Although there are numerous other chemically modified tetracyclines to test, COL-3 is the only one that is now in human trials. In Phase I clinical trials, the drug caused patients to become photosensitive. However, in the Phase II trial at the National Cancer Institute (http://www.nci.nih.gov), it was found that lowering the daily dose below 300 mg alleviated photosensitivity.

Hendrix says this paper only contained a small portion of her findings but is helping to build on two more studies. Working in collaboration with Paul Meltzer and Jeff Trent (as part of the Human Genome Project), Hendrix and colleagues have a manuscript in preparation that show the results of a 15,000 gene chip to find out which genes are being expressed as cells change and become aggressive.

She is also focusing on drug combinations that might work best with COL-3. 'In this paper, we suggest that COL-3 can be used in a combinatory manner, with COL-3 targeting messages or signals in the microenvironment and other drugs focusing on the tumour,' she says. 'So we are looking at the drug combinations which will give us this best outcome.'

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2 Seftor, R.E.B. *et al.* (1998) Chemically modified tetracyclines inhibit melanoma cell invasion and metastasis. *Clin. Exp. Metastasis* 16, 215–225

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4 Lee, H.M. *et al.* (2001) CMT-3, a non-antimicrobial tetracycline inhibits MT-1-MMP activity: relevance to cancer. *Curr Med. Chem.* 8, 257–260

News in brief

Targets and mechanisms

True mechanism of calcium channel blockers discovered

Researchers in America have hailed as 'a leap forward' their discovery of the true mechanism of action of calcium channel blockers [1]. The scientists, led by physiologist Mordecai P. Blaustein of the University of Maryland School of Medicine (http://medschool.umaryland.edu/), have demonstrated that the targets of the drugs are store-operated channels (SOCs), rather than voltage-gated channels as was previously believed.

Calcium has an important role in various functions in the body and alterations are thought to be responsible for disorders such as hypertension and angina. Not only do the new findings provide a real understanding of the function of calcium channel blockers, which are often prescribed to sufferers of these conditions, but they also lead the way for the development of novel drugs targeted specifically to SOCs, with fewer side-effects than therapies currently in use, explained Blaustein.

Using high-powered imaging on rat mesenteric arteries, the group made the discovery that both magnesium, a known blocker of SOCs, and nifedipine, a calcium channel blocker, abolished calcium entry through SOCs.

'Before this work, nobody recognized that [SOCs] were the main target of calcium channel blockers in increasing blood flow and lowering blood pressure,' said Blaustein. 'It may be possible,' he said, 'to identify new anti-hypertensive and anti-angina medications that target only [SOCs].'

1 Zhang, J. *et al.* (2002) Mg^{2+} blocks myogenic tone but not K^{+}-induced constriction: role for SOCs in small arteries. *Am. J. Physiol.* 10.1152/ajpheart.00260.2002 (http://ajpheart.physiology.org/)

Structure of LDL receptor extracellular domain revealed

Days could be numbered for the genetic disease familial hypercholesterolemia (FH) as a powerhouse team of scientists, including three Nobel laureates, revealed the 3D structure of the low-density lipoprotein (LDL) receptor extracellular domain [2].

FH, a disorder characterized by high cholesterol, atherosclerosis and an increased risk of heart attack is one of the most common 'single-gene' inherited diseases and affects around one in every 500 people, according to lead author of the study Gabrielle Rudenko. FH has previously been linked to about 1000 LDL receptor mutations and the recent identification of the receptor's structure will make it easier for scientists to understand how the disorder works, commented Rudenko. 'If you understand the basic biological mechanisms underlying a disease, you can hope to come up with strategies to battle [it],' she explained. 'In some cases, protein structures can even be used to design drugs.'

The team also included University of Texas Southwestern Medical Center (http://www3.utsouthwestern.edu/) researchers Johann Deisenhofer, Michael Brown and Joseph L. Goldstein, who have all won Nobel awards for their contributions to science. Deisenhofer, whose previous work has included the pioneering use of X-ray crystallography to show the structure of cell membrane proteins, said that the latest research would help scientists understand the mechanics of how our bodies absorb cholesterol from the blood.

2 Rudenko, G. *et al.* (2002) Structure of the LDL Receptor Extracellular Domain at Endosomal pH. *Science* 298, 2353–2358

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Cancer targets and mechanisms

Hydrogen fuels spread of gastric cancer microbes

Two scientists think they are on their way to developing drugs that will combat ulcers and cut the rates of gastric cancer in humans. They have shown, for the first time, that *Helicobacter pylori*, a bacterium unique to humans and known to be linked to the diseases, sustains itself by using hydrogen as an energy source [3].

