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News in brief

Targets and mechanisms

New role for GM-CSF in heart patients

Granulocyte–macrophage colony-stimulating factor (GM-CSF) significantly improves blood flow around blocked coronary arteries according to a recent report[1]. The human protein GM-CSF is often used in cancer patients to aid haemopoietic recovery following chemo- or radiotherapy. However, scientists at the University of Bern (Switzerland) have shown in a clinical study that GM-CSF improves collateral blood flow.

The researchers studied 21 patients with coronary artery disease that was too severe to be treated with balloon angioplasty or bypass surgery. Before their treatment, the patients' collateral blood flow was assessed downstream from the artery blockage. The group of 10 men and 11 women with an average age of 75 were randomized to receive either a subcutaneous injection of GM-CSF or placebo every other day for two weeks. After treatment, collateral blood flow was significantly improved in the GM-CSF group, whereas it was unchanged in the placebo group. Furthermore, a reduction in ischaemia (measured using electrocardiography) was observed in patients treated with GM-CSF, in contrast to those treated with placebo, in whom ischaemia was found to increase. The study group will now be followed for one year.

1 Seiler, C. *et al.* (2001) Promotion of collateral growth by granulocyte-macrophage colony-stimulating factor in patients with coronary artery disease: a randomized, double-blind, placebo-controlled study. *Circulation* 104, 2012–2017

Protective role for thrombospondin in cancer

Scientists at the University of California, Los Angeles (UCLA; CA, USA) have proved that the angiogenic inhibitor thrombospondin-1 (TSP-1) has a role in tumour progression[2] and is, therefore, a potential target for anti-cancer therapies.

In mammary-tumour-prone mice that lacked TSP-1, tumour burden and associated vasculature were significantly increased, whereas mammary-tumour-prone mice that overexpressed TSP-1 exhibited delayed tumour growth and, in 20% of the animals, lacked frank tumour development.

Molecular studies revealed that in mice lacking TSP-1, vascular endothelial growth factor (VEGF) was increasingly associated with its receptor, VEGFR. Furthermore, an increase in active matrix metalloprotease-9 (MMP-9), which is involved both in angiogenesis and tumour invasion, was observed. These results suggest that TSP-1 regulates angiogenic events mediated by VEGF and MMP-9 and could have a protective role in tumour growth and invasion.

2 Rodriguez-Manzaneque, J.C. *et al.* (2001) Thrombospondin-1 suppresses spontaneous tumor growth and inhibits activation of matrix metalloproteinase-9 and mobilization of vascular endothelial factor. *Proc. Natl. Acad. Sci. U. S. A.* 98, 12485–12490

Targets and mechanisms in neuroscience

The missing link?

Researchers have discovered the missing link between the two main inherited forms of Parkinson's disease (PD), which could also be connected to the non-inherited forms of the disease. The inherited forms of PD are marked by alterations or mutations in one of two proteins, parkin or α-synuclein. How these two proteins lead to the same disorder is not yet well understood. However, scientists at Johns Hopkins School of Medicine (Baltimore, MD, USA) suggest that both these proteins could interact with a third protein, synphilin, and that the mutations disrupt this interaction[3].

In PD, dopamine-producing nerve cells die, starving the brain of a crucial messenger. Many of these dead cells contain protein clusters, known as Lewy bodies, which could include parkin, α-synuclein or synphilin. Ted Dawson,

Professor of Neurology and Neuroscience and Director of the Program in Neural Regeneration and Repair for the Johns Hopkins Institute for Cell Engineering said, 'We were trying to see if the genetic mutations converge with what is known about the non-inherited disease… And now, all roads in PD seem to lead to α-synuclein.'

The research shows that parkin binds to synphilin, and via synphilin to α-synuclein. Parkin then ubiquitinates these proteins and the result is the formation of Lewy bodies. Dawson suggests that one stimulus behind Lewy body formation could be a malfunctioning α-synuclein. 'We suspect that the destruction pathway and the action of ubiquitin might be very important in PD, that perhaps the altered destruction of α-synuclein could be the common thread in causing these neurons to die.'

3 Chung, K.K. *et al.* (2001) Parkin ubiquitinates the α-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson's disease. *Nat. Med.* 7, 1144–1150

Size does matter in AD predisposition

Researchers at the University of South Florida (Tampa, FL, USA) and the University of Washington (Seattle, WA, USA) have determined the markers for predisposition to Alzheimer's disease (AD)[4]. The risk of developing the disease is increased if people carrying the Alzheimer-related gene also have a small head circumference. The presence of the gene, *ApoE ε4*, in combination with a small head size, increased the likelihood of AD by 14-fold;

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people with small head size alone had no increased predisposition to the disease. Amy Borenstein Graves, one of the researchers at the University of South Florida said, 'Those with large brain reserves may have the same changes in their brains, but they don't show symptoms of the disease until much later.'

