IN BRIEF

KINASE INHIBITORS

Discovery of *S*-[5-amino-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-[3-(2,3-dihydropropoxy)phenyl]-methanone (RO3201195), an orally bioavailable and highly selective inhibitor of p38 MAP kinase.

Goldstein, D. M. *et al. J. Med. Chem.* **49**, 1562–1575 (2006)

Goldstein *et al.* describe the optimization of a series of p38 inhibitors identified by high-throughput screening. X-ray crystal structures of the series bound to p38 revealed the presence of a hydrogen bond between the inhibitor and a threonine residue in the ATP-binding site of p38 that contributes to inhibitor selectivity. This information was used to guide lead optimization, which resulted in a highly selective and orally bioavailable p38 inhibitor with anti-inflammatory activity in cell-based assays.

OSTEOPOROSIS

Denosumab in postmenopausal women with low bone mineral density.

McClung, M. R. *et al. New Engl. J. Med.* **354**, 821–831 (2006)

Osteoclasts, cells that resorb bone, are regulated by receptor activator of nuclear factor-κB ligand (RANKL). This paper reports Phase II trial results in which denosumab, a human monoclonal antibody that targets RANKL and blocks its effects on osteoclasts, was found to increase bone density and decrease bone resorption in a dose-dependent manner.

GENE THERAPY

Effective gene therapy with nonintegrating lentiviral vectors.

Yáñez-Muñoz, R. J. *et al. Nature Med.* **12**, 348–353 (2006)

Gene therapy has been hindered in part by the risk that vector integration into host chromosomes might cause mutations that can lead to cancer and lymphoproliferative diseases. This paper now provides the first *in vivo* evidence of sustained stable transgene expression in rat ocular and brain tissues using an integration-deficient vector, and reports the use of this approach to halt the progression of ocular degeneration in rats.

NEUROLOGICAL DISORDERS

Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number.

Flavell, S. W. *et al. Science* **311**, 1008–1012 (2006)

A calcium-regulated MEF2 sumoylation switch controls postsynaptic differentiation.

Shalizi, A. *et al. Science* **311**, 1012–1017 (2006)

The transcription factor myocyte enhancer factor-2 (MEF2) has emerged as a possible new target for neurological diseases that involve changes in synaptic formation and plasticity, according to two recent reports. The first paper shows that when neuronal activity is increased, the resulting calcium influx into cells causes calcineurin to dephosphorylate and activate MEF2, subsequently upregulating a set of genes that restrict synapse formation. The second paper further dissects the mechanism by which calcineurin regulates MEF2, and implicates MEF2 signalling in the post-synaptic differentiation of dendrites, which is essential for synapse formation. Both papers identify MEF2 as a new transcription factor with possible therapeutic relevance for Alzheimer's disease and autism.

ANTIBACTERIAL DRUGS

Pinpoint attack on resistance

Bacteria have developed numerous ways to resist the effects of antibiotics; in the case of vancomycin — currently one of the few antibiotics that is active against many potentially lethal bacteria — resistance can result from a small but crucial change in the structure of bacterial cell-wall precursors. Now, rationally counter-attacking by making a corresponding small change in the structure of vancomycin through chemical synthesis, Crowley and Boger have produced a compound that is active against vancomycin-resistant bacteria.

Vancomycin inhibits bacterial cell-wall biosynthesis by binding strongly to bacterial cell-wall precursors terminating in D-Ala-D-Ala. However, some bacteria have acquired the capacity to biosynthesize precursors that terminate in D-Ala-D-Lac — a deceptively simple change that greatly reduces the affinity of vancomycin for the modified cell-wall precursor by eliminating an attractive hydrogen-bond interaction between vancomycin and the precursor, and introducing a strongly repulsive interaction instead. This loss in affinity leads to a ~1,000-fold drop in antibacterial activity.

With the aim of counteracting this change, Crowley and Boger set out to construct a derivative of vancomycin in which a carbonyl group of the antibiotic that is involved in both the attractive hydrogen bond to D-Ala-D-Ala and the repulsive interaction with D-Ala-D-Lac was replaced with a non-polar methylene group. Because this group is in the core of the highly complex vancomycin structure, the authors used total synthesis to create the derivative, building on previous synthetic strategies for vancomycin and related antibiotics developed by the Boger group.

As anticipated, the new vancomycin derivative had considerably enhanced affinity for D-Ala-D-Lac, while affinity for D-Ala-D-Ala was reduced to around the same level owing to the loss of the hydrogen-bonding interaction. And excitingly, when tested against bacteria that resist vancomycin by switching from using D-Ala-D-Ala precursors to using D-Ala-D-Lac precursors in the presence of the antibiotic, the derivative showed significant antimicrobial activity reflective of its dual binding characteristics.

The activity of the derivative is not quite high enough for it to be considered a potential replacement for vancomycin, and the current need for total synthesis would also present considerable challenges for drug development. Nevertheless, both limitations are being addressed at present, and the results show that an understanding of the mechanisms of action of, and resistance to, antibiotics can be used to rationally design new agents that overcome resistance, and offer the hope of providing a fast track to much-needed new antibacterial drugs.

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ORIGINAL RESEARCH PAPER Crowley, B. M. & Boger, D. L. Total synthesis and evaluation of [ψ[CH_2NH]Tpg^4]vancomycin aglycone: reengineering vancomycin for dual D-Ala-D-Ala and D-Ala-D-Lac binding. *J. Am. Chem. Soc.* 4 Feb 2006 (doi:10.1021/ja0572912)