IN BRIEF

EYE DISORDERS

Pegaptanib for neovascular age-related macular degeneration.

Gragoudas, E. S. *et al. N. Engl. J. Med.* **351**, 2805–2816 (2004).

Age-related macular degeneration (AMD) is a leading cause of severe vision loss in people older than 55 years of age in the developed world. Gragoudas *et al.* report the results of Phase III trials of pegaptanib, a modified RNA aptamer that binds to and blocks the activity of vascular endothelial growth factor. Pegaptanib was shown to be an effective treatment for neovascular AMD; on the basis of this and other data, it has recently become the first aptamer-based therapeutic to be approved by the FDA.

NEURODEGENERATIVE DISEASE

Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK.

Pedrini, S. *et al. PLoS Med.* **2**, e18 (2005).

Recent evidence suggests that statins, which are widely used as cholesterol-lowering drugs, might be associated with a decreased risk for Alzheimer's disease. The underlying mechanisms are poorly understood, but one idea is that statins modulate the metabolism of amyloid precursor protein, which has a key role in Alzheimer's disease. Pedrini and colleagues provide data that indicate that statins exert these effects by modulating the isoprenoid pathway and Rho-associated protein kinase 1 (ROCK1).

SCREENING

ALARM NMR: a rapid and robust experimental method to detect reactive false positives in biochemical screens.

Huth, J. R. *et al. J. Am. Chem. Soc.* **127**, 217–224 (2005).

Reactive compounds are a major source of costly and time-consuming false positives in high-throughput screening. To address this issue, Huth and colleagues have developed a rapid and reliable method based on nuclear magnetic resonance for identifying reactive compounds, which they show could significantly augment current *in silico* approaches.

INFECTIOUS DISEASES

IL-7 is a potent and proviral strain-specific inducer of latent HIV-1 cellular reservoirs of infected individuals on virally suppressive HAART.

Wang, F. X. *et al. J. Clin. Invest.* **115**, 128–137 (2005).

The persistence of HIV-1 in virally suppressed infected individuals being treated with highly active antiretroviral therapy (HAART) is a key problem in disease treatment. The addition of immune-activating agents has been proposed as a potential strategy to purge the pool of 'latently infected' cells. Wang *et al.* show that interleukin-7 upregulated the expression of HIV-1 in latently infected cells from HIV-1 patients on suppressive HAART more effectively than previous agents tested, and so might be a valuable component of novel immune-antiretroviral approaches.

STRUCTURE-BASED DRUG DESIGN

Seeking selectivity

The goal of designing isoform-selective phosphodiesterase (PDE) inhibitors with improved potency and fewer side effects has been brought one step closer following the recent publication of high-resolution crystal structures of PDEs bound to a selection of inhibitors. In a recent paper in *Structure*, Graeme Card *et al.* report that there are two conserved interactions involved in the binding of PDE inhibitors, and our understanding of these could prove valuable for the future rational design of PDE inhibitors.

PDEs affect the cellular levels of the cyclic nucleotides cAMP and cGMP, which are involved in many physiological processes such as immunity, cardiac- and smooth-muscle contraction, apoptosis, ion-channel conductance and growth control. Inhibiting these enzymes is therefore an attractive strategy in the development of smooth-muscle relaxants and drugs to treat inflammatory diseases, asthma, depression and many other diseases. In particular, there has been much interest in inhibiting the PDE4 and PDE5 isoforms. PDE4B is involved in inflammation and several inhibitors of this isoform are currently being tested in clinical trials for asthma and chronic obstructive pulmonary disease; the most famous PDE5 inhibitor drug, sildenafil (Viagra), is an effective treatment for erectile dysfunction.

However, PDE4 inhibitors cause nausea and emesis, possibly by inhibiting PDE4D in the brain, and sildenafil and related PDE5 inhibitors exhibit cross-reactivity with PDE6 and PDE11, which is thought to be responsible for side effects such as blue-tinged vision and back and muscle pain. Information about the binding mode of PDE inhibitors will therefore be crucial for the design of drugs that target these enzymes in a more selective manner.

The crystal structures of the catalytic domains of several PDEs have recently been made available. However, these structures do not shed light on the key interactions that define the common and selective features of the various inhibitors. In the new paper, Card *et al.* describe the co-crystal structures of PDE4B, PDE4D and PDE5A in complex with 10 known inhibitors. They reveal two common features of inhibitor binding: a planar ring structure of the inhibitor that is held in place within the enzyme active site by a pair of hydrophobic residues (a so-called hydrophobic clamp), and the formation of one or two hydrogen bonds between the inhibitor and an invariant purine-selective glutamine residue of the PDE active site.

These two features — together referred to as the Q site — define a common scaffold for PDE inhibitors. Furthermore, by looking at different inhibitors, the authors suggest that exploiting differences in the shape and hydrophobicity of the binding pockets near the invariant glutamine, and designing substituents to the inhibitor scaffold that have hydrophobic interactions with other elements of the catalytic domain, could improve both the selectivity and potency of the inhibitors.

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References and links

ORIGINAL RESEARCH PAPER Card, G. L. *et al.* Structural basis for the activity of drugs that inhibit phosphodiesterases. *Structure* **12**, 2233–2247 (2004)