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# IN BRIEF

## EPILEPSY

### HSP90 inhibition suppresses seizures

Loss of the glutamate transporter GLT1 (also known as SLC1A2) occurs in temporal lobe epilepsy (TLE), but the mechanisms mediating GLT1 degradation are not understood. Here, Sha *et al.* report upregulated expression of HSP90β in reactive astrocytes of human epileptogenic tissue and in mouse models of TLE and febrile seizures. In cultured astrocytes, HSP90β negatively regulated GLT1 protein levels through proteasome-dependent GLT1 degradation, which was prevented by the HSP90 inhibitor, 17AAG. In mouse models of TLE, long-term systemic administration of 17AAG suppressed spontaneous recurrent seizures and ameliorated astrogliosis.

**ORIGINAL ARTICLE** Sha, L. *et al.* Pharmacologic inhibition of Hsp90 to prevent GLT-1 degradation as an effective therapy for epilepsy. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20160667 (2016)

## ALZHEIMER DISEASE

### Identification of novel Aβ inhibitors

Targeting amyloid-β (Aβ) aggregation and accumulation has been pursued as a major potential therapeutic strategy against AD, but no compound has yet gained regulatory approval. Habchi *et al.* now describe the use of a quasi-structure-based and kinetics-based drug discovery approach to identify a pool of ligands for retinoid acid receptors and retinoid X receptors that inhibit aggregation of the 42-residue form of Aβ ($Aβ_{42}$). The compounds inhibited $Aβ_{42}$ aggregation in human cerebrospinal fluid solutions and rescued $Aβ_{42}$-mediated dysfunction in a *Caenorhabditis elegans* model of $Aβ_{42}$-mediated cytotoxicity.

**ORIGINAL ARTICLE** Habchi, J. *et al.* Systematic development of small molecules to inhibit specific microscopic steps of Aβ42 aggregation in Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **114**, E200–E208 (2016)

## NEURODEGENERATIVE DISEASE

### Pituitary adenylate cyclase activator ameliorates SBMA

Post-translational modifications, such as phosphorylation, modify the toxicity of the polyglutamine (polyQ) expansion in the androgen receptor (*AR*) (polyQ-AR), which occurs in spinobulbar muscular atrophy (SBMA). Here, Polanco *et al.* show in cell models that cyclin-dependent kinase 2 phosphorylates polyQ-AR specifically at Ser96 and this is negatively regulated by the adenylate cyclase–protein kinase A signalling pathway. Chronic intranasal administration of an analogue of pituitary adenylyl cyclase-activating polypeptide to a mouse model of SBMA reduced Ser96 phosphorylation, promoted polyQ-AR degradation and ameliorated the disease outcome.

**ORIGINAL ARTICLE** Polanco, M. J. *et al.* Adenylyl cyclase activating polypeptide reduces phosphorylation and toxicity of the polyglutamine-expanded androgen receptor in spinobulbar muscular atrophy. *Sci. Transl Med.* **8**, 370ra181 (2016)

## HIV

### CRISPR screen identifies novel therapeutic targets

Host proteins, termed host dependency factors (HDFs), are crucial for productive HIV infection but dispensable for cellular viability, thereby representing promising therapeutic targets. Here, Park *et al.* conduct a CRISPR-based genetic screen in a $CD4^+$ T cell line to identify five HDFs (the HIV co-receptors CD4 and CCR5, as well as TPST2, SLC35B2, and ALCAM) that, when inactivated, conferred protection from HIV infection. Using the $CD4^+$ T cell line and primary $CD4^+$ T cells, TPST2 and SLC35B2 were shown to facilitate CCR5 recognition by the HIV envelope, whereas ALCAM mediated cell aggregation, which is required for cell-to-cell HIV transmission.

**ORIGINAL ARTICLE** Park, R. J. *et al.* A genome-wide CRISPR screen identifies a restricted set of HIV host dependency factors. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3741 (2016)