Hold’em for Life

Translating discoveries into breast cancer cures

Progress Report

June 2018

Sinai Health System

Lunenfeld-Tanenbaum Research Institute
Sinai Health System

UHN Princess Margaret Cancer Centre

Executive Summary

With generous funding from the ***Hold'em for Life*** **Charity** we have built a successful integrated multidisciplinary breast cancer research program focused on the interface between the patient (host) and her cancer.

The dynamic team that we have assembled bridges clinical and basic researchers across Mount Sinai (MSH)/Lunenfeld Tanenbaum Research Institute (LTRI) and Princess Margaret Cancer Centre (PMH)/ Research Institute. We have leveraged the funds received from Hold'em (approximately $ 1.5 million per year) multiple times against institutional assets, peer-reviewed funding, pooled funding from multi-center clinical trials and industry.

Underpinning our success is our commitment to jointly aligning and conducting critical clinical and basic breast cancer research, deepening our understanding in the areas of our members' expertise and leveraging that knowledge to advance the central shared objectives of the Hold'em for Life program. The breadth and depth of the combined scientific and clinical expertise with which we approach our research is substantial and includes clinical medicine (medical oncology, radiation oncology and pathology), statistics and basic research (molecular biology and genomics) and is seldom achieved in multidisciplinary teams. Such a collaborative team, working interactively to investigate research questions from multiple perspectives is a major strength of our research program.

The Hold'em for Life funded program has **five inter-related planks** that reflect robust interaction between preclinical and clinical research focused on host hormonal factors (e.g. insulin, estrogen, progesterone) and tumor development and progression. We also provide support for clinical trials infrastructure and for trainees.

In 2017/2018 we initiated a new major plank – **Exploration of factors associated with late recurrence in hormone receptor positive breast cancer** – this work involves a major prospective cohort study with rigorous and serial collection of blood, urine and patient-related factors in order to identify potential predictors of imminent risk of distant relapse. This project is described in detail later in the report. The initiation of this new area of research has taken place as many of our earlier studies have been completed (as described below).

PLANKS

Late Recurrence in Women With Hormone Receptor Positive Breast Cancer - We have initiated an important new study which will tackle the problem of late recurrence of breast cancer. In Canada, almost 5000 Canadian women still die from breast cancer every year. Many of the life threatening/incurable breast cancer recurrences and deaths now take place more than 5 years after diagnosis, after completion of adjuvant therapy, particularly in hormone receptor positive breast cancer. It is a **major unmet need** to understand **who is at risk for these late recurrences** and to **identify interventions to prevent or delay** them.

There is no reliable and validated way to identify which specific women will recur and when a recurrence is imminent (but still potentially avoidable). Overcoming this knowledge gap is important because the majority of women do not recur – treatment needs to be focused on those who are at greatest risk of recurrence in order to maximize benefit and minimize toxicity. Our research is focusing on circulating tumor cells, circulating tumor DNA and tumor markers as potential personalized markers of impending risk of recurrence and it is expected to lead to randomized clinical trials testing treatments that will prevent late recurrences. This research is novel, timely and impactful. Hold'em funding has allowed us to initiate this study in Toronto and to develop a collaboration with the British Columbia Cancer Agency (BCCA). We have leveraged the Hold'em funding ($600,000 in 2017/2018) to obtain additional funding from granting agencies, including the Breast Cancer Research Foundation (New York, ($325,000/year) and funding of associated assays by Epic Science based in the US (approximately $10,000,000 total value of the assays). We are also in negotiation with Genomic Health (US) for funding of Oncotype Dx assays on the primary tumors of our subjects (up to $4,000,000 value over the course of the study).

Obesity & Metabolic Factors - We have been investigating the role of obesity and metabolic factors, by way of clinical trials of the diabetes drug metformin in breast cancer, and by looking at the molecular biology of the obesity-cancer relationship and mechanisms of action of metformin. Drs. Goodwin and Stambolic have led this area, along with Dr. Ryan Dowling. We have reported improved metabolism in women receiving metformin – important because abnormal metabolism (for example, high insulin levels) has been associated with an increased risk of breast cancer recurrence and death. We also have several ongoing translational research activities in CCTG MA.32 (A Phase III Adjuvant RCT of metformin vs placebo n early breast cancer that will provide definitive information regarding the potential therapeutic role of metformin in breast cancer) and we have conducted several translational studies in this area (see below). In 2017/2018, Hold'em funding contributed to the final analysis of a randomized trial of a weight loss intervention in early breast cancer that had been initiated over a decade ago, led by Dr. Pamela Goodwin – the results of this study suggest that a weight loss intervention will lower risk of breast cancer recurrence and provide strong (and much needed) support for continuation of a larger ongoing randomized trial that will provide more definitive evidence.

Liquid Biopsies - The study of metastatic breast cancer demands direct evaluation of tumor material, which is difficult to obtain because of the need for invasive biopsies of metastatic lesions. A promising alternative to tissue biopsies are "liquid biopsies", which sample tumor-derived cells or products present in the blood of affected individuals.

Initially, we examined patient metabolic host (patient-related) factor correlates of circulating tumour cells (CTCs) in metastatic breast cancer. There has been a shift in scientific thinking and we are now working with circulating tumour DNA ("liquid biopsy" or ctDNA). Dr. Scott Bratman, a scientific expert in this area, and Dr. Dave Cescon plan to examine ctDNA spikes post chemotherapy in the neoadjuvant and metastatic setting as potential early markers of tumor response to treatment. These activities have contributed in a major way to the design of our Late Recurrence study. They have also formed the basis for a new collaboration with EPIC Science to measure CTCs in our Late Recurrence study (worth approximately $10 M CAD).

Hormonal and Bone Related Factors – A group of Hold'em scientists have explored hormonal and bone related factors such as estrogen, progesterone and Rank-ligand (RANK-L, a bone-related factor) in the development and treatment of breast cancer. As with our other core activities, this work has contributed to hypotheses that will be tested in our new program of research focusing on late recurrence.

Dr. Khokha's research has provided an explanation for why certain types of hormone replacement lead to increased breast cancer risk while others do not. Purna Joshi (Post-doctoral fellow) has investigated fat and stem cells in the breast, including examination of biologic properties of fat cells. Alison Casey's (Post-doctoral fellow) work has identified drugs that target stem cells which can act as precursors of breast cancers. Dr. Daniel Schramek (LTRI scientist) has investigated bone related trauma as a potential contributor to late recurrence in a mouse model.

Breast Translational Research Resource (BTRR) - The BTRR, an established and growing research resource available to the Hold'em researchers and other University of Toronto investigators, currently includes tumor tissue, normal breast tissue, blood and clinical information. Approximately 840 women with breast cancer have been enrolled into the BTRR with full clinical annotation; key patients (primary invasive cancer and followed clinically at MSH) are being followed annually for clinical outcomes.

This high quality resource will have its greatest value and impact in the next 2-5 years as some of the participants experience a recurrence or metastasis of their cancer. At that time it will become possible to conduct more detailed investigations into why some women develop metastases while others do not – an important complement to our planned late recurrence study. In the meantime, 6 researchers have proposed research utilizing these samples; three of the projects are underway and 1 project (investigating obesity associated blood and tumor markers in hormone receptor positive breast cancer) has been completed.

SUPPORTED ACTIVITIES

Clinical Trials Infrastructure Support - The program also supports clinical trials infrastructure that facilitates participation in multicenter clinical trials. A number of Hold'em funded studies have been completed with preliminary results already presented and manuscripts detailing the final results underway.

Much of the full complement of trials work (over 30 studies) has taken advantage of funding from other sources and/or has been layered onto existing infrastructure for clinical trials – this has allowed the program to have an impact that is greater than would have been possible using only Hold'em funding. The enhanced level of clinical trial activity has facilitated membership of MSH in the Canadian Cancer Clinical Trials Network, which provides additional infrastructure support for oncology clinical trials.

Trainees - Hold'em has engaged 25 trainees and they are exposed to the full spectrum of research. Some of the trainees are now beginning to play a leadership role in their own studies and three trainees have accepted staff positions and continue to work with the group.

SCIENTIFIC ADVISORY BOARD

Our research was reviewed by an international Scientific Advisory Board (Dr. Dan Hayes, Ann Arbor, Michigan; Dr. Fraser Symmans, MD Anderson, Texas; Dr. Morag Park, MGill University, Montreal, Quebec) in November 2017. The day long face-to-face meeting was attended by Andrew Hoffman who received in person feedback. The Scientific Advisory Board was impressed with our focus and progress. They endorsed the importance of our Late Recurrence Study, as well as our recent transitions into Liquid Biopsies; they emphasized the importance of our BTRR and they were supportive of our activities in other areas. It was agreed that the next Scientific Advisory Board meeting take place in 18-24 months.

We are recognized internationally – we have published 46 papers and 30 abstracts (see Appendix 7) and presentations based on our Hold'em for Life funded research.

SUMMARY AND CONCLUSIONS

Over the past six years, the Hold'em team has evolved into a successful multidisciplinary team that has effectively conducted research in five inter-related planks, with plans for ongoing activities in each of these planks. We have also provided support for clinical trials infrastructure and 25 trainees (listed in Appendix 1) and we have published 46 manuscripts and presented 20 abstracts.

In 2017/2018, we embarked on a new, timely and potentially impactful area of research – identification of individual patient factors associated with imminent risk of distant recurrence after hormone treatment for hormone receptor positive breast cancer. This work involves national and international collaborations which has led to almost $14M in matching funding. We anticipate this new project will require about 5 years for completion and that we will obtain funding from multiple sources to conduct this research.

A detailed table of our activities over time is provided in Appendix 2.

STORIES TO TELL

We have selected three "Stories to Tell" this year. More stories can be generated if desired.

1. **Metformin lowers CA15-3, a breast cancer tumor marker found in blood**

In an international study involving 3649 women with early stage breast cancer who were enrolled onto MA32, a multi-country randomized trial of metformin vs placebo, Hold'em for Life funded research has shown that metformin lowered a breast cancer tumor marker, called CA15-3, in blood. This finding provides early evidence that metformin (a well-tolerated generic drug that costs 10 cents per day) may be having a beneficial impact on early stage breast cancer; the effect of metformin on breast cancer recurrence will be known in 2-3 years.

2. **Lifestyle change leading to weight loss may lower risk of breast cancer recurrence**

Hold'em for Life funding supported the final analysis of trial of 338 women with breast cancer who were randomized to receive a telephone based weight loss lifestyle intervention (lower caloric intake and higher physical activity) or educational materials. Those who received the intervention had a weight loss that averaged 5%; their risk of recurrence at 8 years of follow-up was 30% lower than that of women who did not receive the intervention. These results are very encouraging, however, because of the small number of women enrolled onto the study confirmatory research is required.

