PATENT WATCH

Method of treatment must be specific

With US $2.4 billion at stake, there were bound to be arguments as to who owns the rights to the best-selling pain killers Celebrex and Bextra, both of which are COX2 inhibitors. The case concerned a patent owned by the University of Rochester that covered the utilization of a specific biochemical pathway to decrease pain. The university claimed that their patent was infringed by Pfizer, Pharmacia, Monsanto and Searle — manufacturers of the COX2 inhibitors — because these drugs act by targeting the university's patented pathway. However, Judge David Larimer of the US District Court ruled that the university's patent was invalid because it was too vague; and that by not indicating a specific drug compound to inhibit the described pathway, the claim failed to satisfy written-description requirements. Without the drug, it is impossible to practice the claimed method of treatment, and so the ruling went on to say that the patent could not be considered to be an invention, but merely a first step for obtaining a desired result. The implications of Judge Larimer's ruling are enormous, as many patents claim method-of-treatment for a disease without specifically detailing which compounds would be used to inhibit or promote the particular molecular target. The University of Rochester intend to appeal against the district court ruling.

WEB SITE
US District Court ruling: http://www.nywd.uscourts.gov/decision/20030305_00cv6161_larimer.pdf

GSK's Paxil given notice

GlaxoSmithKline (GSK) shares dropped after Chicago Federal Judge Richard Posner ruled that a version of the blockbuster antidepressant Paxil (paroxetine hydrochloride), made by Canadian generics company Apotex, did not infringe the patent on the drug, which is due to expire in 2006. The Chicago case centred on Apotex's anhydrate version — that is, a version without water — of the core molecule in Paxil, which it said was different from GSK's hemi-hydrate version, which contains some water. GSK's claim that the anhydrate version naturally converts into the hemi-hydrate version were rejected by the judge. Although Judge Posner did find it likely that there would be some hemi-hydrate in Apotex's product, he found that GSK did not show that sufficient amounts would be present to infringe the patent under his claim interpretation. GSK disagrees with that claim interpretation and will appeal the ruling of non-infringement. This latest ruling on the hemi-hydrate patent represents one element of the present legal action between GSK and Apotex. In mid-September, a 30-month stay granted under Hatch–Waxman law against regulatory approval of Apotex's generic drug is due to expire, paving the way for the drug to be marketed. With sales of US $3.2 billion, Paxil accounted for about 10% of GSK's total revenue in 2002. In a bid to minimize the threat to Paxil, GSK is promoting a new controlled-release version of the medicine, called Paxil CR, that is protected by separate patents and already accounts for 31% of new US Paxil prescriptions.

ANTICANCER DRUGS

Breaking down resistance

The kinase inhibitor STI571 (Gleevec; Novartis) can induce complete remission in patients with chronic-phase chronic myelogenous leukaemia (CML). Patients whose disease has advanced to blast crisis, however, frequently become resistant to the drug, due to mutations in the BCR–ABL kinase domain. As reported in *Cell*, Azam *et al.* have developed an *in vitro* screen to survey mutagenized forms of BCR–ABL, and have obtained a more comprehensive picture of mutations that confer drug resistance.

Kinases typically exist in equilibrium between 'open' (active) states, or a 'closed' (autoinhibited) state. Co-crystallization studies of STI571 and the ABL kinase domain have shown that the drug achieves its specificity by trapping the kinase in the closed conformation. The majority of patients that become resistant to STI571 therefore harbour mutations within the BCR–ABL kinase domain.

Azam *et al.* reasoned that mutations in other domains of the protein, in addition to the kinase domain, might mediate resistance. To look for these, they randomly mutagenized the *BCR–ABL* gene through propagation of the gene in a bacterial strain that is deficient in DNA repair. The screen led to the identification of 59 protein variants that were resistant to STI571 treatment, of which only 13 had been previously identified in patients with drug-resistant CML.

So how do these mutations confer drug resistance? Twenty-six resistance-associated mutations were found to lie outside the kinase domain. Structural modelling studies indicated that many of these mutations destabilize the closed conformation of the ABL kinase, shifting the protein equilibrium toward the open, active kinase conformation, which precludes drug binding. Some of the mutations were also associated with increased kinase activity and accelerated disease progression.

The *in vitro* screening strategy reported by Azam *et al.* could potentially be used for the many other kinase targets for which compounds are presently in development, to predict the mutations that are likely to be problematic in the clinic. Identification of the most refractory drug-resistant variants could be valuable in the development of next-generation drugs.

Kristine Novak, Nature Reviews Cancer

References and links

ORIGINAL RESEARCH PAPER Azam, M., Latek, R. R. & Daley, G. R. Mechanisms of autoinhibition and STI-571/Imatinib resistance revealed by mutagenesis of *BCR–ABL*. *Cell* **112**, 831–843 (2003)

FURTHER READING Capdeville, R. *et al.* Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nature Rev. Drug Discov.* **1**, 493–502 (2002) | Dancey, J. & Sausville, E. A. Issues and progress with protein kinase inhibitors for cancer treatment. *Nature Rev. Drug Discov*. **2**, 296–313 (2003)