Humanized Peptides for the Treatment of AIDS

Overview

Drug Name	PepTRx anti-HIV
Description	Human immunodeficiency virus (HIV) is a virus that attacks and weakens the immune system, causing acquired immunodeficiency syndrome (AIDS). Most drugs used to treat AIDS inhibit one or more of the enzymes involved in HIV replication. But these enzyme inhibitors may develop resistance over time, increasing enzyme tolerance and forcing patients to use larger drug doses. With the current HIV pandemic causing a global health and economic crisis, PepTRx anti-HIV humanized peptides are developed with the potential to be an effective therapeutic agent for the prevention or treatment of AIDS.
Target	HIV structural and non-structural proteins
Drug Modality	Humanized peptide
Indication	AIDS
Product Category	Immunotherapy
Mechanism of Action	Activating cellular immunity to destroy HIV infected cells and eliminate the virus
Status	Preclinical
Patent	NA

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PepTRx anti-HIV. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

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Multiple Regional HIV Structural and Non-structural Proteins: Asp-Nef-Tat-Vpu-Gag

Structural proteins of HIV make up the outer shell and viral scaffold. In addition to structural proteins, the HIV genome encodes non-structural proteins, including regulatory proteins and accessory proteins. Both structural and non-structural of proteins are pathogenic components that attack host cells. The proteins exposed on the surface of the HIV envelope enable the entry of the virus particles into a host cell through binding to receptors on the host cell.

The genome of HIV consists of at least seven structural landmarks (LTR, TAR, RRE, PE, SLIP, CRS, and INS) and nine genes (GAG, POL, ENV, TAT, REV, NEF, VIF, VPR, and VPU). The tenth gene ASP has been discovered, which encodes the tenth protein. GAG, POL, and ENV genes contain the information required to produce structural proteins for new viral particles. ENV encodes a protein called gp160, which is cleaved by cellular proteases to form gp120 and gp41. TAT, REV, NEF, VIF, VPR, and VPU (an additional VPX in HIV-2) genes are regulatory genes for proteins that control the ability of HIV to infect cells, produce new copies of the virus, or cause disease.

The ends of each strand of HIV sense RNA contains an RNA sequence called a long terminal repeat (LTR). The LTR region acts as a switch to control the production of new viruses and can be triggered by proteins of HIV or host cells. The TAT protein is transcriptional transactivator for the LTR promoter, acting by binding to TAR RNA elements. The TAR can be processed into microRNAs that regulate ERCC1 and IER3 apoptosis genes. The REV protein participates in shuttling RNAs from the nucleus and cytoplasm by binding to RRE RNA elements. The VIF protein blocks the action of APOBEC3G protein. The VPR protein inhibits cell division at G2/M. The NEF protein downregulates CD4 (the main viral receptor) and MHC-I and II molecules. The NEF protein also interacts with the SH3 domain. The VPU protein affects the release of new viral particles from infected cells.

Drug Modality

Humanized Peptides

Based on an AI peptide design platform, dozens of peptides with strong CD4+ T-cell activation ability have been screened to identify more effective and specific viral peptide CD4+ T-cell activators. Several Asp-Nef-Tat-Pup-Gag peptides are found to effectively activate CD4+ T-cells and inhibit HIV virus infection. Targeting MHC-II small molecules can increase the activation of CD4+ T-cells by more than 2000 times. Humanized peptides

are being developed for the treatment of AIDS, which activates cellular immunity to destroy HIV infected cells and eliminate the virus.

Indication

AIDS

HIV is a retrovirus belonging to the Retroviridae family, lentivirus genus, which is the cause of the acquired immune deficiency syndrome (AIDS). HIV-1 and HIV-2 are two strains of the virus that cause human disease. These strains are similar in their genetic structure and modes of transmission, but their DNA sequences differ significantly. HIV-1 is far more prevalent and widespread, and HIV-2 is considered less virulent, progressing to AIDS less frequently and associated with lower mortality.

AIDS cause a gradual deterioration of the immune system, leading to opportunistic infections and ultimately death. An HIV-infected person with access to modern therapeutics can expect to live to old age. The global prevalence of HIV continues to increase as more effective new drug therapies enable patients to live longer. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there were approximately 38.4 million adults and children living with HIV/AIDS worldwide in 2021. An estimated 1.3 million new HIV infections occurred in 2022.

A growing number of antiretroviral agents and combinations are currently on the market. Most agents for the treatment of AIDS are enzymes inhibitors that inhibit actions of one or more enzymes involved in HIV replication. These inhibitors may develop resistance, increasing enzyme tolerance and forcing patients to take higher doses. In addition, once these inhibitors are discontinued, the virus immediately becomes more active, posing a great life-threatening risk.

