

# Executive Summary

**K**inases are enzymes involved in phosphorylation, a biochemical modification mechanism that regulates fundamental cellular processes such as gene expression, cytoskeletal rearrangement and cell movement, growth and differentiation, proliferation, and death. Phosphorylation also regulates the catalytic activity of many target enzymes, causing them to modify additional proteins. Thus, the activation of one kinase can cause a cascade of signaling pathway activation, resulting in significant changes in the behavior or fate of a cell.

There are 518 known human kinases, with a wide range of structures, functions, and locations within the cell. Their role in cellular function and communication, and their sheer number, suggest that any disruption in their activity can have adverse effects. Aberrant or inappropriate kinase activity has been associated with many diseases, in particular those involving inflammatory or proliferative responses. In addition to cancer and inflammatory disorders such as rheumatoid arthritis, compromised kinase activity has been causally linked to diabetes, cardiovascular disease, neurological disorders, and other conditions.

At the end of the 1980s, no protein kinase inhibitors had yet entered clinical trials. Because the adenosine triphosphate (ATP)-binding residues on kinases are conserved throughout the family, researchers were concerned early on that it would not be possible to develop kinase

inhibitors with adequate potency and specificity. These concerns have been allayed to some extent in recent years. Many compounds are more selective than might have initially been expected, and agents with broader specificity have proven their safety and effectiveness. The field of kinase modulation has in recent years become one of the most active in the industry. Most, if not all, big pharma firms have programs in this area, and they are among the leaders in the field. In 2003, approximately 50 kinase-modulating compounds were in clinical trials or beyond, and by 2006 the figure had surpassed 100. Today about 20 kinase inhibitors are approved for marketing in the United States and at least another 250 are in clinical evaluation.

Small-molecule kinase inhibitors are the most promising types of drugs in this class because of their potential for oral delivery, the ease of fine-tuning their chemical structure using classic and combinatorial chemistry techniques, and their amenability to large-scale production. Monoclonal antibodies, antisense, and RNA interference are also being targeted against kinases.

A large proportion of late-stage clinical kinase inhibitor programs target receptor tyrosine kinases. Although only 58 of the 518 human kinases fall into this category, their role in controlling cellular growth and the fact that they possess extracellular binding domains made them early and actively explored targets for the development of compounds for

cancer and other proliferative diseases. Today almost 40% of the kinase inhibitors in clinical trials fall into this category. The role of the PI3K-Akt-mTOR (phosphoinositide 3-kinase–Akt–mammalian target of rapamycin) pathway in cancer is now also generating increased interest, as many pharmaceutical companies are in the early stages of building programs in this area.

Although kinase modulation has shown itself to be a novel and promising approach to treating disease, several limitations have become apparent in studies conducted to date. Some of the challenges to success in the field include:

- Ensuring target relevance and specificity
- Overcoming resistance
- Designing clinical trials to maximize the response to a drug
- Addressing the high cost of novel therapeutics

Kinases make up a veritable treasure trove of targets for a variety of indications. Despite this wealth of opportunity, however, kinase-modulating drugs have begun to progress through clinical trials and onto the market only relatively recently, and the most advanced compounds target only a handful of the best-characterized kinases. Beyond these kinase targets, hundreds more exist that could provide sites for intervention in other disease processes.

This report reviews the considerable array of drug development efforts directed at kinases (organized according to the major groups, the receptor and nonreceptor tyrosine kinases, and the serine-threonine kinases) and profiles the major companies, drugs, and projects. It also surveys the current and emerging technologies being applied to the development of these compounds. It concludes with a discussion of current trends and some of the major challenges faced by the industry.