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Discovery leads to rapid mouse 'personalized trials' in breast cancer

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One person's breast cancer is not the same as another person's, because the gene mutations differ in each tumor. That makes it difficult to match the best therapy with the individual patient.

Using a finding that the genetic complexity of tumors in mice parallels that in humans, researchers at the Duke University Institute for Genome Sciences and Policy and Duke University Medical Center are starting trial studies in mice, just like human clinical trials, to evaluate whether understanding tumor diversity can improve cancer treatment.

"Giving everyone the same few current treatments doesn't take the very different types of tumors into account," said Joseph Nevins, Ph.D., Barbara Levine University Professor of Breast Cancer Genomics at Duke, who directs the Center for Applied Genomics & Technology at Duke. "It's like trying to treat a virus infection without recognizing that it may be HIV, influenza or cold virus."

For a study appearing this week in the *Proceedings of the National Academy of Sciences,* Nevins and colleagues painstakingly examined a large number of mouse breast tumors and performed genomic analyses to differentiate the tumors.

"The genetic pathways in the tumors determine the sensitivity to drugs," Nevins said. "We still have so much to learn about this."

All of the mice were bred to have a Myc gene variant that gave them

tumors; however, additional gene mutations are acquired that contribute to the development of the tumor, including mutations in the Ras gene and others. The spectrum of tumor variation at the genetic level mimicked the complexity of human cancers.

"If we are going to successfully treat a tumor, we must recognize the extensive heterogeneity of what we call breast cancer and match drugs carefully to the characteristics of that particular tumor," Nevins said. "Today breast tumors may be sorted by whether they are estrogen-sensitive or HER-2 sensitive, but that is about the extent of it. We are performing human trials to look at the underlying biological pathways and examine how best to match therapies with the individual patient. But, these are lengthy studies. Now we can develop new strategies to match a therapy with a mouse tumor subtype and have results in a much shorter period of time."

Nevins and colleagues plan to conduct trials in the mice just as they would in humans: find the tumor, perform a needle biopsy, learn all they can about the tumor, and match it to a drug based on scientific data. The mouse studies don't replace human trials, but they can be an important component of advancing a strategy, Nevins said.

"This work highlights the importance of both biological and computational model systems to unravel the complexities and heterogeneity of human cancer," said Daniel Gallahan, Ph.D., program director for the Integrative Cancer Biology Program at the National Cancer Institute. "This type of analysis can be exploited to better align a therapeutic strategy with an individual's specific cancer."

Running parallel to human trials, the mouse trials will show what works well and what doesn't in the trial methods, data collection, analysis and other aspects of the trials. Researchers can then translate these findings immediately to keep the human clinical trials advancing as effectively as

possible.

With so much mouse model research happening around the globe, why weren't these mouse tumor differences noted before? The gene expression analyses performed on mouse tumors simply haven't been large enough, Nevins said.

"We examined a large number, up to 80 samples of mouse tumors. And in the same way that a picture gets clearer when you add more pixels, the information about the tumors became clearer as we examined more samples," he said. "In effect, we went to a higher resolution and could begin to see patterns more clearly."

Source: Duke University Medical Center (news : web)