Garvan Institute of Medical Research

UNSW THE UNIVERSITY OF NEW SOUTH WALES

The *Connie Johnson* Breast Cancer Research Group

Transformative Patient Centric Breast Cancer Research

ST VINCENT'S HOSPITAL SYDNEY

The Kinghorn Cancer Centre

Our research is proudly supported by

Mission Statement

Transformative Patient Centric Breast Cancer Research

Research underpins medical progress.

At the Connie Johnson Breast Cancer Research Laboratory, we work on projects spanning discovery of new treatment concepts in the laboratory to evaluation of treatments in clinical trials in patients.

Patients inspire our research and are key partners in our research endeavour. Our goal is to accelerate the bench to bedside research pipeline, ultimately to improve the outcomes of patients with breast cancers.

We invite you to partner with us in this mission through supporting our research.

The *Connie Johnson* Breast Cancer Research Group

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 Prof Elgene Lim to lead it.

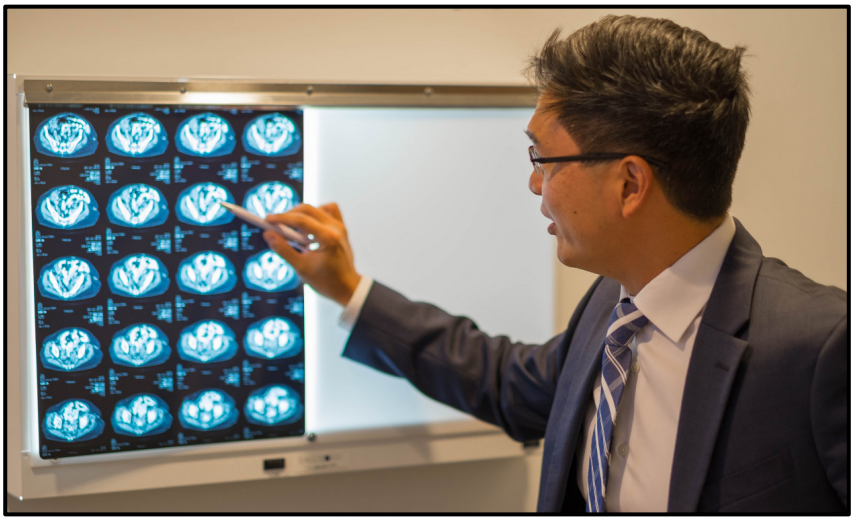
The Connie Johnson Research Laboratory comprise a multidisciplinary team of 10 talented young scientists, clinicians and PhD students whose research is solely focussed on improving the outcomes for patients with breast cancer. Our research spans the biological understanding and therapeutic vulnerabilities of breast cancer in the lab, to clinical trials in patients.

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

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.*

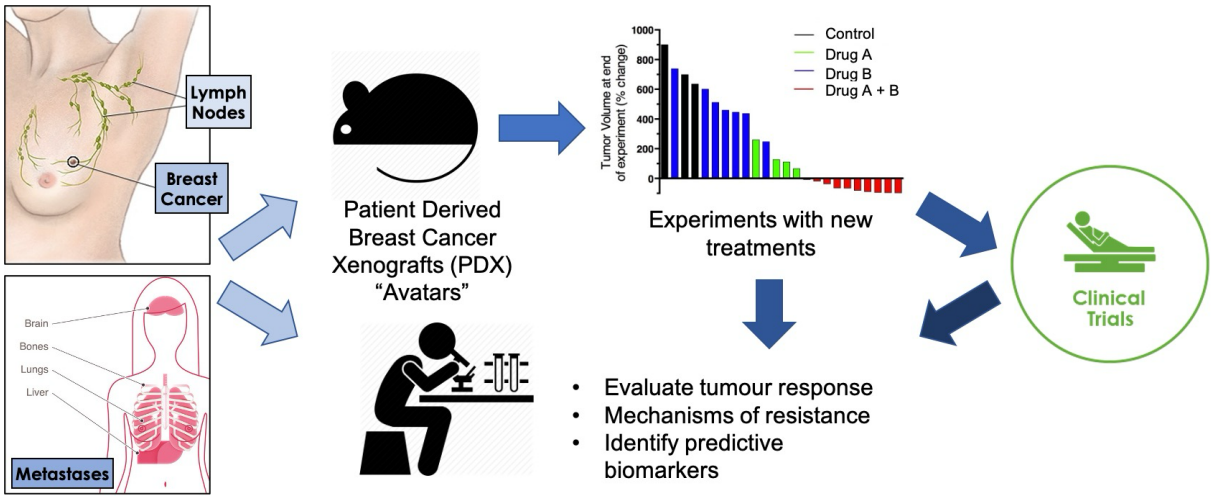
I also head the *Connie Johnson Breast Cancer Research Group* at the *Garvan Institute of Medical Research*, comprising a team of 11 talented young scientists, whose research is solely focussed on improving the outcomes for patients with breast cancer. Our research is funded through the NBCF, Love Your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

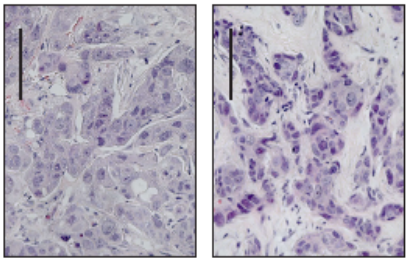
We have a number of research projects in our laboratory at any one time, from laboratory based to clinical trials. Our aim is to accelerate laboratory findings into patient care. We collaborate extensively with other researchers in Australia and Internationally. The major areas of research focus of the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

1) Identify key 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

A key goal of our 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.

