Nature Reviews Drug Discovery | Corrected online 30 April 2012

IN BRIEF

LEAD DISCOVERY

Small-molecule inhibitors of cytoplasmic dynein

Motor cytoplasmic dynein is an ATPase that regulates ciliary trafficking, mitotic spindle formation and organelle transport. Firestone *et al.* described the discovery of the first specific small-molecule antagonists of cytoplasmic dynein, termed ciliobrevins. They showed that ciliobrevins modulate protein trafficking within primary cilia, which leads to blockade of Hedgehog signalling (a pathway that is implicated in cancer). Moreover, the compounds blocked dynein-dependent microtubule gliding and ATPase activity, and so could be useful tool compounds for studying cellular processes and for stimulating the development of further ciliobrevin-like inhibitors.

ORIGINAL RESEARCH PAPER Firestone, A. J. *et al.* Small-molecule inhibitors of the AAA+ ATPase motor cytoplasmic dynein. *Nature* **484**, 125–129 (2012)

CANCER

Intratumour heterogeneity

Gerlinger *et al.* conducted whole-exome sequencing of biopsy samples taken from different tumour regions from patients with renal cell carcinoma. They showed that the individual tumours displayed extensive intratumour heterogeneity. For example, 63–69% of somatic mutations were not detectable across every tumour region, several tumour suppressor genes showed multiple distinct and spatially separated inactivating mutations within a single tumour, and gene expression signatures of good and poor prognosis were detected in different regions of the same tumour. These findings present challenges to the development of personalized medicine and cancer biomarkers.

ORIGINAL RESEARCH PAPER Gerlinger, M. *et al.* Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N. Engl. J. Med.* **366**, 883–892 (2012)

ANTIBACTERIAL DRUGS

Overcoming MRSA resistance

This paper showed that FtsZ, a guanosine triphosphatase involved in bacterial cell division, is a new target for overcoming methicillin-resistant *Staphylococcus aureus* (MRSA) resistance to β-lactam antibiotics. The authors showed that the FtsZ-specific inhibitor PC190723 acts synergistically with a β-lactam antibiotic to reduce infection in a mouse model of MRSA; these effects were due to the concomitant delocalization of FtsZ and the antibiotic target. Although mutations that conferred resistance to PC190723 were identified, combining PC190723 with a β-lactam antibiotic reduced the frequency and virulence of the MRSA mutants.

ORIGINAL RESEARCH PAPER Tan, C. M. *et al.* Restoring methicillin-resistant *Staphylococcus aureus* susceptibility to β-lactam antibiotics. *Sci. Transl. Med.* **4**, 126ra35 (2012)

ANTICANCER DRUGS

Identifying tumour-associated antigens

Activation of T cell responses against multiple tumour-associated antigens could be beneficial in several types of cancer. This paper showed that injection of mice with virus-expressed cDNA libraries from melanocytes could cure established melanoma in 60% of mice, which was achieved through the priming of a tumour-specific interleukin-17 response mediated by heat shock protein 70. Importantly, the authors identified the specific tumour-associated antigens involved in the response. This approach — which has also been used in models of prostate cancer — might be used in antigen discovery for other cancers.

ORIGINAL RESEARCH PAPER Pulido, J. *et al.* Using virally expressed melanoma cDNA libraries to identify tumor-associated antigens that cure melanoma. *Nature Biotech.* **30**, 337–343 (2012)

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