However, even as a preventive strategy in animals, these results fail to impress another researcher who has studied scrapie and AD. The immunization 'clearly isn't very protective,' comments microbiologist Steven Wietgrefe of the University of Minnesota (http://www.umn.edu). Vaccination, he points out, delayed the onset of disease – which has a normal incubation period of perhaps 175 days – by only about 10 days. 'For protecting deer and elk herds,' he says, 'it probably wouldn't be worth the trouble if the vaccine delays, but does not stop, the infection.'

Future work

The NYU researchers are working towards outright protection. The key, Wisniewski hypothesizes, is higher antibody titers. To this end, they are looking for better adjuvants, using mutated variants of the recPrP vaccine. They hope these variants will elicit a stronger immune response while being less likely themselves to take on the β-pleated sheet conformation characteristic of pathogenic prion proteins.

The group is also trying a variety of multi-faceted approaches, such as passively immunizing some test animals with anti-PrP^{Sc} antibody preparations, and to boost the IgA antibody response, they have begun feeding mice with recPrP. (Subcutaneous immunization induces principally IgG2a and IgG2b.) 'Because scrapie infections often arise in nature via the gut,' Wisniewski reasoned, 'we might be able to hinder penetration of the agent into the body.'

Wietgrefe also voiced concern over the lack of any discernable histopathological difference between the brains of vaccinated versus control animals. This could be because of the assays being conducted only on mice that had reached their clinical endpoint, regardless of how long it took them to get there.

Because of the lengthy clinical incubation period of the disease, scientists in this field must wait nearly six months before they can know whether any treatment (or set of treatments) has had any effect. The NYU researchers are gearing up to address this issue by using magentic resonance imaging (MRI) to assess damage to the brains of inoculated mice, which could appear long before any neurological symptoms become apparent. An added benefit is that this approach requires far fewer mice than histological examinations, because it does not require destroying the animals. Thus it is easier to test several treatments concurrently.

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3 Sigurdsson, E.M. *et al.* (2002) Immunization delays the onset of prion disease in mice. *Am. J. Pathol.* 161,13–17

News in brief

Targets and mechanisms

Leads on drugs for controlling obesity?

Researchers have recently found that the appetite-suppressing drug, fenfluramine, acts by targeting the same brain pathways that control appetite, obesity and anorexia [1]. Such results could lead to the development of selective treatments for effective weight control, particularly for the treatment of obesity.

Researchers from the Beth Israel Deaconess Medical Center, led by Joel Elmquist, studied the effects of D-fenfluramine (D-FEN) in the brains of rats. The drug induces anorexia in the rats and this in turn activates melanocortin neurons in the CNS. D-FEN is also known to increase the release of serotonin from the brain, a hormone also thought to be involved in eating disorders such as anorexia nervosa.

The researchers studied activity patterns in the arcuate nucleus region of the hypothalamus, which is an area of the brain in which serotonin is received directly by pro-opiomelanocortin (POMC) neurons. On activation, these neurons stimulate the release of peptide molecules that act on melanocortin receptors, which are crucial regulators of appetite, energy and hormones in the brain. The researchers found that the firing rate of POMC neurons was doubled by the presence of D-FEN and that the neurons depolarized in response to receiving D-FEN, serotonin or either of two serotonin receptor antagonists.

'Our study has linked the serotonin system, a classic brain pathway thought to be involved with eating disorders like anorexia nervosa, to the melanocortin system, a brain pathway involved in obesity', reported Elmquist, who added; 'our work gives a mechanistic explanation of how drugs like D-FEN may inhibit food intake'. These results could lead to the development of novel drugs for the prevention and treatment of obesity that have fewer side effects than D-FEN itself, which was withdrawn by the FDA after reports of cardiac complications.

1 Heisler, L.K. *et al.* (2002) Activation of central melanocortin pathways by fenfluramine. *Science* 10.1126/science.1072327

New tools for diagnosing muscular dystrophies?

