Medical Xpress

Genetically-engineered preclinical models predict pharmacodynamic response

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New cancer drugs must be thoroughly tested in preclinical models, often in mice, before they can be offered to cancer patients for the first time in phase I clinical trials. Key components of this process include pharmacokinetic and pharmacodynamic studies, which evaluate how the drug acts on a living organism. These studies measure the pharmacologic response and the duration and magnitude of response observed relative to the concentration of the drug at an active site in the organism.

A new comparison of four different methodologies for pharmacokinetic and pharmacodynamic testing of the anti-melanoma agent carboplatin, demonstrates that genetically-engineered mouse models provide tumor delivery of drug most comparable to the response seen in melanoma patients.

"These studies are critically important in the case of small-molecule cancer drugs, which often have systemic side effects and can be toxic at high concentrations," said Ned Sharpless, MD, Wellcome Distinguished Professor of Cancer Research and study co-author.

The study, led by Bill Zamboni, PharmD and PhD, Associate Professor of Pharmacotherapy and Experimental Therapeutics at the UNC Eshelman School of Pharmacy and a member of UNC Lineberger Comprehensive Cancer Center, and Ned Sharpless, MD, who is also Associate Director for Translational Research at UNC Lineberger.

The collaborative study, which appears in *The Oncologist*, brought

together a set of unique resources available at UNC to determine which preclinical models best predict delivery of carboplatin to melanoma tumors in patients. "We have a unique opportunity to evaluate an important factor in the treatment of solid tumors because of the outstanding collaborative nature and novel resources at UNC", said Zamboni.

"We have used a pharmacokinetics testing method called microdialysis, which uses a tiny probe to take samples that measure serial drug concentrations in a tumor over time," he added. "We plan to use this method to advance pharmacology studies of anticancer agents in tumors and tissues of patients and to evaluate the tumor delivery of nanoparticles and other classes of delivery agents."

The team used the resources of the preclinical phase I unit at UNC Lineberger to compare how pharmacokenetic levels vary in several preclinical tumor models including a genetically-engineered model, a model where tumor cells are transplanted to the appropriate part of the body (called an orthotopic syngeneic transplant or OST), and a xenograft model, where human tumor tissue is transplanted.

"Because carboplatin is widely used, we have good data on how the drug works pharmacokenetically in humans. For the first time, we were able to compare these various laboratory techniques used in countless labs and the pharmaceutical industry to evaluate how carboplatin was delivered to the tumor and compare it to actual human data. None of these laboratory models are perfect, but the genetically-engineered model is the best in terms of predicting the amount of drug that is delivered to the tumor in human patients," Zamboni added.

"We know that laboratory models are imperfectly predictive of human response and if the tumor models don't predict delivery, they are most likely not an optimal research tools," he noted.

Sharpless added, "We are continually looking for ways to build better laboratory models so that new therapies move from the lab to the patient as quickly and safely as possible. This study provides valuable validation that genetically-engineered models can help us accomplish this objective."

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