Next generation HIV drugs move into late stage development

There are currently 24 drugs approved for treating HIV infection. Of these, 23 are small molecule orally available drugs, or drug combinations, targeting the virus' reverse transcriptase and protease enzymes, targets that have been known for two decades. In reality, only a relatively small number of currently approved drugs are regularly used in clinical practice, as earlier compounds are superseded by drugs with improved dosing regimens, potency and tolerability.

By Dr Graham P. Allaway and Dr Jeffrey M. Jacobson

Today, a major limitation of HIV therapy is treatment failure due to drug resistance. Drugs with the same target typically exhibit cross-resistance, further limiting treatment options. For many years the pharmaceutical industry has sought to identify new classes of drugs acting at different targets in the viral life cycle and having efficacy against strains resistant to the approved reverse transcriptase and protease inhibitors. So far, these efforts have resulted in only one new drug entering the market, namely the fusion inhibitor enfirvutide (Fuzeon), which received US marketing approval in 2003. Fuzeon targets one of the first steps in HIV replication – fusion of the virus to the human cell. Despite its potent antiviral properties, the market for Fuzeon has been limited by the fact that it is a protein-based drug that must be administered by twice-daily subcutaneous injections. These are often associated with injection site reactions, limiting patient compliance. It is also very costly to manufacture, so that treatment with Fuzeon can cost more than twice that of most other approved HIV drugs[1].

While major efforts have been made to identify compounds targeting a number of other steps in HIV replication, many of these have fallen by the wayside based on lack of potency or the occurrence of significant toxicities. However, in the past few years the landscape has started to change as a number of new drug candidates have been successfully moving through Phase II clinical testing. These include several compounds that block the earliest steps in the viral life cycle, the binding of HIV to receptors on the human cell. Another drug candidate moving into late stage development inhibits the viral integrase enzyme. Most recently a completely new target for HIV drug discovery has been identified, called maturation inhibition. The first-in-class maturation inhibitor, PA-457, is currently in Phase II clinical testing. Maturation inhibition is the first new target for HIV drug discovery to be elucidated in nearly 10 years that has been validated by the development of a potent drug candidate. Generating much interest, these new approaches have the potential to transform HIV treatment towards the end of this decade.

Targets for drug intervention in the HIV life cycle

HIV replication offers many potential sites for therapeutic intervention. Some of the major ones are shown in **Figure 1**, which illustrates the HIV life cycle. At the top of the figure is an HIV virus particle about to infect the human cell in the centre of the diagram. The virus particle first binds to its receptor,

