



THE 'PINK' ELEPHANT IN THE ROOM

Once breast cancer spreads to the brain it is inevitably fatal within months, but UQ researchers are working to try and improve this outlook.

Thanks to early detection and advances in treatment, breast cancer survival rates have improved significantly in recent years. However, existing therapies have limited benefit if the disease metastasises or spreads to other sites in the body.

The (pink) elephant in the room, breast cancer metastasis to the brain, for example, causes considerable morbidity and is inevitably fatal, with patients typically surviving four to 18 months from diagnosis.

Head of the Molecular Breast Pathology unit at UQ's Centre for Clinical Research, Professor Sunil Lakhani, says that – because these brain tumours resist existing therapies – it is clear we need to be more innovative in our approach to treating them. So, he and his team are collaborating with scientists around the globe to tackle important and complex questions about breast cancer development at the molecular and cellular level. By taking a multifaceted approach, they hope to find better treatment options for patients.

One of the ways Professor Lakhani helped bring this collaborative approach about was the launch of the Brisbane Breast Bank (BBB) in 2005.

With financial support from UQ, QIMR Berghofer, the RBWH Foundation and Australasian Biospecimen Network, as well as the cooperation and goodwill of staff from Pathology Queensland, QML and Sullivan Nicolaides Pathology, the bank aims to collect a tumour sample from every patient undergoing treatment at the Royal Brisbane

and Women's Hospital. It has become a valuable resource for breast cancer research in Australia and abroad.

The BBB is a repository of frozen breast tissue samples linked to data relating to sample collection and clinical history, such as whether a patient's cancer responded to a particular treatment.

The samples and their byproducts are pivotal to research – for example, validating findings from experimental systems, or correlating tumour features with cancer treatments and patient outcomes. Amassing large numbers of samples gives the statistical power needed to determine whether treatments are really working, and allows researchers to predict which patients would be most responsive to a particular therapy.

Molecular genetics specialist Dr Amy McCart Reed coordinates the BBB in addition to her research portfolio.

“A number of our discoveries would not have been possible without the valuable samples donated by breast cancer patients,” says Dr Reed. “Metastatic brain tumours in particular are not easy to come by.”

For Professor Lakhani's latest project, he and his team have joined with UQ's School of Pharmacy to develop cutting-edge research into the spread of breast cancer to the brain.

“An idea gaining support in the biomedical community is to simultaneously target cancer cells and the so-called ‘tumour microenvironment’, which we are now learning can provide critical support to growing cancers,” he says.

The three-year study builds on previous research suggesting the movement of calcium in cells goes awry in both primary breast cancers and in metastatic tumours in the brain. Understanding how these processes are altered in breast cancer could lead to new ways to reduce the chance of the disease spreading, and arrest the growth of metastatic tumours once they are detected.

The US Department of Defense has committed more than A\$1.3 million to the project through its Breast Cancer Breakthrough Scheme. This is the only research outside North America to receive such funding.

Also taking advantage of the BBB, and working alongside Professor Lakhani to improve breast cancer management and survival rates for women is Dr Jodi Saunus. The multidisciplinary researcher is leading a new clinical trial – ‘BoNSAI’. The study is expected to provide major advances in understanding the dose of drugs needed to target tumours in the brain.

The brain is normally protected from intravenous drugs by unique, impenetrable blood vessels. While the vessels that grow through tumours are ‘leakier’ than the rest of the brain, they are still not as permeable to drugs as blood vessels elsewhere in the body.

The degree to which this blocks the effects of cancer drugs in metastatic brain tumours is hotly debated in scientific literature.

By using cutting-edge medical imaging – made possible by the launch of the Herston Imaging Research Facility – the BoNSAI study will determine how much of a drug

administered to breast cancer patients is absorbed into metastatic brain tumours.

“We will attach a Positron Emission Tomography (PET) tracer to a drug routinely used to treat breast cancer,” Dr Saunus explains.

