Any human tumour antigen chosen for a vaccine in humans will not be a xeno-antigen and additionally must not provoke immune attack on normal cells.

Ronald Levy, Professor of Medicine at Stanford School of Medicine (http://www.stanford.edu) who has reviewed DC vaccines [2], agrees that that this paper offers some interesting possibilities for creating human cancer vaccines. He expressed optimism that tumour markers for at least some cancers would prove to be useful vaccine targets.

Higgins, whose primary interest is bacterial and viral infection, not oncology, noted in earlier work that listeriolysin forced macrophages into a much stronger presentation of antigen to cytotoxic T lymphocytes [3]. When discussing this finding with his co-authors in the UK they resolved to use the approach against cancer. Although gratified by this proof-of-concept work, Higgins says his group is planning significant follow-up studies using listeriolysin-based vaccines against bacteria, viruses and cancers. Choosing the bacterial vector for human vaccines is a major issue, which must be determined not by its ease of use but rather by safety of the resultant bacterium, he says. He notes that the choice of the appropriate target antigen for each variety of cancer is another area that will require much work.

References

1 Radford, K.J. *et al.* (2002) A recombinant *E. coli* vaccine to promote MHC class 1-dependent antigen presentation; application to cancer immunotherapy. *Gene Ther.* 9, 1455–1462

2 Timmerman, J.M. and Levy, R. (1999) Dendritic cell vaccines for cancer immunotherapy. *Ann. Rev. Med.* 50, 507–529

3 Higgins, D.E. *et al.* (1999) Delivery of protein to the cytosol of macrophages using *Escherichia coli* K-12. *Mol. Microbiol.* 31, 1631–1641

News in brief

Targets and mechanisms

Friendly stomach bugs

A specific type of microbe promotes the development of blood vessels in the intestinal lining, according to researchers at the Washington University School of Medicine (http://medicine.wustl.edu/). Jeffrey Gordon and co-workers have discovered that *Bacteroides thetaiotaomicron*, a naturally occurring gut bacterium, interacts with Paneth cells in the intestine and encourage the growth of capillaries [1].

The gut naturally contains a complex collection of bacterial species, some of which are known to be beneficial to the host. This study provides a new example of such symbiosis. The researchers used confocal microscopy to provide 3D views of intestinal tissue sections. This enabled the comparison of capillary density between groups of six-week-old mice with and without gut bacteria. The development of blood vessels stopped early in the group with no gut bacteria, but growth could be reinitiated upon colonization with bacteria from normal mice. Further tests showed that implantation of *B. thetaiotaomicron* was as effective as introducing the whole microbial society, thus implicating the bacterium as the causative agent.

To investigate the pathway of bacterially mediated blood-vessel growth, Gordon and his team engineered mice that lacked Paneth cells, a constituent of the intestinal lining that defends against bacterial attack. Without these cells, blood vessels could not completely develop, even when *B. thetaiotaomicron* was introduced. The team concluded that Paneth cells and *B. thetaiotaomicron* co-operate to stimulate postnatal capillary formation. 'Our findings illustrate the importance of co-evolution of animals and their microbial partners,' said Gordon. 'Unravelling the molecular foundations of these relationships may provide new ways of preventing or treating a variety of diseases.'

1 Stappenback, T.S. *et al.* (2002) Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.202604299 (http://www.pnas.org)

Staph's secret weapon revealed

The secret of *Staphylococcus aureus'* success might be its ability to interfere with T cells, according to research carried out at Texas A&M University System Health Science Center (http://tamushsc.tamu.edu/com/com.html) [2].

Eric Brown and co-workers suspected that *S. aureus* promotes its own survival by expressing MHC class II analog protein (Map), which works by affecting the host animal's immune system. Using mice as hosts, the team compared the incidence of disease in animals infected with two types of *S. aureus*: one group with functioning Map and the other group that was deficient in the protein.

They found that mice infected with Map-deficient *S. aureus* suffered less arthritis, osteomyelitis and abscess formation than control animals. The team went a step further by showing how Map weakens the immune system. 'T cells or mice treated with recombinant Map had reduced T-cell proliferative responses,' they explained. Their data suggests that Map is 'an immunomodulatory protein that may play a role in persistent *S.aureus* infections by affecting protective cellular immunity.'

