News in brief

Targets and mechanisms

Immune system finding could lead to novel diabetes therapy

Researchers at the Dana-Farber Cancer Institute (a teaching affiliate of Harvard Medical School, Boston, MA, USA) have discovered that the manipulation of a cell that controls the response of the immune system to infections, could prevent the onset of diabetes in mice that are predisposed to the disease [1]. The studies showed that diabetes-prone mice were prevented from developing the disease by activating certain immune system cells (iNKT cells) and that this condition is reversible.

The iNKT cells work by regulating the response of the immune system to infections and other disorders, ensuring that only diseased tissue is targeted for attack. Type I diabetes occurs when the immune system attacks healthy insulin-producing cells in the pancreas.

Brain Wilson, senior author of the study and Assistant Professor at Harvard Medical School, said: 'Because iNKT cells work in much the same way in mice and humans, techniques for increasing the production of these cells could be the basis of preventive treatments for people with a genetic risk of diabetes.'

The study examined the mechanism of activation of iNKT cells (which involves dendritic cells) whose role is to alert the immune system to infection or other potential health problems. Located on the surface of dendritic cells are proteins (CD1d) that display lipids, such as α-galactosylceramide, that act as activators of iNKT cells. Administration of α-galactosylceramide prevents diabetes formation in non-obese diabetic (NOD) female mice; if the *CD1d* gene is silenced, α-galactosylceramide is not displayed, and the mice go on to develop full-blown diabetes.

Wilson concluded, 'The success of our work in mice lays the groundwork for a clinical trial of this therapy in people at high risk of diabetes. Preventing pre-diabetic conditions from progressing would be an important benefit to about one in 500 people in the USA.'

1 Naumov, Y.N. *et al.* (2001) Activation of CD1d-restricted T cells protects NOD mice from developing diabetes by regulating dendritic cell subsets. *Proc. Natl. Acad. Sci. U. S. A.* 98, 13838–13843

Pot cure for bellys

Scientists at the University of California, Irvine (UCI; CA, USA), Complutense University (Madrid, Spain) and the Fundaciön Hospital Carlos Maya (Malaga, Spain) have discovered that a marijuana-related compound in the human body could provide effective treatment for obesity and other eating disorders [2]. The compound, oleylethanolamide (OEA), is a natural analogue of the cannabinoid anandamide and is produced in cells when triggered by a stimulus. It does not, however, activate cannabinoid receptors and its biological function is unknown. Administration of OEA causes the induction of an anorexic effect, which results in a reduction in food intake and a decrease in body mass gain: this effect is associated with the discrete activation of regions in the brain that are involved in satiety control.

Almost 30% of Americans are obese (according to the Centers for Disease Control) and the occurrence of obesity has risen by almost 60% since 1991. Daniele Piomelli, Professor of Pharmacology at UCI, said: 'We first saw OEA levels change in rats that had been deprived of food…This suggested to us that OEA is an important regulator of eating behaviour and could be used as a tool to design new anti-obesity medicines.' Piomelli and coworkers were the first to discover the function of OEA in the brain and have been working to assess the range of effects that anandamide has on the body. This study indicates that OEA is a lipid mediator that is involved in the peripheral regulation of feeding.

2 Rodriguez de Fonseca, F. *et al.* (2001) An anorexic lipid mediator regulated by feeding. *Nature* 414, 209–212

Viral infections linked to schizophrenia

Children born of mothers that have herpes simplex virus type 2 (HSV-2) at the time of birth are more likely to develop schizophrenia or other psychotic disorders [3]. The correlative study is the first to do a direct comparison of maternal infections with the development of psychosis in children.

Researchers drew their subjects from a large-scale nationwide study that monitored 55,000 pregnancies at 12 study sites in the USA between 1959 and 1966. The study evaluated infants for physical and mental development in the first seven years of life and also stored blood samples from the mothers for later analysis.

Out of a group of 3804 surviving offspring in the study, 27 children were diagnosed with schizophrenia or another psychotic disease. These results were compared with a matched group of 54 unaffected control mothers and children.

