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News in brief

Targets and mechanisms

Ebola promotes immune response in mice

A mouse strain of the Ebola virus, adapted from the human strain, has unexpectedly been found to induce a strong T-cell immune response. The lethal effects of Ebola were previously generally believed to be due to virus-cased suppression of the hosts' immune system. Researchers at Emory University (Atlanta, GA, USA) and the Centers for Disease Control (Atlanta) detected a high frequency of activated CD4 and CD8 T cells in mice as early as four days post-infection, and high levels of interferon-γ in the spleen, liver and serum.

However, the mouse strain used was no less virulent as it produced 100% mortality in 6–8 days following intraperitoneal injection of a low dose of the virus. The researchers therefore concluded that, despite this strong immune response, the severe and fatal response in mice to Ebola is caused by the fact that the virus is so virulent in mice that it does not allow enough time for the T cells to multiply and attack.

Removal of all CD8 T cells from a subset of mice stopped production of interferon-γ, suggesting that CD8 T cells are the major cytokines induced by Ebola during acute infection. Further research has shown that memory CD8 T cells, in the absence of anti-Ebola antibodies, can protect against Ebola virus infection. Understanding of the mechanism of immune protection is hoped to eventually lead to the development of an Ebola vaccine.

Novel mechanism of action elucidated for brain cancer drug

Four preclinical studies have suggested a novel mechanism of action for Xcytrin (motexafin gadolinium; Pharmacyclics, Sunnyvale, CA, USA), a drug found to enhance the effects of radiation and chemotherapy. Xcytrin is the first of a new class of drugs known as texaphyrins, which selectively accumulates in cancer cells, disrupts cellular metabolism, and interferes with the flow of energy in cancer cells.

The studies were presented at the *92nd American Association of Cancer Research* (AACR) meeting in New Orleans (LA, USA). The results of the studies showed that Xcytrin is a redox mediator that interacts with intracellular reducing metabolites such as ascorbate and dihydrolipoate. This leads to the production of superoxide and hydrogen peroxide in cancer cells, where it localizes. This 'futile redox recycling' was shown to explain the drugs' ability to enhance the effects of radiation and chemotherapy.

Patient enrolment has recently been completed for an international randomized Phase III study of Xcytrin for the treatment of brain metastases. Phase II clinical trials with the drug have recently begun for the treatment of primary brain tumours, and others are planned for the treatment of pancreatic cancer and non-small-cell lung cancer. Richard A. Miller, President and CEO of Pharmacyclics, said, 'More preclinical and clinical studies will be published and presented throughout the rest of the year, culminating with results from our pivotal Phase III trial at the end of this year.'

UCLA researchers solve mystery of latent HIV infection

Researchers at the University of California AIDS Institute (Los Angeles, CA, USA) believe they have discovered how latent HIV infections occur in the human body[1]. The claim, from immunologists studying the thymus gland, is that the HIV virus uses dormant T cells to evade eradication by drugs. They surmise that when antigens in the bloodstream activate T cells, they also trigger new outbreaks of the disease, sometimes years after initial infection.

The researchers have used the mouse model, SCID-hu (Thy/Liv) to study latent infection. This mouse does not have its own immune system and mice generally cannot be infected with HIV, and so this

Markets

Vaccine products pipeline bulging

There are at least 25 new immunotherapy products currently undergoing late-stage clinical trials, with at least another 400 passing through earlier stages of development, announced a recent study by Theta Reports (New York, NY, USA) entitled *Vaccines 2001: The World Markets*. If these products reach the market, they will follow 15 other new immunotherapy medicines that have done so in the past two years. Therapeutic vaccines alone made US$2 billion in 1999, with further growth predicted at 21% per year leading to total sales of US$4.5 billion in 2005. These figures come despite recent controversy regarding clinical trial procedures, conflicting patent positions and the safety of certain paediatric vaccines. Recent recalls of AHP/Wyeth's RotaShield rotavirus vaccine and consumer wariness have prompted the Food and Drug Administration (FDA) to reassess clinical trial procedures.

Glut of novel anticancer drugs

A new report suggests that there are 547 novel anticancer drugs currently undergoing development, with many in late-stage clinical trials. The report by the Oncology KnowledgeBASE (nm/OK; http://www.oncologyknowledgebase.com) states that a dozen of the 300 or so regulatory agents making up this number have already entered Phase III clinical trials. Many of the remaining number of anticancer agents are immunotherapy/vaccine products (such as monoclonal antibodies, small-molecule drugs, gene transfer transfer/activation/therapy constructs) that have also begun clinical trials. Novel mechanisms (such as angiogenesis inhibition, enhancement of apoptosis and growth factor inhibition, tumour-associated antigen targeting) have the potential to treat cancer without many of unpleasant side effects associated with traditional chemotherapy and radiotherapy treatments. However, their most valuable contribution might be to enhance the effectiveness of chemotherapy and radiotherapy as part of combination regimes and as long-term treatment options to suppress tumour re-growth.

