KÜR-2017

Dr. Birgül Mete
İ.Ü. Cerrahpaşa Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Kürde Hedeflenen Temel Prensipler

- ✓ **Viral rezervuarın eradikasyonu**

  aktivasyon

  eradikasyon

- ✓ **İmmünoterapi**

  konağın bağışıklık sistemini HIV'e karşı güçlendirmek

- ✓ **Gen terapileri**

  CD4 + T hücrelerini virüse dirençli hale getirebilmek

Viral Rezervuarın Eradikasyonu

Kür için en büyük engel latent rezervuar

CD4+ T hücreleri
monosit/makrofaj
mikroglia
GİS- ilişkili lenfoid doku makrofajları
dendritik hücreler

Latent hücre

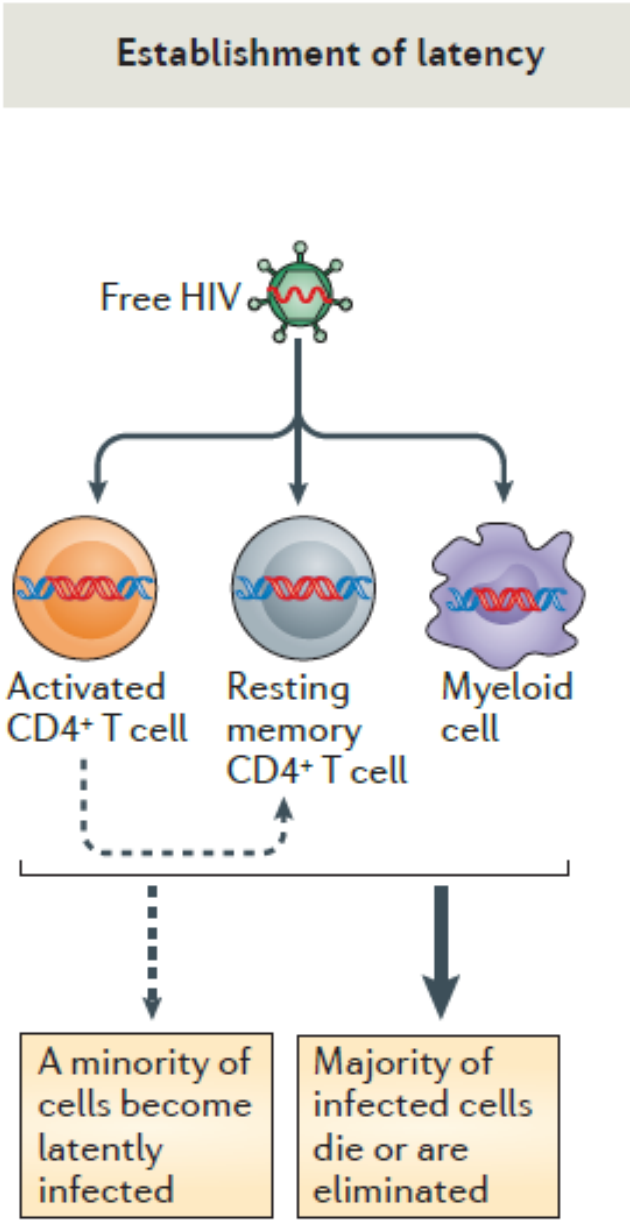
⇩

Replikasyon yeteneği olan
stabil provirüs taşır
Transkripsiyon aşamasında
sesiz
(viral transkript ya da viriyon üretimi yok)

Hücresel uyarı

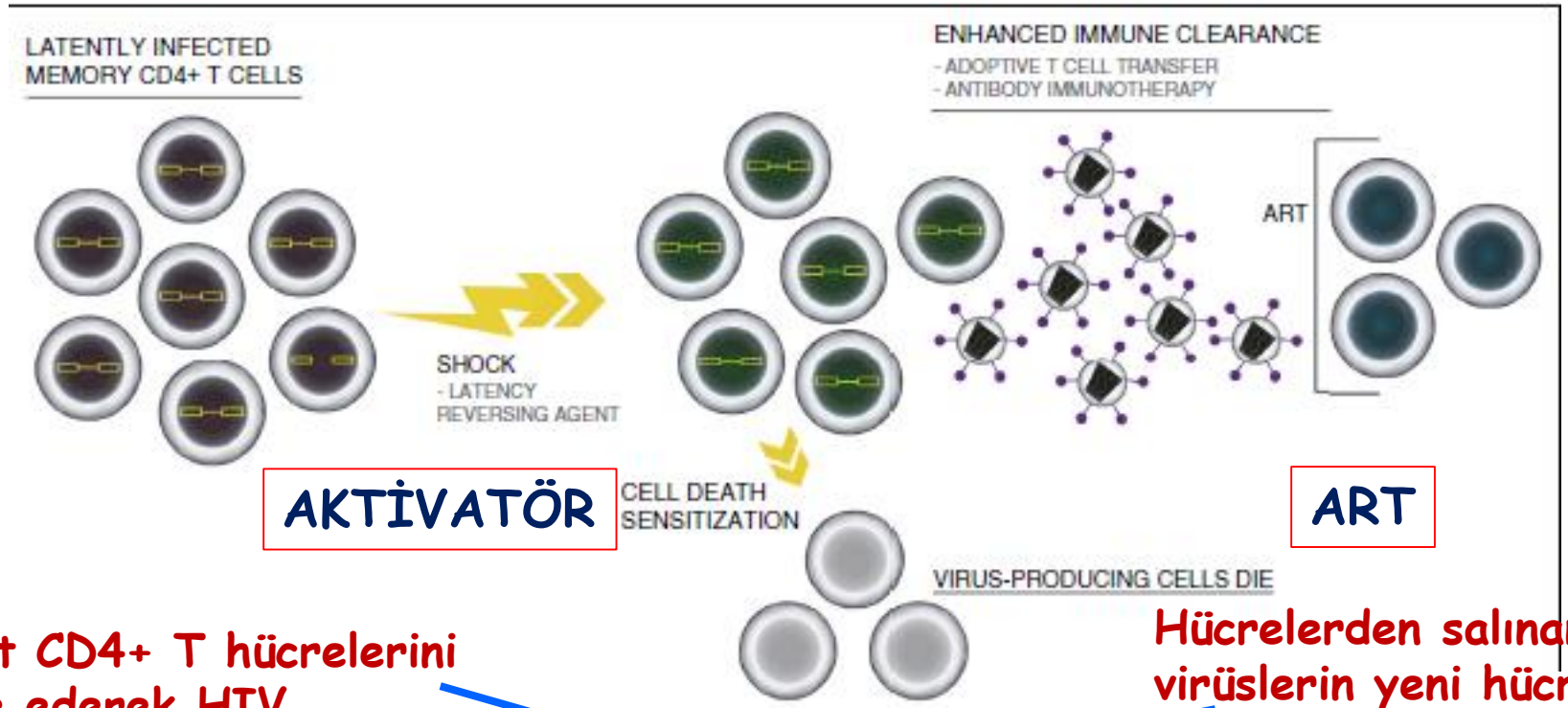
⇩

Viriyon üretimi



Towards an HIV cure: a global scientific strategy.
Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Kumar A, et al. Clin Epigenetics 2015 Sep 24;7(1):103.

