Canadian Cancer Society

January 2019 (i2I-19) Competition
Awarded Innovation to Impact Grants

Listed in alphabetical order by panel

I1b Gene Regulation and Cell Biology

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Identification of novel synthetic lethal therapeutic targets for BRCA1/2-defective and other homologous recombination-deficient breast and ovarian cancers

Background: The tumour suppressors BRCA1 and BRCA2 (BRCA1/2) are essential for homologous recombination (HR) mediated repair of DNA double-strand breaks (DSB) and R-loop resolution. Mutations in BRCA1/2 or defects in HR increase the risk of developing aggressive malignancies, including breast, ovarian and other cancers. For instance, women with *BRCA1*mutations frequently develop aggressive triple-negative breast cancer subtype, which has poor prognosis. While PARP inhibitors and platinum agents are used in the clinic for the therapy of BRCA1/2 cancers, associated resistance and relapse is common. Therefore, novel optimal therapeutic targets are needed for the majority of cancer patients with defects in BRCA1/2 or HR.

Overview of generated data: We have identified that two proteins involved in DSB repair, compensate for the loss of *BRCA1/2* and that their inactivation confers synthetic lethality to human BRCA1/2 mutant breast and ovarian tumours. With the support of the Innovation grant, we have made significant progress toward characterizing the phenotypes and mechanisms underlying this dependency. We have uncovered that HR-defective (HRD) tumours are hyper-dependent on specific mechanisms that restrain their level of DSBs, and that defects in these mechanisms can be lethal to these tumours. *We propose taking advantage*
of the dependence of HRD tumours on these specific mechanisms and exploit it for targeted therapy of HRD cancers.

Hypothesis: We hypothesize that the two proteins we have identified are essential for restraining genomic instability in BRCA1/2 mutant breast and ovarian cancer. We also hypothesize that the identification of novel mechanisms that exacerbate genomic instability can be exploited to kill BRCA1/2-mutant and HRD tumours.

Objectives: We will characterize the mechanisms by which loss of our identified proteins kills BRCA1/2-mutant tumours. We will also conduct a CRISPR-Cas9 screen to identify hits that promote DSBs and synthetic lethality of BRCA1/2 mutant and HRD tumours.

Aim 1- *Identify the mechanisms leading to R-loop accumulation and synthetic lethality of BRCA mutant and HRD tumours in the absence of our proteins of interest*.

Aim 2 - *Characterize the effect of the studied proteins on genome-wide R-loop dynamics in BRCA-mutant*

and HRD cancers.

Aim 3 - *Identify novel synthetic lethal targets for HRD breast and ovarian cancers using CRISPR screening.*

Methodology: In collaboration with experts in the fields of breast cancer, replication stress, chromatin modifiers and bioinformatics, we will examine the role of our two proteins of interest in genome-wide dynamics of our structures of interest in HRD breast and ovarian tumours. We will employ genomic and transcriptomic approaches including ChIP-seq, RNA-seq, and mass spectrometry/proteomic profiling approaches to gain insight into mechanisms underlying synthetic lethality of BRCA1/2 mutant and HRD tumours. *In vitro* and *in vivo* approaches will examine the impact of loss of our proteins of interest on therapies currently being used for treating BRCA1/2 mutant breast and ovarian cancers. Our CRISPR-Cas9 screen paired with an FDA-approved drug gRNA library will identify hits that exacerbate DSBs in HRD tumours, leading to their killing.

Conclusion and impact: Completion of our proposed studies will identify genes which restrain genomic instability in BRCA1/2 mutated and HRD tumours. Importantly, synthetic lethal hits for these tumours, identified using our CRISPR-Cas9 screen, may have FDA approved drugs; thereby accelerating the translation of our discoveries to cancer therapy and ultimately to patients. If there are no available FDA approved drugs or small molecule inhibitors to target the identified genes, our studies will rationalize their development to target these cancers to potentially alter standard targeted and chemotherapy regimens.

Pelletier, Laurence
Mount Sinai Hospital

A centrosome Wnt-PCP signalling axis in cancer cell motility and metastasis

Background: Centrosomes control directed cell motility, polarity and migration that is thought to be mediated by their microtubule-organizing capacity. We found that Wnt signaling drives a distinct form of non-directional cell motility that requires a key centrosome-derived module, but not microtubules nor centrosomes. Upon exosome mobilization of PCP proteins, we show that DVL2 orchestrates recruitment of a CEP192-PLK4-AURKB complex to the cell cortex where PLK4 and AURKB act redundantly to drive protrusive activity and cell motility. This is mediated by coordination of formin-dependent actin remodeling through displacement of cortically localized DAAM1 for DAAM2. Furthermore, abnormal expression of *PLK4*, *AURKB* and *DAAM1* is associated with poor outcome in breast and bladder cancer. Thus, a centrosomal module plays an atypical function in Wnt signaling and actin nucleation that is critical for cancer cell motility and is associated with more aggressive cancers. These studies have broad implications in how contextual signaling can control distinct modes of cell migration. Here, we will use proteomics, advanced imaging methods, and animal models to gain a spatiotemporal and mechanistic understanding of this intricate signalling axis in motility and breast cancer initiation and progression.

AIM1: Spatiotemporal monitoring of exosome mobilization and signaling in breast cancer cell migration. We will investigate, using biosensors and next-generation imaging the dynamic properties of this novel signaling axis. We will investigate early time point in exosome response by monitoring their uptake, modification and cortical delivery to initiate protrusion formation. We will then monitor, with high spatiotemporal resolution, the recruitment of the CEP192/PLK4/AURKB module to the cell cortex and determine how it controls the handover of DAAM1 for DAAM2. Novel factors identified in Aim2 will also be studied. This work will significantly expand our understanding of how this pathway is regulated in both

space and time.

AIM2: Deciphering the molecular mechanisms underpinning the function of the centrosome Wnt-PCP signaling axis. To further delineate the molecular determinants of this signaling axis, we will use next-generation proximity interaction mapping (BioID2 and TurboID) and detailed phenotypic profiling to identify new pathway components. We will build on exciting preliminary data and focus our initial efforts on the identification and characterization of PLK4 and AURKB substrates and reveal how the activity of this pathway is regulated through ubiquitylation by the SCF complex and the HECT-E3 ligase SMURF1. This aim will evolve our understanding of this pathway, illuminate how it is regulated through post-translational modifications and provide insight into the dynamic and *in vivo* studies in *Aim1* and *Aim3*.

AIM3: Development of preclinical models to probe how modulating the activity of this pathway affects metastatic potential of breast cancer. We will use our current understanding of this pathway to deploy preclinical mouse models to ascertain if upregulating or downregulating pathway components alters metastatic capacity of breast cancer. We will use orthotopic models developed by co-applicant Wrana to investigate how exosome mobilization in breast cancer cells can lead to metastasis through activation of this pathway. In addition, we will deploy novel, intraductal mammary gland injections and classic genetic models of breast cancer components of this pathway (and novel ones identified in Aim2) under native immune/stromal contexts. Together, these lines of investigation will highlight how the centrosome Wnt-PCP signalling axis differentially interacts with multiple tumourigenic initiating events.

