News in brief

Targets and mechanisms

Immunity is only skin deep

A new breakthrough in delivering dendritic-cell-based vaccines is set to bring anti-tumour vaccines to a practical reality [1]. The method, which manipulates dendritic cells *in situ* rather than *in vitro,* could reduce the conventional process from 10 days to just 24 h.

Dendritic cells are specialized white blood cells that initiate immune responses to cancer cells. The conventional manufacture of dendritic-cell-based vaccines involves the removal of these cells from the body and then culturing and expanding them *in vitro*. Cells are then loaded with the tumour-associated antigen and, finally, administered in a vaccine.

The epidermis contains immature dendritic cells called Langerhans cells (LCs). In the study, researchers were able to entrap these cells by implanting an ethylene-vinyl-acetate (EVA) rod that released macrophage inflammatory protein (MIP)-3β to attract the LCs. In addition, a topical application of hapten triggered emigration of the LCs from the epidermis. The entrapped cells were then loaded with antigen by implanting a second EVA rod that released tumour-associated antigens (TAAs).

The experiment resulted in a potent cytotoxic immune response and protective immunity with each of the three TAAs tested. 'We thought these Langerhans cells would carry the tumour-associated antigen to the draining lymph nodes and initiate protective immunity against tumour development. Our subsequent experiments with several tumour models have, indeed, demonstrated the preclinical efficacy of this strategy,' said Akira Takashima, of the University of Texas Southwestern Medical Centre (Dallas, TX, USA).

1 Kumamoto, T. *et al.* (2002) Induction of tumor-specific protective immunity by *in situ* Langerhans cell vaccine. *Nat. Biotechnol.* 20, 64–69

Melatonin linked to AD

Melatonin, a naturally occurring hormone in the body, could reverse the formation of a protein complex associated with the development of Alzheimer's disease [2]. The findings suggest that a reduction in brain melatonin, which occurs during aging, is linked to AD, and that effective treatments might, in the future, be administered through dietary supplements.

AD is characterized by the formation of amyloid beta (Aβ) plaques in the brain. Previous research suggests that apolipoprotein E4 (apoE4) binds to Aβ and promotes the formation of amyloid fibrils. Researchers found that in cultured human cells, addition of melatonin to Aβ in the presence of apoE4 results in an inhibition of fibril formation, far greater than the effect observed with melatonin alone. As melatonin has antioxidant effects, its inhibitory effects were compared with other antioxidants; however, all had no effect, thus confirming that the results were structure-dependent. In addition, melatonin was also found to prevent the high toxicity observed in neuronal cells when Aβ and apoE are both present in the cell.

The use of dietary supplements to promote brain function is a growing area of research and, although further research is required to confirm the results, these findings suggest that practical applications in this area might be seen in the near future.

2 Poeggeler, B. *et al.* (2001) Melatonin reverses the profibrillogenic activity of apolipoprotein E4 on the Alzheimer amyloid Aβ peptide. *Biochemistry* 40, 14995–15001

Turning back the cellular clock

Embryonic stem cells can now be created without the ethical concerns of sacrificing embryos [3]. Researchers at the University of Pennsylvania (Philadelphia, PA, USA) have identified a receptor that effectively 'turns back the clock' on cellular development.

The receptor plays a role in restricting pluripotency, which is responsible for the development of embryonic cells into more than 200 tissue types in the body. The research is the first to identify a mechanism whereby pluripotency is lost in mammalian cells. A receptor, termed germ-cell nuclear factor (GCNF), represses the expression of a gene called *Oct4*, which is expressed in pluripotent cells. The repression of *Oct4* activity decreases steadily as embryonic cells differentiate. GCNF eventually restricts the expression of *Oct4* in somatic cells, leaving expression only in the germ cell lineage.

Although scientists can isolate stem cells from embryos, a recent declaration by President Bush now means that research is limited to cells that have already been harvested from frozen embryos. 'This knowledge may permit us to convert ordinary adult cells back to embryonic stem cells for research purposes,' said Hans R. Schöler, senior author of the study. The new stem cell resource has applications ranging from replacing damaged cells that are unable to regenerate, to growing replacement tissues or organs.

