News in brief

Targets and mechanisms

c-MYC gets knotted!

Scientists at Cyternex (http://www.cyternex.com) and the University of Arizona (http://www.arizona.edu) have announced results identifying a specific knot structure of DNA that can inhibit the expression of the oncogene *c-MYC* [1].

Laurence Hurley, from the University of Arizona, said: 'The study provides direct evidence that a 3D 'knot' in DNA, called a G-quadruplex, controls this key cancer gene. In this case, the knot is the shape of a chair.' He continued that, by stabilizing this chair-form G-quadruplex, the transcriptional control region of *c-MYC* was blocked, which effectively inhibits its expression.

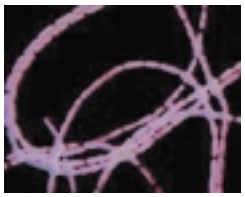
The *c-MYC* gene is seen in 60% of all cancers, including prostate, breast, lung, pancreatic and myeloid leukaemia, said Hurley. In this study, the team reported the identification of a biologically relevant structure of c-MYC and used base mutation analysis to identify the crucial bases involved in formation of the chair structure.

By targeting these unique knot-like structures, Cyternex is developing drug candidates to regulate the expression of oncogenes. Tom Farrell, President and CEO of Cyternex, said: 'Since the original studies were completed, we've developed compounds that are several orders of magnitude more effective than the one cited in the paper.' He added, 'We have also identified 16 other genes controlled by the formation of a G-quadruplex… All 16 genes have been implicated in cancer, as well as other proliferative diseases. We are taking advantage of the structural diversity of our quadruplex targets as we continue the development of small-molecule compounds to repress individual oncogene expression.

1 Siddiqui-Jain, A. *et al.* (2002) Direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11593–11598

Evasion mechanism behind deadly anthrax

A protein complex, called lethal toxin (LT), produced by *Bacillus anthracis* enables



these potentially lethal bacteria to disarm and evade the host immune system, according to scientists at the University of California, San Diego (http://www.ucsd.edu) [2].

LT is a combination of protective antigen (PA) and lethal factor (LF) proteins. The PA component binds to the surface of macrophages enabling bacteria to penetrate, whereas this latest study has shown that LF selectively induces apoptosis in macrophages by cleaving the amino-terminal extension of mitogen-activated protein kinase (MAPK) kinase, MKK, which activates p38. It is thought that p38 is necessary for the activation of genes that protect against apoptosis, and that together, PA and LF disable the signaling mechanisms responsible for immune activation, thus allowing the anthrax bacteria to spread freely and rapidly throughout the body.

Michael Karin and colleagues believe that the next step is to develop an antidote to block LF: 'If we are correct,' he says, 'inhibition of the toxin's activity should give our bodies enough time to detect an infection and fight it.'

2 Karin, M. *et al*. (2002) Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. *Science* 297, 2048–2051

Key CNS communicator identified

Researchers have discovered that the SynCAM protein has a major role in the formation of synapses, which are junctions of communication between neurons in the brain [3]. This study details the initial events that lead to synapse formation in the CNS.

Thomas Biederer, lead author of the study and a postdoctoral researcher in the center for Basic Neuroscience at UT Southwestern Medical Center at Dallas (http://www3.utsouthwestern.edu) said: 'Until this discovery, very little was known about how neurons form synapses with each other. We defined how the initial contact points are being developed and from there we can figure out how the young nervous system grows into an active network'.

The team identified the protein by searching the mouse genome for a molecule that was capable of bridging neurons and recruiting synaptic components. An artificial model was then constructed that induces synaptic transmission. Functional characterization was performed using cultured neurons from mice. Upon overexpression of SynCAM, the team found an increase in spontaneous synaptic structures and activity by as much as threefold; when this SynCAM function was interrupted, synapse number and activity decreased.