Viral rezervuarın eradikasyonu --şok et ve öldür--



Latent CD4+ T hücrelerini aktive ederek HIV ekspresyonunu sağlamak

~~Virüs tetikli sitopatik etki ve/veya konak bağışıklık sistemi etkisiyle hücrelerin ölümü~~

Hücrelerden salınan virüslerin yeni hücreleri enfekte etmesinin engellenmesi

Kimata JT. Challenges and strategies for the eradication of the HIV reservoir . Current Opinion in Immunology 2016, 42:65–70.
Chun TW, et al.Nat Immunol 2015 Jun;16(6):584-9

İmmünoterapi

İmmünoterapi

- ✓**Latent rezervuarı eradike edecek ya da baskılayacak terapötik aşılar**

  Anti-HIV immünitesinin işlev ve yaygınlığını arttıracak aşılar

- ✓**Pasif bağışıklama**

  Nötralizan antikorlar

Mylvaganam GH, et al. Curr Opin Immunol. 2015 Aug;35:1-8.

NEWS RELEASES

Wednesday, February 15, 2017

NIH research helps explain how antibody treatment led to sustained remission of HIV-like virus

Scientists at the National Institutes of Health have found that the presence of the protein alpha-4 beta-7 integrin on the surface of HIV and its monkey equivalent — simian immunodeficiency virus, or SIV — may help explain why an antibody protected monkeys from SIV in previous experiments.

"...our team found that anti-alpha-4 beta-7 antibody binds not only to cells but also to HIV and SIV."

Institute/Center

National Institute of Allergy and Infectious Diseases (NIAID)

Contact

Laura S. Leifman
301-402-1663

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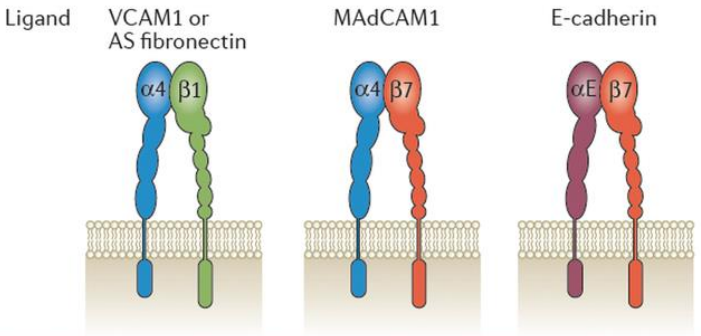
- ✓ **alpha-4 beta-7 integrin** immün sistem hücreleri üzerinde yoğun olarak bulunan bir reseptör
- ✓ HIV ve SIV bu reseptörleri taşıyan hücreleri enfekte ediyor.



Natalizumab	Yes	Yes	No	Yes
Vedolizumab	No	Yes	No	Not observed
Etrolizumab	No	Yes	Yes	Unknown

Nature Reviews | Drug Discovery

Fauci ve ark.'nın 2014-2016 yılları arasında laboratuvarlarında yürüttükleri çalışma sonuçları:

alpha-4 beta-7 integrine karşı laboratuvar ortamında oluşturulan antikorlar

- ✓ SIV'in enfekte olmayan maymunlara bulaşını azaltıyor
- ✓ enfekte maymunlarda SIV remisyonuna yol açıyor

HIV ve SIV yüzeyinde de alpha-4 beta-7 integrin mevcut mu??

- ✓ HIV ve SIV konak hücrelerden tomurcuklanarak salınırken alpha-4 beta-7 integrinin yoğun olduğu bölgeden ayrıldığı için bu reseptörleri de zarf yüzeyine alıyor
- ✓ HIV ve SIV yüzeyinde yer alan protein alpha-4 beta-7 integrin eşdeğer

18 rhesus makak maymunun SIV ile enfeksiyonu

5 hafta

ART (plan: 90 gün)

9 hafta

9 hafta

11 maymun
23 hafta boyunca
3 haftada 1 kez alpha-4 beta-7 integrin antikor infüzyonu

7 maymun
23 hafta boyunca
3 haftada bir kez **plasebo antikor** infüzyonu

32 haftanın sonunda tüm tedaviler kesildi.

3 maymunda antikor gelişimi
8 maymunda ART kesildikten sonra 23 ay boyunca SIV kan ve GİS'te saptanamaz düzeyde

ART kesildikten
2 ay sonra viral rebound

Scientists at NIH and Emory | CT Vedolizumab (Anti-alpha4bet

https://clinicaltrials.gov/ct2/show/NCT02788175

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Example: "Heart attack" AND "Los Angeles"

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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

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Text Size

Vedolizumab (Anti-alpha4beta7) in Subjects With HIV Infection Undergoing Analytical Treatment Interruption

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 1, 2016 by National Institutes of Health Clinical Center (CC)

Sponsor:
National Institute of Allergy and Infectious Diseases (NIAID)

Information provided by (Responsible Party):
National Institutes of Health Clinical Center (CC) (National Institute of Allergy and Infectious Diseases (NIAID))

ClinicalTrials.gov Identifier:
NCT02788175

First received: May 28, 2016
Last updated: January 24, 2017
Last verified: December 1, 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Background:

In most people infected with human immunodeficiency virus (HIV), their immune system cannot control HIV infection. They need drugs called combination antiretroviral therapy (cART) to control the HIV. When people stop cART treatment, their immune system cannot control the infection again. They can also become resistant to cART and have lasting side effects. Researchers want to test if the drug vedolizumab is effective at

