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Development of peptide inhibitors of HIV transmission

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ABSTRACT

Treatment of HIV has long faced the challenge of high mutation rates leading to rapid development of resistance, with ongoing need to develop new methods to effectively fight the infection. Traditionally, early HIV medications were designed to inhibit RNA replication and protein production through small molecular drugs. Peptide based therapeutics are a versatile, promising field in HIV therapy, which continues to develop as we expand our understanding of key protein-protein interactions that occur in HIV replication and infection. This review begins with an introduction to HIV, followed by the biological basis of disease, current clinical management of the disease, therapeutics on the market, and finally potential avenues for improved drug development.

1. Introduction

The human immunodeficiency virus (HIV) is one of the hardest to control, medically manage, and lethal infectious diseases. HIV is a major public health problem globally and domestically. The World Health Organization estimates 37 million people living with HIV or acquired immunodeficiency syndrome (AIDS) worldwide in 2014 with Sub-Saharan Africa accounting for almost 70% of new global HIV infections [1]. About 44,000 people become infected with HIV each year in the United States [2], 350,000 in Asia, 25,000 in the Middle East & North Africa, 94,000 in Latin America, 88,000 in West and Central Europe and North America, 110,000 in Eastern Europe and Central Asia, and 12,000 in the Caribbean [3]. The CDC estimates about 1.2 million people in the United States were living with HIV at the end of 2012 [4]. Of those people, about 12.8% do not know they are infected [5]. The number of new infections continues to rise, particularly in women. HIV treatment is costly. Estimated cost per patient per year in 2010 was $13,251 [6] in the United States, impeding HIV treatment in low-resource settings [7]. Therefore, HIV is still one of the hottest topics in basic science, clinical, and public health research.

Given the magnitude of this pandemic, numerous global efforts have been gathered to fund research needed for HIV prevention and treatment. Over $15 billion has been devoted from 2000 to 2014 [8]. The cumulative HIV/AIDS treatment costs from 1996 to 2010 are estimated to be $242 billion. FY2016 US funding for domestic HIV research is $2.8 billion [9]. North America provides the vast majority of HIV prevention R&D investment (90.9%) [8].

Peptide therapeutics are composed of short amino acid sequences that target protein-protein interactions, such as the critical interaction between the host cell receptors and HIV glycoproteins required for viral entry into host cells. Peptide based therapies offer

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; FY, fiscal year; R&D, research and development; FDA, US Food and Drug Administration; HCV, hepatitis C Virus; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NRTI, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitors; INSTI, Integrase strand transfer inhibitors; RT, reverse transcriptase; LEDGF, lens epithelium-derived growth factor.

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several advantages over small molecule based therapies, including versatility, high potency, and lower side effects [10]. Peptide/Protein based therapeutics can bind a domain more specifically and effectively than small molecule drugs, as it has larger surface area and stronger interaction between the target domain and the drug [11]. It also has fewer medication interactions and toxicity, as it has more specific binding to target domains and is metabolized into nontoxic amino acids [12]. Peptide therapeutics are less likely to encounter drug resistance, as it requires much more drastic changes in the viral structure for the virus to develop resistance against a peptide. However, peptide based therapeutics face challenges, such as poor in vivo stability and difficulty of forming oral formulations [13]. Currently, two peptide based therapeutics are being used for HIV treatment: Enfuvirtide, a fusion inhibitor that binds and blocks conformational change in gp41 [14], and Maraviroc, an entry inhibitor which blocks binding of gp120 to CCR5 [15], with others under investigation for FDA approval.

Treatment of HIV has advanced significantly over the past 3 decades. This review will briefly discuss the etiology of HIV [16], medical management [17], and approved drugs commonly used [18]. An interesting avenue that has gained much traction for HIV treatment is the development of HIV virion inhibitor peptides. The subsequent focus of this review will be to discuss the fundamental facets of peptide based therapeutics, specifically those currently in research. Finally, we provide insight into how these and other novel therapeutics may change the way we treat HIV. Overall, to be an *effective* drug in the treatment of HIV the following are required: 1) Cost-effective synthesis, 2) high potency with minimal side effects, 3) easy administration to enhance patient compliance, and 4) educational outreach for disease management and prevention.