3 Fuhrmann, G. *et al.* (2001) Mouse germline restriction of *Oct4* expression by germ cell nuclear factor. *Dev. Cell* 1, 377–387

Stunning results for MS

A component of the venom used by sea anemones to stun their prey has been found to reverse the paralysis observed in an experimental form of multiple sclerosis (MS) [4]. The finding could lead to a new class of drugs for MS, which is one of the most common diseases of the nervous system.

MS occurs when T cells and other components of the immune system attack the nervous system by stripping away the protective myelin sheath that surrounds neurons and helps to transmit signals around the body. A breakdown of this process leads to a progressive loss of sensation and function.

The active component, ShK, from the venom of the Caribbean sea anemone *Stichodactyla helianthus*, was found to block ion channels in white blood cells, which were activated in an experimental model to cause MS. This prevented cells

  PII: S1359-6446(02)02192-X

from attacking the nervous system and causing paralysis.

However, ShK has a short lifespan in the bloodstream, which could reduce its effectiveness. 'ShK may not last long enough to prevent or treat the disease on a long-term basis,' said Heike Wulff, a researcher at the University of California (Irvine, CA, USA). 'But it appears to match the biochemical structure of the channel well enough to block it and change the T cells' responses. Our group is searching for chemically similar substances that last longer in the body.'

The finding could help to identify ways of treating MS by targeting the specific ion channel while preserving the function of the immune system.

4 Beeton, C. *et al.* (2001) Selective blockade of T lymphocyte K^+ channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. *Proc. Natl. Acad. Sci. U. S. A.* 98, 13942–13947

In utero gene therapy

The use of prenatal gene therapy for the correction of neurological and genetic disorders was presented at the *43rd Annual Meeting of the American Society of Hematology* (7–11 December 2001, Orlando, FL, USA; http://www.hematology.org/meeting/2001/). The researchers, from the University of Minnesota Cancer Center (Minneapolis, MN, USA), delivered two separate presentations [5,6] (http://www.hematology.org/images/pdf/abstracts_oral.pdf), in which the potential for *in utero* gene therapies were described.

Angela Panoskaltsis-Mortari discussed the 'Sleeping Beauty' transposon, which could deliver gene sequences that are capable of correcting congenital blood and immune system disorders that can prove challenging if treated postnatally [5]. The 'Sleeping Beauty' transposon links specific genes with specific functions, and when immune-deficient mice foetuses were injected with the enzyme, the green fluorescent protein (GFP) marker was detected in the liver, lung, heart, kidney, skin and brain. GFP expression was observed in the spleen and bone marrow;

Miscellaneous

Gene Therapy Center awarded US$9.2 million from NIH

The Gene Therapy Center at the Chapel Hill School of Medicine (University of North Carolina, Chapel Hill, NC, USA) will receive US$9.2 million from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH). The grant, to be awarded over five years, will aim to convert existing basic research knowledge of gene delivery into finalised treatments for single-gene defect lung and blood disorders such as cystic fibrosis and haemophilia.

Two of the projects will be aimed at understanding and overcoming inefficient gene delivery related to virus entry into cells and the persistence of expression of the transferred gene. This should provide further knowledge of the safety and biological efficacy of gene delivery, which will be of importance to the design of future clinical trials. Two additional studies will research the cell biology of target tissue and will study animal models for airway and haemophilia disorders, hopefully leading to increasing the access of transferred genes to airway tissue and developing novel models (such as a humanized haemophilia mouse).

The award 'acknowledges the importance of understanding the basic science first before moving into the clinical setting,' said R. Jude Samulski, Professor of Pharmacology and Director of the university's Gene Therapy Center.

Replacement for leeches

A novel device has been designed to promote blood flow to compromised tissue by researchers at the University of Wisconsin-Madison and William S. Middleton Memorial Veterans Administration Hospital (both Madison, WI, USA). This is a job that is normally performed by the blood-sucking leech.

