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News in brief

Targets and mechanisms

Ribosome or ribozyme? New implications for drug discovery

Fundamental research at the UIC Center for Pharmaceutical Biotechnology (Chicago, IL, USA) could lead to the development of a new class of antibiotics to help combat the growing global health problem of antibiotic resistance[1]. Approximately two-thirds of all antibiotics kill bacteria by acting on the ribosome and interfering with protein synthesis. However, researchers found that the ribosome can remain functional even after alterations are made to the one nucleotide understood to be crucial for catalytic activity.

'The expectation was that if you made mutations at this nucleotide you would kill the ribosome and it would no longer be able to synthesize a protein but, in fact, it still could,' said Alexander Mankin, Associate Professor of Medical Chemistry in the UIC College of Pharmacy (Chicago, IL, USA).

The finding makes sense from an evolutionary perspective, Mankin says. According to the RNA-world theory, life on this planet began as RNA molecules that reproduced without protein. Unlike modern cells, in which proteins are catalysts of most chemical reactions, the ancient ribosome was probably made of RNA, which is a poor chemical catalyst but efficient at binding substrates.

The finding suggests that drugs that interfere with binding of ribosomal substrates could block bacterial protein synthesis and, hence, be more effective against antibiotic-resistant bacteria.

1 Polacek, N. *et al.* (2001) Ribosomal peptidyl transferase can withstand mutations at the putative catalytic nucleotide. *Nature* 411, 498–501

New ion channel drug targets

The regulatory mechanism of two members of a novel ion-channel family found in non-excitable cells has been elucidated. This discovery could provide new treatment approaches for immune and blood disorders, liver and kidney failure, strokes, aging and insulin shock.

Compared with ion channels in excitable cells, little is known about these structures in non-excitable cells. Scientists at the University of Washington (Washington, DC, USA), the University of Hawaii (Hawaii, HI, USA), John Hopkins University (Baltimore, MD, USA) and Harvard Medical School (Boston, MA, USA) have published their work in two back-to-back articles in *Nature*[2,3]. These findings will help our understanding of how the influx and efflux of ions such as sodium and calcium is regulated in non-excitable cells. The groups have studied two ion channels, LTRPC2 and LTRPC7.

LTRPC2 is regulated by a mechanism involving ADP-ribose, which was previously thought to be a useless byproduct of cellular processes. However, it has been shown that ADP-ribose can control the entry of sodium and calcium into cells that have LTRPC2 channels[2]. This is significant because several reactions that generate ADP-ribose also generate harmful free radicals and reactive oxygen species, which are implicated in many disease processes.

LTRPC7 is regulated by ATP; in the event of ATP depletion, which occurs when the body is deprived of oxygen or sugar, the channel becomes activated and the influx of calcium into cells is increased[3]. This channel might, therefore, be implicated in strokes and heart attacks in which impaired blood supply results in oxygen starvation and cell death in surrounding tissues.

Excessive calcium influx has long been associated with cell death and tissue damage in stroke and heart attacks as well as several other diseases. Targeting the regulation of these novel, calcium-permeable ion channels could be an attractive approach for new drugs for these diseases.

2 Perraud, A.L. *et al.* (2001) ADP-ribose gating of the calcium-permeable LTRPC2 channel revealed by Nudix motif homology. *Nature* 411, 595–599

3 Nadler, M.J.S. *et al.* (2001) LTRPC7 is a Mg.ATP-regulated divalent cation channel required for cell viability *Nature* 411, 590–595

Pinpointing proteins in neurons

A novel method for visualizing protein synthesis in neurons has been developed by scientists[4]. It is thought that local protein synthesis is required for synapse plasticity. However, until now, it has been difficult to show that protein synthesis occurs in mammalian neurons.

