KÜR HAYAL Mİ?

Dr. Birgül Mete
İÜC-Cerrahpaşa Tıp Fakültesi
Enfeksiyon Hastalıkları ve
Klinik Mikrobiyoloji AD

KÜR

Steril

- Tüm HIV DNA'nın (rezervuar) eliminasyonu

Fonksiyonel

- Latent HIV (+)
- Rezervuar eradike edilmeden immün kontrol
- ART'siz viremi (-) ya da düşük düzeyde viremi

Hibrid

Towards an HIV cure: a global scientific strategy. Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Dahabieh MS, et al. Annu Rev Med .2015;66:407-21.
Cillo Ar, et al. Current Opinion in Virology 2016, 18:14–19

Steril kür

- ✓ **Berlin Hastası-***AML-13 yıl*
- ✓ **Londra Hastası-***HL-4 yıl*
- ✓ **New York Hastası-***AML-14 ay (haplo-kord nakil)*

Ortak özellik----*CCR5-homozigot-delta-32 mutasyonuna sahip kişilerden kemik iliği nakli*

Ding J, et al. Knowledge From London and Berlin: Finding Threads to a Functional HIV Cure. Frontiers in Immunology 1 May 2021 | Volume 12 |
Hsu J et al (Bryson Y presenting). *HIV-1 remission with CCR5Δ32Δ32 haplo-cord transplant in a U.S . women: IMPAACT P1107.* Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

New York hastası

- ✓ IMPAACT P1107 gözlemsel çalışmasına katılan orta yaşlı kadın hasta
- ✓ **2013'te HIV ve 2017'de AML tanısı**
- ✓ CCR5-homozigot-delta-32 mutasyonuna sahip daha önce taranan **göbek kordonu** kanı nakli planlanıyor
  - ➢ Göbek kordon kanı yetişkin kök hücreler kadar yakın bir genetik eşleşme gerektirmiyor
  - ➢ Ancak yetişkin nakli için miktar az ve engraftman yavaş

Hsu J et al (Bryson Y presenting). *HIV-1 remission with CCR5Δ32Δ32 haplo-cord transplant in a U.S . women: IMPAACT P1107.* Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

- ✓ **Haplo-kord nakli:** Kordon kan hücreleri hastanın yetişkin akrabalarından birinin (CCR5 mutasyonu olmayan) kısmen eşleştirilmiş donör kök hücreleriyle birleştiriliyor
- ✓ Timothy Ray Brown gibi, nakilden **önce yoğun kemoterapi ve tüm vücut radyoterapisi**
- ✓ Nakil sonrası graft-versus-host hastalığı gelişmiyor

Hsu J et al (Bryson Y presenting). *HIV-1 remission with CCR5Δ32Δ32 haplo-cord transplant in a U.S . women: IMPAACT P1107.* Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

- ✓ **100 gün içinde**, kordon kanı hücrelerinden türetilen %100 *CCR5*-delta-32 bağışıklık hücreleri ile **tam engraftman**
- ✓ Laboratuvar testleri:
  - ➢ yeni hücreler şaşırtıcı bir şekilde, CXCR4 reseptörüne bile dirençli
- ✓ Yüksek düzeyde duyarlı testlerde:
  - ➢ viral yük (-)
  - ➢ immün hücrelerde HIV DNA (-)
  - ➢ replike olabilen HIV (-)
  - ➢ nakilden bir yıl sonra Anti HIV (-)

Hsu J et al (Bryson Y presenting). *HIV-1 remission with CCR5Δ32Δ32 haplo-cord transplant in a U.S . women: IMPAACT P1107.* Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

- ✓ 3 yıl sonra ART kesildi.
- ✓ 14 ay sonra – kök hücre naklinden 4,5 yıl sonra:
  - ➢ viral yük (-)
  - ➢ AML remisyonda
  - ➢ yaklaşık 75 milyon CD4 hücresinde replike olabilen HIV (-)

Hsu J et al (Bryson Y presenting). *HIV-1 remission with CCR5Δ32Δ32 haplo-cord transplant in a U.S . women: IMPAACT P1107.* Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

Steril kür?