The study involved 1869 Japanese-Americans aged 65+, for an average of 3.8 years, during which time 59 people developed AD. Those who did develop the disease were older, less educated, shorter, lighter and had lower estimated verbal IQ scores than those who did not. They were also more likely to have at least one *ApoE ε4* allelle and fall into the category of head size <21.4 inches. Borenstein Graves continued, 'In our study, 18% of the risk of Alzheimer's was attributed solely to small head size. So, if it were possible to increase brain reserve through prevention of brain damage that occurs across the life span, nearly 20% of the disease…might be preventable.'

4 Borenstein Graves, A. *et al.* (2001) Head circumference and incident Alzheimer's disease. *Neurology* 57, 1453–1460

Cocaine relapse goes to pot

The cannabinoid system that governs the actions of marijuana in the brain might also play a role in the processes underlying relapse to cocaine use[5]. The results of the study could lead to a new generation of treatments to prevent cocaine relapse after long periods of withdrawal.

First, the study showed that in a rat model, a synthetic cannabinoid-receptor agonist provoked cocaine relapse after long periods of withdrawal. Second, and perhaps more importantly, it showed that a cannabinoid-receptor antagonist selectively reduced relapse behaviour in two of the most common conditions associated with relapse – conditioned cocaine cues and cocaine use itself. However, when given alone, the cannabinoid-receptor antagonist did not modify baseline response rates, indicating that the cannabinoid receptors are selectively involved in triggering cocaine craving rather than in mediating the primary effects of the drug.

It is well-known that the liberated feelings accompanying marijuana use are linked to dopamine release in the brain. Although mapping of the cannabinergic pathway in the brain is still tenuous, it is thought that the new results could be interpreted in one of two ways. Raised dopamine levels, initiated by cocaine or cocaine-associated cues, elicit the release of endocannabinoids thereby causing the relapse. Alternatively, the same cues could elevate cannabinoid levels, which then cause relapse by enhancing dopamine release.

Either way, the research could lead to new therapeutic treatments that target cannabinoid receptors, in particular CB_1, to prevent relapse into cocaine seeking.

5 De Vries, T.J. *et al.* (2001) A cannabinoid mechanism in relapse to cocaine seeking. *Nat. Med.* 7, 1151–1154

The long and short of HD

Researchers at the Mayo Clinic (Rochester, MN, USA) have new results that contradict one of the major hypotheses believed to be behind the cause of Huntington's disease (HD)[6]. The research could lead to more effective strategies to help treat the disease.

HD is an inherited neurodegenerative disorder, characterized by involuntary movements, cognitive impairment and mood disturbances. The disease is caused by expansion of a repeated sequence of the amino acid glutamine in the abnormal protein huntingtin (Htt).

It was originally thought that 'clipping' of the mutant protein, by a process known as proteolysis, generated small toxic fragments that accumulate in the brain and become toxic to neurons. Current therapies therefore aim to block the molecules that clip the protein, thereby preventing release of the toxic fragment.

However, the new research has found that the mutant protein is actually resistant to proteolysis, much more so than its normal counterpart. Therefore, the full-length abnormal protein accumulates in the neuron over time. Furthermore, they

Clinical trials

Good publicity for clinical trials?

The incidence of death as a result of clinical trials is low, according to a recent study by CenterWatch. The study, published in the October edition of the CenterWatch newsletter (http://www.centerwatch.com), is the first to investigate the risk of adverse events and death in investigational treatments. The study found that one adverse event per research subject is reported for every new drug application (NDA), and that death resulting from investigational treatments is rare.

The study is the result of the accumulation of 130 randomly selected NDAs that have been approved since 1997 (almost one-third of new chemical entities during this period). Almost 3500 serious adverse events and 13 deaths were reported resulting from studies of drug effects.

Ken Getz of CenterWatch believes that this information is an important part of health consumer education and informed consent. It could also help to reverse some of the bad publicity recently surrounding clinical trials. However, Mary Jo Lamberti of CenterWatch warned that this study fails to convey the wide variability in risk, which is dependent on the type of disease and drug being studied, and the trial duration. The study also does not include the many cases of trials that are terminated before an NDA is filed.

Painless Phase II for PTI555

Pain Therapeutics (South San Francisco, CA, USA) announced recently that its investigational painkiller PTI555, a combination of morphine and low-dose naltrexone, has achieved its primary endpoint in Phase II clinical trials.