Using the stored blood samples, researchers identified maternal HSV-2 infection by elevated levels of antibodies to HSV-2 in the blood. Antibodies to other infectious diseases were found to be low in mothers with both psychotic and non-psychotic children. Because these antibodies to other sexually transmitted diseases were not different between groups, the study concludes that the sexual activity of the mother is not, in itself, a predictive factor for the development of psychosis in children.

Another, separate study has also identified a link between schizophrenia and viral infections in the brain. Hans Moises, from the University of Kiel, Germany, presented his findings at the *8th International Meeting of the Human Genome Project* in Valencia, Spain.

Moises proposes that the most likely cause of schizophrenia is the brain's inability to produce enough proteins that form the building blocks of nerve cells, and that this protein deficiency might be caused by viral infections in the brain.

Although the research has yet to be confirmed, the finding could mean that schizophrenia might be preventable and treatable by a combination of immunization against viruses that attack nerve tissue and new drugs that improve the brain's ability to produce proteins.

3 Buka, S.L. *et al.* (2001) Maternal infections and subsequent psychosis among offspring. *Arch. Gen. Psychiatry* 58, 1032–1037

Old drug stubbs out nicotine addiction

Studies at the US Department of Energy's Brookhaven National Laboratory (Upton,

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NY, USA) have indicated that topiramate, a drug that is currently used for the treatment of epilepsy, can block nicotine-triggered alterations in brain chemistry and could have potential in the treatment of nicotine addiction.

Previous studies at the site have focussed on agents that block drug-induced increases in brain dopamine, a neurotransmitter associated with pleasure and reward. Stephen Dewy, neuroanatomist and coauthor of the study, said '…new theories about nicotine dependence suggest that dopamine isn't the only system involved.' Nicotine stimulates excitory systems in the brain, which in turn excite dopamine and other brain chemicals, such as norepinephrine and serotonin.

The researchers injected rats with topiramate and used saline-injected animals as a control group. Acute doses of nicotine were then administrated and the levels of dopamine, norepinephrine and serotonin were measured in the brain. The control animals showed significantly increased levels of all three chemicals compared with those injected with topiramate, which blocked nicotine-induced increases in norepinephrine and dopamine. By contrast, the effect of nicotine on serotonin levels was unaffected by topiramate.

Wynne Schiffer, lead author of the study said: 'This treatment strategy uses a drug that simultaneously targets two different neurotransmitter pathways, thereby reducing the neurochemical activity believed to underlie nicotine addiction. Since the brain's dopamine and norepinephrine systems are closely linked, the ability of topiramate to reduce increases in both neurotransmitters suggests that this drug has potential for treating nicotine abuse.'

Novel insights from HSP gene identification

Scientists have identified a gene implicated in the childhood form of the rare nerve disease, hereditary spastic paraplegia (HSP) [4] that could provide insights into other spinal cord problems. The finding could also lead to improved diagnosis and treatment of the disease, which affects 10,000–20,000 individuals in the USA.

The childhood form of HSP is often initially identified as a subtle difficulty with walking, but can progress to a complete weakening of the legs as nerves begin to break down in the spinal cord.

Genomics

Whole transcriptome analysis of *Drosophila*

Scientists have for the first time monitored the activity of the entire genome of the fruitfly *Drosophila*, an important model organism in developmental studies. Using a technique called serial analysis of gene expression (SAGE), researchers at the European Molecular Biology Laboratory (EMBL; Heidelberg, Germany) have studied the expression of the fly's genome in response to activators of the Jun N-terminal kinase (JNK) signal transduction pathway [5].

JNKs modulate the cell shape changes and reorganization of the actin cytoskeleton that are involved in morphogenesis. Dirk Bohmann and colleagues at EMBL found that activation of the JNK pathway increased the expression of >300 genes and decreased the expression of >300 others. One of the upregulated genes was the chickadee gene (*chic*), which encodes a *Drosophila* profilin. Further study of the role of this gene in embryogenesis revealed that *chic*-deficient embryos lose the ability to execute JNK-mediated cytoskeletal rearrangements during dorsal closure.