San Fransisko hastası (2020)

- ✓ 1992'de HIV tanısı
- ✓ ART olmaksızın onlarca yıldır virüsün kontrolü
- ✓ **1,5 milyardan fazla kan ve bağırsak hücresinde intact HIV genetik materyaline dair herhangi bir iz yok**

Esperanza hastası (2021)

- ✓ 2013'te HIV tanısı
- ✓ İlk hamileliği sırasında sadece 6 ay boyunca ART aldı
- ✓ **Sekiz yılı aşkın takip, HIV RNA (-)**
- ✓ Ultra duyarlı testlerde **HIV RNA (-)**
- ✓ Plasenta dokusundan 1.19 milyar periferik kan hücresi ve 503 milyon hücre dizilemesi sonucunda **intact HIV genetik materyali (-)**
- ✓ 7 defektiv provirüs saptanmasına rağmen, 150 milyon latent hücrede replikasyon (-)

Turk G et al. A possible sterilizing cure of HIV-1 infection without stem cell transplantation. Annals of Internal Medicine, November 2021.

Curr HIV/AIDS Rep
DOI 10.1007/s11904-016-0296-x

HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

Post-Treatment Controllers: Role in HIV "Cure" Research

Leslie R. Cockerham[1] · Hiroyu Hatano[2] · Steven G. Deeks[2]

Abstract Descriptions of individuals who are able to control viral replication in the absence of antiretroviral therapy after receiving short-term therapy early in infection ("post-treatment controllers") has generated excitement and controversy within the field. As with natural or "elite" controllers, these cases provide hope that a long-term remission or "functional cure" might one day be possible. Here, we review what is known and not known about these cases and discuss the immunologic factors that may allow these unique individuals to be maintain viral control and may be important for future curative strategies.

Keywords HIV infection · HIV latency · HIV viral rebound · T cell activation · Post-treatment controllers · Antiretroviral therapy

Introduction

Individuals who naturally control HIV replication in the absence of therapy provide the strongest evidence that a remission may one day be achievable. Approximately, 1 % of individuals who acquire HIV are able to control the virus to below the level of detection for years to decades [1]. These so-called "elite" controllers have been extensively studied and reviewed elsewhere [1–3]. Here, we discuss a possible new clinical phenotype that has generated both excitement and controversy: individuals who presented with early HIV infection, who appeared unlikely to be heading toward a state of "elite" control, who started and remained on ART for several years, and who stopped therapy and failed to exhibit the expected viral rebound. These "post-treatment controllers" (PTCs) may indeed be a newly described phenomenon or they may simply be elite controllers whose natural history was interrupted by a

CHAMP

Control of HIV after Antiretroviral Medication Pause

- ✓ Kanada ve ABD'den 10 randomize kontrollü ve 4 kohort çalışma
- ✓ Ortalama tedavi süresi 2 yıl
- ✓ 67 post-treatment controller:

  erken tedavi:%13

  kronik enfeksiyon:%4
- ✓ **5 yıl remisyon** (HIV RNA<400 kopya/ml): **%22**
- ✓ Erken tedavi başlanan grupta az oranda **10 yıllık remisyon**

Namazi G et al. *The Control of HIV after Antiretroviral Medication Pause (CHAMP) study: post-treatment controllers identified from 14 clinical studies.* The Journal of Infectious Diseases,

