by activating Th-1 cells. The drug is a novel synthetic dipeptide, D-glutamyl-L-tryptophan, dubbed SCV07.

In co-operation with a Russian biotechnology company, Verta, SciClone has recently tested the effectiveness of SCV07 in a Phase II clinical trial. In addition to standard anti-TB therapy, 44 patients with TB (60% with MDR TB) received 10–100 μg d^{-1} of SCV07 for five days. As controls, 27 other patients received standard therapy only.

Among patients treated with SCV07, 57% had negative sputum cultures after one month and 80% were negative after three months (Fig. 1). Among controls, cultures were negative for only 19% and 37%, respectively. These results imply that SCV07 could potentially reduce the length of TB treatment, according to Cynthia Tuthill, SciClone's Vice President for Scientific Affairs. 'The real benefit, however, is that by reducing the time that patients are contagious, there is less opportunity to spread the infection', she explained.

Although these results are encouraging, this was a relatively small study, warns Martin Bachmann, Chief Scientific Officer of Cytos Biotechnology AG (http://www.cytos.com). 'Side effects are always a major concern with non-specific stimulators. It is quite possible that problems may be encountered when patient numbers are increased', he cautioned.

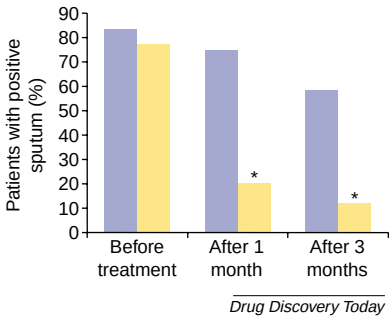


Figure 1. Decreases in positive sputum assays for mycobacteria in Phase II trial of SCV07 (blue bars, controls; yellow bars, patients treated with SCV07. * $P<0.05$). Figure courtesy of SciClone Pharmaceuticals (http://www.sciclone.com).

From missiles to meat

Although it is yet to be tested in Phase III clinical trials, the development of SCV07 could be a significant step in the continuing fight against TB, and perhaps other infectious diseases. This progress might never have occurred without the help of the US Civilian R&D Foundation (CRDF; http://www.crdf.org), which has provided funding for the project and facilitated co-operation between SciClone and Verta.

CRDF is a nonprofit charitable organization that promotes scientific and technical collaboration between the USA and the countries of the FSU. One of its main goals is to give opportunities to scientists and engineers in the FSU (many of whom used to work for the military) to do 'real' science and engineering work, so they would not have to leave their country or their profession to survive, says Tom Owens, a Senior Advisor with CRDF.

According to Owens, any US company is eligible for financial assistance from CRDF 'as long as it has a serious interest and wishes to develop a new relationship with a group in the former Soviet Union on a project in which there could be a decent chance for commercial application in the future'.

'We fund projects up to the time of being commercial', Owens said. Funding might be in the form of travel grants or awards for experiments and other R&D activities that can help people make a decision to enter the commercial market, he explains.

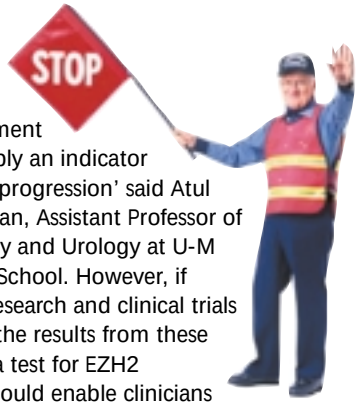
News in brief

Cancer gene expression

EZH2 flags up metastatic prostate cancer

Scientists at the University of Michigan's Comprehensive Cancer Centre (http://www.cancer.med.umich.edu) have shown, through gene expression profiling, that high levels of the polycomb group protein enhancer of zeste homolog 2 (EZH2) could be a warning sign of metastatic prostate cancer [1]. The group compared donated prostate tissue samples and observed that the intensity of EZH2 protein staining steadily increased from benign to clinically localized prostate cancer to metastatic disease. Analysis of EZH2 expression and other clinical indicators, including the Gleason score, tumour stage and prostate specific antigen (PSA) levels, were correlated with clinical outcome and it was found that the most significantly accurate predictor of clinical outcome was EZH2 protein expression in prostate cells.