3. **Hold'em researchers are conducting a study to develop a blood test to identify breast cancer patients who will experience a late recurrence of their breast cancer**

1000 women with hormone receptor positive breast cancer who are being enrolled and followed in Toronto and Vancouver are providing annual blood samples, as well as medical and lifestyle information. Blood will be analyzed for circulating tumor cells (by EPIC Science), circulating tumor DNA and tumor markers. The appearance of these factors in blood will be tested as a marker of upcoming breast cancer recurrence. This study is ongoing and is expected to provide results within 5 years.

Contents

Report of Activities June 2017 to June 2018, including Description of Ongoing and Planned Core Activities

For the past 6 years, the generous support of ***Hold'em for Life*** has allowed us to accomplish much in building a multidisciplinary breast cancer research program. The dynamic team that we have assembled bridges clinical and basic research across Mount Sinai (MSH)/Lunenfeld Tanenbaum Research Institute (LTRI) and Princess Margaret Cancer Centre (PMH)/Research Institute. We have leveraged the funds received from Hold'em multiple times against institutional assets, peer-reviewed grants, and pooled funding from multi-center clinical trials. During the past year we have successfully negotiated leveraged funds from EPIC Science, a commercial entity that has developed state of the art assays for circulating tumor cells. The driving focus of our program is predominantly clinical with an emphasis on prevention and treatment of metastatic breast cancer; this focus also embraces the investigation of earlier stages of breast cancer to facilitate understanding of why some women develop metastases and how these recurrences can be prevented.

Our Hold'em for Life funded research program has focused on the interface between the woman and her cancer, exploring this interface in research spanning the molecular biology of the cancer to the physiology and lifestyle of the patient. Throughout, our focus has been on understanding why some patients develop metastases and how those metastases can be prevented and treated. We continue to focus on research in this area.

Underpinning our success has been the establishment of an integrated multidisciplinary breast cancer research team. This engaged research team has matured over the years to effectively conduct critical clinical and basic breast cancer research, deepening our understanding in the areas of our members' expertise and leveraging that knowledge to advance the central shared objectives of the Hold'em for Life program. The breadth and depth of the combined scientific and clinical expertise with which we approach our research is substantial and includes clinical medicine (medical oncology, radiation oncology, pathology), statistics and basic research (molecular biology and genomics) and is rarely achieved in multidisciplinary teams. Such a collaborative team, working interactively to investigate research questions from multiple perspectives, is both rare and highly prized; it is a major strength of our research program. Our Hold'em for Life program is cultivating the future scientists in this area through the support and mentoring of trainees, several of whom have moved into staff positions and are beginning to take a leadership role in their own breast cancer research programs. We are recognized internationally – having published 46 papers and 30 abstracts and presentations based on our Hold'em for Life funded research.

The Five Major Research Planks of the Hold'em Program

There are **five major planks** in our existing research program.

1. Major New Focus: Investigation of Late Recurrences in Hormone Receptor Positive, HER2 Negative Breast Cancer

During 2017/2018 we began an important new research initiative which will investigate the problem of late recurrence of HR+, HER2- breast cancer. Late recurrences have been defined as those that occur after completion of adjuvant (preventive) hormonal treatment. The evolution of our scientists into a highly functioning inter-institutional multidisciplinary research team has placed us in a unique position internationally to conduct this novel, impactful research. This new initiative arose from advances in the understanding of the magnitude of the late recurrence risk in breast cancer patients (which can be greater than 2% per year) and from the discoveries we have made in our ongoing and completed Hold'em for Life funded research.

Study Goal - To develop a blood test that will identify factors associated with late recurrence in women with hormone receptor positive BC who are about to complete, or have recently completed five to ten years of adjuvant hormonal therapy. The blood test will focus on circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and tumor markers. Our ultimate goal is to use this information to develop treatments targeting these women at imminent risk that will prevent late recurrences and death.

Scientific Background – In Canada, breast cancer mortality rates are at the lowest levels since the 1950s, when statistics were first collected. However, almost 5000 Canadian women still die from breast cancer every year. Earlier diagnosis and better adjuvant therapy have improved breast cancer outcomes, with 5 year survival approaching 90-95%. Unfortunately, many of the life threatening/incurable breast cancer recurrences and deaths now take place more than 5 years following diagnosis, particularly in women with hormone receptor positive (HR+) BC. These women have an ongoing annual risk of recurrence of 1-2% that is fairly constant out to 20 years post diagnosis; subgroups at higher annual risk have been identified and these higher risk groups will be the focus of our study.

Why do these late recurrences happen? By the time a breast cancer is surgically removed, microscopic cancer cells have often spread to other parts of the body; many of these cells are killed by post-operative adjuvant drug treatments, leading to lower risk of future recurrence. Unfortunately some cells are not killed – they remain in a dormant state (in essence, they are inactive, or sleeping) for years. At some point, in some patients, often many years after diagnosis, these dormant cells begin to grow to become incurable metastases. Our study is designed to identify factors in the blood of these patients, notably circulating tumor cells, circulating tumor DNA and specific tumor markers that precede these late recurrences. We will also study medical, surgical and lifestyle factors that may contribute to activation of these dormant/sleeping cells. We believe that this knowledge will allow us to identify women whose cancer is about to recur, before it is incurable, so that we can conduct trials that will identify treatments that will prevent these late recurrences.

The specific factors we will study include:

Blood – circulating tumor cells and DNA, circulating tumor markers (CEA, CA15-3), immune profiles

Patient factors – lifestyle (body mass index, diet, physical activity, smoking, alcohol), stress, medical and surgical illnesses/procedures, trauma, medications

Study Design - 1000 women with HR+ HER2- BC who have not experienced a distant recurrence will be enrolled; half will be enrolled during their final year of adjuvant hormone therapy and half during the first few years after completion of adjuvant hormone therapy,. Blood and patient-related factors will be measured at study entry and annually until recurrence or study end. Breast cancer recurrences will be documented. Statistical analyses will compare those who recur to those who do not.

Participants are recruited from oncologists in Toronto and Vancouver, approximately half in Ontario and half in British Columbia. Informed consent and data collection are conducted by phone and medical record review; blood collection will be done at hospital laboratories.

All blood and data collection are repeated annually until a recurrence is identified or the study ends; follow-up will include ascertainment and confirmation of BC recurrence. Maximum duration of participation is anticipated to be 10 years.

We will enroll 1000 patients over 2-3 years, with follow-up continued for an additional 1-2 years before initial analyses can be performed. This will allow us to have sufficient rigor to determine whether the appearance of circulating tumor cells, circulating tumor DNA or tumor markers in blood can predict a breast cancer recurrence. We will also analyze how patient related medical/surgical/lifestyle data are related to late recurrence. Continued follow-up will allow more robust analyses to be performed in future.

Late Recurrence Study Progress in 2017/2018:

1. Finalization of a study protocol. This was completed in March 2018.

2. Ethics approval – the protocol was submitted to Ontario-wide Ethics board in March 2018 – we have provided additional information in response to their queries – we anticipate full approval in early July 2018. We are currently identifying subjects and will continue with data collection in Ontario as soon as Ethics approval is finalized.

   Note that BCCCA will submit the project to their Ethics committee after Ontario approval has been obtained; their approval is projected for late summer/fall 2018.

3. Development of formal collaborations for recruitment (currently these include medical oncologists Mount Sinai Hospital, Princess Margaret Hospital and Sunnybrook Hospital in Toronto). Our Toronto collaboration has now expanded to include Women's College Hospital which has a large breast cancer follow-up clinic. To develop additional collaborations (which will allow us to recruit, collect data and obtain study results more rapidly, we presented this study at the Canadian Clinical trials Group (CCTG) annual meeting Spring 2018 — multiple centers in four provinces expressed interest in participating - we have chosen to work with the British Columbia (BC) group (led by Dr. Steven Chia) through a collaboration with the BC Cancer Agency who will enroll up to half of our subjects. With this collaboration, we believe our target of 1000 subjects will be met in 2-3 years.

   If additional collaborations are required we will pursue them in the upcoming months, based on accrual during the next 6 -12 months. Additional centers will likely be in Ontario, as the Ethics board of record from this study provides approval that would be acceptable at other Ontario centers.

4. Identification of study subjects is ongoing and will continue to be a focus of our activities, with expansion into data and blood collection once ethics approval is finalized.

5. Establishment of a study biorepository – we have received quotes from multiple potential repositories; we expect to finalize our selection by late summer 2018.

6. We have identified three major sources of leveraged funding:

   (i) Breast Cancer Research Foundation (NY) has funded this project for the past 2 years (including development of the host factor questionnaire that will be used in this study). Their contribution for the upcoming year will be $325,000 (total from BCRF to 2018 is approximately $750,000).

   (ii) EPIC Science (US) has agreed to fund CTC collection, storage and future assays – they are developing/validating a novel assay of inflammatory cells, and plan to support development of

novel genomic assays of CTCs - based on market value of their CTC assays this collaboration will be worth $8 million (US), over $10 million Canadian.

(iii) We are having ongoing negotiations with Genomic Health (US) to perform Oncotype Dx assays on the primary tumors of patients enrolled onto this study. Based on Canadian cost of the Oncotype assay, this collaboration will be worth up to $3-4 million (Canadian) if all tumors are assayed.

7. With funding from BCRF and Hold'em for Life Charities, we held an international Late Recurrence workshop in Toronto in February 2018. This workshop, chaired by Pam Goodwin, Dan Hayes (US), Joe Sparano (US) and Kevin Kalinsky (US), was attended by over 20 international researchers who reviewed the current state of the science as well as ongoing and planned studies of Late Recurrence. Areas of collaboration were identified and a second workshop is planned for 2019 (Chaired by Dan Hayes). A meeting report is under preparation.

Planned Late Recurrence Study Activities in 2018-2019

1. Activation of the study at all remaining centers (in Ontario and British Columbia).
2. Enrolment of 350-400 subjects, with collection of blood, tumor tissue and clinical data.
3. Establishment of recruitment, data and specimen collection and follow-up of eligible women at the British Columbia Cancer Agency.
4. Finalization of a collaboration with Genomic Health to conduct Oncotype Dx assays on tumors obtained from study participants.
5. Establishment of a study database and finalize a study biorepository.

Anticipated Impact of the Late Recurrence Study

Successful development of a blood test that will allow us to identify breast cancer survivors at imminent risk of late recurrence will open up new possibilities for interventional research to test therapies that can prevent these late recurrences and potentially dramatically lower breast cancer mortality rates for hormone receptor positive breast. Our research is also expected to contribute to enhanced understanding of the biologic factors associated with late recurrence.