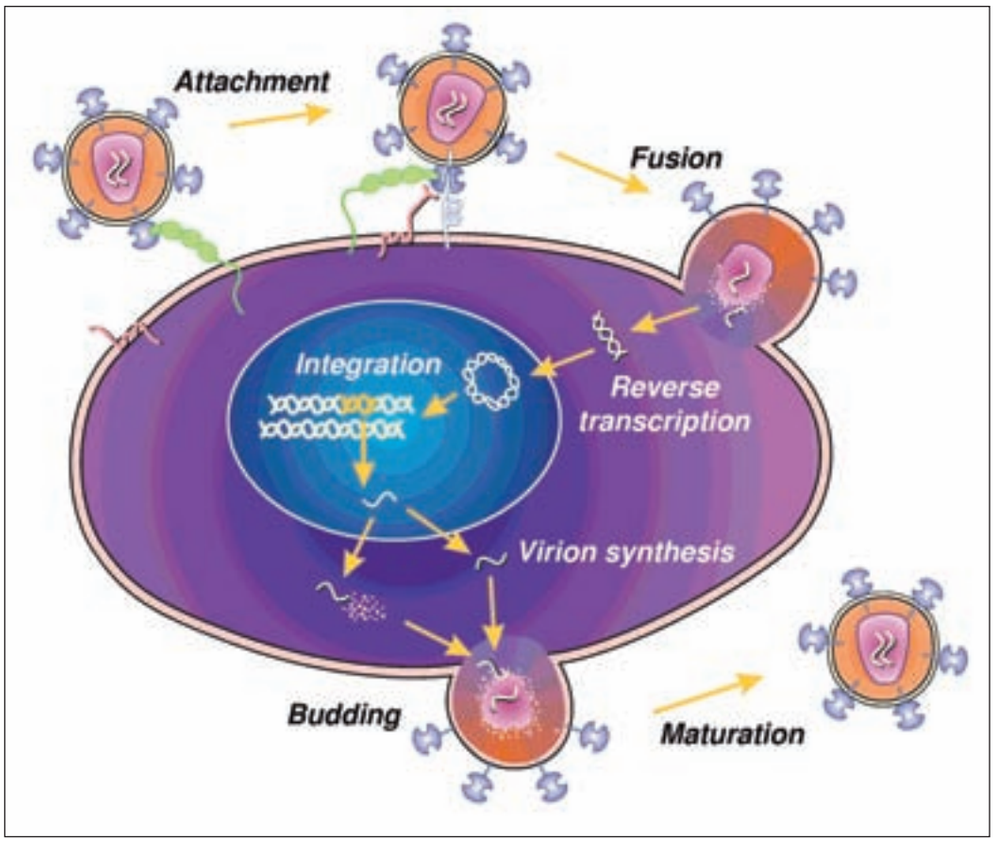

Figure 1
The HIV life cycle: Described in main text

CD4, shown in green, a process known as attachment. The virus next binds to a co-receptor, illustrated in pink, which can be either of two cellular chemokine receptors, CCR5 or CXCR4. These receptor interactions permit initiation of the fusion process, when viral and cellular membranes fuse allowing the viral RNA to enter the cell. The injected HIV RNA is then transcribed into a DNA copy by the viral reverse transcriptase enzyme. Next the viral DNA integrates into the cellular genome, a process mediated by the viral integrase enzyme. New copies of the HIV proteins and genomic RNA are then synthesised from the viral DNA copy, using the cellular synthetic machinery. These components assemble into new viral particles that bud out of the cell, at which time a series of protein processing events occur called maturation, that are required for the viral particles to become infectious and spread infection to new cells around the body.

The biology of HIV replication continues to be elucidated in more detail, revealing numerous potential new molecular targets for drug intervention. An example is our expanding understanding of HIV assembly and budding, when HIV utilises the cellular exocytosis machinery. This involves a complex interaction of viral and cellular proteins that if blocked, can inhibit viral replication. However, most of these new targets have not yet been validated by the discovery of potent inhibitors with suitable development properties.

Table 1 lists the major HIV drugs with new targets that have successfully demonstrated antiviral activity in short term (7-14 day) monotherapy studies in HIV-infected patients, known as Phase I/II or Phase IIa studies, and are now continuing on to longer term (24-48 week) Phase IIb or pivotal Phase III clinical studies of the agents, in combination with approved drugs.

Novel entry inhibitors

The role of CD4 as the primary HIV receptor was established back in the 1980s, but despite substantial efforts, attachment has not been readily amenable to successful therapeutic development. One small molecule attachment inhibitor from Bristol-Myers Squibb (BMS-488043) has shown antiviral activity in a Phase IIa study in HIV-infected patients. However, Bristol-Myers has reportedly terminated development of this compound in favour of identifying more broadly active molecules[2]. In

contrast, several groups have identified protein-based attachment inhibitors, one of the most advanced being Tanox's anti-CD4 monoclonal antibody TNX-355. This compound has demonstrated anti-HIV activity when administered by bi-weekly infusion for 24 weeks to patients on optimised background therapy[3].

While CD4 is the primary HIV receptor, its presence is not sufficient for HIV to enter and infect human cells. Additional co-receptors are required, specifically the chemokine receptors CCR5 or CXCR4. HIV viral strains typically use only one or other of these receptors. CCR5-using strains are generally responsible for HIV transmission and are found most commonly in asymptomatic patients, while CXCR4-using strains are more prevalent later on in the disease process and are generally believed to be more pathogenic than CCR5-dependent strains. Efforts to identify inhibitors of the HIV co-receptor interactions have been under way for nearly 10 years. Early work demonstrated that certain individuals bearing a homozygous mutation in their CCR5 receptors were resistant to HIV infection. The fact that these people were healthy, with no immunological problems, suggested that CCR5 could be a good target for HIV drug development. For this reason, as well as the greater prevalence of CCR5-using viruses, CCR5 antagonists have been the major focus of HIV drug development efforts. However, since patients may be infected by CXCR4-dependent viruses in addition to, or instead of, CCR5-using strains, effective therapy with a CCR5 antagonist will likely require diagnostic testing for viral tropism. Furthermore, there is a theoretical risk, yet to be clearly demonstrated clinically, that inhibiting the replication of CCR5-using viruses may result in the selection of the more pathogenic CXCR4 strains.

