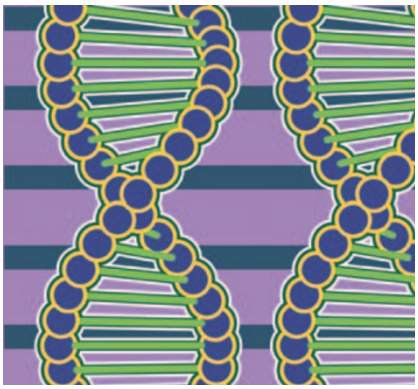
IN BRIEF



DRUG DELIVERY

Efficient gene delivery to pancreatic islets with ultrasonic microbubble destruction technology.

Chen, S. *et al. Proc. Natl Acad. Sci. USA* **103**, 8469–8474 (2006)

One strategy against diabetes is to deliver genes to pancreatic islets that enhance insulin secretion, but most approaches to do this result in variable expression, require invasive techniques or generate an inflammatory reaction. Chen and colleagues report a novel technique that uses gas-filled phospholipid microbubbles containing plasmid DNA, which are then infused into rats and destroyed within the pancreatic microcirculation using ultrasound. Using this method, it was possible to deliver a plasmid containing the rat insulin 1 promoter (RIP) fused to either human insulin or human hexokinase, both of which were able to decrease blood glucose levels.

PARKINSON'S DISEASE

RGS4-dependent attenuation of M_4 autoreceptor function in striatal cholinergic interneurons following dopamine depletion.

Ding, J. *et al. Nature Neurosci.* **9**, 832–842 (2006)

The motor symptoms associated with Parkinson's disease result from reduced striatal dopamine levels, which causes striatal acetylcholine to rise. This was previously thought to be caused by a loss of interneuronal regulation by inhibitory D_2 dopamine receptors. Now, Ding *et al.* challenge that hypothesis with the finding that the increase in acetylcholine is mediated by the M_4 muscarinic autoreceptor. They show that this adaptation results from the selective upregulation of RGS4 — a GTPase accelerator — which attenuates autoreceptor signalling.

ANTIINFECTIVES

Coexpression of virulence and fosfomycin susceptibility in *Listeria*: molecular basis of an antimicrobial *in vitro–in vivo* paradox.

Scortti, M. *et al. Nature Med.* **12**, 515–517 (2006)

Resistance to an antibiotic in *in vitro* susceptibility tests can sometimes be at odds with a successful treatment outcome in the clinic — known as the *in vitro–in vivo* paradox. Scortti *et al.* provide the first mechanistic explanation of this paradox. They identified a virulence factor in *Listeria monocytogenes*, Hpt, that is expressed *in vivo* and is responsible for uptake of fosfomycin into the bacterial cell. The absence of Hpt *in vitro* explains the resistance of *L. monocytogenes* to fosfomycin in susceptibility tests and highlights the need for *in vivo* confirmation of *in vitro* data.

KINASE INHIBITORS

Selective kinase inhibition by exploiting differential pathway sensitivity.

Kung, C. *et al. Chem. Biol.* **13**, 399–407 (2006)

Selective kinase inhibition is a desirable property of many drug candidates but can be challenging to achieve for kinases within the same subfamily. Kung *et al.* provide evidence to show that kinases differ in their intrinsic sensitivity to inhibitors. They used two cyclin dependent kinases — CDK1 and PHO85 — which have distinct functions and found that an oxindole inhibitor is more selective for the PHO85 than the CDK1 pathway. This suggests that hypersensitive kinases might exist that could be promising therapeutic targets for selective modulation of kinase pathways.