PATENT WATCH

UK allows generic version of Amgen's breadwinner

A ruling by the UK Court of Appeal in late July frees Transkarytotic Therapeutics (TKT) and its partner Aventis to market erythropoietin (EPO) in the United Kingdom, a decision that will give a general boost to manufacturers of generic biopharmaceutical products. Last year, Amgen won a patent infringement case against TKT in the UK High Court, although this was widely seen at the time as a surprisingly broad interpretation of Amgen's intellectual property rights over EPO. Although the Court of Appeal did not question the validity of Amgen's patent, they ruled that it did not extend to cover products made by endogenous gene activation, a technique not covered by the patent. Amgen is expected to seek permission to appeal this latest decision in the House of Lords, the highest court of appeal in the United Kingdom, but it is by no means certain that this will be granted. This narrower interpretation of biopharmaceutical patents will leave patent holders more open to attack from generic manufacturers using innovative techniques. An equivalent appeal hearing was recently conducted in the United States, and a decision is due within the next few months.

Full written description might not be necessary

Enzo Biochem's patent for bacterial probes is valid, even though, in defining their invention, it had made only a deposit of a biological sample, in combination with a definition of the function of the invention. So ruled the US Court of Appeals for the Federal Circuit, disagreeing with a previous Appeals Court decision and reversing an earlier judgement from the Federal District Court, which had dismissed the patent because the written description of the claimed invention was not thorough enough. The validation of its patent signifies that Enzo can reinstate the suit alleging patent infringement against Gen-Probe and four other defendants, returning the case to the trial court. The other companies named as defendants are Gen-Probe's parent company Chugai Pharmaceutical, Chugai Pharma USA, bioMerieux and BD (Becton, Dickinson and Company).

WEB SITE US Patent and Trademark Office: http://www.uspto.gov/
Lo, A. Nucleotide sequence composition and method for detection of *Neisseria gonorrhoeae* and method for screening for a nucleotide sequence that is specific for a genetically distinct group. US Patent 4,900,659 (1990)

Mechanism-of-action patent on NF-κB

ARIAD Pharmaceuticals has recently obtained a US patent covering methods of treating disease by regulating nuclear factor-κB (NF-κB) signalling. The patent forms one of a suite of NF-κB-related patents to which ARIAD has exclusive licence, which have been awarded to a team that includes Nobel laureates David Baltimore and Philip Sharp. Several marketed drugs, as well as many in development, act by modulating NF-κB, which is implicated in conditions such as cancer, inflammation and osteoporosis.

WEB SITE US Patent and Trademark Office: http://www.uspto.gov/
Baltimore, D. *et al.* Nuclear factors associated with transcriptional regulation. US Patent 6,410,516 (2002)

LEARNING AND MEMORY

Weeding out memory extinction

If we train a mouse to fear a tone that is paired with an electric shock, the mouse will freeze the next time it hears the tone, expecting to receive another shock. But if we continue to present the tone in the absence of shock, the association between the two stimuli will gradually become weaker, and the mouse will stop freezing.

This phenomenon is called extinction — defined as the reduction of a learned behavioural response on repeated presentations of a conditioned stimulus in the absence of a reinforcer. As the extinction of aversive memories might be affected in states such as post-traumatic stress disorder and in certain phobias, it is important to find the mechanism(s) behind extinction.

So, what are the neural bases of extinction? Reporting in *Nature*, Marsicano *et al.* provide evidence for the crucial involvement of endocannabinoids. Marsicano *et al.* generated mice that lacked the cannabinoid receptor Cb_1 and trained them in the aversive task described above. *Cb1*$^{-/-}$ mice learned to freeze in response to the tone; however, in contrast to wild-type mice, the Cb_1-deficient animals failed to extinguish this behavioural response. Moreover, the Cb_1 antagonist SR141716A had the same effect on extinction if it was administered immediately before the tone.

The area of the brain that is key to learning the tone–shock association is the amygdala. Marsicano *et al.* therefore predicted that the levels of endogenous cannabinoids should rise in the amygdala immediately after presentation of the tone. Indeed, they confirmed this prediction for two endocannabinoids — anandamide and 2-arachidonoylglycerol. But how might these molecules affect synaptic transmission in the amygdala during extinction? We don't yet know, but the authors made an intriguing finding. In wild-type animals, low-frequency stimulation of inhibitory synapses in the amygdala led to a persistent depression of their efficacy. By contrast, this effect was missing in the amygdala of *Cb1*$^{-/-}$ mice or in the presence of SR141716A. So, endocannabinoids seem to participate in this synaptic depression, and it will now be important to determine whether and how this effect is related to extinction.

Juan Carlos López, Editor, Nature Reviews Neuroscience

References and links

ORIGINAL RESEARCH PAPER Marsicano, G. *et al.* The endogenous cannabinoid system controls extinction of aversive memories. *Nature* **418**, 530–534 (2002)
FURTHER READING Wilson, R. I. & Nicoll, R. A. Endocannabinoid signalling in the brain. *Science* **296**, 678–682 (2002) | Medina, J. F. *et al.* Parallels between cerebellum- and amygdala-dependent conditioning. *Nature Rev. Neurosci.* **3**, 122–131 (2002)