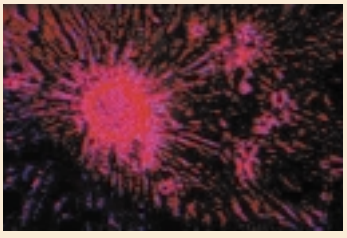
The discovery was made by Jonathan W. Olson, a microbiologist at the North Carolina State University (http://www.ncsu.edu/) and his co-worker Robert J. Maier of the University of Georgia (http://www.uga.edu/). They say that *H. pylori* manufactures the enzyme hydrogenase and makes use of hydrogen in the same way that other bacteria break down carbohydrates to grow. This strategy enables it to survive in hydrogen rich environments, such as agricultural areas and, according to the latest findings, the stomachs of humans.

Using live mice as a model, Olson and Maier found that the gastric mucosa contained up to 50 times more hydrogen than the enzyme was able to use. The pair proceeded to show that in a mutant strain of *H. pylori*, without functioning hydrogenase, only a quarter of the bacteria managed to colonize mouse stomachs, whereas with the enzyme, the pathogen was successful in virtually all cases.

Olson said that thanks to their research, they now had a new target for antibiotics. 'If we were to develop a drug to inhibit the hydrogenase enzyme,' he explained, 'we could eradicate ulcers in humans.'

3 Olson, J.W. and Maier, R.J. (2002) Molecular hydrogen as an energy source for *Helicobacter pylori*. *Science* 298, 1788–1790

'Genetic signatures' explain mystery of metastasis



The potential for metastasis – the spread of tumour cells from primary cancers to other organs – which was, until now, poorly understood and widely believed to be a random and unpredictable process, might be given away by a tell-tale 'genetic signature' detectable at the time of diagnosis, say scientists at the Whitehead Institute (http://www-genome.wi.mit.edu/) and the Dana-Farber Cancer Institute (http://www.dfci.harvard.edu/) [4].

When they analyzed the genetic profiles of 64 primary adenocarcinoma tumours and a dozen cancers that had metastasized from other adenocarcinomas, the group found a collection of 128 genes, whose expression differed between the two groups. Surprisingly, the genes were present in some of the primary tumours, leading them to suspect that far from being unpredictable, metastasis might actually be encoded within the bulk of a primary tumour.

In support of their idea, they showed that several lung cancers contained the genes, and that those patients with the 'signature' survived for a shorter time than those without it. The team now thinks that the 'signature' might be linked to a wide range of cancers, but they point out that it does not have a part in the development of blood lymphomas.

Sridhar Ramaswamy said they had had no reason to believe the 'signature' was so broadly applicable, and stated: 'these results strongly support the idea that some primary tumours are pre-configured to metastasize, and that this propensity is detectable at the time of diagnosis.'

4 Ramaswamy, S. *et al.* (2003) A molecular signature of metastasis in primary solid tumors. *Nat. Genet.* 33, 49–54

Miscellaneous

Man and mouse

As far as scientific milestones go, this one is going to take some beating. Less than two years after the publication of the 'holy grail' of genomics, the human genome, the Mouse Genome Sequencing Consortium, an international team of experts from no less than 27 institutions around the world, has announced a draft sequence of the mouse genome and, for the first time, placed the human side-by-side with another mammal for comparison [5].

It has been an ambitious project, which its participants hope will, amongst other things, highlight similarities between mouse and man, and identify the most functionally important genes that were likely to have been conserved through evolution. Research was carried out on the 20 chromosomes of a female mouse of the 'Black 6' strain, which is commonly used in the study of human disease. It is hoped that understanding the mouse will be like understanding ourselves.

Eric Lander of the Whitehead/MIT Center for Genome Research (http://www-genome.wi.mit.edu/) thinks having the blueprint provides us with 'an opportunity to see ourselves in an evolutionary mirror'. Robert Waterston of the Genome Sequencing Center at Washington University School of Medicine (http://www.genome.wustl.edu/) said that the publication of the mouse genome would spur the development of methods to study many genes in parallel. 'This more detailed molecular understanding of mouse biology,' he suggested, 'will in turn produce new opportunities for understanding human disease and for devising effective therapies.'

One of the consortium's findings is that over 90% of the mouse genome could be lined up with a region of the human genome, despite the 75 million years worth of evolution thought to separate the two. The research also lays to rest the dispute over the number of protein coding genes in humans. The number, says the group, is around 30,000, as in the mouse.

The information is available at http://www.ensembl.org.