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 ours is the study cancers resistant to current therapies, we evaluate combination therapy strategies to overcome key mechanisms of resistance and improve treatment efficacy.

c. Cancer Cell and Tumour Microenviroment 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 **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.

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 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 have completed 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.

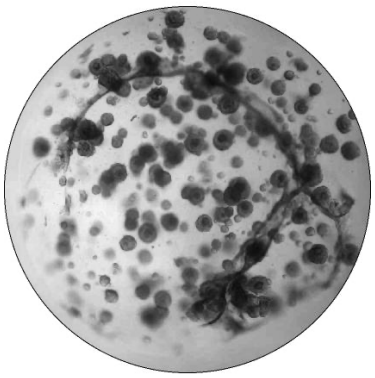
b. Novel therapies for Lobular Breast Cancer.

Approximately 15% of Breast Cancer is the Lobular subtype. It has a poorer prognosis, insidious growth and spread compared with the more common form of ductal breast cancers. Yet, patients are treated in much the same way as ductal cancers. In collaboration with ***Prof Jason Carroll (Cambridge University)*** we will evaluate differences in estrogen signalling biology in a unique cohort of lab models of invasive lobular and the more common ductal breast cancers and demonstrated that the lobular breast cancers are suppressed with estrogen in contrast to our ductal models. The ultimate goal is to develop new therapies specific for lobular cancer.

c. Targeting the Androgen Receptor in Breast Cancer

Our seminal research on Selective Androgen Receptor Modulators in collaboration with ***Prof. Wayne Tilley and Theresa Hickey (University of Adelaide,*** Nature Medicine 2021) has led to the evaluation of this class of therapies in breast cancer (Palmieri et al, Lancet Oncology 2024). We are now evaluating AR directed therapies in the treatment of Ductal Carcinoma in Situ.

Current Research Projects



Mammospheres grown in 3D from patient-derived breast tissue

1) Targeting the Androgen Receptor in Breast Cancer and DCIS

- **Team Members:** Lilly Hatwell (PhD Student), Dr Sarah Childs, A/Prof Ryoko Semba
- **Collaborators:** Prof Wayne Tilley, A/Prof Theresa Hickey (Uni Adelaide), Prof Jason Carroll (Cambridge Uni), Dr Allegra Freelander (University of California, San Francisco)

2) Targeting the Progesterone Receptor in Breast Cancer (WinPro Trial)

- **Team Members:** Dr Lucy Haggstrom, Kate Saw, Jennifer Siu
- **Collaborators:** Dr Davendra Segara, Dr Andrew Parker (St Vincent's Hospital), Dr Andrew Ong (Campbell town Hospital), Dr Janne Bingham (Royal Adelaide Hospital)

3) Novel therapeutic strategies for treatment resistant breast cancer

- **Team Members:** Dr Leila Eshraghi, Dr Vanessa Ramos, Lilly Hatwell, Jessica Jenner
- **Collaborators:** A/Prof Liz Caldon, Prof Susan Clark, A/Prof Clare Stirzaker (Garvan, UNSW), A/Prof Orazio Vittoria (UNSW), Prof Wayne Tilley (Uni Adelaide), Dr Henrik Ditzel (University of Southern Demark)

4) Targeting Stromal epithelial interactions in Triple Negative Breast cancer and the Breast Cancer Single Cell Atlas

- **Team Members:** Dr Julia Chen, Dr Jeremy Mo (PhD student)
- **Collaborators:** Prof Alex Swarbrick (Garvan, UNSW)

5) Project Share: The Breast Cancer and Xenograft Biobank

- **Team Members:** Kate Saw, Jennifer Siu, Jessica Jenner
- **Collaborators:** Dr Davendra Segara, Dr Andrew Parker, Dr Linda Borella (St Vincent's Hospital)

6) Empowering patients to access clinical Trials (Clinicaltrialsconnect.com.au)

- **Team Members:** Ms Kate Saw (Research Nurse)
- **Collaborators:** Dr Frank Lin, Dr Carolyn Mazariego (UNSW)