2. The biological basis of HIV

2.1. Basics of HIV

The origin of HIV has not been clearly understood [19], with wide speculation that includes its evolution from the simian immunodeficiency virus [20]. HIV is the virus that can lead to AIDS. HIV infects and destroys CD4 cells (T cells), and undermines the human immune system in AIDS. In general, HIV cannot be cured at present and therefore requires life-long treatment. When not treated, undermined immunity surrenders to co-infections, such as HCV (hepatitis C Virus) [21], tuberculosis [22], other sexually transmitted infections [23], cytomegalovirus [24], and papillomavirus [25]. It can also result in age associated morbidities, such as myocardial infection and cancer [26], and eventually leading to significant patient mortality.

HIV is highly heterogeneous, mutates quickly, and can be latent for over 10 years, increasing the difficulty in prevention and treatment [27]. Although uncommon, there has been at least one report of a long-term control for HIV reported using CCR5 Delta32/Delta32 stem cell transplantation that is resistant to HIV-1 [28,29]. A number of research efforts are ongoing to find a cure for HIV [30,31]. Efforts have focused on finding treatment and prevention methods through vaccine and other methods of prophylaxis, including anti-retroviral drugs like Tenofovir in topical applications such as vagina gel and ring [32–34], in oral pre-exposure prophylaxis [35], and in implants [36]. Oral pre-exposure prophylaxis has shown effective protection for men who have sex with men by reducing HIV incidence by 44% [37], but not for heterosexual women, potentially due to low pill adherence or low drug concentrations at the genital tract [38]. Preclinical studies have also shown significant reduction of HIV infection by topical pre-exposure prophylaxis [39].

2.2. Clinical treatment and procedures

Antiretroviral therapy (ART) is the treatment for HIV infection. Multidrug regimens are used to reduce the progression of disease to AIDS, occurrence of opportunistic infections, hospitalizations, and death. There are currently more than 25 antiretroviral medications available in 5 drug categories (discussed below). Although a small portion of these are recommended for initial therapy, continuous assessment of the patient for adverse effects and toxicities as well as adherence guides medication choice. Multiple comparative clinical trials have shown that combination therapy consisting of 2 nucleoside reverse transcriptase inhibitors and a third agent from another class is the most effective treatment. The other classes used in initial treatment are non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors [40].

2.3. Clinical presentation of HIV

HIV infection can present early as a mononucleosis-like illness; however, many affected individuals are asymptomatic. Estimates for those who are asymptomatic with HIV are between 10 and 60%, but it is hard to estimate because most diagnoses are made after a symptom has led to a work up. Those who have an acute infection, also known as acute retrovirus syndrome, develop symptoms two to four weeks after infection. However, incubation of up to 10 months has been reported [41]. Symptoms of acute HIV infection include fever, lymphadenopathy, sore throat, rash, myalgia, arthralgia, and headache. None of these symptoms are specific, but the presence of these features for an extended duration or with associated mucocutaneous ulcers is suggestive. Many patients experience nausea, diarrhea, anorexia, and weight loss. Patients can present with aseptic meningitis and rarely self-limited encephalopathy. The peripheral nervous system can also be affected. Opportunistic infections (OIs) usually occur in the later course of the infection and rarely occur during early infection with the transient lymphopenia [42]. Oral and esophageal candidiases are the most commonly occurring OIs. Other OIs in early HIV include cytomegalovirus (CMV) colitis, proctitis, hepatitis, pneumocystis jiroveci pneumonia, and cryptosporidiosis.

The chronic period of HIV infection is the time from acute infection to a CD4 count of <200, and it usually lasts 8–10 years. AIDS is diagnosed when CD4 reaches <200 cells/μL or with the presence of an AIDS defining illness, which includes OIs, recurrent infections, lymphoma of brain, and invasive cervical cancer [43]. Mucocutaneous candidiasis, oral hairy leukoplakia, seborrheic dermatitis, and herpetic infections occur with greater frequency when the CD4 cell count is < 200 cells/μL. Eosinophilic folliculitis, xerosis, prurigo nodularis, molluscum contagiosum, bacillary angiomatosis, exacerbation of psoriasis, and severe scabies are associated with AIDS. Anemia, leukopenia, lymphopenia, or thrombocytopenia is present in 40% of those with CD4 < 200 cells/μL. Polyclonal hyperglobulinemia is another hematologic aberration.

2.4. Severity of HIV and associated diseases

OIs usually occur at CD4 levels <200 cells/μL and less often at levels above that, with approximately 10% of patients developing an AIDS-defining diagnosis with a CD4 count ≥200 cells/μL [44]. Disseminated M. avium infection and CMV infections occur predominantly with a CD4 cell count <50 cells/μL. In the absence of antiretroviral therapy (ART), the median time to an AIDS-defining condition in someone with a CD4 cell count < 200 cells/μL is estimated at 12–18 months [45].