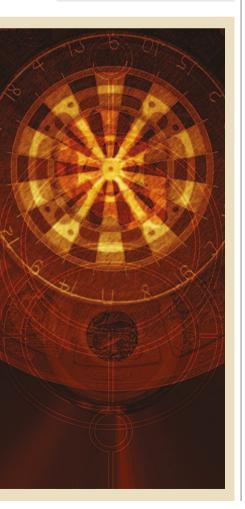
assembly. The use of fluorescent dyes can overcome technical difficulties associated with other assembly assays, such as light scattering, which is more sensitive to the presence of particulates or aggregates in the solution. Furthermore, this technique is both faster and cheaper than cell-based antiviral assays and is not complicated by issues associated with cellular uptake or toxicity of the candidate drug. At present, HBV capsid assembly is one of the better understood systems; however, as we gain improved understanding of viral assembly this approach could translate to other viruses that rely on capsid assembly for replication, including HIV, hepatitis C and avian influenza.

Katherine Whalley

ORIGINAL RESEARCH PAPER Stray, et al. An in vitro fluorescence screen to identify antivirals that disrupt hepatitis B virus capsid assembly. Nature Biotechnol. 24, 358–362 (2006)



## Parallel lines

Screening of compound libraries against cells is usually limited to characterizing the effects of molecules against a single cell line or drug target. The ability to study the effects of a compound on various cellular parameters simultaneously in different cell types could therefore speed up screening and enable parallel studies of drug efficacy and toxicity. Jeremy Caldwell and colleagues describe in *Proceedings of the National Academy of Sciences* a robotic system that does just that, and demonstrate how this system was used to characterize a library of kinase inhibitors and identify novel activities for known kinase inhibitors that could broaden their therapeutic use.

The authors designed an automated compound profiling (ACP) system that enables automated cell culture and which can perform miniaturized cell-based assays in 384- or 1,536-well microplates. The system integrates all stages of cell-line propagation (passaging, splitting, and determination of cell density and viability) with the necessary steps for compound screening (cell dispensing, compound addition, incubation, detection, reagent addition and plate reading). The authors demonstrated the capability of the ACP system by profiling the growth-inhibitory properties of a library of kinase-directed heterocyclic compounds against a panel of cells constitutively expressing a specific tyrosine kinase.

Kinases are often constitutively activated by fusion with other genes, and so Caldwell and colleagues exploited this to generate a cDNA library of tyrosine kinases fused to a common kinase fusion partner, ETV6/Tel, which, when expressed in a haematopoietic cell line, conferred tyrosine-kinase-dependence on cell populations. The library of tyrosine kinase-targeted compounds was supplemented with 10 known tyrosine kinase inhibitors and screened against the kinase-dependent cells. Only 30 of the 1,400 compounds were toxic to the cells, and 282 compounds had no effect on any kinasedependent cell line. However, each kinase tested was inhibited by at least one small molecule in the library, and 5.9% of the compound library selectively inhibited a single kinase.

Clusters of structurally similar molecules showed a modest correlation between potency and selectivity (as is typically identified by conventional kinase screens), and a plot of chemical similarity versus growth inhibition for pairs of compounds suggested that chemical similarity was in most cases an effective predictor of biological activity. Moreover, structure–activity relationship dendrograms compiled from the ACP data confirmed that structurally homologous kinases had comparable inhibition profiles, and could be used to aid target selection.

Perhaps the most therapeutically significant finding was the previously uncharacterized activities of existing kinase inhibitors. In addition to confirming the cross-kinase effects of imatinib (Gleevec; Novartis) on BCR-ABL, platelet-derived growth factor and c-KIT. new activities for less well-characterized kinase inhibitors currently in development were observed. BIRB796, a p38 kinase inhibitor, was also found to inhibit TIE1 and TIE2, kinases involved in angiogenesis and stem-cell guiescence and mobilization during chemotherapy. BMS-354825, a dual SRC and ABL inhibitor currently in trials as a therapy to overcome imatinib-resistant acute lymphoblastic and chronic myelogenous leukaemia. also inhibited multiple additional kinases including the ephrin receptors B1, B2 and B4.

Discovering these activities early on in screening not only highlights the potential for expanding investigative drugs for other indications, but could perhaps also explain off-target effects. Although others have profiled the 'kinome' against chemical space, this paper is the first example of the use of a physiologically relevant cell-based kinase screen used in parallel with a large compound library, and could be adapted to screen other target and drug classes.

Joanna Owens

**ORIGINAL RESEARCH PAPER** Melnick, J. S. *et al*. An efficient rapid system for profiling the cellular activities of molecular libraries. *Proc. Natl Acad. Sci. USA* **103**, 3153–3158 (2006) **WEB SITE** 

Jeremy S. Caldwell's laboratory: http://web.gnf.org/scientific/cellbio/caldwell.html

