Early Breast Cancer Translational Research Initiative Planning Workshop Report

Thursday, February 25, 2016, 8:00 am – 5:00 pm
Location: OICR | West Tower Boardroom 5-20/21

Invitees	
Christina Addison	Ottawa Hospital Research Institute
Irene Andrulis	Lunenfeld-Tanenbaum Research Institute
Angel Arnaout	Ottawa Hospital Cancer Centre, Ottawa Hospital Research Institute
Anita Bane	McMaster University
John Bartlett	Ontario Institute for Cancer Research
Jane Bayani	Ontario Institute of Cancer Research
Dave Cescon	Princess Margaret Cancer Centre
Harriet Feilotter	Queen's University
Aaron Fenster	Robarts Research Institute
Jean Gariépy	Sunnybrook Research Institute
Eva Grunfeld	University of Toronto
Michael Hoffman	Princess Margaret Cancer Centre, University of Toronto
Victoria Hoskin	Queen's University
Katarzyna Jerzak	Sunnybrook Odette Cancer Centre
Mark Levine	McMaster University
Jordan Lerner-Ellis	Mount Sinai Hospital, University of Toronto
Nicole Look-Hong	Sunnybrook Research Institute
Anne Martel	Sunnybrook Research Institute
Kelly Metcalfe	University of Toronto, Women's College Hospital
Steven Narod	University of Toronto, Women's College Hospital
Amadeo Parissenti	Laurentian University & Northeast Cancer Centre
Wendy Parulekar	Canadian Cancer Trials Group
Kathy Pritchard	Sunnybrook Health Sciences Centre
Eileen Rakovitch	Sunnybrook Health Sciences Centre
Jüri Reimand	Ontario Institute for Cancer Research
Azin Sayad	University of Toronto
Melanie Spears	Ontario Institute for Cancer Research
Lincoln Stein	Ontario Institute for Cancer Research
Dongsheng Tu	Canadian Cancer Trials Group
Sonal Varma	Queen's University
Tim Whelan	McMaster University
Martin Yaffe	Sunnybrook Research Institute
Yulia Yerofeyeva	Sunnybrook Research Institute
External Advisors	
Mark Basik	McGill University
Denis Sgroi	Harvard Medical School / Massachusetts General Hospital
OICR & FACIT	
Rob Campos	Head Research Operations, OICR
Jeff Courtney	Chief Commercial Officer, FACIT
Tom Hudson	President & Scientific Director, OICR
Nicole Onetto	Deputy Director & Chief Scientific Officer, OICR
Teresa Petrocelli	Director, Scientific Secretariat, OICR
Jane Sun	Project Manager, Transformative Pathology, OICR
Rebecca Tamarchak	Director, Strategic Planning and Outreach, OICR
Brent Zanke	Executive in Residence, FACIT
Guest	
Dawn Richards	Medical Writer

Please note that this is a succinct summary of the workshop prepared by the organizers. For more details please contact the TRI workshop leaders:

- John Bartlett: john.bartlett@oicr.on.ca
- Mark Levine: mlevine@mcmaster.ca
- Eileen Rakovitch: Eileen.Rakovitch@sunnybrook.ca

Notes

On behalf of the TRI organizers, Dr Eileen Rakovitch, Dr Mark Levine and himself, Dr. Bartlett welcomed everyone to the meeting and expressed enthusiasm for learning more about each other's research and discussing potential ways to collaborate. He introduced everyone to two external participants who will be helping advice on the scope of the TRI Letter of Intent (LOI) preparation – Drs. Denis Sgroi and Mark Basik.

1. Background (Nicole Onetto)

- OICR Strategic Plan 2016-2021: overview
- Translational Research Initiatives

OICR's 5-year strategic plan (2016-2021) was reviewed and the Institute's concept of Translational Research Initiatives (TRIs) was discussed. Important highlights include the aims:

- To advance Ontario's best cancer research to improve cancer care and treatment; enhance Ontario's global leadership in cancer research;
- To work in collaboration with partners; and, for economic development.
- To encourage workshop participants to consider leveraging networks supported by OICR (e.g., Global Alliance for Genomics & Health, Ontario Tumour Bank, Canadian Cancer Clinical Trials Network) as well as OICR's Technology Programs

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 2-5 projects, with at least one mandatory clinical trial which must be started in the first 2 years of a TRI. A budget of up to $10 M over 4 years may be requested for a TRI, with the clinical trial budget comprising at least $2 M over the 4 years (if less than $2 M, then 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. It is important to note that TRI funding will be competitive, with the possibility that all full applications may not be funded.