2. Obesity and Metabolic Factors, Including Metformin

We have been investigating the role of **obesity and metabolic factors**, by way of clinical trials of the diabetes drug metformin in breast cancer, and by investigating the molecular biology of the obesity-cancer relationship and mechanisms of action of metformin. This work has been led by Drs. Pam Goodwin (clinical scientist at MSH/LTRI) and Vuk Stambolic (molecular biologist at PMHRI); Hold'em scientists are recognized as international leaders in this area of research.

Our work in this area reflects our understanding of the obesity-cancer link described in the Figure below.

Impact of the Obesity Epidemic on Cancer

Pamela J. Goodwin and Vuk Stambolic
(Annual Reviews in Medicine 2015)

The emerging understanding of the biologic nature of the association of obesity and cancer suggests a complex interplay of a range of factors at multiple levels: the whole patient, the adipose tissue, and the tumor cell and its fat-containing microenvironment (Figure 2).

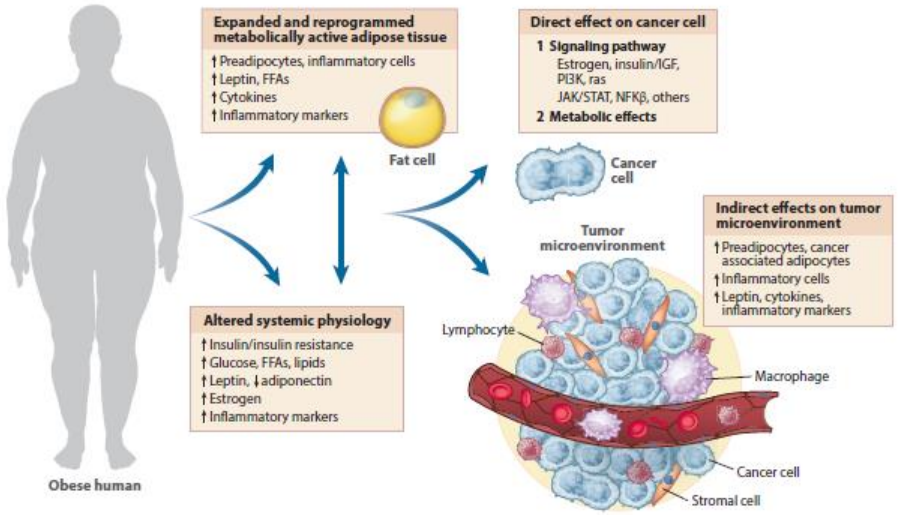


Figure 2
The complex association of obesity and cancer. Obesity is associated with expanded and reprogrammed adipose tissue that is metabolically active, leading to localized inflammation and altered cytokine/adipokine secretion; these local changes contribute to, and interact with, alterations in systemic physiology that reflect the insulin resistance/metabolic syndrome. Local adipose tissue and systemic obesity-associated alterations can impact cancer directly by (1) the activation of key signaling pathways or (2) an alteration in cellular metabolism, reflecting an abundance of glucose, free fatty acids (FFAs), and lipids. They may also act indirectly on the tumor microenvironment to promote proliferation, angiogenesis, invasion, and epithelial-mesenchymal transition.

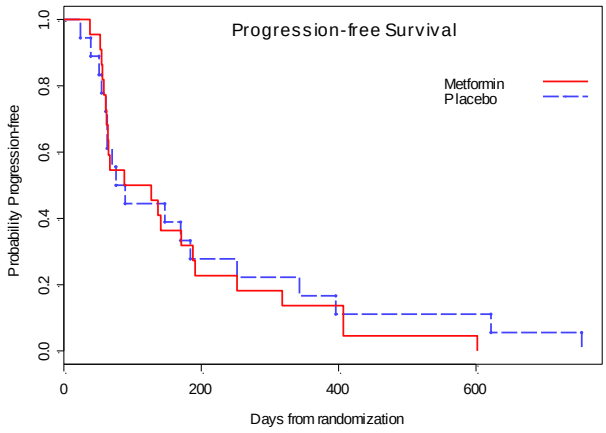
A. OZM 027 – A Phase II Randomized Trial of the Effect of Metformin vs Placebo on Progression Free Survival (PFS) in Women with Metastatic Breast Cancer Receiving Standard Chemotherapy

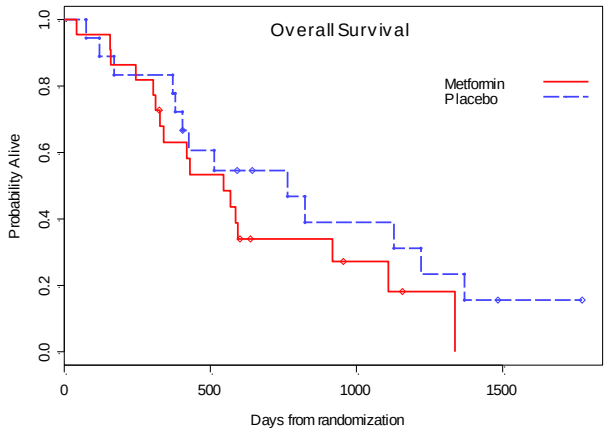
We have recently completed a Phase II trial of metformin (vs placebo) plus chemotherapy in the metastatic setting (OZM 027), and are currently finalizing the analysis of the data collected (see below). This trial was designed to evaluate, in a clinical population, the provocative observation that metformin enhanced the effect of chemotherapy by selectively targeting cancer stem cells in a mouse mammary cancer model (Hirsch H et al, Cancer Res 2009;19:7507-7511).

Study Design: We randomized 40 women starting a new chemotherapy (first, second, third or fourth line standard chemotherapy as selected by the treating physician) for metastatic breast cancer at one of 6 participating Ontario hospitals to metformin (850 mg PO BID) or placebo. Breast cancer response to treatment was examined every 9 weeks and study treatment was stopped when cancer progression was identified.

Results: Most of our patients had cancer that was resistant to multiple types of chemotherapy and hormone therapy before they entered the study. We saw no complete responses, regardless of whether women were on metformin or placebo. Half of the patients (50.0%) receiving metformin and one-third of the patients (33.3%) receiving placebo showed clinical benefit (partial response or stable disease). However, Grade 1 and 2 toxicities (mild and moderate, mainly gastro-intestinal) were more frequent in those receiving metformin. Importantly, there was no evidence that metformin slowed cancer progression (164 days on average to progression in the metformin arm and 192 days in the placebo arm) or prolonged survival (see graph).

Conclusions: Although the clinical benefit rate was somewhat higher in women receiving metformin, metformin led to greater toxicity and did not delay cancer progression or prolong survival. We do not recommend further research be done examining the combination of metformin with chemotherapy in breast cancer that is resistant to other therapies. We do not believe these results should impact other trials in earlier stages of breast cancer (e.g. MA32) will lead to similar findings; those trials should continue to their planned conclusions. These results have been submitted to the 2018 San Antonio Breast Cancer Symposium.





Plans for 2018/2019 – This study is complete. A manuscript will be submitted for publication.

B. Correlative Research in CCTG MA.32, A Phase III Trial of the Effect of Metformin versus Placebo on Invasive Disease Free Survival in Early Stage Breast Cancer

Funding from the Hold'em For Life program has allowed us to make important progress with our correlative work on MA.32, a large phase III clinical trial (NCIC CTG MA.32) investigating the effects of metformin versus placebo on recurrence and survival in early stage breast cancer. This correlative research examines:

(i) Patient factors and physiology that underlie the obesity-cancer link,

(ii) Mechanisms of action of metformin in breast cancer,

(iii) Predictors of metformin benefit.

Approximately $25 million in funding from other funders (including the Canadian Cancer Society, the National Institutes of Health US and Cancer Research UK, amongst others) allowed us to perform this research in a cost-effective and timely fashion. The outcomes of the parent trial are projected to be available in 2020/2021 (the exact timing depends on when women experience recurrences). Much of our work involves blood assays (of metabolic factors, tumor markers and DNA). Dr. Martin Chang (a Mount Sinai based pathologist with the Hold'em group) is characterizing the breast cancers of the women participating in this trial to identify tissue markers of metformin benefit. Progress during 2017/2018 includes the following:

1. We completed analysis of a genetic marker (called a single nucleotide polymorphism or SNP; namely rs1121617) in MA.32 study participants. In work by other investigators this marker was shown to predict metformin effect on insulin and glucose in diabetics (without breast cancer). We have shown that that the genetic marker does not predict metformin effect on insulin and glucose in non-diabetic breast cancer patients, however, the genetic marker is associated with obesity in our patients. This may mean it can be used to identify individuals who are likely to become obese – and that interventions can be developed to avoid obesity in this population. These results will be presented at the Obesity Society meeting in fall 2018.

2. We showed that metformin significantly improved metabolism and physiology and it led to weight loss. These results were presented at ASCO 2018.

3. We also tested levels of CA15-3, a tumour marker that has demonstrated prognostic value in breast cancer patients. Metformin significantly lowered CA15-3 (compared to control) – this may be early evidence of a potential beneficial effect of metformin on breast cancer outcomes. These results were presented at ASCO in 2018.

4. Significant progress has also been made in the analysis of MA.32 tissue samples. Dr. Martin Chang has completed assessment and marking of all tissue slides associated with the trial (over 3500, including both tumour and normal tissue) and tumor microarray (TMA) construction is virtually complete – these TMAs are critical to the study of tumor associated markers and their construction is a major milestone that will now allow us to move forward with tissue based assays – these assays will need to be completed before the trial analysis in 2020/2021. Dr. Chang continues examining these tissue markers (over 20,000 individual marker tests are being scored) – this work will continue over the next 1- 2 years.

