News in brief

Targets and mechanisms

Fatbusters

A cellular mechanism that regulates the formation of fat cells has been identified by researchers at the Department of Radiation Oncology (Stanford University, Stanford, CA, USA) and could provide a new target for therapies against obesity and diabetes [1]. The team, led by Amato Giaccia, examined the effect of low oxygen (hypoxia) on the generation of fat cells in mice. The rationale behind the study was that training at high altitude has been observed to enhance the reduction of body fat.

According to the Centers for Disease Control and Prevention (http://www.cdc.gov), 61% of adults in the USA are clinically obese and, therefore, are at an increased risk of developing serious illnesses, such as diabetes, stroke, heart disease or cancer.

The Stanford scientists used mouse cells that could be stimulated to become fat cells by treatment with certain hormones, and compared cells maintained in hypoxic conditions with those in normal oxygen: low oxygen levels were found to inhibit the development of fat cells. The study showed that the cells that failed to develop into fat cells had the protein HIF-1 (hypoxia-inducible factor-1) present, and also found that the *PPARγ* gene, known to be crucial for the development of fat cells, was inhibited by hypoxia.

The researchers postulate that the HIF-1-regulated gene, *DEC1/Stra1*, represses *PPARγ* promoter activation and affects the inhibition of adipogenesis, mediated by hypoxia. Therefore, agents that are involved in the regulation of HIF-1 activity or oxygen sensing could be used in the control of obesity. 'Our study provides a different perspective on fat cell development in a simplified system,' said Giaccia. 'Nevertheless, our findings suggest a new approach for regulating fat cell generation, which could potentially be beneficial to the development of therapies for obesity and/or diabetes.'

1 Yun, Z. *et al.* (2002) Inhibition of PPARγ2 gene expression by the HIF-1-regulated gene *DEC1/Stra13*. A mechanism for regulation of adipogenesis by hypoxia. *Dev. Cell* 2, 331–341

Sleeping Beauty transposes germline

Researchers at the University of Minnesota (MN, USA) have developed a new, simple and effective way of generating large numbers of genetically modified vertebrates [2], using the Sleeping Beauty transposon system. This system has several advantages over the current method of retroviral infection.

Germline transgenesis can be used to introduce new traits into animals and to evaluate gene function *in vivo*. In lower organisms, transposable elements have been used successfully for insertional mutagenesis. The Sleeping Beauty system enables the introduction of multiple single-copy transposons into chromosomes and is active in a number of vertebrate cells, including humans, and also has the potential for gene delivery in multiple settings.

One-cell mouse embryos were injected with the Sleeping Beauty transposase (SB10) mRNA and the linear transposon vector containing the gene for yellow coat colour, *agouti*. SB10 mediates the transposition of the transposon containing the single-copy *agouti* gene into the mouse chromosome. Evidence of transposition at many sites was obtained by cloning of insertional sites from the multiple transgenic mice produced.

Sleeping Beauty transposons inserted into the mouse genome at TA dinucleotides, but no particular sequences adjacent to TA sites seem to favour insertion. Thus, a large number of TA sites could represent transposon insertion sites – unlike current retroviral infection methods, where the virus cannot integrate into 'cold' sites and prefers 5′ regions.

The potential uses for this technique are diverse: genetically altered farm animals could be created and used as a source for organs, for example. 'One use would be to add genes to germ cells or early embryos in order to produce large amounts of a protein in an animal,' said David Largaespada, Assistant Professor in the University of Minnesota's department of genetics, cell biology and development, and Director of the Universty of Minnesota Cancer Center's Genetic Mechanisms of Cancer research program. 'We… are also working on transferring genes directly into cells of the body, in the liver or lungs,' he continued. 'We hope this procedure could help cure diseases such as cystic fibrosis and hemophilia.'

2 Dupuy, A.J. *et al.* (2002) Mammalian germline transgenesis by transposition. *Proc. Natl. Acad. Sci. U. S. A.* 99, 4495–4499

Soya diet reduces inflammation in rats

New research presented at the *American Pain Society Annual Meeting* in Baltimore (MD, USA) in March 2002 could lead the way to the development of a diet-based treatment for people suffering from inflammatory pain.