EZH2 is one of several proteins that control the genetic memory of a cell and can interfere with the transcription of genetic code. 'At this point, it's unclear whether the gene plays a role in cancer's development or is simply an indicator of lethal progression' said Atul Chinnaiyan, Assistant Professor of Pathology and Urology at U-M Medical School. However, if further research and clinical trials reaffirm the results from these studies, a test for EZH2 protein could enable clinicians to diagnose those men who need immediate clinical intervention to prevent the cancer from spreading.



1 Varambally, S. *et al.* (2002) The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature* 419, 624–629

  PII: S1359-6446(02)02535-7

New genetic marker for colon cancer

Researchers at the Memorial Sloan-Kettering Cancer Center (MSKCC; http://www.mskcc.org) and the University of Michigan (http://www.umich.edu), in collaboration with colleagues at the Carmel Medical Centre/Technion University of Israel (http://www.technion.ac.il), have shown how a genetic mutation can increase the risk of colon cancer [2]. This newly identified genetic marker increases this risk threefold in individuals born with the mutation, known as BLMAsh.

The team of scientists analyzed the frequency of BLMAsh mutations in 1244 patients from New York City and Israel and compared the frequency of mutation with that in 1839 healthy volunteers. They found that almost 2% of patients with colon cancer had this genetic abnormality, compared with less than 1% of healthy volunteers.

'The interesting aspect of this study is the discovery of a possible novel pathway for colon cancer in humans, which had not previously been suggested in laboratory models,' said Kenneth Offit, Chief of the Clinical Genetics Service at MSKCC and senior author of the paper.

It was previously known that people with mutations in their BLM genes were at risk. However, as pointed out by Nathan Ellis, Director of the Laboratory of Cancer Susceptibility at MSKCC, 'this is the first study to show that individuals carrying a single *BLM* mutation are at increased risk for colon cancer.'

Ellis and co-workers cloned the gene for *BLM* in 1995 [3]. Alterations in BLM cause a rare genetic disorder, called Bloom's syndrome, which is associated with a predisposition to cancer. This recent study focused on individuals of Ashkenazi Jewish origin, because the BLMAsh mutation is common in this group, with approximately 1 in 100 carrying the defect.

Offit said: 'Although the finding that BLM mutations are associated with colon cancer risk pertains only to those of Ashkenazi Jewish ancestry, we feel the scientific implications are relevant to understanding the fundamental genetic mechanisms that cause colon cancer in the general population.'

Future studies aim to determine the molecular mechanism of the mutation in BLM that leads to cancer.

2 Gruber, S.B. *et al.* (2002) BLM heterozygosity and the risk of colorectal cancer. *Science* 297, 2013

3 Ellis, N.A. *et al.* (1995) The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell* 83, 544–666

Dual genetic signals behind breast cancer

Researchers have found that breast tissue needs to receive two signals; one, to proliferate and two, to avoid apoptosis in the early development of breast cancer [4]. A team at Harvard Medical School (http://www.harvard.edu) used three-dimensional basement membrane cultures to model the architecture of the epithelium *in vitro*, enabling many features of breast epithelium *in vivo* to be recapitulated, including the morphogenesis of glandular epithelium and modelling of the biological activity of cancer genes.

Lumen formation in healthy breast tissue is formed by selective apoptosis of centrally located cells and is maintained by signals that cause the death of the excess proliferating cells. The researchers introduced genes encoding HER2 or cyclin D1 into cultured breast cells and found that both HER2 and cyclin D1 stimulated proliferation of the breast cells into the lumen. However, the cyclin-D-producing tissues retained hollow areas resulting from cell death by apoptosis. By contrast, HER2 provided a signal that promoted survival and allowed the cells to fill the hollow space. These studies show that tumour cells must not only proliferate but also must overcome the normal signals that promote apoptosis and maintain the epithelial architecture. The discovery that dual genetic signals are required in tumorigenesis in the breast should help to provide a mechanistic framework to identify new diagnostic markers and therapeutic targets for epithelial cancers.

4 Debnath, J. *et al.* (2002) The role of apotosis in creating and maintaining luminal space within normal and oncogene-expressing mammary acini. *Cell* 111, 29–40

To die or not to die?

Chemotherapy causes certain cancer cells to apoptose, whereas others undergo citostasis (stop proliferating) and try to repair the damaging effects of the drug. What pushes cells down one pathway as opposed to the other has for years been a puzzle for scientists. Now, researchers have shown that the transcription factor Myc is a principal determinant in this choice [5].

