ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Patient-Derived Tumor Xenograft Models in Drug Development

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H&O What types of preclinical models are used to predict clinical activity of novel therapies in cancer patients?

MH There are now 4 types of preclinical models. The classic cell-line xenografts have been used for years. They have a high negative predictive value, but a very poor positive predictive value with regard to overall anticancer activity.

Patient-derived xenograft models were developed in the past 10 years. Our group was among the first to study these models, and they appear to be more predictive than cell-line xenografts. More studies are needed, however, to determine their true predictive value.

> A rational approach would be to conduct preclinical studies in patient-derived tumor xenograft models before drugs are evaluated in clinical trials.

Genetically engineered mouse models can offer insight into the biology of a disease. They are less useful for therapeutic development.

The past 3 years have seen the development of organoid models. The potential for these models is exciting, but data are currently lacking. It is necessary to determine how well they predict patient response to treatments.

H&O Could you please describe xenografts, both the standard cell-line models and the patient-derived models?

MH Xenografts consist of human cancer tissues that are implanted into an immunodeficient mouse. Standard cell-line xenograft models are created from cell lines that have been adapted to grow in plastic and other in vitro conditions for many years. It is not known how well standard cell-line xenograft models mirror the cancer properties of the patient from whom they originated. Patient-derived xenograft models are generated from freshly collected tissue, and for that reason, they may better reflect the intrinsic characteristics of the tumor from which they are derived.

H&O How are patient-derived tumor xenografts developed for use in preclinical trials?

MH Pieces of tumors, collected from biopsies or surgery, are implanted into immunodeficient mice. Some groups are developing xenografts from circulating tumor cells.

