News in brief

Targets and mechanisms

Prions to treat prion diseases

The controversial theory that prion diseases can be treated by administering normal prions from another species has recently been supported by results from a computer model[1]. In prion diseases, abnormal PrP (a protein found on the surface of brain cells) enters the brain and creates more of itself by converting normal PrP into the abnormal form. This abnormal PrP then clumps together to form plaques. Daniel Cox and colleagues (University of California, Davis, CA, USA) have devised a model of the plaques that predicts how long the disease takes to develop, which could then be used to assess treatment protocols.

Research has also revealed a species barrier to prion transmission in that abnormal mouse PrP can infect hamsters but not vice versa. According to the model, if normal hamster PrP is injected into the brain of a mouse infected with abnormal PrP, the progression of the disease should be slowed down. However, there are still several obstacles to overcome for this to become a treatment. For example, very large concentrations of the normal hamster PrP are required and, as yet, there is no delivery system for PrP.

1 Slepoy, A. *et al.* (2001) On the statistical mechanics of prion diseases. *New Scientist* http://www.newscientist.com

3D structure of the glucocorticoid receptor elucidated

Researchers at Karo Bio AB (Huddinge, Sweden) and Abbott Laboratories (Abbott Park, IL, USA) have announced that they have determined the three-dimensional structure of the glucocorticoid receptor. The receptor is an important target for drug development, and mediates the inflammatory effects of steroids and regulates glucose metabolism. The elucidation of the structure of this protein target should make identification and optimization of lead compounds against the receptor much easier. The aim of the collaboration between the two companies has been to develop liver-selective antagonists of the glucocorticoid receptor in attempt to normalize the elevated output of glucose from the liver in type 2 diabetes.

New FGF protein identified

A new protein in the fibroblast growth factor (FGF) family has been discovered, which has been found to be inappropriately expressed in human cancer cells derived from the lungs, stomach and colon[2]. Scientists at Curagen Corporation (New Haven, CT, USA) are now developing fully human antibodies against this protein to inhibit its function in the hope of finding a new treatment for malignant tumour cell growth.

The gene encoding this novel protein, identified by using a homology-based genomic DNA mining process, was designated FGF-20 and is expressed in normal brain and some cancer cell lines. The researchers found that recombinant FGF-20 protein induces DNA synthesis in a variety of cell types and is recognized by multiple FGF receptors.

2 Jeffers, M. *et al.* (2001) Identification of a novel human fibroblast growth factor and characterization of its role in oncogenesis. *Cancer Res.* 61, 3131–3138

Are some cases of schizophrenia triggered by endogenous retroviruses?

The molecular footprint of a retrovirus found only in the cerebrospinal fluid (CSF) of people with schizophrenia has recently been discovered[3]. Robert Yolken and colleagues at the Johns Hopkins Children's Center found sequences homologous to the retroviral *pol* genes in cell-free CSF of 29% of people with acute schizophrenia or schizoaffective disorder and 5% of those with chronic schizophrenia. By contrast, these genes were absent in individuals with noninflammatory neurological diseases or with no evidence of neurological or psychiatric diseases.

The nucleotide sequence identified in the CSF of those with schizophrenia or schizoaffective disorder were related to those of the human engogenous retroviral (HERV)-W family and to other retroviruses in the murine leukaemia virus genus. Unlike HIV or other retroviruses, endogenous retroviruses are a natural part of the human genome.

Yolken says: 'While our report doesn't explain why the retrovirus becomes active in the first place, it presents clues as to what may happen when it does become active.'

It is hoped that further characterization of these retroviral elements could lead to improved methods for diagnosis and management of schizophrenia. Yolken adds: 'Our ultimate hope is that we can interfere with the retrovirus by preventing it from becoming active. If we can do that, it may give doctors another method of treating schizophrenia.'

3 Karlsson, H. *et al.* (2001) Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 98, 4634–4639

Anti-inflammatory action of statins

New research has shown that many statin drugs which are used, to lower cholesterol levels, can also directly help the inflammatory symptoms associated with atherosclerosis[4]. Previous research has shown that pravastatin can reduce levels of high-sensitive C-reactive protein (hs-CRP) in the blood, a protein associated with severe arterial inflammation, but this new study suggests that this is also a feature of other statins such as simvastatin and atorvastatin.

The randomized, double-blind study of 22 individuals with elevated levels of low-density lipoproteins (LDL) and triglycerides tested all three statin drugs in the same patients so that the results could be reliably compared. Subjects followed the American Heart Association Step 1 diet and took the three drugs alternately for periods of six weeks. Hs-CRP levels were reduced in 73% of the subjects while taking pravastatin and 82% while taking simvastatin or atorvastatin to below 2.0 mg l^{-1}, the crucial level at which the risk of heart attack or stroke increases dramatically.' There was also no significant correlation between reductions in hs-CRP and LDL cholesterol levels.

Ishwarlal Jialal, Director of the Division of Clinical Biochemistry and Human Metabolism at the University of Texas Southwestern Medical Center (Dallas, TX, USA) said: 'The good thing about all three

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statin drugs is that they lower CRP levels at the same time that they lower LDL and triglyceride levels. This is probably why they are associated with lower mortality from heart attacks and strokes.'

