LEAD DISCOVERY

Guided by nature

Disappointment with the hit rates from combinatorial libraries produced during the 1990s has led to the proposal of a range of strategies aimed at improving the quality of libraries used for screening. One such strategy exploits the idea that the structures of natural products represent biologically validated starting points in chemical space from which to develop combinatorial libraries, because many natural products have evolved to bind to proteins. Writing in the *Journal of Medicinal Chemistry*, Waldmann and colleagues now provide a demonstration of this approach: the discovery of several novel inhibitors of receptor tyrosine kinases (RTKs) from a synthetic library based on the structure of the natural product nakijiquinone C.

Nakijiquinones are inhibitors of the ERBB2 (also known as HER2/neu) RTK, a member of the epidermal growth factor receptor (EGFR) family. So, working on the basis that nakijiquinones possess structural features that have evolved to promote binding to the kinase domain of RTKs, the authors set out to develop novel RTK inhibitors by synthesizing a library of 74 compounds related to nakijiquinone C. In particular, variations were introduced in parts of the nakijiquinone C structure that are thought to occupy less-conserved regions adjacent to the highly conserved ATP-binding site, as interactions with these less-conserved regions are likely to be important in determining activity against different RTKs.

The synthesized compounds were tested against several RTKs, including the vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, Tie-2, EGFR1, ERBB2 and insulin-like growth factor 1 receptor (IGFR1). A high hit rate was observed: seven of the 74 compounds showed inhibitory activity in the low-micromolar range against Tie-2, VEGFR2, VEGFR3 or IGFR1, with two being selective for Tie-2 alone.

These results show that natural inhibitors of particular proteins can be good starting points for the discovery of inhibitors of structurally related proteins. Further extensive molecular modelling studies provided insights into the structural basis of the activity of the identified compounds that should prove valuable in the development of inhibitors of Tie-2 and VEGFRs, which are of particular interest owing to the roles of these enzymes in tumour angiogenesis.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Kissau, L., Stahl, P., Mazitschek, R., Giannis, A. & Waldmann, H. Development of natural product-derived receptor tyrosine kinase inhibitors based on conservation of protein domain fold. *J. Med. Chem.* 2003 Jun 5 (DOI: 10.1021/jm0307943)

FURTHER READING Breinbauer, R., Vetter, I. R. & Waldmann, H. From protein domains to drug candidates — natural products as guiding principles in the design and synthesis of compound libraries. *Angew. Chem. Int. Ed.* **41**, 2878–2890 (2002)

IN BRIEF

INFLAMMATORY DISEASE

Impaired inflammatory and pain responses in mice lacking an inducible prostagladin E synthase.

Trebino, C. E. *et al. Proc. Natl Acad. Sci USA* 2003 Jun 30 (doi:10.1073/pnas.1332766100)

The anti-inflammatory effects of aspirin and related drugs — which block the production of prostaglandin H_2 (PGH_2), the common source of prostaglandins — are thought at least in part to be due to reduction in the levels of PGE_2. However, the loss of other PGs can result in side-effects such as ulceration. Here, mice lacking microsomal PGE synthase 1 (mPGES1), which synthesizes PGE_2 from PGH_2, were found to be healthy and fertile, but showed markedly reduced inflammatory responses, indicating that mPGES1 might be an attractive target .

ANTICANCER DRUGS

Regression of established tumors and metastases by potent vascular endothelial growth factor blockade.

Huang, J. *et al. Proc. Natl Acad. Sci USA* **100**, 7785–7790 (2003)

The key role of vascular endothelial growth factor (VEGF) in blood-vessel growth during tumorigenesis has led to the investigation of VEGF blockade as a strategy for impeding cancer progression. Using a soluble decoy receptor for VEGF, Huang *et al.* show that blockade of VEGF might not only halt tumour growth but also produce regression, and so might be effective in patients with bulky, metastatic cancers, as well as those with minimal residual disease.

CARDIOVASCULAR DISEASE

MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.

Heart Protection Study Collaborative Group. *Lancet* **361**, 2005–2016 (2003)

People with diabetes have a higher risk of cardiovascular events, but their plasma cholesterol concentrations are typically similar to those in the general population, and they do not usually receive cholesterol-lowering drugs, such as statins. This study reports that simvastatin reduced the rate of first major vascular events in a wide range of diabetic patients by about a quarter, indicating that statin therapy should be routinely considered in such cases.

ANTI-ALLERGIC DRUGS

SOCS-3 regulates onset and maintenance of T_H2-mediated allergic responses.

Seki, Y. *et al. Nature Med.* 2003 Jun 29 (doi:10.1038/nm896)

Members of the suppressor of cytokine signalling (SOCS) family are thought to alter the balance of cytokines regulating the onset of T_H1- and T_H2-mediated immune responses. The authors show that SOCS-3 expression correlates with the pathology of T_H2-mediated allergic immune diseases such as asthma, suggesting that it could be a new target for these conditions.