Nature Reviews Drug Discovery | Published online 11 Aug 2017

IN BRIEF

ANTICANCER AGENTS

Fighting resistance

RAF–MEK–ERK pathway inhibitors are used to treat cancers exhibiting *BRAF*^{V600E} mutations, but drug resistance commonly develops. Here, analysis of patient-derived xenograft (PDX) of *BRAF*^{V600E}-mutant cancers and single-cell DNA sequencing showed that following drug treatment, parallel evolutionary tracts enable the selection and propagation of *BRAF*-amplified (*BRAF*^{amp}) subclones. In cells, a fitness threshold model revealed that the level of BRAF-V600E expression required to overcome the drug effect differed between RAF, MEK and ERK inhibitors. Intermittent concurrent targeting of the kinases RAF, MEK and ERK suppressed the expansion of *BRAF*^{amp} subclones and inhibited tumour growth in PDX models.

ORIGINAL ARTICLE Xue, Y. *et al.* An approach to suppress the evolution of resistance in *BRAF*^{V600E}-mutant cancer. *Nat. Med.* http://dx.doi.org/10.1038/nm.4369 (2017).

IMMUNOTHERAPY

CAR T cells in glioblastoma

Chimeric antigen receptor-modified T (CAR T) cells have shown efficacy in leukaemia and lymphoma. Now, O'Rourke *et al.* report on the first clinical trial of CAR T cells targeted to the epidermal growth factor receptor variant III (EGFRvIII) in 10 patients with recurrent glioblastoma. Treatment was well tolerated, and at day 28, nine subjects had stable disease, with one patient remaining stable for over 18 months of follow-up. Analysis of the seven patients undergoing post-CAR T EGFRvIII surgical intervention showed CAR T EGFRvIII trafficking to the tumour and a decrease in EGFRvIII target antigen expression.

ORIGINAL ARTICLE O'Rourke, D. *et al.* A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci. Transl Med.* **9**, eaaa0984 (2017).

SYSTEMS MEDICINE

Understanding wellness and disease

Systems medicine aims to understand the basis of wellness and disease. Here, Price *et al.* report findings from the Pioneer 100 Wellness Project, a collection of data from 108 individuals over 9 months - including whole genome sequences, clinical tests, metabolomes, proteomes, microbiomes and frequent activity measurements. Generation of a correlation network revealed communities of related analytes associated with physiology and disease and enabled the identification of known and candidate biomarkers. Personal data enabled recommendation of individual lifestyle changes, which improved clinical biomarkers.

ORIGINAL ARTICLE Price, N. D. *et al.* A wellness study of 108 individuals using personal, dense, dynamic data clouds. *Nat. Biotechnol.* http://dx.doi.org/10.1038/nbt.3870 (2017).

CANCER

Inhibiting ROCK in neuroblastoma

Neuroblastoma is a childhood tumour originating from the neural crest, for which treatment options are limited. Dyberg *et al.* report a high frequency of mutations in genes associated with RHO–RAC signalling in human neuroblastoma samples. Increased expression of the downstream RHO-activating kinase ROCK2 was associated with poor patient survival. In human neuroblastoma cell lines, ROCK2 inhibition promoted cell differentiation and decreased cell growth, migration and invasion. In mouse neuroblastoma models, the ROCK2 inhibitor HA1077 significantly suppressed tumour growth.

ORIGINAL ARTICLE Dyberg, C. *et al.* Rho-associated kinase is a therapeutic target in neuroblastoma. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1706011114 (2017).