“Participants will then undergo two to three scans over the following week or so. These scans will enable us to see how much of the administered drug actually reaches the tumour and is retained there. Then we can better understand the factors controlling this, such as the patterns of blood flow and pressure inside the tumours.

“It is possible that drugs we thought were not working in the brain could be effective if used in higher doses to overcome the unique barriers to drug uptake. Quality of life for people living with brain tumours can be incredibly poor, so there is a great need for research to improve both manageability and survival rates.”

The research team is hoping to clarify speculation in scientific literature by providing the evidence for guidelines on dosing. This could also provide benchmarking for treatment of metastatic brain tumours originating from cancer types other than breast cancer, such as lung cancer and melanoma.

BBB samples have supported the groundbreaking research into breast cancer genomics, undertaken in collaboration with the International Cancer Genome Consortium.

Centre for Clinical Research Team Leader Dr Peter Simpson has published several high-impact research papers defining the breast cancer genome, together with collaborators at the Wellcome Trust Sanger Institute in Cambridge. In particular, new research investigating mutational signatures has the potential to identify a subgroup of patients who might benefit from additional therapies.

Professor Lakhani says the study has identified a much larger patient group who could benefit.

“It could be an effective way of picking those patients where particular treatments are going to work – and that’s a big step forward in cancer research.”

Professor Lakhani holds an appointment with Pathology Queensland, and was recognised with the 2016 Robert Sutherland Award for Excellence in Translational Research from the ANZ Breast Cancer Trials Group.

“I’ve been fortunate to lead and work with some amazing research teams. We’ve come a long way in improving women’s health outcomes.”

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(Photo credit: Drs Andrew Dalley and Jodi Saunus, UQCCR Molecular Breast Pathology, and adjusted by Craig Oddy, Office of Marketing and Communications)

Progress to date:

2004: Professor Lakhani takes up positions in UQ’s School of Medicine (Head of the Discipline of Molecular and Cellular Pathology), Pathology Queensland (State Director of Anatomical Pathology), and UQ’s Centre for Clinical Research (UQCCR) (Head of the Molecular Breast Pathology Group)

2005: Establishes the Brisbane Breast Bank (BBB) in collaboration with the RBWH Breast Unit

2007: With Professors Georgia Chenevix-Trench and Kum Kum Khanna from QIMR-Berghofer, is successful in bid for National Health and Medical Research Council (NHMRC) program funding for *Pathways to breast cancer development*

2012: Is awarded NHMRC project grant for *Defining therapeutic options for brain metastases*, and NHMRC program funding is renewed for *Molecular determinants of susceptibility and progression in breast cancer* (UQ-QIMRB)

2015: Receives *Distinguished Pathologist Award* from the International Academy of Pathology (Australasian Division)

2015: Is awarded pilot funding from UQ and ANZ Breast Cancer Trials Group (ANZBCTG) for *Repurposing HER2/3 antibodies for treatment of brain metastases from breast cancer* (with Professor Andrew Scott, Olivia Newton-John Cancer Research Institute)

2016: Is awarded the *Robert Sutherland Award for Excellence in Translational Research* from ANZBCTG

2016: Receives *Distinguished Fellow Award* from the Royal College of Pathologists of Australasia, for outstanding contributions to pathology research, teaching and administration

2016: Is awarded seed funding from Metro North Hospital and Health Service for *Improving treatments for brain metastases through advanced imaging* (BoNSAI)

2017: Is successful in bid for third successive NHMRC program grant, *Translating molecular determinants of susceptibility and progression in breast cancer* (UQ-QIMRB)

2017: With Professors Greg Monteith and Sarah Roberts-Thomson and Dr Jodi Saunus, is awarded funding from US Department of Defense Congressionally Directed Medical Research Programs for *Exploiting the remodelling of Ca²⁺ signalling in breast cancer cell microenvironments to control metastasis and to specifically target brain metastases*

2017: Is selected for *The William O Russell Lectureship* and honoured with the *Joanne Vandenberg Hill Award in Anatomical Pathology* at the MD Anderson Cancer Centre, Texas, USA

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