Gen terapileri

Gen terapileri

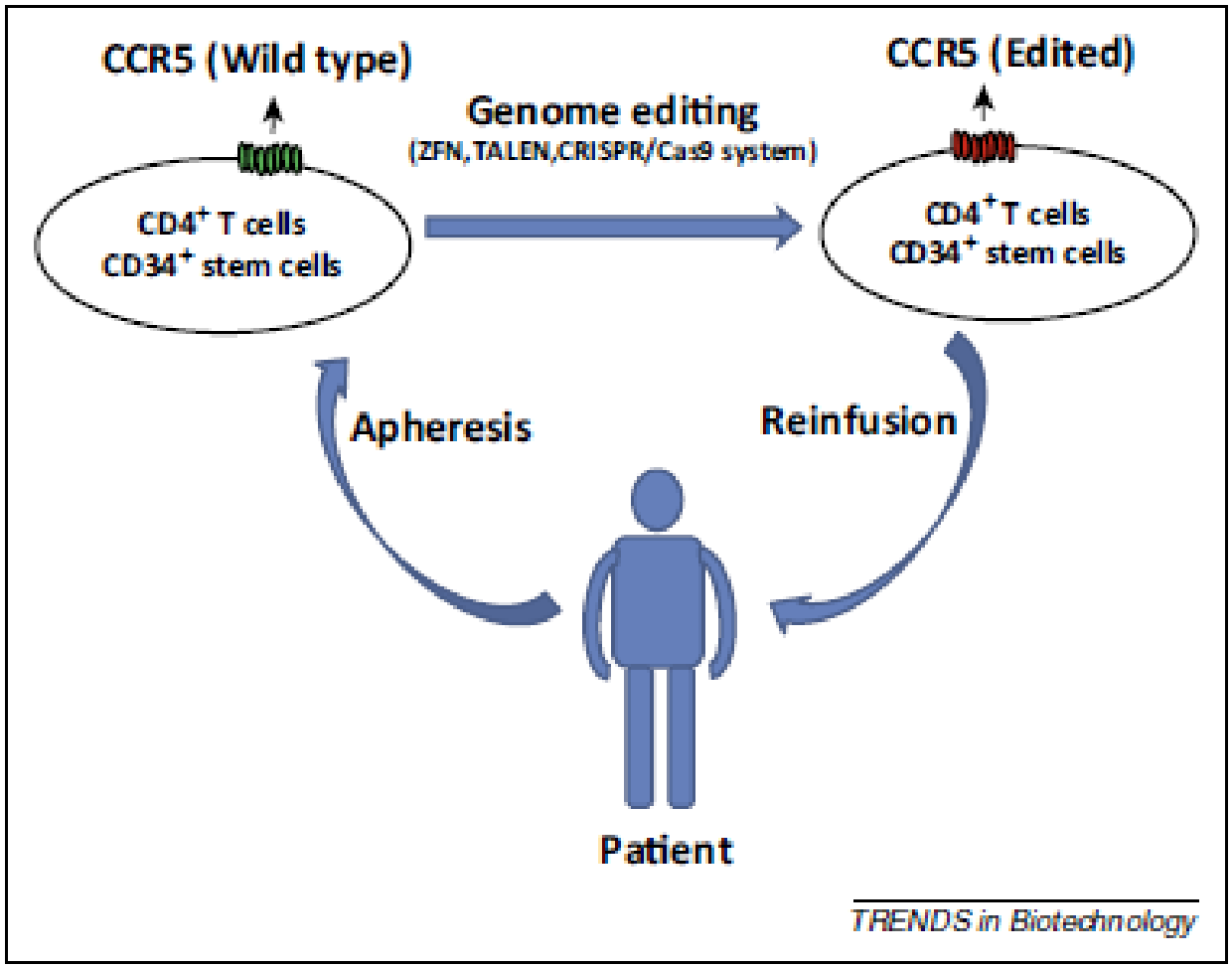
- ✓**Enfeksiyon ilişkili özgül genleri modifiye ederek hücreleri HIV'e dirençli hale getirmek**

  CCR5-defektif hematopoetik hücrelerle repopülasyon sağlamak (CXCR4 kullanan düşük düzeylerde virüs varlığında bile)

- ✓**Entegre olan provirüsün eksizyonu**

Passaes CP, et al. Virology. 2014 Apr;454-455:340-52

HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi



Gu WG.Trends Biotechnol 2015 Mar;33(3):172-9.

