson	President and Scientific Director
David Koehler	Director, Fund Operations, FACIT
Nicole Onetto	Deputy Director and Chief Scientific Officer
Teresa Petrocelli	Director, Scientific Secretariat
Rebecca Tamarchak	Director, Strategic Planning and Outreach
Brent Zanke	Entrepreneur in Residence, FACIT

Guest	
Dawn Richards	Medical Writer

Please note that this is a succinct summary of the workshops, for more details please contact the TRI workshop leaders:

- Glenn Bauman: Glenn.Bauman@lhsc.on.ca
- Andrew Loblaw: Andrew.Loblaw@sunnybrook.ca
- Paul Boutros: Paul.Boutros@oicr.on.ca

1. Opening remarks *(Glenn Bauman)*

- Workshop goals and deliverables/outcomes

Attendees were welcomed and thanked in advance for their input. The workshop is intended to bring together researchers in prostate cancer to discuss opportunities to move current assets and projects forward in a translational capacity, as well as to plan for how to integrate those assets into new project plans. These would form the start of a potential Translational Research Initiative (TRI) Letter of Intent (LOI). The group was asked to consider pressing clinical needs and to refer to the pre-circulated survey results. The group's strengths span the preclinical space including biomarkers, -omics, and basic biology; the clinical space including risk stratification and focal treatment; and the health outcomes space, including knowledge translation of new treatments/paradigms and economic evaluation. There was a reminder that the discussion of leveraging current OICR and Ontario assets should be limited to specific technical questions to ensure the heart of the workshop can include a lengthy and in-depth brainstorm on potential new projects.

2. Background *(Nicole Onetto)*

- OICR Strategic Plan 2016-2021: Overview

OICR's five-year strategic plan (2016-2021) was reviewed, including the Institute's mission and goals. For more details, please click here.

- Translational Research Initiatives

The Institute's concept of TRIs was discussed.

Structure-wise, TRIs represent large scale, multi-disciplinary collaborations between laboratory and clinical scientists to advance Ontario assets and improve cancer patient outcomes. They should be focused on a clinical need that builds on assets or innovations in an area of leadership for Ontario. TRIs will include two to five projects, with at least one mandatory clinical trial that must begin in the first two years of a TRI. A budget of up to $10 M over four years may be requested for a TRI, with the clinical trial budget comprising at least $2 M over the four years (if less than $2 M, the total budget will be reduced accordingly). Additional supplemental funding should be sought at the start of the TRI and continued throughout the course of the TRI.

The timing for TRI development was described as follows:

- TRI workshops - until March 2016;
- Declaration of LOI interest – by April 15, 2016;
- TRI LOI submission – May 2, 2016 which includes an overview, research summary, description of team, and a high level budget;
- TRI LOI selection – July 15, 2016;

    - Only TRI LOI submissions rated medium or high will be invited for a Funding Request (FR) submission.
- TRI FR submission – October 31, 2016;
- TRI FR international review panel – February 2017;
- TRI FR communication – March 2017;
- Funding begins – April 2017.

There was a reminder that all guidelines about the TRI process are available by contacting OICR's Scientific Secretariat at scientificsecretariat@oicr.on.ca.

3. Landscape of existing OICR and Ontario activities, projects and assets

As the TRIs are intended to leverage existing OICR investments in relevant research areas, leaders of OICR funded prostate research projects were invited to provide summaries of their work. It is recognized that there are many Ontario investigators engaged in prostate cancer research in Ontario who also possess a base of expertise to support a TRI.

CPC-GENE (biomarkers) – Paul Boutros

The Canadian Prostate Cancer Genome Network (CPC-GENE) is a focused study of the genomes of intermediate-risk prostate cancer. The primary goal of CPC-GENE is to create clinically-useful prognostic markers, and it is the largest prostate cancer genomics project in the world.

Important points highlighted during the presentation included:

- The project is funded by Movember, Prostate Cancer Canada, and OICR;
- The focus is on an intermediate risk localized group which undergoes definitive treatment, and for which approximately one-third of patients are over-treated and one-third of patients are under-treated. The goal is to sub-stage this group for improved surveillance and to identify those patients who require more intensive therapy;
- To date, 305 prostate whole genomes have been sequenced;
- In some patients, they have found two genetically distinct prostate cancers as indicated by their large genomic heterogeneity;
- Robust copy number aberration (CNA)-based biomarkers have been developed, published and assessed in initial validation. Recent work has shown the strong benefit to integrating other types of genomic information, particularly methylation, into composite multi-modal biomarkers.

PRONTO (biomarkers) – John Bartlett

The PRONTO program is aimed at better identifying men who need or do not need aggressive treatment by providing accurate information about risk to patients diagnosed with early prostate cancer. The program seeks to develop novel molecular diagnostic tests to predict which patients are likely to develop aggressive cancer and support personalized treatment of early cancers.

