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IN BRIEF

POLYPHARMACOLOGY

Repurposing ceritinib

Network-based targeting strategies represent a promising therapeutic approach for the treatment of diseases that lack strong and actionable drivers. Using an integrated phenotypic screening and phosphoproteomics strategy, Kuenzi *et al.* report that the FDA-approved ALK inhibitor ceritinib exhibits activity in several ALK-negative non-small-cell lung cancer cell lines through simultaneous inhibition of multiple non-canonical targets (namely FAK1, IGF1R, RSK1 and RSK2), which is largely dependent on the downstream signalling effector YB1. Ceritinib synergized with paclitaxel, particularly in cells expressing high FAK1 autophosphorylation.

ORIGINAL ARTICLE Kuenzi, B. *et al.* Polypharmacology-based ceritinib repurposing using integrated functional proteomics. *Nat.Chem. Biol.* http://dx.doi.org/10.1038/nchembio.2489 (2017)

INFECTIOUS DISEASE

Fighting influenza B

The use of broadly neutralizing antibodies against the influenza viral surface glycoprotein haemagglutinin (HA) represents a promising therapeutic approach. In mice, Shen *et al.* implemented several immunization regimens to induce cross-reactive antibodies against highly conserved epitopes in the HA protein of influenza B. A functional screening strategy identified the highly potent antibody C12G6, which targeted the receptor binding site in the HA region and inhibited influenza B viruses via multiple mechanisms. *In vitro*, C12G6 neutralized all available influenza B viruses isolated since 1940. Furthermore, C12G6 exhibited broad prophylactic and therapeutic activity in mice and ferrets.

ORIGINAL ARTICLE Shen, C. *et al.* A multimechanistic antibody targeting the receptor binding site potently cross-protects against influenza B viruses. *Sci. Transl Med.* **9**, eaam5752 (2017)

DIABETES

Selective FOXO1 modulation

Inhibition of the FOXO1 transcription factor has beneficial effects on diabetic hyperglycaemia through the suppression of glucose-6-phosphatase (G6PC) activation, but it also suppresses glucokinase (GCK) inhibition, which promotes lipogenesis. Here, Langlet *et al.* identify SIN3A as the corepressor required for FOXO1-mediated inhibition of GCK. SIN3A ablation in mice impaired nutrient regulation of GCK without affecting other FOXO1 target genes. In primary hepatocytes from these mice, insulin-mediated FOXO1 inhibition lowered glucose production but did not induce lipogenesis. A FOXO1 inhibitor was identified which did not clear SIN3A from the GCK promoter, inhibiting glucose production without activating lipogenesis.

ORIGINAL ARTICLE Langlet, F. *et al.* Selective inhibition of FOXO1 activator/repressor balance modulates hepatic glucose handling. *Cell* **171**, 824–835 (2017)

GPCRs

Crystal structure of D4 dopamine receptor

Numerous compounds are reported to interact with dopamine receptors, but the molecular mechanisms mediating dopamine receptor selectivity and activity are poorly understood. Here, Wang *et al.* determine crystal structures of the D4 dopamine receptor (D_4R) in its inactive state bound to the antipsychotic drug nemonapride, with resolutions of up to 1.95 Å. The use of computational modelling to dock a library of more than 600,000 molecules from the ZINC database of commercially available compounds against the 1.95 Å D_4R structure identified an extremely potent and specific D_4R agonist.

ORIGINAL ARTICLE Wang, S. *et al.* D4 dopamine receptor high-resolution structures enable the discovery of selective agonists. *Science* **358**, 381–386 (2017)