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IN BRIEF

CANCER

Understanding resistance to antiangiogenic agents

The molecular mechanisms by which tumours acquire resistance to antiangiogenic therapies — such as small-molecule receptor tyrosine kinase inhibitors (RTKIs) — remain poorly understood. Here, applying global transcriptomic, proteomic and metabolomic approaches to preclinical cancer models, the authors provide mechanistic insights into how tumours adapt their metabolism to antiangiogenic therapy. Following RTKI treatment withdrawal, tumours undergo a metabolic shift from a glycolytic phenotype towards lipid metabolism and increased TCA activity, which is associated with rapid tumour regrowth and accelerated metastatic dissemination. Inhibition of fatty acid synthase reversed this malignant adaptation and prevented tumour relapse, which may have clinical implications.

ORIGINAL RESEARCH PAPER Sounni, N. E. *et al.* Blocking lipid synthesis overcomes tumor regrowth and metastasis after antiangiogenic therapy withdrawal. *Cell Metabol.* **20**, 280–294 (2014)

TRANSPLANTATION

Hydrogel safely delivers immunosuppressant

Widespread clinical use of vascularized composite allotransplantation (VCA) is hindered by the side effects of systemic immunosuppressive drugs, such as tacrolimus. Gajanayake *et al.* loaded tacrolimus into an injectable self-assembled hydrogel, which releases the drug in response to proteolytic enzymes that are overexpressed during inflammation. A single injection of the hydrogel into a rat hindlimb transplantation model significantly prolonged graft survival and reduced the immune response, compared to tacrolimus only-treated recipients.

ORIGINAL RESEARCH PAPER Gajanayake, T. *et al.* A single localized dose of enzyme-responsive hydrogel improves long-term survival of a vascularized composite allograft. *Sci. Transl. Med.* **6**, 249ra110 (2014)

PSYCHIATRIC DISORDERS

Enzyme inhibitor improves cognitive function

Chronic increases in brain levels of kynurenic acid (KYNA) in schizophrenia patients are thought to contribute to impaired cognitive function. Here, the authors identify PF-04859989, the first brain-penetrable inhibitor of kynurenine aminotransferase II (KAT II) — the enzyme responsible for brain KYNA synthesis — and demonstrate it to improve cognitive performance under schizophrenic conditions. In rats, systemic PF-04859989 reduced brain KYNA to 28% of basal levels, and prevented amphetamine- and ketamine-induced disruption of auditory gating. The KAT II inhibitor also prevented ketamine-induced impairment of attentional and working memory processes in rodents and non-human primates, respectively.

ORIGINAL RESEARCH PAPER Kozak, R. *et al.* Reduction of brain kynurenic acid improves cognitive function. *J. Neuroscience* **34**, 10592–10602 (2014)

DRUG DESIGN

Guidelines for macrocycle drug design

Synthetic macrocycles (MCs) have received significant attention for their potential as drugs, largely due to their proposed utility against traditionally difficult targets. Now, Villar *et al.* identify and examine a representative set of MC–protein complexes for which co-crystal structures have been reported, to establish key characteristics of their binding modes. They propose guidelines for designing synthetic MC libraries with favourable structural and physicochemical features for binding to protein targets and for good bioavailability.

ORIGINAL RESEARCH PAPER Villar, E. A. *et al.* How proteins bind macrocycles. *Nature Chem. Biol.* **10**, 723–731 (2014)