Important points highlighted during the presentation included:

- This is a five-year program co-funded by Prostate Cancer Canada;
- It includes two cohorts: a low- and high-risk cohort with the objective to find bio-markers to help customize treatment according to patient risk level;
- At 18 months into the project, RNA profiling has started with methylation assays ongoing.

SPIRIT (imaging validation) – Glenn Bauman

As part of the Smarter Imaging Program currently supported by OICR, a research project co-led by Martin Yaffe and Aaron Fenster, SPIRIT is focused on developing and evaluating new imaging techniques (SPIRIT – Smarter Prostate Imaging and Interventions). SPIRIT seeks to develop four new prostate imaging techniques (Dynamic ^{18}F PET, Hyperpolarized ^{13}C MRI imaging, ^{23}Na MRI imaging and ^{18}F-PSMA PET imaging) for use in clinical trials. An imaging to pathology registration pipeline has been built to allow the highly spatially accurate comparison of intra-prostatic imaging changes against ground truth pathology changes with the hope the new imaging techniques will provide more accurate localization of cancers in challenging locations (like the anterior gland) and allow more complete characterization of cancers (such as identifying high grade foci). The validation of the imaging is occurring through pilot trials with the most promising imaging technique proceeding to a larger validation trial. Within the validation trial, correlation of imaging changes with genetic changes by sequencing spatially corresponding pathology tissue is planned and pilot experiments are underway. In parallel with the validation trials is a prospective trial of focal laser ablation for early prostate cancer based on mpMRI, the intent being to bring the two technologies (better localization of cancer and focal deliver) together in a future trial (out of scope of the current award).

Important points highlighted during the presentation included:

- Utilization of next generation imaging techniques in Ontario to augment standard of care and to provide novel structural and biological information about prostate cancer with more reliable identification of prostate cancer, and specifically aggressive disease;
- Efforts will continue to potentially augment conventional imaging for surveillance protocols using a PSMA peptide probe.

CPDC/PET probes (PSMA/FCH) – John Valliant

The Centre for Probe Development and Commercialization (CPDC) is a not-for-profit national centre of excellence for probe discovery, development and manufacturing. It is funded by the Government of Canada through the Network of Centres of Excellence program and an additional grant from the Province of Ontario through the Ontario Institute for Cancer Research. CPDC is unique in that it bridges the gap between university research and clinical programs, helping researchers to move their innovative discoveries from concept to clinical application. Their team of 80 has the expertise needed to create and manufacture imaging agents and initiate clinical trials. Currently, CPDC is supplying agents for 21 clinical trials. The CPDC has harmonized probe manufacturing amongst multiple sites.

PRECISE (clinical trial) – Andrew Loblaw

The current challenge for early detection/screening for prostate cancer is that the benefits of screening are modest, but the harms and costs are too high. Multiparametric MRI allows for targeted biopsies which potentially can increase the proportion of high-grade (G7+) cancers and decrease the proportion of lower-grade cancers that undergo treatment. Economic modelling suggests this will result in net savings. A recent evidence-based guideline concluded that there is insufficient evidence to offer MR-guided screening at the current time. The clinical trial proposed, "PRECISE", is a multicentre, non-inferiority randomized clinical trial for men suspected of having prostate cancer (elevated PSA) that will be randomized between standard TRUS-guided template biopsies and MRI supplemented by guided targeted

biopsies in case of suspicious MRI images. PRECISE will be proposed for funding by OICR as part of the TRI with a possibility of co-funding by Prostate Cancer Canada.

Medical Instrumentation and Imaging Software (MIIS, targeted biopsy and treatment) – Aaron Fenster

As part of the current OICR strategy, the OICR Smarter Imaging Program is linked to an Imaging Translation Program (ITP), co-led by Aaron Fenster and Martin Yaffe, which is aimed at developing new imaging technologies. ITP seeks to develop new technologies for image guidance of needle biopsy as well as focal ablative therapies for prostate cancer.

Important points highlighted during the presentation included:

- Efforts are underway to decrease the procedure time for the focal laser ablation device;
- Workshop participants were invited to leverage the group's extensive infrastructure for rapid development and projects in the TRI.

4. Potential TRI projects and collaborations

Participants were asked to rank the top three ideas as research priorities that would then be reported back to the group. They were instructed to think specifically about clinical need, scope and how the priority would leverage resources already identified.

Breakout Session: Report back on research priorities:

Breakout groups were asked to discuss research priorities according to the different groups of patients who could be the subject of the TRI:

- Low risk/active surveillance;
- Intermediate risk;
- High risk.