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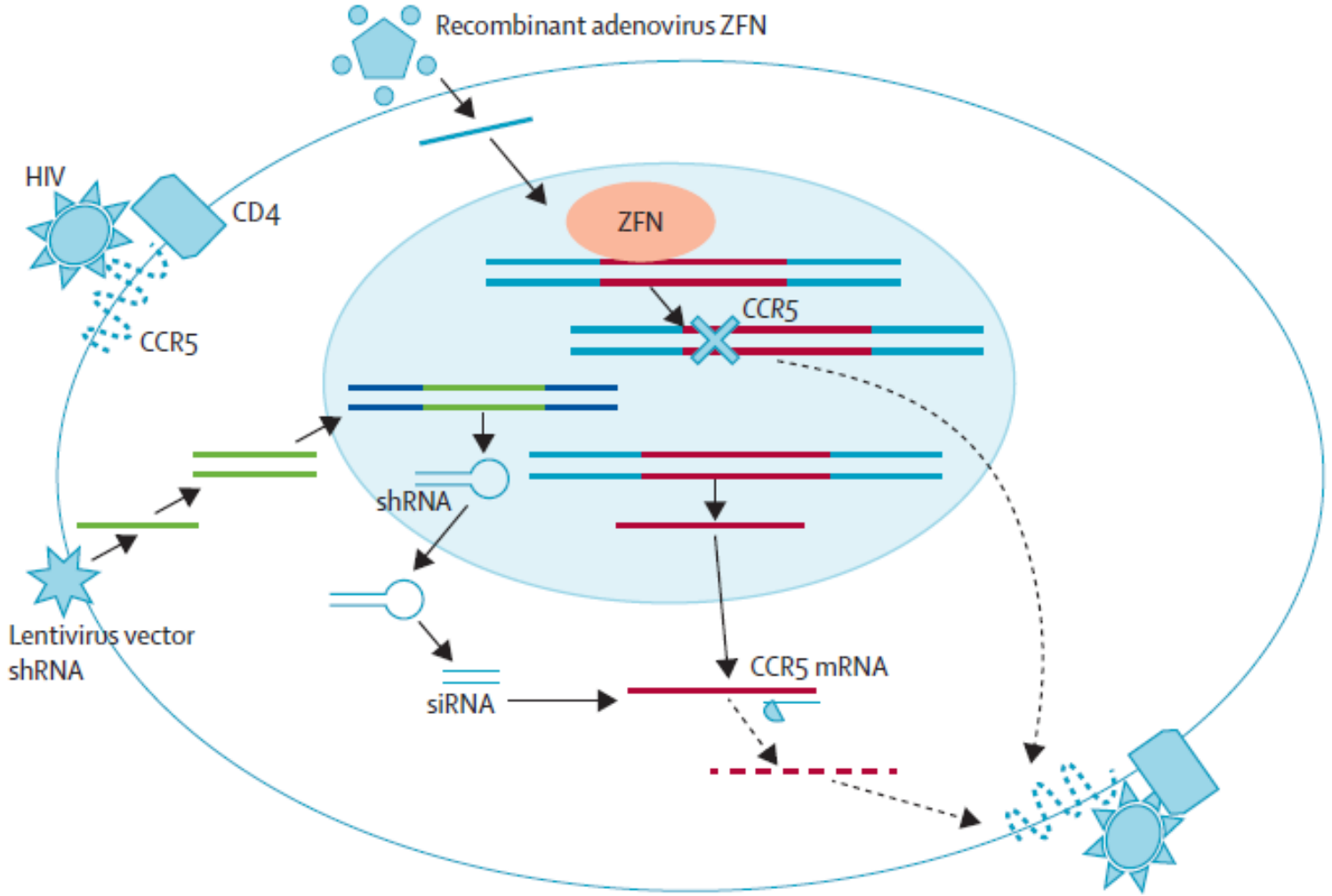
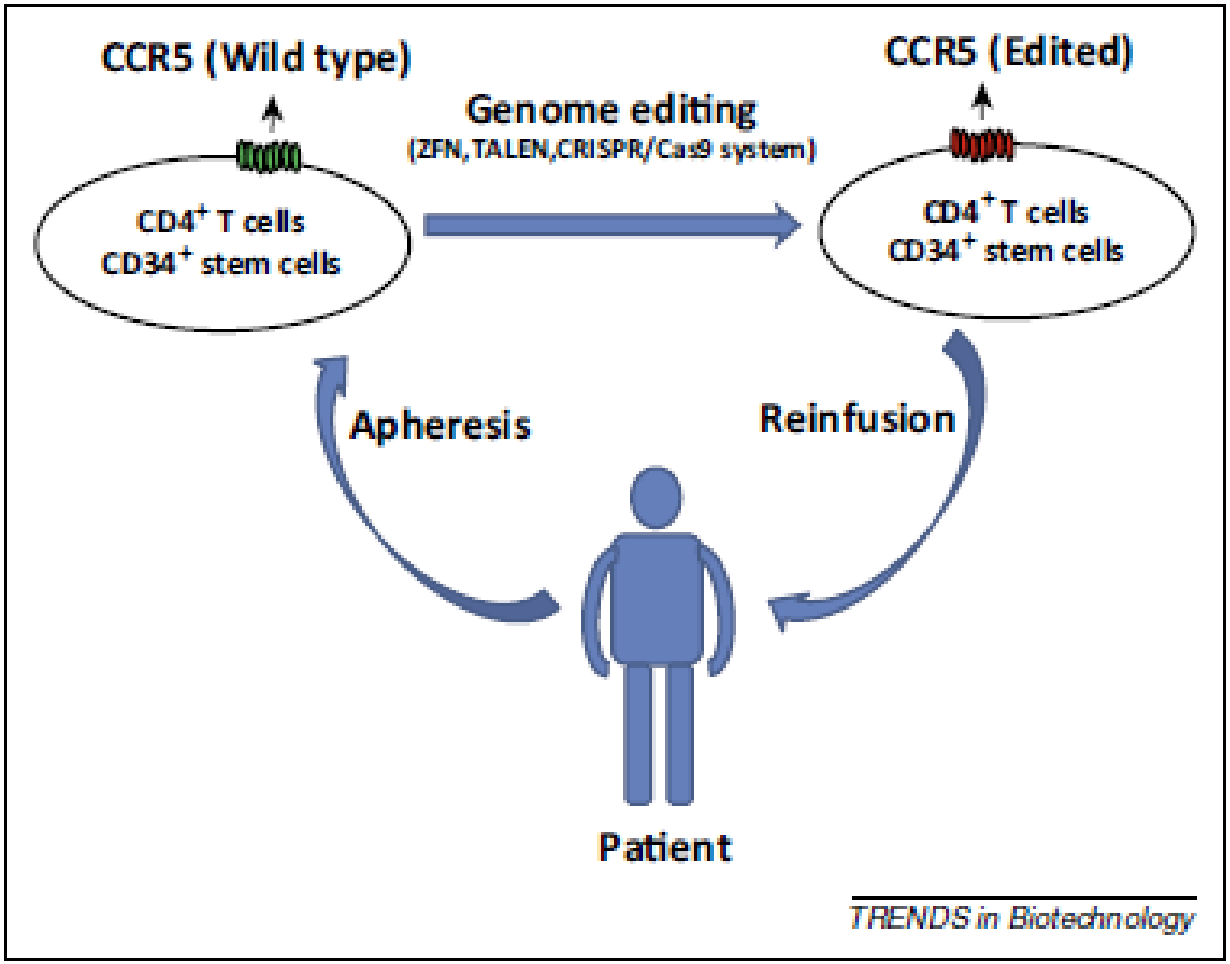


Kent SJ,et al. Lancet Infect Dis 2013 Jul;13(7):614-21.



Orijinal HIV'e duyarlı hücrelerin eradikasyonu için kemoterapi gerekli olabilir

Liu et al. Cell Biosci (2017) 7:47
DOI 10.1186/s13578-017-0174-2

Cell & Bioscience

RESEARCH Open Access

Genome editing of the HIV co-receptors CCR5 and CXCR4 by CRISPR-Cas9 protects CD4$^+$ T cells from HIV-1 infection

Zhepeng Liu[1‡], Shuliang Chen[1,2*‡], Xu Jin[3], Qiankun Wang[1], Kongxiang Yang[4], Chenlin Li[1], Qiaoqiao Xiao[1], Panpan Hou[4], Shuai Liu[1], Shaoshuai Wu[1], Wei Hou[1], Yong Xiong[5], Chunyan Kong[1], Xixian Zhao[1], Li Wu[2], Chunmei Li[1,6], Guihong Sun[1] and Deyin Guo[1,6*]

