Box 1. Currently available anti-obesity drugs

Centrally acting appetite suppressants

Phentermine increases the release of noradrenaline. Because of its stimulant action, it has addictive potential and is only recommended for short-term use of less than three months. Although the drug is still available in the USA, it has been withdrawn from European markets because of concerns that its use could lead to valvular heart disease and pulmonary hypertension.

Sibutramine inhibits the re-uptake of serotonin and noradrenaline, thereby prolonging the effect of these appetite-regulating neurotransmitters. It does not seem to have amphetamine-like abuse potential and has been licensed for the long-term treatment of obesity. However, if patients are already being treated with other psychotropic drugs, there are risks of drug interactions and compliance problems.

Drugs inhibiting nutrient and calorie absorption

Orlistat inhibits the pancreatic lipase, which results in decreased fat absorption. The drug can have serious gastrointestinal side effects, such as steatorrhea (excessive fat in the stools), if taken with fatty foods. Because there is insufficient experience with the long-term use of orlistat, the drug is only licensed for use for up to two years.

Future studies

Susan Jebb at the MRC (Medical Research Council) Human Nutrition Research centre in Cambridge, UK, acts as an independent consultant advising Phytopharm on how to design the dietary aspects of their clinical studies. She agrees that the results of the proof-of-principle study are very encouraging. However, she stresses that it is early days. 'The studies they have done so far are only up to two weeks long. Now, they have to do longer studies in more people to demonstrate that this is a consistent effect. Obesity is a chronic relapsing problem and you need a treatment that is going to work safely and effectively over much longer periods of time.'

Dixey says their next step will be to take a closer look at the dosing interval and other pharmacodynamic parameters. 'In parallel with that, we have a large semi-synthetic programme with other active molecules and we are doing a lot of work on the mode of action'. Phytopharm are hoping to have a drug on the market by 2006.

References

1 Froguel, P. and Boutin, P.(2001) Genetics of pathways regulating body weight in the development of obesity in humans. *Exp. Biol. Med.* 226, 991–996

2 Astrup, A. (2001) Healthy lifestyles in Europe: prevention of obesity and type 2 diabetes by diet and physical activity. *Public Health Nutr.* 4, 499–515

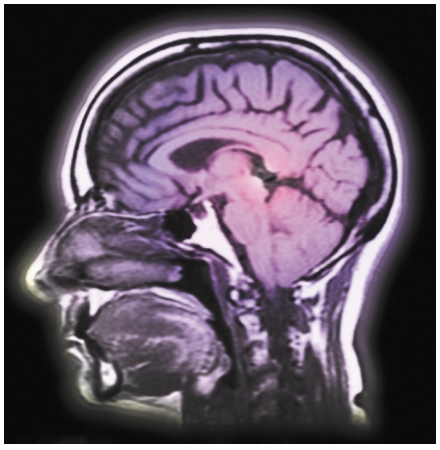
News in brief

CNS disorders

Folic acid deficiency linked to PD

Scientists have found that a deficiency in folic acid could increase the brain's susceptibility to Parkinson's disease (PD)[1]. The study, carried out at the National Institute on Aging (NIA) Gerontology Research Center (Baltimore, MD, USA) provides the first direct evidence that folic acid might have a role in protecting against age-related disease.

Researchers fed one group of mice a diet that included folate, and a second group a folate-deficient diet, followed by moderate amounts of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical that induces PD-like symptoms. The folate-deficient group developed severe PD-like



symptoms in contrast to the group fed with folate, which developed only mild symptoms of PD. Further analysis revealed that the folate-deficient group had elevated levels of plasma homocysteine, an amino acid that exacerbates the effects of MPTP including dopamine depletion, neuronal degeneration and motor dysfunction.

Mark Mattson, Chief of the NIA's Laboratory of Neurosciences, comments: 'It is clear from this study that a deficiency of [folic acid] is associated with increased toxin-induced damage to the dopamine-producing neurons in the mouse brain.' He suggests that consuming folic acid, either though diet or by taking supplements, could be beneficial in the prevention of age-related diseases such as PD.