Bohmann and colleagues believe that this finding suggests a major link between the JNK pathway and the structural rearrangements within cells that enable them to form tissues. 'Getting [the SAGE technique] to work in the fruitfly is a crucial step', Bohmann says, 'because it will allow researchers to understand the effects of multiple genes on a whole animal.'

5 Jasper, H. *et al.* (2001) The genomic response of the *Drosophila* embryo to JNK signaling. *Dev. Cell* 1, 579–586

First draft of pufferfish genome published

The first draft of the genome sequence of *Fugu rubripes*, the Japanese pufferfish, was made public at the *13th International Genome Sequencing and Analysis Conference* (25–28 October 2001, San Diego, CA, USA), which was organized by TIGR (The Institute for Genomic Research; Rockville, MD, USA).

Myriad Genetics (Salt Lake City, UT, USA) has used its high-throughput DNA sequencing facility to generate the 600 million base-pair sequencing data over the past four months. The genome comprises ~30,000 genes, approximately the same number as thought to be present in the human genome, but it is only one-eighth of the length of its human counterpart. This is because the length of non-coding junk DNA between the genes is so small. This makes the identification of genes and their regulatory elements far easier.

The mapping of the pufferfish genome is expected to be an enormous help to the deciphering of the sequences revealed by the Human Genome Project, because the fish is thought to have the same basic set of genes as humans. It will be the third vertebrate genome to be available to the public, but is the most complete sequence of a vertebrate, to date.

Whole genome *Arabidopsis* microarray to weed out junk genes

A whole-genome microarray of the widely used model organism, *Arabidopsis thaliana*, is to be commercialized by Agilent Technologies (Palo Alto, CA, USA) and Paradigm Genetics (Research Triangle Park, NC, USA). The novel microarray, which is the result of using Agilent's Technology Access Program (TAP) together with Paradigm's gene function expertise, is expected to be available by the end of 2001.

All of the relevant genes necessary to conduct a genome-wide expression analysis of *Arabidopsis* will be arrayed using a flexible, inkjet-based microarray design on standard-sized glass slides that can be used with many commercially available microarray scanners.

The research identified a one-letter missense mutation in the gene *SPG3A*, which causes alterations to a newly identified protein termed atlastin. The predicted protein structure of atlastin, based on the genetic sequence of *SPG3A*, has identified the protein as similar to a group of proteins called dynamins, which mediate certain cellular processes, such as nerve cell communication. Disturbances in this process could lead to the nerve degeneration seen in HSP. This could also help the understanding of progressive nerve degeneration in other conditions, such as spinal cord injuries, primary lateral sclerosis and amyotrophic lateral sclerosis (Lou Gehrig's disease).

The team analyzed the DNA sequence of *SPG3A* from HSP-prone families and families with no history of the disease. They identified the mutation in three families at a position on the gene unique to that family but possessed by every family member who had HSP. The same missense mutation was found in three other families with individuals affected by HSP.

Hopes for treatment are centred on understanding how the mutation causes nerve degeneration so that the process can be halted to enable nerve outgrowth. Prenatal diagnosis of the disease could also be possible, based on the genetic type of HSP.

4 Zhao, X. *et al.* (2001) Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nat. Genet*. 29, 326–331

Pungent promise for malaria and cancer

A group of compounds in garlic have been shown to have potent anti-infective activity against malaria, and might also use the same mechanism to fight cancer cells. Researchers from the University of Toronto (Toronto, Ontario, Canada) reported these findings at the *50th Annual Meeting of the American Society of Tropical Medicine and Hygiene* (11–15 November 2001, Atlanta, GA, USA).

Garlic, onions and mahogany trees are known for their antifungal, antibacterial and anticancer properties, which are attributed to the naturally occurring disulfides that they contain. Now, Ian Crandall, Assistant Professor of Laboratory Medicine and Pathobiology at the

University of Toronto, and his colleagues have taken this hypothesis further and studied the response of malaria-infected cells and anticancer cells to 11 different synthetic disulfides. Not all of the disulfides were effective against the malaria parasite, *Plasmodium falciparum*, but significantly, those that were, were also effective at killing the cancer cells.

