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IN BRIEF

CANCER

Targeting minimal residual disease

Cancer relapse is driven by a small subpopulation of drug-tolerant cells, known as minimal residual disease (MRD). To study the biology of solid tumour MRD, Rambow et al. established patient-derived xenografts (PDXs) from *BRAF*-mutant melanoma patients and carried out single-cell RNA-sequencing of malignant cells that had developed resistance to RAF and MEK inhibition. This analysis revealed multiple drug-tolerant transcriptional states, including the neural crest stem cell transcriptional program, driven by RXR signalling. Combining an RXR antagonist with RAF and MEK inhibitor treatment in the PDXs delayed the development of resistance.

ORIGINAL ARTICLE Rambow, F. et al. Toward minimal residual disease-directed therapy in melanoma. *Cell* https://doi.org/10.1016/j.cell.2018.06.025 (2018)

AUTOIMMUNE DISEASE

Reversing vitiligo

The skin depigmentation that is characteristic of vitiligo recurs after discontinuation of conventional treatments, indicating the presence of a persistent autoimmune memory. Here, Richmond et al. confirm the presence of resident memory T cells (TRM) in vitiligo lesional skin of both humans and mice. In a mouse model of vitiligo, inhibition of IL-15 signalling, via long-term systemic treatment of an antibody targeting the IL-15 receptor component CD122, depleted TRM from lesional skin and led to durable disease reversal. Short-term local intradermal treatment with the anti-CD122 antibody inhibited TRM effector function, resulting in long-term skin repigmentation.

ORIGINAL ARTICLE Richmond, J. et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci. Transl Med.* **10**, eaam7710 (2018)

EPILEPSY

Gene therapy safely reduces seizures in rats

A third of patients continue to have seizures using existing antiepileptic drugs, demonstrating the need for novel therapeutic approaches. Although the use of gene therapy to decrease neuronal excitability has shown promise in preclinical models, it is irreversible and may interfere with normal brain function. Now, Lieb et al. describe an autoregulatory antiepileptic lentiviral-based gene therapy which inhibits neurons in response to pathological accumulation of extracellular glutamate. In a rat model of focal epilepsy, the therapy decreased seizures without adverse effects.

ORIGINAL ARTICLE Lieb, A. et al. Biochemical autoregulatory gene therapy for focal epilepsy. *Nat. Med.* https://doi.org/10.1038/s41591-018-0103-x (2018)

CANCER

Overcoming resistance to checkpoint blockade

Although PDL1-directed immunotherapy has yielded promising results, a majority of cancer patients do not respond. Using cancer cells and mice, Sheng et al. now show that pharmacological or genetic ablation of the histone demethylase, LSD1, stimulates endogenous retrovirus expression and downregulates RNA-induced silencing complex, resulting in enhanced tumour immunogenicity and T cell infiltration. In a mouse melanoma model, LSD1 ablation sensitized resistant tumours to PD1 blockade. Furthermore, analysis of The Cancer Genome Atlas revealed an inverse correlation between LSD1 expression and $CD8^+$ T cell infiltration in various human cancers.

ORIGINAL ARTICLE Sheng, W. et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. *Cell* **174**, 549–563 (2018)

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