New treatments stemming from these new findings might provide the body blow needed against *S. aureus,* a pathogen that is becoming increasingly resistant to current drugs and thought to be carried by over 20% of healthy humans.

  PII: S1359-6446(02)02585-0

2 Lee, L.Y. *et al.* (2002) The *Staphylococcus aureus* Map protein is an immunomodulator that interferes with T-cell-mediated responses. *J. Clin. Invest.* 110, 1461–1471

Protection against malaria comes as NO surprise

A recent study reports that children who possess a gene that enables them to produce high levels of nitric oxide (NO) are protected from two of the deadliest forms of malaria [3].

NO is a small molecule that performs numerous functions in the body, from assisting blood flow to killing bacteria and viruses. The amount of NO made by the body during infection is regulated by the gene for NO synthase (NOS2). An international team of researchers studied 179 children in coastal Tanzania, with and without cerebral malaria. They found that children with a variant of NOS2 that enabled them to make greater amounts of NO were 88% less likely to develop the disease than those without the variant. 'This is exciting because it confirms the importance of nitric oxide in the immune response to malaria and could lead to new therapies to protect against its devastating effects', said Maurine Hobbs, a leading member of the research team.

The researchers went on to examine DNA from 1106 Kenyan children and discovered that the same variant of NOS2 protected them from severe malarial anaemia. Targeted interventions to increase NO delivery or production could provide new strategies to treat and prevent this major cause of death in children.

3 Hobbs, M.R. *et al.* (2002) A new NOS2 promoter polymorphism associated with increased nitric oxide production and protection from severe malaria in Tanzanian and Kenyan children. *Lancet* 360, 1468

DNA nanocircles and ageing

Synthetic circles of DNA, dubbed 'nanocircles', are contributing to a better understanding of the ageing process of cells and could have applications in areas as diverse as cancer research and transplantation medicine [4].

Eric Kool and his team from Stanford University (http://www.stanford.edu/) developed the novel, yet simple, nanocircles as a means to prolong the life of cell lines used in everyday laboratory research. Such cell lines are normally derived from tumours, which are essentially immortal because of their continuous division. The ability to readily use non-cancerous cells for research, however, would be of enormous benefit to several areas of biomedical research. Unfortunately, normal cells have limited lifespans, which are associated with the length of single-stranded DNA sequences known as telomeres that cap the ends of chromosomes. After each cell division, the telomeres are reduced by around 100 bases, until a crucial point is reached at which the cell enters senescence and dies.

It is possible to extend the DNA caps by using the telomerase enzyme, a tactic that tumour cells employ, but this enzyme is difficult to produce in the laboratory. This inspired Kool and his team to develop the DNA nanocircles. Each circle consists of DNA base pairs with complementarity to the telomeres. When added *in vitro*, the nanocircles automatically add new sequences, resulting in lengthened telomeres that are visible under the microscope when fluorescently labelled. Kool commented that 'we may be able to make cells live indefinitely and divide indefinitely, so they essentially become refreshed, as if they were younger.'

4 Lindström, U.M. *et al.* (2002) Artificial human telomeres from DNA nanocircle templates. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.252396199

Miscellaneous

Luciferase sheds new light on herpes infection

Researchers at Washington University School of Medicine (http://medicine.wustl.edu/) have used a herpes virus that produces luciferase to illuminate the virus's course of infection in mice and to help monitor the infection's response to therapy [5]. The work will help overcome some of the problems previously encountered in studying the course of virus infection.

The investigators added the gene for luciferase to a strain of herpes simplex type 1 virus and injected the modified virus into several locations in mice. The mice were injected daily for nine days with luciferin, which emits light when it is catalyzed by luciferase in a process termed bioluminescence. The mice were then anaesthetized and photographed using a charged-coupled device (CCD) camera. The camera captures light that is emitted through the tissues of the mouse by the actively replicating virus. The image produced by the camera shows the location and amount of virus in a mouse as areas of colour, ranging from blue (low levels) to red (high levels). This imaging method enabled the investigators to monitor the infection as it spread and receded over nine days.

