Garvan Institute of Medical Research

UNSW THE UNIVERSITY OF NEW SOUTH WALES

# The *Connie Johnson* Breast Cancer Research Group

The Kinghorn Cancer Centre

The Kinghorn Cancer Centre
370 Victoria St, Darlinghurst, NSW 2010

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Constance Johnson OAM (1977 – 8 September 2017) was an Australian philanthropist, author, wife and mother of 2 boys. She suffered from bone cancer at age 11, uterine cancer at age 22 and finally breast cancer at age 33. She was awarded the Medal of the Order of Australia on 7 September 2017 and died the following day, aged 40.

Connie joined with her brother, actor and humanitarian, Samuel Johnson, to start the Love Your Sister charity in 2012, aiming to raise funding for cancer research. In February 2013 Samuel left Melbourne on his unicycle and rode a world record 15,000 kilometres around Australia. The ride ended after 364 days in February 2014 and raised $1.5 million, which provided the seed funding to establish the Connie Johnson Breast Cancer Research Laboratory in 2015 and the recruitment of Professor Elgene Lim to lead it.

The Connie Johnson Research Laboratory comprise a multidisciplinary team of 11 talented young scientists, clinicians and PhD students whose research is solely focussed on improving the outcomes for patients with breast cancer. Our research spans the biological understanding and therapeutic vulnerabilities of breast cancer in the lab, to clinical trials in patients.

*Research underpins medical progress, and patients are vital to this endeavour. We partner extensively with patients in many projects in our laboratory.*

# A brief Biography of Prof Elgene Lim

I was awarded my medical degree from the *University of Melbourne*, and obtained my medical oncology fellowship from the *Royal Australasian College of Physicians* (RACP) in 2006, and subsequently embarked on a PhD as a *National Breast Cancer Foundation (NBCF) Scholar* at the *Walter & Eliza Hall Institute of Medical Research* with eminent Australian breast cancer researchers Professors Jane Visvader & Geoffrey Lindeman. My research identified the aberrant cells in carriers of the BRCA1 mutant gene, a hereditary breast cancer syndrome, which are the likely culprit cells giving rise to breast cancer.

I furthered my research and clinical training in breast cancer as a *Fulbright Scholar* at the *Dana-Farber Cancer Institute* & *Harvard Medical School* in Boston under the mentorship of internationally acclaimed leaders in breast cancer research Professors Eric Winer & Myles Brown, through fellowships from the National Health & Medical Research Council of Australia and RACP.

I was awarded the *NBCF Practitioner Fellowship* in 2014 and returned from Boston to Australia. I was recruited as a Senior Staff Oncologist & Director of translational research at *St Vincent's Hospital* and *The Kinghorn Cancer Centre*, where I oversee the breast cancer department and breast cancer clinical trials portfolio. In 2017, I was awarded the inaugural *NBCF Endowed Chair.*

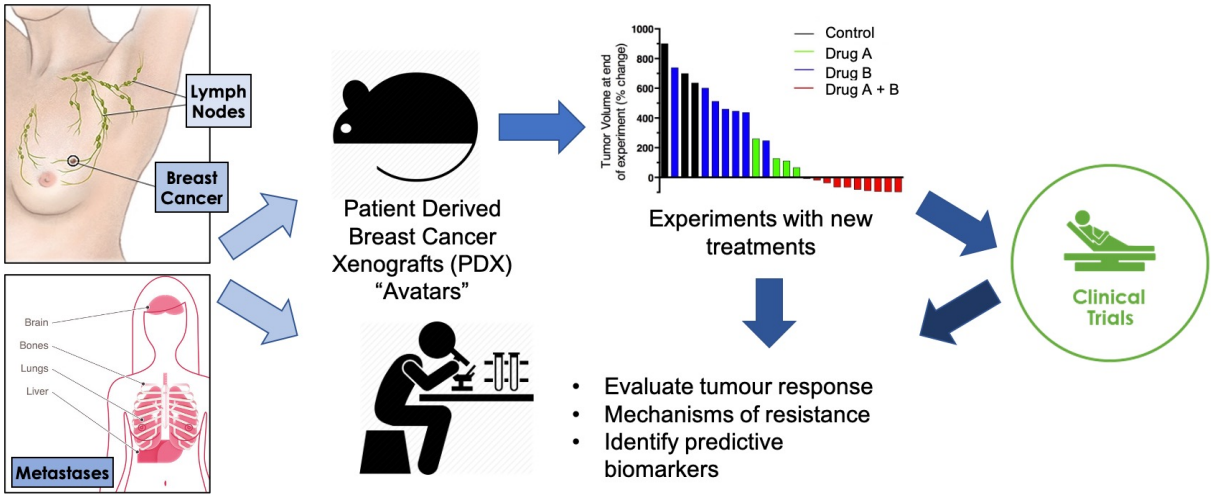
I also head the *Connie Johnson Breast Cancer Research Group* at the *Garvan Institute of Medical Research*, comprising a team of 11 talented young scientists, whose research is solely focussed on improving the outcomes for patients with breast cancer. Our research is funded through the NBCF, Love Your Sister, NHMRC, Cancer Australia, Cancer Council NSW, White Butterfly, Balnaves, St Vincent's Curran and Garvan Foundation.