Researchers at the Howard Hughes Medical Institute (Chevy Chase, MD, USA) have synthesized a protein-synthesis reporter gene in which the gene for green fluorescent protein (GFP) is flanked by a gene encoding calcium/calmodulin-dependent kinase II-α (CAMKII-α), which confers dendritic mRNA localization and translation. Using cultured hippocampal neurons, the researchers showed that a growth factor involved in synaptic plasticity, brain-derived neurotrophic factor (BDNF), could stimulate expression of the reporter gene in intact dendrites and isolated dendrites (detached from the main cell body, the soma). This protein synthesis is blocked by the translation-inhibitor anisomycin, and appears to occur consistently in particular parts of the cells, termed translational hot-spots. The group is now applying this technique to other regions of the brain and to the whole brain to explore the role of protein synthesis in information processing and animal behaviour.

4 Smith, A.G. *et al.* (2001) Dynamic visualization of local protein synthesis in hippocampal neurons. *Neuron* 30, 489–502

Botulinum injections give new hope to sufferers of low-back pain

Injections of botulinum toxin A have been found to ease chronic low-back pain[5]. Thirty-one patients with chronic low-back pain were given injections of either botulinum toxin or a saline solution in the randomized, double-blind study. Patients had experienced pain for at least six months before the study commenced and were taking a variety of analgesic and anti-spasmodic drugs, which they were advised to continue to take during the study.

After three weeks, 73% of patients who received the drug said the amount of pain had decreased by 50% or more, compared with 25% who had received the placebo. After eight weeks, 60% of those who received the drug maintained that pain relief was still decreased by 50% or more,

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compared with 13% of those receiving the placebo.

Patients were also evaluated on their ability to perform activities of daily life. After eight weeks, 67% of the patients who received botulinum toxin showed improvement in their ability to function, compared with 19% of those who received saline.

None of the patients reported any side effects from the injections or any worsening of pain or function. After six months, six of the 10 people who received botulinum toxin reported that the effect of the drug had worn off after three to four months.

Researchers are not sure how the botulinum toxin works, but it might reduce pain by decreasing the input from sensory fibres or by acting on pain receptors.

5 Foster, L. *et al.* (2001) Botulinum toxin A and chronic low back pain. *Neurology* 56, 1290–1293

Clinical trials

MS trials can use placebos in some circumstances

Placebos can ethically be used as a control in trials of new drugs for multiple sclerosis (MS), even though partially effective treatments exist, according to a recent report published in the *Annals of Neurology*[8]. The report, produced by the multi-disciplinary Task Force on Placebo-Controlled Clinical Trials in MS, convened by the National Multiple Sclerosis Society in the US, adds that use or placebos should be limited to MS patients who have been educated about current treatment options but do not appear to have benefited from these drugs of have declined to take advantage of them. The bioethicist, Jonathan Moreno (University of Virginia, Charlottesville, VA, USA) who wrote an editorial to accompany the report[9] said that the report is especially timely in light of the recent statement by the World Medical Association that he suggests tries to preclude the use of placebos in any trials where effective treatment alternatives exist.

Placebo trials are generally agreed to be the most efficient, cost-effective and decisive way to test the safety and efficacy of a drug. However 'most people in the field feel that it is problematic to utilize placebo-controlled trials in lieu of available therapy,' said Fred Lublin, lead author of the report and neurologist at Mount Sinai School of Medicine (New York, NY, USA).

8 Lublin, F.D. and Reingold, S.C. (2001) Placebo-controlled clinical trials in multiple sclerosis: ethical considerations. *Ann. Neurol.* 49, 677–681

9 Moreno, J.D. (2001) Placebos on trial. *Ann. Neurol.* 49, 558–560

HIV targets/mechanisms

Polymorphisms in HIV protease

Polymorphisms in the protease of HIV subtypes A and C – the most prevalent strains in Africa – might cause resistance to HIV protease inhibitors that target the process of virus maturation. Genetic variation in HIV subtype B has already been associated with drug resistance. Researchers at John Hopkins University (Baltimore, MD, USA) characterized HIV-1 proteases using sequences from drug-naive Ugandan HIV+ patients[6]. Several polymorphisms were found in both HIV-A and HIV-C compared with the HIV-B subtype. Significantly, in catalytic studies, the protease inhibitors indinavir, ritonavir, saquinavir and nelfinavir inhibited the HIV-A and HIV-C subtypes with 2.5–7.0-times and 2.0–4.5-times weaker K_i values than HIV-B, respectively. These data suggest that the proteases of HIV subtypes A and C are more biochemically fit in the presence of protease inhibitors. The lead researcher, Ernesto Freire, believes that scientists should, therefore, widen the focus of their research to include strains other than HIV-B. However, he warned that these findings are based on *in vitro* biochemical studies and could not predict the efficacy of protease inhibitors in patients with HIV.