Selected Research Publications *(of 120 to date)*

1) KL Jhaveri… **E Lim**, et al. Imlunestrant with or without Abemaciclib in Advanced Breast Cancer. ***New England Journal of Medicine.*** 11th Dec 2024.
2) K Jhaveri, **E Lim,** et al. Imlunestrant as monotherapy and in combination with targeted therapy in ER+, HER2- aBC: EMBER Ph 1a/1b study. ***J Clin Oncol.*** 10th Dec 2024
3) M Martín, **E Lim,** et al. Giredestrant for ER+/HER2- Previously Treated Advanced Breast Cancer: Results from the Randomized, Phase II acelERA Breast Cancer Study. ***J Clin Oncol. 2024***. Jun 20;42(18):2149-60.
4) C Palmieri, … **E Lim,** … B Overmoyer. A Phase 2 open label randomized study of enobosarm, a novel oral, selective androgen receptor modulator, in AR+, ER+, HER2- advanced breast cancer: Study G200802. ***Lancet Oncology***. 2024 Mar;25(3):317-25.
5) Achinger-Kawecka J, … **Lim E**, Clark SJ. The potential of epigenetic therapy to target the 3D epigenome in endocrine-resistant breast cancer. ***Nature Structural & Molecular Biology*** 2024:31(3):498-512
6) KL Jhaveri, … **E Lim.** Phase Ia/b Study of Giredestrant ± Palbociclib and ±LHRH Agonist in Estrogen Receptor-positive, HER2-negative, Locally Advanced/Metastatic Breast Cancer. ***Clinical Cancer Research.*** 2024 Feb 16;30(4):754-66.
7) Andre F, …, **Lim E,** … Krop I. Trastuzumab deruxtecan versus treatment of physician's choice in HER2-positive metastatic breast cancer: results of the randomised, open-label, phase 3 DESTINY-Breast02 study. ***Lancet.*** 2023 May 27;401(10390):1773-85.
8) Karimi L, … **Lim E,** Ditzel HJ. Triple combination targeting PI3K, ER, and CDK4/6 or CDK2 inhibits tumor growth in ER+ breast cancer resistant to combined fulvestrant and CDK4/6 or Pi3K inhibitor. ***Cancer Communications.*** 2023;43:720–5
9) **Lim E**, et al. An open label, randomized Ph 2 trial assessing the impact of food on the tolerability of abemaciclib in patients with mBC. ***Breast Cancer Research Treatment.*** 2022 Oct;195(3):275-87.
10) N Portman, **E Lim**. A new sophistication for breast cancer PDX. ***Nature Cancers.*** 2022;3;138–40
11) Wu SZ, … **Lim E**, Lundeburg J, Perou CM, Swarbrick A. A single-cell and spatially resolved atlas of human breast cancers**. *Nature Genetics.*** 2021 Sep 6;53:1334–47
12) Alves CL, … **Lim E**, Ditzel HJ. Co-targeting CDK4/6 and AKT with endocrine therapy prevents progression in CDK4/6 inhibitor and ET-resistant breast cancer. ***Nature Comms.*** 2021;12(1):5112
13) Wu SZ, … **Lim E**, Swarbrick, A. Cryopreservation of human cancers conserves tumour heterogeneity for single-cell multi-omics analysis. ***Genome Biol.*** 2021 May 10;13(1):81
14) Hickey TE, … **Lim E**, Carroll JS, Tilley WD. The Androgen Receptor is a Tumour Suppressor in Estrogen Receptor Positive Breast Cancer. ***Nature Medicine.*** 2021 Feb;27(2):310-20
15) Portman N*, Milioli HH* … Caldon CE*, **Lim E***. MDM2 inhibition in combination with endocrine therapy and CDK4/6 inhibition for the treatment of ER-positive breast cancer. ***Breast Cancer Research.*** 2020:22(1):87
16) Kennedy SP, … **Lim E**, Kolch W, Croucher DR. Targeting promiscuous heterodimerization overcomes innate resistance to ERBB2 dimerization inhibitors in breast cancer. ***Breast Cancer Res.*** 2019;21(1):43
17) Chia K, … Hickey TE*, **Lim E***. Non-canonical AR activity facilitates endocrine resistance in breast cancer. ***Endocr Relat Cancer.*** 2019 Feb 1;26(2):251-64
18) Roswall P, … **Lim E**, et al. Microenvironmental control of breast cancer subtype elicited by paracrine platelet derived growth factor-CC signaling. ***Nature Medicine.*** 2018:24(4):463-73
19) Brockwell NK, … **Lim E**, Parker BS. Neoadjuvant Interferons: Critical for effective PD-1 based immunotherapy in TNBC. ***Cancer Immunology Research.*** 2017:5(10):871-84
20) Johnson SF, … **Lim E,** Shapiro GI. CDK12 inhibition reverses de novo and acquired PARP inhibitor resistance in BRCA wild type and mutated models of TNBC. ***Cell Reports.*** 2016:17(9);2367-81
21) **Lim E**, et al. Renewed interest in the Progesterone Receptor in BC. ***British J Cancer.*** 2016:115(8);909-11
22) **Lim E**, et al. Pushing Estrogen Receptor around in breast cancer. ***Endo Rel Cancer.*** 2016;23(12):T227-41

Our Collaborators