Summation: The work proposed in this application will generate much needed molecular insights into the role of this novel signaling axis in the control of cancer cell motility in response to extracellular cue and in the maintenance of cell polarity and tissue homeostasis. Critically, our work will illuminate key modules that can be targeted for the development of next-generation therapeutics in the treatment of breast cancer.

Postovit, Lynne-Marie
University of Alberta

Plasticity and the breast tumour microenvironment

The tumour microenvironment (TME), consisting of stromal cell types including fibroblasts, endothelial, immune and mesenchymal stromal cells (MSC), is an important mediator of breast cancer progression. Breast cancers regulate the composition of the TME by secreting a multitude of factors; however, mechanisms governing the dynamic reciprocity between breast cancer and TME components are largely unknown. NODAL, an embryonic morphogen belonging to the Transforming Growth Factor-beta (TGF-β) superfamily, is clinically associated with breast cancer progression and we and others have found that NODAL sustains breast cancer stem cells (BCSC) and promotes tumour growth, metastasis and vascularization. The extent to which NODAL may alter cells in the TME is not however known. In completing the aims of our previous grant we made two interesting observations that caused us to posit that NODAL may direct phenotypes in stromal cells: 1) NODAL expression emerges at the tumour-stromal interface as breast cancers progress from Ductal Carcinoma *In Situ* (DCIS) to Invasive Ductal Carcinoma (IDC); and 2) Areas of NODAL expression are associated with increased numbers of cancer activated fibroblasts (CAF) in the stroma, marked by alpha smooth muscle actin (aSMA). Recent studies have shown that certain breast cancer cells secrete factors that induce CAF phenotypes, and that this interaction establishes a niche that enables BCSC propagation and tumour progression. Our preliminary studies have

determined that NODAL directly activates primary human fibroblast toward a CAF-like phenotype and that it also signals in an autocrine manner to regulate the levels of chemokines (e.g. CXCL1), growth factors (e.g. Platelet-Derived Growth Factor A) and cytokines (e.g. Interleukin 6) in breast cancer cells. Hence, NODAL may enable BCSCs to communicate with cells in the TME via both direct and indirect mechanisms. *Based on this, we propose that NODAL has a hitherto unappreciated role as a dynamic and apical regulator of breast cancer TME components. We specifically hypothesize that NODAL increases CAFs, which subsequently support BCSC propagation and therapy resistance.* This will be tested in the following concurrent and interrelated aims:

1.To characterize the impact of NODAL on stromal fibroblasts: Studies will combine RNA, ATAC and SMAD2 ChIP sequencing with quantitative proteomics in order to fully characterize NODAL-induced CAFs. Findings will be validated using patient tissues.

2. To determine the role of NODAL in shaping the breast cancer secretome: Studies will use pairs of breast cancer cell lines and cells derived from PDX to determine the extent to which NODAL regulates the breast cancer secretome.

3. To determine the effects of targeting the NODAL-associated niche: Studies will determine whether NODAL-induced CAFs support BCSC phenotypes and chemoresistance to first line therapies. Patient derived xenograft models will also be used to determine whether targeting stromal propagators can increase the efficacy of anti-NODAL approaches and/or first line chemotherapy. These studies will initially focus on the role of IL6.

Targeting NODAL holds promise for the treatment of breast cancer as it would simultaneously affect cancer cells and the stromal compartment; however, such strategies may be limited in efficacy due to heterogeneous expression levels, and the ability of NODAL to instigate a niche that would support BCSC propagation and therapy resistance; even once NODAL has been removed. By illuminating factors in the niche, this grant may reveal targets that may be used to improve outcomes in patients by mitigating BCSC-supporting factors downstream of NODAL.

Sabourin, Luc
Ottawa Hospital Research Institute

Transcriptional reprogramming by Akt-Sox9 in HER2+ SLK-deficient breast cancer

Approximately 90% of all cancer deaths arise from the metastatic spread of the primary tumours to distant sites. We have previously shown that SLK is a critical signaling hub that integrates haptotactic and chemotactic cues to regulate focal adhesion turnover. Supporting a role for SLK in cell migration and invasion, we have recently shown that SLK plays a scaffolding role in TGFβ-induced EMT of mammary epithelium.

Our initial hypothesis was that the deletion of SLK would suppress or delay tumour progression in a HER2+ animal model. Surprisingly, SLK deletion in the mammary epithelium of MMTV-Neu mice results in the more rapid development of mammary tumours. To investigate the mechanisms whereby SLK deletion enhances tumour growth, we have established SLK-deficient ErbB2+ tumour cells from primary tumours isolated from MMTV-Neu mice. Biochemical analysis shows that SLK deletion results in the high expression of markers present in triple negative breast cancer (TBNC), suggesting that the deletion of SLK induce a transcriptional reprogramming in HER2+ tumours. Chromatin IP and transcriptional assays have

uncovered a novel pathway leading to transcriptional reprogramming of HER2+ tumours into triple negative like breast cancers. Our hypothesis is that the deletion of SLK and a critical regulator of this pathway will result in a marked delay or inhibition of tumourigenesis in MMTV-Neu mice. We will further characterize the role of this system using genetic knock outs and transgenic mice. Following gene deletion, the mice will be surveyed for tumour initiation and progression. Cell lines derived from the various genotypes will also be tested for metastatic spread in vivo. We will further explore the mechanisms of genetic reprogramming using transcription assays and chromatin analysis of the target gene involved. This system provides a unique opportunity to test the role of specific factors in the progression of TNBC and to assess potential targeted therapies for this breast cancer subtype.

Yamanaka, Yojiro
McGill University

Developing detection strategies and elucidating mechanisms controlling peritoneal metastasis of ovarian cancer

Ovarian cancer is the fifth leading cause of cancer-related deaths in women. The vast majority of ovarian cancers are epithelial ovarian cancer and high-grade serous carcinoma (HGSC) is the most common and lethal type of this disease. In the last 10 years, it has been recognized that the cell of origin of most HGSCs is within the fallopian tube epithelium, instead of the ovarian surface epithelium. However, the early events in disease progression remain poorly defined, largely due to the fact that HGSC is usually diagnosed at advanced stages and there is a lack of proper animal models recapitulating human disease progression.

During the previous CCS funding period, we have developed a unique strategy for generating mouse ovarian cancer models, which is a combination of *in vivo* fallopian tube electroporation, Cre-mediated lineage tracing and CRISPR-mediated gene modifications. As proof-of-principle, we generated a highly metastatic HGSC model by targeting four tumour suppressor genes, *Lkb1, Brca1, Tp53* and *Pten.* Targeting these four genes in female mice generated ovarian tumours within 5 months after electroporation and peritoneal metastasis within 6 months. After 6 months, ascites formation was observed in two thirds of tumour bearing female mice. Interestingly, similar to human ovarian cancer patients, we observed two metastatic patterns, termed miliary and non-miliary metastases. Although peritoneal metastasis is the biggest challenge in ovarian cancer, its etiology and early pathophysiology are poorly understood. Our hypothesis is that the microenvironment in the peritoneum is an important factor in ovarian cancer disease progression. Using our unique mouse ovarian cancer model, we will develop three aims in this proposal;

Aim1: to elucidate what regulates the two peritoneal metastatic patterns, miliary and non-miliary.

