IN BRIEF

ANALGESIA

Erasing the traces of pain

Opioids are often given to alleviate pain. Although clinically used doses decrease nociceptive neurotransmission, they do not reverse the synaptic changes — namely long-term potentiation — that underlie the features of chronic pain, such as hyperalgesia. This study showed that a brief high dose of a short-acting opioid agonist reversed plasticity at nociceptive synapses in the rat spinal cord and reversed hyperalgesia in rats. These effects, which involved Ca^{2+}-dependent signalling, lasted well beyond the duration of agonist treatment and suggest that opioids can also erase components of chronic pain.

ORIGINAL RESEARCH PAPER Drdla-Schutting, R. *et al.* Erasure of a spinal memory trace of pain by a brief, high-dose opioid administration. *Science* **335**, 235–238 (2012)

GENETIC DISORDERS

A way to prevent heat-induced sudden death?

Mutations that affect the muscle Ca^{2+} release channel ryanodine receptor 1 (RYR1) are associated with life-threatening responses to elevated temperatures. Using mice with a mutant version of *Ryr1*, Lanner *et al.* showed that AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) protected mice against excessive heat responses. Rather than working through its known mechanism of targeting AMP-activated protein kinase, AICAR directly inhibited RYR1-mediated Ca^{2+} leak from the sarcoplasmic reticulum and reduced oxidative or nitrosative stress, which could otherwise lead to sustained muscle contractions.

ORIGINAL RESEARCH PAPER Lanner, J. T. *et al.* AICAR prevents heat-induced sudden death in RyR1 mutant mice independent of AMPK activation. *Nature Med.* **18**, 244–251 (2012)

PARASITE INFECTION

Understanding drug mechanisms of action

The mechanism of action of drugs currently used to treat African trypanosomiasis is largely unknown. Alsford *et al.* used genome-scale RNA interference target sequencing screens in *Trypanosoma brucei* to identify the genes that contribute to the action of currently used drugs. In addition to known drug transporters, they linked over 50 genes to drug action; for example, a bloodstream-stage-specific invariant surface glycoprotein (ISG75) family was found to mediate the uptake of suramin. These findings could aid the rational design of new therapies for African trypanosomiasis and help to combat drug resistance.

ORIGINAL RESEARCH PAPER Alsford, S. *et al.* High-throughput decoding of antitrypanosomal drug efficacy and resistance. *Nature* **482**, 232–236 (2012)

ANTICANCER DRUGS

Angiogenesis drug does not improve chemotherapy

It is generally thought that anti-angiogenic drugs such as bevacizumab temporarily normalize abnormal tumour vasculature and lead to an improved efficacy of subsequent chemotherapy. However, this study showed that bevacizumab did not improve the delivery of a chemotherapy drug to tumours. Positron emission tomography studies in patients with non-small-cell lung cancer determined that bevacizumab reduced the perfusion and net influx rate of docetaxel to tumours. These effects occurred within 5 hours and persisted after 4 days, highlighting the need for further studies to optimize the scheduling of anti-angiogenic drugs.

ORIGINAL RESEARCH PAPER Van der Veldt, A. A. M. *et al.* Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs. *Cell* **21**, 82–91 (2012)