Broad impact

Nonetheless, the findings are being hailed a significant discovery. 'This is really a tremendous contribution in terms of identifying additional candidate substrates,' says Charles Samuel, a biologist at the University of California in Santa Barbara, USA (http://www.ucsd.edu).

'RNA editing is significantly broader in its biological impact than we thought,' adds Carmichael. 'It's not just a local phenomenon, it's a broad one.'

Reference

1 Levanon, E.Y. *et al.* (2004). Systematic identification of abundant A-to-I editing sites in the human transcriptome. *Nat. Biotechnol.* 22, 1001–1005

Promising Phase I results against new HIV target

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The first in a new class of potential antiretroviral drugs known as maturation inhibitors has shown promising results in early Phase I clinical trials. PA-457 acts against a different viral target from existing HIV treatments, and could therefore be useful against the increasing problem of drug-resistant HIV isolates.

'This compound seems to work by a brand new type of mechanism,' says Christopher Aiken of Vanderbilt University School of Medicine (http://www.vanderbilt.edu), whose lab is working on the antiviral action of betulinic acid derivatives. 'It is apparently not targeting the protease, but is inhibiting maturation by specifically blocking the cleavage of one of the sites in the Gag protein. This is a very vulnerable Achilles' heel for HIV, because if you block it then the virus is really crippled, and that is why the compound is so potent *in vitro*.'

Specific

PA-457 (3-*O*-(3',3'- dimethylsuccinyl)-betulinic acid) is thought to disrupt a late step in the processing of the viral protein known as Gag, preventing the capsid precursor protein (p25) from being converted to the mature capsid protein (p24) [1]. Specifically, cleavage of the proteins SP1 and CA at their junction site in the Gag precursor $PR55^{Gag}$ is delayed, causing an intermediate protein to accumulate [2]. SP1 is essential for the correct formation of the viral capsid, and failure to release it means that the cores of virus particles shed from HIV-infected cells are mis-shapen and non-infectious.

As yet there is no direct evidence that PA-457 binds to Gag. 'There is a lot of indirect evidence that it does, but no one has yet convincingly demonstrated its effect in a cell-free system,' says Aiken. 'However, it is very specific to HIV-1, so we know it is not a general cytotoxic effect that is blocking viral activity. It may be that the compound is activated by modification within the cell.'

Clinical trials

PA-457 strongly inhibits the replication of wild-type and drug-resistant strains of HIV-1 *in vitro* [1]. Resistance to currently approved antiretroviral drugs is increasingly common: an estimated 5–10% of infected people are resistant to all available reverse transcriptase and protease inhibitors, and this group is growing rapidly. Because it acts on a different viral target, researchers are optimistic that PA-457 might provide a new treatment option for resistant strains. 'It is promising because the sequence that the drug appears to be targeting is extremely highly conserved in HIV-1 isolates,' Aiken comments. 'Even if this compound turns out to have disadvantages, there may be others that can hit the same target.'

PA-457 is being commercialized by Panacos Pharmaceuticals, Gaithersburg, Maryland (http://www.panacos.com). In a preliminary Phase I clinical trial, reported by Panacos at the XV International AIDS Conference in Bangkok in July 2004, it showed good oral bioavailability and favourable pharmacokinetics, suggesting that it will be suitable for once-daily oral dosing. It was also well tolerated at all the doses given (up to 250 mg as a single oral dose). Panacos also presented preclinical studies which it says suggest that PA-457 is unlikely to cause drug–drug interactions when given in combination with currently approved HIV therapies. A multiple-dose Phase I study is now underway in uninfected volunteers, and Panacos anticipates that a Phase II study in HIV-infected patients will begin before the end of 2004.

References

1 Li, F *et al.* (2003) PA-457: A potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. *Proc. Natl. Acad. Sci. U. S. A.* 100, 13555–13560

2 Zhou, J. *et al.* (2004). The sequence of the CA-SP1 junction accounts for the differential sensitivity of HIV-1 and SIV to the small molecule maturation inhibitor 3-*O*-(3',3'-dimethylsuccinyl)-betulinic acid. *Retrovirology* 1, 15

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