The Journal of Clinical Investigation

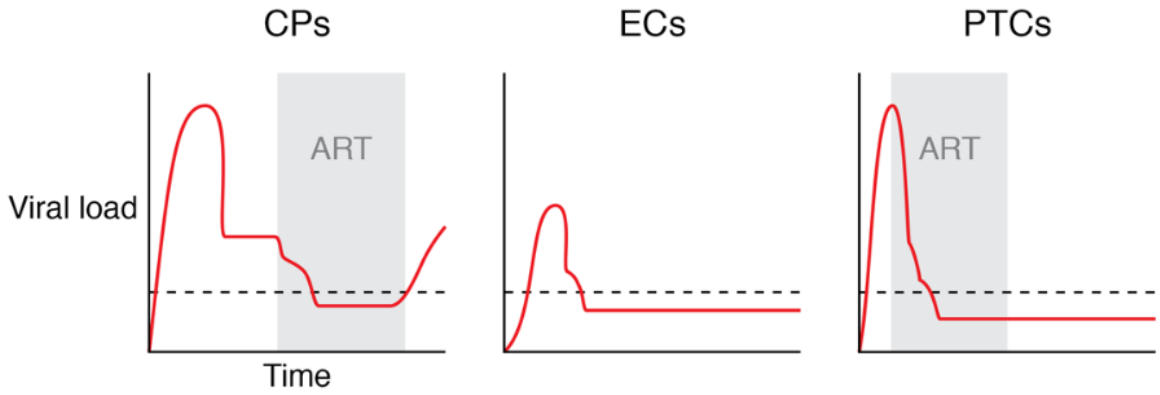
REVIEW

How elite controllers and posttreatment controllers inform our search for an HIV-1 cure

Jonathan Z. Li[1] and Joel N. Blankson[2]

[1]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. [2]Center for AIDS Research, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.

A small percentage of people living with HIV-1 can control viral replication without antiretroviral therapy (ART). These patients are called elite controllers (ECs) if they are able to maintain viral suppression without initiating ART and posttreatment controllers (PTCs) if they control HIV replication after ART has been discontinued. Both types of controllers may serve as a model of a functional cure for HIV-1 but the mechanisms responsible for viral control have not been fully elucidated. In this review, we highlight key lessons that have been learned so far in the study of ECs and PTCs and their implications for HIV cure research.



	CPs	ECs	PTCs
Prevalence*	>80%	<1%	~13%–15% (early-treated) <4% (chronic-treated)
% with protective HLA alleles	10%–20%	40%–80%	10%–20%
HIV-specific $CD8^+$ T cell response	+	+++	+
Reservoir size	+++	+	++
Clonally expanded latent cells	++	+++	++

Figure 1. Virologic and immunologic profiles of CPs, ECs, and PTCs. ART is normally started in chronic progressors (CPs) during the chronic phase of infection, and a rebound in viremia is seen when therapy is discontinued. In contrast, elite controllers (ECs) are ART-naive subjects who control viral replication naturally. Posttreatment controllers (PTCs) are more often patients in whom ART is initiated during primary infection. These patients maintain control of viral replication when ART is discontinued. *Estimates depend on definition of EC and PTC. +, ++, and +++ indicate relative magnitude of each parameter.

Neden Kür Sağlanamıyor?

Latent rezervuar

- ✓ **En önemli neden: Latent rezervuar**

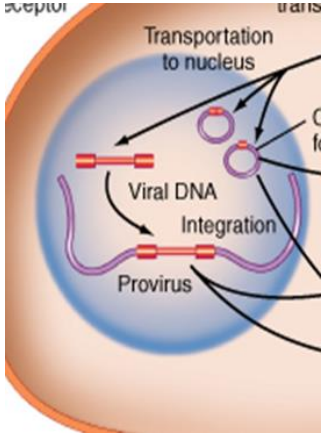
  replike olma özelliğini koruyan virüs CD4 yardımcı T hücrelerinde (özellikle hafıza) latent olarak kalması

- ✓ Hedef hücrelerin de novo enfeksiyonu

  devam eden replikasyon

- ✓ İmmün sistemin enfekte hücreleri eradike edememesi

Towards an HIV cure: a global scientific strategy. Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Dahabieh MS, et al. Annu Rev Med 2015;66:407-21.



