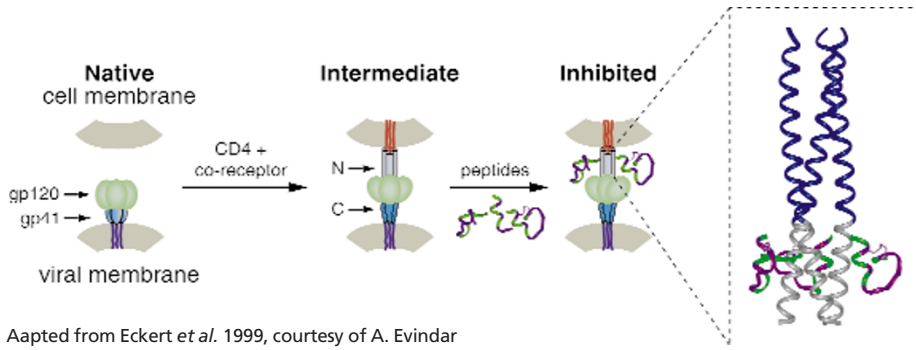
Keeping HIV out

Last month, *Nature Structural Biology* highlighted a paper by Ferrer and coworkers (**6**: 953–960) that reported efforts towards the discovery of reagents that block HIV entry into the cell. In the October issue of *Cell*, Eckert and colleagues (**99**: 103–115) describe work that also validates this approach. Both groups made use of structural information to guide the design of inhibitors that prevent HIV infection by blocking a conformational change of a protein (gp41) on the surface of the virus that is required for membrane fusion. In both cases the inhibitor was targeted to a hydrophobic pocket on the surface of the protein. Ferrer *et al.* used a biased combinatorial chemical library of non-natural binding elements while Eckert *et al.* used mirror-image phage display.

HIV-1 is an enveloped retrovirus and its envelope protein complex, consisting of gp120 and gp41, mediates the early binding and entry steps in infection. Upon binding of gp120 to the target cell receptor (CD4 and a chemokine coreceptor such as CCR-5 or CXCR-4), gp41 undergoes a conformational change in which the fusion peptide regions (dark orange threads) are inserted into the cell membrane and the N-peptide region of gp41 (designated 'N') is exposed. This intermediate leads to the formation of activated gp41 that consists of a six-helix bundle — the N-peptides form the three central helices and the C-peptides form the three outer helices. The intermediate is expected to contain three symmetry-related hydrophobic pockets on the surface of the central three helices formed by the N-peptides. Mutagenesis experiments, together with the finding that synthetic C-peptides (such as T-20) are potent inhibitors of HIV-1 infection, pointed to the hydrophobic pocket as a potential binding site for small molecules that could block the conformational change of gp41 and thus prevent cell fusion.

Eckert *et al.* used a chimeric version of the N-peptide (since the native N-peptide tends to aggregate) as a target to screen for compounds that bind to the hydrophobic pocket. They synthesized the target in the D-amino acid conformation (that is, the mirror image of the naturally occurring L-amino acid form). This D-target was then used to select peptides from a phage-display library expressing random L-amino acid peptides. In theory, D-peptide versions of these phage-displayed peptides should interact with the natural L-amino acid target. The identified D-peptides do indeed bind to the hydrophobic pocket of gp41, as analyzed by NMR and X-ray crystallography (inset). Furthermore, they inhibit gp41-mediated cell-cell fusion and HIV-1 infection. While these D-peptides are effective in the micromolar range, T-20 (the C-peptide that is about to go into Phase II clinical trials), has nanomolar potency. However, the D-peptides have the advantage that they are resistant to proteolytic degradation and they are about half the size of the C-peptides, making them better drug candidates.

The discovery of inhibitors that prevent HIV entry into the cell, as opposed to the currently approved therapies that inhibit viral replication once it has entered the host cell, is a welcome addition to anti-HIV arsenal. While these new studies represent promising steps toward finding new drugs that target HIV entry, the ultimate goal is to identify small molecules that can be taken orally as opposed to the subcutaneous injection required for T-20. Much effort will now be focused on using these identified compounds as leads for the development of small molecule drugs that prevent HIV entry into cells. *Boyana Konforti*



Aapted from Eckert *et al.* 1999, courtesy of A. Evindar

Prebiotic chemistry

The book *The RNA world*, which is reviewed on page 997 of this issue of *Nature Structural Biology*, covers research that seeks to understand the origin of life on Earth and notes that the idea of a 'prebiotic soup' has become part of the mythology of evolutionary research. This Darwinian idea that life arose in a pond containing all of the necessary building blocks is indeed a pleasing concept. However, it seems that there is now little hard evidence, based on current estimations of the primordial atmosphere, to support the idea that a large variety of prebiotic compounds formed at high local concentrations. Thus, the term 'prebiotic soup' is probably not terribly accurate, as it suggests a rich stock of diverse material.

Löb, W. *Z. Elektrochem.* **11**, 282–316 (1906).
Löb, W. *Ber. Dtsch. Chem. Ges.* **46**, 684–697 (1914).
Miller, L.S. *Science* **117**, 528–529 (1953).

Here we highlight some of the work of two researchers whose elegant experiments attempted to recreate early atmospheric conditions. Although the geophysical relevance of the conditions used is questionable, the success of these experiments in producing new compounds from the most basic of ingredients has clearly promoted the idea of a 'prebiotic soup'. Walther Löb (in 1906 and 1914) showed that a few types of aldehydes and the amino acid glycine could be produced in a cold plasma discharge system containing a mixture of compounds such as carbon dioxide, ammonia, and water. S.L. Miller (beginning in 1953) extended this line of experimentation, showing that numerous types of amino acids and other organic compounds could be produced under similar sets of reducing conditions. *Tracy Smith*