The Johns Hopkins researchers fed two groups of rats a different diet each, one based on soya protein and one based on the milk protein casein, for two weeks. The rats were injected at random with either placebo or a compound that induced inflammatory pain in the hind paws. When tested with a painful heat stimulus, those rats on a soya-based diet showed a higher tolerance to the heat and significantly less swelling in their hind paws compared with those rats on a casein-based diet. When the rats were exposed to varying pressures on their paws using nylon threads, there was no difference in the reactions between the two groups.

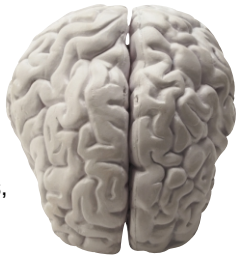
The results suggest that such an alternative and complementary treatment could be developed to help people who suffer from pain, especially those with cancer, when the pain can result from a combination of tissue inflammation and infiltration, and neuropathic pain. Opioids are the most effective medications used to date for inflammatory pain, but these can cause severe side effects, and some patients are unable to tolerate them. 'Our generation is very open to the idea of dietary methods of pain control', says Jill M. Tall, lead author of the study.

1359-6446/02/$ – see front matter PII: S1359-6446(02)02306-1

Future research will determine whether a soya-based diet could be used to reduce the opioid dosage, thus bringing further relief to sufferers of chronic pain.

CNS-related disorders

About turn for AD treatment



Researchers have found that an enzyme that was previously thought to be detrimental to the health of Alzheimer's patients, could in fact be crucial to its future treatment [3].

The study, conducted at the Division of Neurology, Department of Medicine at the University of Alberta (Canada) applied the enzyme galanin to acutely dissociated rat neurons from the basal forebrain, and found that it caused a decrease in whole-cell voltage-activated currents in the majority of cells.

Galanin, which is associated with learning and memory and is involved in brain function and some brain disorders, such as epilepsy, was previously considered to be an inhibitory neuromodulator: when the onset of Alzheimer's disease (AD) occurs, galanin hyperinnervates nerve cells, which depresses acetylcholine (ACh) release and its inhibitor actions at other CNS sites. This is generally accepted as being detrimental; however, this new research suggests that galanin, because of its excitory actions on cholinergic neurons, could have a compensatory role by enhancing ACh release from remaining basal forebrain neurons. This implies that inducing galanin production, for example by nerve growth factor, could have a neuroprotective effect.

The study used dissociated rat cholinergic basal forebrain neurons from the nucleus of the diagonal band of Broca (DBB) using a combination of patch-clamp techniques and RT-PCR. Results show that activation of galanin receptors results in membrane depolarization and an increase in the excitability of basal forebrain neurons and that these actions are specific to cholinergic and not GABAergic neurons.

Two alternative theories have been supplied. The increased galanin innervation of cholinergic neurons could have a role in worsening cognitive function in AD patients. However, this recent study suggests that galanin overexpression could have a compensatory role by enhancing the release of ACh from the remaining basal forebrain neurons.

3 Jhamandas, J. *et al.* (2002) Novel excitatory actions of galanin on rat cholinergic basal forebrain neurons: implications for its role in Alzheimer's disease. *J. Neurophysiol.* 87, 696–704

Potential MS treatment

Scientists have reported the identification of the blood clotting factor fibrin as being crucial in the regulation of the myelin sheath following injury, which could lead to treatment for disorders such as multiple sclerosis (MS) [4]. The team, at the Laboratory of Neurobiology and Genetics at the Rockefeller University (New York, NY, USA), showed that deposition of fibrin in the peripheral nervous system, following injury, is a key regulator of remyelination.

MS is caused by damage to the myelin sheath, which leads to the loss of muscle control that is a characteristic of MS. Under normal circumstances, the myelin sheath is capable of regenerating following damage, but this capacity is regulated by factors made by the nerve and surrounding cells.

