"Preclinical Clinical Trials" Using Patient-Derived Xenograft (PDX) Models of Human Breast Cancer in Immunocompromised Mice

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Background

Serially transplantable patient-derived xenograft (PDX) models of human breast cancer (established and maintained \textit{in vivo} in immunocompromised mice) are rapidly gaining favor over long-established breast cancer cell lines (maintained \textit{in vitro}) for preclinical evaluation of experimental therapeutics. A primary driver behind this trend is the recent availability of comparatively large collections of well-characterized PDX models – collections made possible by the development of new immunocompromised mouse strains, and more efficient methods for establishing such xenograft models (1–7). These xenografts represent the major clinically-defined subtypes of breast cancer (e.g. estrogen receptor positive (ER\(^+\)), HER2 positive (HER2\(^+\)), and "triple negative" (TN) breast cancers). As an aggregate, these collections of PDX models are now sufficiently large, and biologically diverse, to allow conduct of "preclinical clinical trials" in mice using experimental therapeutics. Results from these mouse studies should be relevant to human clinical trials.

Discussion

A cornerstone of translational breast cancer research has been the ability to evaluate experimental therapeutics \textit{in vivo} using long-established human breast cancer cell lines (e.g. MCF7, MDA-MB-231 etc.) transplanted into immunocompromised mice. Advantages such "xenograft" models have over clinical trials conducted using real patients are many. These include the fact that a single treatment-naive tumor can be subjected to multiple candidate therapeutics, whereas a single patient can only be treated with one agent at a time. Further, one can ethically include an untreated control arm in each trial so that the researcher can know what would have happened to the tumor if left completely alone. Finally, since these models are entirely renewable, they can be characterized extensively, at multiple molecular levels (e.g. genomics, transcriptomics, proteomics, metabolomics), and the molecular characteristics used to develop predictive tools of treatment response – studies that have proven extremely difficult in true clinical trials in people.

Unfortunately, at least some long-established cell lines are now known to differ significantly from lab to lab, and indeed between isolates in the same lab, having gained mutations that...
were clearly not present in the original patient. These mutations accumulate as a consequence of
time and inadvertent selection pressures during passage in tissue culture. Thus, there is
considerable debate about the long-term suitability of these models for preclinical studies [see
(8–10) and references therein].

As a potential way around these problems, several groups have developed methods of growing
and maintaining human breast cancers as stably transplantable patient-derived xenografts in a
variety of immunocompromised mouse models (1, 2, 4–7, 11, 12). These xenografts represent
the major clinically-defined subtypes of breast cancer (e.g. estrogen receptor positive (ER+),
HER2 positive (HER2+), and "triple negative" (TN) breast cancers). As part of their efforts,
these groups have demonstrated that the PDX models show remarkable biological and genetic
consistency with the tumor of origin, respond to treatment in very similar ways, and are
phenotypically and genetically stable over several years of passage in mice. Thus, within the
limits of experiments in mice, PDX should serve as useful surrogates for individual patients in
"animal clinical trials."

While the individual PDX collections referenced above are generally not sufficiently large to
provide statistically robust data for response to a given treatment, as a larger collection, they are.
In recognition of this fact, groups responsible for generating PDX models have begun not only
to distribute their PDX models around the world, but have also begun to work together to test
experimental therapeutics in a way that is fundamentally different from anything done
previously.

**Future Directions**

While potentially extremely powerful experimentally, PDX models are not without limita-
tions. For example, even with recent advances, PDX models still do not represent the full
spectrum of human disease with the number of models required to conduct focused animal
clinical trials on defined subsets of tumors (e.g. claudin-low tumors, lobular tumors etc.). It will
be critical to continue to expand our existing collections to include these tumor types. Related to
this issue is the observation that "triple negative" and aggressively metastatic tumors grow with
high efficiency in mice, ER+, HER2+, while less aggressive tumors typically do not. Clearly we
are still missing something. These tumor types and grades may require as yet undiscovered
experimental manipulations to allow their growth in mice. Finally, it is currently unclear the
degree to which the absence of a functional immune system in immunocompromised mice will
influence treatment response of PDX models. Investigation of PDX behavior in mice with
reconstituted human immune systems may answer such questions.

The real impact that PDX models will have on clinical practice will likely not be known for
several years. However, the possibilities are exciting. For example, widespread availability of
PDX models should empower individual researchers and cooperative groups to conduct
"preclinical clinical trials" – trials that test a large number of candidate experimental therapeutics
head-to-head more efficiently, and more inexpensively than traditional clinical trials in patients
can possibly do. Importantly, it should also be feasible to define the correct order of treatment,
or "sequencing" of agents, to achieve maximum treatment response in a more efficient manner
than can be done in traditional human clinical trials. In addition, it should also be possible to
use the animal clinical trial to develop predictors of response/resistance in patients in order to
pick the patient population(s) most likely to respond in an actual clinical trial. Finally, with the decreasing cost of whole genome sequencing – and the subsequent identification of individual “driver mutations” (mutations primarily responsible for tumor initiation and growth), it may be possible to use representative PDX models to realize the ultimate goal of truly personalized medicine for each cancer patient.

References
