Research Unveils the ‘Who’ and ‘Why’ of Gefitinib

When the U.S. Food and Drug Administration (FDA) approved the lung cancer drug gefitinib (Iressa) in May 2003, it was with the knowledge that the drug would be effective in only about 10% of patients. But researchers understood little about the characteristics of this subgroup that made them respond so well.

Sixteen months later, rapid research is providing answers to the “who” and the “why” of gefitinib.

“It’s sort of a dream come true for [lung] cancer therapy,” said Mark Kris, M.D., an oncologist at Memorial Sloan-Kettering Cancer Center in New York, who studies gefitinib. “It’s all about finding the specific defect that causes the cancer or makes it persist, and then countering it.”

Late last year, separate groups at Massachusetts General Hospital and Dana-Farber Cancer Institute, both in Boston, discovered why only a small fraction of patients benefit from gefitinib. After scrutinizing the protein known to be the general target of the drug, epidermal growth factor receptor (EGFR), both teams found that certain acquired mutations neatly tracked drug response.

In the Massachusetts General study, eight of nine patients with non–small-cell lung cancer who benefited from gefitinib displayed mutations in the DNA coding sequence for EGFR. They found no mutations in the seven patients who did not respond to the drug.

“There was such a clear correlation in our initial study between (EGFR) mutation status and response to the drug that we think it explains the vast majority of drug sensitivity,” said Jeffrey Settleman, Ph.D., a researcher on the Massachusetts General team.

That group, led by oncologist Daniel Haber, M.D., Ph.D., published its results in the April 29 online edition of the New England Journal of Medicine. On the same day, the Dana-Farber team reported its results in Scienceexpress, the online early release vehicle for Science. That report detailed EGFR mutations similar to those found at the cross-town hospital. Again, the defects tracked nicely with drug response.

The “who” question was answered, and clinicians were swiftly brought miles closer to identifying patients who will respond to gefitinib. In fact, Kris and other clinicians expect to eventually use diagnostic kits to detect the key mutations. A spokeswoman for the FDA confirmed that commercial tests were in development but declined to estimate when such kits might be available.

Answering “Why?”

Originally, researchers thought that gefitinib completely shut down EGFR, which plays a key role in telling cells when to grow and divide. Because the protein is overabundant in some 40% to 80% of non–small-cell lung cancers, it was a good bet, presumably, that the drug would help all of those patients. Because many other solid tumors overexpress EGFR, logic suggested a role for gefitinib in those tumors, too.

But the clinical trials disappointed. The pivotal U.S. trial found that approximately 10% of patients with chemotherapy-refractory lung tumors improved. Patients in Japan fared better; but even then, only some 20% responded. Patients with brain tumors called gliomas were not helped at all.

“It was obvious that it wasn’t just the amount of EGFR that was important,” said Settleman.

So his team buckled down in the laboratory, transferring normal and mutant EGFR into a variety of cell lines. When they paid close attention to the cascade of signals triggered when epidermal growth factor docked with the receptor, they found a striking bifurcation: Cells with normal receptors lived and died as expected, but those with mutant receptors survived indefinitely. Closer scrutiny revealed that the mutant EGFR seemed to jam the cells’ apoptosis, or death, program. The scientists sought to confirm that observation by blocking mutant EGFR with snippets of RNA. Sure enough, they saw rapid and massive cell death.

“The mutations are driving the antiapoptotic signal, the survival signal,” said Settleman, lead author on a July 29 Scienceexpress paper describing the experiments.

That finding, in effect, answered the “why” of gefitinib. It worked by reversing mutant EGFR’s antiapoptosis meddling. That’s why patients whose cancers harbor the mutation often experience rapid, sometimes dramatic, tumor shrinkage.