A new molecular mechanism recently reported as being the possible cause of a subset of muscular dystrophies [2,3] could lead to the development of improved diagnostic and prognostic tools for patients with this condition.

Muscular dystrophy covers a range of conditions, most of which gradually destroy muscle. However, there is a subset that also cause brain abnormalities that result in severe mental retardation, for example, Fukuyama congenital muscular

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New gene expression tools

SNP consortium completes human linkage map

The SNP consortium has announced the completion of a genome-wide SNP-based human linkage map that is available via the Internet for unrestricted use by researchers worldwide. The linkage map adds value to the SNP database by including details of the location of one SNP relative to another. Almost 800 individuals were genotyped for SNPs and their inheritance through families was analyzed, thus determining the position and ordering of almost 3000 naturally occurring SNPs. This data can now be used to study the association of disease with closely linked SNPs, and could make it easier for scientists to locate the genes involved in the disease.

The SNP Consortium is a non-profit-making organisation that was formed in 1999 with the goal of creating a high density, high quality and highly annotated map of SNPs throughout the human genome. To date, the consortium has mapped more than 1.4 million SNPs.

Researchers now have free access to a tool for genetic analysis that is more dense, informative and much less expensive than existing technologies. The map will also enable faster turnaround time: genetic analysis can be achieved in six weeks rather than 6–9 months. The datasets are available to download in several formats, including a version suitable for bioinformatics, graphical maps for browsing, and several configurations useful to geneticists.

Arthur Holden, Chairman of the SNP Consortium, commented: 'It is our belief that unfettered access to SNP databases and the human linkage map will mean the more rapid development of improved diagnostic techniques and therapeutics.' The map is available at http://snp.cshl.org/

An inGenie-ous toolbox to study disease gene expression

A new set of web-based tools called SAGEGenie has been developed that enables the efficient analysis of data in the SAGE (serial analysis of gene expression) database [9]. The National Cancer Institute (NCI) Cancer Genome Anatomy Project (CGAP; http://cgap.nci.nih.gov/) uses SAGE (which was developed by scientists at Johns Hopkins University) to measure large-scale gene expression and has sponsored a SAGE database for more than four years.

SAGE counts polyadenylated transcripts by sequencing a 14 bp tag at the gene's 3′ end, adjacent to the last restriction site, which is normally *Nla*III. All transcripts with a *Nla*III site can thus be tagged and counted in large numbers. The transcript counts are then electronically archived at the SAGEMap website (http://www.ncbi.nlm.nih.gov/SAGE) for future analysis and digital comparisons.

Gregory Riggins, lead author of the Genie paper, and his colleagues from Duke University went through seven million SAGE transcript tags to see which were the most reliable. Investigators at the Ludwig Institute for Cancer Research then developed a scoring method to alert users whether the tags were of high quality or whether they contained potential flaws. The result is a new set of web-based tools for processing the SAGE data.

Foremost is the SAGE Anatomic Viewer, which enables nearly any gene's transcript levels to be easily viewed in normal and malignant tissues. This anatomic view is based on a growing set of more than 5.2 million SAGE tags from 114 cell types. An enhanced link between the SAGE tag and gene is based on an experimental sample of 6.8 million SAGE tags used to evaluate public transcript databases. These tools provide a rapid view of transcript expression in the human body or brain.

Riggins said: 'Now that most of the human genome has been sequenced, it is important to accurately determine exactly where these genes are expressed, but this information is often hard to use or not available. We have simply improved a good way to study genes and made it available to everyone online.'

9 Boon, K. *et al.* (2002) An anatomy of normal and malignant gene expression. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.152324199 (http://www.pnas.org)

dystrophy, Walker–Warburg Syndrome (WWS) and muscle–eye–brain disease (MEB). 'They are an interesting group of dystrophies because they affect more than just muscle', said Kevin Campbell, corresponding author on both papers.