Abstract

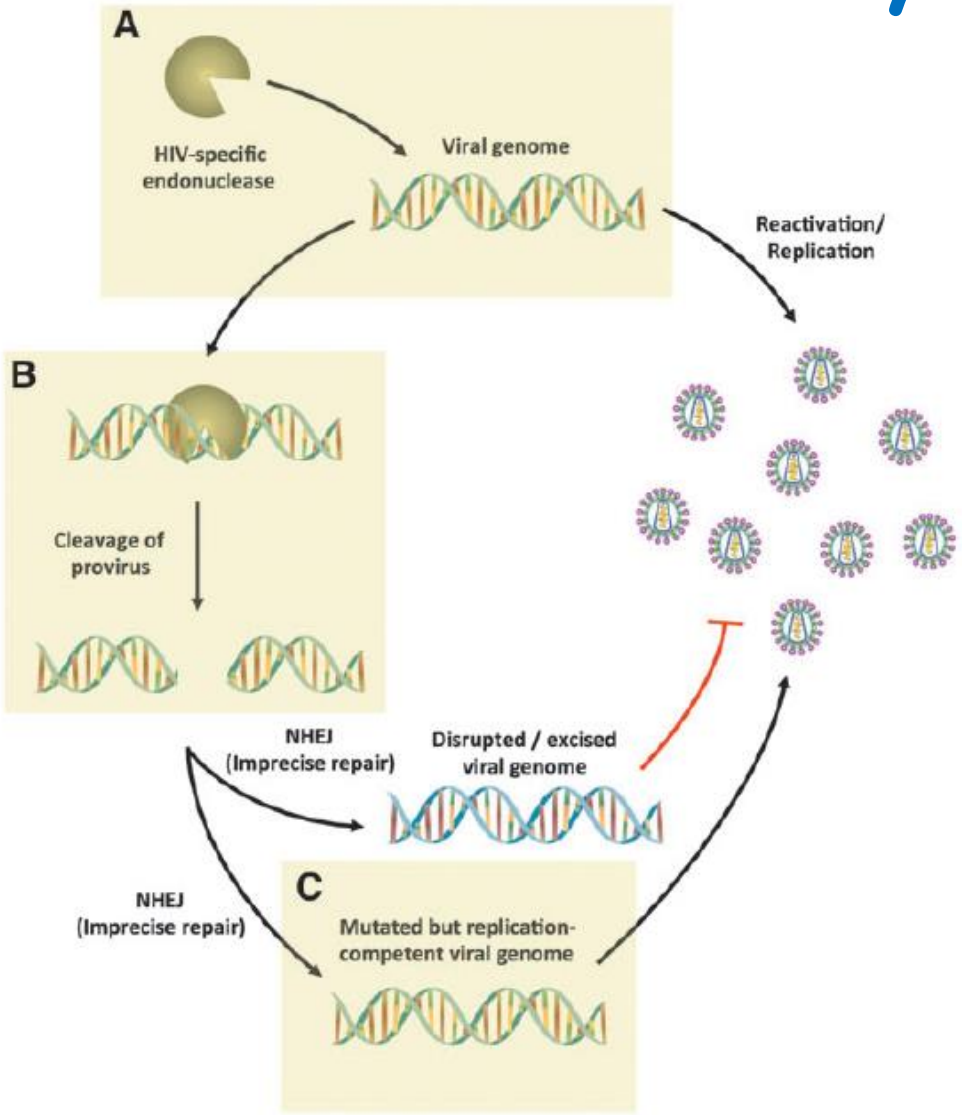
Background: The main approach to treat HIV-1 infection is combination antiretroviral therapy (cART). Although cART is effective in reducing HIV-1 viral load and controlling disease progression, it has many side effects, and is expensive for HIV-1 infected patients who must remain on lifetime treatment. HIV-1 gene therapy has drawn much attention as studies of genome editing tools have progressed. For example, zinc finger nucleases (ZFN), transcription activator like effector nucleases (TALEN) and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 have been utilized to successfully disrupt the HIV-1 co-receptors CCR5 or CXCR4, thereby restricting HIV-1 infection. However, the effects of simultaneous genome editing of CXCR4 and CCR5 by CRISPR-Cas9 in blocking HIV-1 infection in primary CD4$^+$ T cells has been rarely reported. Furthermore, combination of different target sites of CXCR4 and CCR5 for disruption also need investigation.

Results: In this report, we designed two different gRNA combinations targeting both CXCR4 and CCR5, in a single vector. The CRISPR-sgRNAs-Cas9 could successfully induce editing of CXCR4 and CCR5 genes in various cell lines and primary CD4$^+$ T cells. Using HIV-1 challenge assays, we demonstrated that CXCR4-tropic or CCR5-tropic HIV-1 infections were significantly reduced in *CXCR4*- and *CCR5*-modified cells, and the modified cells exhibited a selective advantage over unmodified cells during HIV-1 infection. The off-target analysis showed that no non-specific editing was identified in all predicted sites. In addition, apoptosis assays indicated that simultaneous disruption of CXCR4 and CCR5 in primary CD4$^+$ T cells by CRISPR-Cas9 had no obvious cytotoxic effects on cell viability.

Conclusions: Our results suggest that simultaneous genome editing of CXCR4 and CCR5 by CRISPR-Cas9 can potentially provide an effective and safe strategy towards a functional cure for HIV-1 infection.

Keywords: CRISPR-Cas9, CCR5 and CXCR4 simultaneous, HIV-1, AIDS

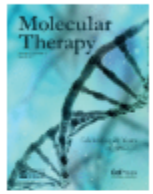
Proviral DNA eliminasyonu



Jerome Kr, et al. Disruption or Excision of Provirus as an Approach to HIV Cure. AIDS PATIENT CARE and STDs Volume 30, Number 12, 2016

