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Cancer cocktails come of age

Novartis teams test combinations of targeted therapeutic agents to combat drug resistance in tumors.

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The oncology world experienced a revolution about 10 years ago as the first targeted therapies came on the scene. Researchers feverishly designed treatments that would spare healthy tissue, tackling the specific molecular defects of cancer cells. But soon a problem cropped up: tumors began to resist the new drugs.

As tumors adapted, so did scientists. They resolved to combine targeted therapeutic agents into drug cocktails to control the evolution of resistance and thwart the persistent cancer cells, a strategy that's finally coming to fruition. A slew of data from early-phase trials—presented by Novartis researchers and others at the American Society of Clinical Oncology (ASCO) meeting in June 2014—is the latest sign that combination therapy is coming of age.

One team, for example, demonstrated activity of the small molecule LEE011 in combination with another targeted agent, MEK162, in patients with a particular type of melanoma. Another team paired the antibody LJM716 with the drug Herceptin® (trastuzumab, manufactured by Genentech) and showed activity in patients with a particular type of breast or gastric cancer. Time will tell if tumors can dodge such cocktails, but the early results are promising.

Reacting to resistance

When resistance first developed in the clinic, it wasn't a complete surprise. After all, one of the hallmarks of cancer is genomic instability. The DNA of each cancer cell changes over time, and that makes tumors—collections of wildly diverse cancer cells—inherently versatile. They're primed for rapid evolution. Yet the first clinical reports of resistance to targeted agents caused alarm. Fierce debates erupted among oncology researchers.

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> **William Sellers**, Global Head of Oncology at the Novartis Institutes for BioMedical Research (NIBR)

"Some questioned the entire targeted therapy paradigm," recalls William Sellers, Global Head of Oncology at the Novartis Institutes for BioMedical Research (NIBR). These naysayers glossed over a striking—and significant—feature of the emerging data. For a given type of tumor, the mutations that confer resistance in patients match those in laboratory models.

"With targeted therapy, you can actually study resistance in cell and animal models to discover the mechanisms in a fairly robust fashion," says Sellers. "That's not the case with chemotherapy."

Labs set out to map the mechanisms of resistance for each targeted therapy, beginning with imatinib, the poster child for molecular medicine. Originally developed as a treatment for a particular type of chronic myelogenous leukemia, imatinib blocks a protein called BCR-ABL, preventing it from initiating a cascade of signals that promote cell growth and division. As researchers studied mutations that confer resistance to the

drug, a pattern emerged. In almost every case, the cancer cells resumed their destructive rampage by re-activating BCR-ABL. They were addicted to the protein.

Studying resistance to other agents proved equally instructive. In many cases, tumors are addicted to a particular protein or molecular pathway, so there are a limited number of ways for them to evade targeted therapies. Time after time, a given type of tumor responds to therapeutic stress by tinkering with a handful of molecules—or even a single molecule. Importantly, scientists learned that while cancer cells may be adaptable, they're also predictable.

Molecular mixology

This discovery inspired scientists to become mixologists, designing cocktails of targeted agents, based on each tumor's dependencies. They select ingredients that disrupt the proteins driving the disease and the proteins or pathways implicated in resistance. The idea is to block a cancer cell's escape routes while attacking the original source of the problem, keeping evolution in check.

It's only recently that scientists assumed the mixology mantle for targeted therapy. When combination of targeted agents was first proposed as a solution to resistance, there was a major hurdle to implementation.

"At the time, we didn't have enough targeted agents to assemble cocktails and test the hypothesis," says Sellers.

By 2009, NIBR had launched a number of programs to address the need, culminating in molecules such as LEE011 and LJM716. From the earliest stages of each project, resistance provided a lens for decision-making, and it ultimately shaped the design of clinical trials. Learn more about these targeted agents below and read about a third molecule—ABL001—that recently reached the clinic.

"The dream is to conquer resistance and achieve cures," says Sellers. "I'm hopeful that rationally designed cocktails of targeted agents will move us in the right direction."

Featured Ingredients

Cancer Cocktails: LEE011 – A Popular Combination Partner

Cancer Cocktails: LJM716 – Closing A Common Release Valve

Cancer Cocktails: ABL001 – Hitting One Target Twice

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