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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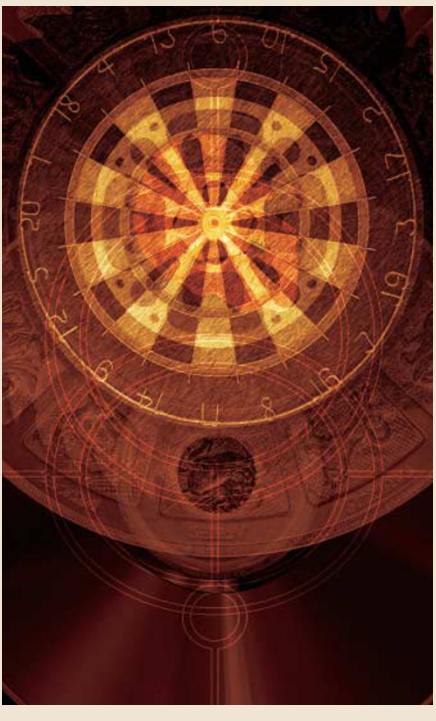

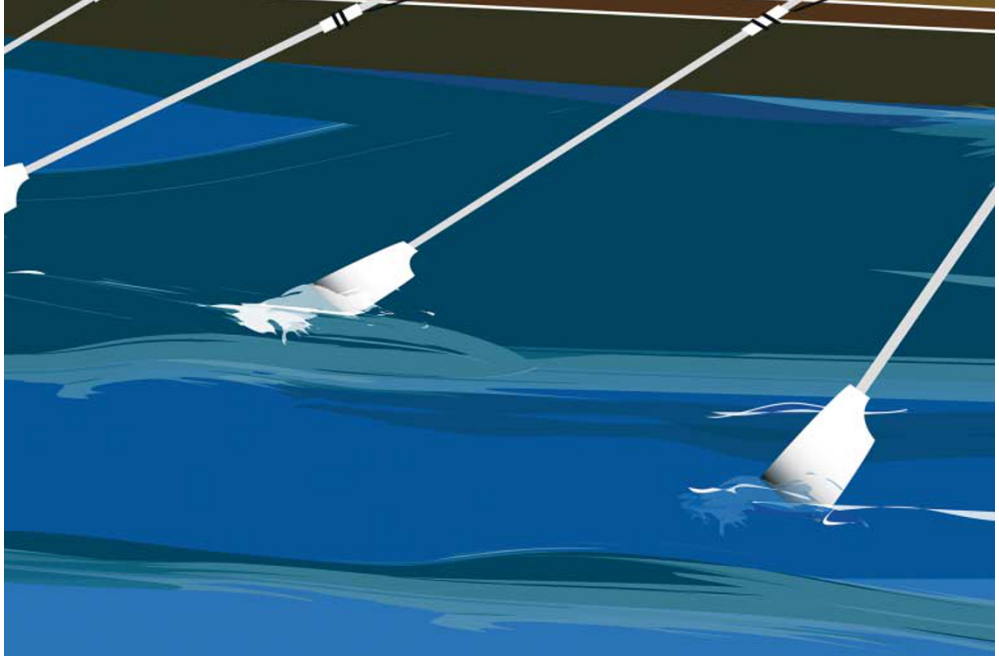

ANTIVIRAL DRUGS

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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