TRI workshops are intended to support development of Letters of Intent (LOIs) for TRIs. TRI's will be led by two co-leaders (preferably not from the same institution), one laboratory scientist and a clinician investigator, while the TRI manager will provide coordination and administrative capabilities.

Workshops are intended to build consensus around the TRI priorities, discuss potential projects, identify collaborations among Ontario scientists, consider how to best leverage OICR Technology Programs, and identify potential sources of co-funding. A workshop report will be generated to inform the community about the workshop and to facilitate LOI applications.

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

2. Opening remarks (Mark Levine)

Dr Levine focused on three key points towards a TRI's envisioned partnership between science and clinical science. The key points are:

- Early Breast TRI workshop and rationale for focused topics
- Workshop goals and deliverables/outcomes
- Funding opportunities and timeline

The planning committee of this workshop (composed of Drs. Levine, Bartlett and Rakovitch) structured the agenda into 3 themes: luminal breast cancer, ductal carcinoma *in situ* (DCIS) and a broad theme that includes chemotherapy, to reflect high priorities in the field of breast cancer with the most potential for short-term/medium term impact with existing available resources. This categorization was empiric and opportune.

A review of the mission and vision launched this TRI workshop and highlights included not only the infrastructure for collaboration but also the unique opportunities and strengths for and with the working groups in the presentation roster.

3. Existing Assets from OICR Programs and Ontario

OCTANE (Tom Hudson, in place of Philippe Bedard)

OCTANE (Ontario–wide Cancer TArgeted Nucleic acid Evaluation) is a new initiative that is part of a personalized medicine program to bridge large scale and clinical genomics. The primary goal of this program is to create a cohort of patients undergoing clinical genomics testing, offering next generation sequencing (NGS) in a CLIA lab, and coordinating informatics tools and sharing of clinical data. Important to achieve this goal is the collaborations with the Princess Margaret Cancer Centre/OICR lab for genomics (Translational Genomics Lab, or TGL) and the infrastructure of The Ontario Tumor Bank at various provincial cancer centers (Princess Margaret Cancer Centre, Juravinski Cancer Centre, London Health Sciences Centre, The Ottawa Hospital, and Kingston General Hospital).

Highlights of this program:

- ✓ To facilitate targeted therapy and immune therapy clinical trials,
- ✓ To identify patient subsets for more advanced genomic profiling,
- ✓ To provide samples/data to ICGCMed.

Presented details included the study process, data collection and consent for research samples. Also discussed was the next steps including phase 1 deliverables such as the launching an NGS panel testing in all 5 OLA clinical labs, developing and launching a secure web portal, adapting OTB infrastructure for OCTANE, enrolling 500 patients in year 1, and starting development and planning for TGL-based on patients.

The Ontario DCIS Cohort (Eileen Rakovitch)

The Ontario DCIS Cohort is a provincial resource for population research and includes all cases of pure DCIS diagnosed in Ontario between 1994-2003. This cohort was developed through linkage with the Ontario Cancer Registry, and treatment and outcomes include deterministic linkage, primary chart review, operative reports to validate surgical treatment, and radiation records. In total there are 8,257 cases including DCIS and DCIS with micro-invasion. The cohort has representative tissue blocks (paraffin embedded) for about half the cases treated with breast conserving surgery. Median follow up is about 11 years. In examination of outcomes of cases treated by breast-conserving surgery, the overall finding was that despite women with lower risk disease having breast-conserving surgery alone, there were still about 20% that recurred, and about half of those were invasive cases.

Ontario Clinical Trial Groups: Canadian Cancer Trials Group (CCTG)/ Canadian Cancer Clinical Trials Network (3CTN)/Ontario Clinical Oncology Group (OCOG) (Wendy Parulekar, Mark Levine)

The CCTG's work spans the development spectrum from preclinical and new drug development to informing guidelines. They have enrolled over 78,000 patients to date, host an annual meeting, and publish high impact results. They have defined standard of care in a breadth of cancers, special populations (elderly, rare cancer settings), and in methods. Bio-specimen collection is an important part of the CCTG, and the breast collections were highlighted for the workshop participants (primarily early breast cancer).

