News in brief

Targets and mechanisms

ACE inhibitors might slow muscle decline

Researchers have found that a drug commonly prescribed as an antihypertensive to patients suffering from congestive heart failure (CHF) might also prevent physical decline in elderly people who do not suffer from CHF [1].

In patients with CHF, angiotensin-converting enzyme (ACE) inhibitors prevent a decline in physical function, mainly through the inhibition of the renin–angiotensin system. This prevents ventricular remodelling, improves peripheral vasodilation and modulates myocardial oxygen consumption. Based on these results, researchers from the Stricht Center on Aging at the Wake Forest University School of Medicine (NC, USA) postulated that similar effects might be seen in patients who do not suffer from CHF.

The group compared rates of decline in walking speed and the strength of the knee extensor muscle among groups of elderly hypertensive women who did not have CHF. Over a three-year period, women who had taken ACE inhibitors continuously showed a smaller decrease in muscle strength and walking speed compared with those who took ACE inhibitors intermittently, those who took other antihypertensive drugs, or those who were not taking any form of antihypertensive medication. In fact, the average three-year decline in walking speed among ACE inhibitor users was ten-times lower than among the other groups. 'This is one of the first studies to suggest that a drug treatment could delay a decline in physical function,' said lead researcher, Graziano Onder.

It is not known exactly how ACE inhibitors could directly affect skeletal muscle. Possible mechanisms might include shifting the myosin heavy chains in muscle to isoforms that are slower, aerobic and more fatigue-resistant; increasing insulin sensitivity, and glucose uptake and storage; lowering the proinflammtory response triggered by angiotensin; and affecting nutritional status by inhibiting interleukin-6, a cytokine that reduces appetite.

Although randomized controlled trials are needed to confirm these findings, they suggest that ACE inhibitors could be used not only for treating elderly patients with hypertension, but also for slowing physical decline in the elderly in general.

1 Onder, G. *et al.* (2002) Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet* 359, 926–930

From genomics to proteomics in yeast

Scientists have completed the largest analysis yet of protein localization in a eukaryote [2]. Mark Snyder and colleagues from Yale University (Newhaven, CT, USA) and Invitrogen (Carlsbad, CA, USA) have reported their efforts to characterize the proteome of baker's yeast (*Saccharomyces cerevisiae*).

The *S. cerevisiae* genome was the first eukaryotic genome to be sequenced, back in 1996. Hence, much information is known about the organism's 6000 genes, but less is known about the function and distribution of the protein products. More than 2000 of the proteins encoded by the yeast's genes are yet to be functionally characterized. To address this problem, Snyder and co-workers have now made a large-scale analysis of the organism's proteome.

Most proteins are synthesized on ribosomes in the cytosol and are then transported to various parts of the cell to perform their function. This subcellular localization can be a strong indicator of protein function. Snyder and co-workers have therefore developed a high-throughput method to tag individual proteins and visualize their movements within living cells. They successfully determined the subcellular localization of over 2700 yeast proteins. Using a combination of various approaches, including a statistical computer algorithm, the researchers were able to predict the localization of all 6100 yeast proteins. This has provided insight into the potential function of nearly half of all previously uncharacterized yeast proteins.

2 Kumar, A. *et al.* (2002) Subcellular localization of the yeast proteome. *Genes Dev.* 16, 707–719

Pumping iron involves a shape change

The three-dimensional structure of a transport protein that actively pumps iron into bacterial cells has been solved [3]. Knowledge of this system could help the design of novel antibiotics. Researchers at the University of Texas Southwestern Medical Center (Dallas, TX, USA) and co-workers have used X-ray crystallography to probe the structure of the FecA protein, both with and without ferric substrate. They noted that the protein undergoes a significant change in conformation while transporting iron through the outer membrane. The structure can be envisaged as a barrel with openings at either end. A plug inside the barrel fills its middle, leaving open pockets at the barrel's top and bottom. When an iron-containing compound enters the top pocket from the extracellular matrix, the top pocket closes, triggering iron absorption.

