mice tolerated very high doses of up to 50 mg kg^{-1} intravenously, without evidence of psychotropic side effects typical of CB-1 agonists. If you give mice THC at high doses they fall over.'

Mode of action

The mechanism of action of CT-3 is unknown, but unpublished research by ATV has shown that, despite its lack of psychoactivity, CT-3 does cross the blood–brain barrier. It does not have a high affinity for either of the known CB receptors, but appears to antagonize some of the actions of THC [2]. 'It is a partial CB1/CB2 agonist,' says Ferrari, 'but we think it might also be acting on a third cannabinoid receptor that has not been cloned yet.'

CT-3's analgesic and anti-inflammatory profile is similar to that of NSAIDs, but animal studies suggest it might lack their characteristic side effects [2]. In contrast to NSAIDs, CT-3 caused no gastrointestinal ulceration in mice at therapeutically relevant doses. One potential indication is rheumatoid arthritis, where CT-3 appears superior to other NSAIDs in preventing joint destruction in a rat model [2].

Future work

The development of CT-3 is going ahead on several fronts. A pilot Phase I/II study has just begun in Germany to test its analgesic properties in patients with neuropathic pain. Upon completion of further safety studies to test the higher dose limits of CT-3, a Phase II study will be carried out in tremor and spasticity in MS. The US Army Medical Research Institute for Chemical Defense is also testing CT-3 as a possible treatment for the chemical warfare blister agent sulfur mustard.

'Route of administration is a big issue with cannabinoids, and no one has really cracked it yet,' says John Zajicek, Consultant Neurologist at the Derriford Hospital (Plymouth, UK) and a principal investigator in the Cannabis in MS study for the UK's Medical Research Council. 'It is difficult to get a consistent dose orally because the high lipophilicity [of cannabinoids] leads to individual variations in absorption, and there is a lot of first-pass metabolism in the liver. Inhalation avoids that, but the technology is difficult and in some studies there has been irritation of the airways.' However, he is optimistic that cannabinoids have a therapeutic role. 'I predict that there will be a whole family of synthetic cannabinoids that will be effective in different indications, and hopefully these will have very few psychoactive effects.'

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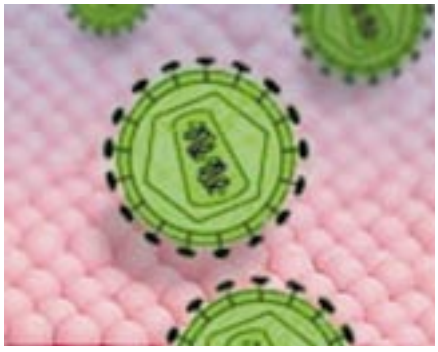
Dumped drugs could prevent HIV

Julie Clayton, freelance writer

Drugs that once held promise as treatments for HIV but were discarded because of their poor oral absorption into the bloodstream are now getting a new lease of life as potential microbicides that prevent the transmission of HIV during intercourse.

One such agent is UC781, which binds tightly to, and inhibits, the HIV replication enzyme, reverse transcriptase. UC781 failed to reach the clinic because of its poor solubility, and hence poor chance of being absorbed by the body. 'But none of those things are relevant to being able to inhibit the virus in a gel in the vagina, for example,' said Joseph Romano of Biosyn in Huntingdon Valley, PA, USA.

Biosyn obtained a license in May 2001 to develop UC781 as a topical microbicide,



one of many such products that are now being investigated for their potential action in the vagina or rectum to block HIV infection from semen.

The first 'tight binder'

UC781 was first developed as a potential fungicide by Uniroyal Chemical (now Crompton), and was one of literally thousands of compounds offered to the US National Institutes of Health (NIH) for testing against HIV. It showed impressively high activity as the first 'tight binding' non-nucleoside inhibitor of the reverse transcriptase enzyme of HIV-1. It targets the same site as nevirapine – now a commonly used systemic drug – but with a thousand-fold higher affinity, according to Israeli researcher Gabi Borkow, who was part of the original team that discovered its activity in the laboratory of Mike Parniak, at the Sir Mortimer B. Davis-Jewish General Hospital in Montreal, Canada (for review see [1]).

'Uniroyal got very excited, but when they tested for bioavailability they quickly lost interest,' said Borkow. Now at

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the Hebrew University Hadassah Medical School in Rehovot, Borkow has continued his interest in UC781, and has tested its effects in a cervical organ culture [2]. Borkow found that UC781 successfully inhibited infection of the explanted cervix by both free virus and virus-infected cells, and abolished the spread of the virus to susceptible cell lines located in another culture chamber below. He presented his findings in a poster at *Microbicides 2002* in Antwerp [3].

Previously, Borkow had found that pre-incubation of cultured cells with UC781 followed by washing, could provide a 'chemical barrier' against infection [4]. This effect was long-lasting, showing 50% protection after five days. In comparison, Borkow's explant model shows complete protection up to 48 h, and partial protection at 72 h.

Broad spectrum activity

Borkow has also found that UC781 enhances the anti-HIV activity both the suspension-based gel BufferGel™, which is about to enter Phase III clinical trials in autumn 2002 as a non-specific microbicide, and Replens™, a commercially available vaginal moisturizer.

Combinations like this are likely to be the best way forward, agrees Jonathan Weber, Professor of HIV research at Imperial College of Science and Medicine, London. 'UC781 does have this interesting quasi-cidal activity: it is so lipophilic it will get into virions. It is completely unsuitable for human use as a drug because it is so lipophilic – you could never take it enterally or parenterally – but in the vagina it may actually work, so that might be one to formulate with dextrin sulphate [a gel with electrostatic properties against HIV],' he explained.

Romano's team at Biosyn has also developed a gel containing UC781 that shows strong *in vitro* activity, and is stable and non-toxic to cells [5]. Furthermore, and broadening its appeal to users worldwide, the team found that UC781 blocks infection by HIV strains belonging to clades A, C, D, E, F and G, which are more typical of the epidemics that are raging in Africa, Asia and South America, as well as against clade B, which predominates in North America and Europe. It does not, however, act against HIV-2.

Biosyn has licensed UC781 from Crompton, and plans to apply for an Investigational New Drug (IND) license from the FDA to begin clinical trials, according to Romano, who also presented his results at *Microbicides 2002*.

Lack of big pharma

Until recently, microbicides research has suffered as the poor relation compared with drug research for treating HIV-infected individuals. 'The problem is that you need a lot of money to validate the concept and clinical trials… it is doubtful that the small biotech companies that have taken these products on by way of license have the pockets to really fund these studies,' said Mark Wainberg, Professor of Microbiology and Director of the AIDS Center at McGill University in Canada.

According to Wainberg, large drug companies have so far shied away from microbicides research, largely because of the pressure they are likely to face to provide successful products to developing countries for little or no cost. 'It is a disincentive, unfortunately, for big pharma to get into the field,' he explained.

Fortunately, however, government and private funds are now coming to the rescue, including the NIH, the UK Medical Research Council, and the Wellcome Trust.

There are now nearly 60 microbicides in the pipeline, mostly at the stage of animal testing and Phase I clinical safety trials, but none has reached the marketplace. However, the most extensively tested compound, nonoxynol-9, has failed to show efficacy against HIV infection in a meta-analysis of Phase III trials, according to David Wilkinson, Head of the Centre for Rural and Remote Health at Adelaide University Medical School.

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