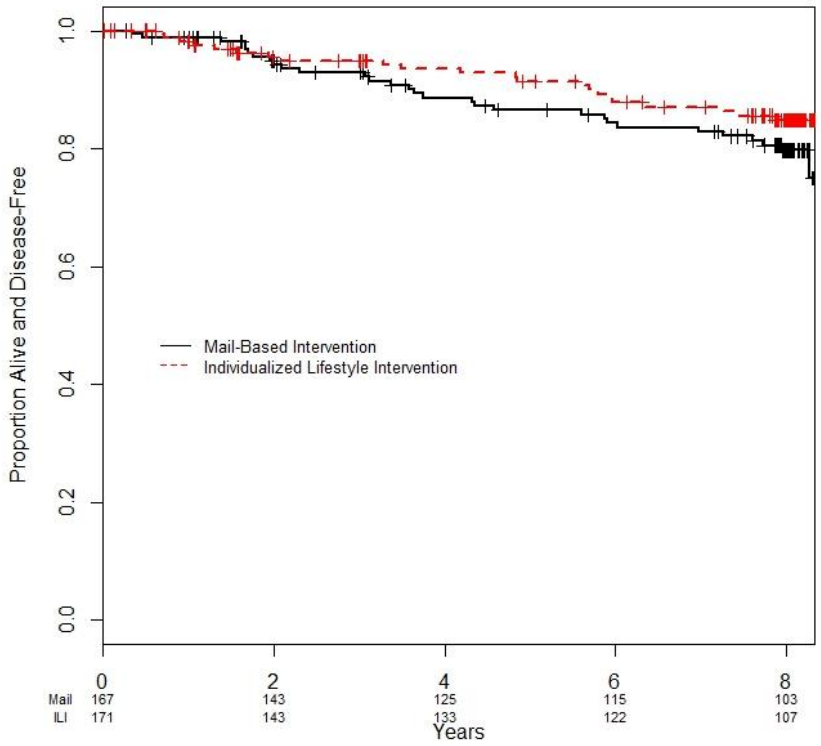
These studies build on our long standing interest in evaluating the use of metformin in breast cancer and characterizing the impact of obesity and hyperinsulinemia on breast cancer, which represents a major theme of our Hold'em research. The results of these analyses will enhance understanding of the effects of obesity and insulin on breast cancer and they may identify new targets for breast cancer treatment. As the proportion of obese individuals in Canada increases, the importance of this work has increased.

Plans for 2018/2019 – Studies 1-3 are complete; manuscripts will be submitted for publication during the upcoming year. Study 4 will continue – Dr. Chang will continue to score tissue assays, with anticipated completion date late 2020/early 2021. Statistical analyses will be conducted at that time.

C. Impact of a Weight Loss Intervention on Breast Cancer Recurrence and Survival (LISA Study)

Hold'em funding has been used to support the final analysis and reporting of a randomized clinical trial of a telephone based weight loss intervention in postmenopausal women with hormone receptor positive early breast cancer. This trial involved 338 women in Canada and the US; it was conducted by the Ontario Clinical Oncology group (based in Hamilton) between 2005 and 2018. This trial, led by Dr. Pam Goodwin, was funded by Novartis Pharmaceuticals (Canada). Funding was terminated in late 2009 (before accrual could be completed) because Novartis Canada lost their patent for a breast cancer drug (letrozole, Femara). Modest Hold'em funding has been leveraged against over $1 million in funding provided by Novartis for this work.

Women randomized to the weight loss intervention were approximately 30% less likely to experience a breast cancer recurrence than those who did not receive the weight loss intervention. This is a large effect, and these results are very promising, however, because of the small number of women enrolled onto the trial (we had planned to enroll 2000 women), they are not definitive. Nonetheless, they provide strong support for a similar trial that is ongoing in the US and Canada (the largest of these trials is the BWEL trial, led by Dr. Jennifer Ligibel from the Dana Farber in Boston- Dr. Goodwin leads the Correlative Science aspect of this new BWEL trial). These results have been submitted to the San Antonio Breast Cancer Symposium, December 2018.



Plans for 2018/2019 – This study is complete; a manuscript will be submitted for publication during the upcoming year.

D. Other Clinical Studies (Hepcidin, ER/PgR Obesity, CLS-B)

(i) Hepcidin

Hepcidin (a marker of iron metabolism in cells and a potential marker of inflammation and predictor of breast cancer recurrence) has been hypothesized to be linked to poor breast cancer outcomes. We studied hepcidin in the blood of 518 women with early stage breast cancer. We showed that hepcidin was not associated with breast cancer outcomes overall, however, among obese women (BMI>30 kg/m^2), higher hepcidin was associated with a shorter time to distant BC recurrence. This work formed the basis of a Master's thesis by Dr. Jerzak (who is now on staff at the Sunnybrook Odette Cancer Center), under the supervision of Dr. Goodwin. This work was presented at the San Antonio Breast Cancer Symposium in December 2017 and it has led to additional international collaborations with researchers in Europe and the US.

Plans for 2018/2019 – This study is complete; a manuscript will be submitted for publication during the upcoming year.

(ii) ER/PgR Obesity

We studied blood and tissue factors related to obesity and metabolism in 129 patients with obesity and non-obesity-associated estrogen-receptor-positive breast cancer who were enrolled onto the BTRR. Obesity was associated with abnormal metabolism and inflammation but it did not impact the type of breast cancer that had developed. An important novel finding was the demonstration that the leptin receptor (a protein on the surface of breast cancer cells) was ubiquitously expressed in these ER+ cancers. Furthermore, the leptin receptor was associated with invasion of cancer into lymph vessels. These observations have stimulated further investigation of leptin receptor and its impact on breast cancer growth. In future, we plan to examine how OB-R is associated with breast cancer recurrence. Data from this study have been presented at the USCAP 2017 meeting.

Plans for 2018/2019 – This study is complete; a manuscript will be submitted for publication during the upcoming year.

(iii) CLS-B

Dr. Martin Chang has explored the association of crown-like structures of the breast (CLS-B) with metabolism and obesity in women with early breast cancer. CLS-B are structures found in the breast of obese women; it has been suggested they may lead to breast cancer development and spread. Dr. Chang began by studying 162 breast cancer patients – in 2017/18 this was expanded to 221 patients. CLS-B were identified in just over one-third (36%) of patient and they were more common in obese women. However, CLS-B were not associated the type of breast cancer that developed nor were they associated with metabolic profiles. Importantly, CLS-B were not associated with breast cancer outcomes, in contrast to findings reported by other researchers. Results from the expanded dataset will be outlined in a manuscript which is under preparation.

Plans for 2018/2019 – This study is complete; a manuscript will be submitted for publication during the upcoming year.

E. Impact of Insulin on Breast Cancer

Emerging evidence indicates that obesity and the associated increase in circulating insulin levels are major adverse factors in the development and severity of breast cancer (BC). Dr. Stambolic is studying the insulin receptor (IR) signaling in BC with a goal to develop new treatments. He is working with Drs. Martin Chang and Ryan Dowling.

In related work these scientists are scoring insulin receptors and other markers in tumor tissue obtained from 949 patients from the NCIC CTG MA.21, a randomized adjuvant BC phase III clinical trial that was completed in 2005 (10,000 of 12,000 scores have been completed). This work forms the basis of similar work that is ongoing and planned in MA.32 where Dr. Stambolic serves as a correlative science chair.

On the basic research front, Dr. Stambolic and his team have shown that deletion of insulin receptor from the breast tissue in mice considerably reduces breast tumor development and growth. Dr. Stambolic is also studying how the insulin receptor action impacts the growth of breast cells and the biology of breast cancer. This work is expected to have far-reaching implications for management of IR positive breast cancers, especially in obese patients. This work will be continued in the coming year.

Completion of this ongoing and planned work could lead to the development of new breast cancer therapeutic strategies (including repurposing of existing, approved therapies targeting these pathways, particularly in obese individuals.

Plans for 2019/2019: In 2018/2019 we plan to continue with these insulin-related translational and basic research projects.

F. New Obesity Project for 2018/2019

We will conduct an investigation of body composition (fat, muscle) in over 330 breast cancer patients enrolled onto the BTRR to examine correlations of muscle and fat with metabolism, sex hormones and, in the future, breast cancer recurrence. Body composition will be determined using a standardized and validated approach based on abdominal CT scans performed at diagnosis of breast cancer. Training for these measurements will take place in Toronto in August 2018 and will involve 5 staff. Ethics approval will be obtained by September 2018 and all body composition estimates and blood assays completed by early 2019. Statistical analyses will be performed in the first quarter of 2019 with an anticipated presentation at a major oncology meeting in Q2/Q3 2019. This work will be conducted by Dr. Isabel Pimentel, a clinical fellow working with the Hold'em group.

3. Liquid Biopsies

The study of metastatic breast cancer demands direct evaluation of tumor material, which is difficult to obtain because of the need for invasive biopsies of metastatic lesions. A promising alternative to tissue biopsies are "liquid biopsies", which sample tumor-derived cells or products present in the blood of affected individuals. The use of circulating tumor DNA (ctDNA) as an early marker of tumour cell death "**liquid biopsy**" could provide clinicians with a tool to rapidly measure treatment efficacy and adjust treatment course accordingly.

Our work initially focused on circulating tumor cells (CTCs) in metastatic breast cancer – with Hold'em funding, Dr. Martin Chang established the first clinical measurement facility in Canada at MSH and we participated in an international study investigating whether the characteristics of the CTCs could be used to predict response to hormonal therapy in metastatic breast cancer.

We have recently completed a study involving metastatic breast cancer patients. This study is part of Dr. Lohmann's PhD thesis, which will be defended in first quarter 2019. Dr. Lohmann studied metabolic/ inflammatory/tumor marker and circulating tumor cells (CTCs) in 96 women with metastatic breast cancer. CTCs were present in 70% of patients. CTCs were more frequent in the presence of bone and liver metastases. CTCs were significantly associated with several inflammatory markers and they were inversely associated with BMI and obesity markers. This work formed part of Dr. Lohmann's PhD thesis work. This project has been completed and published.

In future CTC research in our Late Recurrence study we have partnered with EPIC Science (US) who have developed a more rigorous approach to CTC assays than was possible using the CellSearch technology that we have used for the past 5 years.

In the past year, there has been a scientific shift to novel forms of liquid biopsies, particularly those focusing on circulating tumor DNA (ctDNA) which can be detected in very small amounts thanks to rapid evolution of laboratory techniques. Dr. Scott Bratman is using techniques he developed in other cancers (including head and neck, lung and pancreas) to develop targeted assays in breast cancer patients. He and Dr. Dave Cescon have 3 clinical studies underway that have received Hold'em (and other) funding:

A. Design and Validation of ctDNA Assays to Predict Relapse and Guide Systemic Therapy in Early Breast Cancer

Drs. Cescon and Bratman are leading a multi-center study in the preoperative breast cancer (co-funded by the Canadian Cancer Society who fund clinical aspects of the study), to develop a blood-based assay of ctDNA to monitor response to neoadjuvant chemotherapy and predict subsequent breast cancer recurrence. Hold'em funds the development of novel approaches to quantify ctDNA in this population. 51 (of 100) subjects have been enrolled. Results are expected in 2-3 years.

Plans for 2018/2019 – This study will continue to enroll patients.

B. Characterization of Rapid Release of ctDNA as a Biomarker of Chemotherapy Response in Advanced and Locally Advanced Breast Carcinoma

A second clinical study in advanced/metastatic breast cancer study is examining the release of ctDNA into the blood to test whether a ctDNA spike within the 1st week of treatment may reflect sensitivity of the tumour to treatment (ie: the release of ctDNA is from cells that have been killed by chemotherapy), providing early evidence of a favorable clinical response to treatment. Women with locally advanced (n=20) or metastatic (n=20) breast

cancer who are set to receive neoadjuvant or first line chemotherapy will provide blood for ctDNA analysis at several time points within the first week of initiating chemotherapy.

