PATENT WATCH

Gabbing about gabapentin

In an important ruling, the US Court of Appeals for the Federal Circuit has thrown out a common legal gambit in the case of Warner-Lambert (now Pfizer) versus Apotex Corp — that of listing a new patent on a drug's unapproved use in the FDA's publication of approved drug products, the 'Orange book', a ploy that is often exploited by brand-name pharmaceutical companies against their generic competitors. This particular battle concerns the epilepsy drug gabapentin (Neurontin), which generated Pfizer more than US \$2 billion

in sales in 2002. Even though some of the key patents protecting the drug expired in 2000, no company has overcome Pfizer's legal strategies until now. In 1998, Apotex filed an application with the FDA to market a generic version of gabapentin to treat epilepsy, as key patents covering methods of treating epilepsy were to expire in January 2000. Pfizer then sued Apotex, which resulted in an automatic 30-month stay preventing FDA approval of any generic drug, as it was claimed that such a drug would infringe not only the expiring epilepsy patent, but also a later Pfizer patent covering the use of gabapentin to treat other non-epilepsy neurodegenerative diseases. Even though the FDA had not approved the use of the drug for these neurodegenerative diseases, Pfizer listed this 'off-label-use' patent in the FDA's Orange book. In a three-to-zero decision, the Court of Appeals ruled that Apotex had not infringed the Pfizer patent, and that no infringement occurs when a company seeks FDA approval to market a generic drug for a specific medical use when the only patent at issue is for a use not approved by the FDA.

WEB SITE

US Appeal Court ruling: http://www.ipso.org/2003/IPCourts/Warner_v_Apotex.htm

Pharmacia pilots patent share for HIV drug

At the World Economic Forum, Pharmacia announced the launch of a not-for-profit pilot programme to expand access to medicines that are under patent protection for the poorest populations in the developing world. Together with the International Dispensary Association Foundation (IDA), Pharmacia will grant non-exclusive licenses for the antiretroviral drug delavirdine (Rescriptor) to generic drug companies that agree to manufacture and supply countries where the annual per capita income is less than US \$1,200, or where the HIV infection rate is above 1%, which includes as many as 78 nations. Under the scheme, Pharmacia will transfer its proprietary manufacturing technology and regulatory dossier for delavirdine to IDA, the world's largest non-profit supplier of generic medicines to the developing world, who will appoint generic manufacturers, monitor production quality and receive a 5% royalty fee to cover costs and fund new research. The generic drugs will be different in shape and colour to help authorities track any illegal trade in developed countries.

PROTEIN FOLDING DISEASES

Raising the bar

Raising barriers to provide protection is a familiar form of defence, so it should be no surprise to find out that nature has also adopted this method to protect against diseases. In protein folding diseases, energy barriers control the misfolding of proteins — low barriers allow the protein to misfold rapidly, whereas high barriers prevent this. In one group of protein misfolding diseases — the transthyretin (TTR) amyloid diseases — mutations on one allele can cause TTR protein tetramers to dissociate and misfold, and then misassemble into insoluble amyloid fibrils. However, mutations on the other allele can raise the kinetic barrier of this process, stabilizing the native state and making it harder for the normal TTR tetramer to dissociate and misfold.

Jeffrey Kelly and colleagues report in *Science* how they have taken advantage of this defence mechanism, called *trans*-suppression, to develop small-molecule inhibitors that can carry out the same task. The first step was to understand the mechanism of *trans*-suppression. Looking at engineered tetramers that contained disease-causing subunits and *trans*-suppressing subunits, the authors found that *trans*-suppression is principally mediated through increasing the activation energy associated with the dissociation of the tetramer (the rate-limiting step of TTR amyloid-fibril production) to such a degree that the barrier becomes insurmountable.

Known small-molecule inhibitors of amyloidogenesis are also thought to function by shifting the equilibrium away from the amyloid-fibril state, not by stopping the process of aggregation. Kelly and colleagues looked at five small-molecule inhibitors of TTR amyloidogenesis — including diflunisal and diclofenac, two FDA-approved non-steroidal anti-inflammatory drugs (NSAIDs) — and found that these function similarly to the *trans*-suppressor and stabilize the native protein state in a dose-dependent manner by increasing the activation energy for tetramer dissociation.

This is the first time that small-molecule inhibitors have been shown to stop protein-folding diseases before they begin. Most therapeutic strategies to date have focused on targeting the later stages of the aggregation process, but there is growing evidence that early misfolded intermediates are the toxic form of the misfolded protein, and that therefore the damage might not be influenced significantly by inhibitors that prevent the later stages of amyloid-fibril formation. The hope is that raising the energy barriers of protein misfolding using small-molecule inhibitors could be extended to other protein folding diseases, such as Alzheimer's disease and Parkinson's disease.

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References and links

ORIGINAL RESEARCH PAPER Hammarström, P., Wiseman, R. L., Powers, E. T. & Kelly, J. W. Prevention of transthyretin amyloid disease by changing protein misfolding energetics. *Science* **299**, 713–716 (2003)

FURTHER READING Sacchettini, J. C. & Kelly, J. W. Therapeutic strategies for human amyloid diseases. *Nature Rev. Drug Discov.* **1**, 267–275 (2002)