Aim2: to understand the healthy and malignant peritoneal conditions and investigate cancer-host interactions in the peritoneum.

Aim3: to develop new detection strategies for peritoneal micrometastases.

We believe that our analyses will provide new insights into the mechanisms of peritoneal metastasis. Understanding normal and malignant peritoneal environment is essential for developing better treatment options and new drugs targeting survival of the exfoliated cells before their integration into the peritoneum. Making undetectable cancer cells visible will be highly beneficial for chemotherapy evaluation

and disease control, and has a potential to be used for therapeutic strategies.

I2 Imaging and Technology Development

Reilly, Raymond
University of Toronto

Radiation nanomedicine for local treatment of metastases from triple-negative breast cancer

RATIONALE: We propose an innovative local radiation treatment for limited metastases [oligometastases (OMETS)] in patients with triple-negative breast cancer (TNBC) conceived in our CBCF grant (NanoRad). NanoRad consists of 5 nm gold nanoparticles (AuNPs) labeled with the 2 mm range β-emitter, 177Lu (Eβmax=0.5 MeV) or 12 mm range β-emitter, 90Y (Eβmax=2.28 MeV) incorporated into a calcium alginate seed (nanodepot) with dimensions identical to a conventional brachytherapy seed enabling intratumoural (i.t.) implantation by permanent brachytherapy seed (PSI) techniques. Preliminary studies revealed that i.t. administered NanoRad incorporating 177Lu- or 90Y-AuNPs arrested the growth of murine 4T1 or human MDA-MB-468 TNBC tumours in mice with no normal tissue toxicity. Moreover, treatment of a primary 4T1 tumour with NanoRad caused an abscopal effect that inhibited the growth of a secondary tumour outside the local radiation field. We now propose to study NanoRad for treatment of TNBC tumours and for causing an abscopal effect on the growth of distant metastases when combined with anti-PDL-1 and anti-CTLA-4 immunotherapy.

HYPOTHESIS: We hypothesize that local i.t. implantation of NanoRad will be effective for treatment of TNBC tumours in mice with minimal normal tissue toxicity and combined with anti-PDL-1 and anti-CTLA-4 antibodies, will cause an abscopal effect that inhibits metastases outside the local radiation field.

AIMS:
1.To compare the effectiveness and normal tissue toxicity of NanoRad labeled with 90Y or 177Lu for local treatment of TNBC tumours in immunocompetent mice.
2.To study if local treatment of a TNBC tumour with NanoRad will cause an abscopal effect when combined with anti-PDL-1 and CTLA-4 immunotherapy that will slow the growth of a distant (secondary) tumour outside the local radiation field.
3.To compare the potency of NanoRad and X-radiation for local treatment of tumours and for causing an abscopal effect on distant tumours or metastases when combined with immune checkpoint inhibition.

EXPERIMENTAL DESIGN

Aim 1. NanoRad incorporating 177Lu- or 90Y-AuNPs in a nanodepot will be implanted i.t. in Balb/c mice with 4T1 murine mammary carcinoma tumours in the mammary fat pad (MFP) or in humanized NCG (huNCG) mice with luciferase-transfected MDA-MB-231/Luc tumours. The No Observable Adverse Effect Level (NOAEL) will be determined in preliminary normal tissue toxicity studies that assess the effects of NanoRad on body weight, complete blood cell counts (CBC) and serum alanine aminotransferase (ALT) and creatinine. NanoRad will be administered at the NOAEL and tumour growth and the survival of mice assessed. Control mice will receive a nanodepot with unlabeled AuNPs, an "empty' nanodepot or no treatment. Radiation doses to tumours and normal organs will be estimated by biodistribution studies and dose maps constructed to evaluate intratumoural dose distribution.

Aim 2. Balb/c mice with 4T1 or HuNCG mice with MDA-MB-231/Luc tumours in the MFP will be treated

locally with NanoRad alone or combined with anti-PDL-1 or anti-CTLA-4 antibodies and the effects on the growth of distant metastases in the lungs and liver determined. Histological analysis of the lungs and liver will be performed in Balb/c mice while bioluminescence imaging will be used for HuNCG mice to detect an abscopal effect on metastases from MDA-MB-231/Luc tumours. The survival of treated and control mice will also be compared.

Aim 3. The potency of NanoRad alone or combined with immune checkpoint inhibition for local tumour treatment and for causing an abscopal effect on distant metastases will be compared with that of focused external X-radiation (4 Gy daily for 5 d) in Balb/c mice with 4T1 tumours or HuNCG mice with MDA-MB-231/Luc tumours. The optimal form of radiolabeled AuNPs and immune checkpoint inhibition will be used for these studies.

SIGNIFICANCE OF THE RESEARCH: If successful, the proposed research may lead to a new local radiation treatment for OMETS in patients with TNBC that could improve their long-term outcome. Our team will design and conduct a Phase 1 clinical trial of NanoRad if the proposed research proves successful.

Reznik, Alla
Lakehead University

Incorporating advanced capabilities in best-in-class PEM system for improved clinical outcomes

Although x-ray mammography remains the gold standard of breast cancer screening, there is increasing awareness of large cohort of women for whom anatomical x-ray imaging has reduced sensitivity. This includes women with dense breasts and women with known intermediate and high-risk factors for breast cancer (i.e. have a family history of cancer; carry BRCA1/BRCA2 genetic mutations causing susceptibility to early-onset breast cancer; or use hormone (estrogen and progestin) therapy). Moreover, women undergoing mammography must be given notification of their breast density so that those with dense breasts would be aware of the implications, and could pursue supplemental screening beyond mammography. Legislation to this end exists in some states and has fueled demand for supplemental breast cancer screening.

Our patent-pending technology has enabled the development of a Positron Emission Mammography (PEM) imaging system – a molecular breast imaging tool with improved specificity and sensitivity for breast cancer detection in both diagnostic and high-risk screening settings, alleviating the uncertainty from anatomical breast imaging.

Our innovation improves (1) spatial and energy resolution in comparison with whole-body PET, and (2) sensitivity and deep tumour detectability in comparison with available breast-dedicated nuclear medicine imagers, while simultaneously allowing for a significant reduction of the radiation dose typically associated with PEM imaging. As a result, the proposed PEM technology can be used as (1) a supplemental technique for breast cancer detection for cases when x-ray examination is suspicious but inconclusive; (2) an integral part of the surveillance protocol for women at high and intermediate lifetime risk of breast cancer for whom conventional x-ray mammography is inefficient because of the radiologically dense breast tissue, and (3) as a tool to monitor early responses to chemotherapy. Although chemotherapy is the standard of care for many patients (with chemotherapy being increasingly offered as an alternative to lumpectomy for better outcomes), there is currently no efficient way to monitor early tumour response. In addition, the best-in-class imaging performance of our PEM system will change physicians' ability to characterize the aggressiveness of pre-invasive breast cancers as candidates for stronger therapy, thus

avoiding the more expensive treatment of patients with potentially metastatic disease.