The team, led by Sidney Strickland, studied nerve regeneration in mice that lack fibrin. These mice regenerated crushed nerves significantly faster than mice with fibrin. This was found to be possible because fibrin usually has a key role in keeping sheath cells in an immature state where they are incapable of regenerating the complete myelin sheath. Fibrin induces phosphorylation of ERK1/2 and the production of p75 nerve growth factor low-affinity receptor in Schwann cells, thus maintaining them in a nonmyelinating state; this suppresses fibronectin production and prevents myelin protein synthesis.

These results point towards a potential new treatment for nerve injuries and suggest that preventing the deposition of fibrin could enhance the capabilities of the nervous system for natural regeneration.

4 Akassaglou, K. *et al.* (2002) Fibrin inhibits peripheral nerve remyelination by regulating Schwann cell differentiation. *Neuron* 33, 861–875

Link between AD and Down's syndrome

Researchers have determined that the deposition of protein in the brain of Alzheimer's disease (AD) patients is the same as the deposits found in Down's syndrome [5]. A recent study, conducted at the Department of Neuroscience at the University of Connecticut Health Center (Farmington, CT, USA), showed that prevention of the correct function of mitochondria in normal human brain cells led them to display the characteristic alteration of AD.

There has always been a suspected link between AD and Down's syndrome; people with Down's syndrome typically develop AD by middle-age when their brains often display the deposits that are characteristic of AD. Down's syndrome sufferers inherit an extra copy of chromosome 21; the gene for one of the proteins, APP, which deposits the characteristic plaques of AD, are on this chromosome and mutations in this gene are associated with early-onset AD. Having an extra copy of APP, or a mutation therein, leads to impaired mitochondrial function.

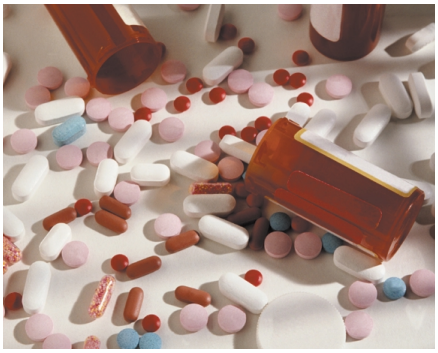
Jorge Busciglio, lead author of the study, said: 'In light of these findings, future therapies for AD or Down's syndrome should seek to restore the normal function of mitochondria.' It could be that restoring the normal function of mitochondria will protect neurons and reduce the cognitive decline caused by AD.

5 Busciglio, J. *et al.* (2002) Altered metabolism of the amyloid β precursor protein is associated with mitochondrial dysfunction in Down's syndrome. *Neuron* 33, 677–688

Cancer targets and mechanisms

Popping NSAIDs protects your prostate

Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) could protect against prostate cancer, according to a recent study [6]. A population-based study, performed by scientists at the Department of Health Sciences Research at the Mayo Clinic (Rochester, MN, USA), found that men aged 60 years or over who used NSAIDs daily reduced their risk of



prostate cancer by almost 60%, and the beneficial effect is thought to increase with age.

The study tracked 1362 Caucasian men for an average of 5.5 years, and 4% of the men taking a daily dose of NSAIDs developed prostate cancer compared with 9% of men who were not taking the drugs. Although these results might be good news for men, Rosebud Roberts, lead researcher on the study, is cautious: 'Although our results provide important information that NSAIDs may protect against prostate cancer, they are not conclusive. More research needs to be done to show that the results we saw in our study…can be confirmed in similar studies.'

The group also needs to find out the optimum dose for this protection, whether this effect is the same for all races, and what the likely mechanism for this protective effect is.

These findings correlate with previous studies that NSAIDs offer protection against breast and colon cancers, but Roberts says that the accompanying negative side-effects of the drugs would have to be carefully monitored and considered in people who take them on a daily basis.