3CTN was created in response to the Report on the State of Cancer Clinical Trials in Canada, specifically to help what is considered to be a broken clinical trial system in Canada. The group's principles and structure were presented, operating on an annual budget of about $8-10 M, and supporting clinical trial activity at the site level at multiple network sites across Canada. The scientific portfolio has very straightforward criteria and the network's innovation includes the areas of science, access and outcomes.

OCOG was established in 1982 with the primary goal of developing academic trials group amongst Ontario cancer centers. For this, OCOG works with networks of investigators to conceive and conduct clinical trials. Over 11,000 cancer patients in a breadth of cancers have participated. The OCOG PET imaging in oncology program (created with the support of the Ministry of Health and Long Term Care and Cancer Care Ontario) has conducted 7 trials to inform government policy on PET. The Oncotype Dx field study evaluated the impact of the 21 gene recurrence score on decision making for chemotherapy in early breast cancer. OCOG works with OICR via their imaging expertise and selective collection of tissue and blood samples, as well as with CCTG collaboratively or by strategically filling CCTG gaps. OCOG is now part of Escarpment Cancer Research Institute (ECRI) affiliated with McMaster and Hamilton Health Sciences.

Medical Imaging Instrumentation & Software (MIIS) Program: Multi-modality Image-Guided Breast Biopsy Imaging (Aaron Fenster)

The OICR Imaging Translation Program (ITP) that has developed expertise in robotics and software modules (have licenses and patents in both areas) and for which workshop participants were invited to leverage their infrastructure for rapid development to clinical translation and commercialization. Highlights include the development of novel imaging probes to identify early cancer allowing accurate biopsy targeting tumors that are not visible by ultrasound alone; and use of a multi-modality approach; the promise of positron emission mammography/ultrasound guided breast biopsy including its potential to improve patient workflow; the advantages of robotic technology, and the MRI/ultrasound fusion guided approach, and the gamma detector/ultrasound guided breast biopsy system.

Reducing the Burden of Breast Cancer in Young Women (RUBY)(Kelly Metcalfe)

RUBY is a prospective cohort of young women (<41 years) that aims to enroll 1,200 women over 4 years at 20 Canadian centers, and for which clinical data, treatment information, and tissue and blood specimens will be collected. At minimum for enrolment, the investigators want access to participants' charts, baseline questionnaires (REDCap), baseline blood and tumor collection (prior to treatment), and blood and chart abstraction at 1 and 3 years. Sample collection will be prearranged for the participants, and to date 13 sites have enrolled at least 1 patient. There are also a number of studies that are funded within RUBY, and workshop participants were informed that this resource will be available to study topics not currently reviewed in cohort study.

Transformative Pathology/IMEC (John Bartlett)
The primary goals of the OICR Transformative Pathology Program include developing fit for clinical and technical diagnostic assays and training the next generation of molecular pathologists. Highlights of this program include collaborations across Canada and in the UK/EU, and with the International Cancer Genomics Consortium; collaboration in the PRONTO program in prostate integrates multiple research groups into one program to facilitate collaboration; a breadth of diagnostic development work that includes discovery, development (evidence to develop in clinical trials) and validation (in another clinical trial); accessibility to clinical trial biobanks suited to develop predictive assays owing to the high quality and, curated samples from patients who are treated uniformly and availability of such resources to conduct meta-analyses and molecular assays to inform stratified trials. Collaboration in the PRONTO program in prostate integrates multiple research groups into one program to facilitate collaboration. PRONTO's model to share intellectual property could be considered for breast cancer.

4. Discussion and other resources

Workshop participants were encouraged to not only formulate questions for which preliminary answers can be sought but also to think downstream about future clinical trials. Discussions included opportunities to link with national and international cancer registries; to collect circulating tumor DNA, and to not forget the Ontario Familial Breast Cancer Registry as a resource. This has been funded by NIH (15 years), is part of an international breast cancer collaboration, and has 2,000 families followed with a history of breast cancer (and 800 population-based controls), collects information in family history, and has extensive genomic information and follow up information on families. Accessibility to this resource is subject to a panel review.

