Peptide Nucleic Acids as Epigenetic Inhibitors of HIV-1

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Introduction

Twenty years after a handful of AIDS cases were first reported in the U.S., today is faced with a global AIDS pandemic, one of the greatest challenges in recent medical history. AIDS is changing the human landscape in many developing countries, where the current highly active anti-retroviral (HAART) treatment is still out of reach for most HIV-1-infected people. Organized distribution of preventive HIV vaccines would be the most effective strategy to stop the spread of HIV-1 infection, especially in these resource-deprived nations. However, despite a tremendous progress in our understanding of HIV-1 and AIDS pathogenesis over the last two decades, a single candidate vaccine has yet to emerge with promising results. Even if an effective vaccine should appear, therapy for people already infected with HIV will continue to be important.

In the mid-1990s, as a result of widespread use of potent combination chemotherapeutics (HAART), a dramatic reduction in the incidence of AIDS and its-related death was reported in the U.S. and other developed countries for the first time in the history of AIDS epidemic. The decline clearly indicated that the disease progression could be delayed if HIV-1 infection was adequately controlled by effective antiretroviral therapy, and invited optimism that HIV disease would become a manageable chronic human disease where HAART was made available. However, an initial steep drop in the incidence of AIDS did not necessarily translate to the conquest of the AIDS epidemic. Rather, a number of alarming signs have begun to surface in recent years. Despite heightened public awareness and systematic prevention activities, HIV-1 continues to spread, especially among minorities and young adults, who may disregard the importance of HIV prevention, falsely believing HIV-1 infection is no longer a life-threatening disease. In reality, the effectiveness of HAART in decreasing viremia is only partial or transient in some individuals, due to emergence of drug-resistant HIV-1 strains and/or difficulty in adhering to complex treatment regimens. The prevalence of multi-drug resistant HIV-1 strains (MDR-HIV) is steadily rising, including among those who are newly infected. The increasing trend in the transmission of MDR-HIV poses a serious threat to the future of epidemic control in the HAART-experienced countries, because at present there are very few alternative agents for MDR-HIV infection.

In the global fight against AIDS, the international community is coming together to gather efforts and resources, some of which will be used to distribute the currently available HAART drugs to as many AIDS-stricken patients as possible worldwide. If successfully implemented, this endeavor will undoubtedly prolong many lives and help reduce the rate of new transmission. Nevertheless, it will only serve as a temporary measure to slow the epidemic for several years, unless we can overcome the limitations of the current antiretroviral strategy. Especially at
HIV-1 Life Cycle and Potential Molecular Targets

HIV-1 is an RNA virus that belongs to the lentivirus genus of the *Retroviridae* family. The virion consists of membranous lipid envelope, gp120/gp41, which surrounds the cone-shaped core. The core, or nucleocapsid, of each mature virion is composed of viral gag proteins that encapsulate viral genome, a 9.2 kb homodimer of single-stranded positive RNA, plus viral enzymes such as reverse transcriptase, integrase, and protease. The principal target cells of HIV-1 are CD4+T lymphocytes and macrophages. The first step of the viral replication cycle (Fig. 1) begins with the attachment of viral envelope protein, gp120, to the CD4 molecule and chemokine receptors, which serve as a viral coreceptor, followed by the uncoating of viral RNA within the cytoplasm. The viral RNA is reverse-transcribed into double-stranded DNA flanked by long terminal repeats at both ends. Following viral DNA synthesis, some of the HIV-1 DNA copies are integrated into the host genome and remain indefinitely as a part of the genome. The integrated viral DNA (provirus) is then transcribed by the host machinery to generate spliced and unspliced mRNAs. Spliced mRNA species encode viral regulatory and accessory proteins, while unspliced mRNA is translated to viral structural precursor polyproteins or gives rise to viral genomic RNA. The structural protein precursors are then transported to the host plasma membrane, where final steps of virion assembly, precursor processing and viral budding take place.