

# New research strategy for understanding drug resistance in leukemia

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UCSF researchers have developed a new approach to identify specific genes that influence how cancer cells respond to drugs and how they become resistant. This strategy, which involves producing diverse genetic mutations that result in leukemia and associating specific mutations with treatment outcomes, will enable researchers to better understand how drug resistance occurs in leukemia and other cancers, and has important long-term implications for the development of more effective therapies.

Findings are reported in the Advance Online Publication of the journal "*Nature*" and are available [here](#).

"In trying to understand why certain cancers respond to drugs while certain other cancers fail to respond, we found that a single gene can be the culprit for [drug resistance](#)," said Kevin Shannon, MD, senior author of the paper and a pediatric cancer specialist at UCSF Children's Hospital. "The subtlety of what makes a cancer cell become resistant to a drug is truly remarkable."

"When treating patients for cancer, clinical specialists usually only have one or two chances to choose the right drug before it is too late. This makes it incredibly important to understand drug resistance so that we can prioritize therapeutic options," said Jennifer Lauchle, MD, the study's lead author and a pediatric blood and cancer specialist at UCSF Children's Hospital.

In the initial stages of the study, the researchers used a strain of mice that developed acute myelogenous leukemia, or AML, to assess the effectiveness of an experimental cancer drug called a MEK inhibitor. AML is an [aggressive cancer](#) that affects both children and adults and causes abnormal [white blood cells](#) to grow rapidly and accumulate in the bone marrow, thereby interfering with the production of normal blood cells.

The researchers created the mouse model of AML through two key steps. First they utilized a strain of mice that had a single gene mutation closely resembling the mutation found in leukemia and some other cancers. Then they introduced an infectious particle called a retrovirus, which produces additional mutations that work together and result in AML. The retrovirus also "tags" these new [genetic mutations](#), which allows researchers to identify them later on. These steps resulted in a model of AML that, like human AML and other advanced cancers, has several genetic mutations that interact with one another.

To assess the effectiveness of the MEK inhibitor, the researchers compared a group of mice with AML that was treated with the drug to a group that was left untreated and found that the drug increased survival time threefold. However, all of the leukemia cells that initially responded to the drug later relapsed, which is similar to what happens in many human patients.

"This shows that even if you make what seems to be a really good drug, resistance is a major problem that must be overcome," said Shannon, who is also a leader of the hematopoietic malignancies research program at UCSF's Helen Diller Family Comprehensive Cancer Center.

In the next phase of the study, the research team set out to uncover the genes that triggered drug resistance by comparing cells from the original drug responsive AML to those of the relapsed AML. Because AML in

the mouse model had been created with a retrovirus, the new mutations that caused the leukemia to relapse could be pinpointed through forward genetic analyses. These analyses identified two new single gene mutations that rendered the MEK inhibitor ineffective and brought about the relapsed AML.

According to the researchers, this same method can be used to study other types of [cancer](#) in order to identify additional genes responsible for drug resistance. "The hope is that this new strategy will enable us to identify more effective therapies and to find ways to anticipate and overcome drug resistance," Shannon added.

Source: University of California - San Francisco

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