IN BRIEF

CANCER

Repurposing SGLT2 inhibitors

Lung adenocarcinoma (LADC) premalignancy remains poorly understood, and diagnostic biomarkers are lacking. Scafoglio et al. analyse 58 human LADC samples and note that sodium glucose transporter 2 (SGLT2) is predominantly expressed in human premalignant and early-stage LADCs. Similarly, both expression and functional activity of SGLT2 were high in premalignant and early-stage LADC in genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDXs). Oral treatment with the SGLT2 inhibitor canagliflozin — used to treat type 2 diabetes — delayed the onset of tumours and increased survival of GEMMs and reduced tumour volume in PDX models of LADC.

ORIGINAL ARTICLE Scafoglio, C. et al. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. *Sci. Transl Med.* **10**, eaat5933 (2018).

OBESITY

Role of BAT in satiation

Inducing brown adipose tissue (BAT) thermogenesis is an attractive approach to treat obesity. Here, Li et al. report that postprandial circulating levels of the intestinal hormone secretin are increased and bind to secretin receptors in BAT, activating UCP-1-dependent BAT thermogenesis, which is sensed by the brain to promote satiation. In diet-induced obese mice, chronic secretin infusion transiently increased energy expenditure at thermoneutrality. In humans, increasing serum secretin levels by single-meal ingestion or secretin infusion, stimulated BAT thermogenesis.

ORIGINAL ARTICLE Li, Y. et al. Secretin-activated brown fat mediates prandial thermogenesis to induce satiation. *Cell* **175**, 1561–1574 (2018).

DRUG DISCOVERY

Targeting transcription factors

Thalidomide analogues bind to cereblon (CRBN) and degrade specific C2H2 zing-finger (ZF)-containing proteins, highlighting a strategy to target this class of transcription factors. Sievers et al. screened the human C2H2 ZF proteome for degradation in the presence of thalidomide analogues and identified 11 ZF degrons. Structural analysis of these degrons followed by computational docking studies revealed that a large number of ZFs with diverse amino acid sequences are likely to bind to the drug–CRBN interface. Introducing specific chemical alterations into thalidomide analogues enabled selective degradation of distinct ZF targets.

ORIGINAL ARTICLE Sievers, Q. et al. Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN. *Science* **362**, eaat0572 (2018).

CANCER

Combating resistance to EGFR inhibitors

Although epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors elicit dramatic initial effects in EGFR-mutant non-small-cell lung cancer (NSCLC), drug resistance commonly develops. Shah et al. modelled acquired resistance in EGFR-mutant lung adenocarcinoma cells, and found that Aurora kinase inhibitors synergistically inhibited cancer cell growth in combination with EGFR inhibitors; findings that were confirmed in mouse and patient-derived xenograft models. In vitro, activation of Aurora kinase A, by its coactivator TPX2, was necessary for acquired resistance and mitigated apoptosis. TPX2 levels were increased in patients with EGFR-mutant NSCLC who had developed erlotinib resistance.

ORIGINAL ARTICLE Shah, K. et al. Aurora kinase A drives the evolution of resistance to third-generation EGFR inhibitors in lung cancer. *Nat. Med.* https://doi.org/10.1038/s41591-018-0264-7 (2018).