4 Jialal, I. *et al.* (2001) Effect of hydroxymethyl glutaryl coenzyme, a reductase inhibitor therapy on high-sensitive c-reactive protein levels. *Circulation* 103, 1933–1935

Neuronal repellant also directs leukocytes

Slit, the secreted protein known for its repulsion of neuronal migration and axon guidance has been found to also inhibit leukocyte chemotaxis induced by chemotactic factors[5].

The study, by a collaboration of scientists from Washington University School of Medicine (St Louis, WA, USA) and Baylor College of Medicine (Houston, TX, USA), showed that when human Slit proteins (hSlit2) were added to leukocytes that had been stimulated to migrate using chemotactic factors, fewer cells migrated. However, this inhibition of leukocyte migration could be reversed using Roundabout (Robo), a Slit receptor containing a single transmembrane domain that enables Slit to act on nerve cells.

Yi Rao, Associate Professor of Anatomy and Neurobiology at Washington University School of Medicine said: 'These results suggest that Slit also is likely to act through a Robo-like receptor on leukocytes to inhibit their migration.' He concluded that: 'This similarity between the immune system and nervous system might suggest new therapeutic approaches to immune system disorders such as inflammation and autoimmune diseases.'

5 Wu, J.Y. *et al.* (2001) The neuronal repellent Slit inhibits leukocyte chemotaxis induced by chemotaxis factors. *Nature* 410, 948–952

Just add water

A method for reviving dried normal human kidney cells has been developed by researchers at the Center for Genomics, Virginia Tech (Blacksburg, VA, USA), and was presented at the recent meeting of the *Society for Experimental Biology* in Canterbury, UK. The method, crucially using nongenetically modified cells, involves adding purified glycan before drying at room temperature. This technique mimics that used by the cyanobacterium *Nostoc commune*, which uses the slimy substance to survive desiccation.

When rehydrated eight days later, half the kidney cells were recovered and started dividing again. Previous successful attempts at drying and rehydrating cells have involved cells genetically modified to produce trehalose, which protects against freezing and drying. This new technique is hoped to enable antibodies and vaccines to have extremely long shelf-lives and enable blood from transfusions to be stored for long periods.

Grants and donations

AstraZeneca donates US$50,000 to fight antibacterial resistance

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID, Taufkirchen, Germany) has received a donation of US$50,000 from AstraZeneca for a clinical infection research programme to fight growing antibacterial resistance. The new partnership was symbolized at the *11th European Congress for Clinical Microbiology and Infectious Diseases* conference by a large mosaic artwork representing man's fight against infection, which is hidden by thousands of bricks.

Carl Erik Nord, ESCMID President, removed the first brick at the official opening of the congress and delegates removing subsequent bricks will have their support acknowledged with entry into a research registry and will receive research bulletins on the project. The specifics of the project are to be decided. ESCMID is a non-profit organization aimed at improving the diagnosis, treatment and prevention of infectious diseases in Europe by promoting and supporting research, education and training in the infection disciplines.

New comprehensive cancer centre for Australia

The Commonwealth Government has given a grant of Aus$20 million to the Queensland Institute of Medical Research (QIMR, Brisbane, Australia) and the Leukaemia Foundation (Fortitude Valley, Queensland, Australia) to provide for a new Comprehensive Cancer Centre at QIMR. The new Centre, also funded by an overseas philanthropist, the QIMR Trust and the Federal Government, will open in August 2001 and offer a combination of cancer research and development of new treatments. Its design will allow multidisciplinary scientific and clinical teams to work together in one location.

'Historically, Australia hasn't gained its rightful share from the development of new technologies such as information technology. Neither has it gained its fair share from the excellent work and discoveries of our medical scientists. This project will help to reverse that trend,' said Phillip Desbrow of the Leukaemia Foundation.

Miscellaneous

Collaboration to map entire human proteome by 2004

Myriad Genetics (Salt Lake City, UT, USA), Hitachi (Tokyo, Japan), Oracle (Redwood Shores, CA, USA) and Friedli (Zurich Switzerland) are to pool their resources to create a US$185 million collaboration aimed at analysing all proteins and their interactions within cells by 2004. Myriad will provide the proteomics expertise necessary to complete the task, along with technologies, which are valued at US$82 million.

Hitachi, Oracle and Friedli will contribute information and electronics technologies, software and financial investment, respectively, valued at a combined US$85 million in cash and US$18 million in technology.

The database and proteomics materials produced will be marketed by a 50% subsidiary of Myriad Genetics named Myriad Proteomics. ProNet®, an industrialized high-throughout version of the yeast two-hybrid system, and ProSpec™, a mass spectrometric technology for the identification of protein complexes, will be used to map the proteome.

Abbott labs offers HIV drugs at cost price

Abbott Laboratories (Abbott Park, IL, USA) are to make their antiretroviral medications,

Kaletra (lopinavir/ritonavir) and Norvir (ritonavir), and their rapid HIV-1/2 test Determine, available for sale in Africa on a non-profit basis.