In a second experiment, mice infected with the modified virus were treated with the antiviral drug valacyclovir. The investigators found that decreases in bioluminescence correlated with the decline in the amount of virus present.

This method avoids the need to sacrifice mice on subsequent days, instead enabling changes in the viral population to be tracked in the same animal day after day. 'This study demonstrates the feasibility of monitoring microbial infections in living animals in real time,' says study leader David Leib, 'The technique enables us to follow an infection over time as it progresses and resolves, and we can do this repeatedly using the same animal.'

The team intend to go on to use the imaging technique to study the course of herpes infection in mice lacking certain elements of the immune system to determine how different elements of the immune system influence the course of an infection.

5 Luker, G.D. *et al.* (2002) Noninvasive bioluminescence imaging of Herpes simplex virus type 1 infection and therapy in living mice. *J. Virol.* 76, 12149–12161

Diabetes drug to treat Cushing's syndrome

Researchers at Cedars-Sinai Medical Center (http://www.csmc.edu/) have found that pituitary tumours express an abundance of a specific protein receptor, peroxisome proliferator activated receptor-γ (PPAR-γ), and showed that treatment with a common diabetes drug was effective in shrinking tumour size and reducing hormone production in Cushing's pituitary tumours in

mice [6]. This work could lead to a new way to treat patients with Cushing's syndrome.

Cushing's syndrome is caused by prolonged high-level exposure of the hormone adrenocorticotropin (ACTH), which is secreted in excess by tumours of the pituitary gland and controls growth, metabolism and reproduction. The disorder is commonly treated with surgery to remove the tumour, but this is often ineffective and tumours frequently recur.

The investigators examined both normal human pituitary tissue and tumour specimens that secreted too much ACTH. They evaluated six ACTH-secreting pituitary tumours that had been surgically removed and found that PPAR-γ was abundantly expressed in all six tumours, compared with modest expression in the normal tissue samples. 'The over-expression of this receptor on pituitary tumour cells indicates that PPAR-γ may play a major role in the causation of Cushing's syndrome,' said Shlomo Melmed, senior author of the study.

On the basis of these findings, the investigators tested whether pituitary tumour cells would respond to thiazolidinediones (TZDs), which are commonly used in the treatment of diabetes and work by activating PPAR-γ. They treated pituitary tumour cells with two different types of TZD drugs — troglitazone or rosiglitazone. Both drugs caused the tumour cells to die and inhibited secretion of ACTH hormone from the cells.

The drugs were subsequently tested in mice with ACTH-secreting pituitary tumour cells. Untreated mice developed large, visible pituitary tumours and typical Cushing's features. In comparison, only one of five rosiglitazone-treated mice developed a small pituitary tumour. Levels of ACTH and other steroid hormones were also considerably lower in the treated mice compared with those not receiving treatment. 'These results indicate that TZDs may be effective in slowing tumour growth in humans,' said Anthony Heaney, lead author of the study.

6 Heaney, A.P. *et al.* (2002) Functional PPAR-γ receptor is a novel therapeutic target for ACTH-secreting pituitary adenomas: *Nat. Med.* 8, 1281–1287

In silico predicts bug drug resistance

Micro-organisms such as *Escherichia coli* might soon be used to manufacture drugs, detergents and other commercial products, following findings that computer models can accurately predict the evolution of bacteria under set conditions [7].

Bernhard Palsson, a researcher at the University of California, San Diego (http://www.ucsd.edu/) and collaborators found that *E.coli* K–12 MG1655 bacteria grew sub-optimally when first placed on a glycerol base, but after 40 days and 700 generations of adaptive evolution, showed growth matching the rate predicted by their *in silico* model. This phase of adaptation to its substrate might explain why past predictions of growth by models have not always been accurate. 'Incorrect predictions of *in silico* models based on optimal performance criteria may be due to incomplete adaptive evolution under the conditions examined,' the team said.

Palsson described as 'revolutionary' the ability to predict a process as complex as adaptive evolution. The group's findings are thought to have far-reaching applications. 'We could use such a system to predict the evolutionary stability of bacteria, and potentially predict the probability of a drug-resistant strain developing,' he said. On the possibility of designing 'commodity microbes' for the production of drugs and detergents, Palsson continued: 'we could design a strain [on] the computer and [calculate its] optimal performance. Once we have a strain that performs to the characteristics we want, we could move on to the real organism, manipulate the genetic content, and then use the adaptive evolutionary process to implement the design.'