Latent hücre

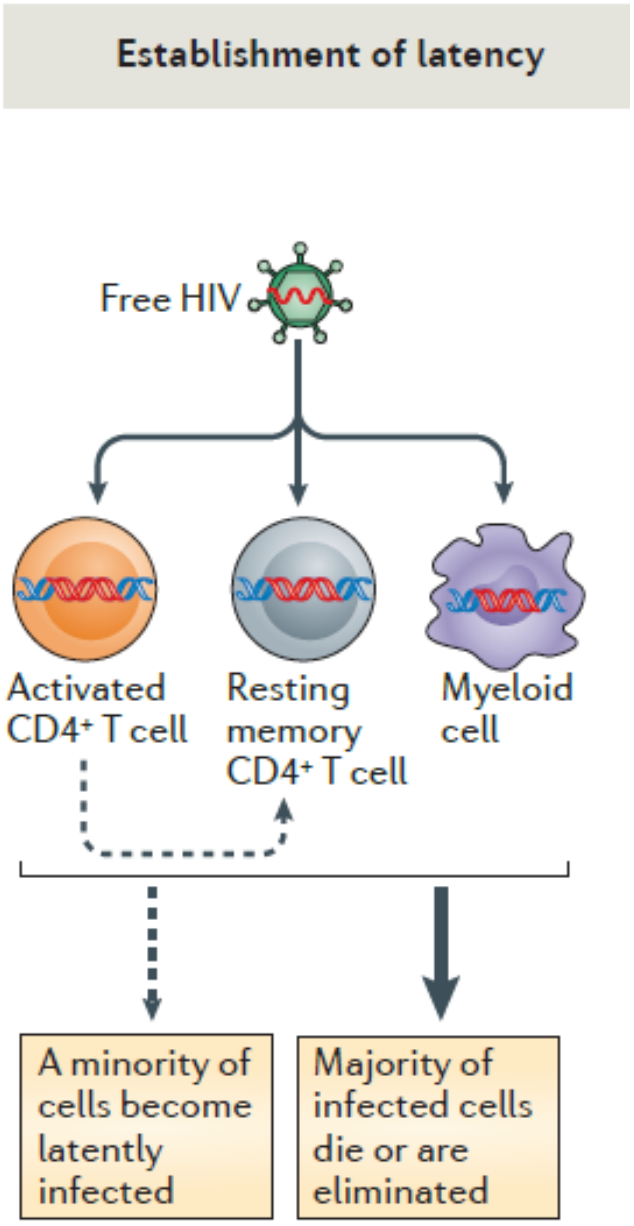
⇩

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

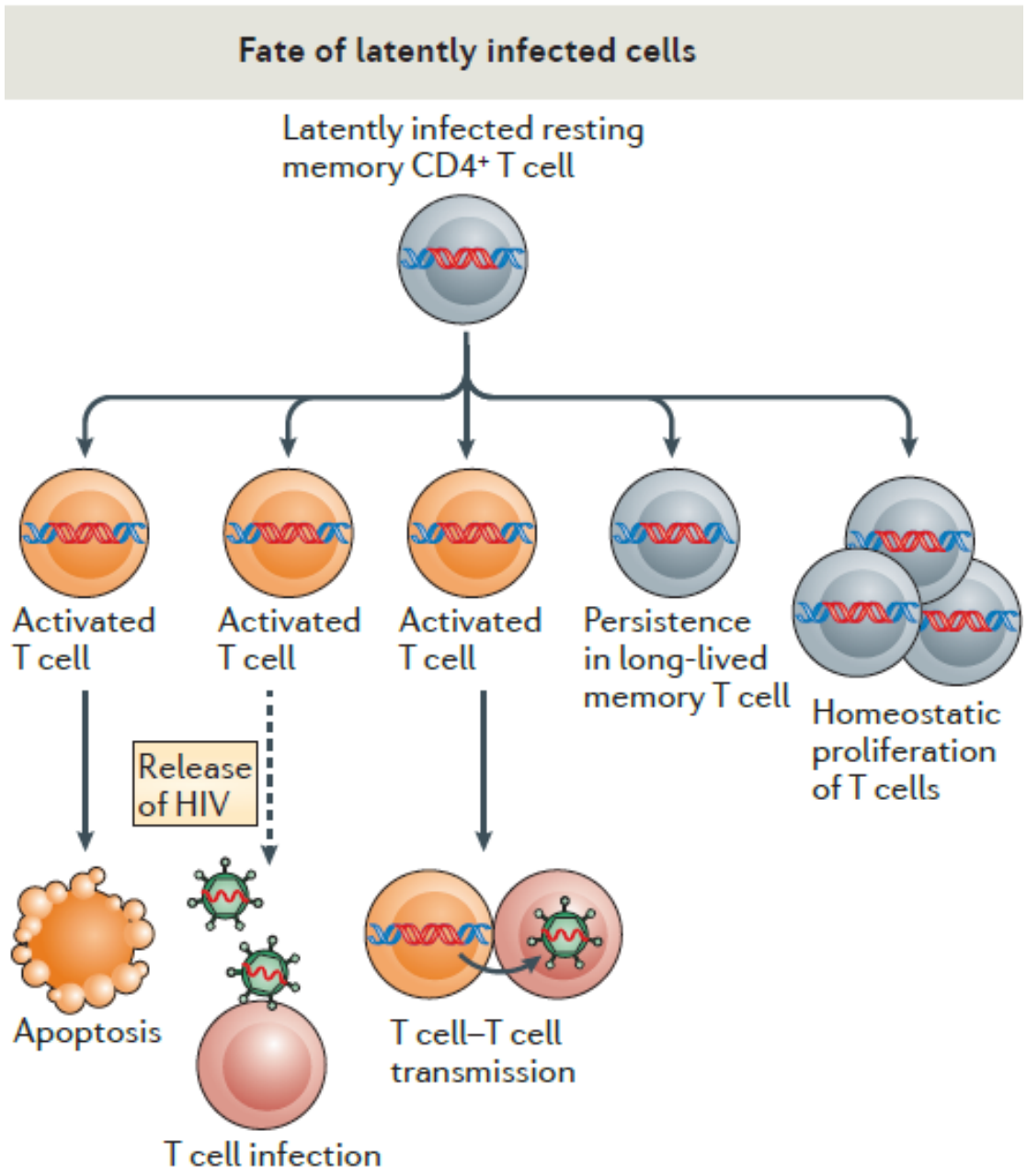
Hücresel uyarı

