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News in brief

Targets and mechanisms

Measles virus implicated in Hodgkin's lymphoma

A recent study by researchers at Ben-Gurion University (Beer-Sheva, Israel) has shown that the measles virus is present in the tumour cells of patients suffering from classical Hodgkin's lymphoma (HL). These results were presented at the *92nd Annual Meeting of the American Association for Cancer Research* (New Orleans, LA, USA). In a study of 68 patients with classical HL, undertaken at the Soroka University Medical Center, 60% of samples were shown to be positive for one or both of the two major proteins (nucleoprotein and haemagglutinin) produced by the measles virus. RNA coding for measles-virus haemagglutinin RNA was also found to be present during a spot check of a few samples.

It has been recognized for more than a decade that individuals who have contracted mononucleosis, a common systemic disease caused by Epstein–Barr virus, have an enhanced chance of developing HL. The study opens the way for a more detailed investigation of the role of measles in Hodgkin's lymphoma. 'The issue of Hodgkin's lymphoma and viral infection, either measles or Epstein–Barr is still much of a riddle,' said Professor Jacob Gopas of Ben-Gurion University. 'Not all biopsies from patients show infection, and the two viruses studied are so different from one another.' The researchers will now study the measles genes found in their HL biopsies to determine whether they originated in measles strains active in Israel or perhaps from the vaccines used to immunize Israeli children.

New cholesterol gene discovered

A genetic investigation of families with autosomal recessive hypercholesterolemia (ARH) has led to the identification of the gene that is mutated in this disorder[1]. ARH is characterized by a 5–10-fold increase in low-density lipoprotein (LDL) levels in plasma. Researchers at the University of Texas Southwestern Medical Center (Dallas, TX, USA) found that the *ARH* gene is located on chromosome 1p35 and that as many as six different mutations on the *ARH* gene can give rise to the disease.

The normal clearance of LDL is achieved predominately by LDL receptors in the liver and, unlike another condition (autosomal dominant familial hypercholesterolemia) that arises from mutation of this receptor, ARH is not caused by direct impairment of the receptor itself. Instead, the *ARH* gene encodes a novel adaptor protein that appears to be necessary for the LDL receptor to function properly. Although ARH itself is rare, the discovery will hopefully increase understanding of the factors that contribute to high levels of cholesterol and highlight potential therapeutic targets.

1 Garcia, C.K. *et al*. (2001) Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science*, 292, 1394–1398

Three genomes sequenced

Mouse genome

The Mouse Sequencing Consortium (MSC; Bethesda, MD, USA) announced that it has now generated threefold coverage of the mouse DNA sequence. The data represent >95% of the full complement of mouse DNA and, because the MSC is an international public–private effort, the data are freely available to all researchers worldwide.

The mouse genome data is essential to further understanding of the human genome because the two are >90% similar. Comparisons of mice and human DNA will help to identify other genetic features of the human genome such as the regulatory regions of DNA that turn gene expression off and on. The sequence was determined using the shotgun sequencing approach, which produces random fragments of the sequence. Identifying disease-related regions in the mouse should make it easier to research new treatments for humans and it is hoped that the success of this private–public consortia will lead to other similar consortia and thus enable rapid results in future projects.

Aspergillus fumigatus

Elitra Pharmaceuticals (San Diego, CA, USA) has announced the complete sequence of the *Aspergillus fumigatus* genome, one of the largest microbial genome sequences. This project was carried out through a contract with Celera Genomics (Rockville, MD, USA).

A. fumigatus is a human fungal pathogen that is a major cause of mortality in immunocompromised patients and currently, the effectiveness of available drugs to treat infection is variable depending on the site of infection. Previously, Elitra Pharmaceuticals used its proprietary technology for identifying essential gene targets in *Candida albicans*, another major fungal pathogen. Now, the same technology (together with the sequence information) will be applied to *A. fumigatus* as an important step towards the development of an effective treatment for *A. fumigatus* infection.