THEME 1: ENDOCRINE REFRACTORY LUMINAL BREAST CANCERS (Moderator: Eileen Rakovitch)

1- Luminal Breast Cancer – Over-treated or Undertreated? Whom to Treat with What and When (Kathy Pritchard)

A review of the clinical landscape on luminal breast cancer converged on a key observation that the drop in mortality by half is accompanied by steady increase in incidence, at least in the UK and Canada between 1950 and 2015. The drop in mortality is due in part to early detection by mostly to adjuvant therapy. The challenge is however, that women with estrogen receptor (ER) positive breast cancer still continue to relapse and die of their disease. Dr. Pritchard presented intriguing data from the meta-analyses from Oxford collaboration on late relapses. Addressed options include adjuvant therapy and chemotherapy with a focus on the biology of early breast cancers and how this knowledge can be leveraged to predict for risk. Targeted therapy showed limited success to date. Future work can work towards closing the gap on predicting better response by the development of better therapies and biomarkers and their validation using large and complete data sets for reproducibility.

2- De-escalating Treatment for Luminal A Breast Cancer (Tim Whelan)

This presentation scoped an approach to the current challenge of adjuvant radiotherapy: all patients are exposed to it and its potential side effects, even though it will only benefit a portion of these patients via prevention of recurrence. Discussions on the Oncotype recurrence score (16 oncogenes plus 5 housekeeping genes) was followed by how it has revolutionized the risk stratification approach and evaluation of adjuvant therapy in practice and clinical trials (TAILOR, RESPONDER). Many women may receive radiotherapy for breast cancer with little benefit. The Ontario and BC-based LUMINA trial uses theimmunohistochemistry subtypes of breast cancer to identify a low risk profile and then avoid radiotherapy to the breast in tumors with a low Ki67. The CCTG MA.20 trial compared regional radiation added to breast radiation versus breast radiation alone in women who had

undergone BCS. An exploratory analysis suggested that benefit if regional irradiation was not observed in low risk patients. A plan for the next trial is to evaluate whether regional radiation is needed in low risk patients. Discussions included studying whether biomarkers can be used to tailor treatment via risk stratification and treatment responsiveness. Emphasis was made on the insight that different trial designs need to be used to include molecular biomarkers.

3- Luminal Breast Cancer – From Residual Risk to Personalized Medicine (John Bartlett)

There is recognition that breast cancers represent cancers with high CAN loads (C-class) and relatively fewer mutations (M-class). Patient selection for chemotherapy and radiation therapy is predicated on clinical risk, and there is a need to balance both risk and biology. Proposed herein is the approach for stratified medicine and integrated diagnostics to identify patients with ER+ breast cancers that are at high risk for recurrence. Such patients could also be candidates for novel treatments. Molecular features could also be used to guide treatment in future. This approach includes development of a biomarker and drug in parallel, showing a response to treatment in the stratified group, followed by a clinical trial; high throughput platforms are needed to translate to the clinic; validation efforts of these stratified targets via molecularly stratified preclinical screening were shown, through selection of cell lines driven by these strata and accessing agents in clinical development against these cell lines. This provides the potential to develop dual targeting approaches that cannot currently be done in the clinic.

4- Functional Drivers in Breast Cancer (Azin Sayad)

A new method sheds light on a path to target undruggable mutations in breast cancer. Work done in genome-scale pooled shRNA screens to determine gene essentiality is possible through the development of a new analytical method based on shRNA vulnerabilities. This represents a significant opportunity for groups to investigate this data (online resource).

5- Potential Role on Ezrin as a Novel Sensitizing Agent and in Blocking Metastasis (Victoria Hoskin)

The knowledge landscape of the metastatic biomarker, Ezrin can be transferred to the early setting as supported by evidence presented by the speaker. Knowledge that supports Ezrin as a potential target include increased cell survival in high expressing cells; sensitization of ER+ breast cancer cells to doxorubicin in vitro; affected cell mobility and migration in a preclinical mouse model and high expression in ER+ subtype samples In the Southeastern Ontario Breast Cancer Cohort (SEOBC).

