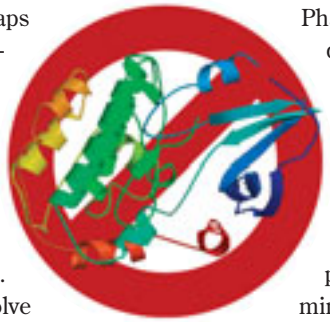
Kinase inhibitors

Researchers eye compounds that prevent or compete with phosphorylation, hoping to find another Glivec.

BY MARK S. LESNEY

With the success of the drug Glivec in the treatment of a specific form of leukemia (see "Focus on phosphate", p 38), the pursuit of kinase inhibitors as therapeutic agents has entered full swing (*1*). Many clinical trials are under way, and more are seeking enrollment in efforts to capitalize on the power of manipulating these major physiological control points involving phosphorylation events. These trials, although mainly focused on controlling a variety of cancers, still encompass a surprising gamut of diseases (though perhaps that should not be unexpected because of the ubiquity of kinases as controlling factors in signal transduction in almost every major physiological pathway, from sugar metabolism to neural transmission).



Many of these trials involve the expanded use or attempts to perfect dosage or delivery of "old favorites" such as Glivec and flavopiridol (a cyclin-dependent kinase inhibitor). In fact, Glivec (referred to as Gleevec or STI571 at *clinicaltrials.gov*) is involved in more than 50 studies for an incredibly wide range of cancers. A significant number of new compounds, however, are being tested as well—drug candidates that companies hope will be the next blockbuster drug or, at the very least, a signpost to hitherto unavailable therapeutic regimes. It would be impossible to do more than highlight a few such studies.

One promising candidate in clinical trials is Iressa (ZD1839), a synthetic selective inhibitor of the epidermal growth factor receptor tyrosine kinase that AstraZeneca is developing. It is currently being tested alone and in concert with other drugs for various cancers, including solid tumors in children (Phase I), non-small-cell lung cancer (Phase II), metastatic squamous cell carcinoma of the skin (Phase II), and breast cancer (Phase II). The results with non-small-cell lung cancer have prompted the company to make Iressa available to patients on a humanitarian, expanded access basis (*www.astrazeneca-us.com/about/iressa_program.asp*).

In another example of kinase inhibitors being studied, in December 2002, Eli Lilly announced the completion of two Phase III clinical trials for its drug ruboxistaurin mesylate, a PKC β inhibitor, also known as LY333531, designed to treat diabetic retinopathy and macular edema. Although not fully meeting its projected end points, the company determined that the results were sufficiently positive to conduct additional trials that it hopes will lead to product registration.

Several companies, including Boehringer Ingelheim, GlaxoSmithKline, and Vertex/Kissei, are preparing or conducting early-stage clinical trials on p38 MAP kinase inhibitors, seeking the next blockbuster drug for rheumatoid arthritis or cardiac inflammation. For example, Phase II-a studies of SCI-469, Scios's p38 MAP kinase inhibitor, which showed promise as an anti-inflammatory in preclinical tests, were conducted in the first quarter of 2003 to determine safety and tolerability of doses in rheumatoid arthritis patients. Follow-up efficacy trials are planned.

Sugen's SU11248, an oral multitargeted kinase inhibitor that showed promise at inhibiting tumor activity and blood supply in preclinical trials, began Phase I studies. In addition, a number of kinase inhibitor compounds are getting significant advanced publicity as a result of their promising preclinical results. The majority of these will likely enter clinical trials in the near future, including Aurora kinase inhibitors developed by Vertex for targeting rapidly dividing cells (such as in cancer).

Whether the majority of these kinase inhibitors being developed and tested prove to be the desired blockbusters, valuable niche drugs for specific cancers, or simply another case of bandwagon hopes dashed, only time will tell.

Reference

(1) Cohen, P. *Nat. Rev. Drug Discov.* **2002,** *1,* 309–315.

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clinicaltrialsweb

Gleevec Phase II trial for advanced ovarian, fallopian tube, or primary peritoneal cancers
www.clinicaltrials.gov/ct/gui/show/NCT00035646;jsessionid=A06CB817A97A66D63C4FB49301BE1908?order=4

Phase III clinical trials for a PKC inhibitor
http://newsroom.lilly.com/news/story.cfm?id=1148

Clinical trials of SU11248
www.sugen.com/webpage_templates/sec.php3?page_name=trials

Preclinical trials: Aurora kinase inhibitors
www.vrtx.com/Pressreleases2002/pr111302.html

Flavopiridol for treating recurrent or metastatic head and neck cancer
www.clinicaltrials.gov/ct/gui/show/NCT00005670;jsessionid=2199F574BC6E1D5B704D068356E9AA9F?order=1

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