PATENT WATCH

Paediatric and generic exclusivity run consecutively

Generic drug manufacturer Barr Laboratories recently received its second piece of good news in five months. Last year, the company won the right to launch its generic version of Prozac, fluoxetine hydrochloride, nearly three years earlier than expected, by successfully mounting a challenge to Eli Lilly's Prozac patents. Barr was the first company to file an application for the production of fluoxetine hydrochloride, and was therefore entitled to 180 days of generic exclusivity, under the Hatch–Waxman Act. Now, following Congressional approval of a section of the Best Pharmaceuticals for Children Act, the US Food and Drug Administration (FDA) confirmed that the clock would start ticking for Barr's generic exclusivity after the completion of Eli Lilly's paediatric exclusivity. Paediatric exclusivity is a period during which protection is extended in return for running drug trials for children. Because there was an overlap between Lilly's paediatric and Barr's generic periods of exclusivity, the FDA has extended Barr's exclusivity by the amount of the overlap. The Congressional action has clarified that paediatric and generic exclusivity are distinct and separate incentives that are intended to be applied consecutively.

Doctrine of equivalents protection to stay or go?

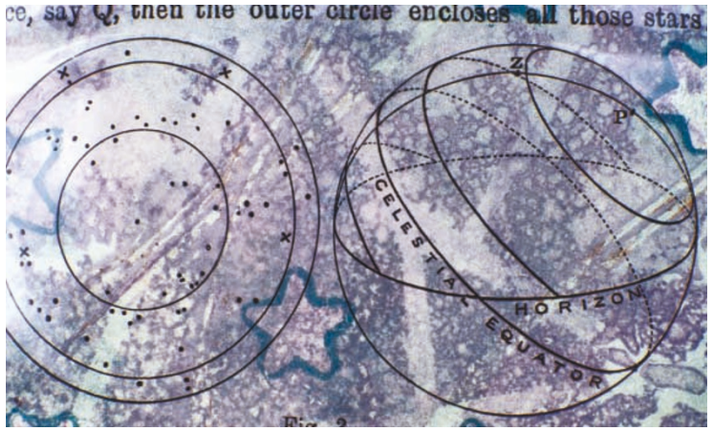
In patent infringement cases, the doctrine of equivalents allows a patent owner to prove infringement even if the claims are not actually infringed. The purpose behind the doctrine of equivalents is to prevent potential infringers from avoiding liability simply by making minor changes to their invention, which might not have been anticipated by the patent owner. Now, the US Supreme Court has agreed to hear the appeal of an important case from the Federal Circuit, *Festo v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, which significantly reduced the protection from the doctrine of equivalents. In late 2000, the Federal Court ruled that the doctrine of equivalents did not apply to amendments added during the patent application process. If this decision is upheld, the doctrine of equivalents will in future apply only to original patent filings and not to later modifications. The outcome of this case is likely to substantially affect the way in which patents are filed and pursued through the US Patent Office, so the ruling of the Supreme Court is anxiously awaited.

WEB SITE Festo v. Shoketsu Kinzoku Kogyo Kabushiki Co.:
http://www.usdoj.gov/osg/briefs/2001/3mer/1ami/2000-1543.mer.ami.html

Pfizer Viagra appeal falls flat

Britains's Appeals Court upheld a ruling that invalidated one of Pfizer's UK patents concerning the impotence drug Viagra. Viagra works by blocking phosphodiesterase 5 (PDE5). The court supported the earlier ruling, which held that because there was prior public knowledge that PDE5 was involved in impotence, Pfizer could not claim to have invented the idea of blocking PDE5 as a therapy for impotence. The legal decision means that Pfizer cannot exclude others from using PDE5 as an anti-impotency target. However, sildenafil, the active ingredient of Viagra, will remain under patent protection until 2013. Although Pfizer were denied permission to appeal further, the company intends to petition the House of Lords.

WEB SITE European patent database:
http://espacenet.com/
Pfizer European patent EP70255



DRUG DELIVERY

Vascular maps

Many therapeutic targets can be expressed in restricted but highly specific and accessible locations in the vascular epithelium. Several peptides that are known to home to blood vessels have been used as carriers to navigate the delivery of drugs to the vasculature. Tapping in on this vascular address system would allow the delivery of targeted therapies to specific locations. In *Nature Medicine*, Arap *et al.* used phage-display technology to identify peptides that home to specific vascular beds in a patient with a B-cell malignancy. This technology fuses peptides to capsid proteins on the phage surface. Libraries of phage-displayed peptides can then be screened for binding to specific ligands. Determination of the gene sequence of the selected phage identifies the peptide sequence.

Screening humans is important, as mouse-derived probes do not always achieve the desired targeted delivery. In this study, the patient received an intravenous infusion of a highly diverse, random phage-display peptide library. After infusion, tissue biopsies were taken to recover and identify phage from various organs. Analysis of the tripeptide sequences showed that some were preferentially recovered from several sites, whereas others were recovered only from a single site. These motifs are likely to represent sequences that are present in circulating ligands that home to vascular receptors. This information was used to compile panels of human proteins that contain these motifs.

One protein containing a tripeptide motif that was recovered from bone marrow is bone morphogenetic protein 3B. This protein is a growth factor that regulates bone development, and so it might be therapeutically useful to mimic the isolated ligand for that tissue. Motifs were also found in extracellular or transmembrane proteins that might operate selectively in the target tissue, such as sortilin in fat. Validation studies showed that some ligand–receptor pairs are detectable in numerous unrelated subjects. Tissue specificity of a phage-displayed peptide that mimics interleukin-11 was found to be associated with prostate. The phage bound specifically to prostate endothelium but not to control organs, and this specificity was confirmed by protein–protein interactions *in vitro*.

Vascular receptors that correspond to the selected peptides have been identified in normal and tumour blood vessels, so it is possible to develop therapeutic strategies based on selective expression of vascular receptors. This work has started to survey some of the uncharted territory in the vascular endothelium.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Arap, W. *et al*. Steps towards mapping the human vasculature by phage display. *Nature Med.* **8**, 121–127 (2002)
WEB SITES Arap's laboratory: http://gsbs.gs.uth.tmc.edu/tutorial/arap.html
Pasqualini's laboratory: http://gsbs.gs.uth.tmc.edu/tutorial/pasqualini.html