Three large Pharma companies (Pfizer, GlaxoSmithKline and Schering-Plough) have taken CCR5 antagonists into mid-stage clinical testing, with impressive results in proof-of-concept studies. However, in recent months GSK terminated development of its lead CCR5 antagonist, aplaviroc, due to severe liver toxicity seen in some patients[4]. Schering-Plough has recently terminated its Phase IIb clinical trial of vicriviroc in treatment-naïve patients following the observation of viral rebound

Table 1: HIV drugs with novel mechanisms that have successfully completed proof-of-concept studies in HIV-infected patients and are in active development*

STAGE IN REPLICATION	MOLECULAR TARGET	DRUG NAME/ DESIGNATION	DOSING REGIMEN**	COMPANY DEVELOPING	CLINICAL STATUS	COMMENTS
Entry	CD4	TNX-355	Biweekly antibody infusion	Tanox	Phase IIb	Antibody-based drug
Entry	CCR5	Vicriviroc	Oral – BID	Schering-Plough	Phase IIb; liver toxicity recently resulted in a decision to focus on resistant patients only	Limited to CCR5-dependent HIV strains
Entry	CCR5	Maraviroc	Oral – BID or QD	Pfizer	Phase IIb/III	Limited to CCR5-dependent HIV strains
Integration	Integrase enzyme	MK-0518	Oral – BID	Merck	Phase IIb	Potential for broad use in patients at all stages of the disease
Maturation	Capsid-SP1 processing	PA-457	Oral – QD	Panacos	Phase IIb anticipated to begin 2006	Potential for broad use in patients at all stages of the disease

** Based on public disclosures at scientific conferences, press releases or other published reports. May not be comprehensive*

*** In recent clinical trials*

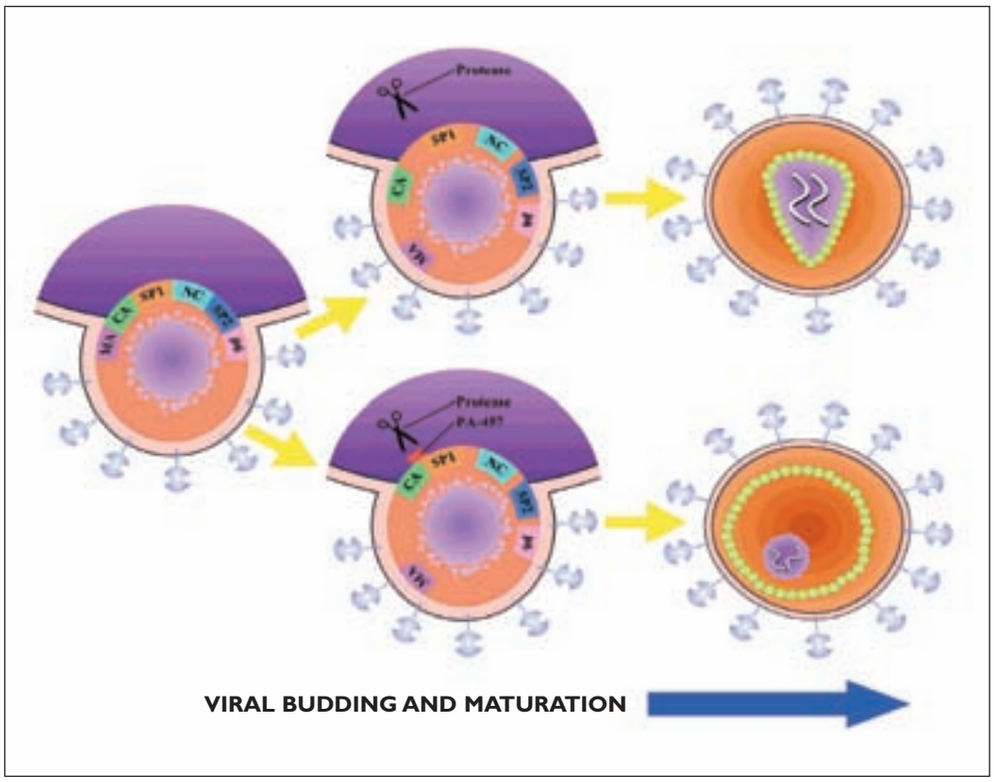

Figure 2
The HIV maturation process and its inhibition by PA-457: Maturation occurs as newly formed virus particles bud out of an infected human cell. The maturation process allows these virus particles to become infectious so that they can spread the infection around the body. Specifically, maturation involves the processing of viral core proteins including Capsid (CA) and Nucleocapsid (NC) and their condensation into a conical core containing the viral RNA genome (top right). PA-457 blocks HIV maturation by preventing the release of Capsid from a linker protein known as SP1. As a result, the virus cannot mature normally, it is has a defective core structure and is non-infectious (bottom right)

in these patients on long-term treatment[5]. Schering is continuing a Phase IIb study of vicriviroc in drug-resistant patients. Pfizer is still developing its CCR5 antagonist, maraviroc, for use in both naïve and treatment-experienced patients. Recently a case of severe hepatotoxicity was reported in a patient receiving maraviroc, but this individual was also simultaneously receiving several other drugs with reported hepatic toxicities, so the causality of this adverse event is unclear[6]. Other companies, including Takeda, also have small molecule CCR5 inhibitors at earlier stages of development. In addition to these small molecule drugs, Progenics Pharmaceuticals and Human Genome Sciences are developing anti-CCR5 monoclonal antibodies with proven *in vitro* anti-HIV activity. Both of these are currently in early phase clinical trials to demonstrate proof-of-concept as injectable therapeutics.

