PATENT WATCH

Balancing patent protection with generic medicines

Loopholes in the 1984 US Hatch–Waxman Act have allowed innovator drug companies to extend their patents far too long. So said the group Business for Affordable Medicine (BAM) at a press conference to Congress earlier this year. BAM, which consists of politicians, employers and labour organizations, is pushing for changes to facilitate faster availability of generics, which would reduce the cost of medicines. The Hatch–Waxman Act was designed to make it easier for generics manufacturers to enter the market by changing the patent rules and FDA testing procedures for generic drugs. One incentive offered to generics companies is the 180-day market exclusivity to the first manufacturer to market a drug previously supplied only as a brand-name drug. However, BAM maintains that brand-name drug companies routinely claim that a generic drug approval infringes the patented drug, which triggers a statutory 30-month delay in the final approval of the generic. No damages are awarded to the generics company should the claim be found groundless. Whereas BAM urges Congress to close the loopholes to prevent these kind of abuses, the Pharmaceutical Research and Manufacturers of America contend that changes to the Hatch–Waxman Act would stifle research and development.

AstraZeneca Losec patent ruled invalid in UK court

The anti-ulcer drug Losec, one of the world's top-selling drugs, accounted for 35% of AstraZeneca's total sales in 2001. Each day that generic competition is delayed, the company earns around US $2.5 million in profits. In March, the Patents Court of the High Court of Justice's Chancery Division ruled in favour of two UK-based pharmaceuticals firms, Cairnstores and Generics, in their challenge to two of the omeprazole (the active ingredient of Losec) formulation patents of AstraZeneca. However, AstraZeneca was given leave to appeal against the decision. Although the main patent on the drug expired last October, several other patents are still in force, which is providing the mainstay of AstraZeneca's defence against the generics companies. The company maintains that the UK decision does not have any implications for a similar case that is now underway in New York.

WEB SITES **European patent database:** http://gb.espacenet.com/
Lovegren, K. I. *et al.*, Haessle AB, EP 247983 | Lovegren, K. I. *et al.*, Haessle AB, EP 496437

Generics companies should challenge patents in court

Interim injunctions, those granted before a dispute is settled, are not often issued by the UK High Court. Last year, an interim injunction was granted on behalf of GlaxoSmithKline (GSK) against Generic UK over the production of a generic version of a GSK drug. The granting of the interim injunction in this case indicates that the Court will not look favourably on those who wait for legal action to come to them as a practical matter, rather than challenging the patent validity in court. The judge took into account that Generic UK had known that legal proceedings were likely if it went ahead with the product in question, but failed to take steps to challenge the validity of the patent that it considered invalid. The GSK patent-infringement case against Generic UK is underway in the High Court.

GENOMICS

Look into the future

Accurate prediction of future clinical outcome could revolutionize cancer treatment by potentially allowing specific therapies to be tailored to distinct tumour types, thus maximizing efficacy and minimizing toxicity. Identifying informative correlations between gene-expression levels in cell populations that do or do not respond to a given treatment offers much promise for this goal, but large differences in expression levels are typically crucial for predictive success. Writing in the inaugural issue of the *Journal of Proteome Research*, Michael Korenberg describes a computational method that can predict long-term treatment response from gene-expression profiles taken from patients at the time of diagnosis of acute leukaemia. The success achieved is in contrast to several previous attempts with the same data, which were hampered by the lack of genes with expression-level differences strongly correlated with clinical outcome.

The data were from a landmark study by Golub *et al.*, which showed that gene-expression profiling could be used to distinguish acute lymphoblastic leukaemia (ALL) from acute myeloid leukaemia (AML). This study also explored the ability to predict response to treatment with anthracycline-cytarabine in a group of 15 AML patients, 8 of whom failed to achieve remission, but statistical analysis found no evidence of a strong gene-expression signature predictive of clinical outcome.

Korenberg exploited a method for modelling nonlinear systems called parallel cascade identification (PCI), which requires only input/output data for the system gathered in an experiment — in this case, expression levels at the time of diagnosis/clinical outcome — to train a model for classifying further data, and has the useful feature that effective classifiers can be created with very few data. Using expression profiles from just one failed treatment and one successful treatment to create a training input, a PCI model was constructed that transformed gene-expression levels from the remaining profiles into output values whose correlation with outcome was clearly significant ($P < 0.0155$). In fact, 5 of the remaining 7 failed outcomes and 5 of the 6 remaining successful outcomes could be correctly classified from their expression profiles. Another identified PCI model could distinguish AML from ALL in a test analogous to that done by Golub and colleagues.

Such success in the prediction of class in the absence of large differences in gene-expression levels between classes could lead to the widespread application of PCI in cancer diagnosis and therapy. Furthermore, the method is just as applicable to images obtained from 2D-gel electrophoresis of proteins, and to many other biological profiles.

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References and links

ORIGINAL RESEARCH PAPER Korenberg, M. J. Prediction of treatment response using gene expression profiles. *J. Proteome Res.* **1**, 55–61 (2002)
FURTHER READING Golub, T. R. *et al.* Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science* **286**, 531–537 (1999)