hoped that the elucidation of the relative contributions of psychological, social and genetic factors that cause obesity will result in the identification of several novel therapeutic targets for this common and complex disorder.

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An SOS for HIV

The development of a safe, effective vaccine against HIV will be crucial to halting the AIDS pandemic. Three years after President Clinton declared that it should be possible to produce one within a decade, many obstacles remain. Such a vaccine would almost certainly require several components, including a subunit vaccine based on the envelope glycoprotein to induce neutralizing antibodies[1].

Although most trials of HIV subunit vaccines to date have used a soluble form of the gp120 subunit, it is a poor immunogen because of its poor stability. Now, John Moore, James Binley and their colleagues at Aaron Diamond AIDS Research Center (ADARC; NY, USA), working in collaboration with Progenics Pharmaceuticals (NY, USA), have produced a genetically engineered, stable envelope glycoprotein complex that mimics the virion-associated structure[2], which they hope to use as a potential component of a vaccine against HIV.

The native HIV-1 envelope glycoprotein, the so-called 'viral spike' familiar from graphical reproductions of the virus, is a non-covalently weakly bonded complex of three gp120 subunits with three gp41 subunits. Hence, the gp120 subunit often dissociates from the complex (Fig. 1a). Consequently, it has proven very difficult to produce a stable recombinant form of this glycoprotein complex (Fig. 1b).

Stabilizing the complex

The virus produces the glycoprotein complex from a larger gp160 monomer by proteolytic cleavage. Although some groups have attempted to generate a stable complex by mutating gp160 to remove the cleavage site[3] (Fig. 1c), this monomer does not elicit antibodies capable of neutralizing HIV-1. Researchers believe that the confor-

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mation of this monomer is different from that of the non-covalently associated viral complex. The strategy developed by Binley, Moore and their coworkers is based on the belief that a soluble antigen would need to be stable and to closely mimic the conformation of the viral spike. They have therefore introduced a disulfide bridge between the gp120 and gp41 subunits to try to stabilize the complex in a near-native conformation.

For this strategy to be successful, the genetically engineered disulfide must form between two residues that are in close contact in the native complex. 'This was a high risk strategy; we did not expect it to work' explains Binley. 'As we do not have the crystal structure of the gp120–gp41 complex, we had no direct evidence of which residues were in contact.' The group made over sixty double-cysteine mutants of the gp120–gp41 complex in the well characterized JR-FL strain of HIV-1. For this, they selected residues from those regions in each subunit that were believed, from earlier site-directed mutagenesis experiments, to contact the other subunit.

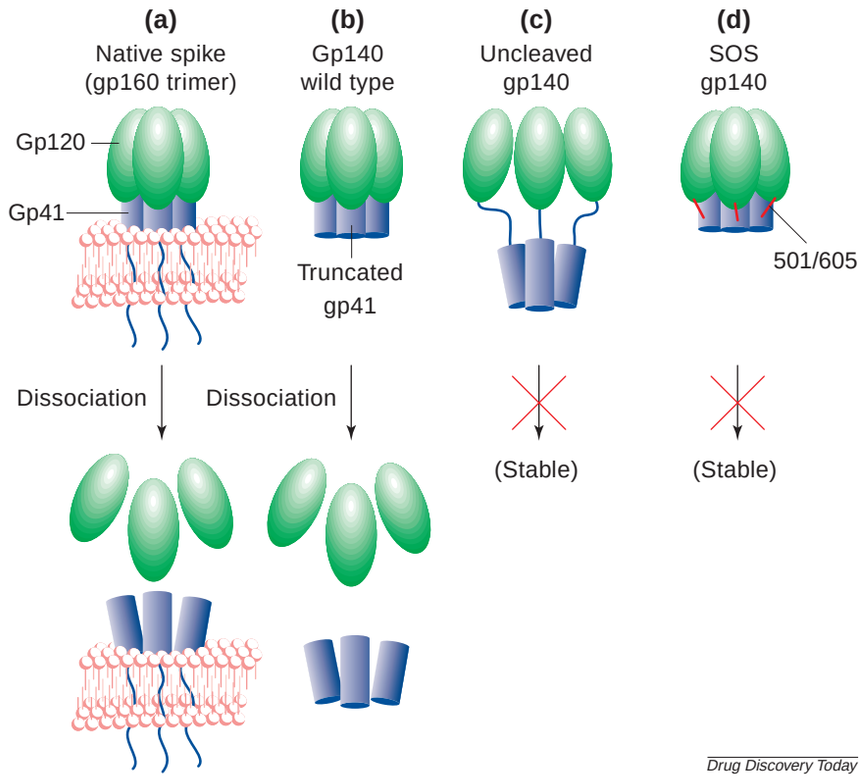

Figure 1. *Schematic representation of various forms of HIV-1 envelope protein and their stabilities. (a) The native envelope trimer as present on virus particles. (b–d) Various forms of soluble gp140, truncated at the membrane spanning domain. The SOS mutant (d) is stable, unlike the wild-type native envelope protein structure (a,b) that easily dissociates. Furthermore, from antigenic studies, SOS (d) resembles the native envelope structure (a,b). Conversely, uncleaved gp140 (c), although stable, does not resemble the native structure. Note that, at present, the SOS gp140 mutant is not yet known to be trimeric, but is known to be oligomeric. Artwork by Daryl Schiller.*

