IN BRIEF

INFLAMMATION

Siglec-targeting nanoparticle treats sepsis

The excessive proinflammatory responses in sepsis and associated acute respiratory distress syndrome (ARDS) are largely mediated by Toll-like receptors (TLRs). Spence *et al.* report a novel approach to harness the TLR inhibitory effects of sialic acid-binding immunoglobulin-like lectin E (Siglec-E) — a transmembrane receptor found on macrophages and neutrophils. Nanoparticles decorated with the Siglec E-specific ligand, α2,8-linked *N*-acetylneuraminic acid, reduced inflammation and prolonged survival in mouse sepsis and ARDS models and attenuated pulmonary oedema in a human *ex vivo* lung perfusion model of lung injury.

ORIGINAL RESEARCH PAPER Spence, S. *et al.* Targeting Siglecs with a sialic acid-decorated nanoparticle abrogates inflammation. *Sci.Transl. Med.* **7**, 303ra140 (2015)

EPIGENETICS

Targeting chromatin regulation in PDAC

Chromatin remodelling and modification pathways are emerging as promising anticancer targets. Mazur *et al.* investigate the potential of targeting the bromodomain and extra-terminal (BET) protein family of chromatin regulators in pancreatic ductal adenocarcinoma (PDAC). The BET inhibitor, JQ1, reduced tumour volume, decreased proliferation and improved survival in mouse models of PDAC. Combination of JQ1 with the small-molecule HDAC inhibitor, SAHA, was synergistic in the PDAC model, without evidence of tumour relapse or metastasis.

ORIGINAL RESEARCH PAPER Mazur, P. *et al.* Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. *Nat. Med.* http://dx.doi.org/10.1038/nm.3952 (2015)

AUTOIMMUNE DISEASE

Novel peptide ameliorates CNS inflammation

Central nervous system (CNS) infiltration of pro-inflammatory effector T cells is critical in the development and progression of multiple sclerosis. Here, Lim *et al.* develop a cationic cell-permeable peptide, dNP2, from the human novel LZAP-binding protein (NLBP), which efficiently delivered proteins into primary mouse and human immune cells in culture, and into the mouse brain *in vivo*. In mice, intraperitoneal injection of the peptide conjugated to the cytoplasmic domain of cytotoxic T lymphocyte antigen 4 (a T cell receptor with immune-suppressive function) inhibited T cell responses and ameliorated disease symptoms in experimental autoimmune encephalomyelitis.

ORIGINAL RESEARCH PAPER Lim, S. *et al.* dNP2 is a blood–brain barrier-permeable peptide enabling ctCTLA-4 protein delivery to ameliorate experimental autoimmune encephalomyelitis. *Nat. Comm.* **6**, 8244 (2015)

CANCER

New RAF inhibitor with broad activity

Oncogenic mutations of BRAF drive ERK-dependent cancer growth. Physiological ERK activation occurs when activated RAS induces dimerization of RAF, a process limited by negative feedback. Yao *et al.* show that all activated BRAF mutants evade feedback inhibition owing to RAS-independence: BRAF V600 mutants signal as active monomers and all other BRAF-activating mutants signal as constitutive, RAS-independent dimers. The approved RAF inhibitor, vemurafenib, only inhibits mutant monomers and is ineffective in non-V600E BRAF mutant tumours. The authors identify BGB659, a type II, ATP-competitive RAF inhibitor which can bind RAF dimers and effectively inhibit tumour growth driven by all RAF mutants in mice.

ORIGINAL RESEARCH PAPER Yao, Z. *et al.* BRAF mutants evade ERK-dependent feedback by different mechanisms that determine their sensitivity to pharmacologic inhibition. *Cancer Cell* **28**, 370–383 (2015)