6- Invasive Lobular Breast Cancer: Markers to Mechanisms (Angel Arnaout / Christina Addison)

Lobular breast cancer comprises about 15% of all breast cancers. The clinical problem for the surgeons is two-fold: Larger margin of the tumor is resected owing to a non-sticky tumor mass rendering it difficult to visualize the tumor periphery. The clinical dilemma is that biologically indolent tumors (low grade, luminal A/B, ER+) have distant metastatic potential (multiple sites common, unusual sites, hard to detect). The approach discussed focused on a microRNA platform on samples using the repository of ILC Tissue Collection and Database (487 cases, collected from 2010-2014). This approach successfully identified biomarkers in potential pathways as shown by validation studies in vitro.

7- Prognostic Importance of Intratumoral T-bet-positive Lymphoid Cells in Breast Cancer (Irene Andrulis)

The immunology component was the focus of this tumor microenvironment presentation with an approach to block the adaptive immune response via turning on the immune system to generate T-cells. Supporting evidence using g samples from the Ontario Familial Breast

Cancer Study was shared. Ongoing studies are addressing why some basal breast cancers with the same features have T-bet+ lymphocyte infiltration and others do not.

8- Stratified Medicine Clinical Trial in Luminal Breast Cancer (Wendy Parulekar)

The primary goal of a potential "window of opportunity" trial is to match the patients tumor to drugs based on combinatorial data including gene mutation, CNV and gene expression. The proposed clinical trial is a phase 2 umbrella study on screening with molecularly-defined strata and a window of opportunity design. The primary outcome measure is Ki67 at 14 days, and secondary outcome measures include adverse events (CTC AE V4.0), treatment compliance, surgical complication rate, etc. Key challenges will include physician and patient acceptance, patient numbers needed to screen for final sample size (about 650), turn-around time for the Prosigna panel and other molecular testing, quality control for molecular assays, and the predictive ability of all molecular strata not tested for each drug. She also emphasized that the CCTG has a history of good potential recruitment and has influential knowledge translation capabilities.

THEME 1: Discussion summary

Much of the discussion focused on the window of opportunity trial, as a novel (to Canada) approach. Overall there was strong support for the linked diagnostic/preclinical work leading to a potential stratified clinical trial. This was seen as a high priority for the TRI with some challenges to be addressed prior to full submission. In the field of radiotherapy there was support to explore the potential for developing a team approach in this area – building on existing resources. Over-treatment by radiation is critical and could lead to significant changes for the healthcare system.

THEME 2:-DCIS- REDUCING OVERTREATMENT/PREDICTING RECURRENCE (Moderator: Mark Levine)

9-DCIS – Challenges in the Management of DCIS Over and Under Treatment (Eileen Rakovitch)

DCIS is commonly diagnosed because of screening mammography in healthy women. There is now consensus that DCIS is often indolent and women are being over treated. DCIS is associated with high survival rates and over the last 50 years there has been no decrease in incidence of invasive breast cancer. Due to the data from 4 randomized trials and a meta-analysis, the potential for recurrence (usually) has all women treated the same who have DCIS (treatment with at least local excision and radiation). It would be most beneficial to stratify low- and high-risk local recurrence post-surgery. ECOG E5194 and Boston study data were reviewed, and the Ontario DCIS Population Cohort showed that despite clinical evidence and guidelines, only half of women with breast conserving surgery received radiation treatment as well. In this cohort, if the women who did not receive radiation therapy post-surgery had received treatments, there would have been a reduction in low risk numbers similar to those who received radiation therapy. There is a need to identify between low- and high-risk recurrence factors via identification of both molecular and pathological factors to impact clinical treatment and decision-making.

10-Developing Biomarkers for improved Management of DCIS (Jane Bayani)

Based on the framing of the clinical management challenges of DCIS, the goal, herein is to use sequencing techniques to find biomarkers to stratify patients accordingly: patients at low risk (conservative therapy) versus those at high risk (more aggressive therapy), thus improving risk assessment and reducing over treatment of DCIS. Interim analysis of 214/500 samples shows that 23 genes with differential expression between patients without recurrence and patients with any recurrence and plotting of these genes with reactome identified putative pathways.