The tumour suppressor p53 is activated by DNA damage, inducing either apoptosis or cell cycle arrest. The apoptotic effect of p53 is mediated by transcriptional activation of mediators including *PUMA* and *PIG3*, whereas the cytostatic effect is mediated by transcriptional activation of the cyclin-dependent kinase inhibitor $p21^{Cip1}$. This latest research demonstrates that cancer cells with a high level of Myc cannot activate the production of the $p21^{Cip1}$ gene, which inhibits cell division. Myc is directly recruited to the p21 promoter by the DNA-binding protein Miz-1, which then blocks $p21^{Cip1}$ induction by p53. Therefore, the p53 response of colon-cancer cells to DNA damage switches from cytostatic to apoptotic.

'Our work reveals a way we might coax cells to favour apoptosis instead of citostasis in order to increase the effectiveness of chemotherapy,' said Joan Massague, of the Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/mskcc/html/44.cfm) and senior author of the study. Although it is not known whether repression of $p21^{Cip1}$ would be beneficial in cancer treatment, the mechanism proposed in this study provides possible ways of influencing the cell's response to stresses resulting in p53 activation.

5 Seoane, J. *et al.* (2002) Myc suppression of the $p21^{Cip1}$ Cdk inhibitor influences the outcome of the p53 response to DNA damage. *Nature* 419, 729–734

Targets and mechanisms

The missing link

Researchers have determined that a protein crucial for development of the immune system acts as a 'landing platform', regulating gene expression by linking chromatin-remodelling factors to DNA [6]. Their findings provide important new information on the way in which gene expression is controlled.

Terumi Kohwi-Shigematsu and colleagues, based at the Lawrence Berkley National Laboratory, University of California (http://www.lbl.gov), have previously shown that special AT-rich binding-protein 1 (SATB1) regulates gene expression in

Malaria

Malaria deciphered

The complex genome sequence of *Plasmodium falciparum,* the parasite that causes the deadliest form of malaria, has been disciphered [11]. Malaria kills over a million people a year in developing countries. 'This achievement has built a solid foundation for a new generation of research to find more effective drugs and vaccines to treat this devastating disease', commented Claire Fraser, President and Director of the Institute for Genomic Research (TIGR) (http://www.tigr.org).

The success of *P. falciparum* depends partly on its ability to avoid elimination by the human immune system by expressing different versions of the proteins on the surface of host red blood cells, thus disguising itself and evading the immune response. The genome analysis identified ~200 parasite genes that produce proteins involved in this elaborate process. The genes for most of these proteins are found near the ends of the chromosomes. This location makes it easier for the parasite to alter the structure of the proteins through changes in the genes that encode them.

In the short time that the *P. falciparum* sequencing data has been made available via the Internet, newly discovered parasite enzymes that could be targeted by anti-malarial drugs have already been reported. Moreover, some of the enzymes identified in *P. falciparum* have no counterparts in the human host, and might make good targets for chemotherapy. Further genome studies of other *P. falciparum* parasites isolated from malaria patients will identify more variants and provide insights into the pathogen's immune evasion process.

11 Gardner, M.J. *et al.* (2002) Genome sequence of the human malaria parasite. *Plasmodium falciparum*. *Nature* 419, 498–511

Found! Mosquito genes that stop malaria

Scientists at the New York University School of Medicine (http://www.med.nyu.edu) have discovered genes that enable mosquitoes to resist infection by the malaria parasite, *Plasmodium falciparum* [12]. This exciting finding could lead to development of new methods to stop the spread of malaria.

The 'parasite-blocking' genes discovered in the mosquito, *Anopheles gambiae,* appear to have significant effects on the growth of *P. falciparum,* which is deadly when transmitted to humans through an insect bite. Mosquitoes with two copies of the form of the gene that makes insects susceptible to the parasite had an average of 50 parasites per mosquito. Whereas in one case, mosquitoes with two copies of a parasite-blocking gene had an average of 0.2 parasites per mosquito.

'The new genes we have found are the first ones that make the *Anopheles* mosquito resistant to real, natural populations of the most deadly of the human malaria parasites, as opposed to laboratory parasite strains, and there are several ways that this basic research finding could help prevent malaria transmission,' says Kenneth Vernick from the Department of Medical and Molecular Parasitology (NYU School of Medicine), who led the research.