⇩

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.



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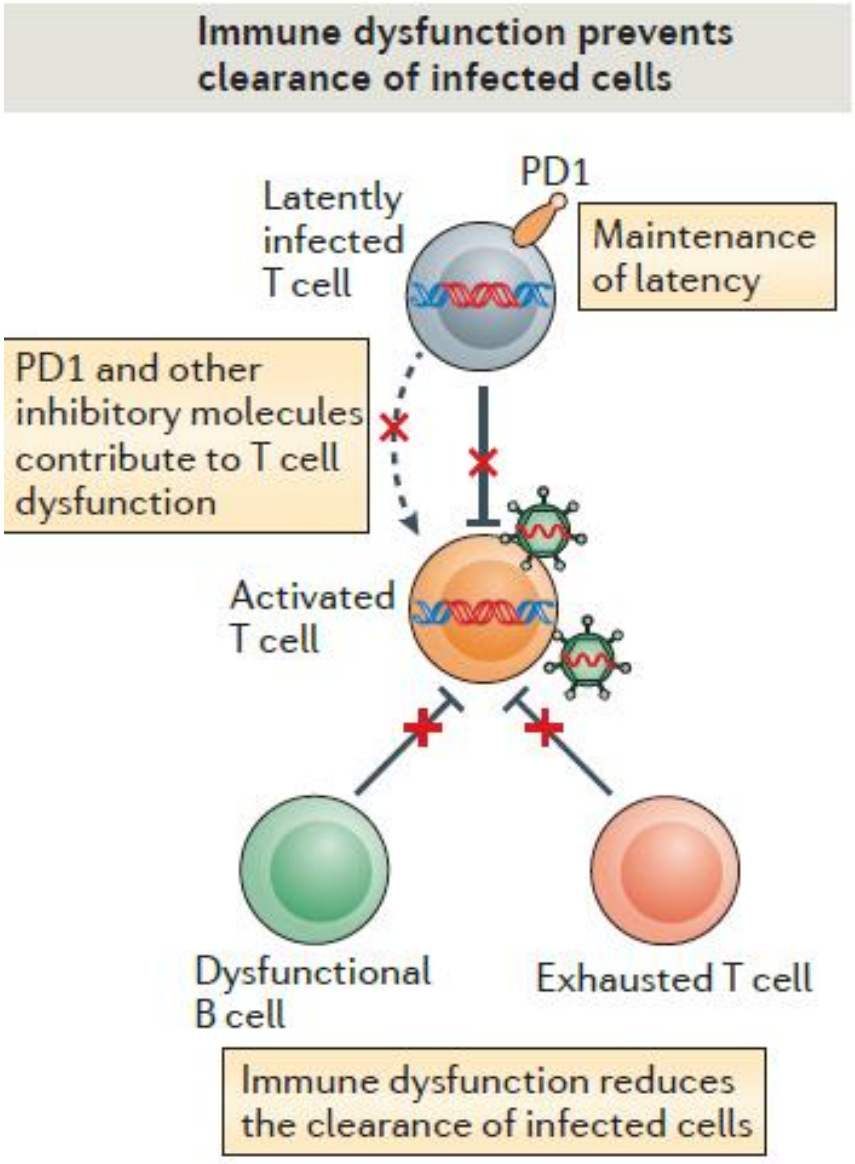