Plans for 2018/2019: This study will continue to enroll patients.

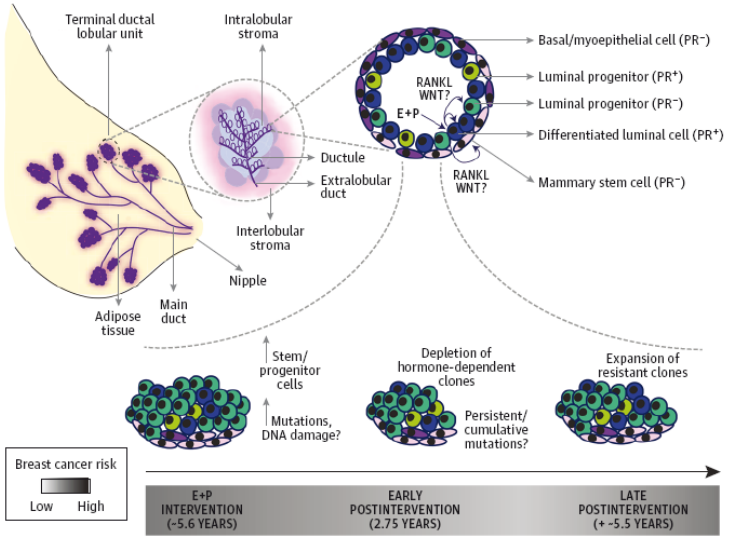
C. Exploration of Factors Associated with Imminent Risk of Late Recurrence in Hormone Receptor Positive Breast Cancer

Dr. Bratman will develop assays for ctDNA detection in women enrolled onto the Late Recurrence study. Given the fast pace of ctDNA technical and commercial developments in this area, the ctDNA analysis platform(s) selected for this study will depend upon perceived accuracy, cost, and plasma requirements at the time of analysis. Results from Projects 1 and 2 described above will also inform the selection of the analysis platform.

Plans for 2018/2019: This work will be ongoing.

4. Hormonal and Bone Related Factors

A. Dr. Khokha's group is unravelling the role of hormones in the development of breast cancer, with a focus on progesterone and RANK-L (a bone-related molecule) and their impact on breast cancer stem cells. Her work has provided an explanation for why certain types of menopausal hormone therapy lead to increased breast cancer risk while others do not.



From an editorial in JAMA Oncology (2015) written by Hold'em scientists Drs. Purna Joshi (Post-doc), Pamela Goodwin and Rama Khokha.

Purna Joshi (Post-doctoral fellow expanded this work to investigate fat and stem cells in the breast, and their potential contributions to breast cancer development. She is using a combination of experimental tools (including mouse models) to conduct this research.

Dr. Alison Casey (Post-doctoral fellow) has identified key regulatory proteins in breast cells and matching these proteins to drugs to test their effects on growth (in the test tube and in mouse models).

Plans for 2018/2019: This work has been completed; manuscripts will be prepared.

B. In laboratory research that is complementary to the clinical late recurrence study, Dr. Daniel Schramek is conducting laboratory research, using mouse models of breast cancer, to understand why late recurrences happen. As part of this research, Dr. Schramek has hypothesized that wound responses or injury might be the "match that lights the fire" of late metastatic recurrence and he has devised experiments in mice to test this hypothesis.

Dr Schramek's research, which is also funded by Komen for the Cure, has three aims:

i. To develop a mouse model of breast cancer spread - this work is well underway. Early findings have demonstrated that it is possible to replicate the conditions of breast cancer spread in the mouse.

ii. Identify mechanisms of breast cancer dormancy and exit from dormancy - the mouse model being developed in aim 1 allows Dr. Schramek to follow cancer cells in the mice to understand where they go, leading to enhanced understanding of breast cancer dormancy and late recurrence. This work is expected to lead to therapeutic interventions designed to prevent cells from exiting dormancy and becoming clinical metastases. It will also inform the assays we perform in patients enrolled onto our Late Recurrence study.

iii. Searching for the trigger of metastasis formation – Dr. Schramek will focus on why cancer cells grow into metastatic lesions, highly relevant to the development of late recurrences.

Plans for 2018/2019: This work will continue in 2018/2019.

5. Breast Translational Research Resource (BTRR)

With Hold 'em funding we have established a **Breast Translational Research Biorepository** that includes tumor tissue, normal breast tissue, blood and clinical information (including follow-up) on over 840 women with early breast cancer – this biorepository is a rich research resource that will have its greatest value and impact in the next 4 years as some of the participants experience a recurrence or metastasis of their cancer. At that time it will become possible to conduct more detailed investigations into why some women develop metastases while others do not – an important complement to our planned late recurrence study.

In the meantime, this resource has already been proven valuable to several groups of investigators at Mount Sinai's Lunenfeld Tanenbaum Research Institute, Princess Margaret and University of Toronto to conduct targeted research into, for example, differences in the characteristics of breast cancer in obese vs. non-obese breast cancer patients.

As of June 2018, a total of 840 breast cancer patients have been enrolled into the BTRR. The BTRR includes annual clinical follow-up. Forty cases have experienced recurrences. In addition, 57 patients have had benign tissues registered with the BTRR in response to investigators' need to examine markers of breast physiology.

The following studies have been approved by the BTRR for access to samples:

- BTRR Obesity: A study of estrogen signaling, insulin signaling, and inflammatory pathways in women with ER+/HER2- breast cancer (Drs. P. Goodwin and M. Chang - described above)
- qTAP in breast cancer tissue: A component of a proteomics study that assess the signaling state of tumours, in particular receptor tyrosine kinase networks in HER2+ cancers and the Hippo pathway in triple negative disease. (Prof. J. Wrana, PI).
- Targeting precursor cell determinants to personalize cancer therapy (Dr. R. Khokha) clinical follow-up

Additional studies are pending approval, including a collaborative integration of BTRR data with an international study on Reducing the Burden of Breast Cancer in Young Women ("RUBY"), led by Dr. Steven Narod (Toronto) and Dr. May Lynn Quan (Calgary) and the above-mentioned study of body composition in relation to obesity and metabolism.

Future Focus

We are committed to ensuring access to BTRR samples is collaborative and free of prohibitive administrative barriers. Dr. Wrana's breast cancer study (see above) was successful in obtaining funding from the CQDM/CIHR Collaborative Funding Program in Personalized Medicine to Accelerate Drug Discovery based on the availability and support of the BTRR. We will continue to emphasize availability of the BTRR to support a wide range of investigations. Information on available holdings can be found in Appendix 6.

This is an important resource for the entire University of Toronto community, developed, curated and maintained using Hold'em for Life funds.

BTRR Holdings

- blood (fasting & non-fasting; aliquots of whole blood, serum, and plasma)
- tissue (tumour & benign)
- clinical annotation (demographics, risk factors, pathology and staging, treatment, recurrence, death)

Biorepository facilities (Lunenfeld-Tanenbaum Research Institute) where BTRR samples are processed and stored.

Sample Access & Utilization

- HIGH QUALITY, COLLABORATIVE & FREE OF PROHIBITIVE ADMINISTRATIVE BARRIERS

Plans for 2018/2019: In 2018-19, work related to the BTRR will continue as in previous years, allowing this resource to mature. We anticipate we will continue to enroll 150-200 women annually (with an ultimate goal of 1250-1500 breast cancer patients, with >5 years average follow-up in another 4 years). This number will be sufficient to conduct a broad range of detailed prognostic and biologic investigations. In the interim, we will continue to support novel research questions as they arise, ensuring that we do not deplete our resources for the critically important prognostic studies that will be possible once this resource matures.

Clinical Trials Infrastructure Support

In addition to these five planks, we have also supported clinical trials infrastructure that facilitates participation in multicenter Phase 2 and 3 clinical trials. To date, this clinical research infrastructure support has been allocated primarily to MSH – a listing of studies/accrual is appended (Appendices 4 & 5). This support has enhanced accrual and will continue to be allocated. We are now expanding our support to three PMH based studies, two of which are led by Dr. Dave Cescon (medical oncologist and clinician scientist, PMH); (i) REFLECT – a prospective study incorporating the generation and pharmacologic testing of patient-derived xenografts (PDX) in the context of a drug development and clinical cancer genomics program for triple negative breast cancer patients with residual disease after neoadjuvant therapy or with metastatic disease and (ii) GENIUS – an exceptional responders (or non-responders) protocol incorporating genomic characterization of clinical tumour material similar to the Exceptional Responders program based at the NIH (US). The third study, led by Dr. Bratman, is the Characterization of Circulating Cell-Free DNA (cfDNA) as a Biomarker of Chemotherapy Response in Advanced and Locally Advanced Breast Carcinoma (described above). These studies are specifically aligned with "treatment of metastatic disease" and will recruit patients from PMH and MSH.

Much of our work has leveraged funding from other sources and/or has been layered onto existing infrastructure or clinical trials – this has allowed us to have an impact that is greater that would have been possible using only Hold'em funding. The enhanced level of clinical trial activity (Appendix 4) has recently facilitated membership of MSH-Oncology in the Canadian Cancer Clinical Trials Network (3CTN) which provides additional infrastructure support for clinical trials.

Trainees

Throughout our Hold'em work we have been dedicated to involving 25 trainees (both basic and clinical) in our research activities. These trainees have been embedded into all of our clinical and basic research and have been given the opportunity to be part of a truly multidisciplinary research team. Support has involved one or more of: salary, access to research subjects and databases, material support for laboratory supplies and other direct research costs, travel to scientific meetings to present results of Hold'em funded research. Some trainees have leveraged this Hold'em support to obtain additional peer-review fellowship/studentship support, freeing up Hold'em funds for additional trainees. The majority of our 20 trainees have been enrolled into Graduate programs and/or post-doctoral positions. Several have gone on to hold academic positions at the University of Toronto and elsewhere.

A list of trainees is provided in the Appendix 1.

