ANTIBACTERIAL DRUGS

Tackling tuberculosis

The causative agent of tuberculosis (TB), *Mycobacterium tuberculosis*, has beset humans for thousands of years. Now, a new agent has been identified that might help in the battle against TB, as described in *Science* by Koen Andries and colleagues.

In the 1940s therapies emerged that led to a drastic reduction in TB incidence in the developed world. The success of these drugs created the impression that TB had been conquered, and, partly because of this, research into anti-TB drugs waned — the most recent novel treatment for TB is more than 30 years old.

However, today TB has a worldwide presence: roughly one-third of the world's population, mostly in poor countries, carry latent TB infections. And of these, 2–3 million die annually. HIV epidemics in many countries have led to the emergence of new waves of TB infection, because co-infection with HIV and *M. tuberculosis* makes latent TB more likely to develop into an active condition, often with fatal consequences. Efforts by the World Health Organization to reduce the incidence of TB have met with limited success, and so any further tool in the arsenal against TB would be welcome — particularly one that could combat the increasing problem of resistance to current anti-TB drugs.

Andries *et al.* report just such a development. The researchers have identified a diarylquinoline compound called R207910 that potently inhibits both drug-sensitive and drug-resistant strains of *M. tuberculosis*. Studies of mutant strains indicate that R207910 inhibits a new bacterial target, the bacterial ATP synthase, and R207910 therefore shows a lack of cross-resistance with current anti-TB drugs.

Studies with mice and humans reveal that R207910 is rapidly absorbed, and in mice has a greater bactericidal activity than the commonly used anti-TB drugs isoniazid and rifampin by at least 1 log. Human studies indicate that the drug is safe and tolerable, and at tolerable doses can reach concentrations greater than that which achieves optimal activity in established disease in mice.

One of the biggest problems with TB therapy at the moment is that patients have to take antibiotics for up to 9 months. As many patients feel better before this time, they prematurely stop their treatment, leaving pools of the most drug-resistant *M. tuberculosis* in their lungs. This contributes to the emergence of complete drug resistance in future patients. Because R207910 seems to act more quickly, patients might not need to stay on the drug so long, making it more likely for drug courses to be completed and reducing the likelihood of resistance developing. There is, however, still a long road of clinical development ahead before this drug can reach those who need it.

Daniel Jones

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LEAD OPTIMIZATION

Improving natural strength

A new and efficient method for genetically manipulating the chemical structure of natural products, a long-established source of drug leads, has been developed, and its success shown in the modification of a polyketide natural product that might provide the basis for the development of potent anticancer agents. This new method, which is described in *Chemistry and Biology*, addresses a major limitation of natural products as leads — the difficulty of incorporating synthetic modifications, owing to their complex structures — and thereby facilitates the optimization of their pharmacokinetic and pharmacodynamic properties.

Polyketides are a large family of natural products that are constructed from acyl-coenzyme A monomers. Geldanamycin is one such polyketide that targets the chaperone protein HSP90, which is overproduced in several types of human cancer. HSP90 chaperones immature kinases, which are important components of signal-transduction pathways, many of which are dysregulated in cancer cells. These immature kinases are rapidly degraded in the presence of geldanamycin, and the subsequent reduction in mature kinases can result in apoptosis and cell death. Geldanamycin might therefore provide an ideal starting point for the generation of anticancer agents to target this pathway.

Several synthetic geldanamycin analogues, including 17-AAG, which is currently undergoing clinical evaluation, have been produced by manipulating the chemically reactive groups of this natural product. However, the modification of the inert groups of this molecule, which might allow further optimization of its pharmacological properties, has until now not been explored.

Geldanamycin is made in *Streptomyces hygroscopicus* by polyketide synthases (PKSs), which are structured in a modular fashion. PKS modules catalyse the step-wise elongation of a polyketide chain, each module being responsible for the incorporation of one acyl group monomer in the final structure. Patel *et al.* developed three approaches (double crossover using bacterial conjugation, double crossover using phage, and gene complementation using bacterial conjugation) to manipulate the inert groups of geldanamycin-related molecules by substituting one of the catalytic

PSORIASIS

STAT3: new target

Signal transducer and activator of transcription 3 (STAT3), a protein involved in transmitting extracellular signals to the nucleus, is crucial to the development of the skin disease psoriasis, according to a study published in the January issue of *Nature Medicine*. Psoriasis is a common inflammatory skin disorder; however, whether its pathogenesis results from abnormal skin cells, keratinocytes or autoimmune responses has remained unclear, until now.