1 Duan, W. *et al.* (2002) Dietary folate deficiency and elevated homocysteine levels endanger neurons in models of Parkinson's disease. *J. Neurochem.* 80, 101–110

DREAM come true for pain relief

A novel genetic mechanism has been discovered that offers a new approach to pain relief [2]. Scientists at the University of Toronto, The Hospital for Sick Children

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Proteomics

Functional yeast map to aid drug discovery

Researchers have mapped the functional units of the *Saccharomyces cerevisiae* proteome [12]. The map contains fundamental information and could lead scientists to make more-informed decisions when choosing drug targets for development.

The goal of the team, from Cellzome (Heidelberg, Germany), was to interpret gene function within the molecular environment of the gene product, and to better understand cellular processes. To this end, they used homologous recombination to modify 1700 genes within the *S. cerevisiae* genome with a double-tag. The resulting expressed proteins were then isolated using these tags. As proteins form complexes, retrieval of the tagged protein led to a recovery of the whole complex comprising the interactive proteins. Matrix-assisted laser desorption–ionization time-of-flight (MALDI-TOF) mass spectrometry and bioinformatics tools were then used to identify the proteins and analyze the networks.

The analysis characterized the functions and interactions of 1440 proteins comprising 232 multiprotein complexes, and identified new roles for 344 proteins. Comparison of yeast and human complexes showed conservation across species extending from single proteins to their molecular environment.

S. cerevisiae is a commonly used eukaryotic model in pharmaceutical development. 'By knowing the molecular context in which targets act, investigators can better predict the effect of drug candidates on the parameters that influence safety and efficacy, while protein interaction maps provide the framework on which to add data mined from the literature and from other experimental approaches,' said Giulio Superti-Furga, Vice President, Biology, Cellzome.

Cellzome have made the data publicly available at: http://www.yeast.cellzome.com

12 Gavin, A-C. *et al.* (2002) Functional organization of the yeast proteome by systematic analysis of protein complexes. *Nature* 415, 141–147

Survey identifies key proteomics products and services

A multi-part survey exploring proteomics in terms of its products and services has been published by the market research company, BioInformatics LLC (Arlington, VA, USA). The survey *The Tools & Techniques of Protein Science: Catalyzing the Future of Proteomics* asked over 1000 members of The Scientific Advisory Board (http://www.scienceboard.net), an online panel of scientific customers, to charactize their experience with a variety of applications and techniques associated with protein science.

Amersham Biosciences (Little Chalfont, UK) were revealed as the company most closely associated by scientists with products and services for protein science and proteomics research. Bio-Rad Laboratories (Hercules, CA, USA) came second but ranked top in several individual categories of products. Other companies that fared well in specific product categories associated with proteomics include: Invitrogen (protein expression and purification; Paisley, UK), Ciphergen (protein microarrays; Fremont, CA, USA), Packard Bioscience (protein microarrays; Meriden, CT, USA), Agilent (microfluidics, Palo Alto, CA, USA), Pierce Chemical (protein visualization; Rockford, IL, USA), Applied Biosystems (mass spectrometry; Foster City, CA, USA), Micromass (mass spectrometry; Manchester, UK) and Clontech (*in vivo* biomolecular interactions; Franklin Lakes, NJ, USA).

Other information obtained from the survey include the fact that the main proteomics technologies that scientists are considering using are protein chips and liquid-phase separation techniques. Furthermore, academic scientists would like to see suppliers focus on improving current separation and detection methods while scientists in the pharma industry want suppliers to focus on automating all procedures to improve reproducibility and throughput.

(both Toronto, Ontario, Canada) and Amgen (Thousand Oaks, CA, USA) identified the novel mechanism involving a gene encoding a protein called DREAM (downstream regulatory element antagonistic modulator), which is a transcriptional repressor of dynorphin [3], an endorphin produced by the body in response to pain or stress.

Michael Salter, Director of the University of Toronto Centre for the Study of Pain and a senior scientist at The Hospital for Sick Children, said: 'We knew about DREAM and its role in dynorphin expression, but the purpose of this study was to determine DREAM's actual physiological function.'