Muscular dystrophies usually have a genetic cause and researchers have found that the genetic mutations affect the protein components of the glycoprotein–dystrophin complex. This protein complex is a bridge between structures outside and inside cells, and might be crucial for maintaining the physical integrity of muscle tissue. Mutations that affect this complex might also be responsible for the brain abnormalities seen in some patients with muscular dystrophies.

Campbell *et al.* have now shown that the main component of these dystrophies is the protein dystroglycan. Although there is no defect in the protein itself, there is a genetic defect in the enzyme that glycosylates it, resulting in certain sugars not being added. The 'unfinished' dystroglycan was unable to interact with its normal partners, such as laminin molecules, at the surface of cells in both brain and muscle. Mice that lacked dystroglycan in their brains had severe brain development defects that were similar to those seen in patients with WWS, MEB and Fukuyama. The absence of dystroglycan disrupted long-term potentiation in the brain of the mice, a process that is associated with strengthening the connections between brain cells, thus influencing learning and memory. Thus dystroglycan might have a role in brain function other than simple neuronal migration.

'These results improve our understanding of muscular dystrophy, and the more we understand, the better equipped we'll be to develop therapies', said Campbell. 'The findings also are important for appropriate genetic counselling.' The results could also be used to develop appropriate tools that could be used to make accurate diagnoses and also precise prognoses for patients with congenital muscular dystrophies.

2 Michele, D.E. *et al.* (2002) Post-translational disruption of dystroglycan–ligand interactions in congenital muscular dystrophies. *Nature* 418, 417–421

3 Moore, S.A. *et al.* (2002) Deletion of brain dystroglycan recapitulates aspects of congenital muscular dystrophy. *Nature* 418, 422–425

Anti-HIV gene discovered

A unique gene has been discovered that acts as a natural defence mechanism against HIV [4]. The research showed how the gene *CEM15* represents natural resistance to viral activity; this gene is normally overcome by the viral infectivity factor (Vif), which suppresses its activity.

'Previous studies have shown that Vif is crucial in infection and neutralizes some sort of defence system in healthy cells,' said Michael Malim, Head of Infectious Diseases at King's College London (http://www.kcl.ac.uk), who was involved with the study. He added that this research identified *CEM15* as a key component of the system and if they can find a way of blocking the action of Vif then it would enable *CEM15* to function properly and thus prevent the spread of HIV.

The scientists, conducted with a team at the University of Pennsylvania School of Medicine (http://www.penn.edu), isolated the gene *CEM15*, the expression of which recreates an innate antiviral phenotype that, in the absence of Vif, makes virions non-infectious.

'There is still a lot to learn about Vif,' said Malim. 'Ongoing work includes identifying substances that bind to and inhibit Vif in the cell… All this will hopefully lead to a way of stopping Vif from working and thus enabling the body's natural defence mechanisms to come into play.' He added that there is further potential for research into Vif as a new way of tackling HIV, which he says is ambitious, but could be developed as a new target for therapy in the next ten years.

4 Sheehy, A. *et al.* (2002) Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* 10.1038/nature00939 (epub ahead of print; http://www.nature.com)

Colon cancer clues

The immune system can identify the natural signs of cancer, a recent study has found [5]. This breakthrough could ultimately make it easier to detect and treat cancer.

The study focused on a specific cancer antigen that circulates in the blood, in an attempt to develop simpler and less invasive methods for the detection of cancer. At present, no such test exists for colon cancer but similar tests exist for the detection of prostate cancer by detecting prostate specific antigen (PSA) and CA125 for ovarian cancer.

The group screened 77 tumour antigens for antibody reactions. No reactions were found in a group of healthy volunteers; however, blood samples from 46% of colon cancer patients detected reactions to one or ore of the 13 specific antigens. Mathew Scanlan, Assistant Member of the Ludwig Institute for Cancer Research at Memorial Sloan-Kettering (http://www.mskcc.org) and lead author of the study, said that these tests would complement regular screening methods and could help to avoid misdiagnoses.