The next step was to determine a common feature of the disulfides that were effective. Crandall believes that the mechanism of action might involve the glutathione system within the cell. Glutathione is an essential antioxidant component of all cells, but it is particularly vital in cells that rapidly reproduce because of their increased production of toxic metabolites. Furthermore, a natural disulfide found in garlic, ajoene, is a known inhibitor of glutathione reduction.

Crandall is optimistic that one day these compounds could be used to treat not only malaria, but cancer too. However, the pungent nature of garlic could be a problem: 'Does this stuff smell of garlic? Well, every time we open a vial of it in the lab, everybody runs!', he said.

Proteasome inhibition looks promising for cancer inactivation

Researchers at Millennium Pharmaceuticals (Cambridge, MA, USA) have reported promising results from their Phase I clinical trial of the investigational drug LDP341 in patients with multiple myeloma. Data from preclinical studies suggest that the compound can block proteasomes, which are responsible for proteolysis of cellular proteins, including those that are involved in cell-division control. On inhibition of proteasomes with LDP341, the dysfunctional regulatory proteins of cancer cells are not lysed, but accumulate to toxic levels, eventually resulting in cancer cell death. It has been shown that healthy cells can be spared cell death (apoptosis) on the inhibition of proteasomes, whereas cancer cells are unable to recover from these effects.

Multiple myeloma – cancer of the bone marrow – is the second most prevalent blood cancer, representing ~1% of all cancers and constituting 2% of cancer deaths. The disease is almost twice as common in males as it is in females; >40,000 Americans are currently afflicted by multiple myeloma and >14,000 new cases are diagnosed in the USA each year.

Although the trial of LDP341, which was studied in 10 patients, was initially designed to define doses and evaluate toxicity, the compound was also shown to have anti-tumour activity. LDP341 reduced the number of myeloma cells in the bone marrow and lowered myeloma protein levels in 70% of cases.

Julian Adams, Senior Vice-President at Millennium Pharmaceuticals, said 'With its unique mechanism of action that targets cancer cells while sparing most healthy ones, LDP341 is a novel potential treatment that has shown anti-tumour activity both alone and in combination with other therapeutic agents in preclinical models and Phase I clinical trials.'

These findings were presented at the American Association for Cancer Research's *AACR–NCI–EORTC International Conference on Molecular Targets and Cancer Therapeutics* (29 October–2 November 2001, Miami Beach, FL, USA).

Business

Top trends for 2002

The creation of highly advanced Internet data centres, the purchase of small technology companies, an increasing active European Commission and a rise in the prominence of neurogenomics will all be strong trends for 2002, reported *Red Herring* (San Francisco, CA, USA) recently [6].

Highly advanced data centres are predicted to replace the current servers that run Internet traffic. These are now out-dated and it is predicted that new networks will facilitate real-time computing

and accelerate the outsourcing of computing resources so that computer networks will function and be distributed across larger distances. IBM (White Plains, New York, USA), Hewlett-Packard (Palo Alto, CA, USA) and smaller companies, such as Egenera (Marlboro, MA, USA) and Ensim (Sunnyvale, CA, USA), have all shown interest in web-hosting, which is predicted to become a US$28.5 billion business by 2005.

The deflation in global stocks is predicted to stimulate merger and acquisition activity in 2002. Name-brand technology companies desperate for cash, and investors keen for a positive return, might be tempted by private-equity firms who have raised multimillion dollar funds to work with, or compete against, private buyout firms.

It is predicted that companies intent on expanding globally through conglomeration will find it increasingly difficult to obtain merger approval in Europe. The European Union's views on privacy and taxation issues are likely to increase costs for US companies, benefiting small European-based technology companies by comparison.

Finally, the profile of neurogenomics among investors will increase next year, with a possible 25% of biotech-related venture capital predicted to be invested in the field by 2004. CNS disorders afflict 73 million people in the US. The size of this potential market is expected to outweigh suggestions that the efficacy of the drugs would make pharmaceutical companies less keen on becoming involved by preventing them 'stringing the patient along to garner a sustained profit,' said Christopher Westphal, Principal with Polaris Venture Partners (Waltham, MA, USA).

