Development in Belgium (http://www.jnj.com) says that combinatorial chemists working in drug discovery should pay more attention to the 'intriguing' structures of these cyanobacterial products. 'Some of these compounds resemble compounds that are actually already in pre-clinical development,' he said.

Haefner gives the example of scytonemin, an ultraviolet sunscreen pigment in cyanobacteria that has recently been found to inhibit several kinases, including one involved in regulating cell division. As a result, scytonemin has sparked interest as an anti-cancer agent. But Haefner has also noticed that scytonemin is structurally similar to nostodione A – an inhibitor of the anti-inflammatory target Ikappa B kinase that is currently under investigation. However, as far as he knows, the anti-inflammatory effects of scytonemin have yet to be tested.

References

1 Gerwick, B. (2003) Intriguing structural features of bioactive marine cyanobacterial natural products. Oral presentation at the *2003 Gordon Research Conference on Natural Products* 27 July–1 August 2003, Tilton, NH, USA

2 Haefner, B. (2003) Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* 8, 536–544

News in brief

Viral Targets and Mechanisms

AIDS vaccine hope

A human antibody with an interesting structure could lead to the development of a vaccine for AIDS, say researchers, including some from Florida State University (FSU; http://www.fsu.edu) [1].

Human antibody 2G12 is able to neutralize the formidable HIV virus quite uniquely by binding a dense cluster of carbohydrate moieties on the 'silent' face of the gp120 glycoprotein envelope. Normally, this thick layer of carbohydrates protects the surface proteins of the HIV virus from antibody attack by tricking the immune system into thinking that the carbohydrates are part of a healthy cell. Even when the virus tries to mutate, the antibody – with its remarkable configuration – can still combat it successfully.

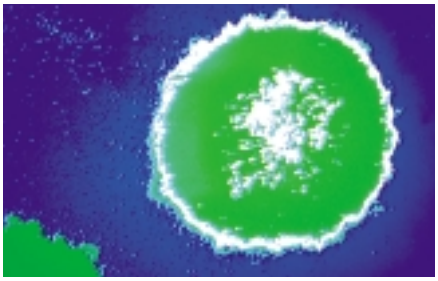
In this study, Kenneth Roux (FSU) and others in a global collaboration, were using different techniques to investigate the unusual binding powers of the antibody, and confirmed Roux's notion that 'we knew we were onto something'.

Roux said that this finding 'suggests that maybe vaccines could be engineered to specifically target the carbohydrates for attack'. He added; 'If we could develop a vaccine that would induce this kind of antibody, it would be quite significant.'

HIV currently affects around 40 million people worldwide, so the prospect of developing a vaccine that could stimulate the human immune system to make 2G12-like antibodies when the HIV virus is present is highly encouraging.

1 Calarese, D.A. *et al.* (2003) Antibody domain exchange is an immunological solution to carbohydrate cluster recognition. *Science* 300, 2065–2071

Link between HLA supertype and HIV virulence



A link has been found between the rapidity with which an individual will succumb to AIDS and the composition of their immune system [2]. Certain individuals with rarer forms of human leukocyte antigens (HLAs) are better protected against HIV than those with more common types.

HLAs are important constituents of the immune system. These highly polymorphic proteins capture antigen fragments from invading viruses and present them on the cell surface. The displayed fragments are then detected by T-cells, leading to a bolstering of the immune system against further antigens of the same type. Because antigen variation is effectively limitless, the structure of HLA proteins likewise must be highly variable. This great variety means that all genetic individuals have a different combination of HLAs.

In this study, researchers at the Los Alamos National Laboratory (http://www.lanl.gov) investigated whether there is a correlation between the HLA repertoire of individuals and their susceptibility to develop AIDS after HIV infection. The group, headed by Steven Wolinsky, studied a group of HIV-positive men enrolled in the Chicago component of the Multicenter AIDS Cohort Study. Because HIV attacks and kills helper T-cells, the number of such cells within an individual is an indicator of the extent of disease.

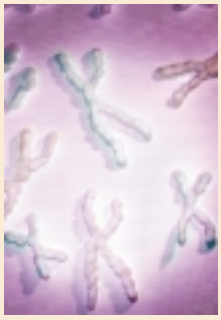
The researchers found that individuals with the most common HLA supertypes generally succumbed to the disease more rapidly than those with rarer HLA supertypes. The findings fit with the idea that HIV evolves to disguise itself from the enemy it encounters most frequently – the most widespread supertypes of HLA. Rarer supertypes present a lesser selective pressure and are more likely to slow the virus. The researchers caution that other, more subtle factors might be at work, however, and stress that further, independent studies are required.

2 Trachtenberg, E. *et al.* (2003) Advantage of rare HLA supertype in HIV disease progression. *Nat. Med.* 9, 928–935

1359-6446/03/$ – see front matter PII: S1359-6446(03)02790-9

Genomics and Proteomics

Chromosome 7 sequence analyzed



Human chromosome 7 has now been mapped and described in exquisite detail. A careful analysis of its sequence has highlighted structural features that might promote genetic changes that can cause disease [6].