Appendix 1: List of Hold'em Scientists, Trainees (those supported by Hold'em in 2017/2018 are highlighted) and Staff

	Mt. Sinai Hospital (MSH) Lunenfeld-Tanenbaum Research Institute (LTRI)	Princess Margaret Hospital (PMH-University Health Network) Princess Margaret Hospital Research Institute (PMHRI)
Medical Oncology/ Surgical Oncology	**Pamela Goodwin** *Trainees* • **Isabel Pimentel, MD** (Clinical Research Fellow, Feb 2018-Mar 2019 – (1) The effect of metformin on sex hormones in non-diabetic breast cancer patients in CCTG MA.32, (2) The association of sarcopenia with BMI and metabolic markers in early breast cancer patients • **Ana Lohmann, MD** (2013-present) - (1) Prognostic associations of vitamin D in NCIC MA.21, a phase III adjuvant randomized trial of three chemotherapy regimens in high risk breast cancer, (2) Pilot study of the association of obesity associated factors with circulating tumour cells in metastatic breast cancer, (3) Anthropometric measurements, metabolic factors, diet and physical activity in long-term breast cancer survivors: change from diagnosis and comparison to non-breast cancer controls. (4) Effects of metformin versus placebo on Vitamin B12 metabolism in non-diabetic breast cancer patients in CCTG MA.32 (5) Association of obesity with breast cancer outcome in relation to breast cancer subtype (6) Association of metabolic, inflammatory and tumor markers with circulating tumor cells in metastatic breast cancer • **Katarzyna Jerzak** (MSc student, 2016-present; MSH & Sunnybrook) Hepcidin in Breast Cancer (Note – Primary Supervisor, MSc) • **April Rose** (2013) - Vitamin D and early stage breast cancer prognosis (Note – Medical Student, McGill University, Montreal)	**David Cescon, MD, PhD**

	Mt. Sinai Hospital (MSH) Lunenfeld-Tanenbaum Research Institute (LTRI)	Princess Margaret Hospital (PMH-University Health Network) Princess Margaret Hospital Research Institute (PMHRI)
	• **Ariadna Tibau, MD** (2012-2014) - (1) Pilot study of the association of obesity associated factors with circulating tumour cells in metastatic breast cancer, (2) Post-surgical highly sensitive C-reactive protein and prognosis in early-stage breast cancer, (3) Non-estrogenic obesity-related variables and breast cancer prognosis – A systematic review and critical appraisal (Note – Primary Supervisor, Clinical Research Fellowship) • **David Cescon, MD** – (2012-2014) - Vitamin D in breast cancer. (Note – Medical Oncology Fellowship Secondary Supervisor) • **Saroj Niraula, MD, MSc** (2009-2012) – Clinical and biologic effects of metformin in early stage breast cancer. (Note – Medical Oncology Fellowship Co-Supervisor 2009-2012; MSc Supervisor 2010-2012; completed MSc in 2012 but is still involved in related publications) • **Ryan Dowling, PhD** (2009-2014) - Biological characterization of patient samples, relationship between obesity, insulin and breast cancer, CTCs (*Note – Research Fellow, Co-Supervisor, Dr. Vuk Stambolic Princess Margaret Cancer Centre Primary Supervisor*) • **Sara Soldera** (2016-2017) – Clinical research fellow – investigation of sexual functioning in breast cancer survivors • **Angela Shellenberg** (2017-2018) – Surgical fellow – The impact of surgery and trauma on risk of late recurrence in breast cancer patients	
Pathology	**Martin Chang** *Trainees*: • **Dr. Zohreh Eslami**- CLSB and Obesity • **Dr. Mahdi Rahimi** - MA.21/MA.32 correlatives (to June 30, 2017) • **Dr. Blerta Starova,** Pathology Resident, 2016-17, HR-Obesity • **Dr. Aysegul Sari,** Research Associate, 2017-2018, BTRR, MA21/MA32 Correlative	

	Mt. Sinai Hospital (MSH) Lunenfeld-Tanenbaum Research Institute (LTRI)	Princess Margaret Hospital (PMH-University Health Network) Princess Margaret Hospital Research Institute (PMHRI)
Radiation Oncology		**Scott Bratman, MD, PhD** Jenna Kara
Statistics	**Marguerite Ennis, PhD**	
Laboratory	**Jim Woodgett** *Trainee*: • **Jennifer Gorman,** PhD (2011-2017) - Evaluation of genes implicated in metastatic spread and circulating tumour cell populations. **Daniel Schramek** *Trainee*: • **Ellen Langille,** PhD student (2016-present), Elucidating genes that drive breast cancer initation, progression and late recurrence • **Jacob Berman,** MSc technician (2017 – present) genetic models of breast cancer	**Vuk Stambolic** **Ryan Dowling** *Trainees*: • **Ryan Dowling, PhD** (2009-2016) - Biological characterization of patient samples, relationship between obesity, insulin and breast cancer, CTCs • **Lauren Podmore**, PhD student • **Yekaterina Poloz, PhD** (2014-2017) - The role of insulin receptor in breast cancer. • **YingJu Chang, PhD** (2013-2015) - Biology of PDZ-RhoGEF, a key regulator of adipose tissue development and a modulator of cancer development and metastasis. **Rama Khokha** *Trainees*: • **Alison Casey, PhD** (2012-2018) - Targeting mammary progenitor cell activity for chemoprevention • **Purna Joshi, PhD** (2012-present) - Host factors in mammary stem cell niche, breast cancer risk • **Pirashaanthy Tharmapalan, PhD Candidate** (2015-present) - Role of progesterone receptor in mammary subsets • **Hyeyeon Kim, PhD Candidate** (2015-present) - DNA damage response in the mammary gland
Program Staff	**Linda Bennett,** Project Manager (2014-current) **Elma Lee,** Project Coordinator **Karman Fazaee,** Clinical Research Coordinator **Lakshmi Rao,** Clinical Research Coordinator	Program Staff provide support at PMH for trials led by MSH and PMH.

	Mt. Sinai Hospital (MSH) Lunenfeld-Tanenbaum Research Institute (LTRI)	Princess Margaret Hospital (PMH-University Health Network) Princess Margaret Hospital Research Institute (PMHRI)
	Bee Ling Lu, Clinical Research Coordinator **Olivera Jugovic,** Clinical Research Coordinator **Maria Chu,** Data Entry **Cary Greenberg** (2012-2014)	

Appendix 2: Hold'em Program Timelines and Progress

Hold'em Supported Research Activities	July 2012 - Mar 2013 (8 mths)			Apr 2013 - Mar 2014				Apr 2014 - Mar 2015				Apr 2015 - Mar 2016				Apr 2016 - Mar 2017				Apr 2017-Mar 2018			
	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar
Basic Studies																							
Khokha Lab	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Stambolic Lab	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Bratman Lab																				P	P	P	P
Translational Studies																							
MA.21 Correlative - Assays									B	B	B/S	Pu	CS										
MA.21 Correlative - Tissue	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
MA.32 Translational - DNA Extraction & SNP Analysis																		B	B	B	B	S	CS
MA.32 Translational - Inflammatory & Metabolic Factors		B/S	B/S	B/S	B/S	B/S	B	B	B	B	B	B/S	B/S	B/S	B/S	B/S	B/S	B/S	B/S	B/S	B/S	B/S	CS
MA.32 Translational - Tumour Marker Ca 15-3/MUC-1																	B	B	B	B	S	S	CS
TRR Obesity									P	P	E/C	A	B	B	S	S	S	Pu	Pu	CS			
NRF Additional Analysis - Inflammatory Markers																P	E	B	S	S	S	S	CS
NRF Additional Analysis - Iron Studies																P	P	B	S	S	S	CS	
NRF Additional Analysis -CLSB & Obesity Protocol	T	T	T	T	T	T	T	T	T	T	T	T	S	Pr								Pr	CS
GENomic Investigation of UnuSual responders (GENIUS)																	C	C	C	O	O	O	O
Clinical Studies																							
AI Host Factor	E/C/A	R	R	R	R	R	R	O	O	O	R/B	B/S	S	S/Pr				Pr			Pu	CS	
OZM-027	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	O	O	CS	S	CS

Hold'em Supported Research Activities	July 2012 - Mar 2013 (8 mths)			Apr 2013 - Mar 2014				Apr 2014 - Mar 2015				Apr 2015 - Mar 2016				Apr 2016 - Mar 2017				Apr 2017-Mar 2018			
	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar
CTC Host Factors	P	E/C/A	R	R	R	R	R	R	R	R	CS	R/B	B/S	Prx 2	CS								
COMETI-P2	P	P/E	E/C	C	R	R	R	R	R	R	R	R	O	CS				Pr	CS				
Pre-Peri						P	P	E/C	A & R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Late Rec PILOT (Questionnaire)														P	P	E/C	R/A	R	R	R	R	CS	
ctDNA in Adv BC																		P	P	P	E/C	E/C	E/C
Exploration of Factors Associated with of Late Recurrence (Late Rec COHORT)																					P	P	E/C
Biospecimen Repository																							
BTRR - Cancer	P	P	E/C	A	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
BTRR - Benign						P	P	E/C	A	R	R	R	R	R	R	R	R	R	R	R	R	R	R
TRR Obesity Study									P	P	E/C	B/S	B/S	S	S	S	PR	CS					
TRR Sarcopenia																							P
Clinical Trials Infrastructure																							
Endocrine Therapy & Cognition_2015 Sept										EC	EC	R	R	R	R	F	F	F	CS				
MA 17.R	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	CS				
MA.24 HERA BO16348_Roche NCIC	R	R	R	R	R	R	R	R	F	F	F	F	F	CS									
MA.32 (activated Oct2010; recruit closed 01-2013)	R	R	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F
MA.32 F (activated dec2011; recruit closed 01-2013)	R	R	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
MA.34 Hoffmann-La Roche APHINITY Study	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
MAC 15 / SWOG 1007	R	R	R	R	R	R	R	R	R	R	F	F	F	F	F	F	F	F	F	F	F	F	F
MAC 18 A221405 POSITIVE NCIC																	E/C	A	R	R	R	R	R
MAC 20 A011401 BWEL NCIC																	E/C	E	P	P	R	R	R
OCOG-2007-LISA	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	S	CS
OCOG-2015-AToM															E	R	R	R	O	O	CS		

Hold'em Supported Research Activities	July 2012 - Mar 2013 (8 mths)			Apr 2013 - Mar 2014				Apr 2014 - Mar 2015				Apr 2015 - Mar 2016				Apr 2016 - Mar 2017				Apr 2017-Mar 2018			
	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar
Metformin in Early BC (KG080358)	CS																						
NSABP B-36 (activated June 2006; recruit closed 07-2008)	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F
NSABP B-42 (activated 2007Aug; recruit closed 01-2010)	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F	O/F
REFLECT PDX post-neoadj TNBC w residual disease																P	P	E	E	P	E	E	E
Survivorship & NRF Studies	CS																						
EMBRACE-MRI Study																				P	E	E	E
Autofluorescent Imaging of BC Using Microendoscopy																				P	E	E	E
Wide-Field Optical Coherence Tomography																				P	E	E	E

Legend:

P = Planning
E/C = Ethics and Contracts
A = Activate
R = Recruitment
O=Ongoing

F= Follow up only
CS= Completed Study
B = Blood Assays
T - Tissue Assays
S = Statistical Analysis