In knockout mice lacking the *dream* gene, the group found increased levels of dynorphin in regions of the spinal cord involved in pain modulation. Furthermore, in models of acute thermal, mechanical and visceral pain, as well as chronic neuropathic and inflammatory pain, dream$^{-/-}$ mice exhibited significantly reduced sensitivity to pain. Importantly, however, the knockout mice had no major defects in motor function, learning or memory, and there was no evidence of addiction to the therapy, which is a common side effect associated with conventional opiate painkillers.

Further analysis revealed that mice lacking DREAM had elevated levels of prodynorphin mRNA and dynorphin A peptides in the spinal cord, and that reduced sensitivity was mediated via dynorphin-selective κ-opioid receptors. These findings could lead to a new approach to pain relief that targets the binding of DREAM to the regulatory element within the dynorphin gene.

2 Cheng, H-Y.M. *et al*. (2002) DREAM is a critical transcriptional repressor for pain modulation. *Cell* 108, 31–48

3 Carrion, A.M. *et al*. (1999) DREAM is a Ca^{2+}-regulated transcriptional repressor. *Nature* 398, 80–84

Vitamin C to treat Alzheimer's disease

Researchers at the University of Ferrara (Ferrara, Italy) have discovered that drugs used in the treatment of Alzheimer's disease appear to enter the brain more easily when a molecule of vitamin C is attached [4]. The study, led by Stefano Manfredini, Professor of Pharmaceutical

Chemistry at the University of Ferrara, focussed on three compounds that are used in the treatment of various brain disorders but which have difficulty passing through the blood–brain barrier (BBB).

A novel receptor, the SVCT2 transporter, has been observed in some cells and is believed to have a role in regulating vitamin C transport into the brain. The theory behind the work of Manfredini and colleagues was that these transporters could facilitate the passage of vitamin C – and hence any drug that is attached to it – into the brain.

The three compounds under investigation were nipecotic acid, kynurenic acid and diclofenamic acid: these were tested using human retinal pigment epithelial cells, which are rich in the same SVCT2 transporter proteins that are present in the BBB. The addition of vitamin C increased the ability of nipecotic and kynurenic acids to interact with the receptors, and diclofenamic acid does not block the transport of vitamin C as it usually would. The compound nipecotic acid was also tested in a mouse model using animals induced to suffer convulsions. The drug alone had no effect, whereas the vitamin C–drug fusion delayed convulsions.

Manfredini says, 'We've opened a door for a promising new way to improve the delivery of drugs into the brain using a natural nutrient, ascorbic acid (vitamin C)'. He says the results are exciting but also cautions that the data is preliminary. Potential applications include drugs for CNS diseases, AIDS, brain lesions and neurodegenerative disorders.

4 Manfredini, S. *et al.* (2002) Design, synthesis and activity of ascorbic acid prodrugs of nipecotic, kynurenic and diclophenamic acids, liable to increase neurotropic activity. *J. Med. Chem.* 45, 559–562

Infectious diseases

Virulent pathogens attack vaccines

A novel theory behind the evolution of pathogenic virulence has been reported by scientists at the University of Edinburgh (Edinburgh, UK) [5]. Previously, studies have focussed on the evolution of vaccine resistance as a result of 'escape mutants' – variants expressing epitopes that are unrecognised by vaccinated individuals. This applies in particular to fast-evolving pathogens such as HIV, but could also be implicated in malarial and trypanasomal parasitic infections.

The researchers studied an alternative counter-adaptation to vaccination, which involves the life-history traits of pathogens, such as virulence and transmission rates. They used mathematical models to elucidate the selection pressures that vaccines could impose on human malaria parasites, and showed that vaccines that are designed to reduce the growth rate of the offending pathogen and/or its toxicity can diminish selection against virulent pathogens. The result is that the pathogen develops an increased intrinsic virulence which, in turn, leads to more severe disease in unvaccinated individuals. This means that overall mortality rates could increase with vaccination. By contrast, vaccines that block infections might select for lower virulence. The models of Gandon and colleagues enable the evaluation of how these consequences of vaccination balance out, and suggest that low coverage with a vaccine that provides some protection against infection can result in an overall increase in malaria mortality, the effects of which could be seen within the next few decades.

