PATENT WATCH

Electronic filing ready to go…

Life for Crystal City's postal facility, which serves the US Patent and Trademark Office (USPTO) and is the world's largest recipient of express mail, is likely to change as the USPTO takes steps to go electronic. As part of its "21st Century Strategic Plan", which aims to transform the USPTO from an inflexible bureaucracy into a system that works for all, its Director, Jim Rogan, awarded contracts to five companies that can offer their electronic-filing services to patent applicants. Although the companies are permitted to charge customers for their services, there will be no cost to the USPTO. At present, ~2–3% of applications are filed in partial electronic form, but these must be converted to paper during processing. Filing fees will be altered to encourage electronic filings. These changes should allow updating and automation of the application procedure, with the hope that the processing time will be reduced. The USPTO's goal is to remove all internal paper processing by October 2003, and for all operations to be completely paperless by 2005. However, all these changes are dependent on the formal adoption of the proposals into law.

WEB SITES US Patent and Trademark Office: http://www.uspto.gov/
21st Century Strategic Plan

Hope for Genentech?

Genentech has been ordered to pay US $300 million dollars in royalty compensatory damages to the City of Hope Cancer Center by a Los Angeles County Superior Court jury after almost a month of deliberation. City of Hope National Medical Center first sued Genentech in 1999, claiming that the biotechnology firm had reneged on an agreement to pay royalties. On that occasion, the jury was deadlocked, and a mistrial was declared. Now, the jury has awarded ~65% of the damages sought. Punitive damages have yet to be determined. Under the terms of their 1976 agreement, Genentech funded research by City of Hope scientists Arthur Riggs and Keiichi Itakura into new ways to make human proteins. The cancer centre would receive a 2% share of future drug sales, whereas Genentech would own any patents stemming from the research. Riggs and Ikatura created the field of using bacteria as protein factories to develop the first recombinant human peptides. Their research led to many patents worldwide, and nearly US $32 billion of new-drug sales, including insulin, recombinant human growth hormone and hepatitis B vaccine. The dispute between Genentech and City of Hope centred around a disagreement as to whether City of Hope was entitled to royalties. Genentech claims that this was not part of the agreement, whereas City of Hope asserts that it is owed 2% royalties on all the sales, and that Genentech concealed billions of dollars of sales between 1980 and 1995. Genentech has not made a decision about a possible appeal, as the trial is still underway.

WEB SITES US Patent and Trademark Office: http://www.uspto.gov/
Genentech, Inc. Recombinant cloning vehicle microbial polypeptide expression. US Patent 4,704,362 | Genentech, Inc. Method and means for somatostatin protein conjugate expression. US Patent 4,563,424

LEAD IDENTIFICATION

Best with both worlds?

Is high-throughput screening (HTS) the best approach to identify new lead compounds? Or is molecular docking more likely to be successful when the target structure is available? Both approaches have their advocates, but have rarely been used on the same target. Doman, Shoichet and colleagues compared the performance of HTS and molecular docking in searches for inhibitors of protein tyrosine phosphatase 1B (PTP1B) — a target for type 2 diabetes — and their findings indicate that HTS and docking could be complementary techniques for lead discovery.

In the HTS experiments, ~400,000 compounds from a corporate collection were screened against human recombinant PTP1B. Those that inhibited PTP1B at 300 μM were chosen for further study, and 85 had IC_{50} values lower than 100 μM — the chosen cut-off value to be considered a hit — which represents a hit rate of 0.021%.

To test the ability of molecular docking, ~235,000 commercially available compounds were computationally screened against the known active site in the crystal structure of PTP1B. In this case, 365 of the highest-scoring molecules in terms of potential for binding were investigated further in inhibition assays, and 127 (34.8%) had IC_{50} values lower than 100 μM. So, docking enriched the hit rate by 1,700-fold over random screening.

Analysis of the hit lists showed that both were dissimilar from the natural ligand — phosphotyrosine — which is important, as phosphate-containing molecules are not good candidates for drug development. Assessment of 'drug-likeness' by considering how many of the hits would pass the Lipinski Rule-of-5 criteria showed that, on average, the docking hits passed 3.49 out of 4 rules compared with 2.73 for the HTS hits, an unexpectedly large difference. Also of particular note was that the two hit lists had no significant structural similarities.

Although the question of whether structure-based methods can compete with random HTS cannot be answered by such a single study (for which there are several caveats, such as the differences between the databases that were screened by each technique), it does provide encouragement for the use of docking and structure-based approaches. But more generally, the diversity of both hit lists and their dissimilarity to each other suggest that the best strategy could be to use both techniques.

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References and links

ORIGINAL RESEARCH PAPER Doman, T. N. *et al*. Molecular docking and high-throughput screening for novel inhibitors of protein tyrosine phosphatase-1B. *J. Med. Chem* **45**, 2213–2221 (2002)