IN BRIEF

MOOD DISORDERS

Alterations in 5-HT$_{1B}$ receptor function by p11 in depression-like states.

Svenningsson, P. *et al. Science* **311**, 77–80 (2006)

Although we know that the 5-hydroxytryptamine (5-HT) receptor family mediates the effects of antidepressant drugs, little is known about the role of individual receptors in the aetiology of depression. Svenningsson *et al.* used a yeast-two-hybrid screen to identify binding partners of the 5-HT receptor family and found that p11, an S100 EF-hand protein, specifically interacts with the 5-HT$_{1B}$ receptor. They also found that p11 is upregulated by antidepressant treatment and is involved in translocation of the 5-HT$_{1B}$ receptor to the cell surface. Correspondingly, p11-null mice had a lower number of 5-HT$_{1B}$ receptors and showed a depressive-like phenotype, suggesting that p11 has a key role in behavioural disorders.

INFORMATICS

DrugBank: a comprehensive resource for *in silico* drug discovery and exploration.

Wishart, D. S. *et al. Nucleic Acids Res.* **34**, D668–D672 (2006)

Wishart and colleagues describe DrugBank — a free, fully searchable database that combines chemical information for >4,100 drug entities with structural and sequence information for >14,000 drug targets. DrugBank has four major categories — FDA-approved small-molecule drugs; FDA-approved biopharmaceuticals; nutraceuticals or micronutrients; and experimental drugs — and has more than 80 data fields for each DrugCard entry. Researchers can search by text, sequence or structure, and can browse or use the 'pharmabrowse' function, which clusters drugs according to class or indication.

STRUCTURE-BASED DRUG DESIGN

Crystal structure of human T cell leukemia virus protease, a novel target for anticancer drug design.

Li, M. *et al. Proc. Natl Acad. Sci. USA* **102**, 18332–18337 (2005)

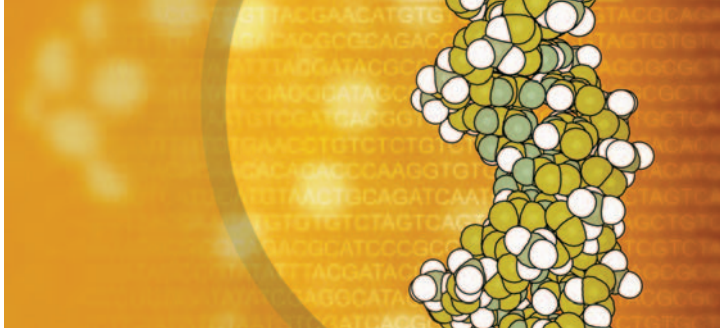
Li *et al.* report the structure of the human T-cell leukaemia virus-1 protease (HTLV-1 PR) bound to a substrate-based inhibitor. Although the overall protein fold is similar to other proteases, the authors found some structural differences that could have functional relevance. In particular, they identified key residues responsible for the resistance of HTLV-1 PR to anti-HIV drugs, which could be important in the rational design of novel antileukaemic drugs.

CANCER

Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients.

López-Lázaro, M. *et al. J. Nat. Prod.* **68**, 1642–1645 (2005)

There have been several observations that the cardiac drug digitoxin also has anticancer effects. In this study, digitoxin and related compounds were screened against several cancer cell lines. In all four cell lines the IC$_{50}$ value for growth inhibition for digitoxin and digoxin were within or below the concentration range used in cardiac patients, and digitoxin was particularly potent against a kidney cancer cell line renowned for its resistance to chemotherapy. Digitoxin's desirable pharmacological profile might therefore warrant its further investigation as a drug to treat kidney tumours and other cancers.



INFECTIOUS DISEASE

Antisense PMOs protect against Ebola virus

A lack of knowledge about the pathogenesis of the filoviruses Ebola virus (EBOV) and Marburg virus, as well as the special containment conditions required to study them, has proved to be a significant obstacle to the development of therapies for these infections. Writing in *PLoS Pathogens*, Warfield and colleagues describe the first use of a new generation of antisense technology that inhibits mRNA translation of specific viral proteins (VPs), an approach that was effective against lethal EBOV infection and has implications for the treatment of other infections caused by viral pathogens.

Warfield and colleagues designed antisense phosphorodiamidate morpholino oligomers (PMOs) — oligonucleotide analogues incorporating a phosphorodiamidate link and a morpholine ring — to target EBOV VP24, VP35 and RNA-dependent RNA polymerase (L protein). In contrast to oligonucleotides, PMOs have several drug-like properties — for example, they are non-ionic in character and therefore permeate cells more easily, are resistant to degradation in cells and do not seem to induce an interferon response, all of which make them attractive as potential therapeutic agents.

Promising results with the three EBOV-specific PMOs from a cell-based assay and survival tests in mice and guinea pigs prompted the authors to carry out a small proof-of-concept study in Rhesus macaques. The monkeys were treated with either the VP35-specific PMO or a combination of the VP24, VP35 and L protein PMOs 2 days before exposure to lethal EBOV infection. Whereas monkeys receiving only the VP35-specific PMO succumbed to lethal EBOV infection, 75% of those monkeys receiving the combination treatment survived. Surviving monkeys developed low to moderate viraemia, and testing of their immune response 28 days after infection showed high levels of anti-EBOV antibodies and T-cell responses, indicating a prominent role for the immune system in protection from lethal infection.

Using a combination of antisense PMOs to target multiple viral genes seems to slow EBOV replication to a level that gives the host's innate immune system time to mount a protective antiviral immune response. PMOs have appropriate safety profiles for use in humans, and can be easily produced in large quantities. Moreover, the hit-to-lead optimization of sequence-based approaches, such as those using antisense PMOs, can usually be done rapidly, and so can accelerate the drug discovery process for such compounds.

Previous strategies to treat EBOV infection focused on inhibiting viral mRNA replication or strengthening the host's immune response, but these approaches had limited success. The results reported by Warfield and colleagues could contribute to the development of a new strategy to combat a wide range of viral infections. The next step will be to enhance the therapeutic potential by targeting the PMOs to the specific locations where viral replication occurs.

Samantha Barton

ORIGINAL RESEARCH PAPER Warfield, K. L. *et al.* Gene-specific countermeasures against Ebola virus based on antisense phosphorodiamidate morpholino oligomers. *PLoS Pathogens* 13 Jan 2006 (doi:10.1371/journal.ppat.0020001)