Export

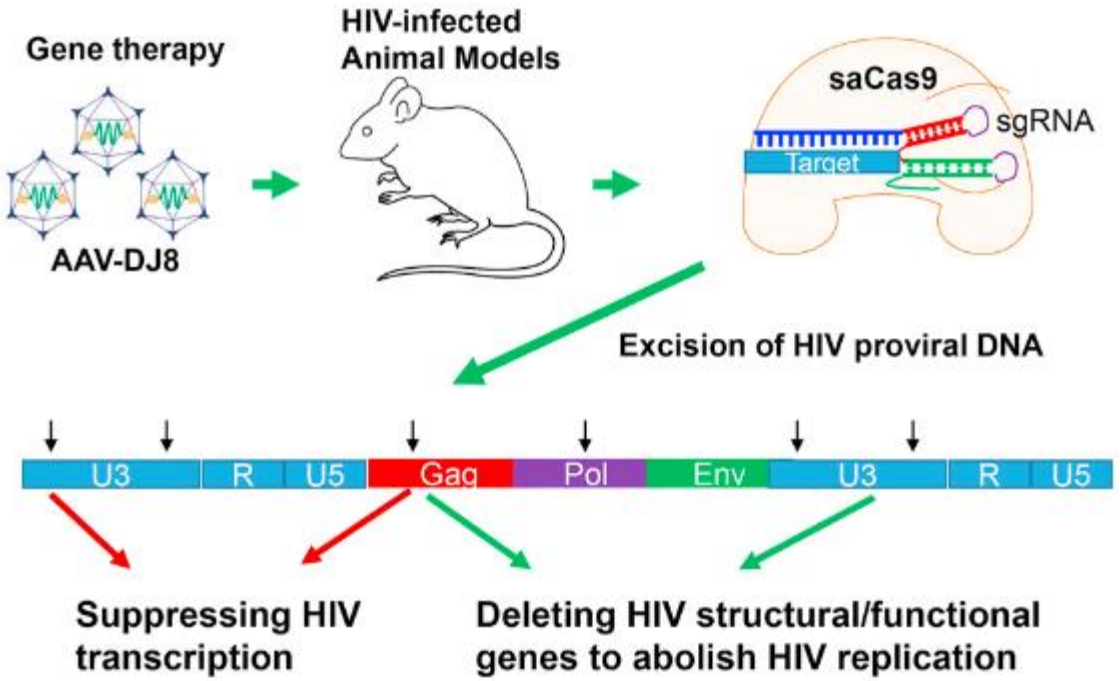
Molecular Therapy



Volume 25, Issue 5, 3 May 2017, Pages 1168-1186

Original Article

In Vivo Excision of HIV-1 Provirus by saCas9 and



Yeni Buluşlar ve Stratejiler

nature International weekly journal of science

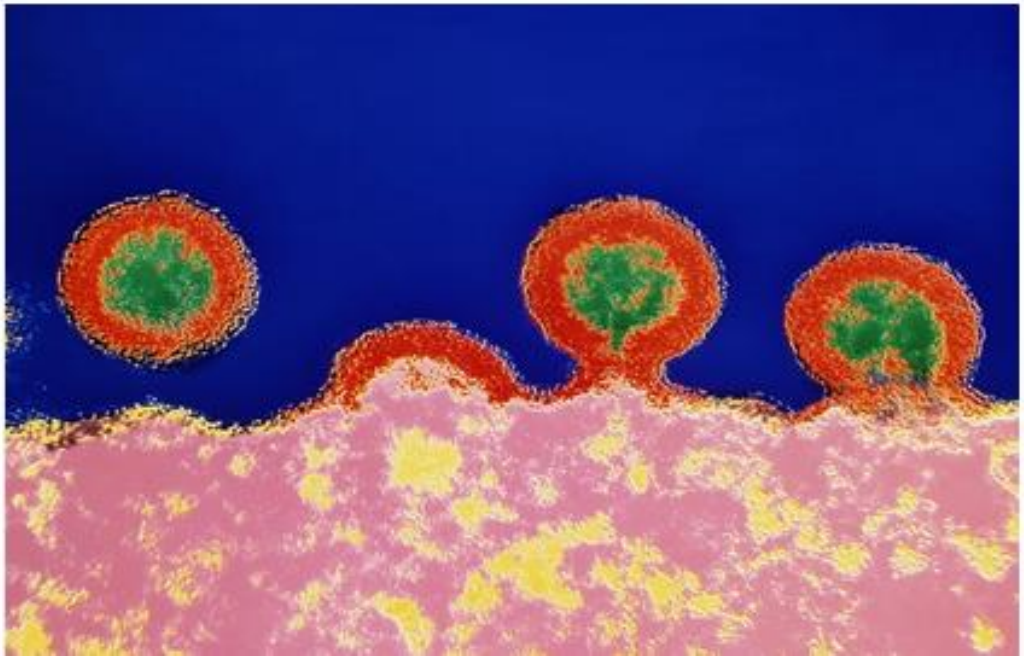
NATURE | NEWS

Hidden HIV reservoirs exposed by telltale protein

The discovery helps to identify dormant infected cells and could one day lead to a cure.

Amy Maxmen

15 March 2017



Virologists lack even basic knowledge of the reservoir, because latently infected cells are exceedingly hard to find in the body. It was Benkirane's quest to solve that problem that led him and his team to the CD32a protein marker. The researchers exposed resting T cells to fluorescently tagged HIV in the lab, and searched for differences in gene expression between cells infected by the marked virus, and those that weren't. A subset of the quiescent infected cells turned on a gene, which coded for CD32a, that was almost undetectable in uninfected cells. The researchers also determined that the protein is not expressed at significant levels in cells actively producing HIV.

Using an antibody that sticks to CD32a, the researchers then pulled cells expressing the protein out of human blood samples from HIV-infected people. As expected, these were quiescent T cells harbouring HIV. "You absolutely could not have done that before now," Benkirane says.

Exposure

Deeks hopes that the new protein target, or biomarker, accelerates research on a cure, in the same way that tests to measure the amount of virus in a sample helped to develop antiretroviral therapy in the late 1990s.

The next steps will be to replicate the findings by screening blood from patients of different genders, ethnicities, ages and stages of the disease, says Tony Fauci, director of the US National Insitute of Allergies and Infectious Disease in Bethesda, Maryland. Scientists will also test tissues

Dekaban and Dikeakos *AIDS Res Ther (2017) 14:53*
DOI 10.1186/s12981-017-0175-6

AIDS Research and Therapy

REVIEW Open Access

HIV-I Nef inhibitors: a novel class of HIV-specific immune adjuvants in support of a cure

Gregory A. Dekaban[1,2*] and Jimmy D. Dikeakos[1*]

Abstract

The success of many current vaccines relies on a formulation that incorporates an immune activating adjuvant. This will hold true for the design of a successful therapeutic HIV vaccine targeted at controlling reactivated virus following cessation of combined antiretroviral therapy (cART). The HIV accessory protein Nef functions by interfering with HIV antigen presentation through the major histocompatibility complex I (MHC-I) pathway thereby suppressing $CD8^+$ cytotoxic T cell (CTL)-mediated killing of HIV infected cells. Thus, this important impediment to HIV vaccine success must be circumvented. This review covers our current knowledge of Nef inhibitors that may serve as immune adjuvants that will specifically restore and enhance CTL-mediated killing of reactivated HIV infected cells as part of an overall vaccine strategy to affect a cure for HIV infection.

