News in brief

Targets and mechanisms

A protein double-act

David Clapham and colleagues (Children's Hospital in Boston and Harvard Medical School, MA, USA) have discovered a novel protein, transient receptor protein-phospholipase C-interacting kinase (TRP-PLIK), which acts both as an ion channel and an enzyme[1]. This protein is involved in cell-signaling pathways, enabling cellular calcium entry and activation of itself and perhaps other proteins. The research team thinks that it might be involved in cell proliferation or cell death, and might therefore be a potential new drug target. It is found in many tissues, including brain, kidney and heart.

'The most exciting part of this finding for us was that TRP-PLIK is bifunctional,' says David Clapham. 'It contains a domain whose opening and closing acts as a gate for calcium and a domain that acts as a kinase.' Although the mechanism of action of TRP-PLIK is known, its biological function remains a mystery. 'Ion channels are targets for perhaps a third of all drugs, either directly or indirectly – including anti-hypertensives, anti-depressants and anti-arrhythmic heart drugs,' says Clapham. 'The bifunctional TRP-PLIK protein could offer a new approach to drugs that turn cell division on or off, or cause cells to go into apoptosis and die.'

1 Runnels, L.W. *et al.* (2001) TRP-PLIK, a bifunctional protein with kinase and ion channel activities. *Science* 10.1126/science.1058519 (http://www.scienceexpress.org)

Nationally tailored vaccines

An experimental HIV-1 vaccine has been developed that is tailored to help fight AIDS in Nigeria [Simon Agwale, University of Maryland Biotechnology Institute (UMBI), MD, USA]. The vaccine studies were conducted by Simon Agwale (UMBI), David Hone and Marv Reitz (UMBI's Institute of Human Virology) and Marcia Kalish (Centers for Disease Control and Prevention, Atlanta, GA, USA). The number of HIV infections has increased steeply over the past few years in Nigeria. This is a serious threat to Nigeria, which is the most heavily populated country in Africa, and wherein anti-HIV drugs are not widely available to the public because they are expensive.

The UMBI's Institute of Human Virology (IHV) has used its most recent vaccine technology to develop a first-generation Nigerian HIV-1 vaccine, which comprises fragments of particular subtypes of HIV that predominate Nigerian infections. These were identified by nationwide analysis of blood from HIV-positive individuals in Nigeria (carried out in association with the Centers for Disease Control and Prevention).

This novel vaccine is now entering preclinical testing in animals, and is designed to be taken orally to eliminate the need to maintain sterile injection needles. Although tailored for applicability in Nigeria, it is potentially relevant to all of Africa because a fragment of DNA from the C-clade variation of HIV-1 was also incorporated into the vaccine, an HIV-1 subtype that is rapidly becoming predominant in Africa.

Mutated HIV attacks protective cells

Recent research at the Children's Hospital (Columbus, OH, USA) has shown for the first time that HIV can mutate to attack human protective cells[2]. This study demonstrated that, in the advanced stages of HIV, the structure of the virus can mutate into a form that can target $CD8^+$ T lymphocytes, which leads to the rapid progression of AIDS. $CD8^+$ T lymphocytes are important in protecting against HIV infection, thus keeping HIV under control in infected people; however, when their protection fails, AIDS develops.

The study indicated that it might be feasible to inhibit the progression of AIDS by therapeutic interventions intended to prevent direct infection of $CD8^+$ T cells with HIV. 'If HIV mutates in infected patients to attack $CD8^+$ T cells, which eventually leads to the development of AIDS, then preventing this from occurring in infected patients may keep them healthy,' says researcher Kunal Saha. The researchers used a novel technique to generate T-cell clones from HIV-infected patients at various disease stages including AIDS. Primate herpes virus was used to clone T cells from normal people in addition to HIV-infected persons.

'The exact reason T cells succumb to HIV is unclear,' added Kunal Saha. 'Our study suggests for the first time that these protective cells may eventually become targets of the virus, which can mutate within the body. These findings, coupled with further study, may enable researchers to understand this occurrence and design a better therapeutic vaccine against AIDS.'

2 Zhang, J. (2001) Isolation of primary HIV-1 that target $CD8^+$ T lymphocytes using CD8 as a receptor. *Nat. Med.* 7, 65–72

Clinical trials

Vascularitis in animal trials cause Pfizer to restrict Capravirine use

Pfizer (Sandwich, Kent, UK) have restricted use of its investigational drug capravirine for some patients participating in clinical trials after a 12-month toxicology study found that animals given very high doses of the drug developed vascularitis. Capravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is currently in Phase II and III clinical trials to determine the drug's efficacy in HIV. To date, no vascularitis events have been reported in trial patients.

The 650 patients involved in these trials across six separate studies will discontinue using the drug unless they are treatment-experienced and, although having previously failed to respond to NNRTIs, are responding well to capravirine. Pfizer is working with the Food and Drug Administration (FDA) to conduct additional animal toxicology studies to further evaluate the drug's safety profile.

