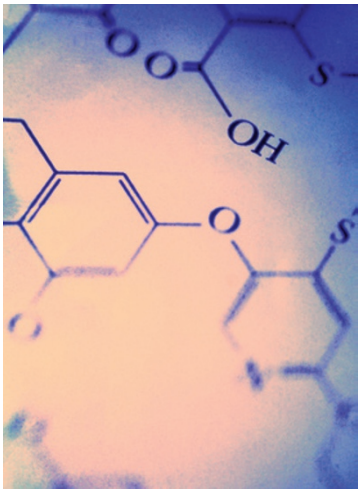
# IN BRIEF




## LEAD IDENTIFICATION

### Pyridopyrimidine derivatives as inhibitors of cyclic nucleotide synthesis: application for treatment of diarrhea.

Kots, A. Y. *et al. Proc. Natl Acad. Sci. USA* **105**, 8440–8445 (2008)

Acute secretory diarrhoea induced by *Escherichia coli* infection involves binding of stable toxin to guanylyl cyclase C (GC-C; also known as GUCY2C). Kots and colleagues identified BPIPP as an inhibitor of GC-C. The compound inhibited chloride-ion transport stimulated by activation of guanylyl cyclases *in vitro*, and suppressed stable toxin-induced fluid accumulation in an *in vivo* rabbit intestinal loop model. So, BPIPP may be a promising lead compound for the treatment of diarrhoea and other conditions involving cyclic nucleotide disturbances.

## G-PROTEIN-COUPLED RECEPTORS

### Structure of a $\beta_1$-adrenergic G-protein-coupled receptor.

Warne, T. *et al. Nature* 25 June 2008 (doi:10.1038/nature07101)

The recent elucidation of the crystal structure of the $\beta_2$-adrenergic receptor (AR) raised questions about the structural basis of subtype specificity of β-AR ligands. Warne and colleagues report the 2.7Å resolution crystal structure of a turkey $\beta_1$-AR in complex with a high-affinity antagonist. Binding of antagonists to $\beta_2$-AR and $\beta_1$-AR involve similar interactions. However, a short helix in cytoplasmic loop 2 — not observed in rhodopsin or $\beta_2$-AR — directly interacts with the highly conserved DRY motif at the end of helix 3 by means of a tyrosine, which is essential for receptor activation.

## PARASITE INFECTION

### Immunity to a salivary protein of a sand fly vector protects against the fatal outcome of visceral leishmaniasis in a hamster model.

Gomes, R. *et al. Proc. Natl Acad. Sci. USA* **105**, 7845–7850 (2008)

Visceral leishmaniasis — transmitted by sandflies — is a fatal disease for which no vaccine is currently available. Gomes and colleagues developed a hamster model of the disease that mimics its natural progression. In this model, immunization with 16 DNA plasmids coding for sandfly salivary proteins resulted in the identification of LJM19, a novel 11 kDa protein. Hamsters immunized with LJM19 were protected against the fatal outcome of visceral leishmaniasis, and mounted a delayed-type hypersensitivity immune response. This highlights the feasibility of using arthropod saliva as a strategy against vector-borne diseases.

## ANTIBODY-MEDIATED DISEASES

### The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis.

Neubert, K. *et al. Nature Med.* **14**, 748–755 (2008)

Autoantibody-mediated diseases — such as systemic lupus erythematosus — are difficult to treat because long-lived plasma cells that produce autoantibodies resist current and experimental approaches. Neubert and colleagues show that the approved proteasome inhibitor bortezomib depletes short-lived and long-lived plasma cells, mainly as a result of activation of the terminal unfolded protein response. Treatment of mice with lupus-like disease with bortezomib decreased dsDNA-specific antibody production, proteinuria and kidney damage, and considerably prolonged survival.