Keywords: HIV-1, Nef, Latency, Vaccines

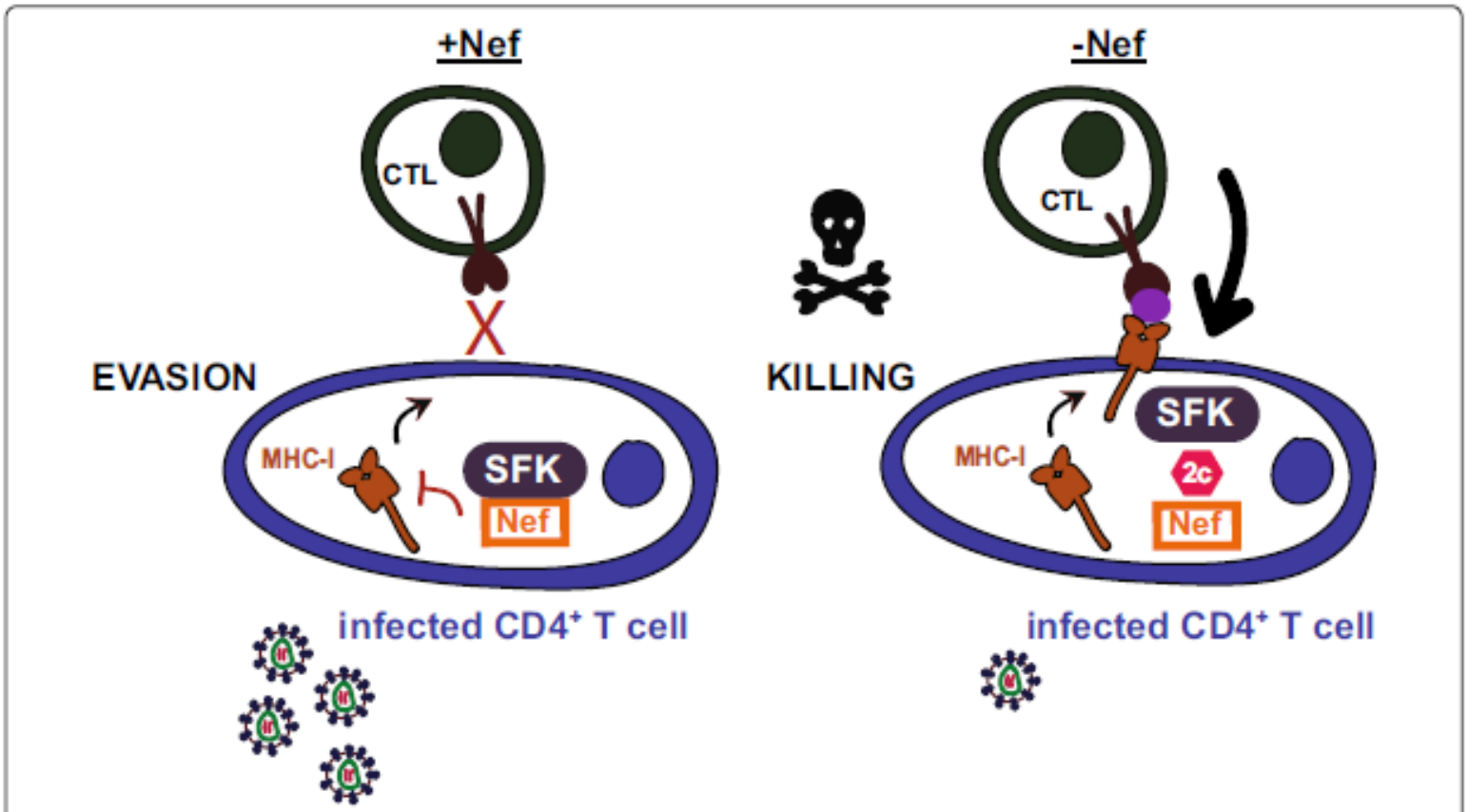


Fig. 1 Shock and kill therapies to cure HIV infection require the inhibition of Nef activity. Shock therapies aim to reactivate latent HIV (shock and to eliminate virus-producing cells (kill). Viral reactivation will enhance Nef activity to evade the immune surveillance system by decreasing cell surface levels of MHC-I on $CD4^+$ T cells (+Nef). Evasion: the interaction between Nef and a Src Family Kinase (SFK) results in the intracellular retention of MHC-I. Subsequently, a $CD8^+$T lymphocyte (CTL) will fail to recognize an HIV infected cell. Killing: conversely, the inhibition of Nef's activity using molecular adjuvants, such as 2c-like compounds (*red hexagon*) that block the interaction between Nef and SFKs (−Nef) will restore cell surface levels of MHC-I which in turn will promote HIV antigen presentation (*purple dot*) and enhance susceptibility to HIV specific $CD8^+$-CTL

SCIENTIFIC REPORTS

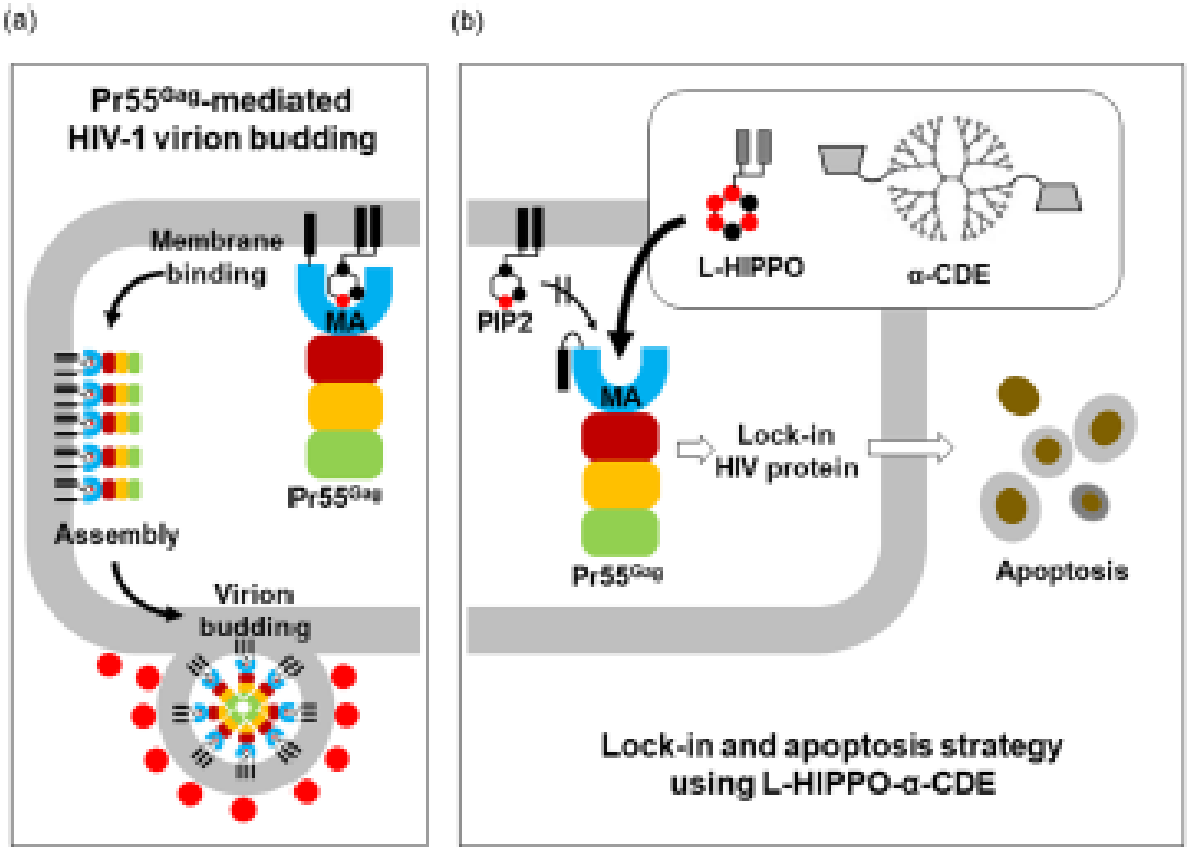
OPEN

A clue to unprecedented strategy to HIV eradication: "Lock-in and apoptosis"

Received: 10 January 2017
Accepted: 24 July 2017
Published online: 21 August 2017

Hiroshi Tateishi, Kazuaki Monde[2], Kensaku Anraku[3], Ryoko Koga[1], Yuya Hayashi[4], Halil Ibrahim Ciftci[1], Hasan DeMirci[5,6], Taishi Higashi[4], Keiichi Motoyama[4], Hidetoshi Arima[4], Masami Otsuka[1] & Mikako Fujita[7]

Despite the development of antiretroviral therapy against HIV, eradication of the virus from the body, as a means to a cure, remains in progress. A "kick and kill" strategy proposes "kick" of the latent HIV to an active HIV to eventually be "killed". Latency-reverting agents that can perform the "kick" function are under development and have shown promise. Management of the infected cells not to produce virions after the "kick" step is important to this strategy. Here we show that a newly synthesized compound, L-HIPPO, captures the HIV-1 protein $Pr55^{Gag}$ and intercepts its function to translocate the virus from the cytoplasm to the plasma membrane leading to virion budding. The infecting virus thus "locked-in" subsequently induces apoptosis of the host cells. This "lock-in and apoptosis" approach performed by our novel compound in HIV-infected cells provides a means to bridge the gap between the "kick" and "kill" steps of this eradication strategy. By building upon previous progress in latency reverting agents, our compound appears to provide a promising step toward the goal of HIV eradication from the body.