The first clinical prototype of the PEM system is assembled, its imaging performance has been characterized in a laboratory setting, and it is now ready for the proposed clinical trials. In parallel, the proposed project will add advanced capabilities to the current PEM prototype, using data from our pilot studies as a guide. The next-generation device will have a better dynamic range to allow for a wide range of clinical tasks (ranging from low-dose screening to high-dose treatment follow-up) and will be tested in multiple clinical centres in both Canada and the United States to prepare data to support widespread deployment. Moreover, we will investigate the performance of novel detector components that would lower the cost associated with PEM imaging.

Overall, our invention addresses important unmet needs in the improvement of breast cancer diagnosis for large cohort of patients, and will provide clinical and economic benefits (through earlier and more effective treatment) that will result in improved breast cancer survival rates.

I3 Immunology, Signalling and Stem Cells

Mossman, Karen
McMaster University

Evaluation of the role of B cells in oncolytic virus therapy that sensitizes triple negative breast cancer to checkpoint blockade immunotherapy

While great strides have been made in treating some forms of breast cancer using targeted therapies and in treating "hot immune" cancers such as lung and melanoma with immunotherapy, little progress has been made in treating triple negative breast cancer (TNBC), which by definition does not express receptors that can be targeted and which is predominantly "immune cold". While the importance of T cells in predicting clinical outcomes is well established, and immunotherapies such as checkpoint blockade have been developed to enhance and sustain effector T cell responses, the role of B cells remains controversial and poorly understood. Moreover, while the recruitment of tumour infiltrating lymphocytes (TILs) and formation of tertiary lymphoid structures (TLSs) within untreated tumours generally serve as prognostic indicators of survival, little to nothing is known about the role of therapies such as oncolytic viruses in increasing TILs and TLSs. In our previous CBCF grant, we found that addition of oncolytic HSV-1 (oHSV-1) to a single administration of a clinical chemotherapy cocktail (FEC) increased survival of mice bearing TNBC tumours and sensitized mice to treatment with checkpoint immunotherapy. Following mechanistic studies, we identified a potential role for B cells and observed formation of TLS-like structures.

Based on these findings, the goal of our i2I grant is to extend findings from our CBCF grant to investigate how the addition of oHSV-1 to clinical chemotherapy regimes sensitizes TNBC tumours to checkpoint immunotherapy. In particular, we will test the hypothesis that B cells are required for oncolytic virus mediated immunotherapy through TILs and TLS formation. We will use new findings to strategically develop clinically useful therapy strategies to generate broadly acting anti-tumour responses that minimize relapse and metastatic disease.

Using the E0771 TNBC model where we have engineered cells to express the SIY T cell epitope to facilitate immune analyses, we propose the following:

Aim 1: Determine if B cells are required for oHSV-1+FEC therapy efficacy. Here, we will treat E0771-SIY

tumour bearing mice with a control isotype or anti-CD20 B cell depleting antibody. Mice will be monitored for tumour growth and survival. In a subsequent experiment, we will harvest tumours at various times post-treatment and perform cytokine analysis on tumour homogenates and quantitative immunohistochemistry on tumour sections to evaluate TILs and TLSs.

Aim 2: Develop oHSV-1 vectors with enhanced immunogenic properties. In this aim, we will engineer oHSV-1 to express cytokines such as CXCL13 that preliminary and new findings identify as key immune modulators that correlate with treatment efficacy. We will determine if these new vectors better synergize with clinical chemotherapies or can eliminate the usage of chemotherapies. Finally, we will determine if optimized vectors can induce a broad anti-tumour immune response to overcome issues of relapse due to antigen loss.

Aim 3: Evaluate correlates of protection in metastatic and spontaneous breast cancer models. Here, we will evaluate our best therapy combination in a metastatic E0771 model and in autochthonous tumours to evaluate the use of our therapy under clinically important conditions.

From this study, we expect to derive new and important information on the role of B cells, TILs and TLSs in oncolytic virus mediated immunotherapy for TNBC, for which virtually nothing is known. While the focus is on TNBC, findings will likely be relevant to multiple cancer types, particularly those that are "immune cold" and offer the greatest challenge within the clinic. A further impact is the development of rationally designed vector to increase therapeutic efficacy. We will leverage knowledge and resources generated by colleagues within the Canadian Oncolytic Virus Consortium to maximize the extent and impact of our findings.

Rafei, Moutih
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Defining the role of interleukin-21 in primary lymphatic organs: towards optimal stem cell transplantation

PROBLEM TO BE INVESTIGATED
Hematopoietic stem cell (**HSC**) transplantation (**HSCT**) is a curative therapy for lympho-hematopoietic cancers. Since T cells recover slowly (if any) following HSCT, treated patients are susceptible to infections and emergence of primary/secondary tumours. The functional recovery of the T-lineage relies on *de novo* generation of naive T cells from the thymus. For this to occur, three conditions must be fulfilled: i) efficient HSC engraftment, ii) active thymic seeding by bone marrow (BM)-derived progenitor cells, and iii) a thymic architecture conductive to progenitors migration/differentiation. We have recently established a role for interleukin (IL)-21 in stimulating thymopoiesis in aged mice and demonstrated that their rejuvenated T-cell pool improved both anti-tumoural responses and survival following vaccination. We further demonstrated that IL-21 depends on endogenous IL-7 to induce *de novo* T-cell development in mice, whereas administering high IL-21 doses blocks thymopoiesis through an unknown mechanism. We further observed that IL-21 displays a dual effect on both BM and thymic compartments, whereas thymic epithelial cell regeneration is impaired in IL-21 receptor (IL-21R) deficient recipient mice. Collectively, these observations demonstrate that: i) the IL-21 mode of action remains ill-defined in the field of thymopoiesis, and ii) host-derived intrathymic stromal cells play a central role in enhancing thymopoiesis post-HSCT. We therefore hypothesize that IL-21 affects both the BM and thymic stromal compartments during thymopoiesis post-HSCT. To validate this hypothesis, further investigations are required to elucidate the impact of IL-21 on primary lymphatic tissues (BM and thymus) in order to decipher its mechanism of action and use this knowledge to develop optimal IL-21-based therapies.

OBJECTIVES & METHODOLOGIES

IL-21 overexpression was previously reported to increase the pool of HSCs in wild-type mice. However, this study did not provide mechanistic insights nor identified any non-hematopoietic responsive population(s) residing in the thymic stroma. Since our studies unveiled an IL-21-based pharmacological effect on the BM and thymic compartments, a three-step approach will be followed to interrogate the mechanism of action of IL-21. Thymic reconstitution is mainly limited by the number of migrating progenitors. Therefore, we will first analyse whether IL-21 administration following HSCT affects thymic settling by assessing the magnitude of BM progenitor migration to the thymus, the nature of the migrating progenitors and whether IL-21 treatment saturates the thymic stromal niche. The dependence of IL-21 on IL-7 will be investigated as well. Second, we will pinpoint the thymic stromal population(s) expressing the IL-21R prior to characterizing the biological/biochemical responses of all IL-21-responsive cells (HSCs, thymocytes and all identified stromal cells). Finally, IL-21 supports thymopoiesis in a dose-specific manner. This suggests a new level of unexpected thymopoiesis regulation. Therefore, we will investigate the impact of administering high IL-21 dose on RORγt, γc receptor expression and IL-7Rα modulation during thymocyte development.