6 Pontin, J. (2001) Ten trends for what's ahead. *Red Herring* 107, 47–66

High goals for BMS

Bristol-Myers Squibb (BMS; New York, NY, USA) recently announced that they plan to submit an unprecedented five potential best-in-class or first-in-class products for regulatory filings in the next 12 months. The products are:

- A novel compound called aripiprazole, which is under investigation for the treatment of schizophrenia and related disorders. BMS aims to file for Marketing Authorisation Application in Europe by the end of 2001.
- Erbitix (cetuximab; formerly IMCC225), a monoclonal antibody. Co-developed and co-promoted with Imclone Systems (New York, NY, USA), a Biologics Licence Application has been submitted to use the drug for the treatment of advanced colorectal cancer that has been shown to be refractory to irinotecan.
- Vanlev (omapatrilat), a novel NEP/ACE inhibitor as a possible alternative treatment for congestive heart failure.
- An oral once-daily protease inhibitor (atazanavir) that possesses a favourable HIV resistance and lipid profile but (unlike other protease inhibitors) does not elevate lipid levels. Global regulatory submission is scheduled for Q3/4 2002.
- A novel quinolone antibiotic, des-6-fluoroquinolone. Submission for multiple indications is expected in Q3/4 2002.

BMS Chairman and CEO, Peter R. Dolan, cited the acquisitions and divestitures the company had made over the past year as the reason for the number of products now planned. 'As a result of these efforts, we believe we have the products that will allow us to achieve our goal of launching three potential blockbuster products a year, for several years, starting in 2003,' he said.

Miscellaneous

Novo Nordisk to go it alone with trials of PPAR agonist

Novo Nordisk (Denmark) has taken over the sole rights to commercialize NN622, a novel dual-acting insulin sensitizer for use in treating Type 2 diabetes, after Novartis Pharma AG pulled out of their collaboration. The CEO and President of Novo Nordisk, Lars Rebien Sorensen, has said that Novartis' decision will not impact on the NN622 development program. Recent results from Phase II studies have shown that the drug produces a substantial lowering of HbA1c (a marker for blood glucose levels) and of fasting plasma glucose levels along with an improvement in insulin sensitivity. NN622 has also been shown to affect lipid levels, producing a significant increase in HDL-cholesterol levels and a decrease in triglyceride levels and free fatty acid levels. Phase III trials are expected by the end of 2001 as originally scheduled.

NN622 is a PPARα (peroxisome proliferator-activated receptor) and PPARγ agonist. In preclinical and early clinical trials, it has been shown to have the potential to regulate diabetic dyslipidemia and blood glucose. However, as its mechanism of action is unlike other PPAR agonists currently being marketed, it would be a member of a new class of insulin sensitizers.

ACS announces major new grants

The American Cancer Society (ACS; Atlanta, GA, USA) has announced it will donate US$46,352,380 in its new research grant program. The program, comprising 84 separate grants, will be divided among Research Scholar Grants for Beginning Investigators (42 grants), Postdoctoral Fellowships (25), Clinical Research Training Awards (4), Physician Training Awards in Preventative Medicine (3), and Research Scholar Grants in Psychosocial, Behavioural or Health Policy and Services Research (2). Two of these grants exceed US$2 million and have been awarded to researchers at the University of California, Los Angeles (UCLA; CA, USA) and Dartmouth College (Hanover, NH, USA) to research some of the social and environmental issues surrounding cancer.

The grants also include a new ACS Research Professorship, which has been awarded to Graham Walker of the Massachusetts Institute of Technology (MIT; Cambridge, MA, USA) for research on the SOS DNA repair system in bacteria. This award is the Society's most prestigious award and is given to outstanding mid-career scientists who have made seminal contributions to their field. The grant provides US$80,000 per year in unrestricted research support for five years, with the option of one five-year renewal.

Walker commented that: 'What touches me more than anything else is that the American Cancer Society recognizes and acknowledges the fundamental research… [which], by its very nature, generally does not make the immediate connection to cancer in humans. What it does do is provide a basic understanding of the important molecular processes and strategies that are important for life.'

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