Key points of the discussion were as follows:

1. *Low risk, active surveillance* – Understand how biomarkers other than PSA could be used to enable clinical decisions in these cohorts. There was a proposal to build a well-curated active surveillance cohort, for example, harmonizing and leveraging provincial activities, and collection at relevant time points etc.;
2. *Intermediate risk* – Work is starting at Princess Margaret Hospital based on MR-guided focal radiation therapy, aiming to find an imaging/radiation link, developing biomarkers from existing CPC-GENE and PRONTO cohorts and understanding the biology to look at how changes observed are mediating resistance or radiation response, radiotherapy, radio-sensitivity. This might be an opportunity for work that will be proposed in the TRI;
3. *Higher risk population* – This refers to a population of patients that undergo prostatectomy and might be candidates for early systemic intervention. Main objectives will be to find relevant molecular/imaging biomarkers to guide treatment. Especially given the promise of PSMA as an imaging agent and using it to detect earlier disease in low- to high-risk patients, deciding when to treat more aggressively or de-escalate treatment, and how existing biomarkers can provide new or complementary information;
4. *Principled priority* – Regardless of research direction, there is a mandate to leverage prospective cohorts, obtain consent for data linkages (for example to

administrative databases), and build in quality of life measurements and cost parameter measurements to perform health services analysis in the future. Ensuring the right degree of planning at the outset will allow for the necessary additional analyses to be done for payers and other stakeholders when promising results are translated.

A brief summary from the discussions was provided. The main potential research activities and projects that were highlighted included:

- Active surveillance with a potential focus on high risk surveillance on patients with companion diagnostics development (longitudinal);
- Focal radiation approaches (including radiotherapy, ablation, etc.);
- High risk treatment sensitivity prediction (radio-sensitivity or chemo-sensitivity);
- Companion diagnostics for the PRECISE trials.

Attendees ranked each of these potential projects according to what they felt should be the top priorities, with the following final order:

1. Active Surveillance (highest priority)
2. PRECISE companion studies
3. High-risk treatment sensitivity
4. Focal radiation (lowest priority)

5. Next Steps/Wrap Up

Attendees were thanked for their time and input. Meeting notes will be shared with the attendees and people who were not able to allow them to be involved in development of the TRI LOI moving forward.

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Early Prostate Cancer TRI Planning Workshop

Wednesday, January 20, 2016
8:30 a.m. – 4:30 p.m.
Light breakfast will be served at 8:00 a.m.
Location: OICR | West Tower Boardroom 5-20/21

TIME	AGENDA ITEM	PRESENTER
8:00 a.m.	**Arrivals and light breakfast**	
8:30 a.m. – 8:40 a.m.	**Opening remarks** • Workshop goals and deliverables/outcomes.	*G. Bauman*
8:40 a.m. – 9:00 a.m.	**Background** • OICR Strategic Plan 2016-2021: overview; • Translational Research Initiative (TRI): overview, available funds, linkages to platforms and existing projects; and • Letters of Intent: Declaration, submission.	*N. Onetto*
9:00 a.m. – 10:00 a.m.	**Existing Ontario early prostate cancer projects and assets** • CPC-GENE (biomarkers) • PRONTO (biomarkers) • SPIRIT (imaging validation) • CPDC/PET probes (PSMA/FCH) • PRECISE (clinical trial) • MIIS (targeted biopsy and treatment)	*P. Boutros* *J. Bartlett* *G. Bauman* *J. Valliant* *A. Loblaw* *A. Fenster*
10:00 a.m. – 10:20 a.m.	**Break**	
10:20 a.m. – 12:00 p.m.	**Breakout 1:** **Defining research priorities considering** • Critical clinical needs in prostate cancer management particularly within diagnosis and localized disease; • Within a given clinical need, what is the key research question that would address that need and what is the scope of that research (preclinical discovery vs. first in man trial (N<20) vs. single arm trial (N<100) vs. medium sized randomized trial (ASIST size, N<300); and • Available Ontario expertise and research assets that could be leveraged to address the clinical need. **Report back from tables of research priorities** • Each table identifies up to 3 priorities including a description of scope and assets leveraged.	*A. Loblaw* *All (table discussion)*

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12:00 p.m. – 12:45 p.m.	**Lunch**	
12:45 p.m. – 3:00 p.m.	**Planning Committee Feedback** • Report on the consolidated research priorities; • Blinded voting on the top 3-5 priorities (if needed); and • Investigators self identify to participate in brainstorming. **Breakout 2 - Brainstorming around the priorities** • Suggest a hypothesis; • Sketch out a research plan; • Identify OICR/Ontario assets leveraged; • Identify other potential collaborators/research team; and • Interested project leaders can self-identify at this step.	*P. Boutros* *All (table discussion)*
3:00 p.m. – 3:20 p.m.	**Break**	
3:20 p.m. – 4:20 p.m.	**Group Feedback:** • Reports from breakout groups on proposed research plan and team for their priorities; and • Blinded voting to refine list of research priorities.	*G. Bauman*
4:20 p.m. – 4:30 p.m.	**Next steps/wrap up** • Workshop report; • Declaration of interest; • LOI.	*N. Onetto/ G. Bauman*