STAT proteins transmit signals from cytokines or growth factors that have cell-surface receptors associated with tyrosine kinase activity. Kinases, such as members of the Janus kinase family or SRC family, phosphorylate these receptors and provide docking sites for inactive STAT monomers, which are in turn phosphorylated and form activated dimers. Activated STATS move to the nucleus and are involved in regulating many genes that control fundamental biological process including apoptosis, cell proliferation and immune responses.

John DiGiovanni and colleagues report that keratinocytes in psoriatic lesions express STAT3. The authors generated a mouse model in which keratinocytes express large amounts of constitutively active STAT3. Within 2 weeks of birth, these mice developed a skin phenotype that closely resembles human psoriasis. Histological, immunochemical and gene-expression analyses revealed many features of psoriasis, including epidermal hyperplasia, increased keratinocyte replication, inflammatory cell infiltration within the dermis and epidermis, and increased expression of molecules such as VEGF, ICAM-1, TGF-α, cyclin D1 and IκB-α.

Blocking the function of STAT3 using antisense oligonucleotides inhibited the onset of, and reversed, established psoriatic lesions. Further analysis revealed a dual requirement for both activated STAT3 in keratinocytes as well as in T cells, indicating that the pathogenesis of psoriasis is rooted in a co-operative process involving STAT3-regulated genes in both skin cells and the immune system.

The results of this study indicate that inhibiting the activation of STAT3 could be beneficial in the treatment of psoriasis. Interestingly, constitutive activation of STAT3 has been observed in several tumours, and antagonising its expression induces apoptosis of cancer cells and inhibits angiogenesis.

Melanie Brazil

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domains — the acyl transferase domain — at several positions on the PKS modules with those that would lead to the incorporation of different acyl group monomers. This led to the efficient production of unique geldanamycin analogues that would be very difficult to produce through conventional chemical modification.

In developing this method, the authors generated a geldanamycin analogue, KOSN1559, which binds to HSP90 with a fourfold greater affinity than that of 17-AAG. This analogue also lacked the quinone moiety that is believed to lead to hepatotoxicity of 17-AAG. This work demonstrates the success of a method that could be used to develop more potent and safer analogues of geldanamycin with improved cellular uptake while maintaining the enhanced HSP90-binding affinity through chemical modification.

Alison Rowan

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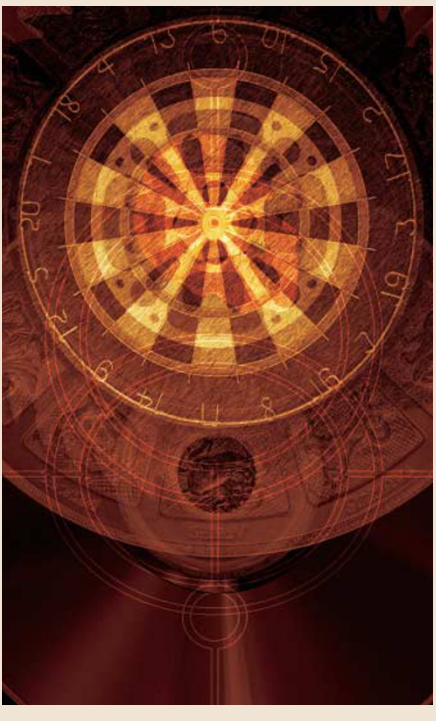

