IN BRIEF

ANTICANCER DRUGS

Light-activated destruction of cancer cell nuclei by platinum diazide complexes.

Bednarski, P. J. *et al. Chem. Biol.* **13**, 61–67 (2006)

To improve the specificity and safety of platinum-based anticancer drugs, Bednarski *et al.* used light to induce photochemical changes in non-toxic platinum prodrugs which then release the active drug within the tumour. Two photolabile prodrug complexes of cisplatin and an analogue were evaluated for their capacity to inhibit the growth of human bladder cancer cells in light and dark conditions. Light activation of the prodrugs caused adducts in tumour DNA more quickly than cisplatin and caused disintegration of cancer cell nuclei. The prodrugs were also active against cisplatin-resistant cell lines, and could prove useful against several tumour types that are light-accessible.

MODEL ORGANISMS

Conservation of gene expression signatures between zebrafish and human liver tumors and tumor progression.

Lam, S. H. *et al. Nature Biotechnol.* **24**, 73–75 (2006)

Because little is known about how similar zebrafish and human cancers are at the molecular level, Lam and colleagues set out to identify gene signatures for particular tumour phenotypes in zebrafish and humans, and compare their similarity. They generated liver tumours in zebrafish and identified a set of genes that were differentially expressed in these tumours compared with normal liver tissues. The deregulated genes were found to be homologues of human proteins involved in processes related to tumour progression, such as cell-cycle regulation and DNA repair, indicating that the zebrafish tumours have similar hallmark genetic changes to human tumours.

CHEMICAL BIOLOGY

SMM-chemokines: a class of unnatural synthetic molecules as chemical probes of chemokine receptor biology and leads for therapeutic development.

Kumar, S. *et al. Chem. Biol.* **13**, 69–79 (2006)

Developing selective inhibitors of specific chemokine receptors has proved challenging. This paper describes a method of creating synthetically and modularly modified (SMM)-chemokines using 'total chemical synthesis' to incorporate an unlimited range of unnatural amino acids and chemical modifications into novel peptide ligands. The authors were able to convert the non-selective vMIPII inhibitor into ligands with high selectivity for CXRC4 or CCR5 and improved pharmacokinetic and toxicity profiles.

MOOD DISORDERS

Leptin: a potential novel antidepressant.

Lu, X.-Y. *et al. Proc. Natl Acad. Sci.* USA **103**, 1593–1598 (2006)

Although leptin is known to be involved in energy homeostasis, it has also recently been implicated in depression. Lu and colleagues now show that circulating leptin is downregulated in rats suffering from conditions that produce behavioural deficits similar to depression. Evaluation of the antidepressant effect of leptin showed that behavioural alterations in the decreased sucrose preference test and the forced swim test were overcome by leptin administration.

DRUG METABOLISM

Crystals clarify metabolism

The crystal structure of cytochrome P450 2D6, one of the most important drug-metabolizing enzymes, has been solved. With the exception of cytochrome P450 3A4, whose structure was reported in 2004, 2D6 metabolizes the largest fraction of known drugs — at least 20% — and furthermore shows considerable inter-individual variation that can have a major impact on the rate of drug metabolism.

As Rowland and colleagues describe in their paper in the *Journal of Biological Chemistry*, the structure of 2D6 has the characteristic P450 family fold, and the lengths and orientations of the individual secondary structure elements are very similar to those in cytochrome P450 2C9, another important drug-metabolizing enzyme. However, there are six main regions that show large differences between 2D6 and 2C9, three of which are directly involved in defining the shape and character of the active site of 2D6.

Compounds recognized by 2D6 typically have a basic nitrogen and a planar aromatic ring, features that are common in central nervous system and cardiovascular drugs that act on G-protein-coupled receptors. The 2D6 structure, which has a well-defined active site cavity above the haem group, helps to explain how a crucial residue previously implicated in substrate recognition — Phe120 — could act to control the orientation of the aromatic ring of substrates with respect to the haem. In addition, the role of several other key residues involved in substrate interactions previously identified from site-directed mutagenesis and modelling studies, such as Asp-301 and Glu-216, is now clearer.

The authors also use the structure to explain earlier observations about the metabolism of important 2D6 substrates, such as the antihypertensive drug debrisoquine. Work in progress to determine the structure of 2D6 in complex with substrates and inhibitors will clarify details of ligand recognition, which will further aid the design of compounds with reduced susceptibility to metabolism by 2D6 and could also provide a structural basis for the study of the effects of various 2D6 polymorphs on substrate metabolism.

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ORIGINAL RESEARCH PAPER Rowland, P. *et al.* Crystal structure of human cytochrome P450 2D6. *J. Biol. Chem.* doi: 10.1074/jbc.M511232200
FURTHER READING Williams, P. A. *et al.* Crystal structures of human cytochrome P450 3A4 bound to metyrapone and progesterone. *Science* **305**, 683–686 (2004)