nature biotechnology



# A dose of reality for rational therapies

Many of biotech's greatest therapeutic successes are drugs used as adjuncts to conventional cancer therapies. Erythropoietin-α and granulocyte-macrophage colony stimulating factor are blockbusters that ameliorate the harmful effects of cytotoxic chemotherapy regimes. Interferon-α was for many years the therapy of choice for use with traditional chemotherapy in certain leukemias and multiple myeloma. Now, 'molecularly targeted' biotech drugs—monoclonal antibodies and small molecules that inhibit protein kinases activated by mutations and chromosomal rearrangements occurring in tumors—have investors and analysts purring about their potential as cancer therapies. The approvals of monoclonal antibodies Herceptin (trastuzumab) and Erbitux (cetuximab) and of the small molecule Tarceva (erlotinib)—all of which target mutated receptor tyrosine kinases—are further fueling the enthusiasm.

Several talks at last month's Miami Nature Biotechnology Winter Symposium highlighted the expanding number of kinases—phosphatidylinositol 3-kinase, Akt, PTEN, mTOR, the Ras/Raf/MEK pathway and cell cycle proteins CDKs/cyclins—being targeted by drug developers. With over 30 kinase inhibitors currently in clinical development and around 518 protein kinases identified in the human genome, there appears to be plenty of 'low-hanging fruit' for companies to pick. One industry speaker at Miami went so far as to suggest that kinase inhibitors are the main reason for the biotech industry's continued success.

There are reasons to question, however, whether the spectacular clinical results of trailblazing drugs such as Gleevec (imatinib mesylate) and Herceptin may be repeated. Kinase targets clearly are 'low hanging,' in that they are identifiable and addressable. But the real issue is whether they can be 'fruitful' when there is only limited knowledge of their molecular roles. Already, several of the following pack of kinase inhibitors have shown less than impressive clinical efficacy; AstraZeneca's Iressa (gefitinib) has also been associated with an unexpectedly high number of adverse events in non-small cell lung cancer patients. Concerns are sufficiently serious that the US Food and Drug Administration is considering whether to withdraw the drug.

Even kinase inhibitors that are initially effective have had to contend with the emergence of resistance in patients to monotherapy, most often as a result of mutations in the ATP-binding pocket of the kinase. One way around resistance may be to use combinations of inhibitors either that target inactive and active conformations of the same kinase or that compete for binding with both ATP and the kinase's protein substrate.

When combined with conventional cytotoxic agents, certain kinase inhibitors, such as Gleevec and Iressa, have in certain cancers failed to confer significant therapeutic benefit. One explanation for this is that many kinase inhibitors target molecules that participate in signal transduction pathways with many redundant and uncharacterized components. To make matters worse, several kinases whose role in cell proliferation is well characterized appear to have additional moonlighting roles—and this implies potential unpredictable side effects for drugs that inhibit them.

The reality is that concerted efforts to identify the number and promiscuity of interactions in cell signaling systems remain in their infancy. According Miami keynote speaker Al Gilman of the Alliance for Cellular Signaling (http://www.signaling-gateway.org/)—a multicenter effort to investigate 'nonadditivity' in signal transduction that studies the effects of pairs of ligands (rather than single ligands) on cell behavior—almost every ligand pair tested so far (203 of 231) has at least one statistically significant nonadditive interaction. Results so far indicate that many receptor signaling pathways converge early on into common transduction modules—a finding that will encourage drug developers that they may one day be able to identify pivotal points in signaling cascades for intervention.

Until that time, however, drugs will be developed against a background where the underlying cancer biology (and the role of kinases in that biology) remains poorly understood. Even when preclinical work establishes a mechanism of action, new targets often emerge. In the case of Gleevec, which was initially touted as a specific inhibitor of the kinase stemming from the BCR-ABL fusion in chronic myelogenous leukemia, several other kinase targets have subsequently been identified. This in itself is not necessarily a bad thing: with so much functional redundancy in cancer signaling pathways, multi-action kinase inhibitors may be more effective, as long as the range of targets is germane to cell proliferation. Inhibitors that target multiple kinases may also be applicable to new cancer types (e.g., the application of Gleevec to c-KIT positive gastrointestinal stromal tumors). In this context, assays that screen drug candidates against entire arrays of many kinases (see p. 329) may allow more rapid mapping of inhibitor specificity, help predict those cancers in which inhibitors will be effective and raise flags for potential toxicity problems.

In the meantime, companies that rush inhibitors into trials without a molecular rationale for selecting patients with tumors responsive to therapy are playing a dangerous game. The clinic is a crowded arena where molecularly defined therapies jostle for attention with cytotoxic therapies, life-cycle-managed variants of those therapies, cellular and genetic approaches, 'alternative medicine' methods and a host of pretender nostrums whose place on the roster is based as much on clinical despair and hope as on any form of underpinning scientific rationale. If compounds that interact with kinases (or other molecular targets) are to distinguish themselves as rational therapies, then their molecular basis must be well founded.

Genentech broke new ground in 1998 when it introduced Herceptin, a breast cancer treatment for patients selected on the basis of an immunohistochemical test for HER2 in tumor biopsies. Seven years later, diagnostics for epidermal growth factor receptor are only just starting to be tested to predict patient responses to Erbitux, Iressa and Tarceva. Pharmacogenetic tests to identify the mutations in intracellular kinase domains remain a distant prospect. That is snail-paced progress for an industry that claims to be innovative and producing rational therapies. And it ill serves cancer patients who are being offered inappropriate therapies when diagnostics could be developed to spare them from fruitless treatment and debilitating drug toxicities.