Moving Ahead with Personalized Mouse Models

Patient-derived xenografts advance research in breast cancer but need further validation

The first whole-genome study of drug-resistant breast cancer in patient-derived xenografts (PDX) in mice produced several major surprises, says Matthew Ellis, MB, BChir, PhD, professor of medicine at Washington University School of Medicine in Saint Louis, MO.

One was the discovery of endocrine-therapy–resistant mutations of the estrogen receptor-1 gene (*ESR1*), including a translocation and an amplification (Cell Reports 2013; 4:1116–30). "Understanding these types of mutations is a potential game-changer in medical practice," says Ellis. "Depending on whether *ESR1* is wild-type, point-mutated, translocated, or amplified, you could do different treatments."

Another surprise from the study, Ellis says, was the "astonishing" fidelity with which the PDXs reflected genomic variants found in the original human tumor.

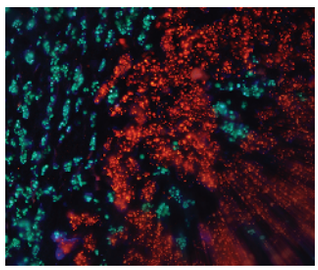
Moreover, that fidelity included "remarkably consistent" allele frequency distributions in the originating tumor and PDXs. "In the competition model we're all brought up on, a rare allele is about to die out or it's about to dominate, but that's not what you see here," he comments. "What that observation suggests is not a competition model; it's a cooperation model, in which somehow minor clones and major clones must be talking to each other to maintain a hierarchy of frequencies."

Findings such as these highlight the potential advantages of PDX models, created from individual patients' tumors, over traditional cell lines and animal models. The *ESR1* translocations, for instance, aren't present in the conventional ER-positive cell lines and thus hadn't been detected. "So it really shows the advantage of going to the PDX system and trying to link it directly with patient experiences," says Ellis. "Because we wouldn't have made these discoveries if we carried on studying T47D cells and MCF7 cells for the rest of our lives."

PDX models for breast cancer, while slower to emerge than models for some other cancers, such as colon and pancreatic cancers, are now becoming established. "I can only imagine that PDX research will increase massively in significance, and perhaps almost become a mandatory step in drug development," Ellis says.

Among signs of growing acceptance of PDX-based research, "reviewers for both journals and grants are already starting to demand use of these models," says Alana Welm, PhD, associate professor of oncological sciences at Huntsman Cancer Institute at the University of Utah in Salt Lake City. She estimates that her lab has given its PDX models of breast cancer to about 100 labs since publishing a *Nature Medicine* paper in 2011 (Nat Med 2011;17:1514–20).

BUILDING ON STRENGTHS



Matthew Ellis, Washington University

Sequencing has shown that the genomes of patient-derived xenografts can closely match those of originating human tumors. Here, human breast cancer cells (red) are growing amid mouse cells (green).

PDXs can tackle any questions that can be handled with cell lines or other animal models but may be particularly suited to studying metastasis, treatment resistance, biomarkers, and the role of stem cells, proponents say.

"We're doing a very nice job of capturing high-grade cancers as xenografts," says Michael Lewis, PhD, associate professor at Baylor College of Medicine in Houston, TX. Lewis is senior author on a recent paper describing 32 stably transplantable xenograft lines that showed drug treatment responses comparable to those seen in the clinic (Cancer Res 2013;73:4885–97).

However, he adds that "I don't think we're doing a very good job of modeling lower-grade cancers, and we still have trouble with ER-positive and HER2-positive tumors with the exception of really aggressive metastatic tumors."

Currently, PDXs "are an enormous investment in time and money," Welm cautions. "They are not easy to grow. They are not easy to manipulate."

Another constraint is the requirement for actively engaging surgeons and other clinical staff in obtaining the patient tumors, emphasizes Carol Sartorius, PhD, assistant professor of pathology at the University of Colorado School of Medicine in Aurora. "It involves an incredible number of people, and it's extra work for all of them."

Additionally, scientists underline the need to validate findings from PDXs with clinical results. "All the data so far point to these xenografts being extremely high-fidelity models, but no model is perfect, and they haven't really been validated prospectively in the clinic," Welm says. "If they have some critical pitfalls that we may not be aware of yet, we're better off knowing that before we make a huge investment in this relatively new technology."

Fortunately, "as a community we finally have enough types of PDX models of breast cancer to start to do such clinical validation," says Lewis.

In addition to learning how to make PDX models more efficiently, scientists hope to develop models better representing the human immune system. Welm's lab is among a few pursuing this line of research.

Another long-term goal for some researchers is using PDXs to aid in individual patient treatment, but experts caution that this typically will not be practical anytime soon, if ever. "These first-generation xenografts take a long time to grow—up to a year or more—and some patients don't have that kind of time," Lewis points out. More generally, researchers say, knowledge gained from working with a broad spectrum of PDXs will help to identify likely agents for clinical interventions. —*Eric Bender* ■

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