6 Velaquez-Campoy, A. *et al.* (2001) Catalytic efficiency and vitality of HIV-1 proteases from African viral subtypes. *Proc. Natl. Acad. Sci. U. S. A.* 98, 6062–6067

Methadone might raise risk of HIV infection

Methadone, the drug that is used widely to treat heroin addicts, has been shown to stimulate HIV infection of human immune cells studied in cell cultures. Researchers at the Children's Hospital of Philadelphia (Philadelphia, PA, USA) reported the results at the *International Conference of the PsychoNeuroImmunology Research Society* meeting in Utrecht, The Netherlands.

It is well known that intravenous drug users are at high risk of HIV infection and AIDS but, in addition to the threat of virus transmission by needles, the group report that drugs such as morphine and heroin (opiates) stimulate HIV replication. Methadone is a synthetic opiate but has also been found to increase HIV infection of human microglial cells and macrophages. When added to blood cells taken from HIV-infected patients, methadone triggered latent HIV infection into active replication. The drug was shown to increase the expression of CCR5 receptors on the cell membrane, allowing HIV to enter the cells. In addition, methadone might activate HIV LTR, a promoter that causes HIV infection to switch from latency to an active state. Further research is necessary to assess whether the laboratory results accurately reflect HIV progression in patients receiving methadone. Meanwhile, patients receiving methadone to treat drug abuse who are also HIV-infected are advised to have their viral load and CD4 counts closely monitored for possible adverse effects of the treatment.

The thymus: a challenge too much for drug-resistant HIV

Drug-resistant HIV is less able to replicate in thyroid cells and thus halt the production of T cells than non-resistant virus[7]. These latest findings mean that patients that have protease inhibitor (PI)-resistant HIV and high viral loads can still fight the infection by producing a humoral immune response.

Researchers at the Gladstone Institute of Virology and Immunology (University of California at San Francisco, San Francisco, CA, USA) discovered this phenomenon after observing that patients who have developed resistant HIV after treatment with protease inhibitors do not display any concurrent decrease in T-cell count. The group studied recombinant HIV-1 clones containing wildtype or PI-resistant

protease domains in cultures of peripheral blood mononuclear cells, human thymic organ cultures and human thymus implants in severe combined immunodeficiency (SCID)-hu Ty/Liv mice. In the mononuclear cells, both HIV clones replicated to a similar extent. However, in thymocytes, the replication of the PI-resistant clones, but not wild-type clones, was significantly reduced[7]. Further, computed tomography showed that patients with PI-resistant HIV-1 had abundant thymus tissue. These findings suggest that replication of PI-resistant HIV in thymus cells contributes to the maintenance of T-cell counts in individuals infected with drug-resistant HIV.

7 Stoddart, C.A. *et al.* (2001) Impaired replication of protease inhibitor-resistant HIV-1 in human thymus. *Nat. Med.* 7, 712–718

Miscellaneous

GlaxoSmithKline rationalizes e-procurement

GlaxoSmithKline (GSK; London, UK) is to implement a World Wide Web-enabled procurement strategy, announced the company recently. The newly merged company now has 1200 procurement professionals worldwide purchasing £8.16 billion of goods, services and supplies annually. The group, led by Willie Deese, has the remit of reducing total spending on purchased goods and services by 10% over the next three years. They will also coordinate the supply-chain implications of the company's new procurement strategy and ensure that all business requirements are still met. The new system implemented by GSK will allow detailed tracking of spending and savings, as well as contract management and creation.

