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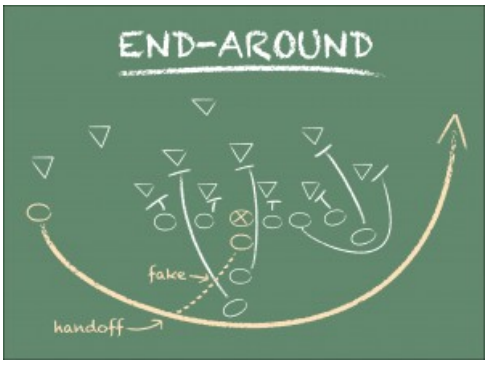
Researchers aim to beat trick play by tumors with drug combo

By Elizabeth Dougherty | Feb 17, 2015

When a team of researchers started testing BYL719—an experimental targeted drug—in breast cancer patients at Massachusetts General Hospital (MGH) in 2012, they expected solid results. They had reason for high hopes. Other targeted drugs have been therapeutic game changers for some types of cancer, causing tumors to vanish in the vast majority of patients with mutations that match the target. This new drug's target, PI3K, plays a role in 70 percent of breast cancers and was thought to be driving the tumor growth machinery of the patients selected for the Novartis-sponsored trial.

"But we didn't see what we expected," says Alan Huang, senior director in Oncology Translational Research at the Novartis Institutes for BioMedical Research. Rather, the drug shrank tumors only in about one in four patients, though it did show prolonged results over several months in some cases.

To better understand the gap between expectation and reality, the researchers went back to the laboratory. The resulting investigation led them to find a second target that appears to help tumors resist treatment with the PI3K inhibitor. When this target is inhibited along with PI3K, the two-drug combo can potentially shut down the cancer. This approach represents a new strategy for battling drug resistance with smart blends of targeted drugs. The results appeared in *Cancer Cell*, and the combination—BYL719 plus a second compound—is now being tested in a clinical trial.



The End-Around: In this American football play, while defenders block a key pass receiver, another player skirts behind them, takes an unexpected hand-off and moves the ball forward. Image: PJ Kaszas

The protein PI3K is potentially a promising cancer target because it sits at the top of a cascade of cellular signals that control cell growth. The researchers had expected that blocking it with BYL719 would stop the downstream signals, too, halting cell growth. But in the trial, cancer growth didn't always stop. This observation made them wonder if tumor cells were executing a trick play similar to one used in American football – the end-around. In this play, while defenders block a key pass receiver, another player skirts behind them, takes an unexpected hand-off and moves the ball forward. Similarly, while the inhibitor blocks PI3K, another protein goes in motion to drive cell growth.

The research team's first step was to confirm that the cell cycle machinery downstream of PI3K was still active in the drug resistant tumors. Sure enough, it was. Samples of cells from the tumors of patients who had shown

resistance to BYL719 contained biological markers indicating cell cycle activity, while samples from patients who responded to the drug did not.

The end-around theory was looking good, but the team needed to figure out what protein, or proteins, were running the trick play. To do this, researchers at MGH grew three cell lines resistant to the PI3K inhibitor on plates, each plate with 96 wells, and handed the cell lines over to Huang and his colleagues at Novartis for a screening experiment. Huang's team paired a PI3K inhibitor (either BYL719 or another company's inhibitor) with an array of compounds with known targets to see if any of the additional drugs would stop the end-around.

One pairing stood out. Blocking CDK4/6 and PI3K synergistically reduced cell viability.

"At that moment, we knew we were onto something," says Huang. "It was quite bizarre to see the two drugs working together. If PI3K is shut down, CDK4/6 should be, too, because it's downstream in the signaling pathway."

The researchers do not yet know the exact mechanism enabling dual control of the cell cycle, but CDK4/6 is clearly driving drug resistance in many cases. Another protein that sits downstream from PI3K, mTOR, also appears to be capable of running an end-around play. Blocking it also stopped the cell cycle machinery when combined with the PI3K inhibitor. But that compound has side effects that are similar to the PI3K inhibitor, while the CDK4/6 inhibitor does not.

"Combining two compounds with non-overlapping side effects is obviously more desirable," says Huang.

Clinical trials of the two-drug combo—BYL719 plus a CDK4/6 inhibitor—have begun in breast cancer patients with PI3K mutations. The strategy of attacking two targets in the same pathway at the same time is becoming more and more common in oncology. Designing rational combinations of targeted agents, based on work like this team's, might be the best way to combat the drug resistance that often plagues therapy with a single targeted agent.

Main image: Getty Images/iStockphoto

Novartis researchers chase down breast cancer's clever evasion of a new experimental drug by hitting two targets at once.

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