site, occluding it in gp120s (such as HxBc2) that bind only CXCR4.

Importantly, creation or exposure of the highly conserved co-receptor-binding site requires that gp120 first binds CD4 (refs 11–13). This is another way for HIV-1 to evade humoral immunity — by the time the co-receptor site is ready to bind CCR5 or CXCR4, the virus is already attached to CD4. Steric constraints will hinder access of antibodies to the co-receptor site under these conditions, explaining why primary isolates are poorly neutralized by the 17b antibody[2,3]. The CD4-induced conformational changes in gp120 involve movement of the V1/V2 structure and, to a lesser extent, the V3 loop, away from the underlying co-receptor-binding site[11]. Although these variable loops are not present on the crystal structure, they have been modelled[10] as a protuberance above the gp120 core. One way to view them is as an umbrella that shields the critical regions of gp120 from the rain of antibodies thrown at it by the humoral immune response; if a neutralizing antibody succeeds in binding to the variable loops, the virus will simply mutate the non-essential residues involved, and escape.

The virus has additional protection from humoral immunity by the extensive glycosylation of gp120. The authors[1–3] modelled many of the glycans onto the crystal structure, clearly revealing how they shield receptor-binding regions of the peptide backbone from antibodies. This makes sense from the virus's perspective — with rare exceptions, HIV-1 is neutralized by inhibition of its attachment to cellular receptors[14]. The same protective devices will also reduce the binding of gp120 to the immunoglobulin-like B-cell receptor, meaning that HIV-1 can also limit the production of neutralizing antibodies in the first place. Throw in observations that some strains of HIV-1 can even use anti-gp120 antibodies to increase their ability to fuse with host cells[15] — presumably by occupying one of the three subunits of an assembled envelope glycoprotein trimer and inducing structural changes in the other two — and the war between HIV-1 and the humoral immune system takes an even more perverse twist.

The trimeric nature of the assembled gp120–gp41 complex can only be inferred from the crystal structure because the inter-subunit contacts are between the gp41 moieties. But there is really only one way for all the components to fit together[1,2]. The immunogenicity and antibody reactivity of the assembled complex are even less than those of the gp120 monomer, perhaps because of steric considerations[16,17], and this provides yet another level of protection — the immune system is decoyed into making antibodies to disassembled gp120 that are poorly reactive, and hence ineffective, with virions. These protective measures may reduce HIV-1 infectivity *in vivo*, but they provide an overall advantage in the face of the immune response. *In vitro*, HIV-1 can afford to discard some of its protective armour, increasing its ability to bind receptors and infect its target cells at the (now irrelevant) expense of becoming neutralization sensitive[18].

So what can be done to overcome the defences of HIV-1, given that an antibody response may be necessary to supplement vaccine-induced cellular immunity? There seems little to be gained by continuing to use simple gp120 subunits of whatever strain, alone or in combination. Antibodies elicited by such proteins play into the virus's hands because they attack its defences head-on. If an arrow bounces off a tank, why use a quiver-full of the same design? Instead, we need to use the crystal structure to design a smart bomb with armour-piercing capacity, perhaps by modifying the antigenic structure of gp120. Already, there are indications that this may be possible. When glycosylation sites were deleted[19] from the V1/V2 loops of the simian immunodeficiency virus gp120, not only was a neutralization-sensitive virus created, but the immunogenicity of the mutant virus was altered so that a better immune response was raised to the wild-type virus. Similarly, removing the V1/V2 loops from HIV-1 gp120 renders the conserved regions underneath more vulnerable to antibodies[11,20], although it is not yet known whether this will translate into improved immunogenicity. These and other approaches that will be stimulated by the new information on the structure of gp120 are part of the way ahead on the long road to developing an HIV-1 vaccine. □

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Daedalus

Thermal noise

How to get rid of our mounting piles of organic waste? Oxidation is the obvious reaction for the job; but burning in air generates highly unpopular smoke. Water-based oxidation would be far better. Sadly, it either needs ferocious reagents, such as fuming nitric acid, or extremely high temperatures and pressures, as in supercritical aqueous oxidation. Daedalus is looking for another way.

He notes that sonolysis, subjecting a reaction to intense high-frequency sound, can speed it up hundreds of times. The violent pressure-swings of the sound cause the liquid to cavitate, that is, to form tiny transient bubbles of vacuum. Their collapse produces vast temperatures and pressures; these create energetic free radicals which speed the reaction.

Sonolysis can certainly accelerate the oxidation of organics in solution. But Daedalus wants to destroy solids as well — old newspapers, plastic rubbish, food residues, discarded clothing, and the rest of our organic detritus. He points out that bubbles form easily on solid surfaces, especially irregular ones. Hence the 'boiling stones' used by chemists to aid smooth boiling, and the cavitation suffered by ships' propellers. A propeller can stir the water violently enough to cause cavitation; the bubbles form right on the metal where they can do the most damage.

In principle, therefore, a suspension of solid waste should oxidize if stirred with sufficient vigour — provided the waste itself was used as the stirrer. Now an object suspended in a conducting liquid threaded by a magnetic field experiences a force when a current is passed through the liquid: a sort of differential motor effect. So Daedalus will oxygenate his rubbish suspension, put it in a strong magnetic field, and pass high-frequency a.c. through it. The violent vibration of the solids against the surrounding water will cause cavitation at their interface. Bubbles will form and collapse on the solid surfaces, exactly where they are needed; the suspended waste will erode and oxidize rapidly.

Daedalus's waste-cavitation plant will suspend its shredded waste in air-saturated sea water, the cheapest oxidizing conducting solvent. The rubbish will simply fizz away to gas and ash, and the sterile effluent will be returned to the sea. The process should work on domestic sewage, too. Those lazy seaside towns that just pump the stuff out to sea will not even have to change their outfall pipe.

David Jones