Historically, the leech was used as a treatment for a variety of ailments, ranging from headaches to stomach aches and more. In modern medicine, the leech has emerged as a valuable tool to treat venous congestion. Nadine Connor, a scientist on the team that developed the novel device, said: 'Venous congestion is a post-surgical complication that can occur after reconstructive surgery…excess blood in the tissue, if severe enough, can deprive the tissue of oxygen and other nutrients and can cause it to die.' Venous congestion is most common after reconstructive surgery to the head, neck, breast, or attachment of limbs or digits, where tissue is moved from one part of the body to another.

Leeches were employed to promote the flow of blood in tissues where this had been affected. Even after detachment of the leech from the affected body part, the anticoagulants that it secretes enable the tissue to release blood for hours. During leech therapy, which can last for up to ten days, new veins can grow into the reconstructed tissue, from healthy tissue, thus re-establishing adequate blood drainage.

However, the leech does have its disadvantages! Many patients would not be comfortable having a blood-sucking animal attached to their body; leeches are not sterile and can cause bacterial infections; and the leech can sometimes reattach itself to other parts of the body not requiring therapy.

The mechanical device has several other advantages over its natural counterpart. Michael Conforti, a scientist at the Hospital, said, 'The real leech can only penetrate so deep. Our device can act at a deeper level under the skin, tapping into larger blood vessels and treating a larger area of tissue.' Connor added, 'But perhaps the mechanical device's biggest advantage is that it is not a leech.'

this indicates that it can localize to haematopoietic organs *in vivo*, which is important for the correction of lymphohaematopoietic disorders.

Jakub Tolar showed, for the first time, that multipotent adult progenitor cells (MAPCs), or bone marrow stem cells, can differentiate into brain and liver cells following gene transfer *in utero*. The combined results suggest future possibilities for the clinical use of adult bone marrow stem cells in an attempt to correct neurological, hepatic, muscular and other congenital disorders prenatally.

5 Panoskaltsis-Mortari, A. (2001) *In utero* delivery of Sleeping Beauty transposon results in long term multi-organ expression: potential for prenatal gene therapy of genetic disorders. *43rd Annual Meeting of the American Society of Hematology*, 7–11 December 2001, Orlando, FL, USA, Abstract 3105

6 Tolar, J. (2001) The *in utero* transfer of murine multipotent adult progenitor cells (MAPCs) results in brain and liver differentiation. *43rd Annual Meeting of the American Society of Hematology*, 7–11 December 2001, Orlando, FL, USA, Abstract 1985

Gone today, hair tomorrow

Researchers have identified an important causative factor in the disease alopecia areata [7]. The group, at the Technion–Israel Institute of Technology (Haifa, Israel), found that a way of treating the hair loss disorder, which often affects children, is to desensitize the immune system to substances that are found to provoke an attack.

The researchers showed that proteins produced by hair cells that produce pigment can trigger the start of an alopecia attack, when the body mistakes cell molecules for foreign bodies. Previous work had shown that in the disorder, white blood cells attack hair follicles, but the cause of the attack was not clear.

Leader of the study Amos Gilhar, Associate Professor of Medicine at the Technion Faculty of Medicine, said: 'Alopecia areata can be a very challenging condition emotionally, and it currently has no cure.' The research findings indicate that injecting high doses of potential triggering substances could desensitize the body to further attacks but, according to research collaborator Richard Kalish of Stony Brook University (Stony Brook, NY, USA), further research is necessary to fully clarify these findings. The disorder affects four million people in the USA and commonly starts with small, round, smooth bald patches on the scalp, according to the National Alopecia Areata Foundation, which supported the study (http://www.naaf.org/).

7 Gilhar, A. *et al.* (2001) Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on Prkdc^{scid} mice. *J. Invest. Dermatol.* 117, 1–6

Saying NO to drug resistance

Nitric oxide (NO) donors could decrease resistance to chemotherapeutic drugs in cancer cells [8]. The results of a recent study suggest that NO donors could also be used as adjuvants to increase the potency of chemotherapeutic agents.

