IN BRIEF

ANXIETY DISORDERS

Selective anxiolysis produced by ocinaplon, a $GABA_A$ receptor modulator.

Lippa, A. *et al. Proc. Natl Acad. Sci. USA* **102**, 7380–7385 (2005)

Individuals with anxiety disorders are commonly prescribed benzodiazepines, which act via $GABA_A$ (γ-aminobutyric acid A) receptors but cause side effects such as sedation, muscle relaxation and ataxia. Compounds with selectivity for type I receptors have been shown to elicit anxiolytic effects at lower concentrations than those producing benzodiazepine-type side effects in animals. Lippa *et al.* report a compound, ocinaplon, which is anxio-selective in humans. A double-blind placebo-controlled trial of at least 40 patients showed that a 2-week regimen of ocinaplon caused a significant reduction in scores from the Hamilton rating scale for anxiety with no benzodiazepine-like side effects.

HIV

Antigenic conservation and immunogenicity of the HIV coreceptor binding site.

Decker, J.M. *et al. J. Exp. Med.* **201**, 1407–1419 (2005)

Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies.

Trkola, A. *et al. Nature Med.* **48**, 3122–3125 (2005)

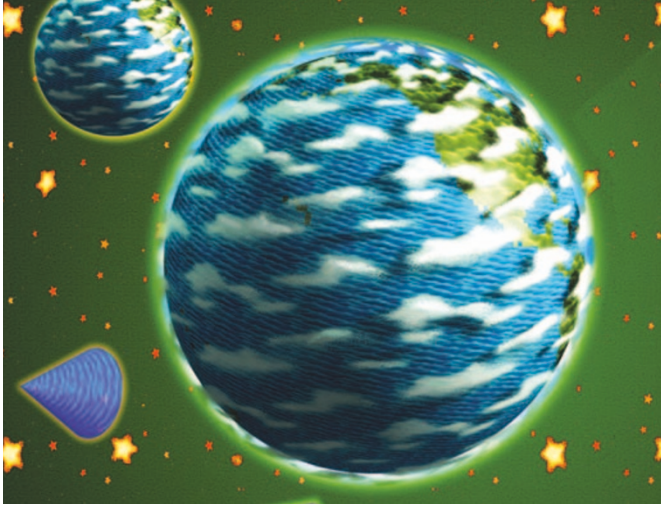
Two papers on HIV published recently provide insights into the potential of treating the infection with neutralizing antibodies or vaccines. Decker *et al.* provide new information about the immunogenicity of the HIV-1 envelope glycoprotein and suggest that, in contrast to previous reports, the co-receptor-binding site on HIV-1 is strongly immunogenic and elicits high titres of antibody that neutralize HIV-1 as well as multiple strains of HIV-2. Their results will aid the development of neutralization assays for HIV vaccine assessment. In the second paper, Trkola *et al.* studied the ability of the humoral immune response to delay HIV-1 rebound after withdrawal of antiretroviral therapy. They found that passive immunization with neutralizing antibodies had little effect in delaying viral rebound in patients with chronic infections, whereas those acutely infected fared better. The antibody 2G12 was found to be crucial to the activity of the neutralizing antibody cocktail *in vivo*.

GENE EXPRESSION

MicroRNA expression profiles classify human cancers.

Lu, J. *et al. Nature* **435**, 834–838 (2005)

MicroRNAs (miRNAs) are a class of small non-coding RNAs with diverse regulatory functions. In this paper, Lu *et al.* provide evidence that miRNAs have unexpected diagnostic potential in cancer. A bead-based flow cytometry miRNA-expression profiling method was developed to perform a systematic expression analysis of 334 different human cancer samples using 217 mammalian miRNAs. The majority of miRNAs had lower expression in tumours than in normal tissue, and hierarchical clustering reflected both developmental lineage and differentiation state of tumours. Moreover, when used to classify poorly differentiated tumours, miRNA expression was far more accurate than conventional mRNA profiling. Unlike mRNAs, miRNAs remain intact in formalin-fixed paraffin sections, and so this method might be easily implemented in the clinic.



MEDICINAL CHEMISTRY

Best of both worlds?

A new approach that tackles a key issue in medicinal chemistry — how to achieve maximum diversity in chemical libraries used for screening, while minimizing the size of the libraries — has been recently reported in the *Journal of Medicinal Chemistry*. The developers of the strategy, Didier Rognan and colleagues, describe how it can be used to increase the potency of a known phosphodiesterase 4 (PDE4) inhibitor by a factor of ~10^3 by computationally evaluating just 320 compounds, and synthesizing and testing only 9.

The authors' approach, dubbed the SLF approach, is based on the combinatorial assembly of three types of molecular 'building blocks': a conserved scaffold (S), a variable linker (L) and a variable functional group (F). Importantly, and in contrast to some other general strategies for combinatorial scaffold-based library design, all the building blocks are user-selected. In particular, carefully selecting a limited number of functional groups that do not overlap in 'pharmacophoric space' helps to create maximal chemical diversity while keeping the overall library size down. Furthermore, the combinations were also selected so as to ensure synthetic accessibility.

To demonstrate their strategy, Rognan *et al.* used the scaffold of the known PDE4 inhibitor zardaverine to build a virtual library by combining 4 closely related such scaffolds, 5 linkers and 16 functional groups. The 320 resultant molecules were then docked into a crystal structure of PDE4, and ranked by predicted binding strength. Inspection of high-ranking molecules suggested that two additional binding pockets in PDE4 not occupied by zardaverine could be targeted by a number of such compounds in the library, and nine of these compounds were selected and synthesized for testing.

Of the nine compounds, five were stronger inhibitors of PDE4 *in vitro* than zardaverine, and one had an IC_{50} value of 0.9 nM — ~900-fold greater than zardaverine. Also, as one of the additional binding pockets identified by the authors shows some degree of variation between different PDEs, these compounds could represent good starting points for attempts to overcome the selectivity problems that have so far limited the clinical development of PDE4 inhibitors. And more generally, the ability of the SLF approach to facilitate rapid and efficient lead optimization could lead to its application for many other targets.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Krier, M. *et al.* Design of small-sized libraries by combinatorial assembly of linkers and functional groups to a given scaffold: application to the structure-based optimization of a phosphodiesterase 4 inhibitor. *J. Med. Chem.* **48**, 3816–3822 (2005)
FURTHER READING Rees. D. C. *et al.* Fragment-based lead discovery. *Nature Rev. Drug Discov.* **3**, 660–672 (2004)