IN BRIEF

G PROTEIN-COUPLED RECEPTORS

Cloud computing gives insights into activation

Molecular dynamics simulations can reveal important information about receptor activation, but often require specialist hardware. To overcome this limitation, Kohlhoff *et al.* used cloud computing to investigate the mechanism that underlies β_2-adrenergic receptor activation. Tens of thousands of independent simulations were run on Google Exacycle, which were then integrated into a single statistical model. This captured multiple previously unidentified discrete conformational states of the receptor, which were linked to different activation pathways; agonists and inverse agonists interacted differentially with these pathways.

ORIGINAL RESEARCH PAPER Kohlhoff, K. J. *et al.* Cloud-based simulations on Google Exacycle reveal ligand modulation of GPCR activation pathways. *Nature Chem.* **6**, 15–21 (2014)

CHEMICAL GENETICS

Genome-wide target identification

Many small-molecule drugs target DNA-associated processes such as transcription, modification and replication. This paper devised a method — called Chem-seq — based on ligand-affinity capture and massively parallel DNA sequencing to identify the genome binding sites of a bromodomain inhibitor (JQ1), a cyclin-dependent kinase 9 inhibitor (AT7519) and the DNA intercalator psoralen in multiple myeloma cells. The authors note that this method could be used to help understand the action and specificity of many small molecules.

ORIGINAL RESEARCH PAPER Anders, L. *et al.* Genome-wide localization of small molecules. *Nature Biotech.* **32**, 92–96 (2014)

ANTICANCER DRUGS

A novel way to hit the proteasome

The proteasome inhibitors bortezomib and carfilzomib are approved for the treatment of multiple myeloma, but their effectiveness can be limited by the development of resistance. Anchoori *et al.* identified a novel proteasome inhibitor that covalently bound to cysteine 88 of the human proteasomal ubiquitin receptor ADRM1 and reduced the viability of bortezomib-resistant multiple myeloma cells. In mice, oral administration of the compound inhibited proteasome function in skin and muscle, and reduced the growth of multiple myeloma and ovarian cancer xenografts.

ORIGINAL RESEARCH PAPER Anchoori, R. K. *et al.* A bis-benzylidine piperidone targeting proteasome ubiquitin receptor RPN13/ADRM1 as a therapy for cancer. *Cancer Cell* **24**, 791–805 (2013)

INFECTIOUS DISEASE

New leads for resistant tuberculosis

This study described a new class of compounds — the indolcarboxamides — that could hold potential for the treatment of *Mycobacterium tuberculosis*. Two lead compounds, NITD-304 and NITD-349, were active against drug-sensitive and multidrug-resistant clinical isolates of *M. tuberculosis* and reduced infection in acute and chronic mouse models following oral administration. Mechanistic studies showed that the compounds target the trehalose monomycolate transporter MmpL3, which is essential for mycobacterial cell wall biosynthesis.

ORIGINAL RESEARCH PAPER Rao, S. P. S. *et al.* Indolcarboxamide is a preclinical candidate for treating multidrug-resistant tuberculosis. *Sci. Transl. Med.* **5**, 214ra168 (2013)