*Nature Reviews Drug Discovery* | Published online 31 Dec 2015

# IN BRIEF

## CANCER

### Disrupting protein homeostasis

Cancer cells can be highly dependent on protein homeostasis pathways for their growth and survival. Here, Anderson *et al.* identify a potent and selective small-molecule inhibitor of p97 — a member of the AAA family of adenosine triphosphatases and a key regulator of protein homeostasis — named CB-5083. In cancer cells, CB-5083 blocked major protein-degradation functions, activating the unfolded protein response and apoptosis. CB-5083 significantly inhibited tumour growth in mouse haematological and solid tumour xenograft models and is currently in Phase I clinical trials.

**ORIGINAL ARTICLE** Anderson D. J. *et al.* Targeting the AAA ATPase p97 as an approach to treat cancer through disruption of protein homeostasis. *Cancer Cell* **28**, 653–665 (2015)

## ALZHEIMER DISEASE

### Aβ-targeting antibodies aggravate neuronal dysfunction

Clearance of pathogenic amyloid-β (Aβ) deposits from patient brains is being investigated as a treatment approach for Alzheimer disease (AD). However, Phase III trial results of Aβ-targeting monoclonal antibodies have been disappointing. Using AD transgenic mice, Busche *et al.* reveal that although Aβ-targeting antibodies reduce amyloid pathology, they unexpectedly aggravate neuronal dysfunction, increase numbers of pathologically hyperactive neurons and promote abnormal synchrony of cortical activity.

**ORIGINAL ARTICLE** Busche, M. A. *et al.* Decreased amyloid-β and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. *Nat. Neurosci.* **18**, 1725–1728 (2015)

## CANCER

### Novel PDL1 inhibitor identified

Monoclonal antibodies against the receptor programmed cell death protein 1 (PD1) and its ligand PDL1 have shown impressive clinical activity in various cancers. However, the effectiveness of these antibodies is limited by poor tumour penetrance and immune cell depletion. Maute *et al.* engineer a non-antibody-biologic competitive antagonist of PDL1 — named HAC-PD1 — based on the PD1 ectodomain. Compared with PDL1-specific antibodies, HAC-PD1 exhibited enhanced tumour delivery without depleting peripheral effector T cells, resulting in superior antitumour efficacy in syngeneic mouse tumour models.

**ORIGINAL ARTICLE** Maute, R. L. *et al.* Engineering high-affinity PD-1 variants for optimized immunotherapy and immuno-PET imaging. *Proc. Natl Acad. Sci. USA* **112**, E6506–E6514 (2015)

## ANTIVIRAL DRUGS

### HSP70 inhibitor blocks virus replication

Host molecular chaperones are reported to facilitate the replication of flaviviruses such as dengue virus (DENV). Here, Taguwa *et al.* show that cytosolic heat shock protein 70 (HSP70) isoforms and their DNAJ cofactors facilitate multiple steps of the DENV life cycle, including viral entry, RNA replication and virion biogenesis. The allosteric HSP70 inhibitor JG40 potently inhibited replication of different DENV serotypes as well as other flaviviruses in primary cultures of human blood cells, without signs of viral resistance or host cell toxicity.

**ORIGINAL ARTICLE** Taguwa, S. *et al.* Defining Hsp70 subnetworks in dengue virus replication reveals key vulnerability in flavivirus infection. *Cell* **163**, 1108–1123 (2015)



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