SIGNIFICANCE TO CANCER

Besides providing mechanistic insights, this proposal will reveal whether IL-21 exert beneficial effects mostly on the BM and/or thymic compartment. Unveiling the importance of IL-21 in primary lymphoid tissues will lead to the development of strategies, which will certainly localize the cytokine to where it is mostly needed in order to improve engraftment while diminishing all cytoablation-associated complications.

I4 Novel Therapeutics

Chan, Warren
University of Toronto

Artificially increased nanoparticle delivery efficiency for solid tumours

Nanoparticles have been extensively developed as drug carriers for the treatment of cancer but few of them have advanced to clinical use. The main problem is that less than 0.7% (median) of administered nanoparticles are delivered into solid tumours in mouse models. If the nanoparticles do not get delivered to the tumour, they cannot function as designed. In mouse, killing of tumours can be achieved by increasing the amount of nanoparticles (to compensate for the low delivery efficiency) but human patients are much bigger and require significantly more injected nanoparticles (by mass comparison). An increase in the amount of therapeutic nanoparticle injection for human use would lead to problems with manufacturing, cost, and toxicity. With the 2-year CCS innovation grant, we addressed this problem head-on. We developed a technique that can increase the delivery efficiency of nanoparticles to the solid tumour. This method led to enhanced therapeutic outcome in 4T1 mouse tumour models. Our i2I grant application is focused on optimizing the pre-clinical parameters (e.g., pharmacokinetics, biodistribution, tumour delivery efficiency and toxicity) with respect to the parameters of this technique. The results of these studies can guide our design of phase I clinical trial. This development should accelerate the clinical translation of cancer-fighting nanoparticles, which can lead to better therapeutic outcome and reduce side effects in patients, and fulfil the promise of nanomedicine research. Our findings are also important from an academic perspective as the paradigm of improving delivery could be

applied to the design of nanoparticles for other diseases.

Egan, Sean
The Hospital for Sick Children

Modelling hormone resistant Invasive lobular breast cancer as a platform for development of novel treatment strategies

Problem to be investigated: Invasive Lobular Carcinoma (ILC) of the breast is an estrogen receptor positive (ER+) disease, representing ~10% of Breast Cancer (BC) cases. In contrast to other forms of BC, the slope of survival for ILC never flattens out. By approximately ten years post diagnosis, ILC patients show worse survival than patients with many other forms. Death from ILC is associated with recurrent, therapy resistant and metastatic disease. Recent genomic analysis has identified dominant mutations (such as Y537S) in the estrogen receptor alpha gene (*ESR1*) as a major driver of progression from benign ILC at diagnosis to deadly, recurrent disease. While ER+BC cells expressing these mutants are resistant to standard hormone therapies such as tamoxifen, they retain sensitivity to a distinct ER inhibitor Bazedoxifene, which is well tolerated in humans. Also, Bazedoxifene can synergize with Palbociclib, a Cdk4/6 (cell cycle) inhibitor to block the growth of ER+BCs.

Cancer therapy has been revolutionized by the realization that evasion of the immune system may represent an essential step in progression. Some diseases including lung cancer and malignant melanoma, which were almost universally lethal are now being successfully treated with immune-checkpoint blockade (ICB) therapy or combination therapy targeting oncogenic signaling proteins together with immune-checkpoint regulators. As a group, BCs have relatively few mutations and do not appear to engage the immune system in the same way as high mutational burden tumours. Despite this, there is increasing evidence that therapies like Palbociclib can increase immune surveillance. In addition, a subset of ILC, the Immune Related form (IR-ILC), show evidence of immune infiltration as well as suppression and exhaustion of anti-tumour immunity.

Some models have been established for *ESR1*mutant and metastatic BC, but these are based on injection of human BC cells into immunocompromised mice. As a result, the potential for identification of immune checkpoint and combination therapy is compromised. We have developed a mouse model for IR-ILC and a distinct transgenic line which can be programed to express the mouse version of *ESR1Y537S* (*Esr1Y541S*). These strains will be intercrossed to yield an immune competent model for recurrent ILC, which can then be used for the development of immune-based combination therapy.

Objectives and Methods: In this project, we will i) define how an activated ESR1 mutant promotes progression of lobular BC, ii) how it effects immune surveillance in tumour bearing animals, and iii) how mutant receptors, the cell cycle and the immune system can be targeted for effective therapy against otherwise lethal and metastatic disease. These objectives will be pursued through the following specific aims:

1) To determine how dominant alleles of *ESR1*promote progression, metastasis and immune evasion in ILC, we will cross our new transgenic model for ectopic Esr1Y541S to IR-ILC model mice. We will then test for enhanced tumour initiation, growth, invasion, metastasis and immune evasion in the resulting model for recurrent disease.

2) We will create a Luciferase expressing version of this model as a platform to test how Bazedoxifene and Palbociclib affect tumour growth, dissemination as well as immune surveillance using quantitative bioluminescence, CyTOF and IMC. Results from this analysis will be used to identify the best candidate ICB therapy to synergize for elimination of recurrent disease.

Significance: Through this project, we will identify combination therapy focused on mutant *Esr1*, CDK4/6 and reactivation of an anti-tumour immune response. Based on data from our project, we will engage clinical collaborators in Toronto to provide such therapy on a compassion basis. This approach can represent a stepping stone to inspire larger clinical trials to treat recurrent hormone therapy resistant and metastatic ILC. As ILC represents ~10% of all BC cases, results from this study will have the potentially to positively affect the lives of thousands of Canadian women.

Jiang, Xiaoyan
BC Cancer, part of the Provincial Health Services Authority

A novel treatment approach to overcome TKI resistance in BCR-ABL+ human leukemia

Treatment of BCR-ABL+ human leukemia, especially for early phase CML patients, has been greatly improved by ABL tyrosine kinase inhibitor (TKIs) therapies. However, very few TKIs completely eradiate the leukemic clone, and early relapses and acquired drug resistance remain problems. This is mainly due to both intrinsic and acquired resistance properties of leukemic stem/progenitor cells. We and others have demonstrated that leukemic stem cells (LSCs), including primitive *quiescent* cells, are genetically unstable, are less responsive to drug treatments and are a critical target population for TKI resistance. Evidence also suggests protection within the bone marrow (BM) microenvironment, by stromal cells that surround LSCs, as a potential mechanism of disease persistence on TKI therapy. Using RNA-seq analysis, we discovered that integrin-linked kinase (ILK), a serine/threonine kinase, is highly upregulated in CML LSCs and that TKIs in combination with a pre-clinically validated ILK inhibitor (QLT0267) inhibit growth of TKI-nonresponder cells. In 2014, we received a 2-year Innovation Grant to investigate whether combined suppression of BCR-ABL and ILK activities, to target both leukemic stem/progenitor cells and their associated BM niche, might present a new therapeutic approach to overcome TKI-resistant CML. Indeed, we have since extensively demonstrated that knockdown of ILK expression by lentiviral shRNAs or inhibition of ILK activity, by the ILK inhibitor QLT0267, in LSCs and TKI-resistant cells significantly impairs their survival and sensitizes them to TKI treatments, while sparing healthy stem/progenitor cells, *in vitro* and in pre-clinical xenograft models. These results strongly support the notion that targeting both BCR-ABL-dependent and independent survival pathways effectively eliminate TKI-nonresponder cells, which is not achievable by TKI alone. Strikingly, QLT0267 specifically targets *quiescent* LSCs. We have further demonstrated, by RNA-seq analysis, that inhibition of ILK activity in *quiescent* LSCs uniquely downregulates mitochondrial oxidative phosphorylation (OXPHOS) and reactive oxygen species (ROS) networks and that synergistic loss of gene expression in the OXPHOS network is also observed in the same cells treated with QLT0267 and a TKI. These new, exciting findings offer a solid basis to functionally pinpoint how inhibition of ILK-mediated metabolic networks selectively targets drug-resistant, dormant LSCs, which will provide molecular insights into novel combination treatment strategies for improved treatments for CML, particularly for a subset of currently fatal leukemias.

