# **IN BRIEF**

#### MALARIA

Malaria-infected mice are cured by a single dose of novel artemisinin derivatives.

Posner, G. H. et al. J. Med. Chem. 50, 2516-2519 (2007)

There is a need for new low-cost effective therapies for drugresistant malaria. Posner and colleagues describe the curative activity of a new generation of plant-derived trioxane dimers that were easily prepared in four or five chemical steps. When given to malaria-infected mice, four of the trioxane dimers cured the mice after a single subcutaneous dose, and two other dimers cured after three oral doses. The use of these artemisinin-derived dimers provide an efficient and economical use of the natural product.

## **CANCER**

*MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling.

Engelman, J. A. et al. Science 316, 1039-1043 (2007)

Although the kinase inhibitor gefitinib is effective in cancer that has epidermal growth factor receptor (EGFR)-activating mutations, these tumours invariably develop drug resistance. Engelman and colleagues describe a gefitinib-sensitive lung-cancer cell line that developed resistance to gefitinib as a result of focal amplification of the MET kinase proto-oncogene, which led to the ERBB3-dependent activation of phosphatidylinositol 3 kinase. Inhibition of MET signalling restored gefitinib sensitivity. Thus, clinical combination of MET-kinase and EGFR-kinase inhibitors could be therapeutically beneficial.

## **OBESITY AND DIABETES**

Pharmacological inhibition of glucosylceramide synthase enhances insulin sensitivity.

Aerts, J. M. et al. Diabetes 56, 1341-1349 (2007)

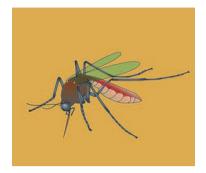
Ceramide and its metabolites are implicated in the pathogenesis of insulin resistance. Aerts and colleagues developed a specific small-molecule inhibitor of glucosylceramide synthase, an enzyme involved in the conversion of ceramide to glycosphingolipids. In rodent models of diabetes, treatment with the inhibitor normalized elevated levels of tissue glucosylceramide, lowered circulating glucose levels, improved oral glucose tolerance and improved insulin sensitivity in muscle and liver. These findings suggest that interference with glycosphingolipid biosynthesis might present an approach to the development of therapies for type 2 diabetes.

## AMYLOID DISEASES

Connecting TNF- $\alpha$  signaling pathways to iNOS expression in a mouse model of Alzheimer's disease: relevance for the behavioral and synaptic deficits induced by amyloid  $\beta$  protein.

Medeiros, R. et al. J. Neurosci. 27, 5394-5404 (2007)

Increased brain deposition of amyloid  $\beta$  protein (A $\beta$ ) and cognitive deficits are characteristic markers of Alzheimer's disease (AD) that are associated with inflammatory alterations. In a mouse model of AD, Medeiros and colleagues determined a link between tumour-necrosis factor (TNF), a neuroinflammatory cytokine, and inducible nitric oxide synthase (iNOS), a molecule involved in oxidative-stress pathways. Blockade of either TNF or iNOS reduced cognitive deficits. These results suggest that TNF and iNOS are central mediators of  $A\beta$  action, and might be a target for AD drug discovery.



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