In neurological disorders such as Parkinson's and Alzheimer's diseases, there is a loss of neurons and synapses, said Biederer. Thus, a better understanding of trans-synaptic signalling could lead to potential new treatments for these disorders. 'One can speculate that the detrimental effects of these diseases can be balanced by a molecule such as SynCAM that can induce new synapses,' said Biederer. 'Other possible applications could include therapies for spinal cord injuries.'

3 Biederer, T. *et al.* (2002) SynCAM, a synaptic adhesion molecule that drives synapse assembly. *Science* 30, 1525–1531

An end to immortal cancer cells?

New research has revealed one way in which cancer cells can multiply unchecked that could, ultimately, lead to therapies for controlling cancer growth [4].

Telomerase is a key player in unrestricted cell growth, maintaining the telomeres that cap the ends of chromosomes so that DNA replication and cell division can occur unhindered. If the telomeres get too short, the cell becomes unable to divide, and thus growth is stopped.

Researchers at UC Berkeley (http://www.berkeley.edu) have now shown that, in a normal cell, the telomerase is confined to the nucleolus and only comes into contact with chromosomes when cell division is occurring. The telomerase is then returned to the nucleolus once cell division has finished. The researchers, led by Julie M.Y. Wong and Kathleen Collins, looked at cancer cells and found that their telomerase is always present in the nucleus, enabling the cells to divide almost continuously, while maintaining the length of the telomeres.

Although it is still unknown how cancer cells are able to maintain a continuous presence of telomerase in the nucleus, discovering a way to gather them up and return them to the nucleolus could halt the unchecked growth of cancer cells.

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Not only could such methodology be used to treat patients with cancer, but it could also be used to treat patients with HIV or who are undergoing chemotherapy. In HIV, there is a continual turnover of immune cells, which results in an exhausted immune system, because the cells can only undergo a certain number of divisions. Finding a way to stop or slow down such division could be a potential treatment strategy for HIV patients.

4 Wong, J.M.Y. *et al.* (2002) Subnuclear shuttling of human telomerase induced by transformation and DNA damage. *Nat. Cell Biol.* 4, 731–736

TIMHC II molecules caught on camera

A novel video technique has revealed a pathway that enables dormant immune cells to become active [5]. This discovery provides new insights into how the immune system is mobilized to fight disease and could eventually lead to new ways to treat diseases such as arthritis, Crohn's disease and cancer.

Researchers at Yale University (http://www.yale.edu) and the Ludwig Institute for Cancer Research (http://www.licr.org) used confocal video microscopy to watch activated dendritic cells search lysosomes to salvage unused major histocompatibility complex class II (MHC II) molecules. These molecules bind with antigen fragments from invading microbes and then present the material on the dendritic cell surface, where they prompt immune defences to launch an attack. Exactly how the MHC II molecules make it from lysosomes to the surface has long been a mystery. The video shows dendritic cells generating special tubules that transport the molecules and antigen fragments to the cell surface. By capturing the action live on tape, the study documents a pathway that could only be guessed at before.

'We have had all sorts of theories on why dendritic cells behave in certain ways, but at the end of the day, you want to see them in action,' said Ira Mellman, who led the team. 'Visualizing how cells work can provide for remarkably creative insights.' Dendritic cells might be a key target for promoting more favourable immune responses. In fact, a new treatment for arthritis and Crohn's disease might work by inhibiting the ability of dendritic cells to rescue intracellular MHC II.'There are still a number of outstanding questions on how this transport system works,' said Mellman, 'But these issues can now be easily

Stem cells

Blood cells developed from adult progenitor cells

Scientists at the Mayo Clinic (http://www.mayo.edu) have shown for the first time that an adult stem cell variant that circulates in adult human blood can form smooth muscle cells, which are key components in the formation of blood vessels [10].

'Previous studies have shown that endothelial cells, which line blood vessels, can be grown from progenitors in blood,' said David Simper, first author of the paper. 'Smooth muscle cells are the essential building blocks of arteries, and until now we have not had a way to create them.' He said that the study could be a significant step for the development of potential new vessels to provide blood circulation in diseased hearts.