Saccharopolyspora erythraea

One of the largest bacterial genomes, that of *Saccharopolyspora erythraea*, has now been sequenced at the University of Cambridge (Cambridge, UK). *S. erythraea* is used industrially to produce the broad-spectrum antibiotic erythromycin, which is also the starting material in the production of semi-synthetic derivatives. Analysis of the sequence data of this genome is hoped to help in the search for novel antibiotics, immunosuppressants and anti-cancer compounds. The group, led by Peter Leadlay, worked in collaboration with the Biochemistry Sequence Facility (also at Cambridge University) led by John Lester. The data is already proving useful, providing insights into metabolic regulatory processes. Now, functional genomics tools will be used to investigate the molecular basis of overproduction of erythromycin and other polyketide antibiotics.

MMPs stimulate cell migration

The movement of cancer cells through tissues is incompletely understood, but the results of a recent study have added another piece to the puzzle. It is generally accepted that migratory cells, including those that are cancerous, possess special enzymes (matrix metalloproteinases; MMPs) that serve to break down the extracellular matrix, thus clearing a path through which they can move. However, MMPs have also now been found to process specific cell adhesion molecules and to promote cell migration[2].

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The research shows that the membrane-type 1 MMP (MT1-MMP), commonly expressed by invasive cancer cells, directly cleaves the CD44 adhesion protein from the surface of cells, effectively removing the anchor that keeps them immobilized. Furthermore, the process of CD44 degradation by proteolysis stimulates cell movement. The molecular interaction between MT1-MMP and CD44 provides additional clues to understanding the events that regulate melanoma cell invasion and metastasis, and with it, improved prospects for the development of selective compounds that could help to control the spread of cancer in patients.

2 Kajita, M. *et al.* (2001) Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. *J. Cell Biol.* 153, 893–904

New insight into HIV resistance

New findings from a unique and much studied cohort of individuals – commercial sex workers in Kenya – could help in the search for an effective vaccine against HIV. This group of individuals is unusual in that, despite repeated exposures to the virus, some of these women remain seronegative. It has been thought that a persistent HIV-specific immune response, in particular the generation of cytotoxic T lymphocytes (CTL), underpins this immunity but this new study[3] provides novel insight into this theory.

The study shows that ~10% of previously HIV-resistant individuals in this cohort seroconverted to HIV^+ status, despite the expression of CTL epitopes in the blood that are specific for the sequence of the infecting virus. Interestingly, they also found that this late susceptibility to the infection was correlated with decreased exposure to the virus, raising the possibility that reduced antigenic stimulation led to the loss of the CTL response. It is currently unclear whether particular CTL epitopes are responsible for HIV resistance, but these findings, and the possible relationship between antigenic stimulus and immunological state, could provide additional strategies towards the development of effective HIV vaccines.

3 Kaul, R. *et al.* (2001) Late seroconversion in HIV-resistant Nairobi prostitutes despite pre-existing HIV-specific $CD8^+$ responses. *J. Clin. Invest.* 107, 341–349

Gleevec shows promise for treatment of GIST

Gleevec, the cancer-fighting drug recently approved by the Food and Drug Administration to treat leukaemia patients, has also shown remarkable results in the treatment of gastrointestinal stromal tumours (GIST). GIST is a deadly cancer that affects the wall of the intestine and for which traditional cancer treatments are not effective.

The first two of four patients to participate in the ongoing study, which is being carried out at the Edward Cancer Center (Naperville, IL, USA), showed reductions of >50% in tumour size in patients with GIST. The patients had both received daily doses of Gleevec (also known as STI571) for eight weeks before scanning by confocal tomography. Neither participant experienced any side effects normally associated with oncology treatment.

'Early indications are nothing short of remarkable,' said Alexander Hantal, Medical Director at the Edward Cancer Center. 'This drug is effectively attacking an aggressive, non-responsive form of cancer without the debilitating side effects of so many other cancer fighting agents.'

