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Kill the cancer, not the patient: New toxicity testing approach could make chemo drugs safer

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For cancer patients on chemotherapy, the "cure" can be as deadly as the disease itself. Adverse drug reactions are one of the leading causes of death among patients receiving cancer treatment.

Jackson Laboratory Professor Gary Churchill wants to change that. With a new two-year, $1 million grant from the National Cancer Institute, Churchill is launching a radical new approach to testing three chemotherapeutic drugs for potential toxic effects.

Chemo drugs are supposed to be toxic—to cancer cells. But they're notorious for their unpredictable effectiveness and for causing systemic toxic reactions in patients.

"Adverse drug reactions can be difficult to study in humans," Churchill says. "Every individual is genetically unique and lives in an uncontrolled environment. That's why we need animal model systems to fully understand the genetic basis of drug response."

Testing chemo drugs in animal models is not new, but Churchill's approach is. Instead of working with one hybrid strain of mouse, as is the pharmaceutical industry standard, The Jackson Laboratory is developing a new mouse variety that is designed to maximize genetic diversity. Each one of these "Diversity Outbred Mice" will be genetically unique and, as a whole, the population approximates the genetic diversity

observed in human populations.

To develop the Diversity Outbred Mice, Churchill is teaming up with Neal Goodwin, Ph.D., who directs cancer studies at JAX—West, The Jackson Laboratory's facility in Sacramento, Calif.

Sophisticated genetic mapping and live-animal imaging techniques will enable Churchill and Goodwin to home in on the gene variations found in mice that exhibit a toxic reaction. "So in terms of the information we're getting, it's almost like testing chemo drugs on every person on Earth," Churchill says. "This sets the scene for future, highly reliable screens for cancer patients."

The three drugs in the study—doxorubicin, cyclophosphamide, docetaxel—were chosen because of their well-known myelotoxic effects. Myelotoxicity or bone marrow suppression reduces the production of blood cells, hampering the body's ability to fight infection and causing anemia and other severe problems.

"We have chosen myelosuppression as the physiological response for this study," Churchill says, "because this adverse effect is a major contributor to morbidity, mortality and costs associated with cancer treatment. Mice are known to respond to these agents in a manner similar to humans, and the response can be measured using standard clinical hematological methods."

Imogen Hurley, Ph.D., an associate research scientist in Churchill's laboratory, notes that the approach behind these experiments will be relevant to all types of drugs. "Cancer drugs are an important test case. We expect to show that researchers will be able to use the genetic diversity of these mice to understand why individuals have different reactions to a wide range of drugs."

Source: Jackson Laboratory