The experiments also bolstered a relatively new theory of tumorigenesis, “oncogene addiction,” a term coined two years ago by I. Bernard Weinstein, M.D., from the Herbert Irving Comprehensive Cancer Center at Columbia University, New York. Oncogene addiction explains the origin of cancer in simple, familiar terms. While cancer cells typically carry mutations in multiple genes, gross chromosomal abnormalities, and wholesale changes in gene expression, Weinstein argued in a July 2002 Science perspective that a single altered gene may, in fact, drive the entire process.

If the theory is correct, then “every tumor cell has an Achilles heel, a particular molecule that it has become addicted to,” said Sloan-Kettering’s Kris. “But once that signal is withdrawn, the cell can no longer proliferate or survive.”

Cousin Drugs

The EGFR family of proteins has become a popular target for cancer drugs. The monoclonal antibody trastuzumab (Herceptin), approved for use against breast cancer, targets Her2/neu, another EGF receptor. Other drugs in development include erlotinib (Tarceva), a small-molecule drug like...
gefitinib. It received FDA fast-track status in May 2002 and may be approved later this year, depending on phase III trial results. An article published in August in the Proceedings of the National Academy of Sciences early edition confirms that, like gefitinib, erlotinib targets EGFR mutations. Published by a Sloan-Kettering team led by William Pao, M.D., and Nobel prize winner Harold Varmus, M.D., the article concludes that further work will determine if the two drugs target the same or overlapping sets of patients. It is possible, too, they write, that certain mutations will confer greater sensitivity to specific EGFR-targeted drugs.

The most successful targeted cancer therapy to date, imatinib (Gleevec), garnered massive attention for improving the chances of patients with chronic myelogenous leukemia (CML), which is notoriously difficult to treat. But only a few thousand people in the United States develop CML each year, leaving open the question whether targeted cancer therapy would ever work for the majority of people with cancer.

Gefitinib provides a tantalizing preview of what clinicians hope will be a major targeted-therapy assault on common cancers. Lung cancer is the leading cause of cancer death among both men and women, responsible for an estimated 160,440 deaths in the United States this year. Some 80% to 85% of lung cancers are non–small-cell cancers, the type treated by gefitinib.

“Gefitinib is a huge deal. It confirms that the paradigm of targeted therapy is going to work for major common tumors, and not just rare ones,” said Dana-Farber Cancer Institute pathologist Matthew Meyerson, M.D.

Despite Myerson’s enthusiasm, though, the tumors of patients treated with gefitinib eventually start growing; survival times are only a few months longer than without the drug.

The mechanism behind this tumor resistance is one mystery surrounding gefitinib. Another: what to make of patients who respond to the drug but do
not carry the key mutations. The Pao and Varmus article identifies six (19%) such patients out of 31 who responded to gefitinib or erlotinib.

And without a practical laboratory test for the key mutations, clinicians are left searching for a reliable way to identify patients to treat with gefitinib. In the August 4 Journal of the National Cancer Institute (Vol. 96, No. 15, p. 1133), an Italian team proposed a simple immunohistochemical test. A group called the Interuniversity Consortium of Bologna found that 50% of 103 patients tested positive for a molecule called phosphorylated Akt. As a link in the apoptosis signaling chain, the molecule makes sense as a possible surrogate for EGFR mutation status. However, the test may not be discriminating enough: While 50% of the Italian patients had phosphorylated Akt, about 10% of U.S. patients ultimately respond to gefitinib. Testing for Akt status, then, would probably capture a large number of patients who do not stand to benefit from the drug.

Two other factors appear important for response: nonsmoker status and Asian heritage. In a Japanese phase II clinical trial, 19% of patients responded to gefitinib, while the parallel statistic in the U.S. trials is 10%. An analysis by Kris and colleagues also found that nonsmokers were more likely to respond to gefitinib than smokers. Scientists are just beginning to explore the biological mechanisms behind these observations.

So despite the high-tech promise of targeted therapy for lung cancer, and despite the progress in determining who will benefit from gefitinib, Kris provides a well-worn prescription: “The bottom line in 2004 is this: There is really only one absolute certain way to know if this drug is going to help, and that’s to give it to the patient.”

—Brian Vastag