IN BRIEF

IMMUNOTHERAPY

A lethal storm

The use of cancer immunotherapies can result in severe toxic effects. As cancer is primarily a disease of ageing, Mirsoian *et al.* have examined the toxicity of immunotherapy in aged mice. The authors previously showed that treatment of young mice with an immune-stimulatory therapy including interleukin-2 (IL-2) and a monoclonal antibody against CD40 (anti-CD40) reduced tumour growth and was well tolerated. However, in aged mice this treatment induced a cytokine storm that was 100% lethal. They have now found that levels of visceral fat in mice increase with age. Young obese mice have similar levels of visceral fat to aged mice, and IL-2 and anti-CD40 treatment also induces a lethal cytokine storm in these mice, whereas calorie-restricted aged mice have less visceral fat and are protected from treatment toxicity.

ORIGINAL RESEARCH PAPER Mirsoian, A. *et al.* Adiposity induces lethal cytokine storm after systemic administration of stimulatory immunotherapy regimens in aged mice. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20140116 (2014)

LEUKAEMIA

Explaining gender bias

T cell acute lymphoblastic leukaemia (T-ALL) develops more frequently in males than females. Van der Meulen *et al.* found that the X chromosome gene *UTX*, which encodes a demethylase of histone H3 lysine 27 trimethylation contains loss-of-function somatic mutations exclusively in males with T-ALL but escapes X chromosome-inactivation in females. They further showed that *UTX* acts as a tumour suppressor *in vitro* and *in vivo*, and that T-ALL with *UTX* loss is sensitive to a histone methyltransferase inhibitor.

ORIGINAL RESEARCH PAPER Van der Meulen, J. *et al.* The H3K27me3 demethylase UTX is a gender-specific tumor suppressor in T-cell acute lymphoblastic leukemia. *Blood* http://dx.doi.org/10.1182/blood-2014-05-577270 (2014)

TUMOUR SUPPRESSORS

Take it up a Notch

Cyclin C (CCNC) has been shown to promote cell cycle progression and transcription, but little is known about its functions *in vivo*. Li *et al.* used conditional *Ccnc* knockout mice to show that CCNC and cyclin-dependent kinase (CDK) complexes phosphorylate the NOTCH1 intracellular domain (NICD) to promote its degradation; therefore, mice lacking CCNC have higher NICD levels. *Ccnc* knockout or heterozygosity promoted development of T cell acute lymphoblastic leukaemia (T-ALL) in collaboration with T-ALL oncogene expression in mice. In human T-ALL samples, heterozygous deletions of *CCNC* were frequently observed, as were point mutations that prevented NICD phosphorylation by CCNC–CDK.

ORIGINAL RESEARCH PAPER Li, N. *et al.* Cyclin C is a haploinsufficient tumour suppressor. *Nature Cell Biol.* **16**, 1080–1091 (2014)

THERAPEUTIC RESISTANCE

Blocking the gatekeeper

Tan *et al.* have identified covalent inhibitors of the fibroblast growth factor receptor (FGFR) that can block the proliferation of cells expressing FGFR1 or FGFR2 gatekeeper mutants, which are resistant to the first generation FGFR inhibitors that are being tested clinically for a variety of cancers. They used structure-based drug design to develop inhibitors that covalently target cysteine residues in the ATP binding pocket.

ORIGINAL RESEARCH PAPER Tan, L. *et al.* Development of covalent inhibitors that can overcome resistance to first-generation FGFR kinase inhibitors. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1403438111 (2014)