Because the CXCR4 receptor is found on many cell types and is required for normal immunological function, CXCR4 antagonists have the potential for greater mechanism-based toxicities than the CCR5 drugs. This has limited progress on CXCR4 inhibitors, although Anormed recently initiated Phase IIa testing of a small molecule oral CXCR4 antagonist, AMD-070. If successfully developed, this could open the opportunity to combine CXCR4 and CCR5 antagonists into a therapeutic cocktail with activity against all HIV strains regardless of co-receptor tropism.

One other target within entry is the fusion mechanism itself, as distinct from the receptor inhibitors discussed above. The peptide drug Fuzeon acts by inhibiting conformational changes in the viral gp41 protein that drive fusion of the viral and cell membranes. Theoretically it may be difficult to find small molecule drugs that act on exactly the same target as the Fuzeon peptide, although recently Panacos Pharmaceuticals and the New York Blood Center have separately reported the identification of compounds that block HIV fusion by inhibiting conformational changes in gp120 and gp41[7,8].

Integrase

The HIV integrase enzyme is a potential HIV drug target that has been the focus of considerable attention for the past 15 years. For most of this time HIV integrase inhibitors discovered in the laboratory had not moved far through clinical development for various reasons, including lack of suitable pharmaceutical properties or toxicity issues. Recently, however, Merck announced completion of a successful Phase IIa trial demonstrating proof-of-concept with its MK-0518 integrase inhibitor which is being

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Continued on page 48

Continued from page 47

advanced into Phase IIb testing[9]. This twice-daily oral drug showed potent anti-HIV activity and a good tolerability profile in the proof-of-concept study. Other companies, including Gilead in collaboration with Japan Tobacco, are also pursuing this target, albeit at an earlier stage. Their compound is currently in Phase I/II clinical testing.

Maturation

Maturation inhibition is the first validated new HIV drug target discovered for many years. PA-457, the first-in-class maturation inhibitor under development by Panacos Pharmaceuticals, was recently shown to have potent antiviral activity in a Phase IIa clinical study[10]. The discovery of maturation inhibition by Panacos and its collaborators was first published in 2003[11]. Maturation inhibition involves blocking the last step in infection, the processing of the HIV Gag protein that is required for the virus particle to become infectious. Acting at the same point in the viral life cycle as protease inhibitors, the target for maturation inhibitors is quite distinct as shown in **Figure 2**. The normal HIV maturation process involves the processing of a viral polyprotein called Gag into its separate core protein components, matrix (MA), capsid (CA), nucleocapsid (NC) and p6. This processing, which is carried out by the viral protease, also results in the release of two linker proteins, SP1 and SP2, and allows the core of the virus to condense normally.

PA-457 blocks one step in this processing cascade – the separation of capsid from SP1. It does this by interacting with the Gag substrate rather than the protease enzyme. Thus maturation inhibitors are a new class, distinct from any other approved drugs or drugs in development by other companies. As anticipated based on its novel mechanism of action, PA-457 has activity against all HIV strains resistant to approved drugs. Its other promising features include once daily oral dosing and a good tolerability profile in clinical studies completed to date. Furthermore, PA-457 is metabolised by a different pathway from most other approved or development stage HIV drugs, reducing the likelihood of significant drug-drug interactions when used in combination therapy, a major problem for many HIV inhibitors. In addition to PA-457, Panacos has a pipeline of second and third generation maturation inhibitors at earlier stages of development.

Novel treatment paradigms – what will be the role of the new generation drugs?

HIV therapy involves the use of several drugs in combination, making for very potent cocktails and reducing the potential for drug resistance to develop. First line therapy typically involves a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with an non-nucleoside RT inhibitor (NNRTI) or a protease inhibitor (PI). When resistance occurs, patients are switched on to alternative regimens. Because of extensive cross-resistance in the classes of drugs currently approved, the treatment options available become progressively more limited.

There is a clear need to develop new therapies to treat patients failing therapy due to resistance. Many of the new drugs discussed above may be first used in that setting, adding them to cocktails of currently approved drugs. The availability of multiple novel agents targeting different steps of the HIV life cycle will improve the chances of achieving potent viral suppression in patients with multi-drug resistant virus, similar to what is now achieved with first-line therapy. In addition, the new treatments may be able to unseat some of the first line regimens if they have suitable properties, including once- or twice-daily dosing, good potency and reduced toxicities or drug interactions. It may even be possible to develop fixed-dose combinations of the new and older therapies to improve compliance and efficacy in first and second line therapy.

In summary, the development of these new HIV inhibitors, alone or in combination, could dramatically improve the outlook for HIV-infected patients within the next several years. DDW

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