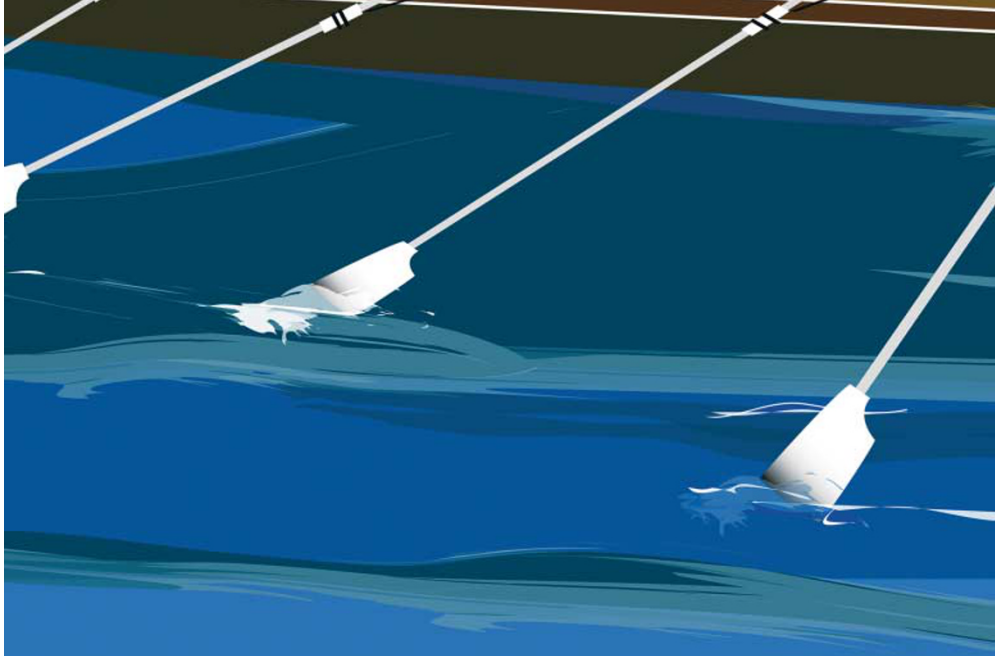

ANTIVIRAL DRUGS

Coordinated effort targets resistance

The story of the discovery of a promising new anti-HIV compound that could alleviate the problems of drug resistance has recently been reported in the *Journal of Medicinal Chemistry* in a paper from the late Paul Janssen and colleagues. The compound, which is a non-nucleoside inhibitor of the key HIV enzyme reverse transcriptase, is the culmination of more than a decade of research by investigators at Janssen Pharmaceutica, Tibotec, Johnson & Johnson Pharmaceutical R&D and Rutgers University.

The first non-nucleoside reverse transcriptase inhibitors (NNRTIs) were discovered in 1987 by screening the Janssen compound library. So far, three NNRTIs have been approved for clinical use: nevirapine, delavirdine and efavirenz. However, although antiviral regimes that include these drugs are initially very effective, resistance to the NNRTIs can emerge relatively easily compared with other anti-HIV drug classes, often through just a single mutation in reverse transcriptase.

The authors describe the discovery, under the guidance of Paul Janssen, of new NNRTIs that are not only highly active against wild-type HIV, but which also retain activity against mutant strains associated with resistance to NNRTIs. In parallel, they define several other criteria that are important for an ideal anti-HIV drug, including minimal adverse effects, ease of synthesis and formulation, and pharmacokinetic properties compatible with once-daily dosing, which is important for drug compliance.

Optimization of the original NNRTIs with the aid of molecular modelling and virological profiling led to the discovery of the diarylpyrimidine (DAPY) family of NNRTIs in the late 1990s, including the compounds TMC120 (dapivirine) and TMC125 (etravirine), which have shown promising results in Phase II trials. Analysis of crystal structures of various NNRTIs in complex with HIV reverse transcriptase, and further molecular modelling studies, identified possible interactions between the inhibitors and reverse transcriptase. Importantly, the newest DAPY derivative reported — known as R278474 or TMC278 (rilpivirine) — is thought to bind to a highly conserved residue in reverse transcriptase, reducing the likelihood of resistance evolving. Moreover, it seems that some additional flexibility in R278474 could further increase its resilience to mutations, as it could allow the compound to bind in multiple modes, in a sense attaining an effect comparable to several compounds binding in different modes used in combination.

Assessment of R278474 against the criteria specified for an ideal anti-HIV drug showed that it is more active against wild-type HIV-1 and all single and double mutants tested than approved NNRTIs, and virus 'breakthrough' occurred much less readily. Furthermore, R278474 has the desired pharmacokinetic properties for once-daily dosing, a satisfactory safety profile in animals, and can be easily synthesized and formulated, suggesting that it could become a valuable weapon in the battle against HIV.

Peter Kirkpatrick

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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.

Joanna Owens

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