(a)
(b)
Pr55Gag-mediated
HIV-1 virion budding
Membrane
binding
MA
Pr55Gag
Assembly
Virion
budding
L-HIPPO
α-CDE
PIP2
MA
Lock-in
HIV protein
Pr55Gag
Apoptosis
Lock-in and apoptosis strategy
using L-HIPPO-α-CDE

- ✓ Tüm viral rezervuarı reaktive etmek sorunlu
- ✓ **Yakın vadede latent viral rezervuarı kontrol altında tutmak daha gerçekçi bir hedef??**

tat bağımlı transkripsiyonun baskılanması

HAT inhibitörleri: garcinol türevleri, curcumin, celastrol (tat blokeri), **cortistatin A analoğu**

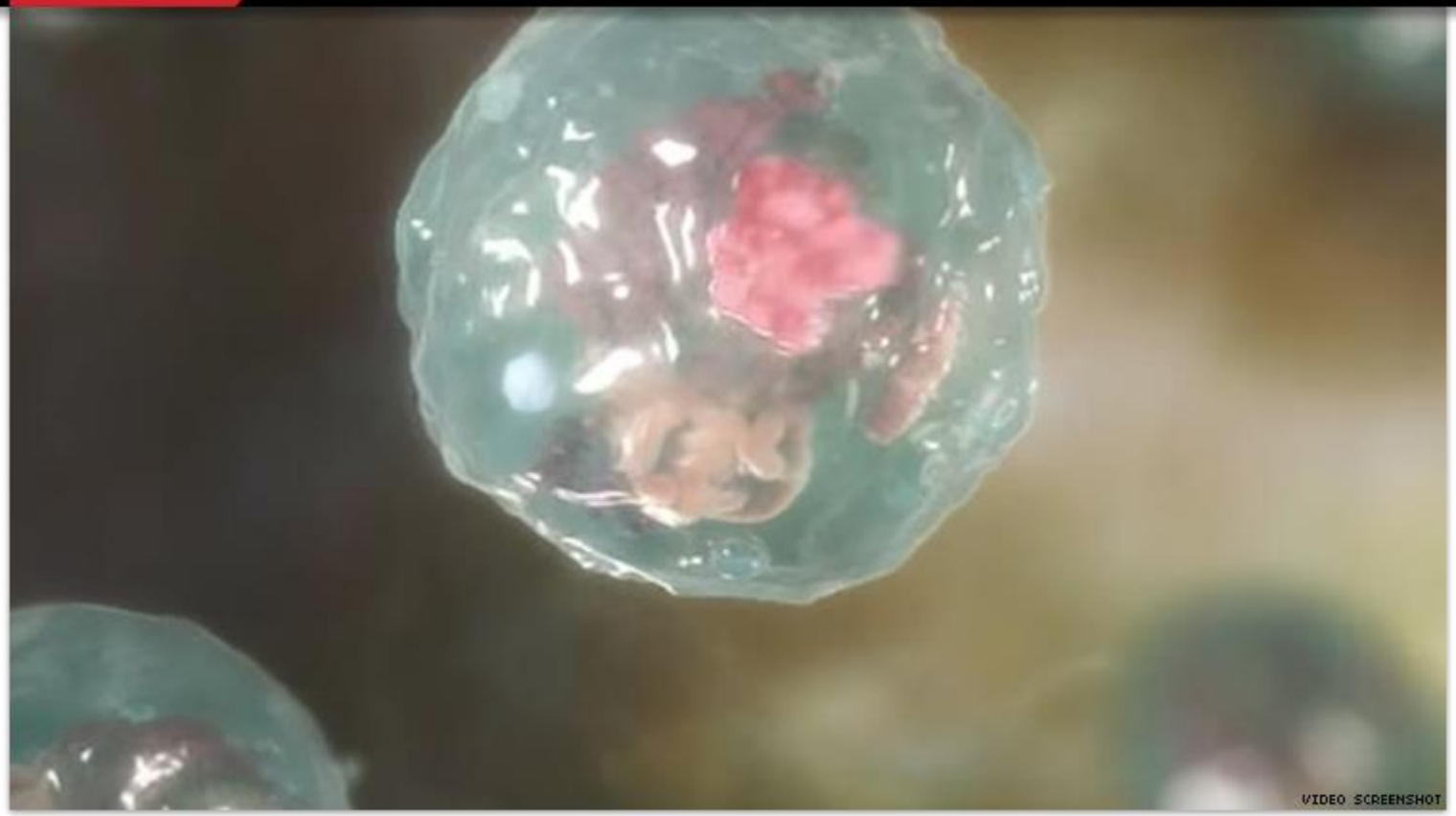
Passaes CP, et al. Virology 2014 Apr;454-455:340-52

~~Şok et ve öldür?~~
Bloke et ve kilitle?

At IAS 2017, Valente presented the results of experiments **in mice** adapted so they can be infected with human HIV. Adding dCA to standard ART resulted in a significant **1.5 to 10.5-fold reduction in viral expression from reservoir cells and showed a degree of persistence when ART was withdrawn.**
However, Valente warned that even adapted mice were not the same as humans, and the tricks HIV uses to co-opt the human immune system into making more HIV could in theory neutralise the effect of dCA. Human studies are planned.

ABX464

TRENDING TasP PrEP I Am a Warrior Amazing HIV+ People



After completing Phase II trials, a pill called ABX464 has proven to reduce HIV reservoirs, which can ultimately become part of an HIV cure.

- ✓ ABX464 **Rev'in aktivitesini engelleyerek replikasyonu inhibe eder.**
- ✓ **ABX464 altında yeni virüslerin oluşumunda kullanılamayan kısa RNA parçaları oluşur.**
- ✓ **Replikasyon sırasında bu küçük fragmanlar hücre yüzeyine göç eder ve immün sistemi uyarır ve hücreler immün sistem tarafından elimine olabilir.**

Vandekerckhove L et al. *ABX464 decreases total HIV DNA in PBMCs when administered during 28 days to HIV-infected patients who are virologically suppressed.* 16th European AIDS Conference, 25-27 October, Milan, abstract PS 1/7, 2017.

TEŞEKKÜR EDERİM