I am an Associate Professor with the *University of New South Wales* School of Medicine and continue to maintain strong links with the Dana-Farber Cancer Institute. I am on the scientific advisory committee of *Breast Cancer Trials*, the peak Breast Cancer Trials Co-operative group in Australia, and the Medical Faculty Board of UNSW. I am a member of the American Association of Cancer Research and American Society of Clinical Oncologists.

*More details can be found on the following websites*

- *https://www.elgenelim.com*
- *https://www.sydneyoncology.com.au*
- *https://www.garvan.org.au/research/cancer/connie-johnson-breast-cancer-research/elglim*

# Research Themes




**Reducing the timeline for the development of new therapies for breast cancer**

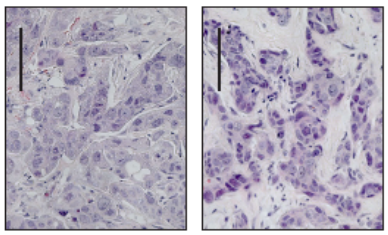
We have a number of research projects in our laboratory at any one time, from laboratory based to clinical trials. Our aim is to accelerate laboratory findings into patient care. We collaborate extensively with other researchers in Australia and Internationally. The major areas of research focus of the Connie Johnson laboratory are as follows.

## 1) Identify key clinical challenges in breast cancer where new therapies are needed

Our laboratory is focussed on identifying the current and future challenges that face patients with breast cancer. The treatment landscape is in constant evolution, and similarly, the challenges patients face and how the cancer behaves constantly evolve. As cancers learn how to evade currently used therapies, new treatment strategies are required. Patients are therefore key stakeholders and research partners in this endeavour.

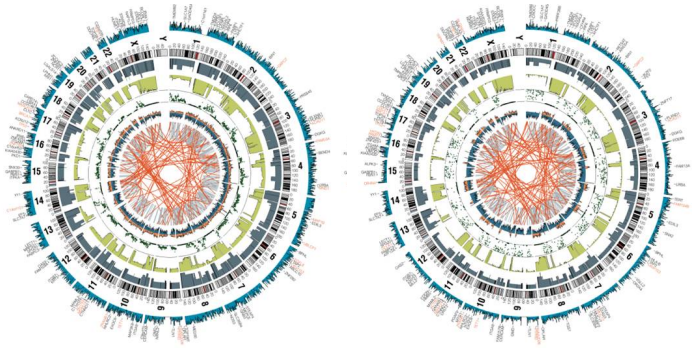
In partnership with our patients, we have established Australia's largest breast cancer **patient derived xenograft (PDX) biobank** of clinically relevant preclinical models to study resistance to cancer therapies and evaluate novel therapies. This serves as a resource for national and international breast cancer researchers.

### Histology



Patient Tumour | PDX (Avatar) Tumour

### Whole Genome Sequencing



Patient Tumour | PDX (Avatar) Tumour

**Preservation of patient tumour characteristics in PDX Avatar models**

## 2) Conduct preclinical studies to identify new therapeutic strategies and biomarkers

A key goal of my research program is to understand the underlying mechanisms of therapeutic resistance and identify new therapeutic strategies and biomarkers in order to maximise the success of bringing a therapy into patient care and rationalize the cost of drug development. An important platform are our patient derived xenograft avatar models.