The Phase II double-blind, randomized, placebo-controlled trial enrolled 210 patients with moderate to severe pain that required opiate therapy following oral surgery. Immediately after surgery, patients received a single dose of morphine, PTI555 or placebo. The primary endpoint, pain relief within eight hours, was achieved in 25% of patients given PTI555. Furthermore, patients given PTI555 experienced more pain relief after four hours than those patients taking morphine or placebo, with no significant change in side effects (http://www.pathtrials.com).

show that the full-length protein could target its normal counterpart and knock out its function – a process that would be lethal to normal cell functioning. As a result of these findings, new therapies could be focused on developing molecules that prevent the mutant protein from grabbing other normal cellular targets.

In a separate study, researchers at the University of California, Irvine (CA, USA), provide molecular clues as to how neuronal loss in HD occurs[7]. The polyglutamine domain of the mutant protein, termed Htt exon 1 protein (Httex1p) has been found to bind to the acetyltransferase domains of important proteins, such as CREB-binding protein, and inhibit their action, of which normal functioning is essential for brain cells.

Acetyltransferases and deacetylases have opposing functions to increase and decrease the levels of genetic activity, respectively. As Httex1p affects this balance, researchers sought to redress this by reducing histone deacetylase (HDAC) activities to compensate. They found that administrating inhibitors of HDAC arrested progressive neuronal degeneration and reduced lethality in two *Drosophila* models of the disease.

'By reversing the key changes in these pathways, we have identified a potentially effective way to slow or prevent the disease. What's especially exciting is that the existing drugs, known as HDAC inhibitors, have the potential to provide this treatment,' said Leslie Thompson, College of Medicine, University of California, Irvine, and co-author of the study.

6 Dyer, R.B. and McMurray, C.T. (2001) Mutant protein in Huntington disease is resistant to proteolysis in affected brain. *Nat. Genet.* DOI:10.1038/ng745 (www.nature.com/ng/)

7 Steffan, J.S. *et al.* (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature* 413, 739–743

Miscellaneous

Research network to share brain imaging data

A consortium of universities has been awarded US$20 million to build the first computer environment to study diseases of the brain. The award was given by The National Center for Research Resources

(NCRR), a component of the National Institutes for Health (NIH), and the consortium was coordinated by the University of California, San Diego (UCSD; CA, USA). Researchers, linked over a nationwide network, will have access to high-resolution animal and human brain images, which will enable the cross-institutional integration of data and expertise to advance research in diseases such as Alzheimer's and Parkinson's disease, multiple sclerosis and schizophrenia.

The director of NCRR, Judith Vaitukaitis, said, 'Biomedical research is undergoing a rapid transformation that can be traced to the explosion in the size of datasets ranging from DNA and protein sequences to high-resolution images mapping the architecture of cellular components, cells, tissues, organs and whole organisms. Information technology is becoming essential for management and analysis of these data.'

The Biomedical Informatics Research Network (BIRN) will be the first such network for effective data mining and sharing for basic and clinical research. BIRN Principal Investigator and Director of the UCSD Center for Research on Biological Structure, Mark Ellisman, said 'BIRN will create an environment for organizing and presenting data in a way that makes it accessible and useful to other researchers. All of us will be able to study linkages between animal models for human diseases and data from patients suffering with these diseases.'

Initially, data from ongoing experiments will be divided between two major BIRN projects: (1) the Mouse BIRN project (led by G. Allan Johnson, Director of the Center for *In Vivo* Microscopy, an NCRR Resource at Duke University, Durham, NC, USA), which will extend two mouse models of human disease – one that develops a neurological disorder similar to mulitiple sclerosis and another where the gene altering dopamine levels has been altered, which is implicated in several brain disorders; and (2) the Brain Morphology BIRN project is based on ongoing human studies and is led by Bruce Rosen (Director of the Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging, Massachusetts General Hospital–MIT–Harvard Biomedical School) and colleague Anders Dale, with the initial focus being on depression and Alzheimer's disease.

New supercomputing power in Japan

The Institute for Chemical Research (ICR) at Kyoto University (Kyoto, Japan) has recently bought a 768-CPU supercomputing system from SGI (Mountain View, CA, USA), formerly known as Silicon Graphics, thereby making it the site of one of the biggest supercomputing systems in Japan.

The two SGI™ Origin™ 3800 systems have 512 CPUs dedicated to computational chemistry and 256 CPUs for use in computational biology, and the ICR will use these systems to further their research in those areas. SGI is also including an SGI™ Onyx® 3400 visualization system that has 32 CPUs and an SGI™ TP9400 35TB storage system.

SGI has previously delivered several systems to the ICR over the past 10 years. These computers have been used in genomics research and have helped to launch GenomeNet, a group of genomics databases [including the Kyoto Encyclopedia of Genes and Genomes (KEGG)] available to researchers around the world.