5 Gandon, S. *et al.* (2001) Imperfect vaccines and the evolution of pathogenic virulence. *Nature* 414, 751–756

Human genome sequence aids hunt for microbes

Researchers have developed a novel technique for detecting foreign bacteria and viruses in human tissue samples [6]. The team, at the Dana-Farber Cancer Institute (Boston, MA, USA), developed a computational subtraction approach to detect microbes by filtering human tissue samples against the human genome.

Traditionally, microbes were identified by culturing them from infectious tissue samples; however, not all disease-causing organisms can be cultured and detected in this way. Senior author of the study, Matthew Meyerson says, 'The technique is good for investigating all these chronic diseases of unknown origin.' He believes that many diseases that have previously been attributed to other causes, such as stomach ulcers – which were originally blamed on stress and diet but were discovered to be linked to bacterial infection – could be a result of bacterial or viral infections. He says this could apply to several inflammatory and autoimmune diseases and cancers including lymphomas, bladder cancer and some lung cancers.

The research involved determining the sequence of a portion of DNA in a sample from diseased tissue, which was then compared with the DNA of the entire human genome, using the MEGABLAST computer program [7]. The team tested 3.2 million expressed sequence tags (ESTs), which are gene segments collected from healthy and diseased human tissues. Approximately 2% of the DNA did not match that in the human genome; some of these sequences were from infecting bacteria, viruses and fungi, including DNA from organisms such as the hepatitis B and C viruses, and Kaposi's sarcoma herpesvirus. A positive control was used, whereby tissue infected with human papillomavirus – the cause of cervical cancer – was tested, and successfully identified.

'So, if you sequence the DNA and compare your sequences to the human genome, you eliminate anything that matches. What's left of the DNA is the infectious agent,' says Meyerson.

6 Weber, G. *et al.* (2002) Identification of foreign gene sequences by transcript filtering against the human genome. *Nat. Genet.* 10.1038/ng818 (http://www.genetics.nature.com)

7 Altschul, S.F. *et al.* (1990) Basic local alignment search tool. *J. Mol. Biol.* 215, 403–410

Novel thinking behind immune response

A recent report could alter the way that scientists understand immune response mechanisms [8]. T cells in the immune system form one of the major defences against disease and infection. Recent research by a team at the Dana-Farber Cancer Institute (Boston, MA, USA) has found that a signal from the *Tob* gene keeps the T cells in a dormant – quiescent – state. When an infection is discovered, the gene is switched off and the T cells become activated against disease. Vassiliki Boussiotis, leader of the research, said: 'The quiescent state isn't something the cells lapse into, as had been previously thought, but one they must actively maintain.'

The research determined that induced expression of TOB inhibited T cell proliferation and the transcription of cytokines. Suppression of TOB increased CD3-mediated responses and cancelled the requirement of costimulation for maximal proliferation and secretion of cytokines.

Currently, cancer vaccines induce an immune response in the immune system. By contrast, the success of organ transplantation relies on the desensitization of the immune system to foreign tissue. Therefore, the elucidation of the switching mechanism of *Tob* would be essential in enabling the switching of the cells to 'off' or 'high alert'. This research could lead to the development of more potent vaccines and transplantation techniques that require fewer anti-rejection drugs.

8 Tzachanis, D. *et al.* (2001) Tob is a negative regulator of activation that is expressed in anergic and quiescent T cells. *Nat. Immunol.* 2, 1174–1182

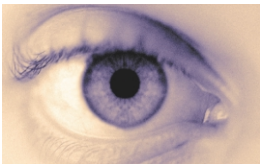
University of Pittsburgh consolidates its immunology programs

The University of Pittsburgh School of Medicine (Pittsburgh, PA, USA) is to create a dedicated immunology department in an attempt to streamline basic immunology research and strengthen training programs. The University will bring more than 30 faculty members currently working across various departments under one roof.