'Based on a patients own specific tumour profile, we could design treatments that go after the best targets without harming healthy tissue,' said Scanlan. He added, 'What we need to do now is find more antigens. It could then be possible to harness the immune systems own ability to detect disease and use it as a diagnostic tool.'

5 Scanlan, M.J. *et al.* (2002) Cancer-related serological recognition of human colon cancer: identification of potential diagnostic and immunotherapeutic targets. *Cancer Res.* 62, 4041–4047

Cause of defective heart valves revealed

Researchers have identified a key component of the cause of defective heart valves, which is one of the most common causes of congenital heart problems [6]. They also identified a key component in cancer that was also present in heart abnormalities.

John A. McDonald, Professor of Internal Medicine at the University of Utah Medical School (http://www.med.utah.edu/som/), said that this discovery changes the fundamental understanding of how the heart is formed, and continued: 'We now have the potential to look at genes in patients who have these heart defects and see if they're abnormal.'

The problem – atrioventricular septal defects (AVSD) – arises because of the absence of the polysaccharide, hyaluronan (HA), during early heart formation. In AVSD, the heart's valves are faulty, resulting in blood pooling in the lungs, high blood pressure and weakened blood vessels.

McDonald and co-workers discovered a family of genes responsible for the production of HA. In this study, the team used knockout mice and deactivated the gene that encodes HA; when this is absent, the septum and valves were not present in the developing hearts of mice. The team has also shown that HA communicates with the ErbB receptor family and these have a crucial role in heart valve genesis. The surprise, said McDonald, was that you need both HA and the ErbB system to build a normal heart.

This discovery of the involvement of HA also has significance in the fight against cancer because ErbB is present in some breast cancers and models have shown HA engaging ErbB2 in ovarian cancers. This means that an HA-related reagent could possibly be used to as a potential cancer growth inhibitor.

6 Camenisch, T.D. *et al.* (2002) Heart-valve mesenchyme formation is dependent on hyaluranon-augmented activation of ErbB2–ErbB3 receptors. *Nature* 10.1038/nm742 (epub ahead of print; http://www.nature.com/nm/)

Miscellaneous

Bile acid has neuroprotective activity in HD

Tauroursodeoxycholic acid (TUDCA), a hydrophilic bile acid, has been shown to protect against Huntington's disease (HD) in a mouse model [7]. Researchers at the University of Minnesota (http://www.umn.edu) found that systemically administered TUDCA resulted in significantly reduced striatal neuropathology in the R6/2 transgenic HD mouse. HD is an untreatable disorder caused by the selective and progressive degeneration of neurons.

It has been previously shown that TUDCA prevents neuropathology and associated behavioural deficits in the 3-nitropropionic acid rat model of HD [8]. Walter Low and colleagues therefore decided to investigate whether the bile acid would be neuroprotective in a genetic mouse model of HD.

The transgenic mice were given TUDCA from six weeks of age, and exhibited reduced striatal atrophy and apoptosis, and fewer and smaller intranuclear huntingtin inclusions. Further, the treated mice had significantly improved locomotor and sensorimotor deficits.

C. Dirk Steer, first author on the paper, commented: 'What's exciting about TUDCA, in addition to its remarkable anti-apoptotic quality, is that it's made in our own bodies and causes virtually no side effects when given as a drug. TUDCA may even have potential for treating other chronic neurodegenerative conditions such as Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS).'

7 Keene, C.D. *et al.* (2002) Tauroursodeoxycholic acid, a bile acid, is neuroprotective in a transgenic animal model of Huntington's disease. *Proc. Natl. Acad. Sci. U. S. A.* 99, 10671–10676
8 Keene, C.D. *et al.* (2001) Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. *Exp. Neurol.* 171, 351–360

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People

Caliper Technologies announces changes to its management team

The microfluidics company Caliper Technologies (http://www.calipertech.com) has revealed a new organizational structure and announced several new appointments. Michael Knapp will take on the role of Chief Executive Officer, whereas James L. Knighton has been appointed as President, with Daniel L. Kisner relinquishing these roles in favour of becoming Chairman of the Board. David Milligan, currently Chairman of the Board, will become Vice-Chairman.

