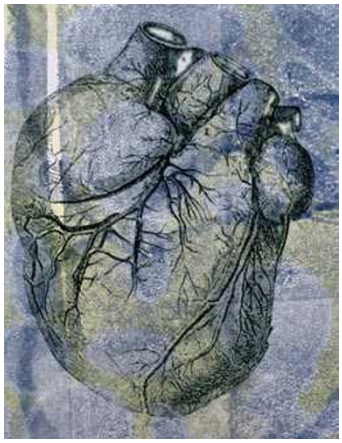
IN BRIEF



LEAD IDENTIFICATION

Sodium late current blockers in ischemia reperfusion: is the bullet magic?

Le Grande, B. *et al. J. Med. Chem.* **51**, 3856–3866 (2008)

In ischaemic myocardia, the late sodium current is a main source of sodium, which is a driving force for calcium overload that contributes to cell damage and death. Le Grand and colleagues describe the discovery of the first selective, potent and voltage-dependent inhibitor of the late sodium current mediated by the cardiac sodium channel $Na_v1.5$. In an animal model, the compound had potent anti-ischaemic activity that was not associated with any haemodynamic changes. The unique pharmacological profile of this inhibitor suggests new opportunities for the treatment of ischaemic heart diseases.

BIOTECHNOLOGY

Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index.

Junutula, J. R. *et al. Nature Biotech.* **26**, 925–932 (2008)

To limit the potential toxicity associated with conventional drug conjugation strategies, Junutula and colleagues developed a new drug–antibody conjugation strategy using site-specific engineered reactive cysteine residues. A conjugated antibody against an ovarian cancer antigen was efficacious in xenograft models and was tolerated at higher doses than the same conjugate prepared by conventional approaches. So, this strategy offers a general approach to retaining the antitumour efficacy of antibody–drug conjugates while minimizing their systemic toxicity.

NEUROLOGICAL DISORDERS

Small-molecule protein tyrosine phosphatase inhibition as a neuroprotective treatment after spinal cord injury in adult rats.

Nakashima, S. *et al. J. Neurosci.* **28**, 7293–7303 (2008)

Spinal-cord injury causes progressive secondary tissue degeneration, leaving many individuals with neurological disabilities. Because protein tyrosine phosphatases (PTPs) inactivate neurotrophic factor receptors, Nakashima and colleagues studied the neuroprotective activity of a PTP inhibitor — bpV(phen) — in a rat model of spinal-cord injury. Intrathecal infusions, including those started 4 hours after contusion, rescued dorsal column sensory axons at the injury epicenter, greatly improved sensorimotor function and provided complete axonal protection over 6 weeks.

RNA INTERFERENCE

Coexpression of Argonaute-2 enhances RNA interference toward perfect match binding sites.

Diederichs, S. *et al. Proc. Natl Acad. Sci. USA* **105**, 9284–9289 (2008)

RNAi is widely used to inhibit expression of specific genes, but it is limited by variable efficiency and specificity of empirically designed siRNA or shRNA constructs. Diederichs and colleagues showed that ectopic expression of the RISC slicer Argonaute-2 enhanced RNAi specifically for mRNA targets with perfectly matched binding sites. Co-expression of Argonaute-2 with shRNA targeting the EGF receptor in lung cancer cells resulted in uniform and highly specific gene suppression. This technique provides a strategy to enhance RNAi efficacy and specificity in experimental and potentially therapeutic settings.