11- Predicting Recurrence Risk in Individuals with DCIS Treated by Breast-Conserving Surgery (Eileen Rakovitch)

The Oncotype Dx DCIS score can provide a Recurrence Score from 12/21 genes and individualized estimates of the 10-year risk of local recurrence in patients with DCIS treated by breast-conserving treatment alone. The use of this score in the ECOG E5194 study was reviewed and compared to very similar findings from the Ontario Population Cohort. The DCIS score is associated with risk of local recurrence in patients who received breast-conserving surgery alone and compared to those patients who received surgery and radiation, and there was no interaction between the DCIS score and radiation therapy. Patients with a low DCIS risk score fell into a subset treated with breast conserving surgery with a smaller absolute benefit from radiotherpay when compared to patients with a high DCIS score.

12- Developing new Predictive and Prognostic Biomarkers using Digital Pathology (Anne Martel)

Histopathology in the diagnosis of breast cancer is important and challenging in a large cohort when extracting reproducible measures of well-established H&E stained section biomarkers, at low cost. This challenge presents an opportunity for automated analysis of whole section images to synthesize a computation pathology approach. Outcomes of such an approach for DCIS include determination of whether histopathological characteristics in stroma can be used to stratify patients, features derived from pathologists' knowledge, and deep learning/convolutional neural networks used to learn features automatically and provision of an open source platform to annotate, share, and quantitatively analyze digitized pathology image data.

13- Reducing Mortality and Morbidity from Breast Cancer: The Role of Imaging (Martin Yaffe)

There is an important opportunity for OICR to do work in screening to find breast (and other) cancers earlier and when the tumors are smaller. New approaches to improve sensitivity or specificity, can identify cancers that are likely more lethal and to reduce over-screening (or under-screening) by risk stratification. Collaborative work with GE Global was highlighted with respect to reducing overtreatment by characterizing the potential aggressiveness of cancers. There is a need to develop a reliable way to follow women with minimal treatment for DCIS, which may include using the whole mount slides and other types of analyses they can offer this group. Finally, there are needs to reduce toxicity of therapies to normal tissues via image-guided therapies and activatable drug delivery systems, and to determine response to therapy as soon as possible.

14- Current and Upcoming Trials in DCIS Active Surveillance (Nicole Look-Hong)

In the area of overtreatment, for some the approach would be how atypical ductal hyperplasia and atypical lobular hyperplasia are treated via either active surveillance or chemoprevention. There are challenges to active surveillance including limited validation of biomarkers and tools to predict risks for invasive cancer, the need to educate and gain acceptance from providers and patients, and the requirement for accurate imagining. Reviewed were 3 similar active surveillance trials (LORD lead by the Dutch, LORIS lead in the UK, COMET which is funded by PCORI) that are currently at various stages. There may be some potential difficulties in the Canadian setting for these trials including patient acceptability and enrollment, routine vacuum core biopsies, routine ER/PR status, and funding. Also reviewed was the CALGB 40903 study which is a phase 2 study now accruing in the US and which may inform the active surveillance concept with respect to the potential to use MRI.

THEME 2: Discussion summary

The existing DCIS data generated through the Ontario cohort and Oncotype Dx study were seen as strong assets. Significant opportunity to mine this existing data for a novel prognostic or potentially predictive nomogram was highlighted. Engagement with strong statistical teams in Hamilton and elsewhere was suggested.

THEME 3- ANTHRACYCLINE/TAXANE RESISTANCE IN BREAST CANCER (Moderator: John Bartlett)

15- Predicting Responsiveness to Chemotherapy. Reality or a Pipe Dream (Mark Levine)

A brief history of adjuvant chemotherapy trials over the last 40 years was provided, including anthracycline, paclitaxel, and targeting HER2. This included a review of current chemotherapy regimens that are based on underlying risk (DDACT, FECD, TAC, TC, AC, CMF, etc.). An OICR-funded project found that in Ontario FECD is the most common regimen followed by ACT. The pressing need for precision medicine was illustrated via an examination of breast cancer patients whose data were linked to administrative databases and which showed a striking number of ER visits; at least 1 visit per patient on average. The major toxicity issues were reviewed, and the fact that treatment decisions are being guided by population level data indicates that treatment is somewhat odds-/chances-based. More research on rational approaches is required - both to tailor chemotherapy to risk as well as response to treatment.