'We are extremely excited about the formation of the new department,' said Arthur S. Levine, Senior Vice-Chancellor for Health Sciences and Dean of the School of Medicine at the University of Pittsburgh. 'It will provide a needed academic home for the innovative research in immunology we are currently conducting,' he said.

Other targets and mechanisms

Nature's own gene therapy candidate for blindness



Two recent reports have shown that recombinant fragments of a human tyrosyl-tRNA synthetase (TyrRS) are angiostatic in mammalian cells [9] and inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis and naturally occurring retinal angiogenesis in the adult and neonatal mouse, respectively [10]. In addition to revealing a potential anti-cancer target, this finding could lead to new therapies for age-related macular degeneration (AMD) and diabetic retinopathy, which result from inappropriate neovascularization and affect 12–15 million people aged over 65 years in the USA.

TyrRS is an aminoacyl-tRNA synthetase (an enzyme that catalyzes the first step of protein synthesis) that has recently been shown to have a role in cytokine signalling [11]. Researchers at the Scripps Research Institute (SRI; La Jolla, CA, USA) demonstrated that TyrRS can be split into two fragments with distinct cytokine activities [11]. A close homologue of TyrRS, tryptophanyl-tRNA synthetase (TrpRS) is a naturally occurring alternative splice product, the expression of which is stimulated by the angiostatic cytokine, interferon γ (IFN γ). By contrast, the full-length protein has no anti-angiogenic activity.

In preclinical studies using a recombinant carboxy-terminal fragment of TrpRS, the Scripps group has demonstrated 100% inhibition of vessel formation in 70% of neonatal mice. This is significantly better than the 20–40% inhibition seen with anti-angiogenic compounds currently in clinical trials, according to Martin Friedlander, Associate Professor in the Department of Cell Biology at SRI. This natural molecule has advantages over other potential compounds because it is unlikely to provoke an immune response or cause toxicity. Moreover, Friedlander hopes that this is one therapy that they can teach the cell to make: 'One clinical approach to treating angiogenic vision loss could be to deliver the TrpRS molecule directly into the eye through gene- and cell-based vectors.'

In addition to exploring ways to apply this therapy, the group is now concentrating on finding out what role this alternatively spliced fragment has in nature and, importantly, identifying its receptor.

9 Wakasugi, K. *et al.* (2002) A human aminoacyl-tRNA synthetase as a regulator of angiogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 99, 173–177

10 Otani, A. *et al.* (2002) A fragment of human TrpRS as a potent antagonist of ocular angiogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 99, 178–183

11 Wakasugi, K. and Schimmel, P. (1999) Two distinct cytokines released from a human aminoacyl-tRNA synthetase. *Science* 284, 147–151

News in Brief was written by *Joanne Clough*, *Joanna Milburn*, *Joanna Owens* and *Ben Ramster*

People

New leadership at Memorial Sloan-Kettering Cancer Center

Memorial Sloan-Kettering Cancer Center (New York, NY, USA) has announced the appointment of Robert E. Wittes as Physician-in-Chief of Memorial Hospital and Thomas J. Kelly as Chairman of the Sloan-Kettering Institute. Wittes is currently Director of the Division of Cancer Treatment and Diagnosis and Deputy Director for Extramural Science at the National Cancer Institute. He has previously worked as Senior Vice-President of Cancer Research at Bristol-Myers Squibb and as Chief of the medicine branch at the National Cancer Institute.

Meanwhile, Kelly is Boury Professor and Chairman of the Department of Molecular Biology and Genetics at Johns Hopkins University. He was also the founding director of the university's Institute for Basic Biomedical Sciences. He is a member of the National Academy of Sciences and the Institute of Medicine, and was previously Assistant Professor of Microbiology at Johns Hopkins. Harold Varmus, President of Memorial Sloan-Kettering Cancer Center said: 'Memorial Sloan-Kettering is beginning a period of extraordinary growth and development across our full panoply of clinical and

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