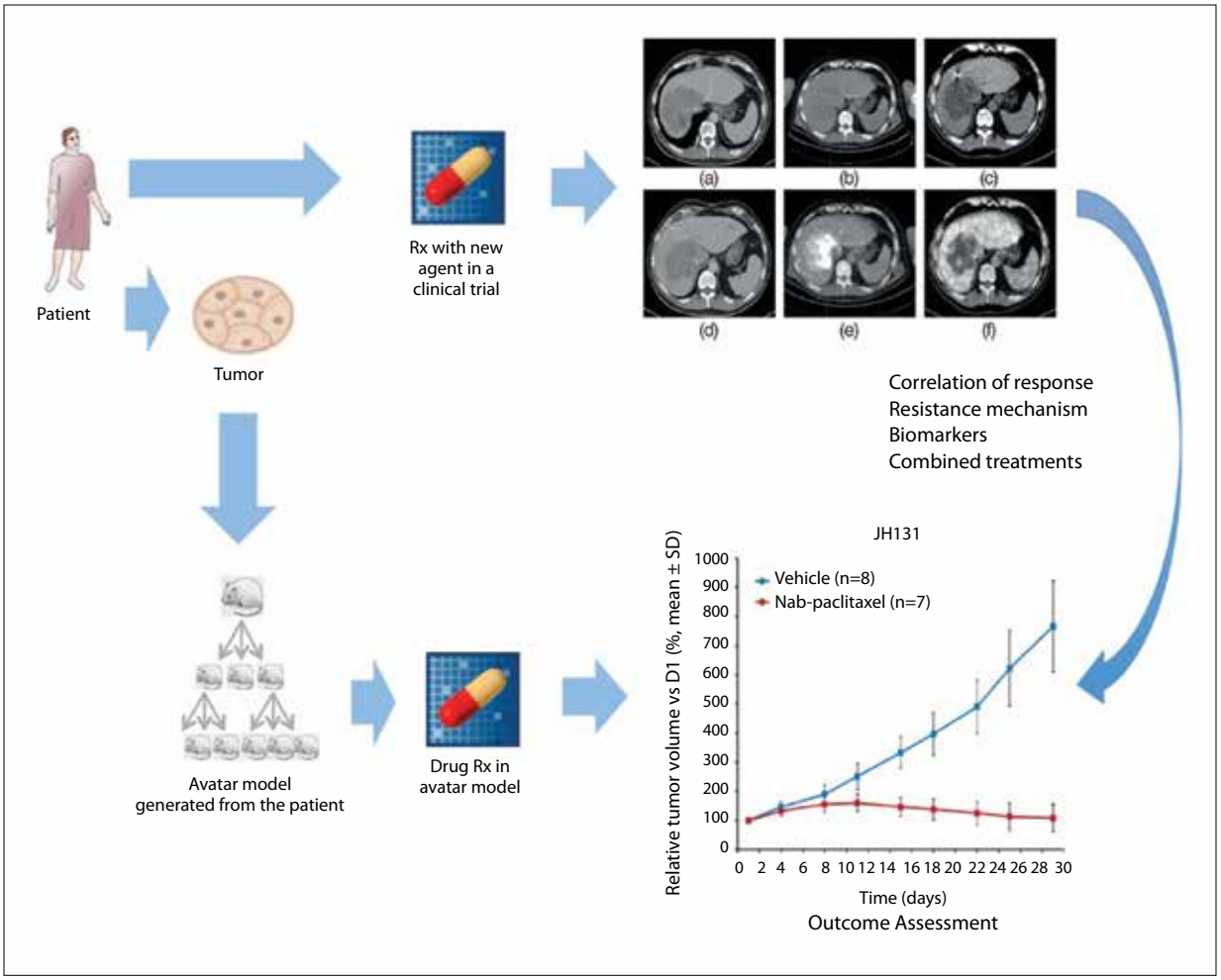

Figure. A new version of the co-clinical trial concept incorporates a patient-derived xenograft model developed from a patient who is treated with a novel agent in a clinical trial. This approach permits the development of models with validated clinical outcome data that can be used to interrogate mechanisms of response and resistance and to develop strategies (eg, combination therapies) to increase response and overcome resistance. D1, day 1; Rx, prescription; SD, standard deviation. Reprinted with permission from Hidalgo M et al. Patient-derived xenograft models: an emerging platform for translational cancer research. *Cancer Discov.* 2014;4(9):998-1013. Copyright © 2014 American Association for Cancer Research.

Patient-derived tumor xenografts are used in preclinical studies. If there is an interesting level of activity, then the drug might be moved to a clinical trial.

H&O Does engraftment and expansion appear to change a tumor's genetic features?

MH There are no significant changes. Most studies suggest that these tumors faithfully recapitulate the genetics of the originator tumor.

H&O What kind of information can patient-derived tumor xenograft models provide?

MH Patient-derived tumor xenograft models are useful for drug screening. For example, patient-derived tumor xenograft models clearly showed that nab-paclitaxel (Abraxane, Celgene) was effective in pancreatic cancer. These models can also be used in the development of biomarkers. A rational approach would be to conduct preclinical studies in patient-derived tumor xenograft models before drugs are evaluated in clinical trials.

H&O What are the challenges to the use of patient-derived tumor xenografts?

MH There are several challenges. In approximately 20% of patients, the tumor sample does not grow in the mouse. Therefore, the process inherently selects a certain group of patients. Not much is known about which tumors grow

better in mice. Cells from some diseases, such as prostate cancer, are notoriously difficult to grow in mice. More aggressive cancers appear to grow better.

Development of patient-derived tumor xenografts can take 6 months, which may be too long for patients with a poor prognosis. In addition, the development of these models is expensive and requires substantial resources.

H&O Are there certain cancer types in which the use of patient-derived tumor xenografts have been especially successful?

MH They have been most successful in colon cancer, pancreatic cancer, and lymphoma. In pancreatic cancer, for example, we and other researchers have observed a very nice correlation between responses seen in patient-derived models and clinical outcome. This observation helped in the development of nab-paclitaxel for pancreatic cancer. In colon cancer, studies performed in patient-derived models have been used to identify mechanisms of resistance to targeted agents and to develop rational combinations of agents subsequently evaluated in clinical trials.

H&O Are patient-derived tumor xenograft models useful for the newer approaches to treatment?

MH They are useful for targeted therapy. They are not suitable for immunotherapy because they have been generated in an immunodeficient model.

H&O Do you have any suggestions on how to use patient-derived tumor xenografts in trials?

MH At my institution, we have been using patient-derived tumor xenograft models mainly in so-called co-clinical trials, in which we generate tumor xenograft models from patients who are then enrolled into a clinical trial (Figure). We attempt to mirror the treatment that the patient is receiving to learn about mechanisms of resistance. This information can then be used to adapt treatment.

H&O Do you anticipate that the use of patient-derived tumor xenografts will evolve?

MH It will evolve. An important area of research is the development of patient-derived tumor xenografts in immunocompetent backgrounds, so that they can be used to exploit immunotherapy. Another exciting area is the use of organoids to provide an easier way of obtaining individual patient models for all the applications just discussed.

Disclosure

Dr Hidalgo is a founder and shareholder of Champions Oncology.

Suggested Readings

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