Former FDA director calls for reduction in patent litigation

A former Food and Drug Administration (FDA, Rockville, MD, USA) deputy director called on members of industry, the Food and Drug bar, and congressional committees to work out a fair system to determine how long patent protection should last and from what point generic versions can be marketed, it was reported by the Regulatory Affairs Professionals Society (Rockville, MD, USA; June 2001 issue).

Gerald Meyer, former Deputy Director of the Center for Drug Evaluation and Research, said that the misdirected energy and dollars being spent on litigation or circumventing intellectual property rights was 'exceptional and unfortunate – and generally destructive in terms of drug development [in the USA].'

'We need to find a way to better use the energy and funds now being directed at gimmicks and litigation,' he continued. He cited that although the 1984 Hatch–Waxman legislation was a significant step towards achieving a fair balance, it has become clear that the protections provided have 'not always been adequate' in the intervening period since its introduction.

Double activist trouble at GSK AGM

Directors attending GlaxoSmithKline's (GSK; London, UK) recent Annual General Meeting (AGM) were the focus of demonstrations by several activist groups, it was reported in the European Pharmaceutical Intelligence Bulletin (EPIB) recently. Oxfam, the international charity, handed shareholders material calling on GSK to make the essential medicines it produces cheaper for poor countries. The board also heard the same message from some of their investors.

Defending his company's protection of its patent rights, Jean-Pierre Garnier, GSK's Chief Executive, said GSK is not to blame for the limited access to essential medicines in some countries. Instead he blamed poor healthcare infrastructure, inadequate healthcare budgets, failure to prevent the spread of fatal diseases and lack of political will.

Animal rights groups were also present at the meeting protesting over GSK's continued support for the research company Huntingdon Life Sciences.

Consumer groups start class actions

The Stop Patient Abuse Now (SPAN; Washington, WA, USA) coalition is to organize consumer and patient groups in the USA to initiate a series of class action lawsuits against pharmaceutical companies that are perceived to be endangering public health by stifling competition in the market place, the coalition recently announced.

One of the groups to take part is the National Organization for Women (NOW, New York, NY, USA). NOW is taking Bristol-Myers Squibb (New York, NY, USA) to court because the company allegedly prevented access to a lower-priced version of the breast and ovarian cancer drug Taxol. A federal court ruled in March 2000 that the tactics included 'an intent to deceive' the US Government.

AstraZeneca (London, UK) is also a target for SPAN following its alleged attempts to delay competition for the ulcer medicine Prilosec. Patent protection for the drug expires in October 2001, but the company has indicated that it might try to extend this.

Abbott Laboratories (Abbott Park, IL, USA) could be the focus of a similar lawsuit if it refuses to remove its thyroid disease drug, Synthroid, from the market. In April 2001, the Food and Drug Administration (FDA; Rockville, MD, USA) issued a letter that Synthroid 'cannot be generally recognized as safe and effective'.

'Consumers have no regulatory avenue for relief from market abuses by pharmaceutical companies', stated Tim Fuller from SPAN and the Gray Panthers (Washington, DC, USA), another consumer organization. 'This strategy will shift the balance of power from drug industry executives and their friends in Congress to the consumers who need relief.'

Support for stem cell research overwhelming

Public approval of stem-cell research in the USA is at 70% and includes that of fundamentalist Christians and opponents of abortion, reveals a recently survey conducted by Caravan OCR International for the Coalition for the Advancement of Medical Research (Washington, WA, USA).

Survey participants were asked their initial opinion of stem cell research that comes from fertilized eggs. They were then given a series of arguments used by both supporters and opponents of the research. Of the 1010 adults surveyed, the ratio of people supporting the research to those against was 3:1. Respondents strongly favouring National Institutes of Health funding for stem cell research outweighed those against by 2.5:1.

Meanwhile, Catholic supporters of stem cell research outnumbered opponents by 3 to 1, and among fundamentalist Christians, the ratio was 2.5:1, and those describing themselves as pro-life, 1:1.

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