Tumour suppressor gene as new biological drug

The Rb2/p130 tumour suppressor gene has been implicated in the inhibition of angiogenesis in tumours following studies conducted by researchers at the Jefferson Medical College (Thomas Jefferson University Hospital, Philadelphia, PA, USA)

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and colleagues at the University of Naples (Naples, Italy), the University of Siena (Siena, Italy) and the Sunnybrook and Women's Health Science Centre (Toronto, Ontario, Canada)[3].

The putative antiangiogenic property of Rb2, a member of the retinoblastoma tumour suppressor family, was discovered when studying glioblastoma and lung tumours in mice. Treatment with Rb2 appeared to cause calcification of the tumours, which indicated restricted blood flow to the tumour cells. Further investigation has shown that the level of vascular endothelial growth factor (VEGF), which promotes cell growth and is a marker for angiogenesis, is reduced by injecting increasing levels of Rb2 into tumour cell lines, resulting in a tenfold reduction in angiogenesis and, thus, restricted blood flow. Although there is no evidence of a direct interaction between Rb2 and VEGF as yet, Antonio Giordano (Jefferson Medical College) believes that 'Rb2 has a say in the relation that is occurring between angiogenetic factors'. The researchers now hope that Rb2 will be a new biological 'smart' drug, with the potential for sophisticated delivery, such as by aerosol to lung tumours. Work is currently under way to design small molecules that can effectively deliver the desired portion of the Rb2 gene.

3 Claudio, P.P. *et al*. (2001) Rb2/p130 gene-enhanced expression down-regulates vascular endothelial growth factor expression and inhibits angiogenesis *in vivo*. *Cancer Res.* 61, 462–468

Mice model could help to iron out Parkinson's disease

Mice unable to effectively metabolize iron could provide a model for studying Parkinson's disease and similar disorders. A study by the National Institute of Child Health and Human Development (NICHD; Bethesda, MD, USA) has shown that knockout mice lacking the gene for iron regulatory protein-2 (IRP-2) accumulate iron deposits in the cerebellum and basal ganglia, the areas of the brain that control movement[4]. These deposits are similar to the progressive deterioration seen in Parkinsonism and related diseases. Further, although the mice developed normally at first, they were subsequently found to have difficulty with movement and walking.

High levels of iron can be cytotoxic and, therefore, machinery exists within the cell to prevent its build-up. This machinery includes IRP-2, which is a key protein in regulating cellular iron levels by modulating the activities of proteins directly involved in iron metabolism and transport, such as the transferrin receptor, ferritin and iron exporters. Duane Alexander (Director, NICHD) thinks that the accumulation of iron in IRP-2-deficient mice is 'a strong clue that iron may play a causative role in Parkinson's and similar disorders'.

The areas of the brain affected in mice differ to those that are involved in the majority of human nervous system disorders and, therefore, no direct link with IRP-2 has been established. However, this latest finding could lead the way to identifying other genes involved in iron metabolism that might prove to be worthy targets for the treatment of human brain disorders. Indeed, the NICHD are already planning a follow-up study to test patients with Multiple System Atrophy for defects in the IRP-2 gene.

4 LaVaute, T. *et al*. (2001) Targeted deletion of the gene encoding iron regulatory protein-2 causes misregulation of iron metabolism and neurodegenerative disease in mice. *Nat. Genet*. 27, 209–214

'Spanner in the works' thought to cause cancer

Cancer is a result of a disruption in the highly complex spindle apparatus during cell division, a scientist from the University of California has proposed. Peter Duesberg (University of California at Berkeley, CA, USA) has disputed the accepted belief that cancer develops from a series of mutations that result in aberrant cell growth. Instead, he proposes that the sensitive balance of proteins that comprise the spindle apparatus during cell division is perturbed, resulting in the unequal splitting of chromosomes and consequent generation of aneuploid daughter cells (cells with an abnormal number of chromosomes) with inappropriate phenotypic characteristics.

It is well known that tumours consist of predominantly aneuploid cells, but this was

Markets

US cancer vaccines finally set to reach market

Therapeutic vaccinations against cancer are reaching the end of Phase III trials in the US, prompting predictions that the market will be worth $60 million in 2002, and is expected to grow at a rate of >100% in 2007, reported Frost and Sullivan (London, UK) recently. Three cancer vaccines are already commercially available in other parts of the world but long approval processes by the Food and Drug Administration (FDA) mean it is yet to approve any cancer vaccines for the US. However, there are more than 150 cancer vaccines in different stages of development. The commercial potential of the market is increased by the fact that cancer vaccines are being designed to be used in addition to existing therapies and so will be suitable for use in all patients for which it is efficacious.

Changes in medical practice will increase the use of expensive breast cancer treatment drugs

An emphasis on aggressively treating patients with early stage (I and II) breast cancer and high-risk tumour recurrence will lead to a rise in the use of expensive drugs such as taxanes and the monoclonal antibody trastuzumab (Genentech/Roche's Herceptin), concludes a recent Decision Resources (Waltham, Massachusetts, USA) study entitled *Breast Cancer*. The number of patients diagnosed with, and treated for, early-stage disease is far greater than that involved in traditional approaches to intensive systemic therapy, which generally focus on metastatic (stage IV) disease.