*Major areas of focus include:*

### A) Targeting Hormone Receptors in Breast Cancer

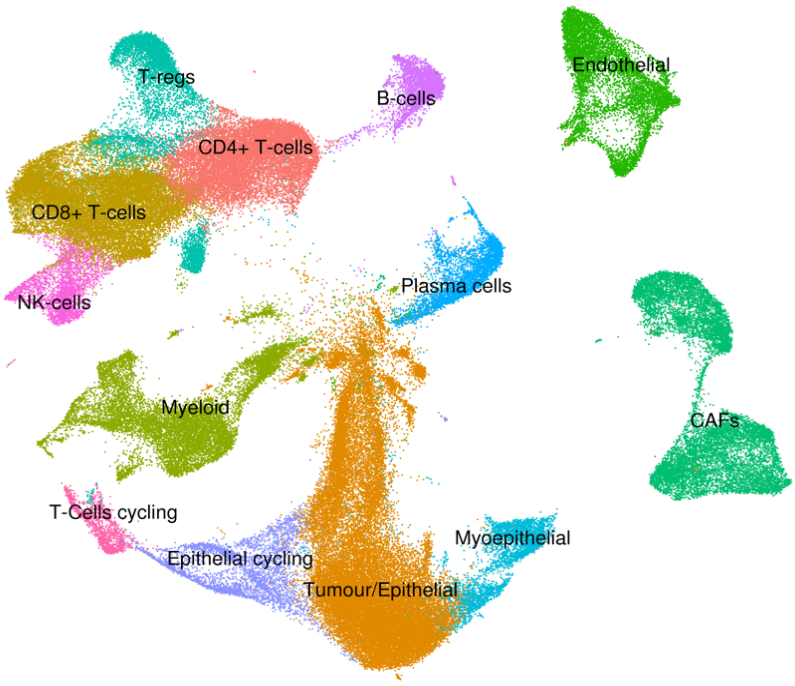
The estrogen receptor (ER) is perhaps the most well-known therapeutic target in breast cancer. Related hormone receptors such as the progesterone and androgen receptor (PR and AR) are also present in the majority of breast cancer but its role is still unclear. We are evaluating therapies that target PR and AR not currently used to treat breast cancer.

### B. Combination therapeutic strategies in breast cancer.

A major focus of our research is to study cancers that are resistant to current therapies, we evaluate combination therapy strategies to overcome key mechanisms of resistance and improve treatment efficacy.

### C. Stromal Epithelial interactions

It is increasingly clear that the tumour microenvironment plays an important role in tumour progression and response to therapy. Other than cancer cells, there is a village of other cells that interact with the cancer cells, including a patient's own immune cells, fibroblasts and blood vessels. In close collaboration with **A/Prof Swarbrick (Garvan Institute, UNSW)**, we have also started an ambitious project, the **Breast Cancer Single Cell Atlas** to dissect the complex molecular environment of breast cancers, and the discover new therapeutic strategies for metastatic triple negative breast cancer.




Breast Cancer Single Cell Atlas from 25 patients

## 3. Translating Therapeutic Strategies into Clinical Trials

This theme represents the ultimate goal of our labs research efforts. Our research starts with patients and does not stop in the laboratory. The development of a sound preclinical rationale and identification of predictive biomarkers would enable us to translate our therapeutic concepts to be evaluated in clinical trials in patients.

### A. Targeting the Progesterone Receptor in Breast Cancer

We are currently leading a Cancer Instituted NSW funded National clinical trial (WinPro) to evaluate Progesterone in early stage breast cancer building on seminal preclinical findings in which the clinical implications suggest that progesterone may be used to enhance the efficacy of currently used anti-estrogen therapies. This trial progressed to from publication to trial accrual in 2 years and is the first trial of its kind in Australia in the field of breast cancer.

