IN BRIEF

LEAD DISCOVERY

Assessment of the consistency of medicinal chemists in reviewing sets of compounds.

Lajiness, M. S. *et al. J. Med. Chem.* 21 Aug 2004 (doi:10.1021/jm049740z)

Medicinal chemists are often asked to evaluate lists of compounds for their suitability as potential leads, but how consistent are the opinions of different medicinal chemists? To address this question, the authors performed an experiment in which a subset of 250 compounds rejected as unsuitable by a very experienced medicinal chemist were added to lists of ~2,000 compounds. These combined lists were then evaluated by 13 other medicinal chemists, and, interestingly, it was found that they were not very consistent in the compounds that they rejected as undesirable.

HIGH-THROUGHPUT SCREENING

Nonspecific enhancement of gene expression by compounds identified in high-throughput cell-based screening.

Cunningham, S. C. *et al. Biotechniques* **37**, 120–122 (2004)

Artefacts in high-throughput screening can be a major problem. Cunningham *et al.* investigated the ability of compounds to nonspecifically up- or down-regulate reporter plasmids in cell-based screening assays. Their results indicated that typical compound libraries can be expected to contain a group of compounds that nonspecifically modulate gene expression, which would be useful to take into account when performing such assays.

BIOTECHNOLOGY

DNA-templated organic synthesis and selection of a library of macrocycles.

Gartner, Z. J. *et al. Sciencexpress* 19 Aug 2004 (doi:10.1126/science.1102629)

Evolution-based approaches can be powerful for creating molecular function, but can only be applied to molecules that can be translated from amplifiable information carriers; for example, the translation of DNA into proteins. Recent efforts have focused on extending the possibilities of such approaches to small molecules (for example, see p737 of the September issue). Gartner and colleagues describe an approach based on DNA-templated organic synthesis that allows the translation, selection and amplification of DNA libraries into synthetic small molecules.

TUBERCULOSIS

Synthesis and biological evaluation of new inhibitors of UDP-Gal*f* transferase — a key enzyme in *M. tuberculosis* cell wall biosynthesis.

Cren, S. *et al. Org. Biomol. Chem.* **2**, 2418–2420 (2004)

Cren *et al.* describe the first inhibitors of a key enzyme involved in the biosynthesis of D-galactans found in the cell wall of *Mycobacterium tuberculosis*: UDP-Gal*f* transferase. These compounds could represent promising leads for the development of new antituberculosis drugs that lack serious side effects, because the main constituents of D-galactans are not found in mammalian metabolism.

CHEMISTRY

Stabilizing staples

A technique called hydrocarbon stapling has been shown to improve the pharmacological properties of peptides used to manipulate interactions between proteins. Writing in *Science*, Loren Walensky and colleagues describe how using these stapled peptides to modulate the BCL2 pathway in apoptosis provides both an attractive anticancer strategy and a tool for modulating protein interactions in many biological contexts.

Despite the attraction of modulating protein interactions, achieving this has proved difficult. Protein-interaction surfaces that are shallow, hydrophobic and extensive can present a challenge for targeting by small molecules. An alternative approach is to use peptides, but their use *in vivo* is hindered by poor permeability and sensitivity to proteases.

Focusing on the BCL2 pathway, Walensky *et al.* generated a panel of hydrocarbon-stapled peptides that mimic the so-called death domain (BH3) of the pro-apoptotic BCL2 family member BH3-interacting death domain agonist (BID). The BH3 domain is an essential feature of all BCL2 members and comprises an amphipathic α-helical segment that mediates many protein interactions. However, when taken out of their biological context, these helices lose their secondary structure, and *in vivo* function is compromised.

Most approaches to stabilize peptides leave them susceptible to degradation or unable to penetrate cells, and so the authors developed an alternative method. The reaction (a ruthenium-catalysed olefin metathesis) essentially stabilizes the helical conformation of the BH3 mimics, referred to as stabilized α-helix of BCL2 domains (SAHBs). Insertion of the staple also has another benefit: it shields the amide backbone, making the peptide less sensitive to proteolysis. Indeed, the SAHBs displayed improved serum stability *in vitro* and *in vivo* in a comparison with unmodified peptide.

The authors then studied the effects of SAHBs in an assay of cytochrome *c* release from mouse liver mitochondria (an early apoptotic event) and found that they caused a dose-dependent increase in cytochrome *c*, whereas the unmodified peptide caused a negligible effect in the low-dose range used. Furthermore, in Bak-null mitochondria (which do not release cytochrome *c* in response to a pro-apoptotic signal) a SAHB also failed to induce cytochrome *c* release, thereby proving that the peptide exerts its effects through the expected pathway. SAHBs also inhibited the growth of a wide variety of leukaemic cell lines and leukaemic xenografts in mice, and therefore offer not only a new method for manipulating biological pathways, but potentially a new class of anticancer drugs.

Joanna Owens

References and links

ORIGINAL RESEARCH PAPER Walensky, L. D. *et al.* Activation of apoptosis *in vivo* by a hydrocarbon-stapled BH3 helix. *Science* **305**, 1466–1470 (2004)

WEB SITE

Stanley Korsmeyer's lab: http://www.dana-farber.org/res/physician/detail.asp?personID=119&RD=True&group=%28Researcher%29

Gregory Verdine's lab: http://glviris.harvard. edu/people.d/GLVBiosketch.htm