Gleevec is the first oncology drug to be developed through rational drug design, based on an understanding of how cancer cells work. The positive clinical results from trials in leukaemia patients prompted the FDA to grant a priority review, resulting in an approval after only two-and-a-half months, the fastest time to market of any cancer treatment.

Vitamin C-derivative protects against stroke

A recent study has shown that dehydroascorbic acid (DHA) is effective in reducing the extent of brain damage, neurological deficits and reduced mortality by 66% when administered up to 3 h after a stroke. The results of the study by researchers at the New York Neurological Institute of Columbia University and Memorial Sloan-Kettering Cancer Center were presented at the *53rd Annual Meeting of the American Academy of Neurology* (Philadelphia, PA, USA).

Currently, tissue plasminogen activator represents the only FDA-approved treatment. The new compound (licensed by Progenics Pharmaceuticals), which is a vitamin C-derivative, is converted into vitamin C after crossing the blood–brain barrier. Once in the brain, it acts as a powerful antioxidant, neutralizing the toxic effects of free radical accumulation, which arise during stroke when the brain's blood supply is compromised. The ability of DHA to protect tissue, even when given hours after a stroke, is encouraging because antioxidants of this nature could represent a useful therapeutic tool for preventing the detrimental effects of stroke and of other conditions that lead to ischemic tissue damage.

Clinical trials

Phase III trial fails

IOMED (Salt Lake City, UT, USA) has announced that the Phase III confirmatory clinical study of its G-II product, formerly called ProDex™ did not meet the primary endpoints in the treatment of epicondylitis (Golfer's elbow), which causes inflammation and tenderness. The results showed a positive response in patients treated with the drug but increased efficacy in the placebo group was also observed. The results of the confirmatory study were inconsistent with those from earlier pivotal Phase III studies, in which the symptoms associated with epicondylitis and plantar fasciitis were reduced. IOMED had planned to file a New Drug Application (NDA) with the Food and Drug Administration for G-II in mid-2001 but now the G-II database of all the clinical trial data will be analyzed to determine the next step in product development.

Novel platelet-derived growth factor discovered

Published in back-to-back articles in *Nature Cell Biology*, the fourth member of the platelet-derived growth factor (PDGF) family, PDGF-D, has been discovered and characterized by two independent laboratories[4,5]. By mining databases of human expressed genes, both groups of researchers identified gene sequences that were highly homologous with known PDGFs and generated full-length cDNA sequences for PDGF-D.

Human and mouse PDGF-D encodes a 370-amino acid polypeptide, the sequences of which are highly conserved (85% amino acid identity) across the two species. Expression of PDGF-D was absent from the brain but was found in many peripheral tissues, including the heart, pancreas, adrenal glands and reproductive organs. As with the other growth factors, PDGF-D forms disulfide-linked homodimers and requires proteolytic processing to unmask its receptor-binding sites. PDGF-D is a unique agonist in that it represents the only growth factor that binds to the PDGF β-receptor but not the α-receptor; however, PDGF-D appears to bind to both receptors when co-expressed on the same cell.

Based on its widespread distribution in the body, unique receptor pharmacology and ability to induce DNA synthesis, together with its over-expression in cancer tissues and cell lines, PDGF-D could be important in many physiological processes and might prove to be useful as a therapeutic agent in some pathophysiological conditions.

4 Bergsten, E. *et al*. (2001) PDGF-D is a specific, protease-activated ligand for the PDGF β-receptor. *Nat. Cell Biol.* 3, 512–516

5 LaRochelle, W.J. *et al*. (2001) PDGF-D, a new protease-activated growth factor. *Nat. Cell Biol.* 3, 517–521

Miscellaneous

Novartis–Roche merger to be ignored 'for now'

Novartis (Basel, Switzerland) and Roche (Basel, Switzerland) are not to merge in the near future but will be discussing concrete ways in which to cooperate, announced Daniel Vasella of Novartis recently. Vasella, whose company has recently taken a 20% share in the rival healthcare group, stated that the subject of a merger was 'not up for discussion' and would remain ignored 'for now'.