This high-affinity iron-uptake system could have clinical applications. So-called 'Trojan Horse' drugs could be designed that mimic natural iron-transport proteins, such as transferrin. These would be specifically recognized and actively pumped into the cell where they would disrupt some aspect of bacterial function. 'Understanding the mechanism of iron transport is an important first step toward this goal', said 1988 Chemistry Nobel Laureate, Johann Deisenhofer, who is Professor of Biochemistry and an investigator in the Howard Hughes Medical Institute at UT Southwestern, and an author of the study.

3 Ferguson, A.D. *et al.* (2002) Structural basis of gating by the outer membrane transporter FecA. *Science* 295, 1715–1719

Leukaemia model leads the way to new cancer therapies

A mouse model of acute myeloid leukaemia (AML) has been developed that could help scientists find treatments for

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several different types of human cancer [4]. Researchers at the St Jude's Children's Research Hospital (Memphis, TN, USA) have generated a mouse strain with a conditional *AML1–ETO* knockin allele that mimics human AML caused by the t(8:21) translocation and avoids the embryonic lethality seen with previous models.

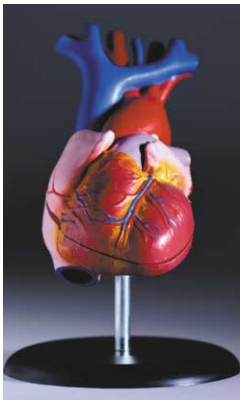
Their experimental strategy involved the insertion of a loxP bracketed transcriptional stop cassette 5′ to the AML1–ETO fusion site, which enabled the allele to be activated *in vivo* by Cre-mediated recombination. Activation of the knockin allele in this manner was insufficient to induce leukaemia; however, induction of cooperating mutations resulted in AML that closely mimicked that seen in humans.

This mouse model will enable scientists to identify the mutations that cooperate with *AML1–ETO* to induce leukaemia and could reveal targets for therapeutic intervention of this pathway. Furthermore, the knockin strategy used here could be applicable to many other animal models of human malignancies.

4 Higuchi, M. *et al.* (2002) Expression of a conditional AML1–ETO oncogene bypasses embryonic lethality and establishes a murine model of human t(8:21) acute myeloid leukaemia. *Cancer Cell* 1, 63–74

Cardiovascular targets and mechanisms

Angina gene therapy is safe



Gene therapy for the treatment of angina appears to be safe, a recent study has shown [5]. The Angiogenic Gene Therapy (AGENT) trial is the first placebo-controlled, double-blind trial of the therapy in humans. Researchers tested the safety and effectiveness of injecting a human fibroblast growth factor (FGF) gene into the heart and discovered significant improvements in exercise times for patients.

'There is no product approved to stimulate the growth of new blood vessels,' says Cindy Grines, lead author of the study and director of the cardiac catheterization laboratories and the interventional cardiology training program at William Beaumont Hospital in Royal Oak (MI, USA). 'We think the growth factor gene used here restarts this natural response. This is a completely new and different approach.' Grines adds that gene therapy could be a better approach than protein therapy because the heart can incorporate the gene and allow continued production of the angiogenic protein for weeks.

The team studied 79 men and women with coronary artery disease and mild to moderate angina. An inactive virus, Ad5, was infused into the heart blood vessels of 60 patients; the remaining 19 patients received placebo. The virus contained the human *FGF4* gene, which stimulates collateral blood vessel development. The researchers determined that 87% of the gene therapy agent stayed in the heart and none of the protein product was detected elsewhere in the circulatory system.

The patient's exercise treadmill time (ETT) was tested at baseline and at four and 12 weeks following treatment. At the start of the study, the average ETT was 9.0 min for the treatment group, compared with 9.4 min for placebo. At four weeks, the ETT of treated patients increased by 1.3 min compared with 0.7 min for placebo. In many patients, the improvement over baseline ETT was comparable to that seen after surgical interventions or angioplasty, says Robert L. Engler, a cardiologist at the Veterans Administration San Diego Health Care System (San Diego, CA, USA).