It isn't yet known how many parasite-blocking genes exist in the *A. gambiae* mosquito, or how common these genes are in nature. But it is estimated that at least 50% of the mosquitoes in natural populations might carry genes for resistance. At this stage, it is uncertain whether research will result in new treatments or prevention strategies, but it might be possible to spread the parasite-blocking genes among mosquito populations, thereby denying the parasite its host. Furthermore, the genes might also produce a parasite-killing compound that could be developed into a drug for human use.

12 Christophides, G.K. *et al.* (2002) Immunity-related genes and gene families in *Anopheles gambiae*. *Science* 298, 159–165

thymocytes. The protein binds along the minor groove of double-stranded DNA, to sequences known as base-unpairing regions (BURs), which are rich in adenine and thymidine and that readily become base-unpaired in supercoiled DNA. When SATB1 binds, the chromatin is remodelled and transcription of genes as far as 50 kb away can be affected. Now, Kohwi-Shigematsu's group has revealed how SATB1 exerts its effects.

The researchers used affinity chromatography to demonstrate that SATB1 binds enzymes that are known to remodel chromatin, including components of the chromosome assembly complex (CHRAC) and the nucleosome-remodelling and histone-deacetylation (NURD) complex. Chromatin immunoprecipitation confirmed that this allows SATB1 to recruit remodelling enzymes to BURs. Yasui *et al*. showed that this recruitment can regulate nucleosome positioning and repress gene expression.

These results shed new light on the action of SATB1, which has been implicated in the correct regulation of hundreds of genes in thymocytes. Furthermore, as the authors suggest, this action could represent 'a general guiding process by which multiple chromatin remodelling factors find entry sites into chromatin… providing a mechanism for global gene regulation in higher eukaryotes'.

6 Yasui, D. *et al.* (2002) SATB1 targets chromatin remodelling to regulate genes over long distances. *Nature* 419, 641–645

Caspase-8 mutation causes immunodeficiency

From studying only two individuals, new insights into the complexity of the immune system have been gleaned. Researchers at the US National Institute of Allergy and Infectious Diseases (http://www.niaid.nih.gov) have found that caspase-8, a known trigger of apoptosis, plays a role in activating the immune system [7].

The scientists studied the immune systems of a brother and sister who had symptoms similar to those of autoimmune lymphoproliferative syndrome (ALPS). ALPS is caused by a defect in the gene for caspase-10 and causes an overabundance of lymphocytes as a result of insufficient apoptosis, resulting in swollen lymph nodes and an enlarged spleen. Puzzlingly, however, there was no defect in the caspase-10 gene in the siblings.

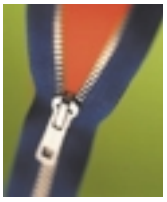
Further study showed that both siblings carried mutations on their caspase-8 genes,

rendering the enzyme ineffective. Various immune-system cells were also inactive. Although caspase-8 has long been implicated in triggering apoptosis, this was the first sign that its mutation could cause immune system defects. Introduction of functional caspase-8 into the siblings' immune system caused lymphocytes to regain their ability to respond to antigens.

'Caspase-8 deficiencies might explain why some people don't respond as well as others to vaccines, or why some people's immune systems don't fight off infections as well as others', said Michael Lenardo, senior author of the study, 'Caspase-8 may be a useful target for a new class of anti-inflammatory or immunosuppressive therapies.'

7 Chun, H.J. *et al.* (2002) Pleiotropic lymphocyte activation defects due to caspase-8 mutation cause human immunodeficiency. *Nature* 418, 395–399

It takes two to unzip…



It now seems that the unzipping of DNA requires at least two helicase molecules. The finding resolves a long-running debate on how helicases function and also demonstrates that single-molecule fluorescence assays can be used to study protein–DNA interactions at resolutions as low as 10 bp [8].

Helicases are motor proteins that travel along DNA, separating the two strands. Because they can move along DNA as monomers, many researchers have previously thought that the monomers would also be sufficient for separation of the DNA strands. This assumption has now been dismissed by workers at the University of Illinois (http://www.uiuc.edu/), Washington University (http://www.wustl.edu/) and Stanford University (http://www.stanford.edu/).