16- Novel Targets for Chemorefractory Breast Cancer (Melanie Spears)

There are risks associated with all chemotherapies and there is a critical need to better identify these risks that have traditionally been hampered by a lack of: clinically-validated biomarkers, targeted conventional therapies due to lack of understanding about key events/pathways, understanding of which patients will respond to which treatments. Data from clinical trials have shed light to better understand treatments for patients including work on the genomics of anthracycline biomarkers. This work has been coupled with functional analysis and testing in preclinical cell lines. Interim investigations include t a potential novel therapy in collaboration with the OICR Drug Discovery Group.

17-Inhibition of Thyroid Hormone Receptor Alpha 1 (THRα1) - A Novel Treatment Strategy for Breast Cancer? (Katarzyna Jerzak)

Endocrine pathways are important in hormonally-driven breast cancer, which has led to the examination of thyroid hormone as a potential target. The THR Splice forms are variants that are very similar but have opposite effects (in short, 1 can be considered 'bad', and 2 can be considered good). In women with the THR 1 receptor, those who also expressed THR had better survival than those without THR . This v in a triple negative breast cancer cohort of 158 women. Work was performed in cell cultures to see the effect of adding T3 and T4 thyroid hormones, showing that adding T3 increased proliferation of cancer cells especially with a low dose in Luminal A cell lines. Testing previously approved and available compounds in triple negative breast cancer cell lines showed a profound effect on the proliferation of the cancer cells. This work has led them to continuing studies on THR 1 as a targ to take to a mouse xenograft model.

18-Tumor RNA Disruption as a Novel Endpoint (Amadeo Parissenti)

The clinical utility of novel biomarkers was presented especially to address the luminal patient population thought to be over treated. They have observed that chemotherapy agents can induce degradation of ribosomal RNA, observed as degradation products over time. Many drugs create this effect as doses of radiation therapy, and they have observed this phenomenon in many cell lines. They have created a measure called the RNA disruption index (RDI) that is a ratio of abnormal to normal rRNA bands on a gel, and in their screens, cells with RDI greater than 0.5 are nonviable. They initially observed this in patients and

subsequently moved to cell lines to validate and further understand. Some work was presented in breast tumor biopsies (early and mid-treatment) that indicate how RDA may identify more chemotherapy responders and non-responders compared to tumor volume measurements by calipers.

19-Triple Negative Breast Cancer: the Hamilton Health Sciences Experience (Anita Bane)

Recent findings were presented on *in silico* work done with a cohort of 1,000 breast cancer patients. Reviewed data included the triple negative breast cancer criteria as well as how genomics has identified subtypes as well as there being seven molecular subtypes. The triple negative group in particular has poor prognosis. Their goal was to identify genes associated with prognosis, overlay these on a protein interaction network and cluster it with survival. They identified seven basal-like breast cancer groups and validated these *in silico* with another cohort. They found that the 3 modules regulating good outcomes were related to the immune system (T-cell, B-cell and apoptosis). From this they utilized the pan-cancer immune profiling panel on the NanoString system in a pilot with 22 patients (10 with recurrence, 12 without) and further identified 3 subgroups based on their immune system (immune high/activated, immune moderate, and immune excluded). They are currently examining these cells and their functionality, hypothesizing that these immune subtypes could be used to target with therapy, for example with immune checkpoint inhibitors.

THEME 3: Discussion Summary

Strong evidence of biomarker development needs an integrated approach to drive forward to a clinical medicine approach. Prior to LOI, there is a need to demonstrate a clear sightline to clinical implementation – which may be some years away – but this should be the focus. For this, engaging a medical oncologist in the network would be a very strong positive.

WORKSHOP SUMMARY & NEXT STEPS (John Bartlett, Mark Levine, Eileen Rakovitch)

On behalf of his co-chairs Dr. Bartlett thanked everyone for their attendance and input and thanked the OICR staff that helped coordinate the workshop. Next steps were discussed including the need to assemble a team to prepare a structured approach for the LOI; to ensure that the proposal addresses highlights, key opportunities (scientific /capacity /training) and outputs; and to focus on unmet needs where the group can leverage pan-Ontario resources to have the biggest impact- both short- and long-term but remembering that the mission of the TRI is translational.