In this Innovation to Impact grant, we hypothesize that inhibition of ILK-mediated survival and mitochondrial networks, to target specific vulnerabilities and metabolic dependencies of LSCs, sensitizes both *quiescent and dividing* LSCs and drug-resistant cells to standard targeted therapies and that the

combined suppression of ILK and mitochondria activities, by ILK/OXPHOS inhibitors in combination with TKIs, may represent a novel therapeutic approach to overcome drug-resistance. We will undertake the following studies: (1) Identify metabolic biomarkers and therapeutic targets by validation of differentially expressed genes in LSCs and drug-resistant cells. (2) Assess biological effects of genetic or pharmacological inhibition of ILK and OXPHOS on key metabolic processes *in vitro*. (3) Investigate the efficacy of ILK/OXPHOS inhibitors in sensitizing LSCs to TKIs and blocking leukemia development *in vivo*. This translational study will provide new functional and molecular insights into how inhibition of ILK-mediated metabolic networks selectively targets drug-resistant, dormant LSCs, which will lead to more effective treatment strategies for management of drug-resistant CML/ALL and other cancers, and ultimately to improved quality of life and reduced healthcare costs.

Khokha, Rama
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Targeting cell-of-origin in the high-risk breast for molecular interception

Despite our increasing ability to pre-emptively identify women at high risk of developing breast cancer, options remain limited both with respect to personalized risk assessment and molecular-guided treatment of aggressive cancers. It is now generally accepted that stem and progenitor cells are the putative cell(s)-of-origin in breast cancer, thus targeting these precursors is a promising strategy to combat disease. We have already completed multi-modal molecular profiling of FACS purified mammary populations enriched in stem/progenitors in the mouse as well as normal human breast epithelial proteomes. Now our efforts in the i2I program centre on leveraging our unique collection of >60 primary breast specimens to focus on high-risk patients. Our objectives are: 1) to develop a new personalized method for assessing high-risk breast tissue; and 2) to use our OMICs-driven high-risk drug testing platform to pinpoint new therapeutic strategies. We envision our work will have clinical utility and impact cancer burden, especially for high-risk women, by informing breast cancer risk and by transforming breast cancer therapy.

Preneoplastic breast tissue from BRCA1 mutation carriers contains an abnormally expanded number of luminal progenitors, yet there are no baseline 'reference points' for human breast composition or clonogenicity. Our working hypothesis is that phenotypic profiling by flow cytometry coupled with clonogenic assays will enable patient-specific tissue assessment. We anticipate distinctions will emerge between normal and high-risk patients, which may serve as surrogate indicators of risk. Therefore, our first objectives is to phenotypically and functionally characterize high-risk breast specimens in a systematic manner, which to our knowledge has not been previously performed. Specifically, we will generate baseline measurements for progenitor capacity using specimens from normal and high-risk groups, taking patient heterogeneity into account as well as progenitor colony type distribution. This reference index for the breadth of progenitor capacity will be the first step towards the high-risk, high reward endeavour of developing a standardized, personalized assay that assesses clonogenicity as a surrogate indicator for breast cancer risk. Additionally, our analysis of high-risk patient material will reveal novel markers with clinical utility. In parallel to analysing breast epithelium, we will also enumerate and analyze stromal cells in large cohorts of patients as our pilot data has revealed an expansion of the stromal compartment in BRCA patients.

Our OMICs discovery efforts combined proteomics with GSEA analysis to uncover new features specific to each mammary lineage that can be therapeutically targeted. Our working hypothesis is that cell lineage dictates drug vulnerability and combining drugs with distinct lineage targets will enhance therapeutic

effectiveness in the cancer setting. Having identified classes of drugs that selectively target a single mammary lineage or stem/progenitor pool, our second objective is to develop new rationalized combinations and achieve better clinical outcomes. Leveraging knowledge from our datasets, we have prioritized combinations of FDA approved drugs that greatly potentiate existing monotherapy inhibitors to limit normal clonogenicity. As a first step, we will examine if these therapeutic vulnerabilities are also retained in breast cancer cells. The most promising combinations will be evaluated in our preclinical platform of breast cancer cell lines and patient-derived xenografts (PDXs), which represent distinct breast cancer subtypes. Additionally, we have constructed proteome-based bioinformatic signatures for basal and luminal progenitor subpopulations and these correlate with known drug sensitivities. We will apply these proteome signatures to known BRCA1/2 PDX RNAseq expression profiles to pinpoint PDXs most likely to respond to our rationalized drugs, individually and in combination. Altogether, our work will provide strong rationale to move novel and targeted combinations towards clinical trials in the near future to ultimately impact breast cancer therapy.

Liu, Fei-Fei
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Developing an anti-fibrosis treatment to improve cancer survivorship

Detailed summary of problem: Within the coming decade, there will be >1M Canadian cancer patients treated with radiation. Half of these patients will develop significant radiation-induced fibrosis, leading to painful scarring and doubling the rate of subsequent surgical complications. To date, there are no effective treatments for fibrosis.

Based on the promising results from the initial Connectivity Map-based pharmacogenomics screen conducted in the Innovation Grant, transcriptional regulation of fibrosis (at gene and epigenetic levels) would be an effective approach to develop therapeutic strategies for radiation fibrosis. However, a lead compound with the maximum effectiveness and minimum toxicity would need to be first identified, and then evaluated in a clinical trials context before it can benefit cancer patients.

Objectives: The goals of this project are to identify a new drug treatment for radiation-induced skin fibrosis to reduce tissue scarring, and to evaluate the safety and efficacy of the new drug in a clinical trial for head and neck cancer patients, who are at high risk of developing radiation fibrosis.

Methods:
Aim 1: To identify lead therapeutic compounds for radiation-induced fibrosis treatment (Months 1-12): We will apply our established pharmacogenomics screening methods to search >20,000 additional small molecule drugs, investigational tool compounds, and screening library compounds for their ability to normalize the fibrotic tissue transcriptome. These drug candidates include compounds with clinical uses, known mechanisms of action, or NIH Molecular Libraries Program nomination as previously described1. The top 25 candidate compounds with greatest predicted transcriptomic effect and acceptable LD50 toxicity will proceed to *in vitro* screening. The *in vitro* screen will assess for: a) limited cytotoxicity, b) effectiveness of fibrosis reduction; and c) drug kinetics (absorption, distribution, metabolism, and excretion).

