



Bridging the Translational Gap: How PDX Models are Transforming Breast Cancer Research, Drug Discovery and Precision Oncology

Breast cancer is the most common cancer in women worldwide. It is highly heterogeneous with distinct breast cancer subtypes, posing challenges for diagnosis and treatment. There are four key molecular breast cancer subtypes classified based on the expression of hormone and growth factor receptors.¹

Luminal A subtype tumours are characterised by the expression of oestrogen receptor (ER+) and/or progesterone receptor (PR+) and the absence of human epidermal growth factor receptor (HER2-). Clinically, they are low grade, slow growing and have the best prognosis with less incidence of relapse and higher survival rate. Luminal B subtype tumours are of higher grade and have a worse prognosis than Luminal A tumours. They are ER+, can be PR+ or PR- negative and HER2- and are generally of intermediate/high histologic grade. These tumours may benefit from hormonal therapy along with chemotherapy. The HER2-positive subtype is characterised by high HER2 expression and is ER- and PR-. They grow faster than the luminal ones and prognosis has improved after the introduction of HER2-targeted therapies.

The triple-negative breast cancer (TNBC) subtype is characterised by the lack of expression of any of the above receptors (ER-/PR-/HER2-). This is the most challenging breast cancer subtype as it is more aggressive and does not respond to hormonal therapies or HER2-targeted therapies. Treatment usually involves chemotherapy, and patients have a higher risk of early recurrence.

There is therefore a need for breast cancer models that capture its heterogeneous subtypes to uncover novel disease mechanisms underlying its complexity and for more precise drug development. Patient-Derived Xenograft (PDX) models have emerged as a leading breast cancer *in vivo* system to study the intricacies of cancer biology and are created by transplanting patient tumour tissue into immunodeficient mice.

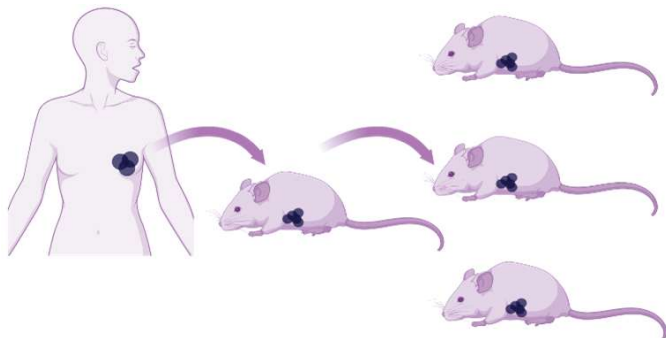


Image: Schematic illustrating the establishment of PDX models by grafting tumour tissues from a patient into immunodeficient mice, created with Biorender.

PDX models faithfully recapitulate patient tumour characteristics, including more representative intratumour heterogeneity, genomic features, metastatic patterns and drug

responses than traditional cell line and animal models. These highly translatable models are ideally suited to support more accurate advanced tumour modelling and preclinical *in vivo* drug validation studies. At the forefront of this field is Professor Alana Welm, based at the University of Utah, who has shared insights from her group's groundbreaking research with us in this article.

Journey into Breast Cancer Research

Professor Welm's journey into breast cancer research began after her PhD, with a desire to make an impact on human health. She explains, "I wanted to do some research that was more directly applicable to human health. So, for my postdoc, I joined J. Michael Bishop's laboratory in UCSF, where I got to learn a lot about oncogenes and started working on breast cancer metastasis."



Image: Professor Alana Welm, University of Utah

Here, she discovered the difficulties in studying metastatic disease: "One of the challenges I realised was that human breast cancer cell lines are poorly metastatic. This is why I set out to make PDX models."

Professor Welm hypothesised that growing these cancer cells *in vivo*, as opposed to on plastic, might enable a "metastatic memory" in the cells or allow them to "interact with their environment in a more physiologically relevant way."

Pioneering Complex Breast Cancer PDX Models at the Huntsman Cancer Institute

In 2007, Professor Welm established her own laboratory at the University of Utah's Huntsman Cancer Institute and began developing novel breast cancer PDX models. These spanned different breast cancer types. Her research focuses on solving the problem of breast cancer metastasis, using *in vivo* PDX modelling of complex and heterogeneous breast cancers.

