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.
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
Tamoxifen is a mainstay of treatment for many women with breast cancer, but when the drug stops working, tumors can progress rapidly. In a recent study that could lead to new options for such patients, Ludwig Chicago Director Geoffrey Greene and his colleagues discovered why some of the most advanced cases of breast cancer become resistant to this drug.

Tamoxifen binds the estrogen receptor, and in so doing blocks its activity, choking off the ability of estrogen to fuel tumor growth. Many late-stage, metastatic tumors contain the estrogen receptor but fail to respond to tamoxifen. Greene asked why by closely looking at a battery of 36 such tumors.

He and his colleagues found that about one-quarter of the tumors contained mutations that made the receptor hyperactive. The hyperactive receptors drove tumor cell proliferation even in the absence of estrogen.

In cell culture experiments, the researchers found that it took extremely high doses of tamoxifen—doses too toxic for patients—to shut down metastatic tumors containing the mutations. The findings suggest that compounds that block the estrogen receptor more potently, gram for gram, than tamoxifen may keep breast cancer at bay for longer. The findings were bolstered by similar findings last year by other groups.

“Drug companies and researchers are now actively developing and testing next-generation compounds,” says Greene, A CHINK IN BREAST CANCER’S ARMOR

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

GEORGE DEMETRI
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.

REFERENCES
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial.
Lancet. 2013 Jan 26;381(9863):295-302. PMID: 23177515

Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, Nam BH, Ramaiya N, Jagannathan J, Demetri GD.
Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial.
Lancet Oncol. 2013 Nov;14(12):1175-82. PMID: 24140183

Greene, cancer biology serves up its surprises. “This was an unexpected result,” he says of the team’s recent discovery, “and it is making quite an impact on our field.”

REFERENCE
ESR1 ligand-binding domain mutations in hormone-resistant breast cancer.
Nat Genet. 2013 Dec;45(12):1439-45. PMID: 24185512