6 Roberts, R.O. *et al.* (2002) A population-based study of daily non-steroidal anti-inflammatory drug use and prostate cancer. *Mayo Clin. Proc.* 77, 219–225

Prostaglandin E_2 and EGFR linked to colon cancer

Prostaglandin E_2 (PGE_2) has been shown to activate epidermal growth factor receptor (EGFR) and trigger a signalling cascade that causes cell growth in gastric epithelial and colon cancer cell lines [7].

The well known role of prostaglandins in the growth of colon polyps and cancer, and the increased expression of EGFR observed in many tumours, prompted researchers at the University of California, Irvine (UCI; CA, USA) and the Department of Veterans Affairs Medical Center (Long Beach, CA, USA) to investigate whether prostaglandins can activate EGFR. They found that PGE_2 causes rapid phosphorylation of EGFR which, in turn, activates the mitogen-activated protein kinase pathway.

Inactivation of EGFR kinase with specific inhibitors significantly reduced PGE_2-mediated induction of the MAPK pathway, c-fos mRNA expression and cell proliferation. Furthermore, inhibition of matrix metalloproteinases (MMPs), transforming growth factor-α (TGF-α) or c-Src blocked PGE_2-induced EGFR activation, suggesting that PGE_2 acts on EGFR via its ligand, TGF-α, which is released by Src-activated MMPs.

Prostaglandins are produced by the COX-2 enzyme, which is highly expressed in colon cancer cells compared with non-cancerous cells. These results suggest that blocking EGFR and preventing the action of prostaglandins could be a strategy for treating colon cancer.

7 Pai, R. *et al.* (2002) Prostaglandin E_2 transactivates EGF receptor: a novel mechanism for promoting colon cancer and gastrointestinal hypertrophy. *Nat. Med.* 8, 289–293

Miscellaneous

University of Iowa names college after benefactor

The University of Iowa (IA, USA) has named its medical school the Roy J. and Lucille A. Carver College of Medicine in recognition of US$63 million recently donated to the College by the late Roy J. Carver, his widow Lucille A. Carver and the Roy J. Carver Charitable Trust (Muscatine, IA, USA).

University President Mary Sue Coleman expressed her gratitude to the family. 'They have been extremely supportive of the University of Iowa. We are honoring the Carvers' faith in, and commitment to, our university,' she said.

The US$63 million, which will be provided over 15 years, will be used to fund new research programs, a new biomedical research building, to renovate existing facilities and to establish research-related faculty endowments associated with specific department or division headships and professorships within the college.

Development halted after antibody fails to treat psoriasis

Protein Design Labs (Fremont, CA, USA) has halted development of Zenepaz (daclizumab), a humanized antibody, after preliminary results from Phase II clinical trials showed that it did not prolong the time to recurrence of psoriasis. The randomized, double-blind, placebo-controlled clinical trial assessed 127 patients from 12 centres in the USA and Canada with moderate-to-severe psoriasis who had experienced remission of their symptoms when treated with cyclosporin. These patients were randomized to receive either five doses of 1mg kg^{-1} daclizumab or a placebo.

However, daclizumab, which affects the α-chain of the human interleukin IL-2 receptor (CD25), will continue to be tested in trials against asthma, multiple sclerosis, type 1 diabetes and uveitis.

Cell Genesys discontinues collaboration with GPC Biotech AG

Cell Genesys (Foster City, CA, USA) has given notice that it is discontinuing its research collaboration and licence agreement with GPC Biotech for the p27/p16 gene therapy for cancer and cardiovascular disease. The company has decided that gene therapy for cardiovascular diseases such as restenosis is a less compelling opportunity in light of the success of other new treatment strategies, such as drug-coated stents.

'Cell Genesys is in the fortunate position to have multiple clinical and preclinincal product candidates in the cancer area,' said Joseph P. Vallner, President and Chief Operating Officer of Cell Genesys. 'While we achieved positive results... our other programs including oncolytic viruses and antiangiogenesis gene therapy will receive a higher priority... based on the strength of the preclinical data,' he said.

News in Brief was written by *Joanne Clough*, *Lisa Deakin*, *Joanna Owens*, *Ben Ramster* and *Linsey Stapley*