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New public repository of patient-derived cancer models aims to improve drug testing

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Testing experimental cancer drugs in mouse models with patient-derived tumors could reduce the high failure rate of drugs in early clinical trials, according to a report from Dana-Farber Cancer Institute scientists performed in collaboration with investigators at multiple other centers.

To share this technique widely, Dana-Farber has established an open-source public repository of biopsy tissue collected from patients with leukemia and lymphoma. Called the Public Repository of Xenografts (PRoXe), it has a Web portal so it can be accessed by researchers worldwide, the investigators report in *Cancer Cell*.

These patient-derived xenograft (PDX) models, created by transplanting cells from different types of cancers into mice, where they take hold and grow, have many advantages over standard methods, say the scientists. Most importantly, their response to experimental drugs can be used to identify the right drugs or combinations of drugs to test in human patients.

"About 90 percent of compounds that show anti-cancer activity in pre-clinical tests don't work when given to patients. By trying drugs in PDX models, we can 'mimic' large and expensive human clinical trials and get answers about efficacy more quickly, less expensively and without the need for patients to get investigational drugs that won't work," said David Weinstock, MD, senior author of the publication and a clinician and researcher at Dana-Farber.

Based at Dana-Farber, the repository contains biopsy material from bone marrow, peripheral blood, and lymph nodes of the mice, along with information on the patients from which the cancer tissue was removed and on the characteristics of the tumor itself.

"Using this repository, we demonstrate that large studies of acute leukemia PDXs that mimic human randomized clinical trials can characterize drug efficacy and generate transcriptional, functional, and proteomic biomarkers in both treatment-naive and relapsed or refractory disease," the authors said. Weinstock lab members Mark Murakami, MD, and Elizabeth Townsend, PhD, are co-first authors.

Cancer investigators who register with PRoxE can access the repository from anywhere and search for PDX models of specific subtypes of blood cancers, Murakami explained. If they find relevant models, they can have frozen cells shipped and transplant them into mice to create models for testing drugs.

Standard pre-clinical assessments test drugs against "lines" - cultures of cancer cells derived from a single type of cancer cell grown in a petri dish - but they have many limitations. For one, these isolated cells don't replicate how tumors behave in their microenvironment in the body. Drugs can also be tested in mouse models developed to have gene mutations similar to human cancers, but these models are available for only a few of the 100s of cancer types, and also have many limitations, the authors explained.

PDX models are relatively new and overcome many of these shortcomings, according to the scientists. Cancer cells from patient biopsies are injected into mice that lack a defensive immune system; the human cancer cells "take" or engraft with a high rate of success. Each xenograft can be injected into multiple animals, so researchers can compare overall survival or time-to-progression in untreated mice with

those given the experimental drug, as in a human clinical trial, and they can study the development of resistance if it occurs.

"These studies allow us to analyze what a drug is doing in many phases of treatment," said Townsend.

To demonstrate how the system can be used, the researchers tested an experimental agent against a type of leukemia called B-ALL in two groups of mice: One group had a mutation in the TP53 tumor suppressor gene and the others had a normal gene. Survival was increased in the mice harboring the normal P53 gene compared to those harboring the mutation. The authors said these results provide strong preclinical evidence for testing the drug in patients who have been extensively treated for B-ALL and still have a normal P53 gene.

The report notes a number of limitations of the PDX system currently, one being that blood cancers are easier to transplant successfully than solid tumors and repeated biopsies over time are more feasible.

Weinstock said the leaders of the repository are negotiating with a number of academic centers to incorporate their PDX models into ProXe. The manuscript had 95 different authors from 14 different centers that contributed samples, models and/or effort to the project.

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