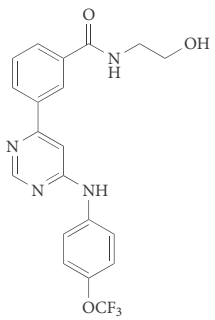
KINASE INHIBITORS

A winning combination against BCR–ABL

In chronic myelogenous leukaemia (CML), a reciprocal translocation between chromosomes 9 and 22 results in a gene encoding BCR–ABL, a fused deregulated kinase that stimulates cellular proliferation and mediates resistance to apoptosis. Although inhibitors directed against the ATP-binding site of the kinase, such as imatinib (Glivec/Gleevec; Novartis), lead to clinical remission in the early stage of the disease, most patients with advanced disease develop drug resistance associated with mutations in the ABL kinase domain. Reporting in *Nature*, Gray and colleagues identify and characterize a selective allosteric inhibitor of BCR–ABL, GNF-5, that cooperates with ATP competitive inhibitors to inhibit both wild-type and mutant forms of the kinase.



GNF-5

In 2006, the authors reported GNF-2 as a BCR–ABL inhibitor, and provided initial evidence that it binds to the autoregulatory myristate binding cleft of ABL, which is spatially distant from the ATP-binding site of ABL kinase. Using nuclear magnetic resonance spectroscopy and X-ray crystallography, they have now confirmed these findings, identifying the precise binding site of GNF-2 in the myristate cleft.

By selecting for *BCR–ABL* alleles that are resistant to GNF-2 *in vitro*, they also identified residues both within and outside the myristate cleft that are required for drug efficacy. It seems that mutations in the myristate cleft prevent GNF-2 binding, whereas non-myristate-site mutants probably prevent the enzyme from adopting its inhibited conformation.

The authors then found that combining GNF-2 with imatinib suppressed the emergence of resistance mutations *in vitro*. Using GNF-5, an *N*-hydroxyethyl carboxamide analogue of GNF-2 with similar inhibitory activity but with more favourable pharmacokinetic properties, they further investigated this cooperative effect. When GNF-5 was administered in combination with imatinib or the related compound nilotinib (Tasigna; Novartis), an additive inhibitory effect on BCR–ABL was observed *in vitro* and in a CML mouse model. Even in mice transplanted with bone-marrow cells bearing the BCR–ABL imatinib-resistant T315I mutation, administration of GNF-5 and nilotinib resulted in significant antitumour activity and improved survival compared with treatment with either agent alone.

Using hydrogen-exchange mass spectrometry, the authors were able to examine the mechanism underlying this cooperative effect. Their results suggest that GNF-5 binding at the myristate-binding site influences the conformation of the ATP-binding site and support further exploration of treatments that combine ATP and non-ATP competitive inhibitors in the treatment of diseases that are characterized by deregulated kinases.

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ORIGINAL RESEARCH PAPER Zhang, J. *et al.* Targeting Bcr–Abl by combining allosteric with ATP-binding-site inhibitors. *Nature* **463**, 501–506 (2010).

FURTHER READING Adrian, F. J. *et al.* Allosteric inhibitors of BCR–ABL-dependent cell proliferation. *Nature Chem. Biol.* **2**, 95–102 (2006) | Quintás-Cardama, A., Kantarjian, H. & Cortes, J. Flying under the radar: the new wave of BCR–ABL inhibitors. *Nature Rev. Drug Discov.* **6**, 834–848 (2007).