Hypoxia in tumours is often associated with increased resistance to radiotherapy and chemotherapy. Molecular oxygen is required for the cellular production of NO, which might block components of the adaptive response to hypoxia. It was, therefore, thought that the hypoxic state inhibits endogenous NO production, thereby increasing drug resistance in tumour cells.

The *in vitro* study used human breast cancer cells and mouse melanoma cells, which were made drug resistant to two chemotherapeutic agents by inducing a hypoxic state following incubation with a NO synthase inhibitor. Results showed that the cells were made susceptible to the chemotherapeutic agent when exposed to nitroglycerin, an NO donor. This suggests that hypoxia-induced drug resistance might result from downstream suppression of NO production.

The findings open up new therapeutic possibilities for nitric oxide donors such as nitroglycerin. New treatments might include administering small doses of NO mimetics to produce an adjuvant effect in chemotherapy.

8 Matthews, N. *et al.* (2001) Nitric oxide-mediated regulation of chemosensitivity in cancer cells. *J. Natl. Cancer Inst.* 93, 1879–1885

Tomatoes and peanuts combat prostate cancer

In separate studies, the benefits of tomatoes and peanuts have been

highlighted in the treatment of prostate cancer. The consumption of tomato products, which contain high levels of the antioxidant lycopene, has been reported to lower the risk of prostate cancer. The recent study [9] examined the effects of tomato-sauce-based pasta dishes on the uptake of lycopene, oxidative DNA damage and prostate-specific antigen (PSA) levels in patients diagnosed with prostate cancer. In this intervention study, 32 patients who were scheduled for prostatectomy were fed the equivalent of 30 mg of lycopene, daily, for three weeks before surgery.

The results showed that the consumption of tomato-sauce-based dishes reduced DNA damage to prostate cancer cells by 28.3% and to leukocytes (white blood cells) by 21%, and also resulted in a reduced level of PSA (~17.5%). Hence, in men, the consumption of high levels of lycopene-containing sauces can slow or prevent the progression of prostate cancer.

In a separate study, phytosterols, which occur naturally in plant sources such as peanuts, beans and olive oil, were shown to reduce prostate tumour growth by >40%, and appear to decrease the occurrence of cancer spreading to other parts of the body, such as the lymph nodes and lungs, by almost 50% [10].

The most common phytosterol, β-sitosterol (SIT), can inhibit cancer growth, as well as protecting against heart disease. Atif Awad, Professor of Nutrition at the State University of New York at Buffalo (NY, USA) and co-investigator of the study, said, 'These studies demonstrate for the first time that phytosterols that exist naturally in our diet, in foods like peanuts and beans, can protect against prostate cancer.'

In the study, severe combined immunodeficient (SCID) mice were fed one of two diets; one supplemented with phytosterols and the other supplemented with cholesterol, designed to simulate the Asian and Western diets, respectively. The results support the evidence of a correlation between a high incidence of prostate cancer in Western males, compared with Asian men.

9 Chen, L. *et al.* (2001) Oxidative DNA damage in prostate cancer patients consuming tomato-sauce-based entrees as a whole-food intervention. *J. Natl. Cancer Inst.* 93, 1872–1879

10 Awad, A.B. *et al.* (2001) *In vitro* and *in vivo* (SCID mice) effects of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells. *Eur. J. Cancer Prev.* 10, 1–6

Infectious diseases

Drug resistance to macrolides overtaken penicillin

Bacterial resistance to macrolides has now overtaken penicillin bacterial resistance in the USA, according to a surveillance study by Protekt US, the US wing of the worldwide study, Prospective Resistant Organism Tracking and Epidemiology of the Ketolide Telithromycin. Macrolides are used to treat several infections including community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, and acute bacterial sinusitis.

The study was set up to assess the spread of antibiotic-resistant phenotypes and genotypes. The results, which were presented at the *41st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC; 16–19 December 2001, Chicago, IL, USA), found that almost 31% of *Streptococcus pneumoniae* were resistant to the macrolide, erythromycin, compared with ~26% being resistant to penicillin.