Pr = presentation
Pu = preparing publication

Appendix 3: Hold'em Funded Clinical Studies

Study	Description	Enrollment/Target	Centres	Status
Host Factor – CTC Goodwin/Chang	Observational study examining the association of CTCs with host factors (notably BMI, insulin, glucose) in metastatic BC with progressive disease.	96 evaluable/100	MSH (Mar 2013); PMH (Feb 2013); LHSC (Aug 2013); SMH (Mar 2014)	study completed; assays and analysis ongoing
Host Factor – AI Cescon/Sridhar	Two step study in women receiving adjuvant letrozole. Part A- association of Vitamin D, BMI and estrogen levels at standard dose. Part B (BMI > 25) - change in estrogen levels with double-dose letrozole.	Total 113 evaluable/106 **Grp A** (BMI ≤ 25) = 65 completers **Grp B** (BMI>25) = 34 completers Std dose = 113; Dbl dose = 34	MSH (Nov 2012); PMH (Oct 2012); WCH (Feb 2013); SHSC (Apr 2014)	Mar 2015 – interim (futility) analysis completed study completed; analysis ongoing & manuscript preparation
OZM027 Goodwin	Phase II RCT of Metformin vs placebo in addition to 1st, 2nd, 3rd or 4th line CXT in metastatic BC; endpoint PFS.	40/40	MSH (Aug 2011), PMH, London, Windsor, SMH	Study completed; assays & analysis completed. Manuscript in preparation
COMETI Goodwin/Amir	Phase II multicentre trial of CTC characterization in metastatic ER+, Her2 neg BC	6 at MSH (1 screen fail; 4 ET) 6 at PMH (0 active; 6 ET) Study recruitment ~110 subjects	MSH (open Aug 13) PMH (open May 2014)) Multiple USA sites	study completed
Pre-Peri - Chang, Escallon, Goodwin, Stambolic, Dowling	Biomarker evaluation in pre-operative and peri-operative tissues	28/40 16-completed;11 IDL; 1 early term (surgery elsewhere; pt withdrew)	MSH (open Jul 2014)	recruitment ongoing
MA 32 Correlative Stambolic, Dowling, Chang, Goodwin	Phase III Intergroup Adjuvant Trial of Metformin vs placebo in early BC Blood – metabolic factors Tissue – TMA construction & IHC analysis DNA extraction and SNP analysis	3649 Pts Paired Blood Specimens: 2,586 Pts Baseline Only Blood Specimens: 370	> 200 sites in 4 countries	study completed; assays and analysis ongoing
CLSB & Obesity Protocol NRF 2014 Chang	Tissue Biomarkers Associated With Obesity: A Retrospective Pathology Analysis for Crown-Like Structures of the Breast and Adipocyte Size	99	MSH	study completed; scoring ongoing

Study	Description	Enrollment/Target	Centres	Status
BTRR-Cancer	Translational Research Resource for Breast Cancer	Enrolled 840 Surgery completed 806	MSH UHN (recruitment only)	recruitment ongoing
BTRR Benign	Translational Research Resource for Benign Breast Cases	Enrolled 58 Surgery completed 57	MSH UHN (recruitment only)	recruitment ongoing
BTRR-Obesity Goodwin	Association of Obesity and Associated Physiologic Factors with Estrogen, Insulin and Inflammatory Signaling in Estrogen Receptor Positive, HER2 Negative Primary Breast Cancer	129/129 Bloods 120/129 Tissue	2014Oct1-2015Sept30	blood assays completed; data extraction completed; tissue assays completed; analysis ongoing
BTRR - Sarcopenia	The association of sarcopenia with BMI and metabolic markers in early breast cancer patients	320 eligible cases	2013 May – 2018 Apr	Planning and protocol revision ongoing

Appendix 4: All Hold'em Supported Clinical Studies

HOLD'EM SUPPORTED PROGRAMS	DESCRIPTION	Status
CTC Platform & ctDNA		
Chang-Bratman - CTC & cDNA in Adv BC_2015Sept	Characterization of Circulating Cell-Free DNA (cfDNA) as a Biomarker of Chemotherapy Response in Advanced and Locally Advanced Breast Carcinoma	protocol written REB review
Goodwin - Janssen COMETI P2 Trial	CTC characterization in metastatic ER+, Her2 neg BC	study completed
Goodwin - CTC Host Factors Study	CTCs with host factors (notably BMI, insulin, glucose) in metastatic BC with progressive disease	study completed assays/analyses ongoing
Metabolism - Clinical & Signaling		
Goodwin-Cescon – Host Factors in ER+ Late Recurrence	Exploration of Factors Associated with Imminent Risk of Late Recurrence in Hormone Receptor Positive Breast Cancer **(Late Rec COHORT)**	ethics review
Goodwin - Host Factors in ER+ Late Recurrence	Patient (Host) Factors Associated with Late Recurrence in ER+ Breast Cancer (Late Rec PILOT)	study completed
Lohmann - Inflammatory Markers - NRF Additional Analysis	Inflammatory Markers [Nutrition Related Factors in Breast Cancer: Continuation of Survivorship Study (CT158) Clinic In LIS: CT318]	assays completed; analysis ongoing
Jerzak – Hepcidin - NRF Additional Analysis	Hepcidin in Breast Cancer [Nutrition Related Factors in Breast Cancer: Continuation of Survivorship Study (CT158) Clinic In LIS: CT318]	assays completed; analysis ongoing
Chang-Biomarkers in Pre- and Peri-Op tissues Study	Biomarker evaluation in pre-operative and peri-operative tissues	study ongoing
Goodwin - OZM 027	RCT Metformin vs placebo plus 1st, 2nd, 3rd or 4th line CXT in metastatic BC; CTC measurement added June 2013	recruitment completed; assays & analysis ongoing
Cescon-Sridhar - AI Host Study	Vitamin D, BMI and estrogen levels in women receiving adjuvant letrozole	study completed assays/analyses completed. Manuscript in preparation.
Chang-CLSB & Obesity Protocol NRF 2014	Tissue Biomarkers Associated With Obesity: A Retrospective Pathology Analysis for Crown-Like Structures of the Breast and Adipocyte Size	study completed assays/analyses ongoing
Goodwin - MA 32 Correlative	Metformin Versus Placebo on Recurrence and Survival in Early Stage Breast Cancer	study completed assays/analyses ongoing

HOLD'EM SUPPORTED PROGRAMS	DESCRIPTION	Status
Goodwin - MA.32 – DNA extraction/SNP	Correlative Research in NCIC MA.32 (Adjuvant RCT of Metformin vs Placebo): DNA extraction and known SNP analysis	study completed assays completed; analyses ongoing
Goodwin-Dowling - MA.21 Correlative	Combination Chemotherapy With or Without Colony-stimulating Factors in Treating Women With Breast Cancer	study completed assays/analyses ongoing
Goodwin - Metformin in Early BC (KG080358)	Clinical and Biologic Effects of Metformin in Early Stage Breast Cancer	study completed assays/analyses completed
Hormone Factors		
Khokha (Elser) Proteomics/progesterone	Reproductive hormones; identify in radiology; blood testing	planning
Genetics		
Cescon - GENomic Investigation of UnuSual responders (GENIUS)	Sequencing "exceptional responders" or those who responded poorly will elucidate functional mechanisms of tumour behavior and drug response	ongoing
Cescon - REFLECT PDX post-neoadjuvant TNBC with residual disease	PRospective Evaluation of Freshly ImpLantEd Cancers in Mice to Test Drug Response in Matching Host	Open (UHN); REB submission (MSH)
BTRR - Translational Research Resource		
*BTRR - Cancer (including PABC)	Translational Research Resource for Breast Cancer	ongoing
*BTRR – Benign	Translational Research Resource for Benign Breast Cases	ongoing
Participation – Hold'em Enabled		
Elser - MAC 18 A221405 POSITIVE NCIC	A Study Evaluating the Pregnancy Outcomes and Safety of Interrupting Endocrine Therapy for Young Women with Endocrine Responsive Breast Cancer who Desire Pregnancy	ongoing
Elser - Endocrine Therapy & Cognition_2015 Sept	Cognitive Sequelae of Adjuvant Endocrine Therapy for the Treatment of Breast Cancer in Older Women [Cognition in 60+ on Tam]	completed; analysis ongoing
Elser- Decision Aid Incidental Genomic Findings_2015Dec	Randomized Controlled Trial of a Decision Aid for Incidental Genomic Findings	planning
Goodwin - A011401-BWEL	Phase III Trial Evaluating the Role of Weight Loss in Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer	initiation
Elser - OCOG-2015-AToM_2015Aug10	Pragmatic Cluster-Randomized Trial of Ambulatory Toxicity Management in Patients Receiving Adjuvant or Neo-adjuvant Chemotherapy for Early Stage Breast Cancer (AToM)	completed
OCOG-2007-LISA	Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer (LISA)	ongoing

HOLD'EM SUPPORTED PROGRAMS	DESCRIPTION	Status
Elser - B-42	A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer	ongoing
MA.34 APHINITY	A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	ongoing
B36	A Clinical Trial of Adjuvant Therapy Comparing Six Cycles of 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) to Four Cycles of Adriamycin and Cyclophosphamide (AC) in Patients With Node-Negative Breast Cancer	ongoing
MA.17R	A Double Blind Randomization to Letrozole or Placebo for Women Previously Diagnosed with Primary Breast Cancer Completing Five Years of Adjuvant Aromatase Inhibitor Either as Initial Therapy or After Tamoxifen	ongoing
Goodwin - MAC 15 Study	RCT ADJUVANT ENDOCRINE THERAPY +/- CHEMOTHERAPY IN PATIENTS WITH 1-3 POSITIVE NODES, HR+ & HER2-NEGATIVE BREAST CANCER WITH RECURRENCE SCORE (RS) OF 25 OR LESS. RXPONDER	enrollment closed; study ongoing
Goodwin - Survivorship & NRF Studies	Survivorship in a Long-Term Breast Cancer Cohort: Integration of Biologic, Psychological and Health-Related Quality of Life Factors / Nutrition Related Factors in Breast Cancer	study completed assays/analyses ongoing
Elser - MA24 HERA BO16348_Roche	Randomised Three-Arm Multi-Centre Comparison of 1 Year and 2 Years of Herceptin* Versus no Herceptin* in Women with HER2-Positive Primary Breast Cancer Who Have Completed Adjuvant Chemotherapy	study completed assays/analyses ongoing