Ha *et al.* followed the unzipping process using fluorescence resonance energy transfer (FRET), tagging both strands of a DNA duplex with fluorescent molecules that display different energy transfer efficiencies according to their proximity. They showed that, although Rep can attach to and translocate along DNA as a monomer, it cannot separate the DNA strands. However, increasing the concentration of Rep caused the FRET efficiency to decrease, indicating strand separation. Ha and colleagues interpreted this as more than one additional Rep molecule joining in, so that a functional helicase unit was formed.

As Ha explains, 'a single helicase can move along the single-strand tail of a DNA [molecule], but once it hits the junction of the one-way and two-way streets, it cannot go any further. It will dissociate at the junction unless you have another coming in to bind to it.' Helicases have been linked to an increased risk of cancer and to premature aging, and these new insights could help those seeking to target helicases in human cells or viruses. Furthermore, this study paves the way for FRET to be used in the study of other protein–DNA interactions.

8 Ha, T. *et al.* (2002) Initiation and re-initiation of DNA unwinding by the *Escherichia coli* Rep helicase. *Nature* 419, 638–641

Miscellaneous

Receptor implicated in paracetamol toxicity

Overdoses of acetaminophen (paracetamol) are the leading cause of hospital admission for acute liver failure in the USA. Ingestion of only 2–3 times the maximum recommended daily dose can cause hepatotoxicity, and the US Food and Drug Administration has recently been advised to require stronger warning labels on products that contain acetaminophen. Recent research points to a xenobiotic receptor known as CAR (constitutive androstane receptor), which can regulate liver toxicity, as a possible new target for treating acetaminophen poisoning [9].

When CAR is activated, the ability of the liver to metabolize xenobiotics and eliminate them from the body increases; however, it can also result in the increased production of toxic intermediates. Researchers used a CAR-null mouse to demonstrate the crucial role of CAR in acetaminophen toxicity [9]. 'We found that high doses of acetaminophen activate CAR, and that CAR then activates target genes that increase toxicity,' said David D. Moore of Baylor College of Medicine (http://public.bcm.tmc.edu/) and senior author of the study. 'This generates a vicious circle in which acetaminophen actually worsens its own toxicity. The absence of this cycle means that CAR-null mice are partially resistant to high doses of acetaminophen.'

The current treatment for acetaminophen overdose uses a compound that replenishes glutathione in the liver, and needs time to be effective. These results suggest that blocking CAR might prove an innovative therapeutic approach for treating the adverse effects of acetaminophen and potentially other hepatotoxic agents. Studies to identify an inhibitor of CAR in humans are currently underway.

9 Zhang, J. *et al.* (2002) Modulation of acetaminophen-induced hepatotoxicity by the xenobiotic receptor CAR. *Science* 298, 422–42

Vitamin D analogue grows bone

A vitamin D analogue, 2-methylene-19-nor-(20S)-1$_{\alpha}$,25(OH)$_2$D$_3$ (2MD), has been shown to induce bone formation both *in vitro* and *in vivo* [10].

Even at concentrations as low as 10^{-12}M, 2MD caused primary cultures of osteoblasts to produce bone *in vitro*, a process essential to both bone resorption and formation. This effect was not found with normal vitamin D at higher concentrations, 10^{-8}M, indicating that 2MD could be osteogenic *in vivo*.

The researchers used ovarectomized rats to show that 2MD increased total body bone mass by 9% over a 23-week period. This finding could aid the development of a class of drugs that would reverse bone loss in humans suffering from osteoporosis, a condition that 44 million people in the USA already suffer from, or are at risk from developing.

Hector F. DeLuca from the University of Wisconsin-Madison (http://www.wisc.edu/) believes that 2MD is the first vitamin D analogue that has demonstrated an increase in bone mass without any toxicity or side effects. However, he stressed that it could be several years before a drug reaches the market place because 2MD has yet to be tested in clinical trials.

10 Shevde, N.K. *et al.* (2002) A potent analog of 1α, 25-dihydroxyvitamin D$_3$ selectively induces bone formation. *Proc. Natl.Acad. Sci. U. S. A.* 10.1073/pnas.202471299

News in brief was written by *Vicky Ashton, Matt Brown, Joanne Clough, Morag Robertson, Sheema Sheikh and Heather Yeomans*