The recent increase in resistance to widely prescribed macrolides suggests an immediate need to explore new options for the treatment of these infections,' commented Charles Stratton of Vanderbilt University School of Medicine (Nashville, TN, USA) and lead investigator of Protekt US. Results varied across the USA, with resistance ranging from 23% in the northwest of the country to 41% in the southeast. The Protekt study is an international study involving more than 72 centres in 25 countries worldwide.

New hope for HIV treatment

Researchers have identified a protein in human cells that could lead to new treatments for HIV and AIDS [11]. The protein, HP68, is crucial to the formation of the outer shell, or capsid, of the AIDS virus. Drugs designed to specifically target the protein could avoid the severe side effects that are seen with current treatments.

HIV is a retrovirus, which has genes made of RNA as opposed to DNA. Without DNA, the virus must infect a host cell to produce DNA. To become infectious, the virus must assemble Gag (group-specific antigens) proteins into a capsid, which then protects the virus.

The newly identified protein was found to temporarily associate with the Gag protein to help form the capsid. If HP68 is mutated or absent, the capsid is unable to form, thereby rendering the virus incapable of infecting other cells.

Current treatments that either stop the production of HIV RNA into DNA, or interrupt production of the virus often have severe side effects. 'The identification of HP68 will allow us to develop drugs that interrupt its interaction with Gag, and therefore stop HIV production,' said Bonnie Firestein of Rutgers University (Piscataway, NJ, USA). 'Since we may be able to develop drugs that are specific for HP68, we may be able to avoid the intolerable side effects found with the drugs currently used in other courses of treatment.'

11 Zimmerman, C. *et al.* (2002) Identification of a host protein essential for assembly of immature HIV-1 capsids. *Nature* 415, 88–92

Fast track for AIDS vaccines

A new international laboratory for the co-ordination and evaluation of AIDS vaccine candidates has opened at the St Stephen's Centre, Chelsea and Westminster Hospital (London, UK). The centre, which will pick up vaccine candidates from other centres worldwide as they complete human trials, was opened by The International AIDS Vaccine Initiative (IAVI, New York, NY, USA) and Imperial College of Science, Technology and Medicine (London, UK), and is part-funded by Becton, Dickinson and Co. (Franklin Lakes, NJ, USA). Vaccines in early human trials will be compared head-to-head so that the best designs can to be prioritized for further development and testing. Over the next few years, IAVI plans to sponsor human trials of at least 12 AIDS vaccine candidates, two of which are already in trials in Kenya and the UK.

The new laboratory will also provide training and equipment for technical staff in developing countries to ensure they have the supplies and training necessary to conduct their own vaccine trials. Initially, teams from Kenya, Uganda, South Africa, India and China will receive training to carry out their own IAVI-sponsored programs. The London facility will act to standardize vaccine assessment across the centres. 'Co-ordination among vaccine researchers is critical,' said Wayne Koff, Senior Vice-President for R&D at IAVI. 'Until now, the global effort to find AIDS vaccines has been fragmented, with researchers unable to compare their results and learn from each other because they are using different methods to assess their vaccines. A breakthrough product is likely to emerge only through a joint effort.'

New international body publishes White Paper on antibiotic use

A new multidisciplinary group of world experts, the International Forum for Antibiotic Resistance (IFAR) has been formed to discuss the growing problem of resistance to antibiotics. The group, including infectious disease specialists, microbiologists, epidemiologists and the International Alliance of Patients Organisations (IAPO; London, UK), detailed their recommendations in a White Paper presented at the *41st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC; 16–19 December 2001, Chicago, IL, USA), entitled *Bacterial Resistance in Community-Acquired Respiratory Tract Infections*.

'Despite numerous international and national recommendations for resistance control, few large-scale interventions have

been implemented,' said Professor Roger G. Finch, President of the European Society for Clinical Microbiology and Infectious Diseases (Basel, Switzerland) and Professor of Infectious Diseases at City Hospital (Nottingham, UK) and the University of Nottingham (Nottingham, UK). 'The Global White Paper…is long overdue and has come at a crucial time.'

