IN BRIEF

NEURODEGENERATIVE DISEASE

NSAIDs and enantiomers of flurbiprofen target γ-secretase and lower Aβ42 *in vivo*.

Eriksen, J. L. *et al. J. Clin. Invest.* **112**, 440–449 (2003).

Recent findings indicate that the apparent ability of nonsteroidal anti-inflammatory drugs (NSAIDs) to protect against the development of Alzheimer's disease (AD) might be due to NSAID-induced reductions in the levels of the 42-amino-acid form of amyloid-β (Aβ42), which seems to have a key pathogenic role in AD. Building on this, Eriksen *et al.* provide data that indicate that the *R* isomer of the NSAID flurbiprofen reduces Aβ42 levels by targeting γ-secretase (the complex that produces Aβ42) and represents a good candidate for clinical testing, as it has low activity against cyclooxygenase, therefore reducing the risks of gastrointestinal side effects.

ANTIMALARIAL DRUGS

Artemisinins target the SERCA of *Plasmodium falciparum*.

Eckstein-Ludwig, U. *et al. Nature* **424**, 957–961 (2003).

Artemisinins are natural products that are important in the treatment of multidrug-resistant malaria, but they have to be administered frequently as they are quickly degraded *in vivo*. Artemisinins were thought to kill the malaria parasite through non-specific radical-mediated damage, but this paper provides strong evidence that they act by inhibiting a crucial parasite enzyme, the sarco/endoplasmic reticulum Ca^{2+}-ATPase — knowledge that should speed the development of longer-lasting artemisinin derivatives.

VIRAL DISEASE

Molecular characterization, reactivation, and depletion of latent HIV.

Brooks, D. G. *et al. Immunity* **19**, 413–423 (2003).

Antiretroviral therapy is unable to eliminate HIV infection in a small, long-lived population of latently infected T cells, providing a source for renewed viral replication if therapy is stopped. Brooks *et al.* demonstrate a potential strategy to address this problem — activating the latently infected cells to make them susceptible to therapy and then targeting them with an anti-HIV immunotoxin — which depleted the bulk of the reservoir of latently infected T cells in mice.

OBESITY

Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-α.

Fu, J. *et al. Nature* **425**, 90–93 (2003).

Fu *et al.* identified the nuclear receptor PPAR-α as the molecular target of oleylethanolamide (OEA), a naturally occurring lipid that regulates eating behaviour. Their data indicate that PPAR-α activation not only mediates OEA-induced weight stabilization, as might be expected from the established metabolic roles of PPAR-α, but is also responsible for OEA-induced satiety.

VIRAL INFECTIONS

Targeting the dog to kill the fleas

There is presently no effective therapy for the most severe form of hepatitis, which is caused by hepatitis delta virus (HDV). The failure of classical antivirals in halting HDV replication might be due to its unique features, as revealed by recent studies. Jeffrey Glenn and colleagues have capitalized on these fresh insights and developed a new method of preventing HDV replication. In *The Journal of Clinical Investigation*, the team presents the first evidence of the *in vivo* efficacy of their strategy.

HDV requires hepatitis B virus (HBV) surface antigens to enter and exit host cells. Derived from co-infecting HBV, these antigens are incorporated into the HDV envelope through interactions with large delta antigen, a product of the HDV genome. Large delta antigen contains a unique amino-acid motif — the 'CXXX box' — which is the substrate for prenyltransferases. Members of this family of host-derived enzymes — the farnesyltransferases — catalyse the covalent addition of the prenyl lipid farnesyl to the cysteine of the CXXX box, a modification that is essential to the assembly of HDV virions. Glenn's group speculated that disrupting this reaction with farnesyltransferase inhibitors (FTIs) might abrogate the HDV life cycle at the crucial stage of viral assembly.

Investigation of this hypothesis was hampered by the lack of a practical animal model of HDV viraemia. So, the authors created their own, by transfecting HBV-transgenic mice with an HDV-encoding plasmid. The proportion of infected hepatocytes in these mice was equivalent to that in HDV-infected humans, and HDV replication within these cells produced mature virions that were released into serum. But would this viraemia succumb to treatment with FTIs?

Transfected mice were injected with one of two FTIs at 50 mg per kg per d for seven days. Both FTI-277 and FTI-2153 — peptidomimetics of the CXXX box of Ras signal transduction GTPases — suppressed HDV viraemia to undetectable levels. As the levels of intrahepatic HDV RNA were similar in treated and control cohorts, the authors concluded that the prenylation-dependent step of virion assembly had been successfully targeted. FTIs that target Ras have been well tolerated in Phase I/II oncological trials, so the potential for their application to medically important viruses, including HDV, is good — Glenn's group is keen to spearhead such efforts with appropriate partners.

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References and links

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Hepatitis delta virus