postmortem examination in some HK patients dying from SARS revealed the presence of vascular thrombosis in the pulmonary vessels [5]. Taken together, these findings warrant further investigation of the role of Fgl2/fibroleukin prothrombinase in the pathogenesis of SARS.'

References

1 Marsden, P.A. *et al.* (2003) The Fgl2/fibroleukin prothrombase contributes to immunologically mediated thrombosis in experimental and human viral hepatitis. *J. Clin. Invest.* 112, 58–66

2 Maupas, P. and Melnick, J.L. (1981) Hepatitis B infection and primary liver cancer. *Prog. Med. Virol.* 27, 1–5

3 Hoofnagle, J.H. and di Bisceglie, A.M. (1997) The treatment of chronic viral hepatitis. *New Engl. J. Med.* 336, 347–356

4 Rich, J.D. *et al.* (2003) A review of the case for hepatitis B vaccination of high-risk adults. *Am. J. Med.* 114, 316–318

5 Peiris, J.S.M. *et al.* (2003) Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 361, 1767–1772

Fishing for novel drugs

Laura Spinney, l.spinney@elsevier.com

Marine cyanobacteria are unusual in that they generate molecules in which sub-units of fatty acids are structurally linked to amino acids. This polyketide–peptide backbone generates enormous chemical diversity, which researchers at Oregon State University in Corvallis (OSU; http://oreganstate.edu) are now beginning to mine for novel drug action [1].

Tailored to fit

'There are just two microbial groups that really integrate those two types of pathways with the abundance and frequency that we see in cyanobacteria: the cyanobacteria and the myxobacteria,' said Bill Gerwick, whose group at the College of Pharmacy at OSU, is now screening the products of cyanobacterial secondary metabolism for anti-cancer effects, among others.

The team is also exploring novel 'tailoring' functions by which the cyanobacteria appear to modify the basic polyketide–peptide backbone of these metabolites. 'After the backbone is made, these [tailoring functions] come in and create unusual little functional groups along it,' said Gerwick.

'In particular, we find abundant use of halogen atoms in cyanobacteria. So they incorporate chlorine, bromine and even iodine into some of these molecular structures, and they do so creating chemical functional groups that have really never been seen before in nature.'

Novel therapeutic actions

Not surprisingly, it turns out that those novel functional groups have novel therapeutic actions. Having fractionated a crude organic extract from one Puerto Rican collection of the cyanobacterium *Lyngbya majuscula*, for instance, Gerwick's group succeeded in isolating three new secondary metabolites, including a tryptophan derivative, as well as several potent neurotoxins.

Tryptophan is an essential amino acid that is used in the treatment of migraine, among other things. The neurotoxins could turn out to be useful as tool compounds, says Gerwick, because they could act as biochemical inhibitors in the study of cell biology.

Using MS and NMR spectroscopy to elucidate the structures of the three metabolites, Gerwick's team found that they all showed evidence of this convergent fatty acid-amino acid pathway.

Anti-cancer drugs

Gerwick's lab is currently involved in a large anti-cancer drug-screening program in collaboration with Novartis (http://www.novartis.com) and the National Cancer Institute (http://www.nci.nih.gov), part of the US National Institutes of Health. Three of their compounds have already progressed through this program to clinical trials.

Although their best success to date has been with compounds isolated from sponges, says Gerwick, new research suggests that some of these might actually have been produced by cyanobacteria living symbiotically with the sponges. His team is also following up cyanobacterial candidates for neuroprotective compounds, as well as insecticides, antibiotics and anti-inflammatories.

Some intriguing structures

Burkhard Haefner [2] of the Department of Inflammatory Disease at Johnson & Johnson Pharmaceutical Research and

  PII: S1359-6446(03)02839-3

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.

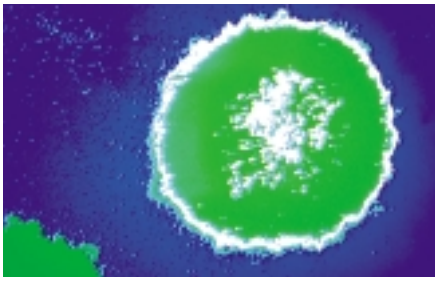
In this study, Kenneth Roux (FSU) and others in a global collaboration, were using different techniques to investigate the unusual binding powers of the antibody, and confirmed Roux's notion that 'we knew we were onto something'.

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