### B. Evaluating the role of exercise in breast cancer

We are evaluating the role of exercise in breast cancer. The beneficial role of exercise following a cancer diagnosis is increasingly recognised as an important lifestyle modification to improve outcomes in cancer. However, the precise mechanisms underpinning these benefits are still not known. Furthermore, it is unclear how it interacts with current systemic therapies used clinically. In parallel with a preclinical project to study the molecular pathways and biomarkers of the interaction of exercise with systemic therapy in our preclinical models, we have embarked on a feasibility study in patients undergoing preoperative chemotherapy in patients to undergo a supervised exercise program immediately following chemotherapy. The findings from this study are critical in the next step to develop a larger intervention trial.

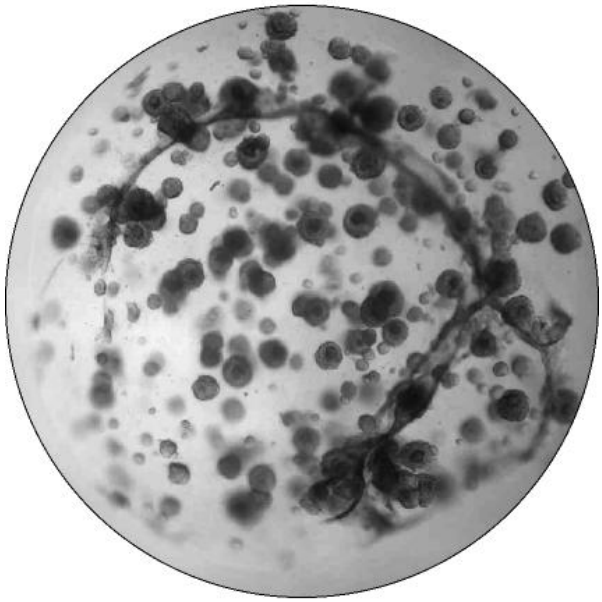
*Preclinical Mouse Experiments*

*Exercise Study in patients undergoing preoperative chemotherapy*

### C. Repurposing anticancer therapies to treat ectopic pregnancy

Ectopic pregnancies are a life-threatening medical emergency, most requiring surgery. In collaboration with obstetric colleague **Prof Stephen Tong (University of Melbourne)**, we demonstrated that Vinorelbine, an oral chemotherapy could be repurposed to be used as a treatment for ectopic pregnancy. Our preclinical work demonstrated that it potently induces placental cell death and did not harm fertility in preclinical models. These results directly led to an NHMRC funded clinical trial to evaluate vinorelbine as a tablet-based therapy to cure ectopic pregnancies, revolutionizing its current management. If successful, this concept has a potential for use in a global scale, as it repurposes a single dose oral chemotherapy to reduce the morbidity and mortality of a disease that disproportionately affects countries with less developed health systems.