The companies were suggested as complementing each other's product range pipelines well, and Vasella continued by saying that, 'the important thing is that the relationship is, and stays, constructive'. In a separate interview, Franz Humer of Roche said, 'I do not feel hemmed in at all pursuing our strategic goals including acquisitions, alliances, licensing and business development in the broadest sense. Novartis is a large and important shareholder, but we treat all… equally.'

Novartis is not opposed in principle to introducing a unified share at Roche but do not wish to dilute its voting rights. The founding families at Roche have a majority vote on the board despite owning <10% of the overall equity. Novartis is expected to discuss the possibility of a supervisory board seat.

Cipla could reduce cost of AIDS drugs still further

Cipla (Mumbai, India) has applied to the Indian government for permission to manufacture a generic AIDS tablet containing the protease inhibitors lamivudine, nevirapine and stavudine, that could reduce the price of these drugs still further. The pill, named Triomune-LNS, will be the first combination pill of the three treatments and could lead to further price reductions for charities such as Medecins Sans Frontieres (Brussels, Belgium).

The three medicines are already available separately at one-thirtieth (US$350 per patient per year) of the price in the US. Yusuf Hamied, Managing Director of Cipla, described AIDS as a 'foreseen tragedy'. 'I represent the Third World and its needs and aspirations, he continued, …[and] the capabilities of a country with a billion population (*Times of India*).' GlaxoSmithKline (Essex, UK), Boehringer Ingelheim GmbH (Ingesheim, Germany) and Bristol-Myers Squibb (New York, NY, USA) currently hold the patents for LNS, respectively, but these patents only apply to the processes by which the drugs are made and not the drugs themselves.

Vaccine report retracted as data found to be faked

The authors of a vaccine research report, published in the 4 January 2000 issue of the *Proceedings of the National Academy of Sciences*, have issued a retraction of their data following the admission by its lead author that he rigged the experiment . The retraction, published on the journal's website in the 8 May 2001 [Vol. 98 (10)] edition of the journal, states that Tatsumi Arichi 'spiked some of the ovary homogenates…with calculated quantities of stock vaccinia virus' so that it appeared to have taken hold and be growing. Arichi, who worked at the National Institutes of Health from December 1995 to May 1999, admitted his part when his colleagues unsuccessfully tried to repeat the experiment (developed to test the ability of a DNA vaccine to block the hepatitis C virus). The matter is being investigated by the NIH Office of Research Integrity (courtesy of John P. Stewart, Quebec, Canada).

South Korea aims to play active role in post-genome era

An adviser to the South Korean President, Song Hae-bok, has recommended that the country's current biological research budget (US$228 million) be doubled for the year 2002 so that the country can play a more active role in the post-genomic era, it was recently reported in *The Nikkei Weekly* (Tokyo, Japan; courtesy of John P. Stewart, Quebec, Canada). A relative latecomer to the field of biology, South Korea is making efforts to broaden and strengthen its national research facilities by investing in technologies that can harness the information produced by the Human Genome Project.

At the root of this initiative is the South Korean Research Institute of Bioscience and Biotechnology (KRIBB), created in 1999 and headed by Song. Comprising 14 laboratories covering protein engineering, immunology and microbiology R&D, the Institute also has five research centers focusing on the human genome, molecular and cellular biology and genetic resources. In addition to advertising internationally, the facility aims to fill its projected staff expansion by actively targeting US and UK scientists as well as Korean scientists who have gone abroad. In 1999, the Government also launched the Human Genome Functional Research Corporation, a facility designed to bring together 400 of South Korea's scientists in one organization aimed at conducting human genome-related R&D.

Aventis and Bristol-Myers Squibb commit aid to WHO sleeping sickness program

Aventis Pharma (Basel, Switzerland) has agreed to donate five-year supplies of the sleeping sickness (trypanomiasis) drugs pentamidine, melarsoprol and eflornithine to the World Health Organization (WHO), six years after it ceased production because

it was deemed unprofitable. In a separate arrangement, Bristol-Myers Squibb has agreed to cover the cost of bulk-materials for 60,000 vials (approximately a one-year supply) of eflornithine.

