IN BRIEF

GENE SILENCING

Effective RNAi-mediated gene silencing without interruption of the endogenous microRNA pathway.

John, M. *et al. Nature* **449**, 745–747 (2007)

Gene silencing using short hairpin RNA in mice results in toxicity due to saturation of the cellular microRNA (miRNA) pathway, but it is not known whether administration of other inhibitory RNAs also produces adverse effects. John and colleagues show that systemic administration of synthetic small interfering RNA (siRNA) produced efficient (~80%), long-term gene silencing in rodent liver without any effect on miRNA activity. This study demonstrates siRNAs as safe and effective tools for gene silencing and supports the advancement of siRNA therapeutics.

DOI:
10.1038/nrd2475

HYPERLIPIDAEMIC DISEASE

Targeting thyroid hormone receptor- β agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index.

Erion M. D. *et al. Proc. Natl Acad. Sci. USA* **104**, 15490–15495 (2007)

The therapeutic potential of thyroid hormone receptor (TR) agonists as lipid-lowering agents remains unexplored because of dose-limiting side effects. Erion and colleagues describe a cytochrome P450-activated prodrug of a phosphonate-containing TR agonist that exhibits increased TR activation in the liver. The compound was cardiac sparing in normal rats and reduced cholesterol and triglycerides in diet-induced obese mice at doses devoid of effects on body mass, glycaemia and the thyroid hormone axis. These results indicate that targeting TR agonists to the liver has the potential to lower cholesterol and triglyceride levels with an acceptable safety profile.

NEURODEGENERATIVE DISEASE

Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins.

Ray, S. *et al. Nature Med.* **13**, 1359–1362 (2007)

Early detection of Alzheimer's disease could lead to better treatment and therapies. Ray and colleagues found 18 signalling proteins in blood plasma that could be used to classify blinded samples from subjects with Alzheimer's with almost 90% accuracy, and could also identify patients who had mild cognitive impairment that progressed to Alzheimer's disease 2–6 years later. Biological analysis of the 18 proteins suggested that systemic dysregulation of haematopoiesis, immune responses, apoptosis and neuronal support occurs in presymptomatic Alzheimer's disease.

BIOTECHNOLOGY

Simultaneous targeting of multiple disease mediators by a dual-variable-domain immunoglobulin.

Wu, C. *et al. Nature Biotech.* **25**, 1290–1297 (2007)

For complex multifactorial diseases, simultaneous blockade of multiple targets may yield better therapeutic efficacy than inhibition of a single target. Wu and colleagues describe a dual-specific, tetravalent immunoglobulin G-like molecule — termed dual-variable-domain immunoglobulin (DVD-Ig) — that could be engineered from any two monoclonal antibodies while preserving activities of the parental antibodies. DVD-Igs exhibited good physicochemical and pharmacokinetic properties, and in a mouse model of arthritis a DVD-Ig inhibited the progression of the disease.