# IN BRIEF

ADME

## Characteristic physical properties and structural fragments of marketed oral drugs.

Vieth, M. *et al. J. Med. Chem.* 26 Nov 2003 (doi:10.1021/jm030267j).

Understanding how the physical properties of molecules influence their pharmacokinetics is important for improving the probability of selecting successful clinical candidates, and so has been the subject of considerable study. Vieth *et al.* have compiled both structural and route-administration information for 1,729 marketed drugs — which they have made freely available online — to provide a basis for developing a new perspective on the characteristics of orally administered drugs.

ANTICANCER DRUGS

## A small-molecule antagonist of CXCR4 inhibits intracranial growth of primary brain tumors.

Rubin, J. B. *et al. Proc. Natl Acad. Sci. USA* **100**, 13513–13518 (2003).

Malignant brain tumours are a major cause of cancer mortality in both adults and children. Rubin *et al.* show that antagonism of the chemokine receptor CXCR4 by the small molecule AMD 3100 inhibits the growth of brain tumours *in vivo* in mice. This finding could rapidly lead to clinical trials, as AMD 3100 is already known to be well tolerated in humans from studies of this agent as a potential anti-HIV treatment.

LIVER DISEASE

## Hepatoprotection by the farnesoid X receptor agonist GW4064 in rat models of intra- and extra-hepatic cholestasis.

Liu, Y. *et al. J. Clin. Invest.* 17 Nov 2003 (doi:10.1172/JCI200318945).

Cholestasis, an impairment or cessation in the flow of bile, causes hepatotoxicity as a result of the accumulation of bile acids and other toxins in the liver. As activation of the farnesoid X receptor (FXR), a member of the nuclear receptor superfamily, is known to induce transcription of genes involved in promoting bile-acid clearance and to repress genes involved in bile-acid synthesis, the authors tested the synthetic FXR agonist GW4064 in rat models of cholestasis, and their results indicate that FXR agonists could be useful in the treatment of cholestatic liver disease.

SCREENING

## Competitive binding assays made easy with a native marker and mass spectrometric quantification.

Höfner, G. & Wanner, K. T. *Angew. Chem. Int. Ed.* **42**, 5235–5237 (2003).

Competitive binding assays are a key method in drug discovery, but typically require the use of marker ligands labelled either with a radioisotope or a fluorophore, which can have several limitations. The authors describe a simple competitive binding assay based on mass spectrometry that does not require labelled ligands.

ADVERSE DRUG REACTIONS

# A broader perspective

**Adverse drug reactions (ADRs) have, so far, been classified only on the basis of properties of the drug in question — that is, on the known pharmacology and the dose-dependence of the drug effects — although other factors, such as the delay in occurrence of the ADR and failure of therapy, are also sometimes taken into account.**

**But Jeffrey Aronson and Robin Ferner argue in the *British Medical Journal* that this approach gives limited insight into ADRs and that a comprehensive classification should take into account additional factors that relate to the drug, the patient and the reaction itself. For example, corticosteroid-related osteoporosis depends on the dose and the duration of treatment, and some reactions, such as asthma caused by β-adrenoceptor antagonists, do not occur in all patients, who have differing susceptibilities.**

**Aronson and Ferner therefore propose a three-dimensional classification system called DoTS, based on dose relatedness (Do), the time course of the reaction (T) and the susceptibility (S) of the patient. Dose relatedness is defined in terms of reactions that occur at supra-therapeutic doses (toxic reactions), standard therapeutic doses (collateral reactions) and sub-therapeutic doses (hyper-susceptibility reactions). Timing is divided into time-dependent and time-independent effects: time-independent reactions occur at any time during a treatment course, whereas time-dependent reactions can occur at six stages — rapid, first dose, early, intermediate, late (including withdrawal reactions) and delayed. Susceptibility factors alter the risks of ADRs in individuals, and include age, sex, physiological and genetic variation, and drug interactions.**

**Three examples of DoTS classifications of ADRs are given. For instance, the classification of osteoporosis due to corticosteroids is: dose-relatedness, collateral; time-course, late; suceptibility factors, age and sex. A more sophisticated analysis is also possible, which requires an estimate of the probability of an ADR at different doses and times after administration for different degrees of susceptibility, and can be displayed as a series of three-dimensional graphs or nomograms. The authors conclude that their proposed classification "should provide important insights for drug development and regulation, for pharmacovigilance, for monitoring patients, and for the prevention, diagnosis, and treatment of adverse drug reactions."**

*Simon Frantz*

### References and links

**ORIGINAL RESEARCH PAPER** Aronson, J. K. & Ferner, R. E. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* **327**, 1222–1225 (2003)

**FURTHER READING** Rawlins, M. D. Clinical pharmacology: adverse reactions to drugs. *BMJ* **282**, 974–976 (1981) | Roden, D. M. & George, A. L. Jr. The genetic basis of variability in drug responses. *Nature Rev. Drug Discov.* **1**, 37–44 (2002)