Sales of breast cancer therapeutics are expected to grow by 10% a year in the seven major pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom and Japan) until 2009. A second driver for this growth is the prospect of new molecules in late-stage development becoming available in the next 1–5 years for clinical use.

thought to be as a result of mutations, not as the cause of the tumour. Duesberg and colleagues have shown that aneuploid cells respond differently to chemotherapy: those with a 50% increase in chromosome number developed resistance in as little as nine days, compared with normal cells that remained sensitive to treatment[5]. This led to the conclusion that frequent rearrangement of chromosomes results in the high levels of mutation observed in cancer cells[5,6], which subsequently might lead to drug resistance. This finding could help to explain why only cancer cells and not normal cells develop resistance to chemotherapy, and how this resistance might be prevented or treated.

5 Duesberg, P.H. *et al*. (2000) Explaining the high mutation rates of cancer cells to drug and multidrug resistance by chromosome reassortments that are catalyzed by aneuploidy. *Proc. Natl. Acad. Sci. U. S. A.* 97, 14295–14300

6 Bialy, H. (2001) Aneuploidy and cancer – the vintage wine revisited. *Nat. Biotechnol*. 19, 22–23

Miscellaneous

Johns Hopkins launches Cell Engineering Institute

The John Hopkins University School of Medicine (Maryland, USA) is to launch an Institute for Cell Engineering (ICE) with the aid of an anonymous $58.5 million donation and a $23.8 million grant from the State of Maryland. The Institute will be designed as a multidisciplinary research incubator where scientists from various departments at the university will be able to come and conduct stem cell research related to their fields of expertise.

The site will occupy one third of the 40,000 square feet basic research facility that is planned to be completed by 2003. Until then, temporary laboratories will be made available. The Institute's research is expected to focus on modifying and reprogramming human cells to be used as potential transplants for conditions such as Parkinson's disease, stroke, diabetes, heart failure and spinal cord injury.

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People

Two new executive appointments created at Quintiles

The Informatics section of Quintiles (Quinternet Informatics; Research Triangle Park, NC, USA) has appointed two new executives to its team. Peter Hoover has been promoted to the new position of Chief Operating Officer, while Thomas Halzer has been brought into the new position of Senior Vice-President of Sales and Marketing.

Hoover was previously Executive Vice-President of Quinternet Informatics, having moved from being President of Rx Remedy in 1999. Hoover has also held a number of positions at IMS America, including Senior Vice-President and General Manager of the Healthcare Division.

Balzer has come from being Senior Vice-President of Pharmaceutical Services at NDC Health Information Services. Previously, he was a manager for the consulting firm ZS Associates and prior to this, a partner with Management Technologies.

Baddour joins Merlin Board

Raymond Baddour has been appointed to join the Board of Directors of Merlin Technologies (Boston, MA, USA). Baddour has extensive expertise in the pharmaceutical industry, having been a cofounder of several companies including Amgen, Hyseq and Ascent Pediatrics. He is also a Business Advisory Committee member of Medical Science Partners, which invests in technologies developed at Harvard Medical School and its affiliated hospitals. Chalom Sayada, CEO of Merlin Technologies hopes that Baddour's scientific and clinical development experience will help Merlin as it prepares to commercialize its *Chlamydia pneumoniae* detection technology.

Baddour is also currently Lammot du Pont Professor of Chemical Engineering, Emeritus at MIT and has previously been the head of this department for seven years. He has served on many committees for national professional organizations, the government and MIT.

New CEO for Avidex

James Noble has been appointed as the new CEO of Avidex Ltd (Oxford, UK), a company that develops T cell-based therapies. Noble has previously held several non-executive Board positions in companies including Oxford Glycosciences, Powderject Pharmaceuticals, Advanced Medical Solutions, Oxagen Ltd and AdProTech Ltd. Previous appointments include Finance Director at British Biotech, Director of Kleinwort Benson Ltd and Chairman of Avidex Ltd. This comes at the same time as the announcement that the company has secured £10 million in funding from Advent Venture Partners and private investors and shareholders.

Cancer and cardiovascular research experts join ExonHit

ExonHit (Paris, France) has appointed two additional members, Pierre Corvol and Dominique Stehelin, to its scientific advisory board. Corvol is currently Professor of Experimental Medicine at the College de France (Paris, France) and Stehelin is currently Director of the Development and Cancer Mechanisms, CNRS unit of the Pasteur Institute (Lille, France). Their expertise in the cardiovascular and cancer fields is hoped to help the company to extend its tools and services based on its DATAS splicing technology.

Corvol is also currently Chairman of the INSERM Counsel and is known for his work on the genetics of human hypertension and cardiovascular research. Meanwhile, Stehelin is known for his work on the molecular basis of cancer, especially through his discovery of the first oncogene that led the group's laboratory at the Medical Center, San Francisco (CA, USA) to receive a Nobel Prize.

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