5 Mouse Genome Sequencing Consortium (2002) Initial sequencing and comparative analysis of the mouse genome. *Nature* 420, 520–562

New gene boosts immunogenicity of flu vaccine

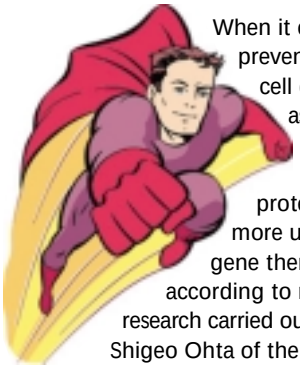
Alexander Bukreyev, of the National Institute of Allergy and Infectious Diseases (http://www.niaid.nih.gov/default.htm/), and his research team have made a discovery that promises to boost the effectiveness of vaccines without bringing on unwanted side-effects [6].

By inserting an extra gene, coding for granulocyte-macrophage colony-stimulating factor (GM-CSF), into live, attenuated parainfluenza virus type 3 (HPIV3) vaccine, and administering it to a group of rhesus monkeys, the researchers found a virus-specific serum antibody response 3–6 times stronger than that seen with a control. What excited Bukreyev and collaborators more was an immune response matching that observed with an equivalent dose of full-strength wild virus, except that their candidate did not lead to more replication of the virus. In response to the vaccine, the monkeys also released more protective T lymphocytes, specific to the virus, into their peripheral blood.

'These findings show that the immunogenicity of a live-attenuated vaccine virus in primates can be enhanced without increasing the level of virus replication,' they concluded. 'It might be possible to develop live-attenuated vaccines that are as immunogenic as parental wild type virus or, possibly, even more so.' They hope their findings will help in the fight against other viruses, including influenza, measles, dengue and respiratory syncytial virus.

6 Bukreyev, A. *et al.* (2002) More antibody with less antigen: Can immunogenicity of attenuated live virus vaccines be improved? *Proc. Natl. Acad. Sci. U. S. A.* 99, 16987–16991

'Super' protein prevents massive cell death



When it comes to preventing massive cell death associated with strokes and other injuries, proteins might be more useful than gene therapy, according to recent research carried out in Japan [7]. Shigeo Ohta of the Nippon Medical School (http://www.nms.ac.jp/) and collaborators engineered super anti-apoptotic factor FNK, a protein known to have strong cytoprotective properties, and fused it to the protein transduction domain (PTD) of the HIV/Tat protein, which helps the HIV virus to enter cells. When introduced into a model of ischemic brain injury, they found that the protein (PTD–FNK) took as little as an hour to localize to mitochondria and protect neurons against toxin-induced cell death. It was so effective that it even prevented cell death at concentrations as low as 0.3 pM.

The most promising results come from what they observed when they used the preparation on live gerbils. When they injected it into the animals' abdominal cavities and induced a stroke, they found that the protein prevented delayed neuronal death in the hippocampus region of the brain.

Unlike gene therapy, which relies on transport via inactivated viruses, proteins have the advantage that they can be delivered directly and in a relatively short period, explained the team. They think their protein works by affecting the movement of calcium ions in the cytosol. They suggested that 'PTD–FNK has potential for clinical [use] as a protein therapeutic strategy to prevent cell death in the brain'.

7 Asoh, S. *et al.* (2002) Protection against ischemic brain injury by protein therapeutics. *Proc. Natl. Acad. Sci. U. S. A.* 99, 17107–17112

News in brief was written by *Peter Chan*

People

Appointments

Hunneyball to oversee Evotec's British and German operations

With more than 24 years' experience in the pharmaceutical and biotechnology industries, Ian M. Hunneyball is to lead the German company Evotec OAI (http://www.evotecoai.com/), in the newly created position of President of Discovery Services. Hunneyball, also a member of the management board, is expected to oversee Evotec's chemistry operations in the UK and its biology services in Germany. 'His excellent team leadership skills and strong commercial awareness will strengthen our management team and make a significant contribution to the continued growth of our business as a partner for pharma and biotech customers,' said President and CEO Joern Aldag. Hunneyball joins Evotec OAI from French company Entomed, where he was Director of R&D. Before that he worked for Knoll Pharmaceuticals, where he managed the development of flosequinan and sibutramine from discovery to registration.

Pharmacopeia subsidiary welcomes new boss

Pharmacopeia (http://www.pharmacopeia.com/), a US developer of science and technology for drug discovery, has welcomed a new president to its subsidiary company Accelrys (http://www.accelrys.com/). He was named as Mark J. Emkjer, an experienced manager, most recently president and CEO of IT firm Sunquest Information Systems, and formerly an executive of Pace Health Management Systems. He is now expected to lend his expertise, developed over 20 years in the business, to Accelrys, a software company with offices in San Diego, USA and Cambridge, UK. According to Pharmacopeia Chairman, President and

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