PATENT WATCH

A new twist on the chiral switch

Patents covering Sanofi-Synthelabo/BMS's oral antiplatelet chiral drug Plavix (clopidogrel bisulfate) are under legal fire in the United States from generics companies, Apotex and Dr Reddy's Laboratories. Plavix was approved by the FDA in 1997 as the (+)-enantiomer, and its five-year exclusivity period, granted for all New Chemical Entities, expired last year. The first patent — US 4,529,596, which was filed in 1983 and expires in July 2003 — claims both enantiomers and their mixture, whereas a later patent — US 4,847,265, due to expire in 2011 — claims only the (+)-enantiomer. Interestingly, although the case might be played out as if it were a chiral switch[1], this drug has never been marketed as a racemate, so the switch is operating at the level of the intellectual property. The likely crux of the generic challenge is that the '265 patent for the single enantiomer does not satisfy the key requirements of being novel and inventive.

Is the '265 patent novel — that is, not part of the prior art? The earlier patent claimed, but did not describe, the (+)- and (–)-enantiomers, although it states that "the invention relates both to each enantiomer and their mixture". In the description of the activities of each enantiomer in the '265 patent, data show that the (+)-enantiomer is pharmacologically superior in activity and less toxic than both the (–)-form and the racemate. However, this is not listed in the claims section of the patent. Even if it were, the court would need to decide if these differences were large enough to qualify as novel and inventive.

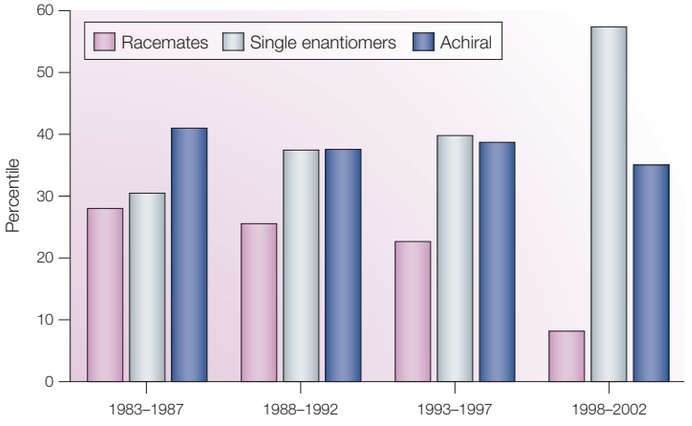
Was the development of Plavix as a single enantiomer in the 1980s non-obvious — that is, was there an inventive step? In the years 1983–1987, before the 1988 filing of the '265 patent, the distribution of worldwide approved drugs was 30% single enantiomers, 29% racemates and 41% achirals (see below: Israel Agranat and Hava Caner, The Hebrew University of Jerusalem). One fact that will undoubtedly come into play during the deliberations is that, in the 1980s, single enantiomers were already a significant and important component of approved drugs.

These issues have been assigned to Judge Robert Sweet of the Southern district of New York, who is not expected to make a decision until mid-2004, and the outcome could have far-reaching implications for the chiral switch strategy.

WEB SITE

US States Patent and Trademark Office: http://www.uspto.gov/patft/index.html

1. Agranat, I., Caver, H. & Caldwell, J. Putting chirality to work: the strategy of chiral switches. *Nature Rev. Drug Discov.* **1**, 753–768 (2002).



Israel Agranat and Hava Caner, The Hebrew University of Jerusalem. Analysis based on data taken from To Market, To Market in *Annual Reports in Medicinal Chemistry*, Vols **19**–**37** (1984–2002) (eds Bristol, J. A. & Doherty, A. M.); and Frantz, S. & Smith, A. Data of New Drug Approvals for 2002 (by the FDA and EMEA). *Nature Rev. Drug Discov.* **2**, 95–96 (2003).

DRUG DELIVERY

Container traffic

Micelles — biocompatible nanoparticles in which poorly soluble drugs can be encapsulated — represent a possible solution to the delivery problems associated with such compounds and, furthermore, as highlighted in two recent papers, could be exploited to target the drugs to particular sites in the body, potentially alleviating toxicity problems.

Block-copolymer micelles, which were used in both studies, are spherical supramolecular assemblies of amphiphilic copolymers that have a core–shell-type architecture. The core is a loading space that can accommodate hydrophobic drugs, and the shell is a hydrophilic brush-like corona that makes the micelle water soluble, thereby allowing delivery of the poorly soluble contents. However, a key issue — particularly if the drug contained is cytotoxic, as is often the case with cancer drugs — is understanding how the micelle and the micelle-incorporated agent are distributed, and so far information on this has been limited. This issue is addressed in the first of the two papers, reported in *Science* by Savic and colleagues. By using fluorescently labelled polymer and organelle-specific dyes in combination with confocal microscopy, they were able to show that their micelles localized in several cytoplasmic organelles, including the mitochondria, but not the nucleus. Further experiments confirmed that the micelles increased the amount of a model agent delivered to the cells, indicating that these micelles might be worth investigating for their potential to deliver drugs to particular subcellular targets.

There is also considerable interest in targeting micelles to particular cell populations, such as tumour cells. As described by Torchilin and colleagues in their paper in the *Proceedings of the National Academy of Sciences*, one strategy for achieving this is to attach antibodies to the polymers that make up the micelles. Using an antibody called 2C5, which is known to recognize the surface of numerous tumour (but not normal) cells, the authors constructed 'immunomicelles' that specifically attached to a variety of tumour cells *in vitro*. Administering immunomicelles loaded with the sparingly soluble anticancer drug taxol to mice with lung carcinoma resulted in increased accumulation of taxol in the tumour compared with free taxol or taxol in non-targeted micelles, and enhanced inhibition of tumour growth, illustrating the therapeutic potential of such micelle-based approaches.

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References and links

ORIGINAL RESEARCH PAPERS Savic, R. *et al*. Micellar nanocontainers distribute to defined cytoplasmic organelles. *Science* **300**, 615–618 (2003) | Torchilin, V. P. *et al.* Immunomicelles: targeted pharmaceutical carriers for poorly soluble drugs. *Proc. Natl Acad Sci. USA* **100**, 6039–6044 (2003)