7 Ibarra, R.U. *et al.* (2002) *Escherichia coli* K–12 undergoes adaptive evolution to achieve *in silico* predicted optimal growth. *Nature* 420, 186–189

Anti-androgens: both friend and foe

Researchers have begun to understand why anti-androgens can do harm as well as good in the treatment of prostate cancer [8]. Their finding helps to explain why the success of treatment with anti-androgens is often only temporary, and suggests new ways in which prostate cancer might be fought.

Prostate cells are usually dependent on testosterone. Cutting off the supply of this androgen is a common strategy for ridding men of prostate cancer cells that have spread throughout the body. Often, such treatment involves drugs that block testosterone function at androgen receptors. However, some of the cancer cells can remain resistant to anti-androgens and such treatment becomes ineffective within a couple of years. After this time, it can even be beneficial to withdraw the anti-androgens.

Now, researchers led by Chawnshang Chang of the George Whipple Laboratory for Cancer Research (http://www.urmc.rochester.edu/ChangARLab/links.html), have published results that help to explain this apparent paradox. They found that mitogen-activated protein (MAP) kinase – which is known to promote cell growth and has been implicated in cancer – was more commonly activated in prostate tumours from patients being treated with the anti-androgen hydroxyflutamide than in those from untreated patients. Hydroxyflutamide also activated MAP kinase in prostate cancer cells *in vitro*, even in cells without androgen receptors. This suggests that the pro-cancer activity of hydroxyflutamide involves receptors other than those used by androgens.

The paper by Lee *et al.* has implications for those treating prostate cancer with anti-androgens. 'These drugs are necessary for patients who otherwise have few options. However, these findings do raise some concerns that should be investigated further', explained Lee. 'Perhaps these findings will help lead to a new drug target so that men with this disease can be treated more effectively.'

8 Lee, Y-F. *et al.* (2002) Activation of mitogen-activated protein kinase pathway by the antiandrogen hydroxyflutamide in androgen receptor-negative prostate cancer cells. *Cancer Res.* 62, 6039–6044

New weapons against bone metastasis

Scientists have identified new weapons against bone metastasis and hypercalcaemia [9], conditions that are often linked to common cancers and which can go on to cause the deaths of patients.

While an estimated 10–20% of cancer sufferers are prone to developing hypercalcaemia, it is also common for cancer of the breast to lead to osteolytic bone disease. Both disorders are thought to be caused by elevated levels of parathyroid hormone-related peptide (PTHrP), secreted by tumour cells when they pass to other parts of the body. Once PTHrP has started to act in bone, tumour cells and osteoclasts, which specialize in breaking down bone, work together,

leading to the destruction of more bone and the accelerated growth of the tumour.

Using nude athymic murine models, workers led by Wolfgang Gallwitz at Osteoscreen (http://informagen.com/Resource_Informagen/Full/8/3748.php), have shown that guanine-nucleotide analogues might be the key to preventing these complications and saving the lives of patients. Unlike bisphosphonates, another group of compounds, which work by inhibiting osteoclasts, the compounds highlighted by Gallwitz and collaborators inhibit the production and secretion of PTHrP by tumours.

The team thinks their compounds might also be effective against hypercalcaemia. 'These results suggest that the PTHrP gene promoter may be a suitable target for treating the skeletal effects of malignancy,' they said.

9 Gallwitz, W.E. *et al.* (2002) Guanosine nucleotides inhibit different syndromes of PTHrP excess caused by human cancers *in vivo*. *J. Clin. Invest.* 110, 1559–1572

Raise a glass to good health

A tipple a day keeps dementia at bay is the message from a new study published by researchers at the Institute of Preventive Medicine at Kommunehospitalet in Copenhagen, Denmark (http://www.ipm.hosp.dk/) [10]. The study, which identified the drinking patterns for wine, beer and liquor of 1709 people in the 1970s and then assessed them for dementia in the 1990s, showed that people who drank wine weekly or monthly were more than two times less likely to develop dementia, including Alzheimer's disease.