The White Paper calls for: more studies to assess the impact of resistance on the health of patients with community acquired respiratory tract infections (RTIs); greater consideration by organizations responsible for resistance control of the factors driving bacterial resistance, including antibiotic use; further education in the prescription of antibiotics for RTIs; and greater patient involvement in measures to control resistance.

News in Brief was written by *Joanne Clough*, *Joanna Milburn* and *Ben Ramster*

People

Awards

The 2001 Brinker International Awards for Breast Cancer Research

Bert W. O'Malley (Professor and Chairman of the Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA) and Jay R. Harris (Chief of Radiation Oncology, Dana-Farber Cancer Institute and Professor of Radiation Oncology, Harvard Medical School, Boston, MA, USA) have been awarded the 2001 Brinker International Awards for Breast Cancer Research. This award was established by the Susan G. Komen Breast Cancer Foundation and recognizes significant advances in basic research concepts or clinical application in the fields of breast cancer research, screening or treatment.

The award for O'Malley recognizes his contributions to research on the pathway and mechanism of steroid hormone action, which has led to the understanding of how the hormones work. This work has had a significant impact on the fields of endocrinology, reproduction, genetic disease, and endocrine cancers of the breast and prostate. He is also a founder of the field of molecular endocrinology as part of the National Academy of Sciences and the Institute of Medicine, and is a fellow of the American Academy of Arts and Sciences, and the American Academy of Microbiology.

Meanwhile, Harris is being recognized for his contributions in the area of clinical evaluation of breast cancer treatments, in particular, radiation therapy and conservative surgery for early breast cancer. He is Program Director of the Joint Center for Radiation Therapy Residency Program and was an active member of President Clinton's Special Commission on Breast Cancer and served on the National Action Plan for Breast Cancer.

Appointments

Barbara Wallner joins BioTransplant as CSO

BioTransplant (Charlestown, MA, USA) has appointed Barbara Wallner as Chief Scientific Officer. She comes to the company from Point Therapeutics, where she was co-founder and spent five years as Senior Vice-President of R&D and Chief Scientific Officer. Before this, Wallner worked at Immulogic in a variety of positions including Vice-President of Research. She has also previously spent ten years at Biogen leading several research projects. Elliot Lebowitz, Chief Executive Officer of BioTransplant, said 'Barbara brings to BioTransplant substantial expertise in the areas of autoimmune diseases and cancer, which will considerably strengthen our efforts to advance our portfolio of products through the developmental process.'

Key appointments at Sequenom

Following the division of Sequenom into the defined business units, Sequenom Genetic Systems and Sequenom Pharmaceuticals, the Sequenom Pharmaceuticals unit has announced several changes to key management positions.

The Chief Medical Officer for Sequenom (San Diego, CA, USA), Andreas Braun, will now lead the newly formed Sequenom Pharmaceuticals. Braun has been with the company since 1995 and was the architect of the company's disease gene discovery program. Meanwhile, Jay Lichter joins the company as Executive Vice-President of Business Development from being CEO of the new start-up company, XenoPharm. He also co-foundered Sequana Therapeutics and previously held management positions at Pfizer and Geneset.

Charles Rodi has also been promoted to Executive Vice-President of Genomics in which he will lead the direction and operation of the company's internal High-Throughput Genotyping Center. Rodi was previously Vice-President of Molecular Biology with the company and has also been Director of the Genome Sequencing Center at Monsanto.

Finally, Richard Macdonald has been promoted to the position of Senior Vice-President of Corporate R&D. Macdonald joined the company in 1998 and has played a leadership role in establishing the company's bioinformatics group and software.

Toni Schuh, President and CEO of Sequenom said: 'Sequenom has established a strong leadership position in the high-throughput genotyping market. We are using our leadership position to build a profitable Genetics Systems business and, in addition, will develop a pharmaceutical business to commercialize proprietary diagnostics and pharmaceutical products.'

Two key appointments at Lipocine

Lipocine (Salt Lake City, UT, USA), a drug delivery biotechnology company, has

1359-6446/02/$ – see front matter PII: S1359-6446(02)02196-7