# Research Projects



Mammospheres grown in 3D from patient-derived breast tissue

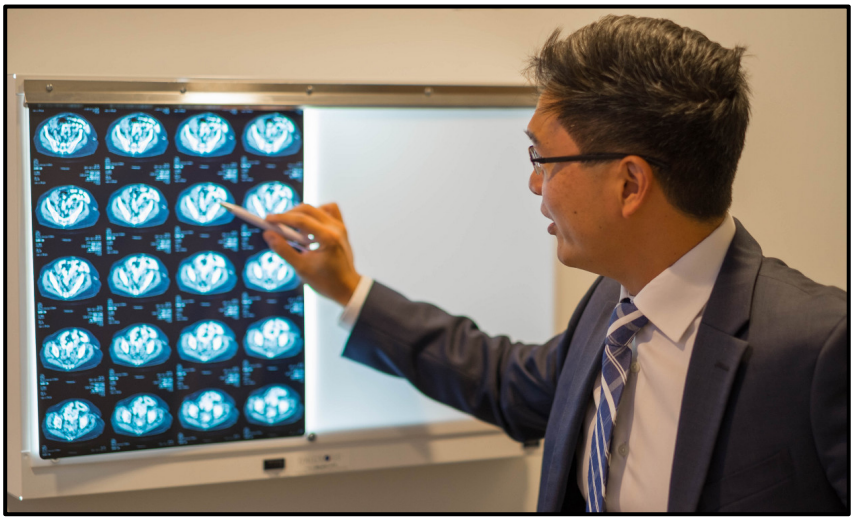
1) Targeting the Androgen Receptor in Breast Cancer
   - **Team Members:** Dr KeeMing Chia, Dr Sanjeev Kumar, Allegra Freelander (PhD Student)
   - **Collaborators:** Prof Wayne Tilley, A/Prof Theresa Hickey (Uni Adelaide), Prof Jason Carroll (Cambridge Uni), A/Prof Beth Overmoyer (Dana-Farber Cancer Institute, Boston)
2) Targeting the Progesterone Receptor in Breast Cancer *(WinPro Trial)*
   - **Team Members:** Dr Brandon Lau, Dr Sanjeev Kumar, Ms Lauren Armstrong
   - **Collaborators:** Dr Davendra Segara, Dr Andrew Parker (St Vincent's Hospital), Dr Andrew Ong (Campbell town Hospital), Dr Janne Bingham (Royal Adelaide Hospital), Prof Bruce Mann, Prof Geoffrey Lindeman (Victorian Comprehensive Cancer Centre)
3) Novel therapeutic strategies for treatment resistant breast cancer
   - **Team Members:** Dr Neil Portman, Allegra Freelander (PhD Student), Katherine Manakas (PhD Student), Sheena Nunag.
   - **Collaborators:** Dr Liz Caldon, Prof Susan Clark, A/Prof Clare Stirzaker (Garvan, UNSW), Prof Shudong Wang (Uni South Australia), Dr Sarat Chandarlapaty (Memorial Sloan Kettering Cancer Institute, NYC), Dr Violetta Serra (Vall D'Hebron, Barcelona), Dr Shom Goel, Prof Ygal Haupt (Peter MacCallum Cancer Centre)
4) Targeting Stromal epithelial interactions in Triple Negative Breast cancer and the Breast Cancer Single Cell Atlas
   - **Team Members:** Dr Julia Chen (PhD student), Sheena Nunag.
   - **Collaborators:** A/Prof Alex Swarbrick (Garvan, UNSW)
5) Project Share, The Patient Derived Breast Cancer Xenograft and Breast Cancer Biobank
   - **Team Members:** Denise Attwater, Aliza Yong, Ashleigh Wilkinson
   - **Collaborators:** Dr Davendra Segara, Dr Andrew Parker, Dr Linda Borella (St Vincent's Hospital), Dr James Black (MedScan)
6) Evaluating the role of exercise in breast cancer
   - **Team Members:** Dr Sara Wahlroos (PhD student)
   - **Collaborators:** Dr David Ortega Gallego (Garvan, UNSW)
7) Empowering patients to access clinical Trials *(Clinicaltrialsconnect.com.au)*
   - **Team Members:** Dr Emma Carson (PhD student)
   - **Collaborators:** Mr Gio Kalender (NBCF), Optus Australia

# Supporting Research

## 1) Project Share

We invite patients to *partner* with us and donate their tissue to be used for research through Project Share, whereby tissues in excess of diagnostic requirements are donated to the laboratory for research purposes. We use these tissues to study the biology of breast cancer, and to create cancer avatars in mice to evaluate new therapies. We have collected in excess of 250 patient tissues from every stage of cancer development. These critical samples not only allow us to study mechanisms of tumour development and progression, but also therapeutic resistance as patients in whom these were obtained from would have received a range of different systemic therapies. These tissues form the critical starting blocks for our research program and the establishment of patient derived breast cancer xenografts (Avatars) and are used by research laboratories across Australia and internationally.

## 2) Clinical Trials



Clinical trials are scientific studies in which new treatments – drugs, diagnostic procedures, and other therapies – are tested in patients to determine if they are safe and effective. We have a large suite of Clinical trials in which some patients are eligible to participate in. Such trials help us answer questions about new cancer therapies, including: what diseases should they be used for? What doses of new drugs are safe and most effective? And which patients can benefit the most from them? Nearly all cancer drugs in use today were tested and made available to patients through clinical trials. Patients play a critical role in improving the standards of care for the next generation of breast cancer patients through clinical trials, just as patients who have previously participated in trials have helped define the current treatment paradigms that are used today.