Validation of the complex

The group found that mutation of the residues Ala501 in gp120 and Thr605 in gp41 to cysteine formed a complex (which they named SOS glycoprotein) that showed the same migration on SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) gels as the uncleaved gp140 protein. This indicated that it had formed a correctly processed and folded envelope glycoprotein complex (Fig. 1d). Boiling with SDS could not dissociate its components; this was only possible using agents that could reduce a disulfide bridge.

If the SOS glycoprotein is to be useful as a vaccine component it must bind to those antibodies that neutralize the native virus. The ADARC group tested the glycoprotein with a panel of antibodies to gp120 and gp41 epitopes. It was recognized efficiently by the CD4–IgG2 molecule, indicating that its CD4 binding site was intact. They found that neutralizing antibodies that bind to the native virus spikes also bind to the SOS glycoprotein while non-neutralizing antibodies that do not bind to these spikes also do not bind to SOS.

Future studies

A team based at Progenics Pharmaceuticals is now producing the SOS glycoprotein in milligram quantities for immunogenicity tests in animal models. Moore explained that one of the next crucial stages is the development of a component that would induce the production of cytotoxic T lymphocytes.

Paul Maddon, CEO of Progenics, says, 'What makes this such an exciting discovery is that the SOS glycoprotein is a faithful mimetic of the immunogenic viral spike, with the correct epitopes exposed. Our goal for 2000 is to demonstrate that the candidate vaccines generate immunity in small mammals and primates'. If these experiments are successful, they hope to establish the first clinical trials of the vaccine component in Africa using the clade C variant of HIV-1 (a variant that is prevalent in sub-

Saharan Africa) in 2001. Furthermore, President Clinton has recently announced the Millennium Vaccine Initiative to promote the affordable development and deployment of vaccines against diseases, including AIDS, that are prevalent in the Third World.

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Clare Sansom

News in brief

Japan could adopt US R&D model

Japanese pharmaceutical firms and investors have shown interest in the unique university-based R&D business model operated by Immtech International (Vernon Hills, IL, USA). The model involves the partnership of biotechnology companies with research scientists and universities and has been used for the cost-effective development of thousands of compounds in the US. The Japanese government is currently pledging billions of US dollars to stimulate the development of a life science and biotechnology industry in Japan.

The business model is cost-effective because it transfers the costs of research and development from biotechnology companies to universities. Biotechnology companies provide the service of licensing and marketing compounds produced, facilitating a rise in the number of new drugs being developed. While the new company grows on the basis of the ownership of the new compounds, the universities involved receive performance-related stock warrants and see their products rapidly reach the marketplace.

EC to increase scientists 'quality of life'?

Growth and job creation in new sectors such as biotechnology are driven essentially through the setting-up and development of new companies. As part of the European Commission's *Quality of Life* program, a series of business-planning workshops are to be held across Europe with the aim of helping scientists launch their own biotechnology companies.

The Biobiz® initiative has received an EC grant of EURO 100,000 as well as financial support from Arthur Andersen and Eurobiobiz (Saint Beauzire, France).

Intensive three-day training workshops will include instruction in basic management and finance skills. The course is designed for (potential) entrepreneurs in the biotechnology sector and applicants should have a clear start-up project as well as a basic understanding of what is involved in starting and running a business. The course is only available to researchers from EU Member or Associated States.

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Virtuoso performance by Siemens

A new diagnostic tool for viewing the vascular system has been developed by Siemen Medical Systems (New York, NY, USA) in conjunction with Alejandro Berenstein of New York's Beth Israel Medical Center (New York, NY, USA), and Michel Mawad from The Methodist Hospital (Houston, TX, USA).

The tool, 3D Virtuoso, is a computer program that uses computed tomography (CT), magnetic resonance (MR) and digital subtraction angiography (DSA) data to construct two images, which are then viewed through a headset. The two images, one for each eye, are set six degrees apart and give such an impression of depth and perception to the wearer that even very small venous anomalies can be distinguished. The software can also be made to effectively 'place' the wearer inside the blood vessel itself.

Berenstein points out that, 'This new technology enables us to assess whether and how well problems such as aneurysms, stroke or vascular problems can be treated… We eliminate the risk of side effects associated with traditional endoscopy such as perforation, infection and haemorrhage.'

The software also has wider implications for use in research, where it could be used to assess the efficacy of test treatments.

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