Knapp, a co-founder of Caliper and currently Vice-President of Corporate Development, has previously served as President and Senior Director at Molecular Tool, a genetics technology company that he co-founded in 1988. As VP of Corporate Development at Caliper, Knapp configured the company's technology access program and drove the creation of partnerships with several important pharma and biotech companies. Knapp also co-founded Amphora Discovery group, a chemical genomics company that was spun out of Caliper with independent funding and management.

Knighton leaves his position as Executive Vice-President and Chief Financial Officer, where he has been responsible for raising ~US$200 million in capital, as well as playing a key role in the formation and funding of Amphora. Previously, Knighton was Senior Vice-President and Chief Financial Officer at Sugen and before this held several management positions at Chiron Corp. Kisner, who before joining Caliper had served in several senior positions at Isis Pharmaceuticals, Abbott Laboratories and Smithkline Beecham, said: 'The joint leadership of Mike [Knapp] and Jim [Knighton] provides the ideal combination of talents to take Caliper to the next stage of its corporate development.'

Trevor Nicholls moves to Affymetrix

Trevor Nicholls is to join Affymetrix (http://www.affymetrix.com) as Chief Commercial Officer, Global Operations. Nicholls was previously CEO of Oxagen, the clinical genomics company that he founded. Before setting up Oxagen (a spin-out company from Oxford University, UK) he was Commercial Director of the Life Science business of Amersham International. In this role he was involved in the company's move into the high-throughput sequencing and drug discovery markets. Nicholls has also been a management consultant with McKinsey and Co. and has held several sales and marketing posts in the diagnostic, radiopharmaceutical and chemical industries.

Susan S. Siegel, President of Affymetrix, commented: 'Trevor is an experienced executive with significant expertise in the Life Science industry and a demonstrated record of commercial success. His strengths in international commerce, technology and operations will be tremendous assets as Affymetrix continues to grow its business.'

Key management appointments at Evotec AOI

Evotec AOI (http://www.evotec.com) has announced several key management appointments. John Kemp has joined the company as Chief Executive Officer of Evotec Neurosciences (ENS), a subsidiary of Evotec OAI that focuses on Alzheimer's disease. Kemp joins the company with 18 years of research experience in CNS diseases, and was previously Vice President and Head of Preclinical CNS Research at Hoffmann-La Roche. Sean Marett, Commercial Director at Evotec, has been promoted to Chief Business Officer and Member of the Management Board. Marett joined Evotec in April 2001 and has been responsible for many of the company's new partnership or extension contracts, including those with Merck and Co., Roche, Amgen, Pharmacia, Serono and Vertex. Before joining Evotec, Marett was Director of New Product Development, US Operating Division, at GlaxoSmithKline.

New Vice President of Drug Discovery at Structural GenomiX

Ian McDonald has been appointed as Vice President of Drug Discovery at Structural GenomiX (SGX; http://www.stromix.com), where he will head the Chemistry team and be responsible for directing the discovery of drug candidates both for partners and internal research programs.

McDonald has more than 24 years of experience in medicinal, combinatorial and analytical chemistry, and has held senior positions in biotechnology and pharmaceutical companies over the past 11 years. He joins SGX from Structural Bioinformatics (SBI) where he was Vice President of Drug Discovery. Before this, he was Vice President of Chemistry at Merck Research Laboratories (formerly SIBIA Neurosciences). Tim Harris, President and CEO at SGX, commented: 'Ian will play a critical role in the structure-guided drug discovery process at SGX…to leverage our structure determination technology for drug discovery and build upon our strategy in the areas of new target selection, drug candidate screening and lead optimization.'

People was written by *Joanna Owens*

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