IN BRIEF

KINASES

A minimalist approach to fragment-based ligand design using common rings and linkers: application to kinase inhibitors.

Aronov, A. M. & Bemis, G. W. *Proteins* **57**, 36–50 (2004)

Fragment-based approaches to lead discovery, in which low-affinity, low-molecular-mass chemical 'fragments' are combined to give high-affinity leads, are becoming increasingly popular. Aronov and Bemis present a novel fragment-based approach to the discovery of kinase inhibitors, which utilizes an analysis of the structures of ~40,000 known kinase inhibitors that indicates that their structures can be largely described by a small number of rings and linkers.

BIOTECHNOLOGY

Antidote-mediated control of an anticoagulant aptamer *in vivo*.

Rusconi, C. P. *et al. Nature Biotechnol.* 17 Oct 2004 (doi:10.1038/nbt1023)

Current agents used to inhibit pathological blood clotting have to be carefully monitored to reduce the risk of serious bleeding. However, with the exception of heparin, no anticoagulants have a rapidly acting 'antidote' that can neutralize such side effects if they occur. Rusconi and colleagues describe an aptamer targeted at coagulation factor IXa, which has anticoagulant effects in animals that can be rapidly reversed using a rationally designed oligonucleotide antidote.

LUNG DISEASES

Imatinib mesylate inhibits the profibrogenic activity of TGF-β and prevents bleomycin-mediated lung fibrosis.

Daniels, C. E. *et al. J. Clin. Invest.* **114**, 1308–1316 (2004)

Profibrotic cytokines, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), are thought to be important in the pathogenesis of idiopathic pulmonary fibrosis (IPF), a progressive and fatal fibrotic disease of the lungs. Daniels *et al.* provide data that indicate that fibroblasts respond to TGF-β by stimulating c-ABL kinase activity. Furthermore, imatinib (Gleevec; Novartis), which inhibits ABL family kinases and the PDGF receptor tyrosine kinase, was shown to obviate fibrotic changes in a mouse model of pulmonary fibrosis, and so could be a potential therapy for IPF.

ANTITHROMBOTIC DRUGS

Disruption of protein–membrane binding and identification of small-molecule inhibitors of coagulation factor VIII.

Spiegel, C. P. *et al. Chem. Biol.* **11**, 1413–1422 (2004)

Highly specific interactions between proteins and lipid membranes are essential in many biological pathways and processes; for example, the interaction between factor VIII and the membranes of platelets has a key role in blood coagulation. Spiegel and colleagues have developed an enzyme-linked-immunosorbent-assay (ELISA)-based high-throughput screen, which they used to identify small molecules that inhibit the binding of factor VIII to lipid membranes. These compounds could be leads for the development of novel antithrombotic drugs.

ANTIVIRAL DRUGS

Inside the envelope

Drugs that target key enzymes in the life cycle of human immunodeficiency virus (HIV) have revolutionized the treatment of HIV in the past decade. Nevertheless, drug resistance remains a major problem. Writing in *Chemistry and Biology*, Schiffer and colleagues propose a novel structure-based strategy for combating drug resistance, using HIV-1 protease — for which several active-site inhibitors are approved — as an example.

HIV-1 protease cleaves the HIV Gag and Pol precursor proteins in at least nine different locations to allow viral maturation. It was originally speculated that this multiplicity of enzyme substrates would make the development of resistance to protease inhibitors unlikely, because the protease would be unable to accommodate mutations necessary to decrease the affinity of drug binding in its active site without seriously compromising its ability to bind at least one of its substrates. However, this has not turned out to be the case.

So, to understand how drug resistance can emerge while the protease retains its ability to recognise its substrates, the authors determined the crystal structures of an inactive variant of HIV-1 protease in complex with six of its known substrates. Using computational analysis to assess the overlap between the volumes in the active site occupied by these substrates, they identified an 'envelope' within the active site that apparently must be made available for substrate binding.

An analogous analysis with HIV-1 protease in complex with eight different inhibitors also revealed an envelope within the active site occupied by inhibitors. However, overlaying the 'inhibitor envelope' and the 'substrate envelope' revealed several regions where the inhibitor envelope protrudes beyond the substrate envelope. And crucially, many of the residues that have been reported to mutate in drug-resistant HIV-1 strains contact these regions.

It therefore seems that if future drug design focuses on developing inhibitors that interact strongly only with residues within the substrate envelope of HIV-1 protease, the chances of drug resistance developing would be reduced. Indeed, recent inhibitors indicate that this might be possible. Furthermore, this strategy could also be extended to other enzymes important in viral pathogenesis, such as the serine protease of hepatitis C virus.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER King, N. M. *et al.* Combating susceptibility to drug resistance: lessons from HIV-1 protease. *Chem. Biol.* **11**, 1333–1338 (2004)

FURTHER READING Prabu-Jeyabalan, M. *et al.* Substrate shape determines specificity of recognition for HIV-1 protease: analysis of crystal structures of six substrate complexes. *Structure* **10**, 369–381 (2002) | Prabu-Jeyabalan, M. *et al.* Viability of a drug-resistant HIV-1 protease variant: structural insights for better anti-viral therapy. *J. Virol.* **77**, 1306–1315 (2003) | King, N. M. *et al.* The structural and thermodynamic basis for the binding of a next generation HIV-1 protease inhibitor, TMC114. *J. Virol.* **78**, 12012–12021 (2004)