'The results of this study are very encouraging because the response that we saw was far in excess of what we would have expected,' says Engler. He stressed that the small number of participants in the trial prohibits any final conclusions and added, 'Proving effectiveness will take a much larger pivotal trial, called AGENT 3, which is currently under way in 100 centers in the USA.' Thus, angiogenic gene transfer with Ad5–FGF4 shows promise as a novel therapeutic approach to the treatment of angina pectoris.

5 Grines, C.L. *et al.* (2002) Angiogenic gene therapy (AGENT) trial in patients with stable angina pectoris. *Circulation* 105, 1291–1297

Antibiotics to improve CV function

Researchers have shown that an antibiotic improved vascular function in people with angina who tested positive for *Chlamydia pneumoniae* (*CPn*) in the blood [6]. The scientists, at the Department of Cardiological Sciences (St George's Hospital Medical School, London, UK), performed a randomized double-blind, placebo-controlled trial in 40 male patients (average age 55 years) with coronary artery disease and positive *CPn*-IgG antibody titres, using the antibiotic azithromycin.

The patients showed improved blood flow in the brachial artery and reduced blood levels of two known markers for endothelial dysfunction (E-selectin and von Willebrand factor) and a marker for inflammation (C-reactive protein) after five weeks of daily treatment with azithromycin. Juan Carlos Kaski, co-author of the study and a Professor of Cardiovascular Science at St George's, says that once a microbe was identified that could cause damage to the endothelium, which leads to atherosclerotic plaque formation and, ultimately, angina and heart attacks, researchers tried to find an antibiotic to eradicate it. *C. pneumoniae* was a good candidate because it has been discovered in plaque removed from the arteries of people with coronary artery disease.

'We have found in this study that treatment with azithromycin improved the function of the endothelium,' says Kaski. After treatment, patient's average flow-mediated dilation (FMD) of the bronchial artery improved from 2.66% at baseline to 4.78%: the placebo group showed 3.11% at baseline and at five weeks it was 3.09%. Kaski says that the benefit of the antibiotic might not be a direct result of pathogen eradication because patients with high levels of *C. pneumoniae* antibodies had the same benefit as those with low levels. 'Thus, whether the beneficial effects of azithromycin were due to its antibacterial or anti-inflammatory actions is unresolved by our study.'

The next step, says Kaski, is to design a study to enable researchers to 'identify the mechanism responsible for the beneficial effect of antibiotics so that we arrive at a more rational treatment, which might include developing even more effective antibiotics or perhaps a vaccine, or just appropriate anti-inflammatory agents.'

6 Parchure, N. *et al.* (2002) Effect of azithromycin treatment on endothelial function in patients with coronary artery disease and evidence of *Chlamydia pneumoniae* infection. *Circulation* 105, 1298–1303

Possible treatment for congestive heart failure

By blocking a key protein in the regulation of calcium levels in heart cells, researchers from the Cardiovascular Research Center (CVRC) and Heart Failure Center at Massachusetts General Hospital (MGH; Boston, MA, USA) have found a way of improving the function of failing heart muscle cells [7].

Congestive heart failure occurs because of abnormal levels of calcium in muscle cells in the heart, and often the only way of correcting such failure is by heart transplants. The researchers studied the protein phospholamban, levels of which might be reduced in failing hearts. This protein regulates the activity of the sarcoplasmic reticulum Ca^{2+} ATPase pump (SERCA2a), which controls the flow of calcium within cells. It is thought that the natural inhibitory actions of phospholamban in a failing heart might stop the heart muscle from relaxing by blocking the normal regulation of calcium, therefore preventing the heart from filling with blood properly.