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model containing implanted human thymus tissue is convenient for studying T cell production. In mice with a thymus implant infected with HIV, T cells were harvested once infection had spread. These T cells were then placed into solution containing protease inhibitors and AZT to simulate the conditions of a person receiving antiretroviral therapy.

Recording the amount of AIDS virus expressed before and after stimulation with agents that imitate confrontation with a T cell specific antigen, researchers were surprised to see that expression increased 30-fold. Within three days, nearly 20% of T cells were expressing HIV proteins. '[The experiment]…shows that thymus cells contain dormant HIV infection,' said Jerome Zack of UCLA. 'Second, it confirms that HIV exploits the thymus as a breeding ground for latently infected immune cells.'

The UCLA model has several other advantages. The number of latent cells produced is high at one in five, compared with HIV-infected patient's blood (less than one per million). This high frequency should make future studies of how latent viruses behave in T cells and how to target latent HIV in the body much easier and faster.

1 Brooks, D.G. *et al.* (2001) Generation of HIV latency during thymopoiesis. *Nat. Med.* 7, 459–464

Substance P-receptor antagonist inhibits HIV

The novel compound CP96345 has been shown to potently inhibit HIV (strain R5)-infected human mononuclear phagocytes[2]. Scientists at The Children's Hospital of Philadelphia believe the compound works by binding to receptors on the surface of monocyte-derived macrophages (MDM) and somehow interrupts the process by which HIV enters these cells, where they create a reservoir of viral DNA for future infections.

CP96345 is thought to be an antagonist at the neurokinin-1-receptor, a primary substance P receptor. Substance P is a neurotransmitter and has been previously shown to enhance HIV replication in human blood-isolated mononuclear phagocytes. However, how this inhibition of substance P–neurokinin-1-receptor binding affects the CCR5 receptor on the macrophage cell surface to inhibit viral entry is still unknown. One suggestion is that the interaction could affect the regulation of CCR5 expression in the monocyte-derived macrophages.

As substance P is found in both the immune system and the nervous system, CP96345 might also provide a future avenue for investigating AIDS-induced dementia and other neurological damage caused by HIV.

2 Lai, J.P. *et al.* (2001) Substance P antagonist (CO-96,345) inhibits HIV 1 replication in human mononuclear phagocytes. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3970–3975

Rice bran and Shiitake mushrooms could arrest tumour cell growth!

MGN-3, a recommended supplement for stimulating the immune system, has been shown to dramatically arrest tumour cell growth *in vitro*, it was announced at the *92nd American Association for Cancer Research* (AACR) meeting held in New Orleans (LA, USA) recently.

Researchers from the Charles Drew University of Medicine (Los Angeles, CA, USA) and University of California, Los Angeles (UCLA) showed that the patented Japanese compound, consisting of hydrolysed rice bran extracts modified by Shiitake mushroom enzymes, directly affected the proliferation of a breast tumour cell line (MCF-7) when compared with control (MCF-12A) cells, completely suppressing growth during a 16-h incubation period.

Flow cytometric analysis revealed a marked stimulation in production of interleukin 10 (IL-10) CIL-101. ELISA analysis of the culture media bathing the cells 16 h post-treatment with MGN-3 showed increases in the production of IL-10 and IL-12 but little change in tumour necrosis factor-γ (TNF-γ) concentrations.

'This is the first time a natural biological response modifier has been shown to go beyond immune system enhancement,' said Mamdooh Ghoneum of Charles R. Drews University of Medicine and Science and UCLA.

MGN-3 has previously been shown in human trials to dramatically increase the activity of natural killer (NK) cells, B cells and T cells without toxic side effects (common to other immune modifiers). In a study of 27 cancer patients with very low levels (10.8–40.0%) of basal NK cell activity, a two-week course of the drug increased NK cell levels to 100–385%. It has also been shown to mediate gross pathological changes and improve quality of life when administered in tandem with cisplatin and adriamycin (two popular chemotherapy drugs) and to potentiate the immune-enhancing effects of IL-2 in the production of TNF-α and interferon-γ (IFN-γ). Researchers are now investigating whether the compound can decrease serum triglycerides, total cholesterol and polyurea in patients with diabetes (see http://www.publishedresearch.com for research abstracts).

'Sponge' implant could solve problem of controlled release

An ex-researcher at Ohio State University (OH, USA) is marketing the idea of using porous hydrogels to control the release of drugs into the human body[3]. Marc Madou, and his company ChipRx, struck on the idea when observing a children's toy that expands when wet. He mused that a similar concept could be used to control the release of drugs from a reservoir implanted into the human body.

Madou's implant, approximately the size of a matchstick, is covered in microscopic holes that open and close due to small rings of artificial muscle. 'The hydrogel is like a miniature sphincter,' he said. Applying a voltage to the gel makes it contract, releasing the contents of the implant. Madou's next step is to develop a biosensor that will project outside the capsule and control the flow of current from an attached battery. Other work in this field includes investigating how genetically engineered proteins that bind to sugar molecules could be used. A resultant change in shape could activate a current.