Professor Welm's group have generated a large biobank of PDX models² that represent breast cancer patients affected by the most advanced and lethal forms of the disease. This includes aggressive, metastatic and treatment-resistant subtypes, providing a truer representation of the entire spectrum of disease than previously available.

Capturing the Complexity of Breast Cancer

Professor Welm's work focuses on the importance of studying metastatic disease, the killer in breast cancer. She endeavours to make sure her models are representative of metastatic disease and highlights the challenges faced and strategies used to ensure this.



Welm said, *"We try really hard to make sure that our models are representative of metastatic disease, but it is hard to get metastatic samples from patients... What we really try to get are the pairs, primary metastatic pairs or longitudinal samples, because then people could use them to study how the tumour evolves in the patient or how it evolves resistance to therapies."*

These matched samples provide researchers with the tools needed to study the biology underpinning metastases. In addition to representing metastatic disease, Professor Welm and her team have worked hard to capture the spectrum of disease experienced across breast cancer. When asked about key subsets in her collection, she notes, *"I think a really unique set are the oestrogen-receptor positive (ER+) tumours because they are harder to grow, so there are only a few of them. We characterise all of them for their oestrogen dependence."*

She further explains that the collection also includes: *"models of ER+ breast cancers with naturally occurring mutations in the oestrogen receptor, which occur in humans with hormone therapy."*

The biobank also contains a vast collection of triple-negative breast cancer (TNBC) models, which is essential. Professor Welm explains further: *"TNBC is a vastly heterogeneous subtype. It's really the absence of a subtype, I guess. We need a lot of those as well to just represent human breast cancer."*

Unlocking Unexpected Discoveries Using These Models

Professor Welm shared with us one of her most unexpected discoveries from using these PDX models: *"I think the biggest finding that we didn't expect was that the ability to generate a PDX model actually predicted distant recurrence for TNBC patients. That was a complete accident. It's like a functional test for aggressivity."* This discovery led to further innovations, Professor Welm explains: *"It inspired our functional precision oncology trials. We knew these patients would have a bad outcome and yet we were growing their tumours. So, we thought we need to do something about this."*

This work evolved into developing matching organoids for higher throughput *in vitro* drug screening, enhancing the potential for personalised treatment responses.

Advancing Breast Cancer Research Through Collaboration

When asked about her goals for implementing PDX models in breast cancer research, Professor Welm emphasised the importance of addressing unmet clinical needs.

"Well, I think for us, the goal is to use these models to research areas of the greatest medical need in breast cancer, which are the recurrent drug-resistant metastatic tumours. There are a lot of primary tumours that we could study, we could make models of, but those might not represent the disease where we need to make new therapies."

Professor Welm has deposited 53 of these PDX models, including models of the most advanced and lethal forms of breast cancer, such as aggressive, metastatic and treatment-resistant subtypes, with CancerTools, a global, non-profit research tools provider. CancerTools, part of Cancer Research UK, connects scientists worldwide with academic-developed

cancer research tools, accelerating discovery and innovation through open, collaborative science. This partnership aims to further accelerate breast cancer research, drug discovery and precision oncology by making these breast cancer PDX models more accessible to the global cancer research and drug discovery community.

For Professor Welm, sharing these models through CancerTools honours both scientific principles and patient wishes: *"It's important to us that these patient-derived models are made available to the scientific community to advance research on breast cancer, not only because it's our obligation as cancer researchers to do so, but because this is what the patients wanted when they donated their tissue to research."*

However, some remaining challenges with PDX models include low take rates, high costs and long timelines involved in generating and maintaining these models. The development of new immunodeficient mice and/or better methods of tumour transplantation should help to overcome these limitations.³ The lack of a functional immune system in current PDX models is another challenge, since tumour-immune interactions are an important part of tumour behaviour and therapeutic response. To overcome this disadvantage, mice engrafted with a human immune system are expected to be a promising tool for the next generation of PDX models.³

In conclusion, these highly translatable breast cancer PDX models enable scientists to study how different breast cancer subtypes respond to potential therapies and provide more predictive responses than traditional models, thereby derisking preclinical drug validation. Moreover, these models also offer scientists unprecedented opportunities to study breast cancer metastasis, drug resistance and tumour evolution in a physiologically relevant context. This paves the way to developing more effective personalised treatments and better outcomes for breast cancer patients.

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