A summary of the workshop would be provided to participants along with next steps.

Workshop participants were advised that they should contact John Bartlett, Mark Levine, or Eileen Rakovitch with projects that they wish to see be part of the proposal.

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Thursday, February 25, 2016
8:00 a.m. – 5:00 p.m.
Location: OICR | West Tower Boardroom 5-20/21

TIME	AGENDA ITEM	PRESENTER/ MODERATOR
8:00 a.m.	**Registration and light breakfast**	
8:30 a.m.	**Background** • OICR Strategic Plan 2016-2021: Overview • Translational Research Initiatives	*Nicole Onetto*
8:45 a.m.	**Opening Remarks** • Early Breast TRI workshop and rationale for focused topics • Workshop goals and deliverables/outcomes • Funding opportunities and timeline	*Mark Levine* *John Bartlett*
9:00 a.m.	**Existing Assets from OICR Programs and Ontario** *(10 min. each)* • OCTANE • DCIS Cohort • Ontario Clinical Trial Groups: CCTG/3CTN/OCOG • Imaging (3D, MR/3D, gamma) in early breast cancer • Young Women's Program • Transformative Pathology/IMEC	*Tom Hudson* *Eileen Rakovitch* *Wendy Parulekar/ Mark Levine* *Aaron Fenster* *Kelly Metcalfe* *John Bartlett*
10:00 a.m.	**Discussion and other resources**	
10:15 a.m.	**Break**	

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10:30 a.m.	**Endocrine Refractory Luminal Breast Cancers:** *Clinical Presentations:* • Luminal breast cancer – over-treated or undertreated? Whom to treat with what and when?: Kathy Pritchard (15 min.) • De-escalating treatment for Luminal A Breast Cancer: Tim Whelan (10 min.) *Translational Presentations:* • Luminal breast cancer – from residual risk to personalized medicine: John Bartlett (15 min.) • Functional drivers in breast cancer: Azin Sayad (10 min.) • Potential role of ezrin as a novel sensitizing agent and in blocking metastasis: Victoria Hoskin/Sonal Varma (10 min.) • Lobular breast cancer: Christina Addison/Angel Arnaout (10 min.) • Prognostic importance of intratumoral T-bet-positive lymphoid cells in breast cancer: Irene Andrulis (10 min.) • Stratified Medicine Clinical Trial: Wendy Parulekar (10 min.)	*Moderator:* *Eileen Rakovitch*
12:00 p.m.	**Discussion**	
12:30 p.m.	**Lunch**	
1:00 p.m.	**DCIS – Reducing Overtreatment/Predicting Recurrence** *Clinical Presentation:* • DCIS – over treatment/under-treatment: *Eileen Rakovitch* (15 min.) *Translational Presentations:* • Developing Biomarkers for improved management of DCIS: Jane Bayani (10 min.) • DCIS OncotypeDx study: Eileen Rakovitch (10 min.) • Digital pathology to develop new predictive and prognostic biomarkers: Anne Martel (10 min.) • Imaging for surveillance of women with DCIS: Martin Yaffe (10 min.) *Clinical Trial Presentation:* • Trials in DCIS (LORIS, LORD, COMET): *Nicole Look-Hong (15 min.)*	*Moderator:* *Mark Levine*
2:10 p.m.	**Discussion**	

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2:40 p.m.	**Break**	
3:00 p.m.	**Anthracycline/Taxane Resistance in Breast Cancer** *Clinical Presentation:* Chemo-refractory breast cancer: Mark Levine (15 min.) *Translational Presentations:* • Novel targets for chemotherapy resistant breast cancer: Melanie Spears (10 min.) • Thyroid Hormone Receptor Alpha 1 (THRα1): A new target for cancer therapy?: Katarzyna Jerzak (10 min.) • Tumour RNA disruption as a novel endpoint: Amadeo Parissenti (10 min.) • Triple negative breast cancer: Anita Bane (10 min.)	*Moderator:* *John Bartlett*
3.55 p.m.	**Discussion**	
4:25 p.m.	**Workshop Summary & Next Steps**	*John Bartlett, Mark Levine, Eileen Rakovitch*
5:00 p.m.	**Adjourn**	