The researchers used platelet-derived growth factor BB (PDGF-BB) and converted previously undiscovered circulating smooth muscle progenitor cells (SPCs) into smooth muscle outgrowth cells (SOCs). SPCs reside in bone marrow and are stem cells that have started on the path of differentiation.

This study is the first to prove the existence of SPCs in humans; in the presence of PGDF-BB, the cells rapidly proliferated into smooth muscle cells, and also had adhesive properties that potentially steer the cells to areas of blocked vessels.

These new findings could help address some of the key problems in interventional cardiology. Noel Caplice, director of the Mayo Clinic laboratory that conducted the study, said: 'About 30% of patients with heart disease who have stents implanted during angioplasty have problems with renarrowing, or restenosis, within the stents…This study may enhance our efforts in achieving therapeutic angiogenesis.'

10 Simper, D. *et al.* (2002) Smooth muscle progenitor cells in human blood. *Circulation* 106, 1199–1204

Doubt about the potential of adult stem cells

New research from Stanford University Medical Center (http://www-med.stanford.edu) shows that trying to coax adult blood-forming stem cells in mice to form tissues other than blood and immune cells has failed [11].

This research strikes a blow for the idea that stem cells from adults have the same differentiation potential as those from embryos and adds to the debate over the fate of embryonic stem-cell research. Several groups have stated that adult stem cells have the same differentiation potential as those from embryos, hence some policy-makers want to ban the controversial embryonic stem-cell research and use adult cells instead.

Irving Weissman, Professor of Cancer Biology at Stanford and lead author of the study, who has long argued that only embryonic cells have the ability to form all adult tissues, said: 'This is the first time somebody injected a single adult stem cell and showed that it made only blood.' He emphasized that, in light of this work, other researchers and members of the public should wait for all data before rushing to judge: 'Especially when you are jumping to a political judgment that has big policy repercussions'.

Weissman, together with postgraduate student Amy Wagers, studied whether mice adult stem cells could integrate into adult tissues. They isolated stem cells from mice bone marrow and engineered them to make green fluorescent protein (GFP); a single stem cell was then injected into mice whose bone marrow had been knocked out by irradiation. After several weeks, the GFP stem cell had repopulated the blood and immune cells of the mice; however, when over 15 million cells from muscle, brain, liver, kidney, gut and lung were analyzed, only eight cells were green when viewed under the microscope. The scientists said that, even if these cells were differentiated from the adult stem cell, the level is so low as not to be any useful form of therapy. Wagers added, 'I hope [this research] tempers the enthusiasm for adult stem cell plasticity. Maybe it's not the answer that it appeared to be.'

11 Wagers, A.J. *et al.* (2002) Little evidence for developmental plasticity of adult hematopoietic stem cells. *Science* DOI 10.1126 (epub ahead of print; http://www.sciencemag.org)

addressed through similar experiments using live cell imaging.'

5 Chow, A. *et al*. (2002) Dendritic cell maturation triggers retrograde MHC class II transport from lysosomes to the plasma membrane. *Nature* 418, 988–994

Cyclopamine stops Hedgehog on its tracks

Blocking growth signals from Hedgehog (Hh) stops medulloblastoma tumours in mice and kills medulloblastoma cells taken from human patients [6]. This discovery could be crucial to the development of an effective treatment for the most common malignant brain tumour in children.

The Hh gene encodes a signalling protein that is essential during embryonic development. If the signal is switched on during later life, it could lead to cancer. Scientists at Johns Hopkins University (http://www.jhu.edu) and the Fred Hutchinson Cancer Research Center (http://www.fhcrc.org) used a plant chemical, cyclopamine, to block the Hh signal. The compound reduces the growth of mouse medulloblastoma cells *in vitro* and also reduces the size of tumours implanted into mice.

In addition, the team studied medulloblastoma tumour samples from seven patients. Cyclopamine actually killed up to 99.9% of the cancer cells. The cells from these cancer patients had abnormal activation of the Hh pathway, but the scientists do not know whether mutations in the Hh gene are responsible. Because cyclopamine does not cause regression of other types of brain tumour, a specific role for Hh pathway activity in medulloblastoma growth has been established.