Multiplexing and miniaturization

A new approach to miniaturization for multiple biochemical analysis has been described by researchers from SurroMed (Mountain View, CA, USA) and Pennsylvania State University (PA, USA)[8]. The Nanobarcodes™ particle technology aims to accelerate research into the molecular basis of disease, and could be a key step to developing novel diagnostic products and key therapeutic approaches.

Nanobarcodes™ are cylindrical striped metal nanoparticles in which the stripes comprise different metals, such as gold,

copper and zinc. Like traditional barcoding, the technology enables the creation of extremely large sets of uniquely identifiable particles by the width and composition of their stripes.

Suspensions of barcoded particles are prepared by sequential electrochemical reduction of metal ions into pores on the membrane templates. The structure of each particle is governed by membrane pore diameter, the sequence of ions used, and the charge. Individual particles can then be identified by an optical microscope.

The approach, known as multiplexing, means that large numbers of biological assays can be performed simultaneously in a small volume of liquid. With the advent of genomics, proteomics and metabolomics, the new technology holds great promise for the future.

8 Nicewarner-Peña, S.R. *et al.* (2001) Submicrometer metallic barcodes. *Science* 294, 137–141

Genetic basis of adverse drug reactions

GlaxoSmithKline (GSK; Stockley Park West, Uxbridge, UK) and First Genetic Trust (FGT; North Deerfield, IL, USA) have announced a collaboration to study genetic variations that could influence the adverse reactions some people experience when taking medication. This would hopefully lead to the development of diagnostic tests to screen for patient susceptibility to further prevent the risk of exposure.

Serious adverse drug reactions (ADRs) are the primary reason why effective medicines are subsequently removed from the market, yet they are so uncommon that they do not become apparent until the drug is used in the general population. At present, less than 1% of the population is at risk from ADRs and this study will potentially reduce the occurrence of side effects and facilitate product prescription.

GSK is sponsoring the study and will do all the analyses while FGT is providing its genetic banking services for the storage of biological samples, as well as medical data. FGT will also be responsible for patient confidentiality and privacy and for obtaining informed consent.

Allen Roses, Senior Vice-President of Genetics Research at GSK, said 'This study to investigate the genetic basis of ADRs will have important implications for drug development and clinical use. Pharmacogenetic studies such as this one will not only increase patient safety but also provide a scientific basis to understand ADRs at the molecular level.'

Financial boost for French biotech

The French government has agreed new plans proposed by the French Biotechnology Industry Association (France Biotech) to boost investment in the French biotechnology industry. The proposal, coined 'Plan Biotech 2002', will be backed jointly by France Biotech and an association of entrepreneurs, Objectif 2010.

The main objective of Plan Biotech 2002 is to create an increasingly favourable climate for investment in France by facilitating the creation of biotech start-ups and accelerating growth of the more established companies. Accordingly, 90 million will be spent on bank loan guarantees to finance acquisitions of foreign biotech companies and R&D investments. In addition, a further 60 million will be channelled into a seed-financing venture to promote start-ups. Hopes are that if the plan grows in 2003, it should result in several billion Euros of investment by 2006.

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People

Awards

Founding Chairman of amfAR honoured

Mathilde Krim, Founding Chairman and Chairman of the Board of the American Foundation for AIDS Research (amfAR; New York, NY, USA), has recently been awarded the Eleanor Roosevelt Val-Kill Medal in recognition of her leadership role in the research effort against HIV/AIDS. Previous recipients of the award include Dorothy Height (President Emerita of the National Council of Negro Women) and Christopher Reeve (Chairman of the Board of the Christopher Reeve Paralysis Foundation).

Krim also holds 13 doctorates *honoris causa* and was awarded the Presidential Medal of Freedom in August 2000 in recognition of her 'extraordinary compassion and commitment'.

The 2001 Albert Lasker Awards

Mario Capecchi (University of Utah, UT, USA), Martin Evans (Cardiff University, Cardiff, UK) and Oliver Smithies (University of North Carolina, Chapel Hill, NC, USA) have been awarded the 2001 Albert Lasker Award for Basic Medical Research for pioneering the use of mouse embryonic stem cells to create animal models of human disease. Meanwhile, the 2001 Albert Lasker Award for Clinical Medical research went to Robert G. Edwards (University of Cambridge, UK) for the development of *in vitro* fertilization. Finally, William H. Foege (Emory University, Atlanta, GA, USA) was awarded the Mary Woodard Lasker Award for Public Service in Support of Medical Research and the Health Sciences for improving worldwide public health and playing a key role in eradicating smallpox and preventing river blindness.

Appointments

Hamner announces retirement from leading the North Carolina Biotechnology Center

Charles E. Hamner, President and CEO of the North Carolina Biotechnology Center (Research Triangle Park, NC, USA) recently announced that he plans to retire on

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