IN BRIEF

KINASES

Disabling poxvirus pathogenesis by inhibition of Abl-family tyrosine kinases.

Reeves, M. P. *et al. Nature Med.* **11**, 731–739 (2005)

Cell-associated enveloped virions (CEVs) rely on actin to be able to move from just outside the host-cell nucleus to the cell surface, where they fuse with the cell membrane, detach and move on to infect another cell. This study shows that the CEVs require Abl and Src-family tyrosine kinases for actin motility, and specifically Abl tyrosine kinase when detaching from the cell. The authors found that the Abl-family kinase inhibitor imatinib (Gleevec; Novartis) blocks the release of CEVs and reduced viral dissemination and improved survival of infected mice.

INFECTIOUS DISEASES

Small-molecule inhibition of siderophore biosynthesis in *Mycobacterium tuberculosis* and *Yersinia pestis*.

Ferreras, J. A. *et al. Nature Chem. Biol.* **1**, 29–32 (2005)

The causative agents of tuberculosis and plague, *Mycobacterium tuberculosis* and *Yersinia pestis*, respectively, both share a common method of pathogenicity. Both use 'siderophores' to chelate iron from the host with extremely high affinity. This paper reports the identification of a class of non-hydrolyzable acyl-AMP analogues that inhibit a crucial step in siderophore biosynthesis called domain salicylation. One particular inhibitor, salicyl-AMS, is a promising lead compound for the development of novel antibiotics against tuberculosis and plague.

ANTICANCER DRUGS

Synthesis and identification of small molecules that potently induce apoptosis in melanoma cells through G1 cell cycle arrest.

Dothager, R. S. *et al. J. Am. Chem. Soc.* **127**, 8686–8696 (2005)

The very features of melanocytes that protect cells against DNA damage in normal skin also protect against cell-cycle arrest caused by chemotherapy. To search for more effective melanoma therapies, the authors of this study synthesized a combinatorial library of potential pro-apoptotic compounds and identified a class of small molecules called triphenylmethylamides (TPMAs) that potently induce cell death in melanoma cell lines without causing death to normal bone-marrow cells.

PARKINSON'S DISEASE

Sumanirole, a highly dopamine D2 selective receptor agonist: *in vitro* and *in vivo* pharmacologic characterization and efficacy in animal models of Parkinson's disease.

McCall, R. B. *et al. J. Pharm. Exp. Ther.* 24 Jun 2005 (doi:10.1124/jpet.105.084202)

The first dopamine D_2-receptor-selective agonist has been reported and shows promise in animal models as a potential drug against Parkinson's disease. Sumanirole was shown in radioligand binding assays to have more than 200-fold greater selectivity for the D_2 receptor subtype than any other dopamine receptor subtype. The authors describe how sumanirole causes many physiological responses in animals that are attributable to D_2-receptor activity, and improved disability scores and locomotor activities in rodent and primate models of Parkinson's disease.

SCREENING

Won't get fooled again

The prevalence of nonspecific or 'promiscuous' inhibitors that seem to be hits in multiple high-throughput screening (HTS) campaigns, but which turn out to be dead ends when attempts are made to optimize their activity, is a key problem in the field of HTS. Shoichet and colleagues, writing in *Nature Chemical Biology*, now describe two high-throughput assays that aim to address this issue by aiding the detection of promiscuous inhibitors.

Various explanations have been put forward to account for promiscuous compounds, including chemical reactivity and interference with assay readouts. Recent work from the Shoichet lab has also identified another possible mechanism to explain promiscuous inhibition: formation of colloid-like aggregates of the compounds, which sequester and thereby inhibit enzymes nonspecifically. Hits from HTS, leads and even some drugs seem to inhibit various enzymes through this mechanism at the micromolar concentrations typically used in HTS.

To facilitate investigation of the extent of this problem, the authors developed two rapid assays based on a standard 96-well format for detecting aggregate-based inhibition. The first assay exploits the detergent-sensitive nature of aggregate formation; compounds that only inhibit β-lactamase in the absence of detergent are considered likely to be promiscuous. The second assay uses dynamic light scattering to detect aggregate formation.

Shoichet *et al.* then selected 1,030 drug-like compounds and screened these molecules at micromolar concentrations in both assays, and a number of significant results were obtained. First, 19% of a subset of the compounds selected at random were detergent-sensitive inhibitors at screening-relevant concentrations (30 μm) — a percentage sufficiently high that it could dominate a screen that did not control for this effect. Second, both assays (whose reliability was confirmed using more sensitive, low-throughput versions of each assay) were able to robustly detect promiscuous aggregates, although of the two the detergent-sensitive assay seems best-suited for larger-scale applications. Finally, computational models for predicting aggregation-based promiscuity exploiting the results from the assays also showed some potential, and the data provided freely by the authors should aid the development of further such models.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Feng, B. Y. High-throughput assays for promiscuous inhibitors. *Nature Chem. Biol.* 3 Jul 2005 (doi:10.1038/nchembio718)

FURTHER READING McGovern, S. L. *et al.* A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. *J. Med. Chem.* **45**, 1712–1722 (2002) | Walters, W. P. & Namchuk, M. Designing screens: how to make your hits a hit. *Nature Rev. Drug Discov.* **2**, 259–266 (2003)