Mechanism of Action

Activating CD4+ T cells to Form Cytotoxic T lymphocytes

MHC-II targeted humanized HIV peptides can selectively enter CD4+ T lymphocytes, because CD4+ T

lymphocytes bind to major histocompatibility complex (MHC) molecules. CD4+ T lymphocytes recognize viral peptides presented on MHC class II molecules, thereby activating CD4+ T lymphocyte subsets Th1 polarized cells, which are responsible for controlling intracellular pathogens such as viruses and some bacteria. IL-12 and IFN-γ are important cytokines involved in Th1 response, and intracellular transcription factors T-bet and STAT-4 are crucial for the differentiation and function of Th1 cells. After CD4+ T lymphocytes are activated, CD8+ cytotoxic T lymphocytes can then be activated, which release various granzymes and perforins. Perforin forms a pore on the membrane of the target cell and this pore allows granzymes, including granzymes A, B, H, K, and M, to enter infected or malignant cells. Granzymes are proteases that cleave proteins within cells, shutting down the production of viral proteins and ultimately leading to apoptosis of target cells.

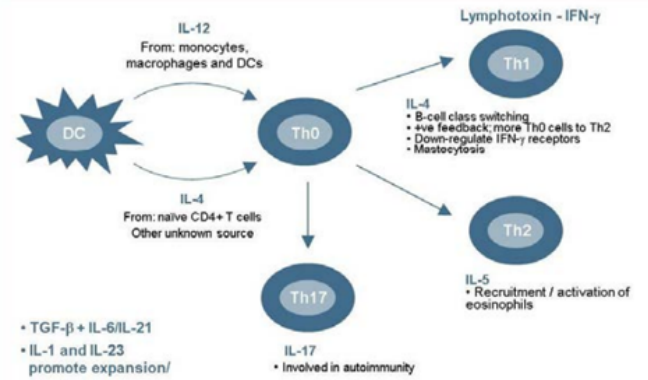

Figure 1. Different interleukins involved in Helper T cell differentiation

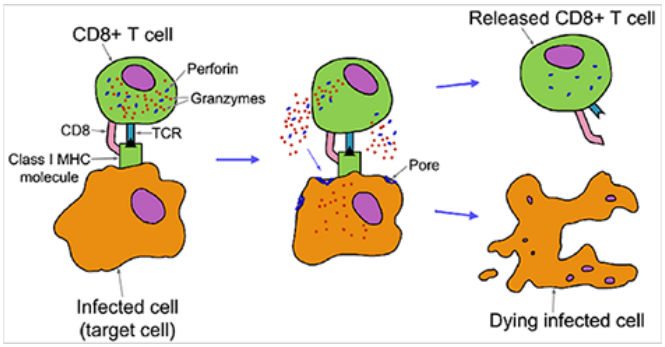

Figure 2. Interaction between CTL and its target cells

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Status

The Status of PepTRx anti-HIV

Preclinical studies have been not completed, but the characteristics of each humanized peptide have been analyzed both individually and combined. The IIT studies found that the combined solution has no local effects and no systematic effects.

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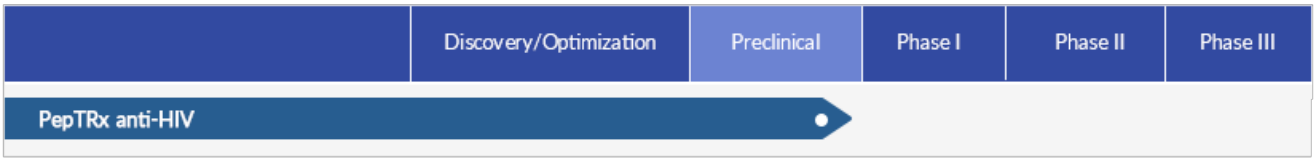

Date

Properties and Effects of PepTRx anti-HIV humanized peptides

Name	ASP102	Nef77	Tat40	VIF147	VPR57	Vpu3	Gag298	Gag16	GP248
Target	1*0701 1*0101 1*1501	H2-Ad	H2-Ed H2-Ek	1*0401 H2-Ek 1*0101 H2-Ed	1*0301 1*0401 1*0701	1*0101 H2-Ad	H2-Ad 1*0101	H2-Ed H2-Ek	1*0101 1*0401 1*0701 1*0301
Immunogenicity	0.6636	NON	1.2513	0.7666	0.5133	0.5750	0.5997	0.8404	NON
Allergenicity	No	No	No	No	No	No	No	No	No
Toxicity	No	No	No	No	No	No	No	No	No
Adverse reactions (local/systemic)	No/No	No/No	No/No	No/No	No/No	No/No	No/No	No/No	No/No
Side-effect	No	No	No	No	No	No	No	No	No

Effect of PepTRx anti-HIV Peptides on PBMC Activation In Vitro

Name	ASP102	Nef77	Tat40	VIF147	VPR57	Vpu3	Gag298	Gag16	GP248
Base	-0.0024	-0.0213	0.2154	-0.5644	0.1799	0.6559	0.0325	0.5286	0.1528
humanized	2.2458	2.6032	2.9019	2.1101	2.5252	2.4620	2.2462	2.7426	3.0819
Increased	×22482	×26245	×13.5	×26745	×14	×3.7	×65	×5	×20

Anti-HIV-1 Activity of the Mixed Peptides

CD4+ cells were treated with released supernatant from PBMCs that treated with or without the mixed peptides

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at the times of dilution for 3 h, and were then infected with HIV-1. Cell lysates were collected and quantified for HIV-1 RNA by RT-PCR. The result showed that the mixed peptides significantly inhibited the viral yield.

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