The sequence of chromosome 7 is the largest to be published so far. The multi-institutional team who achieved this feat was led by Washington University School of Medicine (http://medicine.wustl.edu/). They reported that 99.4% of the gene-containing region of the chromosome had been sequenced to an accuracy of >99.99%. To speed things along, the researchers compared the human chromosome 7 to the recently sequenced mouse counterpart. This comparative genomics approach enabled them to rapidly distinguish between protein-coding genes and non-coding pseudo-genes. They found 1150 protein-coding genes, ~20% fewer than previously predicted.

One of the more insightful discoveries is that chromosome 7 contains an unusually high amount of duplicated sequence segments. Such duplications – duplicons – are known to encourage deletions and rearrangements of genetic material, leading to disease. For example, Williams-Beuren syndrome is associated with large deletions in the long arm of chromosome 7, presumably a consequence of the duplicon structure in this region.

Francis Collins, one of the main proponents of the Human Genome Project and Director of the National Human Genome Research Institute (NHGRI; http://www.genome.gov), explained the significance of this chromosome. 'Besides containing many genes that are crucial to development, this chromosome also holds the gene for cystic fibrosis and is frequently damaged in some types of leukaemia and other cancers,' he said. This is the sixth human chromosome to be described in detail, joining chromosomes 14, 20, 21, 22 and Y.

6 Hillier, L.W. *et al.* (2003) The DNA sequence of human chromosome 7. *Nature*, 424, 157–164

Unravelling protein–DNA interactions

By measuring changes in the force required to unzip the double helix, a new analytical technique can be used to detect points at which proteins bind to DNA [7]. Assessing the affinity of DNA-interacting drugs is just one of the many proposed applications.

The technique, called 'unzipping force analysis of protein association' (UFAPA), was invented by researchers at Cornell University (http://www.cornell.edu/). First, one strand of the DNA is anchored to a microscope coverslip and the other strand is attached to a polystyrene microsphere. The microsphere is immobilized in an optical trap created by a laser beam. Then, as the cover slip is moved away from the microsphere, the two stands of DNA begin to unzip. The force required to effect the dissociation is monitored throughout. When the unzipping fork reaches a bound protein, there is a sudden increase in DNA tension, followed by a sudden relaxation. Hence, the technique can be used to locate protein-binding sites on the DNA.

As well as being a potentially invaluable tool for biochemists, UFAPA might also find applications in the therapeutics industry. Lead researcher, Michelle Wang, suggested one such opportunity: 'We're still in the laboratory-development stage now, but the process could be automated so that in drug development, for example, pharmaceutical companies could use UFAPA to screen libraries of small molecules for affinity to DNA.'

7 Koch, S.J. and Wang, M.D. (2003) Dynamic force spectroscopy of protein–DNA interactions by unzipping DNA. *Phys. Rev. Lett.* 91, DOI:10.1103/PhysRevLett.91.028103

Cancer Targets and Mechanisms

How COX-2 steers cells towards cancer

Cyclooxygenase-2 (COX-2) is overexpressed in many colorectal tumours, and blocking its function using non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin can reduce incidence colon cancer. Important new research reveals details of how COX-2 promotes tumour development, providing potential new targets for drugs to treat colorectal cancer, among others [3].

In healthy intestines, cells are continually generated and destroyed; inhibition of scheduled apoptotic cell death can lead to overgrowth of harmful cells and ultimately to cancer. Researchers led by Paul Insel and Lars Eckman, of the University of California at San Diego (http://www.ucsd.edu/), have now elucidated how COX-2 can steer cells away from death and towards a cancerous fate. The enzyme catalyzes the production of prostaglandins, which increase levels of cAMP. The group showed that cAMP induces inhibitor-of-apoptosis protein 2 (IAP2), which blocks activity of the key apoptotic enzyme caspase 3. Inhibiting COX-2 decreased IAP2 expression and promoted apoptosis, explaining the anti-cancer effects of NSAIDs.

These results answer crucial questions about how COX-2 pushes cells towards cancer. They also suggest new therapeutic targets that might enable the avoidance of undesirable side effects of NSAIDs, such as stomach irritation. And, as Insel explained, 'Although colon cancer was studied, the findings have potential implications for understanding non-intestinal cancers where COX-2 or related enzymes play a role similar to that in colorectal cancer'.

3 Nishihara, H. *et al.* (2003). Inhibition of apoptosis in normal and transformed intestinal epithelial cells by cAMP through induction of inhibitor of apoptosis protein (IAP)-2. *Proc. Natl. Acad. Sci. U. S. A.* 100, 8921–8926

Silenced gene identified in colon cancer

A gene that is switched off early in the development of colon cancer has been identified [4]. Gene SLC5A8 is silenced by aberrant methylation in almost 60% of primary colon cancers. In normal colon

mucosa, this gene is unmethylated and SLC5A8 transcript is expressed.

Sanford Markowitz, a Professor at the Ireland Cancer Center (http://www.irelandcancercenter.org) and a Howard Hughes investigator at Case Western Reserve University (http://www.cwrs.edu) and University Hospitals of Cleveland (http://www.uhhs.com), explains that this transcript 'suppresses the growth of colon cancer tumors, both in the test tube and when grown in mice'.

