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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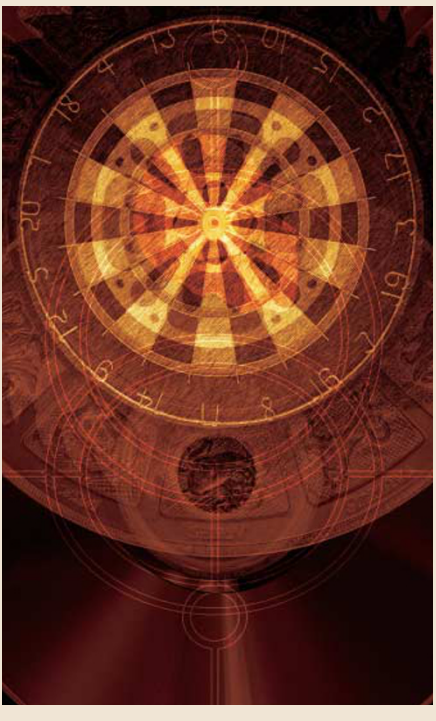

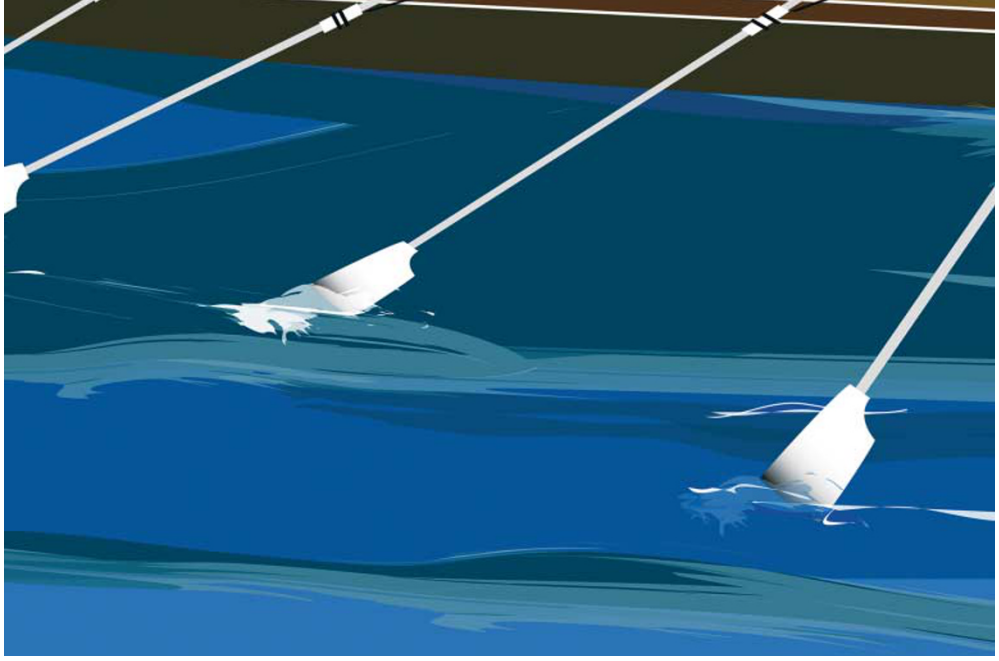

ANTIVIRAL DRUGS

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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