Aim 2: To evaluate lead therapeutic compounds for radiation fibrosis treatment *in vivo* (Months 12-24): From Aim 1, top performing drugs already in clinical use will be prioritized. Drugs will be evaluated to ensure no tumour promoting effects (exclusion criterion), efficacy as preventive and treatment agents,

and efficacy in treating damage from single-and multi-fractionated radiotherapy. Ultrasound elastography will be piloted as a companion imaging tool for a more comprehensive temporal and spatial assessment of the fibrosis outcome alongside traditional physical and histologic measures of skin fibrosis.

Aim 3: To deliver the lead therapeutic compound in a clinical trial for cancer patients (Months 24-36): The lead compound will be evaluated in a single-centre randomized, double-blinded, placebo-controlled Phase 2 trial to determine the efficacy of the drug. Head and neck cancer patients who have completed all of their cancer treatments will be administered the lead compound or placebo for 12 months starting 1 month after completing their radiation therapy. The primary outcome will be the reduction in the proportion of participants with clinically-diagnosed skin fibrosis at 12 months after treatment. Secondary outcomes include severity of radiation-induced skin fibrosis as measured by a skin stiffness *via* cutometry and ultrasound elastography at 6 and 12 months, and severity of radiation-induced skin fibrosis as quantified by tissue collagen, a histologic marker of fibrosis, at 12 months.

Significance to cancer research: Developing an effective treatment for fibrosis will lead to: i) decreased toxicity; ii) more effective radiation dosing (focused on tumour kill rather than limited by normal tissue tolerance); and iii) potential expansion of radiation treatment to patients who have vulnerabilities to radiation fibrosis, who are currently excluded from radiation treatments.

Meloche, Sylvain
Université de Montréal

Identification and preclinical development of small molecule inhibitors of the cancer-related ubiquitin-conjugating enzyme UBCH10

Problem to be investigated:
Similar to protein kinases, components of the UPS are often dysregulated in cancer, making them attractive drug targets. The approval by the FDA of the proteasome inhibitor bortezomib for the treatment of multiple myeloma has heralded an entirely new class of cancer drugs and validated the therapeutic potential of the UPS. Beyond the proteasome, the UPS offers multiple other potential targets for pharmacological intervention. To identify small molecules that block the UPS-mediated degradation of the tumour suppressor p21, we have screened the IRIC library of small molecules using a robust cell-based p21-Rluc reporter protein assay, resulting in the identification of 6 chemical series with confirmed activity. Initial SAR optimization of one chemotype series led to the synthesis of UM129480, which induces the accumulation of p21 and inhibits cancer cell proliferation. Using a chemical proteomic strategy, we identified the E2 ubiquitin-conjugating enzyme UBCH10 as the cellular target of UM129480. UBCH10 is the cognate E2 of the anaphase-promoting complex E3 ligase, a key regulator of the cell division cycle. It is overexpressed in many cancer cell lines and primary tumours, and is emerging as a significant prognostic marker in cancer. Genetic depletion of UBCH10 drastically reduces the proliferation of cancer cell lines, while transgenic overexpression is sufficient to induce tumour formation in mice. Importantly, high UBCH10 mRNA expression predicts adverse prognosis in a variety of solid tumours. Together, these observations provide strong rationale for targeting UBCH10 in cancer.

Objectives:
The overall objective of this proposal is to develop a first generation of small molecule inhibitors of UBCH10 with *in vivo* efficacy in preclinical models. The specific aims are: (1) to optimize the potency, efficacy and pharmaceutical properties of UM129480 and novel chemical classes of UBCH10 inhibitors; (2) to determine the mechanism of action of UBCH10 inhibitors and demonstrate their on-target activity; and

(3) to evaluate the therapeutic potential of UBCH10 inhibitors using clinically relevant human cancer cell lines and mouse models of cancer.

Methodology:
In the first aim, we will undertake HTL chemistry efforts to optimize the potency, efficacy and pharmaceutical properties of UM129480 and of novel chemical classes of UBCH10 inhibitors. Using a recently developed UBCH10 biochemical assay, we have screened a diversity set of small molecules and identified several novel classes of hit compounds. The "drug-likeness" of the new scaffolds will be initially explored in small-scale SAR studies to identify the most promising chemotypes for HTL optimization. In the second aim, we will determine the binding mode of UM129480 and of other classes of inhibitors to UBCH10 by NMR spectroscopy to understand its mechanism of inhibition and guide SAR studies. We will also use a combination of biochemistry, pharmacology and genetics to rigorously validate the on-target activity of UBCH10 inhibitors. Finally, in the third aim, we will evaluate the therapeutic potential and anti-tumour activity of the most promising UBCH10 inhibitor leads using a panel of human cancer cell lines and established mouse models of cancer. PK/PD studies will be implemented to demonstrate efficacy and improve translation of preclinical data.

Significance to cancer:
Despite the major impact that proteasome inhibitors had on the treatment of multiple myeloma, these drugs have failed to show clinical activity in solid tumours, in large part due to adverse effects resulting from lack of selectivity. It is generally anticipated that targeting E2s and E3s will yield better specificity and less toxicity. Here, we report the identification of the first small molecule inhibitor of the E2 enzyme UBCH10. Evidence from *in vitro* studies of human cancer cell line models, mouse transgenic studies and analyses of clinical samples strongly suggest that UBCH10 is a viable cancer drug target. This project has the potential to lead to the development of a first-in-class generation of UBCH10 inhibitors for advanced preclinical evaluation in cancer.

I5 Prevention and Quality of Life

Klassen, Anne
McMaster University

Phase 2 field-test study to validate new BREAST-Q scales

The last two decades have seen an increasing use of economic evaluation studies to inform resource allocation in healthcare systems. The most widely used technique of economic evaluation is cost-effectiveness analysis, and the most common measure of effectiveness is the quality adjusted life years (QALY). Once the cost per QALY is determined with a preference-based measure (PBM), interventions or services with the lowest cost per QALY are typically chosen and funded. Traditionally, generic preference-based measures (PBM) such as EQ-5D or SF-6D have been used to calculate QALYs for breast cancer interventions. However, generic tools have been found to be insensitive (lack content validity) as they do not capture the unique concerns of patients, such as body image issues or the physical, psychological, sexual and emotional impact of cancer. Overlooking these issues is critical in the measurement of cost-effectiveness of two competing interventions and can led to the acceptance of a costly intervention with marginal benefits or rejection of a worthy one.

PBMs are composed of a descriptive health system classification system (HSCS) and a scoring algorithm (ie, preference weights for health states described by the HSCS). The focus of our CBCF grant was to

create a breast cancer-specific HSCS, with the view to applying for funding in the future to create the valuation component. With CBCF funding, we conducted 58 in-person interviews with a heterogeneous sample of women with breast cancer in Canada and the USA. An interpretive descriptive analysis approach was used, which led to the development of a conceptual framework from concepts elicited, and an item pool with 4445 items. The draft version of the descriptive HSCS of the PBM (see Appendix 2) was refined through input from experts and cognitive interviews with patients.