3 Martindale, D. (2001) Saved by sponge man. *New Scientist* http://www.newscientist.com/tech/spongeman.jsp

Miscellaneous

New international mouse research consortium launched

Deltagen (Menlo Park, CA, USA) and the Centre for Modeling Human Disease (CMHD) at the Samuel Lunenfield Research Institute, Mount Sinai Hospital (Toronto, Canada) have joined forces to create an international genome research consortium. CMHD will provide Deltagen, who specialize in the discovery and characterization of gene functions in mammalian models, with access to additional mouse gene function data and intellectual property. In return, the consortium (led by Jane Rossant) will gain certain rights to access and utilize the mouse model systems, data and intellectual property created.

By using three complementary approaches to the high-throughput genome-wide generation of mouse models [chemical mutagenesis by ethylnitrosourea (ENU), targeted deletion mutagenesis and gene trap mutagenesis], CMHD aims to gain an understanding of the functional role of mammalian genes, their corresponding phenotypes and the use of such genes in pharmaceutical and biotechnology development programs.

New *E. coli* database placed on Web

Experts in the field of *E.coli* research have come together to form the EcoReg (http://gobi.lbl.gov/~ecoreg/) Consortium, a body designed to construct and maintain a free database of all relevant information relating to genetic regulation of the organism. The Consortium will include scientists from Genencor International (Palo Alto, CA, USA), Peter Karp (SRI International, Menlo Park, CA, USA), Milton Saier (University of California, San Diego, CA, USA), Tyrrell Conway (University of Oklahoma, Norman, OK, USA) and Adam Arkin (University of California, Berkeley, CA, USA) and is funded initially by Genencor.

The database will aim to succeed the book '*Escherichia coli* and *Salmonella*. Cellular and Molecular Biology', which organised the initial knowledge of the bacteria and included the complete sequence of *E. coli* K-12. It will also be designed to complement the SRI's existing EcoCyc pathway/genome database. Initial information on the site includes the 2D-gel protein information (formerly known as the *E. coli* Gene–Protein Database and ECO2Dbase) donated by Ruth Van Bogelen (Pfizer Global R&D) and Fred Neidhardt (University of Michigan Medical School, MI, USA).

Clinical trials

Promise for first enothelin-receptor antagonist

The first endothelin-receptor antagonist has shown promising results in a Phase III trial for the treatment of acute heart failure (AHF). The results of this trial were presented at the *50th Annual Scientific Session of the American College of Cardiology* in Orlando (FL, USA). Veletri (tezosentan), developed by Actelion (Allschwil, Switzerland) and Genentech (San Francisco, CA, USA), produced a statistically significant hemodynamic effect as shown by improvement in the cardiac index and in pulmonary capillary wedge pressure (PCWP).

This RITZ-2 (Randomized Intravenous TeZosentan) trial is a randomized, double-blind, placebo-controlled, multicentre trial of 292 patients. Patients treated with the drug were compared with placebo on top of conventional therapy over a period of 24 h. A statistically significant change in the cardiac index was seen after 6 h at both the lower dose (50 mg h^{-1}; 21.4%) and the higher dose (100 mg h^{-1}; 21.5%) compared with placebo (2.0%). There were also improvements in PCWP and in dyspnea. The effects of the drug on cardiac index and PCWP were maintained over the 24 h period and for at least 6 h post-treatment.

However, the overall pattern of serious adverse events was similar across all three treatment groups over the following 28 days, although the lower dose of the drug produced more cases of moderate to severe headache being reported while the higher dose led to more reports of symptomatic hypotension, nausea, renal impairment and vomiting but with no improvement in treatment benefits.

This study is the first of the pilot studies to be carried out with Veletri. RITZ-1 is a 670-patient study that will evaluate the ability of the lower dose of Veletri to alleviate the symptoms of AHF, including dyspnea. RITZ-4 will look at the effects of the drug in AHF patients with acute coronary syndrome while RITZ-5 will evaluate the therapy in patients with pulmonary oedema.

First evidence for anti-atherosclerotic efficacy of β-blockers in humans

Treatment with β-blockers has been shown to slow the thickening of carotid artery walls in healthy individuals, recent research has shown[4]. A three-year randomized, double-blind, placebo-controlled trial conducted by Malmo University Hospital (Lund University, Lund, Sweden) studied the effects of low-dose treatment with metoprolol succinate or fluvastatin (a hypocholesterolaemic agent) on the progression of intima-media thickness (IMT) in almost 800 patients with carotid plaques, but with no symptoms of carotid artery disease. The patients were all white Swedish individuals participating in the Malmo Diet and Cancer study and were between 49 and 70 years of age.

Progression of IMT was significantly reduced by both β-blockers tested, although women in the group treated with fluvastatin had an elevated level of transient liver enzyme induction. Although studies in animals have previously shown that β-blockers have a direct anti-atherosclerotic effect, this is the first evidence of efficacy in humans.

4 Hedblad, B. *et al.* (2001) Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima media thickness: main results from the β-blocker cholesterol-lowering asymptomatic plaque study (BCAPS). *Circulation* 103, 1721–1726

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