Appendix 5: Hold'em Funded Research – Peer Review and Funding Partners

Type of Study	Hold'em Role	Name of Project	PI PI(s) (Institution)	Current Status	Peer review	Other Funders
Clinical Study	Full Funder	ctDNA in Adv BC	Cescon (UHN), Bratman (UHN) Chang(MSH)	protocol written, REB submission prepared	SAB	CCSRI $450,000
Clinical Study	Full Funder (Breast pts)	GENomic Investigation of UnuSual responders (GENIUS)	Cescon (PMH)	up to 10 breast patients to be enrolled	SAB	PMRI
Clinical Study	Full Funder	MA.21 Correlative - Tissue**	Goodwin (MSH) - Chang (MSH)	TMA construction and scoring ongoing	CTEP, CCTG, CCSRI	CTEP (NIH), CCSRI
Clinical Study	Full Funder	NRF Additional Analysis - Inflammatory Markers	Lohmann	assays completed & analyses ongoing	SAB, UofT Grad Student Committee	BCRF, MRC (currently CHRI), NCIC (currently CCSRI) ($1.3Million)
Clinical Study	Full Funder	NRF Additional Analysis - Hepcidin	Jerzak (SHSC) Goodwin (MSH)	assays completed & analyses ongoing	UofT Grad Student Committee	See above
Clinical Study	Full Funder	NRF Additional Analysis - CLSB & Obesity Protocol	Chang (MSH)	assays completed; manuscript in preparation	SAB	See above
Clinical Study	Full Funder	Pre-Peri biopsy study	Chang, Escallon, Goodwin, (MSH) Stambolic, Dowling (PMH)	accrual ongoing	Hold'em SAB	
Clinical Study	Joint Funder	Patient (Host) Factors Associated with Late Recurrence in ER+ Breast Cancer **(Late Rec PILOT)**	Goodwin (MSH;	study completed; analyses ongoing	BCRF	BCRF ($325,000)

Type of Study	Hold'em Role	Name of Project	PI PI(s) (Institution)	Current Status	Peer review	Other Funders
Clinical Study	Joint Funder	Exploration of Factors Associated with Imminent Risk of Late Recurrence in Hormone Receptor Positive Breast Cancer **(Late Rec COHORT)**	Goodwin (MDH; Cescon (UHN); Jerzak (SHSC)	Ethics review	BCRF, Hold'em SAB	BCRF $750,000 EPIC Science $14,000,000 (over 4 years)
Clinical Trial	Joint Funder	OZM 027**	Goodwin (MSH)	study completed; analyses ongoing	BCRF, Health Canada	BCRF $475,000
Laboratory	Full Funder	Human Atlas of Insulin Receptor Expression in Cancer	Stambolic (UHN)		PMHRI	
Clinical Study	Full Funder	BTRR - Benign	Goodwin (MSH) Chang (MSH)	ongoing accrual	SAB	The BTRR is a resource for researchers funded by Hold'em - researchers obtain external funding for specific projects that utilize the BTRR resources - those granting agencies review the specific projects - for example, see "Obesity associated signalling and pathway activation in ER+ breast cancer" below
Clinical Study	Full Funder	BTRR-Cancer	Goodwin (MSH) Chang (MSH)	ongoing accrual	SAB	See above
Clinical Study	Joint Funder	Obesity associated signalling and pathway activation in ER+ breast cancer - BTRR study	Goodwin	study completed; analyses ongoing	BCRF	BCRF ($135,000)
Clinical Study	Full Funder	The association of sarcopenia with BMI and metabolic markers in early breast cancer patients- BTRR study	Goodwin	Planning and protocol revision	Pending	

Type of Study	Hold'em Role	Name of Project	PI PI(s) (Institution)	Current Status	Peer review	Other Funders
Clinical Trial	Joint Funder	MA.32 Translational - DNA Extraction & SNP Analysis	Goodwin (MSH)	assays & analyses ongoing	BCRF, NCI (US), CTEP, CCT-CCS, CBCF	BCRF $155,000 (in addition to MA.32 funding from BCRF, CTEP, CCSRI, CBCF, Apotex Ttl: $25million for conduct of the clinical trial)
Clinical Trial	Joint Funder	MA.32 Translational - Inflammatory & Metabolic Factors	Goodwin (MSH) Stambolic (UHN) Dowling (UHN)	assays & analyses ongoing	BCRF, NCI (US), CTEP, CCT-CCS	BCRF $125,000 (in addition to MA.32 funding from BCRF, CTEP, CCSRI, CBCF, Apotex Ttl: $25million for conduct of the clinical trial)
Clinical Study	Joint Funder	MA.32 Translational - Tumour Marker Ca 15-3/MUC-1	Goodwin (MSH)	translational assays & analyses ongoing	BCRF, NCI (US), CTEP, CCT-CCS	BCRF ($325,000 (in addition to MA.32 funding from BCRF, CTEP, CCSRI, CBCF, Apotex Ttl: $25million for conduct of the clinical trial)
Clinical Study	Joint Funder	MA.32 - The effect of metformin on sex hormones in non-diabetic breast cancer patients in CCTG MA.32	Goodwin (MSH)	Protocol Review CCTG	CCTG, NCI (US)	BCRF ($325,000 (in addition to MA.32 funding from BCRF, CTEP, CCSRI, CBCF, Apotex Ttl: $25million for conduct of the clinical trial)
Clinical Study	Joint Funder	REFLECT PDX post-neoadjuvant TNBC with residual disease	Cescon (PMH)	ongoing at UHN; awaiting protocol to open at MSH	PMHRI	PMHRI $50,000
Clinical Study	Joint Funder	Survivorship & NRF Studies	Goodwin (MSH)	study completed; assays/analyses ongoing	MRC, CCSRI, BCRF	BCRF $420,000 (in addition to NRF funding listed above)
Laboratory	Joint Funder	Human Atlas of Insulin Receptor Expression in Cancer	Stambolic (UHN)	Study complete	CCSRI	CCSRI $200,000
Laboratory	Joint Funder	Insulin Receptor and Signalling Pathways in Human Cancer	Stambolic (UHN)	Complete	CCSRI	CCSRI $200,000
Laboratory	Joint Funder	Insulin Receptor and Human Breast Cancer	Stambolic (UHN)	Ongoing	CCSRI	CCSRI $449,910

Type of Study	Hold'em Role	Name of Project	PI PI(s) (Institution)	Current Status	Peer review	Other Funders
Laboratory	Joint Funder	Modelling the Role of the Insulin Receptor in Breast Cancer	Stambolic (UHN)	Ongoing	CCSRI	Principal Applicant - "Insulin receptor signalling in human cancer" Funder - Canadian Cancer Society Research Institute, operating grant, Impact Period: 2016-19; Total Awarded $ 449,910
Laboratory	Joint Funder	Hormone signalling in mammary cells informs breast cancer risk and treatment	Khokha (UHN)	Complete	CCSRI	CCSRI $1222,500
Laboratory	Joint Funder	Identifying dependencies of normal and cancer breast stem cells	Khokha (UHN)	Complete	CCSRI	CCSRI $40,000
Laboratory	Joint Funder	Proteome-based target discovery to impact stem and progenitors in high risk and breast cancer	Khokha (UHN)	Ongoing	CBCF	CBCF $450,000
Laboratory	Joint Funder	Rationalized depletion of breast cancer precursor cells as a strategy for breast cancer prevention	Khokha (UHN)	Ongoing	CBCF	CBCF $450,000

Appendix 6: BTRR Holdings

BTRR Asset Summary - May/2013 to May/2018						
Baseline (entry) characteristics	**Cancer**	**Key Patients**	**Non-Key patients**	**Deceased**	**Status TBD**	**Benign**
Total Screened	1837					169
Excluded/Declined	971					58
Consented	8					19
Considering	0					12
Missed/Withdrew	18					7
All BTRR Ca Participants Enrolled (May 2013-May 2018)	**840**					**73**
IDL	**24**					**15**
Withdrawn from study	**4**					**0**
Active	**812**					**58**
OR completed	**806**	**433**	**342**	**5**	**26**	**57**
Current BC Dx						
Insitu Only	**97**	**0**	**97**			
Phyllodes	**1**	**0**	**1**			
Ipsilateral New Primary Invasive	**2**	**0**	**2**			
Loco-regional recurrence	**25**	**0**	**25**			
Primary IDC	**560**	**360**	**182**	**5**	**13**	
Primary ILC	**53**	**36**	**17**			
Primary Invasive Other	**24**	**17**	**6**		**1**	
Primary Mixed Invasive	**29**	**19**	**10**			
# subjects with Mets tissue	**4**					
Age [range; mean]						
BMI [range; mean; median]	**17-45; 27; 26**					
Pre-diabetesl type 1 & type 2	**107**	50	54		3	
Currently Pregnant (Pregnancy within 12 months of diagnosis) = Yes	**6**	3	3			
Breast Ca (Invasive or insitu) PRIOR to entry = yes	**96**	8	86		2	
Other Ca PRIOR to/at entry = yes	**101**	40	60		1	
Fam Hx (1st/2nd/3rd) BC = YES	**372**	197	168	3	4	
Fam Hx (1st/2nd/3rd) BC = NO	**425**	240	175	2	8	
Genetic Testing	**217**	131	82	3	1	
BRCA1 pos	**11**	8	3			
BRCA 2 pos	**17**	7	10			
BRCA 1&2 pos	**1**	1				
Deceased	**5**					

LOCR/New primary or Distant Mets. within 2 yrs. of primary diagnosis	40
Developed LOCR after within 2 yrs. Of PIBC	6/40
Developed Metastases within 2 years of PIBC	15/40
Developed LOCR followed by Metastases in within 2 years	6/40
Developed LOCR & new primary breast cancer within 2 years	1/40
Developed new primary breast cancer within 2 years	1/40
Developed other cancer within 2 years	11/40

Primary invasive cases (666)*	N	Pre-/Peri-menopause	Post-menopause	Neo yes	Neo no	Blood	Fasting Blood	BSR Tissue	Tissue & Blood
HER2- & ER+ and/or PR+ (Key)	285	91	194	36	248	215	120	150	106
HER2- & ER+ and/or PR+ (Non-Key)	154	35	119	16	137	111	49	78	56
HER2-/ER-/PR- (TNBC) (Key)	39	15	24	14	25	33	17	15	12
HER2-/ER-/PR- (TNBC) (Non-Key)	21	5	16	3	18	20	12	12	11
HER2+ & ER+ and/or PR+ (Key)	51	20	31	22	29	41	27	24	20
HER2+ & ER+ and/or PR+ (Non-Key)	14	6	8	3	11	13	4	5	5
HER2+/ER- & PR- (Key)	17	6	11	9	8	13	8	5	4
HER2+/ER- & PR- (Non-Key)	5	1	4	2	3	3	1	1	0

May 2013- May 2018	Cancer	Benign
Completed Surgery	806	57
*Blood specimens stored in BSR	617	52
Fasting	326	28
Non-fasting	291	24
*Sufficient tissue for storage in BSR	347	47
Second tissue donation	9	5

Appendix 7: Hold'em Publications and Abstracts

Publications

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