Given the richness of our qualitative dataset, we were able to push beyond our initial study aims. Specifically, in addition to the PBM, we created 10 new scales that measure concepts not covered by BREAST-Q, a patient-reported outcome measure for breast cancer developed by our team. These concepts include sleep impact, fatigue, work impact, cancer worry and for patients with lymphedema, arm function, arm symptoms, quality of life impact, psychological distress, information needs and satisfaction with arm sleeve.

With the conclusion of our Phase I study, the objectives of our current research proposal are: 1) to conduct a Phase II field-test study to further refine the descriptive component of the PBM; and 2) to validate the 10 new BREAST-Q scales. This study will utilize the Army of Women community, an online community that works with researchers towards the common goal of the prevention and treatment of breast cancer. Women 18 years and older with confirmed diagnosis of breast cancer (Stages 0-4) at any stage of treatment will be recruited through a AOW recruitment e-blast. Based on previous AOW studies by our team, we anticipate that 7500 women will complete the BREAST-Q survey, of which 15% (n=1125) will have arm lymphedema. Data collected will be analysed to refine the HSCS of the PBM. Psychometric analysis, using a modern approach (Rasch Measurement Theory) will be conducted to refine and finalize the 10 new BREAST-Q scales and create their scoring algorithms. This approach uses a range of statistical and graphical tests to examine how scales perform.

At the completion of our proposed study, the 10 new validated BREAST-Q scales will be made available to researchers and clinicians to use in research and clinical practice free of cost. The development of the scoring algorithm of the PBM using valuation techniques (such as discrete choice experiments, best worst scaling) (Phase III) will be the focus of a future funding application.

Once developed, end-of-grant and integrated knowledge translation efforts will be used to promote the uptake of the new BREAST-Q scales in research/clinical practice and policy through knowledge products designed for specific stakeholders (i.e. patients, clinicians, healthcare funding bodies and policy makers).

Sabiston, Catherine
University of Toronto

Connecting breast cancer survivors for exercise: extending the impact of ActiveMatch

Background
Nearly 90% of Canadian breast cancer survivors (BCS) are not exercising at levels that accrue health benefits. For BCS, a common barrier to exercise is a lack of social support. For cancer clinicians, a common barrier is lack of knowledge of where and how to refer BCS for appropriate and safe exercise. In our Innovation Grant, we addressed both of these barriers with an online platform that connects female cancer survivors with 'ideal' exercise partners. Based on our evaluation of over 250 users, we know this platform successfully identifies and connects exercise partners, is integrated in a cancer care pathway for exercise, and is gaining awareness among clinicians. We know that this platform addresses many exercise

barriers and increases exercise in those who participate. While BCS continue to benefit from the ongoing exercise partnership emanating from the platform, the challenge is to keep them engaged to improve the quality of their exercise and long-term adherence. In these ways, we have little understanding of *how* women support each other and how different methods and functions of social support relate to different types or doses of exercise. To address these gaps, *we will conduct an intensive study to explore daily social support and daily exercise behaviour.* Furthermore, in our evaluations, women suggest the platform can be improved with trustworthy exercise information and tailored exercise programming from a qualified exercise professional (QEP). Addressing this need, *we will develop and implement a dyadic exercise program as part of the platform and will test the effectiveness on increasing exercise among BCS.* Overall, with the current research landscape aimed at patient-centered care and translational science, the platform will be the evidence-based, community outreach, one-stop platform for exercise among BCS across Canada.

Objectives and Methodology

Two distinct research phases will be completed with BCS who register for the platform. Phase I is an ecological momentary assessment (EMA) study exploring the acute naturally occurring social support and the relationship to exercise among dyads. The main goal of this study (Aim 1) is to improve an understanding of the association between social support and exercise, and to use this information to inform motivational messaging in the platform. For this study, 40 BCS will complete daily surveys and wear an accelerometer (a device that measures exercise) for three non-consecutive weeks (21 days). The data will be analyzed using multilevel modeling.

Phase II is an experimental trial with the goal of testing the delivery of a distance-based dyadic exercise program by a qualified exercise professional (QEP) on increases in exercise, social support, and quality of life (Aim 2). BCS dyads (*N*=74 or 148 BCS) will be randomly assigned to the platform ("usual care" control; *n* = 37) or the platform plus QEP remotely-supervised 12-week exercise program (EX; *n* = 37). The primary outcome is change in minutes of exercise, and secondary outcomes include change in social support and quality of life, and cost effectiveness. All outcomes will be assessed at baseline, 12 weeks [end of program], and 24 weeks [follow-up] and analyzed using multilevel modeling. It is hypothesized that the EX group will have higher exercise minutes compared to control at 12 and 24 weeks. Higher social support and quality of life are also expected in the experimental group, and the program is expected to be cost-effective when compared to an in-person delivered program.

Significance

Currently, our platform successfully addresses a common survivor barrier to exercise by helping women find an exercise partner. To maximize long-standing impact, the platform needs to provide support and exercise. The BCS are asking for this, and clinicians need to know that the platform is safe and tailored for their patients to streamline the referral process. This is an evidence-based, real-world implementation of an exercise support platform that will help augment exercise opportunities for BCS to improve health, well-being, and survivorship outcomes.

Sawka, Annie
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Active surveillance of low risk papillary thyroid cancer: program expansion in Quebec

Treatment of low risk cancers that are detected early must be balanced with the possible risks of negative effects of therapy. Low risk cancers are those that cause no symptoms and are highly unlikely to become

life-threatening. A traditional approach in managing low risk solid tumours is surgery with the intent to cure the cancer. An alternative approach to reduce potential over-treatment of low risk cancers that may never cause harm, is to consider close monitoring, with the intent to perform curative surgery if there is evidence of disease progression; this approach is referred to as active surveillance (AS). AS may reduce the risk of treatment-related complications and associated potential quality of life impairment, in individuals whose disease is unlikely to progress. Very low risk papillary thyroid cancer (VL-PTC) is defined as papillary thyroid cancer that is smaller than 2 cm in maximum diameter, which has not spread outside the gland and is not near critical structures. In this prospective multi-centre long-term follow-up study, we will determine how often disease management goals are met in patients with VL-PTC who choose AS or surgery, respectively. We will build on our ongoing single-centre pilot study conducted at being conducted at University Health Network in Toronto, to recruit a larger number of patients at multiple sites across Canada. In this application, we focus on expanding our study to three high volume thyroid cancer hospitals in the province of Quebec. This study will involve French-Canadian translation and language validation of key study materials, including information for patients about disease management options, patient questionnaires, and a qualitative interview script. In our study, the disease management of goals will be defined as follows for respective groups: active surveillance group – survival without thyroid surgery (in absence of significant growth of the primary tumour or development of metastatic disease), and for the surgical arm – an excellent response to therapy (defined by established guidelines, which is analogous to cure). Our study will also compare the following outcomes in AS and surgical groups: quality of life, psychological distress, quality of life, rate of requirement for long-term thyroid hormone treatment, and healthcare resource utilization. We will also conduct an in-depth qualitative analysis of the experiences of a subgroup of study participants in the AS and surgical groups. This study will inform future patients, healthcare practitioners, and health policy makers about the outcomes of patients with VL-PTC choosing surgery or AS. Furthermore, our results our framed to ensure that individual patients' disease management needs are understood and met, respecting both official languages and varied cultural contexts.