KEEPING AN OPEN MIND

There was once considerable scepticism about kinase inhibition as a therapeutic strategy. But, as reflected in this month's focus issue on kinases in cancer, kinases are now the second most important class of drug targets. Could this transition hold general lessons for drug research?

The approval of the kinase inhibitor imatinib mesylate (Gleevec; Novartis) in 2001 heralded a new era in cancer therapy. Not only did the remarkable success of imatinib in treating chronic myelogenous leukaemia (CML) validate the concept that a molecular understanding of cancer can lead to more effective and less toxic drugs, it also finally dispelled the myth that modulation of specific kinases with small molecules was not a feasible therapeutic strategy.

Such scientific breakthroughs can sometimes make previous standpoints appear foolish, but in this case, without the benefit of hindsight, the three issues underlying initial scepticism about kinase inhibitors as therapeutics still seem reasonable. Biochemists argued that developing compounds with sufficient potency to compete with the high intracellular concentrations of ATP would be too challenging, chemists argued that the high degree of similarity among kinase ATP-binding pockets would preclude the development of specific inhibitors, and biologists argued that the key role of kinases in normal cells would lead to unacceptable side effects.

In part owing to concerns about these issues, kinase-inhibitor research in industry did not start to become widespread until the mid-1980s, when staurosporine, an antifungal natural product, was identified as a nanomolar inhibitor of protein kinase C. Although staurosporine is now known to lack specificity, the proof that sufficient potency was achievable encouraged the testing of many other compounds, and, indeed, it was an inhibitor of protein kinase C that became the lead compound in the development of imatinib. With the first of the three hurdles cleared, medicinal chemistry efforts succeeded in addressing the second — providing high specificity for the Bcr–Abl kinase that drives CML — and now many inhibitors that are specific for other kinases have been developed. Finally, fears related to the third issue were laid to rest by the extremely rapid clinical success of imatinib. Furthermore, as imatinib inhibits at least two other kinases with high potency, this success showed that some lack of specificity in kinase inhibitors can be tolerated, and might even be beneficial. Imatinib has now been approved for other indications on the basis of its ability to target these additional kinases, and some of the most exciting anticancer agents in development have been selected because they simultaneously inhibit several kinases implicated in tumour growth and progression.

So, what might we learn for future drug discovery from the change in the perception of the tractability of kinases as targets during the past 20 years? First, it could be good to keep in mind that unexpected breakthroughs can quickly dispel what seems to be well-justified scepticism. A pertinent emerging example is the development of small-molecule drugs that target protein–protein interactions. Such interactions are still viewed, as kinases once were, as highly challenging targets, in this case owing to issues such as the lack of well-defined binding pockets. Nevertheless, several small-molecule antagonists of protein–protein interactions have recently been identified, often through the use of innovative screening approaches, and it is becoming apparent that at least some types of protein–protein interaction might be tractable targets owing to the presence of unexpected small-molecule binding sites.

Second, as in all fields of science, it is important that some research is directed at trying to extend the boundaries of what is thought to be achievable. The financial pressure on the pharmaceutical industry may inevitably constrain the amount of effort devoted to trying to develop drugs that modulate 'risky' targets outside the current major classes, unless the therapeutic rationale is compelling. But academia is not so restricted in this respect. Recent initiatives, such as the NIH Molecular Libraries Initiative, which is seeking to promote the development of 'chemical tools' that modulate targets that are currently viewed as 'undruggable' — and which itself has been the target of some scepticism — could open new doors for drug research. The use of staurosporine as a tool had a key role in catalysing the research that established kinases as a major target class, and compounds of similar importance could well emerge from the research facilitated by such initiatives.

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