Our updated list of clinical trials can be found at
https://www.garvan.org.au/research/clinical-trials/breast-cancer-clinical-trials

## 3) Research Advocacy

Patients provide vital consumer input into our grant submissions and mobilise government support for research funding. Each year in March, we hold the annual *Garvan Breast Cancer Public Symposium* to provide the public with an update of breast cancer research progress.

## 4) Funding research

Research funding is increasingly challenging in Australia. The funding success rate with the National Health and Medical Research Council (NHMRC) is approximately 10%, and the amount of research funding through this scheme has not increased for a decade. Patients and the Public are critical in supporting research funding.
You can support our research efforts directly through a tax-deductible donation directed to the Connie Johnson Research Lab made through

- the *St Vincent's Curran Foundation* Tel: 1800 800 595 or
- the *Garvan Foundation* Tel: (02) 9295 8100.

### *Estimates of research costs*

- Research Officer Salary $110,000 per year
- Experiments to evaluate new therapies $50,000 per compound
- Tissue Banking and PDX "Avatar" establishment $10,000 per model
- Research Biopsy from Patients $1,000 per biopsy

# Selected Research Publications *(of 74 as of 2020)*

1) Portman N, Milioli HH … Caldon CE, Lim E. Synergistic targeting of estrogen-receptor positive breast cancers by MDM2 inhibition in combination with endocrine therapy or CDK4/6 inhibition. ***Breast Cancer Research.*** 2020.

We identified the p53 gene and its suppressor protein MDM2 as potential therapeutic targets in treatment refractory breast cancer. We were the first to demonstrate that the combination of MDM2 inhibitors with endocrine therapy is an effective treatment strategy that reduces tumour growth in preclinical models of both endocrine- and CDK4/6i-resistant breast cancer, representing a novel therapeutic combination that is effective in a clinical scenario faced by the majority of patients with treatment refractory ER+ breast cancer in today's therapeutic landscape. This is now being developed for a clinical trial concept.

2) Chia K, Milioli H, Portman N … Hickey TE, Lim E. Non-canonical AR activity facilitates endocrine resistance in breast cancer. ***Endocrine Related Cancer.*** 2019

This work dissected the role of the Androgen Receptor in Breast Cancer, which is expressed in the majority of estrogen positive breast cancer, but not used targeted therapeutically. Our findings implicate non-canonical AR activity in facilitating an endocrine therapy-resistant phenotype in breast cancer, the therapeutic strategy best used to target AR, and is the springboard for subsequent major research in our lab.

3) Portman N, Alexandrou S, Carson EK … Lim E*, Caldon CE*. Overcoming CDK4/6 inhibitor resistance in ER positive breast cancer. ***Endocrine Related Cancer.*** 2019

This work dissected the interaction between estrogen receptor therapies and CDK 4/6 inhibitors, the current gold standard therapy for patients with metastatic ER+ breast cancer. It highlights mechanisms of resistance to these therapies, and potential novel therapeutic strategies when resistance to these therapies develop.

4) Young AR, Coulson R … Mathivanan S, Lim E, Meeusen E. Immunoprofiling of Breast Cancer Antigens Using Antibodies Derived from Local Lymph Nodes. ***Cancers.*** 2019

This research demonstrated that lymph node-derived ASC-probes provide a highly specific source of tumour-specific antibodies. Marrying technology used successfully in veterinary science and infectious diseases, we applied this novel approach to breast cancer. In this translational study, we found that each breast cancer patient reacts with a different antibody profile which indicates that targeted immunotherapies may need to be personalized for individual patients.

5) Chen J … Lim E*, Segara D.* Window of Opportunity Treatment in Breast Cancer. ***ANZ Journal of Surgery.*** 2019.

This work describes a novel strategy to evaluate new therapies, utlisiing the window of opportunity between diagnosis and surgery to trial a short duration of novel treatment. It is the trial design used in a number of trials being evaluated at St Vincent's Hospital.

6) Kennedy SP, Portman N … Lim E, Kolch W, Croucher DR. Targeting promiscuous heterodimerization overcomes innate resistance to ERBB2 dimerization inhibitors in breast cancer. ***Breast Cancer Research.*** 2019.