The product lines will only be made available to qualified entities (such as the United Nations and other national and international health institutions) that are able to provide sustainable therapeutic programmes.

'Abbott has taken this action to give people most affected by this disease a better opportunity to access care. The next step in the global response is to develop the infrastructure necessary to deliver effective treatment,' said Miles D. White of Abbott.

Schering-Plough to contest illegal payment accusations

Schering-Plough (Kenilworth, NJ, USA) is to contest a suit filed by the Federal Trade Commission (FTC; Washington DC, MA, USA) alleging that patent settlements between it and the drug companies Lederle (of American Home Products, Madison, NJ, USA) and Upsher-Smith (Minneapolis, MN, USA) included illegal payments to delay a low-cost generic drug reaching the market.

The delay, which the FTC allege has cost the consumer US$100 million, surrounds a generic version of the drug K-Dur 20, often prescribed to patients with high blood pressure or cardiac problems. Schering deny the charges saying that it 'believes the settlements…complied with the law'. American Home Products and Upsher-Smith have also refuted the allegations and vowed to fight them.

'When payments are made to discourage entry, enormous potential for consumer harm exists,' said Molly Boast of the FTC.

Clinical trials

Drugs that won't let you down

Vardenafil

Results of the first large-scale patient trial of the selective phosphodiesterase 5 (PDE5) inhibitor, vardenafil, look promising as a new treatment for erectile dysfunction. These results were presented by Bayer at the *36th Annual European Association of Urology* (EAU) meeting in Geneva, Switzerland and showed that the drug was effective at improving erectile function irrespective of age or severity of erectile difficulty[6].

The placebo-controlled trial involved 580 patients (21–70 years) who had experienced difficulty with erectile function of organic, psychogenic or mixed aetiology for an average of 2.8 years.

Vardenafil enabled better penetration, as well as improved ability to maintain erection and complete intercourse (regardless of severity of the disorder) and was reported to have a good safety profile with no evidence of cardiovascular or other serious drug-related problems.

In preclinical studies presented in another poster at the *EAU* conference, vardenafil was shown to have greater pro-erectile activity than the Pfizer drug, sidenafil (Viagra)[7]. Vardenafil has now entered Phase III trials, the results of which will be published later this year.

6 Porst, H. *et al.* A new highly selective PDE5 inhibitor, improves erectile function irrespective of the baseline severity and etiology of ED or age of patient. *36th Annual European Association of Urology* (EAU) meeting, April 2001, Geneva, Switzerland

7 Tejada, I.S. *et al.* Potentiation of the NO-mediated relaxation of human trabecular penile smooth muscle by the PDE-V inhibitor, vardenafil. *36th Annual European Association of Urology* (EAU) meeting, April 2001, Geneva, Switzerland

IC351

Another PDE5 inhibitor, IC351, has been developed by Lilly ICOS LLC (Bothwell, WA, USA) to treat erectile dysfunction in diabetic men. Results of the Phase III study of IC351 were also announced at the *EAU* meeting[8].

Of the 216 men in the placebo-controlled, randomized trial with mild-to-severe diabetes-related erectile dysfunction, 64% of men reported improved erections with the drug compared with 25% who took the placebo. These results were independent of age, duration or severity of either the erectile dysfunction or the diabetes.

This was a lower success rate than reported in Phase II trials, in which up to 88% of men taking the drug reported significantly improved erections compared with 28% of those taking placebo[9].

Although some of the men included in the study had diabetes-related complications, few side effects were reported with no significant changes in clinical laboratory values, ECGs or blood pressure. Further results from the Phase III study will be released at meetings later this year.

8 Sánez de Tejada, I. *et al.* The effect of on-demand Cialis™ (IC351) treatment of erectile dysfunction in men with diabetes. *36th Annual European Association of Urology* (EAU) meeting, April 2001, Geneva, Switzerland

9 Brock, G. *et al.* On-demand administration of IC351 is effective and well tolerated in men with mild-to-severe erectile dysfunction. *36th Annual European Association of Urology* (EAU), April 2001, Geneva, Switzerland

Human trials for Traveller's diarrhoea vaccine begin in 2001

Preclinical studies have been completed for a vaccine to prevent diarrhoea caused by *Shigella sonnei*, announced its developers Antex Biologics (Gaitherburg, MD, USA) recently. The multicomponent vaccine, Activax, which protected 100% of animals from infection and disease, is viewed as an important step toward the development of a multivalent vaccine to prevent Traveller's diarrhoea, caused by *Shigella*, *Campylobacter* and enterotoxigenic *Escherichia coli*.

Four oral doses of the vaccine were given to animals, with two other groups receiving the vaccine plus a mucosal adjuvant or a placebo. All groups were then inoculated with live *Shigella sonnei* bacteria. All the animals given the vaccine alone or the vaccine plus adjuvant were protected against the disease, compared with none of the placebo group.

Antex Biologistics have successfully completed two Phase II clinical trials on the *Campylobacter* component of the Activax vaccine and trials of the multivalent formulation will be initiated after the completion of trials of each of the separate components.

The company estimates that the market for a Traveller's diarrhoea vaccine exceeds US$750 million.

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