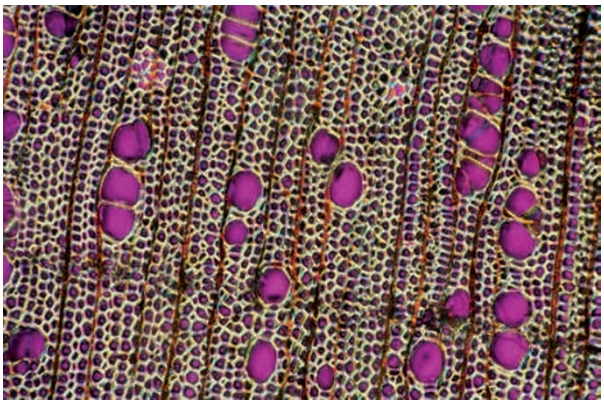
IN BRIEF

LEAD DISCOVERY

Allosteric non-bisphosphonate FPPS inhibitors identified by fragment-based discovery

Jahnke, W. *et al. Nature Chem. Biol.* **6**, 660–666 (2010)

Bisphosphonate-based inhibitors of farnesyl pyrophosphate synthase (FPPS) — currently used in the treatment of bone diseases — could have potential antitumour effects. However, their high affinity for bone mineral is not ideal for this indication. This paper reports the discovery of the first potent non-bisphosphonate FPPS inhibitors, which bind to a previously unidentified allosteric site on FPPS. The identification of this site and its associated lead compounds facilitates the development of a new generation of FPPS inhibitors.



CANCER

CD13 is a therapeutic target in human liver cancer stem cells

Haraguchi, N. *et al. J. Clin. Invest.* **120**, 3326–3339 (2010)

Cancer stem cells are thought to be involved in resistance to chemotherapy and in tumour progression but their identity in many cancers is not defined. This study showed that CD13 (also known as amino peptidase N) is a marker for semiquiescent cancer stem cells in human liver cancer cell lines and in clinical samples. $CD13^+$ cells generated resistance to genotoxic agents through reduced levels of reactive oxygen species. In mouse xenograft models, combining a CD13 inhibitor (either a CD13-neutralizing antibody or the CD13 inhibitor ubenimex) with the genotoxic chemotherapeutic fluorouracil, drastically reduced tumour volume compared with either agent alone.

NEURODEGENERATIVE DISEASE

Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in Huntington's disease

Miller, J. P *et al. Neuron* **67**, 199–212 (2010)

Proteolytic cleavage of huntingtin (HTT) is key in the pathogenesis of Huntington's disease. To identify proteases involved in HTT proteolysis and toxicity, Miller and colleagues screened over 500 small interfering RNAs that target the repertoire of human protease genes. This identified three matrix metalloproteinases (MMPs) that, when inhibited, reduced HTT fragment accumulation. MMP10 directly cleaved HTT and prevented cell death when knocked down in cell models. In addition, MMPs were activated in mouse models, and loss of function of *Drosophila melanogaster* homologues of MMPs suppressed HTT-induced neuronal dysfunction.

DEMENTIA

A noncompetitive BACE1 inhibitor TAK-070 ameliorates Aβ pathology and behavioral deficits in a mouse model of Alzheimer's disease

Fukumoto, H. *et al. J. Neurosci.* **30**, 11157–11166 (2010)

The β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) is a rate-limiting protease for the generation of amyloid-β peptides that cause Alzheimer's disease. Fukamoto and colleagues identified a nonpeptide, orally available BACE1 inhibitor — TAK070 — that lowered levels of soluble amyloid-β, increased levels of neurotrophic soluble APP, inhibited cerebral disposition of insoluble amyloid-β and normalized behavioural impairments when given prior to amyloid-β accumulation in a transgenic mouse model of Alzheimer's disease.