# IN BRIEF

ANTICANCER DRUGS

## Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.

Hurwitz, H. *et al. N. Engl. J. Med.* **350**, 2335–2342 (2004)

Bevacizumab is an antibody against vascular endothelial growth factor, a key regulator of normal and abnormal blood-vessel growth, which, in February this year, became the first agent designed to inhibit tumour angiogenesis to be approved by the FDA. This paper reports the results of a key Phase III trial that formed part of the basis for the approval of bevacizumab, which showed that adding bevaciuzmab to chemotherapy significantly improves survival among patients with previously untreated metastatic colorectal cancer.

LEAD IDENTIFICATION

## Integrating fragment assembly and biophysical methods in the chemical advancement of small-molecule antagonists of IL-2: an approach for inhibiting protein–protein interactions.

Raimundo, B. C. *et al. J. Med. Chem.* **47**, 3111–3130 (2004)

## Identification of a small molecule that inhibits herpes simplex virus DNA polymerase subunit interactions and viral replication.

Pilger, B. D., Cui, C. & Coen, D. M. *Chem. Biol.* **11**, 647–654 (2004)

Identifying inhibitors of protein–protein interactions has long been viewed as highly challenging, but significant progress has been made in this endeavour recently. In the first of these two papers, Raimundo and colleagues report a fragment-based approach to the discovery of a 60-nM inhibitor of the interaction of interleukin-2 (IL-2) and the IL-2 receptor, which is a therapeutic target for immune disorders. And in the second paper, Pilger *et al.* describe the development of a fluorescence-based high-throughput screen for inhibitors of an interaction between subunits of the herpes simplex virus DNA polymerase, and the identification of a small-molecule inhibitor that could provide a starting point for a new class of antiviral drugs.

IMAGING

## Imaging the pharmacodynamics of HER2 degradation in response to Hsp90 inhibitors.

Smith-Jones, P. S. *et al. Nature Biotechnol.* **22**, 701–706 (2004)

Many inhibitors of key signalling pathways involved in cancer are now in clinical trials, and a few have shown considerable success. However, in general, the clinical development of such agents has been hampered by the difficulty of assessing the effect of an agent on its target in patients. The authors of this paper describe a method for non-invasively imaging the pharmacodynamics of 17-allylaminogeldanamycin (17-AAG) — an Hsp90 inhibitor that is in Phase I trials as an anticancer agent — in mice, which could in principle be easily adapted for human use.

CARDIOVASCULAR DISEASE

# All roads lead to GSK-3β

**Many signalling pathways have been shown to mediate cardioprotection, but the identity of a master effector molecule at the end of these trails remains to be determined. Targets that endow cardioprotection would be extremely valuable because patients do not receive much advance notice of an impending heart attack! Now, research published in the *Journal of Clinical Investigation* shows that many cardioprotective drugs converge on the enzyme glycogen synthase kinase-3β (GSK-3β), indicating that the inhibition of this enzyme might be a good target to endow cardioprotection.**

**Our understanding of cardioprotection has been enhanced by studies of preconditioning (PC), the phenomenon in which brief intermittent periods of ischaemia (lack of oxygen) protect against a subsequent prolonged period without oxygen. A number of studies show that activation of mitochondria-regulated cell-death pathways at the start of reperfusion can reduce ischaemia/ reperfusion-related cell death. One of the outstanding issues in this field is how signalling cascades interact with mitochondrial components of cell death.**

**GSK-3β is involved in the control of glycogen metabolism and has key roles in regulating a wide range of cellular functions. Sollott and colleagues showed that PC and cardioprotective agents result in the phosphorylation and inhibition of mitochondrial GSK-3β, which leads to inhibition or delayed activation of the key regulators of apoptosis and, in particular, the mitochondrial permeability transition pore, which they identified as the end-effector of protection signalling. Furthermore, the authors demonstrated that mice possessing a constitutively active mutant form of the enzyme do not exhibit cardioprotection when treated with cardioprotective drugs or GSK-3β inhibitors.**

**In addition to its role in cardioprotection, GSK-3β is a target for diabetes and neurodegenerative disease, and there are a number of potent and specific inhibitors of the enzyme.**

*Melanie Brazil*

### References and links

**ORIGINAL RESEARCH PAPER** Juhaszova, M. *et al*. Glycogen synthase kinase-3β mediates convergence of protection signaling to inhibit the mitochondrial permeability transition pore. *J. Clin. Invest.* **113**, 1535–1549 (2004)

**FURTHER READING**

Cohen, P. & Goedert, M. GSK3 inhibitors: development and therapeutic potential. *Nature Rev. Drug Discov.* **3**, 479–487 (2004) | Vlahos, C. J., McDowell, S. A. & Clerk, A. Kinases as therapeutic targets for heart failure. *Nature Rev. Drug Discov.* **2**, 99–113 (2003) | Marks, A. R. & Wehrens, X. H. T. Novel therapeutic approaches for heart failure by normalizing calcium cycling. *Nature Rev. Drug Discov.* **3**, 565–573 (2004)