IN BRIEF

PROTEIN–PROTEIN INTERACTIONS

Structural conservation of druggable hot spots in protein–protein interfaces

Kozakov, D. *et al. Proc. Natl Acad. Sci. USA* 1 Aug 2011 (doi: 10.1073/pnas.1101835108)

Kozakov *et al.* used computational solvent mapping, which probes protein surfaces using small fragment molecules, to identify druggable sites in protein–protein interfaces. Using this technique on the unliganded structures of 15 target proteins, including interleukin-2, B cell lymphoma X_L and the eukaryotic translation initiation factor 4E (eIF4E)–eIF4G complex, they showed that the druggable sites comprise a cluster of binding 'hotspots' that bind compounds with a hydrophobic scaffold that contain some polar groups. Moreover, it was possible to detect druggable targets on protein–protein interfaces from structural data alone.

MALARIA

Chemical genomic profiling for antimalarial therapies, response signatures, and molecular targets

Yuan, J. *et al. Science* **333**, 724–729 (2011)

This study used quantitative high-throughput screening and genome-wide association and linkage analyses to identify >30 potential new antimalarial drugs, including some that are already approved for human use. The compounds had differential efficacies between parasite lines, and 96% of the differential responses were linked to just three genes, indicating that these genes dominate the response of *Plasmodium falciparum* to different drugs. Moreover, testing of drug combinations with responses that mapped to *pfcrt* alleles identified compounds that could overcome chloroquine resistance.

CANCER

Validation of MdmX as a therapeutic target for reactivating p53 in tumours

Garcia, D. *et al. Genes Dev.* **25**, 1746–1757 (2011)

MDMX blocks the tumour suppressor function of p53, so inhibiting MDMX could be beneficial in some cancers. Using genetically modified mice, Garcia *et al.* show that MDMX is continuously required to buffer p53 activity in adult normal tissues and stem cells, and that the effects of transiently restoring p53 function in the absence of MDMX are non-lethal and reversible. In a lymphoma model, restoring p53 activity in the absence of MDMX increased lifespan, suggesting that MDMX inhibition is a potential strategy for restoring p53 function in tumours.

NEUROPSYCHIATRIC DISORDERS

Role for the membrane receptor guanylyl cyclase-C in attention deficiency and hyperactive behavior

Gong, R. *et al. Science* 11 Aug 2011 (doi: 10.1126/science.1207675)

Dysfunctions in midbrain dopamine neurons are linked to attention deficit hyperactivity disorder (ADHD). This study showed that such neurons in mice express guanylyl cyclase C (GCC), a receptor thought to be expressed mainly in the intestine. Activation of GCC potentiated responses mediated by glutamate and acetylcholine receptors via the activity of protein kinase G (PKG). Knockout mice had symptoms of ADHD, which were reversed by a PKG activator, suggesting that the GCC–PKG signalling pathway in the brain could be targeted to restore the function of midbrain dopamine neurons.

PHOTODISC