A WINDOW INTO GIST'S RESISTANCE

A rational approach to drug design and development yields life-saving results

George Demetri has a knack for finding new cancer drugs.

Over the last ten years he has helped develop several drugs that hit a key family of molecular targets, receptor tyrosine kinases (RTKs). Though the drugs have helped patients worldwide, Ludwig Harvard Director Demetri has been frustrated by their lack of long-term effectiveness for most individuals. Ludwig Harvard's research focuses on understanding and overcoming resistance to these therapies, which target signal transduction pathways, as well as others. By elucidating how resistance is induced by structural changes in the targets of the first two agents he helped to develop, imatinib and sunitinib, Demetri and his colleagues identified a promising compound that hits the same molecular target, but in a different manner—one that might circumvent resistance.

That experimental drug, regorafenib, was owned by the pharmaceutical company Bayer. But the company was evaluating its efficacy as a treatment for colorectal cancer without a clear focus on its mechanism of action across many kinases. Demetri approached the company about collaborating to develop the drug with an eye on how it affects the two kinases that directly drive gastrointestinal stromal tumors (GISTs). He and his team had long studied these deadly tumors. "I said, this thing you have on the shelf looks pretty good," he recalls.

Demetri has not been disappointed. He swiftly obtained the agent in 2010, completed studies in mice and, by the end of 2011, finished testing it in patients with GIST. Within three years—a sprint in the slow-moving world of drug-testing—the US Food and Drug Administration (FDA) approved regorafenib as a proven therapy for GIST resistant to imatinib and sunitinib. The approval came on the heels of a successful phase 3 clinical study, published in 2013 in *The Lancet*.

Behind this success is a research enterprise built for speed and efficiency and focused on applying the best science to real-world clinical problems.

"We have a lot of scientific ammunition behind us," says Demetri. His team harnesses a suite of carefully developed cell-based and human-in-mouse "avatar" xenograft models that accurately predict eventual outcomes in patients. They also routinely assess the molecular profile of a patient's tumor to determine which cellular factors have gone awry. This approach, which is now becoming more common, helps tailor the scientific understanding of a cancer and its treatment to each individual patient.

George Demetri, Ludwig Harvard

Demetri's rational approach to drug design and development is making a difference in the lives of patients. With access to imatinib, sunitinib and regorafenib, patients diagnosed with GISTs today can expect to survive, on average, for five years or more, in contrast to the prognosis of less than a year of survival that was typical 14 years ago, before any of these drugs were available. Additionally, nearly one-quarter of patients with advanced metastatic GISTs can survive for more than a decade on targeted therapy.

Demetri is now rallying his lab's considerable resources to test new RTK inhibitors and combinations, and to develop drugs that kill cancer cells by hitting other targets. The studies have the potential to extend life in patients with GIST and benefit patients with other tumors.

DRUGS IN A BASKET

Receptor tyrosine kinase inhibitors choke off tumors by shutting down molecules that prompt cells to survive and proliferate. But as cancer cells evolve to evade treatment with successive

George Demetri and Joan Brugge, Ludwig Harvard

"The next step is all about discovering and developing the right combinations for the right patients."

GEORGE DEMETRI

RTK inhibitors, much as bacteria do in response to antibiotics, patients can run out of options.

To circumvent such resistance, Demetri is working on ways to simultaneously hit tumors with drugs that kill cancer cells in different or complementary ways. Even endlessly adaptable cancer cells would be hard pressed to escape all these drugs at once, he reasons. "The next step is all about discovering and developing the right combinations for the right patients," he says.

Demetri is developing a new class of agents to target a protein called MDM2, which helps drive cancer cell proliferation by inhibiting the tumor suppressor protein p53. Compounds that silence MDM2 "wake up" p53, which can then do its work to eliminate cancer cells.

Demetri's group is now testing such agents in patients selected based on the molecular profile of their tumors, particularly the levels of MDM2 in cancer cells along with those of a normal p53 gene. They are initially applying the strategy to address cancers of fat known as well-differentiated or de-differentiated liposarcomas, which harbor amplifications of the MDM2 gene. But Demetri says that patients with many other

types of tumors may also benefit from this strategy, especially if it is used as a sensitizer in combination with another drug to induce synergistic anticancer effects.

About ten years ago, Demetri was one of the first to author a pathway-oriented "basket" clinical trial based on such molecular profiling. When used judiciously, with appropriately chosen targets and patients, this approach can efficiently establish the effectiveness of one therapy against several unrelated forms of cancer that share a particular molecular characteristic. Demetri's application of this basket trial methodology led to the simultaneous FDA approval of imatinib for five different forms of cancer in 2006. Since then, many other research groups have adopted this approach.

Meanwhile, Demetri's team is developing new kinase inhibitors. They include pazopanib, the first FDA-approved therapy for soft-tissue sarcomas other than GISTs since the early 1980s. "We are now understanding resistance at a very deep level," he says, "and with the expansion of Ludwig Harvard, Joan Brugge and I plan to engage the Harvard community in a scientific 'social networking' experiment to bring together even more creative solutions to the problems of drug resistance in cancer." Demetri is hopeful that in the next ten years his quest to develop new targeted cancer drugs will yield an even better record, and, most important, even better outcomes for patients facing many different forms of cancer.

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