'If blocking Hedgehog kills all medulloblastoma cells, that would be tremendously important', says Philip Beachy, Professor of Molecular Biology and Genetics at Hopkins' Institute for Basic Biomedical Sciences. It is probable that with more research, other Hh blockers will be discovered that kill medulloblastomas but have better characteristics than the plant compound cyclopamine

6 Berman, D.M. *et al.* (2002) Medulloblastoma growth inhibition by Hedgehog pathway blockade. *Science* 297, 1559–1561

Miscellaneous

High starch diet linked to pancreatic cancer

US researchers have discovered a possible link between a diet high in starch and pancreatic cancer in overweight women with a sedentary lifestyle [8]. The study implies that excess insulin production could promote the development of pancreatic cancer.

Previous laboratory studies showed that insulin encourages the growth of malignant pancreatic cells. Separate studies found that obese people who are physically inactive or have adult-onset diabetes mellitus tended to be 'insulin resistant'. To compensate for this, they produced abnormally high amounts of insulin, increasing their risk of developing pancreatic cancer.

The US researchers hypothesized that if insulin increases the growth of pancreatic cancer cells then foods, such as potatoes, rice and white bread, that cause the body to produce large amounts of insulin could be associated with a higher occurrence of the disease.

Researchers reviewed the dietary and health records of ~89,000 women (data from the Nurses' Health Study at Brigham and Women's Hospital; http://www.brighamandwomens.org/). The intake of sucrose, fructose and carbohydrate were measured and the glycemic load (the amount of glucose-stimulating foods) calculated. It was discovered that physically inactive obese women, whose insulin and glucose levels were above normal, were more than twice as likely to develop cancer of the pancreas if they had a high glycemic load. Significantly, a high glycemic load

did not increase the risk of pancreatic cancer among lean and physically fit women. 'Our findings add to the growing body of evidence that suggests that insulin may have a role in the development of pancreatic cancer,' stated Charles Fuchs from the Dana–Farber Cancer Institute (http://www.dana-farber.org), senior author of the paper.

Although the study only involved women, the researchers think that there is no reason to suggest that the findings do not apply equally to men.

8 Michaud, D.S. *et al.* (2002) Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J. Natl Cancer Inst.* 94 1293–1300

Successful use of gene therapy in a large animal

Gene therapy has been used successfully for the first time to treat a disease that affects multiple organs within the body of a large animal, in this case a dog [9].

Although gene therapy has been used before in dogs to treat diseases that affect just one organ system, it is the first time that such therapy has been used to treat a condition with multisystemic effects.

Researchers led by Mark E. Haskins (University of Pennsylvania School of Veterinary Medicine; http://www.vet.upenn.edu) and Katherine Parker Ponder (Washington University School of Medicine; http://www.washington.edu/medical/som), conducted experiments with dogs suffering from mucopolysaccharidosis VII (MSP VII). MSP VII is a lysosomal storage disease caused by a deficiency in the activity of β glucuronidase. Similar diseases occur in humans, such as Gaucher disease and Tay Sachs disease. In dogs, MSP VII causes corneal clouding, bone abnormalities and cardiac disease, resulting in a loss of mobility by the age of six months.

The dogs were treated with hepatic gene therapy as soon as they were born via four intravenous injections of a retroviral vector that expressed canine β glucuronidase, and were then monitored for 17 months. A normal pattern and level of enzyme activity was recorded for up to 14 months following injection, and the dogs gained weight normally and avoided the serious side effects that normally occur as a result of lysosomal storage diseases.

The researchers are hopeful that such treatment could be used to treat other lysosomal storage diseases, although not those that affect the CNS.

9 Parker Ponder, K. *et al.* (2002) Therapeutic neonatal hepatic gene therapy in mucopolysaccharidosis VII dogs. *Proc. Natl. Acad. Sci. U. S. A.* 99, 13102–13107