Using cells taken from hearts that were about to be transplanted, the researchers used gene therapy to see whether contraction and relaxation in these failing cells could be improved. They injected single-stranded DNA into the cells that binds to the RNA encoded by the phospholamban genes. 'When we knocked down the amount of protein that was formed, the heart cell contractions became normal,' commented Roger Hajjar of the CVRC and the Heart Failure Center at MGH, and the principal investigator of this study. This prevented the formation of phospholamban and resulted in the cells contracting normally.

The strategy is now undergoing clinical trials in animal models to see whether it could become a treatment for congestive heart failure in humans. Such treatment could reduce the need for heart transplants and overcome the problem of waiting lists for such transplants.

7 del Monte, F. *et al.* (2002) Targeting phospholamban by gene transfer in human heart failure. *Circulation* 105, 904–907

Miscellaneous

Manchester cancer centre to be most advanced in field

The world's first purpose-built molecular imaging cancer research centre will open in 2003 in Manchester, UK. The Wolfson Molecular Research Centre (http://www.wmic.man.ac.uk) will be based at Christie Hospital (Manchester, UK) and is being funded by £22 million from the Wolfson Foundation (London, UK), Cancer Research UK (London, UK), the Christie Hospital Trust Charitable Fund, and the University of Manchester (Manchester, UK). The key equipment is being provided by Medical Research Council (London, UK) and the Engineering and Physical Sciences Research Council (Swindon, UK) through the Government's North West Science Initiative.

'The new centre will reinforce Manchester's status as one of the world's leading players in cancer research and is an example of how partnership can take us forward,' said Trevor Hince, Cancer Research UK's Director of Research Management and Planning. Hince described the appointment of Pat Price as Director of the Centre as ensuring 'not only terrific facilities, but also unrivalled expertise.'

Singapore council endorses Institute of Bioengineering

The Singapore Biomedical Science International Advisory Council (IAC) has endorsed the formation of a new Institute of Bioengineering (IBE) to focus on tissue and stem cell engineering, biomaterials and scaffolds, medical devices and delivery systems. The institute will also be actively involved in new technologies in the fields of computational biology, imaging and analysis of biological systems, and nanotechnology.

The IBE is to be established in 2002 and will be funded and supervised by Singapore's Agency for Science, Technology and Research (A*STAR; Singapore, Republic of Singapore) and will be sited at a new research park in Singapore dedicated to the biomedical sciences named Biopolis.

'Singapore has made tremendous progress in developing the Biomedical Sciences industry in a relatively short span of time,' said Sir Richard Sykes, Chairman of the IAC. 'The Council is greatly impressed with Singapore's cohesive and integrated approach … and is confident that Singapore is headed for success in this field,' he said.

The IAC was appointed in 2000 to advise the Singapore Government on how to make biomedical sciences as key a pillar of economic growth as the electronics, chemical and engineering industries have been. Biopolis, which is due to open in 2003, will also house the Genome Institute of Singapore, the Bioprocessing Technology Centre, the Bioinformatics Institute, the merged Institute of Molecular & Cell Biology, and the Institute of Molecular Agrobiology.

Forest ends joint development with European partners

Forest Laboratories (New York, NY, USA) have withdrawn from a joint agreement to co-develop the osteoarthritis treatment ML3000 in the USA after some of the first results from Phase III clinical trials failed to meet Food and Drug Administration (FDA; Rockville, MD, USA) standards. The company, which had agreed to develop the treatment in the USA in parallel with a consortium of European firms, said they did not wish to provide further investment in the extra trials required to achieve FDA approval.

However, the remaining members of the consortium, named EuroAlliance and comprising Merckle (Ulm, Germany), Alfa Wassermann (Bologna, Italy) and Lacer (Barcelona, Spain), believe ML3000's mechanism-of-action is innovative enough to attract important licences and attribute the poor results to unexpectedly high placebo response rates in some of the Eastern European trials.

'We recognise that the US market is not an easy one to crack,' said Giuseppe Persani, President of EuroAlliance. '[ML3000] will be up against the powerful marketing operations of Pharmacia and Merck … [so] … we obviously need a partner who is totally committed,' he said.

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