IN BRIEF

AMYLOID DISEASES

Targeting filamin A reduces Alzheimer's signalling

In Alzheimer's disease (AD), toxic amyloid-β_{42} ($A\beta_{42}$) binds to and aberrantly signals through the α7-nicotinic acetylcholine receptor (α7nAchR). Using tissue from both mouse models of AD and patients with AD, this study showed that $A\beta_{42}$ signalling is dependent upon the recruitment of the scaffolding protein filamin A to the α7nAchR. An orally available small molecule that bound to filamin A (PTI-125) reduced abnormal signalling of α7nAChRs, decreased levels of tau phosphorylation and Aβ aggregates, and prevented Aβ-induced inflammatory cytokine release. PTI-125 greatly reduced the affinity of $A\beta_{42}$ for α7nAChRs and could dissociate existing $A\beta_{42}$–α7nAChR complexes.

ORIGINAL RESEARCH PAPER Wang, H.-Y. *et al.* Reducing amyloid related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. *J. Neurosci.* **32**, 9773–9784 (2012)

HIV

Waking up latent HIV

The persistence of latent HIV within T cells, which is maintained in part by the activity of histone deacetylases (HDACs), means that it is difficult to eradicate HIV infection. Archin *et al.* investigated the effects of the HDAC inhibitor vorinostat in patients with HIV who were receiving antiretroviral therapy. Following initial safety and tolerability dosing, each of eight patients given a single dose of vorinostat had increased HIV RNA expression (a proximal measure of reduced latent infection) in resting T cells. This suggests that HDAC inhibitors — which are already approved for cancer indications — could be used clinically to awaken latent HIV.

ORIGINAL RESEARCH PAPER Archin, N. M. *et al.* Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. *Nature* **487**, 482–485 (2012)

ANTICANCER DRUGS

Reactivating p53 tumour suppressor function

These two papers investigated indirectly restoring p53 tumour suppressor function as an anticancer strategy. Gembarska *et al.* showed that the p53 pathway is inactivated in ~65% of human melanomas as a result of increased expression of MDM4 (a negative regulator of p53). Inhibition of the MDM4–p53 interaction — using a specific cell-permeable stabilized peptide — restored p53 function in melanoma cells, resulting in increased sensitivity to cytotoxic chemotherapy and to inhibitors of the *BRAF*^{V600E} oncogene. This suggests that because it improves p53 function, MDM4 inhibition could be useful in combination therapy for melanoma. Bywater *et al.* showed that in lymphoma, activation of p53 RNA can be achieved through inhibition of RNA polymerase I, an enzyme that increases transcription of ribosomal RNA genes in cancer. A small molecule inhibitor of RNA polymerase I (CX-5461) selectively killed B-lymphoma cells and reduced tumour burden in a mouse model, and induced apoptosis in human leukaemia and lymphoma cell lines. These effects were shown to be a result of nucleolar disruption and activation of p53-dependent apoptotic signalling. This suggests that inhibiting RNA polymerase I, which activates p53, is a potential strategy for the treatment of haematological malignancies.

ORIGINAL RESEARCH PAPERS Gembarska, A. *et al.* MDM4 is a key therapeutic target in cutaneous melanoma. *Nature Med.* **18**, 1239–1247 (2012) | Bywater, M. J. *et al.* Inhibition of RNA polymerase I as a therapeutic strategy to promote cancer-specific activation of p53. *Cancer Cell* **22**, 51–65 (2012)