Molecular Cancer Therapeutics

The Discovery of Lapatinib (GW572016)

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Commentary on:
David W. Rusnak, Karen Lackey, Karen Affleck, Edgar R. Wood, Krystal J. Alligood, Nelson Rhodes, Barry R. Keith, Doris M. Murray, W. Blaine Knight, Robert J. Mullin, and Tona M. Gilmer. **The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines *in vitro* and *in vivo*.** Mol Cancer Ther 2001;1:85–94.

In the mid-1980s, it was recognized that overexpression of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2) adversely affected the prognosis of some cancer patients. Because EGFR and HER2 are key regulators of cell growth, differentiation, and survival, it was believed that inhibition of these receptors would block downstream signaling and would be antiproliferative. Indeed, by the late 1980s, researchers were creating some of the first targeted inhibitors of tyrosine kinase activity. It was in this context that we began our efforts to develop potential disease therapies using a small-molecule approach to selectively target EGFR and HER2.

The challenge for developing small-molecule EGFR/HER2 inhibitors lay in determining the potency and selectivity specific to their kinase domains. Several key components of our study permitted us to drive discovery efforts. First, novel chemistry produced numerous compounds for testing. Second, a broad-based kinase biochemical screening platform allowed us to examine compounds on multiple kinase targets. Third, the creation of a cell-based panel included lines dependent on EGFR or HER2 signaling as well as suitable control cell lines. This cell panel not only provided automated evaluation of molecules for potency and selectivity in the cell's complex environment but also made the investigation of players downstream of EGFR and HER2 possible, linking EGFR and HER2 inhibition to cell-cycle arrest and apoptosis. The last component, *in vivo* xenograft models, enabled us to continue this research by using pharmacokinetic and pharmacodynamic markers. Our work with a highly committed and motivated team of scientists ultimately resulted in the innovative discovery of GW2016, also known as GW572016, which later became the cancer therapy lapatinib.

The selectivity of lapatinib for HER2 and EGFR kinase domains and its activity in HER2-overexpressing cell lines (e.g., breast and gastric cancer) and EGFR-overexpressing cell lines (e.g., head and neck cancer) provided a foundation to test lapatinib in selected patient populations. The U.S. Food and Drug Administration's approval in 2007 of lapatinib, in combination with capecitabine for treatment of advanced or metastatic HER2-overexpressing breast cancer, provided another option for patients whose disease progressed on trastuzumab (a humanized monoclonal antibody directed against the extracellular domain of HER2). Ongoing clinical trials are examining lapatinib activity in HER2-overexpressing breast cancer, HER2-overexpressing gastric cancer, and head and neck cancer.

Looking ahead, an HER2- and EGFR-targeted strategy will be similar to most future cancer therapies (i.e., in combination with other agents). Recent clinical evidence has shown the synergy of dual blockade with the combination of lapatinib and trastuzumab in patients with HER2-positive metastatic breast cancer. In addition, dual blockade of the HER2-signaling pathway is also being examined in the neoadjuvant and adjuvant settings. Other clinical studies are evaluating HER2 and EGFR agents in combination with other signaling agents and chemotherapies. Since our first publication on lapatinib 10 years ago, we have been excited about the impact of our efforts, and we remain committed to improving the lives of cancer patients.

Disclosure of Potential Conflicts of Interest

T. Gilmer and D. Rusnak declare an ownership interest, including patents, with GlaxoSmithKline.

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