Although Thomas Truelsen, author of the study, warns that: 'These results do not mean that people should start drinking wine or drink more wine than they usually do', he does stress that, '…the results are exciting because they could mean that substances in wine reduce the occurrence of dementia. If this is the case, we could potentially develop treatments or prevention methods based on these substances.'

The substances that might be responsible for the beneficial effect could be the natural flavonoids that are found in high amounts in red wine. The flavonoids have an antioxidant effect that work to 'mop-up' free radicals that are released when oxygen is converted to energy and this could be responsible for lower incidence of stroke and other cerebrovascular diseases among wine drinkers.

During the 20 years of this study, 83 of the participants developed dementia and their alcohol intake was compared to those who did not develop dementia. Neurologist John Brust, of Harlem Hospital Centre in New York (http://www.ci.nyc.ny.us/html/hhc/html/harlem.html), points out that there is research to suggest that: 'wine drinkers may have better dietary habits than beer and liquor drinkers, there is also evidence that dietary vitamin E may reduce the risk of developing Alzheimer's' and these factors were not accounted for in this study. 'Nonetheless, this is a provocative report providing evidence that there is indeed something specifically beneficial about wine' he concluded.

10 Truelsen, T. *et al.* (2002) Amount and type of alcohol and risk of dementia: The Copenhagen City Heart Study. *Neurology* 59, 1313–1319

Revolution in heart disease screening

Metabonomics, a new, noninvasive procedure developed by the Imperial College Laboratories (http://www.ic.ac.uk) [11] is set to revolutionize screening for heart disease, which is responsible for thousands of deaths in the UK each year.

Currently used angiography is a costly and invasive screening technique. Furthermore, epidemiological studies have not been effective in diagnosing the presence of heart disease on an individual-by-individual basis, despite pinpointing the detrimental effects of unhealthy diet and smoking in whole populations. Metabonomics, however, should help to resolve this.

Requiring only standard preparations of serum, plasma and urine, and no specialist preparations, 'it is the closest that science has come so far to the hand-held diagnostic analyser used by Dr McCoy in Star-Trek – but that is still a very long way away', says Jeremy Nicholson, a Professor at Imperial College. Pattern-recognition techniques applied to proton nuclear magnetic resonance ([1]H-NMR) spectra of human serum can correctly diagnose not only the presence, but also the severity, of coronary heart disease.

By providing information on drug toxicity and efficacy, clinical diagnostics and gene function, the technique will also be useful clinically, enabling the effective targeting of treatments such as statins. Trials are under way at Papworth hospital, a specialist cardiothoracic centre based in Cambridge, UK, and if successful, the test could be widely available in two years. As revealed by Elaine Holmes of Imperial College, this technology can be expanded to 'potentially help detect a wide range of clinical problems from bone disease to cancer'.

11 Brindle, J.T. *et al.* (2002) Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using [1]H-NMR-based metabonomics. *Nat. Med.* 8, 1439–1445

Blood test for ovarian cancer

A technique involving a simple blood test has been developed by scientists at the Kimmel Cancer Centre at Johns Hopkins (http://www.hopkinskimmelcancercenter.org) that could potentially detect ovarian cancer [12].

Previous screening techniques have been based on measuring the total amount of DNA in the blood, but this is not specific enough because elevated DNA levels can be found in blood samples from patients without cancer. This latest study used a test based on the digital analysis of SNPs to enable the ratio of maternal:paternal alleles present in a blood sample to be determined; thus identifying any 'allelic imbalances', which are typical of cancer cell DNA. However, the tests still need to be improved to single out ovarian cancer samples, because employing a standard ovarian cancer marker (CA125) added little improvement in detection rates.

Ie-Ming Shih from the Kimmel Cancer Centre commented 'Digital SNP appears to detect cancers very well and is far more precise than other available tests'. Although, at present, the technique is very costly, it might be useful for screening high risk individuals.

12 Chang, H.W. *et al.* (2002) Assessment of plasma DNA levels, allelic imbalance, and CA125 as diagnostic tests for cancer. *J. Natl. Cancer Inst.* 94, 1697–1703

News in Brief was written by *Matt Brown, Peter Chan, Carrie Viccars, Catherine Wild and Heather Yeomans*