The donations, which also include funding of £17 million from Aventis for the WHO's treatment and research programmes into the disease, follows recent poor publicity for large pharmaceutical companies regarding their sale of AIDS drugs to the South African Government. 'This agreement is excellent news for patients and a major step in the struggle to control sleeping sickness', said Bernard Pecoul, Director of Medecins Sans Frontieres (Brussels, Belgium). He then asked for an additional £25 million per year from international donors to support the project. In 2000, Aventis offered the license to produce the drug to the WHO but the organization was unable to find a manufacturer.

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People

Gordon Gill named UCSD Interim Dean for Scientific Affairs

Gordon Gill has been named the UCSD Interim Dean for Scientific Affairs after the Nobel Laureate George Palade retired from the position. However, Palade will remain Professor Emeritus with the School.

The position was created by Palade in 1990 after transferring from Yale University where he received the Nobel prize in 1974 for his contributions to the understanding of cell structure, chemistry and function.

Gill comes to the job from being Professor of Medicine, Chair of the Faculty of Basic Biomedical Sciences and a UCSD physician and scientist for 32 years. He has previously been Associate Chair for Scientific Affairs in the Department of Medicine and before this was Chief of the Division of Endocrinology and Metabolism in the Department of Medicine.

Gill is hoping to expand the School, not only in personnel numbers but also in facility space: 'We have been constrained in our ability to recruit new faculty by lack of research space. The development plans are there, but we need to build from a science/research standpoint. Then, we will be able to make the right recruitments, bringing in the creative young investigators that are our future.'

Currently, UCSD is developing a School of Pharmacy and a new Institute for Molecular Medicine, together with new facilities for each.

George Wellman joins Ricerca Scientific Advisory Board

George Robert Wellman is joining the Scientific Advisory Board of Ricerca LLC (Concord, OH, USA) to provide knowledge from his extensive background in developing commercial processes for new drugs. Wellman recently retired (in January 2001) from SmithKline Beecham Pharmaceuticals (SKB) where he was Vice-President, Chemical Development Worldwide. He also held several other senior positions at SKB before this including: Vice-President, Chemical Development; Group Director of Development Chemistry; and Director of Synthetic Chemistry.

Arachnova appoints new Director of New Project Opportunities

Arachnova (Cambridge, UK) has appointed Hazel Bardsley to the position of Director of New Project Opportunities. Bardsley joins the company from eight years at Celltech Chiroscience. This new role will involve identifying new therapeutic switch projects based around new uses for partly or fully developed compounds. The company is a virtual pharmaceutical company that specializes in therapeutic switching.

Peter Read joins Synaptica

Peter Read has been appointed as Non-Executive Director of the neuroscience company, Synaptica Ltd (Oxford, UK). Read was formerly Chairman of Hoechst UK and has previously been President of the ABPI. Read's experience of the industry is hoped to help the company in its expansion programme, which includes refurbishing new laboratories at the Harwell International Business Centre, which will be used to concentrate research on novel therapeutics and diagnostics for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Obituary

John Dorst dies at 74

John Phillips Dorst, Director of Pediatric Radiology at Johns Hopkins Medical Institute has died of brain tumour complications at the age of 74. Not only was he an eminent clinician and a key figure in bringing X-rays to maturity as a diagnostic tool, but he was also an expert on mucopolysaccharidosis and mucolipidosis, and helped to identify some of the underlying biochemical defects in inherited bone disorders. He also authored many papers on subjects ranging from lung cancer diagnosis to heart disease, Down's syndrome and inherited bone malformations.

Dorst was also an avid lover of classical music and visual art and enjoyed canoeing, sailing, hiking and cross-country skiing.

People was written by *Rebecca N. Lawrence*

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