This work describes a novel strategy to overcome treatment resistance to currently used therapies in HER2-positive breast cancer through treatment sequencing using currently used HER2-directed therapies.

7) Hastie R, Lim E … Kaitu'u-Lino TJ, Tong S. Vinorelbine potently induces placental cell death, does not harm fertility and is a potential oral treatment for ectopic pregnancy. ***EBioMedicine.*** 2018.

We demonstrated that Vinorelbine, a chemotherapy, could be repurposed to be used as a treatment for ectopic pregnancy. Our preclinical work demonstrated that it potently induces

placental cell death and did not harm fertility in preclinical models. These results directly led to an NHMRC funded clinical trial to evaluate vinorelbine as a tablet-based therapy to cure ectopic pregnancies, revolutionizing its current management.

8) Brockwell NK … Lim E, Parker BS. Neoadjuvant Interferons: Critical for effective PD-1 based immunotherapy in TNBC. ***Cancer Immunology Research.*** 2017

This research demonstrated the role of IFN in improving triple negative breast cancer (TNBC) response to immunotherapy. This finding has important clinical translation potential for TNBC and a clinical concept is currently being developed to trial this in patients.

9) Robinson DH … Lim E*, Seah D*. Attitudes of patients with metastatic cancer towards research biopsies. ***Asia Pacific Journal of Clinical Oncology***. 2017

This research formed the basis of the establishment of Project Share, allowing us to understand patients' attitudes towards partnering with us in research through providing research biopsies. It enabled us to understand the altruistic motivation of many patients.

10) Johnson SF, … Lim E*, Shapiro GI*. CDK12 inhibition reverses de novo and acquired PARP inhibitor resistance in BRCA wild type and mutated models of triple negative breast cancer. ***Cell Reports.*** 2016.

This research demonstrated the role of extending the use of PARP inhibitors which has been shown to be very effective in patients with BRCA mutant tumours, but only constitute about 5% of all breast cancers, to more broadly non-BRCA mutant tumours. It identified a synthetic lethal approach with the combination of CDK12 inhibitors with PARP inhibitors. This finding has important clinical translation potential and a clinical trial of this concept is underway in patients.

11) Lim E, Tarulli G, Portman N, Hickey T, Tilley W, Palmieri C. Pushing Estrogen Receptor around in breast cancer. ***Endocrine Related Cancer.*** 2016.

This work dissected the interaction between estrogen receptor and other hormone receptors that are commonly present in breast cancer, in particular the progesterone and androgen receptors. It highlights potential novel therapeutic strategies to target these other receptors and has shaped the development of our subsequent research and clinical trials with these novel therapies.

12) Lim E, Metzger O, Winer EP. Natural history of hormone receptor positive breast cancer. **Oncology**. 2012.

This highly cited work describes the changing natural history of hormone receptor breast cancer, including the evolution and change that has occurred with the changing therapies used to treat breast cancer.

13) Lim E, Wu D, … Visvader E. Transcriptome analyses of mouse and human mammary cell subpopulations reveal multiple conserved genes and pathways. ***Breast Cancer Research.*** 2010.

This work found for the first time that the mammary cell hierarchy in a mouse is identical to women, providing the biological rationale for the utility of mice to study human breast cancer.

14) Lim E, Valliant F… Lindeman G, Visvader E. Aberrant luminal progenitors as a likely target population for basal tumor development in BRCA1 mutation carriers. ***Nature Medicine.*** 2009.

This seminal work dissected the mammary epithelial cell hierarchy in women with and without BRCA1 and BRCA2 germline mutations and identified key differences between them. It also identified the putative cell of origin of BRCA1 mutation associated breast cancer, and potential therapeutic targets for cancer prevention. It has directly led to prevention trials currently underway.

# Our research is proudly supported by


National Breast Cancer Foundation

THE BALNAVES FOUNDATION

Cancer Council NSW

Australian Government
National Health and Medical Research Council
N H M R C

Australian Government
Cancer Australia

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BREAST CANCER TRIALS

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# Our Collaborators