Colon cancer is the second leading cause of death in adult Americans, but is highly preventable and is treatable if discovered early in development, the main problem being a lack of initial symptoms.

SLC5A8 methylation is an early event, which is detectable in colon adenomas and in even earlier microscopic colonic aberrant crypt foci. The abnormal DNA in the blood is a marker of the disease and, thus, the abnormal gene is suggested as a candidate for a new diagnostic test for the early detection of colon cancer.

Structural and functional investigations also revealed that SCL5A8 is a member of the family of sodium solute symporters, therefore, they have been added as a class of candidate colon cancer suppressor genes. In this role, SCL5A8 transports a mystery substance into the colon cell. Future studies might elucidate this substance; as Markowitz suggests, '[the substance] could be a potential target for the development of new anti-colon cancer drugs'.

4 Li, H. *et al.* (2003) SLC5A8, a sodium transporter, is a tumor suppressor gene silenced by methylation in human colon aberrant crypt foci and cancers. *Proc. Natl. Acad. Sci. U S A* 100, 8412–8417

Miscellaneous

mAbs available for cytochrome P450s

The National Cancer Institute (http://www.nci.nih.gov) and the National Institutes of Health (http://www.nih.gov) is making available specific inhibitory monoclonal antibodies (mAbs) against human cytochrome P450s, for researchers interested in drug metabolism, adverse drug reactions (ADRs) and drug discovery. Antibodies available are those to cytochrome P450 1A1, 1a2, 2A6, 2B6, 2C8, 2C9, 2C19 the 2C family, 2D6, 3A4/5 and 2E1.

Requests for specific mAbs and the Material Transfer Agreement (MTA) should be sent to Patrick Twomey, Technology Transfer Branch (TTB) on twomeyp@mail.nih.gov. Requests for larger amounts can be obtained by license through Fatima Sayyid, Office of Technology Transfer (OTT) on sayyidf@ot.nih.gov.

A gene to treat blood disorder

Selective, *in vivo* enrichment of transplanted hematopoietic stem cells could overcome limiting gene transfer efficiency in patients with β-thalassemia. Researchers at St. Jude Children's Research Hospital (http://www.stjude.org) used an oncoretroviral vector to transfer a methylguanine methyltransferase drug-resistance gene into normal bone marrow cells, which were then transplanted into β-thalassemic mice [5]. Subsequent chemotherapy, with temozolomide (TMZ) and O^6-benzylguanine (BG), led to a specific increase in these normal cells to levels that diminished or cured the disease.

As Derek Persons, lead author of the report explains, 'the technique…will allow us to enrich the population of cells carrying the normal gene by eliminating competing, defective cells, without using radiation or intensive chemotherapy'.

β-Thalassemia is an inherited disorder that causes under-production of β-globin protein, resulting in insufficient levels of haemoglobin and, thus, life-long anaemia. In the absence of adequate treatment, this can be fatal.

Currently, the most common treatment for the disorder is red blood cell transfusion, a temporary measure that, in severe cases, depletes up to 52 pints of blood per year and can also lead to iron overload and organ failure. The alternative – bone marrow transplantation – is not always possible and carries added risks.

The findings could also be applied to other genetic blood disorders. Stephen Emerson, Chief of Haematology/Oncology at the University of Pennsylvania (http://www.upenn.edu), concludes that, 'haematology research can lead to solutions to the problems that remain before gene-modified stem cells can be safely and successfully used in medical therapy'.

5 Persons, D.A. *et al.* (2003) Successful treatment of murine β-thalassemia using in vivo selection of genetically modified, drug-resistant hematopoietic stem cells. *Blood* 102, 506–513

The first predictive hERG ion channel

Tripos (http://www.tripos.com) – a leading provider of drug discovery informatics products and chemistry research – and ChanTest (http://www.chantest.com) – the premier ion channel platform company providing drug safety testing services – have announced a collaboration to develop a model to predict which drugs are likely to produce cardiac liability caused by blockage of the hERG channel.

This combined model of hERG ion channel optimization and lead rescue service is the first of its kind and will assist pharma and biotech companies in meeting FDA (http://www.fda.gov) clinical trial mandates for hERG ion channel testing.

John P. McAlister, President and Chief Executive Officer of Tripos, said: 'This collaborative venture with ChanTest will not only simplify and streamline the drug discovery process, but will also address a current unmet need in the industry to reduce attrition in the development process.'

Arthur M. Brown, President and Chief Executive Officer of ChanTest, said: 'The need for earlier identification of liabilities in the drug discovery process has never been more necessary… We are aware that FDA and IHC guidance recommends hERG ion channel testing for all new drugs, which puts our collaborative venture ahead of the curve.'

Tripos will select and provide compounds for testing by ChanTest: based on these results, Tripos will develop the predictive model and will employ it to examine data that results from the analysis – by ChanTest – of lead candidates to identify any hERG ion channel liability.

News in brief was written by *Matt Brown, Joanne Clough, Clare Rathbone, Georgina Smyth* and *Heather Yeomans*