IN BRIEF

ANTICANCER DRUGS

A non-ATP-competitive inhibitor of BCR–ABL overrides imatinib resistance.

Gumireddy, K. *et al. Proc. Natl Acad. Sci USA* **102**, 1992–1997 (2005)

Imatinib (Gleevec; Novartis), an ATP-competitive inhibitor of the BCR–ABL kinase, has shown great success in the treatment of chronic myelogenous leukaemia, but a significant proportion of patients eventually develop resistance to the drug owing to mutations in the kinase domain of BCR–ABL. Gumireddy *et al.* describe an inhibitor of BCR–ABL that is substrate-competitive, rather than ATP-competitive, and which shows activity against imatinib-resistant leukaemias and a desirable safety profile.

COMPUTATIONAL CHEMISTRY

Greater than the sum of its parts: combining models for useful ADMET prediction.

O'Brien, S. E. & de Groot, M. J. *J. Med. Chem.* 1 Feb 2005 (doi: 10.1021/jm049254b)

Computational tools for predicting the adsorption, distribution, metabolism, excretion and toxicity (ADMET) properties of compounds are important in helping to reduce late-stage attrition in the drug discovery process. This paper shows how ADMET models can be combined to produce better predictions, using prediction of hERG-channel blocking and inhibition of cytochrome P450 2D6 as examples.

NEURODEGENERATIVE DISEASE

Anti-Aβ antibody treatment promotes the rapid recovery of amyloid-associated neuritic dystrophy in PDAPP transgenic mice.

Brendza, R. P. *et al. J. Clin. Invest.* **115**, 428–433 (2005)

The neuritic plaques that are a defining feature of Alzheimer's disease are composed of extracellular accumulations of amyloid-β (Aβ) and other plaque-associated proteins, surrounded by dystrophic neurites and activated glia. It is thought that dystrophic neurites disrupt neuronal function, but it is not known whether this damage is static, dynamic or reversible. Using anti-Aβ antibody treatment, Brendza *et al.* provide evidence that clearing Aβ in the brain can promote the rapid recovery of existing amyloid-associated neuritic dystrophy in mice, providing encouragement for Aβ-clearance as a therapeutic strategy for Alzheimer's disease.

LEAD DISCOVERY

Development of K_iBank, a database supporting structure-based drug design.

Zhang, J. *et al. Comput. Biol. Chem.* **28**, 401–407 (2004)

Various publicly available databases of chemicals and relevant biological data have been launched in recent years, such as the PDSP K_i database (http://pdsp.cwru.edu/pdsp.php), Pubchem (http://pubchem.ncbi.nlm.nih.gov/) and Chembank (http://chembank.med.harvard.edu/). This paper describes the development of K_iBank, a database of inhibition constant (K_i) values with three-dimensional structures of target proteins and chemicals designed to support structure-based drug design.

ANTIVIRAL DRUGS

A step ahead of drug resistance

A promising new target for the development of antiretroviral therapies to treat HIV-1 has been identified, according to a recent study published in *The Journal of Clinical Investigation*. At present, patients are treated with various combinations of drugs that inhibit the HIV-1 life cycle by targeting the viral proteins HIV-1 reverse transcriptase, HIV-1 protease and gp41. These drug combinations have markedly reduced death rates caused by HIV-1 infection during the past few years. However, HIV-1 can acquire resistance to all existing drugs, and the number of patients who are infected with multidrug-resistant strains is rising, limiting future treatment options. So, there is a pressing need for new anti-HIV drugs, particularly those that have a novel mechanism of action, as these might be less likely to show cross-resistance with current therapies.

Hauber and colleagues now report that blocking a host-cell factor — human deoxyhypusine synthase (DHS) — provides a successful means of preventing the replication of HIV-1, including strains that are resistant to highly active antiretroviral therapy (HAART). CNI-1493, a small molecule that is currently undergoing Phase II trials for Crohn's disease, was found to be a potent inhibitor of DHS, and therefore viral replication. Inhibition of DHS by RNA interference also showed antiviral effects in cell culture and primary cells. These authors then cultured T-cell-tropic and macrophage-tropic laboratory strains, peripheral blood mononuclear cells from patients infected with HIV-1 and a series of antiretroviral-resistant viruses in the presence of CNI-1493, which effectively suppressed viral replication, indicating that this compound would make an ideal inhibitor of drug-resistant viruses.

Normally, DHS activates eukaryotic initiation factor 5A (eIF-5A) by initiating the first of two reactions that convert inactive eIF-5A to its active hypusine-containing form. eIF-5A is involved in the metabolism of specific cellular RNAs, and is a cellular cofactor of the HIV-1 viral regulatory protein Rev, which is essential for the replication of HIV-1. Blocking DHS therefore suppresses viral replication by interfering with eIF-5A activity. Nevertheless, the precise mechanism of action of the anti-DHS activity of CNI-1493 remains to be determined.

Importantly, it seems that the action of CNI-1493 is restricted to inhibition of DHS, because there were no detrimental effects on apoptosis, cell-cycle progression and cytotoxicity, as seen in some other studies of inhibitors of eIF-5A activity, at concentrations that effectively prevented viral replication. This new work therefore supports the idea that small-molecule inhibitors of DHS could be developed as successful antiviral therapies to combat strains of HIV that are resistant to currently available drugs.

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References and links

ORIGINAL RESEARCH PAPER Hauber, I. *et al.* Identification of cellular deoxyhypusine synthase as a novel target for antiretroviral therapy. *J. Clin. Invest.* **115**, 76–85 (2005)

FURTHER READING De Clercq, E. Strategies in the design of antiviral drugs. *Nature Rev. Drug Discov.* **1**, 13–25 (2002)