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Review

Novel targets for HIV therapy

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ABSTRACT

There are currently 25 drugs belonging to 6 different inhibitor classes approved for the treatment of human immunodeficiency virus (HIV) infection. However, new anti-HIV agents are still needed to confront the emergence of drug resistance and various adverse effects associated with long-term use of antiretroviral therapy. The 21st International Conference on Antiviral Research, held in April 2008 in Montreal, Canada, therefore featured a special session focused on novel targets for HIV therapy. The session included presentations by world-renowned experts in HIV virology and covered a diverse array of potential targets for the development of new classes of HIV therapies. This review contains concise summaries of discussed topics that included Vif-APOBEC3G, LEDGF/p75, TRIM 5α, virus assembly and maturation, and Vpu. The described viral and host factors represent some of the most noted examples of recent scientific breakthroughs that are opening unexplored avenues to novel anti-HIV target discovery and validation, and should feed the antiretroviral drug development pipeline in the near future.

Contents

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1. Introduction (José A. Esté)

Twenty-five years after the first isolation of the human immunodeficiency virus (HIV), antiretroviral therapy has moved from fast-track licensing of the first effective drug against HIV, zidovudine (AZT) in 1987 to combination therapy with 25 approved drugs belonging to 6 different classes (Table 1). As disease progression is associated with higher HIV RNA levels in blood (viral load), an important objective of antiretroviral therapy is to reduce viral loads below the limit of detection of approved assays. All but one anti-HIV drugs target viral enzymes and proteins that are indispensable for the virus to complete its replication cycle (Fig. 1), but none alone is able to achieve an undetectable viral load for sustained periods of time. Experience has shown that combinations of three or more active drugs, including at least two classes of antiretrovirals, may achieve maximal suppression of plasma viral load and delay the selection of drug resistance mutations.

Table 1
Approved antiretroviral drugs for the treatment of HIV infection

	Approval date
Entry inhibitors	
Maraviroc (UK-427,857, Selzentry®)	06 August 2007
Fusion inhibitors	
Enfuvirtide (T20, Fuzeon®)	13 March 2003
Integrase inhibitors	
Raltegravir (MK-0518, Isentress®)	12 October 2007
Reverse transcriptase inhibitors	
Nucleoside/nucleotide analogues	
Abacavir (ABC, Ziagen®)	17 December 1998
Didanonise (ddI, Videx®)	09 October 1991
Emtricitabine (FTC, Emtriva®)	02 July 2003
Stavudine (d4T, Zerit®)	24 June 1994
Lamivudine (3TC, Epivir®)	17 November 1995
Tenofovir (DF, Viread®)	26 October 2001
Zalcitabine (ddC, Hivid®)	19 June 1992
Zidovudine (AZT, Retrovir®)	19 March 1987
Non-nucleoside inhibitors	
Delavirdine (DLV, Rescriptor®)	4 April 1997
Efavirenz (EFV, Sustiva®)	17 September 1998
Etravirine (TMC125, Intelence®)	18 January 2008
Nevirapine (NVP, Viramune®)	21 June 1996
Protease inhibitors	
Amprenavir (AMP, Agenerase®)	15 April 1999
Atazanavir (ATZ, Reyataz®)	20 June 2003
Darunavir (TMC-114, Prezista®)	23 June 2006
Fosamprenavir (GW-433908, Lexiva®)	20 October 2003
Indinavir (IDV, Crixivan®)	13 March 1996
Lopinavir (ABT-378, Kaletra® (trade name in combination with RTV))	15 September 2000
Nelfinavir (NFV, Viracept®)	14 March 1997
Ritonavir (RTV, Norvir®)	01 March 1996
Saquinavir (SQV, Fortovase®, Invirase®)	07 November 1997
Tipranavir (TPV, Aptivus®)	22 June 2005

A number of factors may influence the safety and efficacy of antiretroviral therapy in individual patients, including non-adherence to therapy, adverse drug reactions, drug–drug interactions, and development of drug resistance. Long-term management of HIV patients is complex and multifactorial; with time, potent drugs may fail because chronic adverse effects may outweigh the initial benefits. With patients failing current antiretroviral drug regimens, the emergence and transmission of drug-resistant variants increase and become a public-health concern. It is therefore essential that new antiretroviral agents become available.

Antiviral drug development has not waned. On the contrary, the pharmaceutical industry has shown a continued interest in further exploiting existing drug targets, reaching proof of concept for new ones and initiating new drug development programs. In recent years, we have witnessed the advent of two HIV-1 protease inhibitors with improved resistance profiles (tipranavir and darunavir) (Clotet et al., 2007; Hicks et al., 2006), and a new non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (TMC125) (Lazzarin et al., 2007) with antiviral activity in treatment-experienced patients showing resistance to existing NNRTIs. Furthermore, two additional drugs have been approved, each representing a new class of antiretroviral inhibitors: raltegravir, targeting the viral integrase enzyme (Grinsztejn et al., 2007) and maraviroc, targeting the cellular HIV-1 entry cofactor CCR5 (Fatkenheuer et al., 2005).

Complementary to industry, academic research labs are providing an overwhelming amount of new data. Basic research aimed at understanding the biology and pathogenesis of HIV is also revealing new targets for antiretroviral therapy. Protein–protein interaction technology and RNA interference gain wider use to identify host proteins required for HIV-1 infection (Brass et al., 2008) and a high through-put genomic analysis is now used to understand host genetic control of virus infections such as HIV-1 (Fellay et al., 2007).

G-protein coupled receptors (GPCR) are preferred pharmacological targets for many diseases. Moreover, the discovery of chemokine GPCR, not as mere cofactors, but primordial virus receptors, and the observation that host defects in CCR5 expression