Towards an HIV cure: a global scientific strategy.
Nat Rev Immunol 2012 Jul 20;12(8):607-14.

Kür için en büyük engel latent rezervuar

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

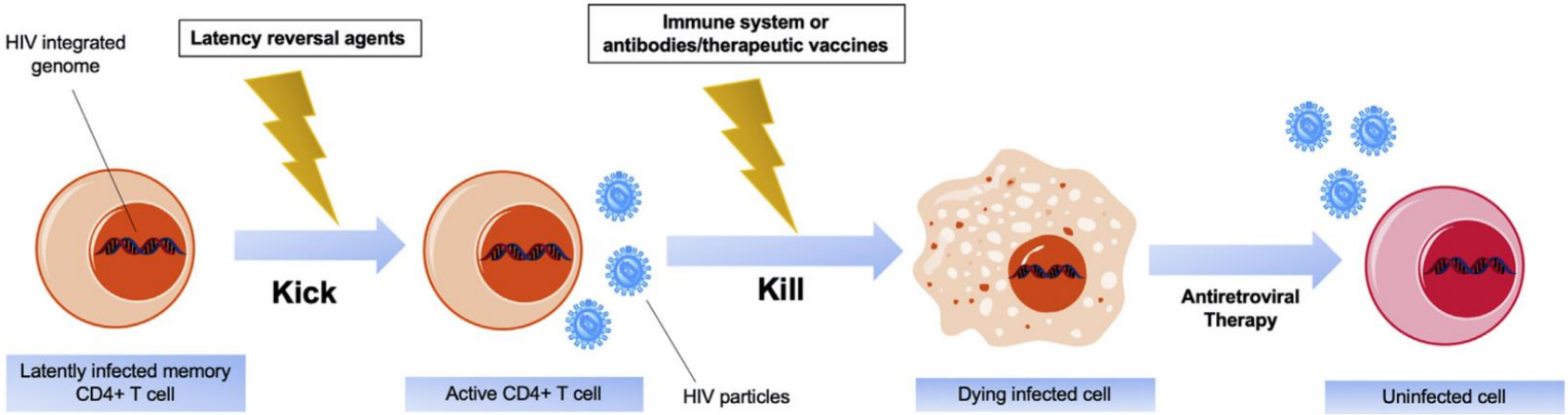
Kürde Temel Yaklaşımlar

Temel Hedefler

- ✓ Viral rezervuarın eradikasyonu
- ✓ Viral rezervuarın baskılanması
- ✓ Gen terapileri ile hücrelerde değişim

Viral Rezervuarın Eradikasyonu

Viral rezervuarın eradikasyonu --şok et ve öldür--



AKTİVATÖR

ART

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
Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (2021)

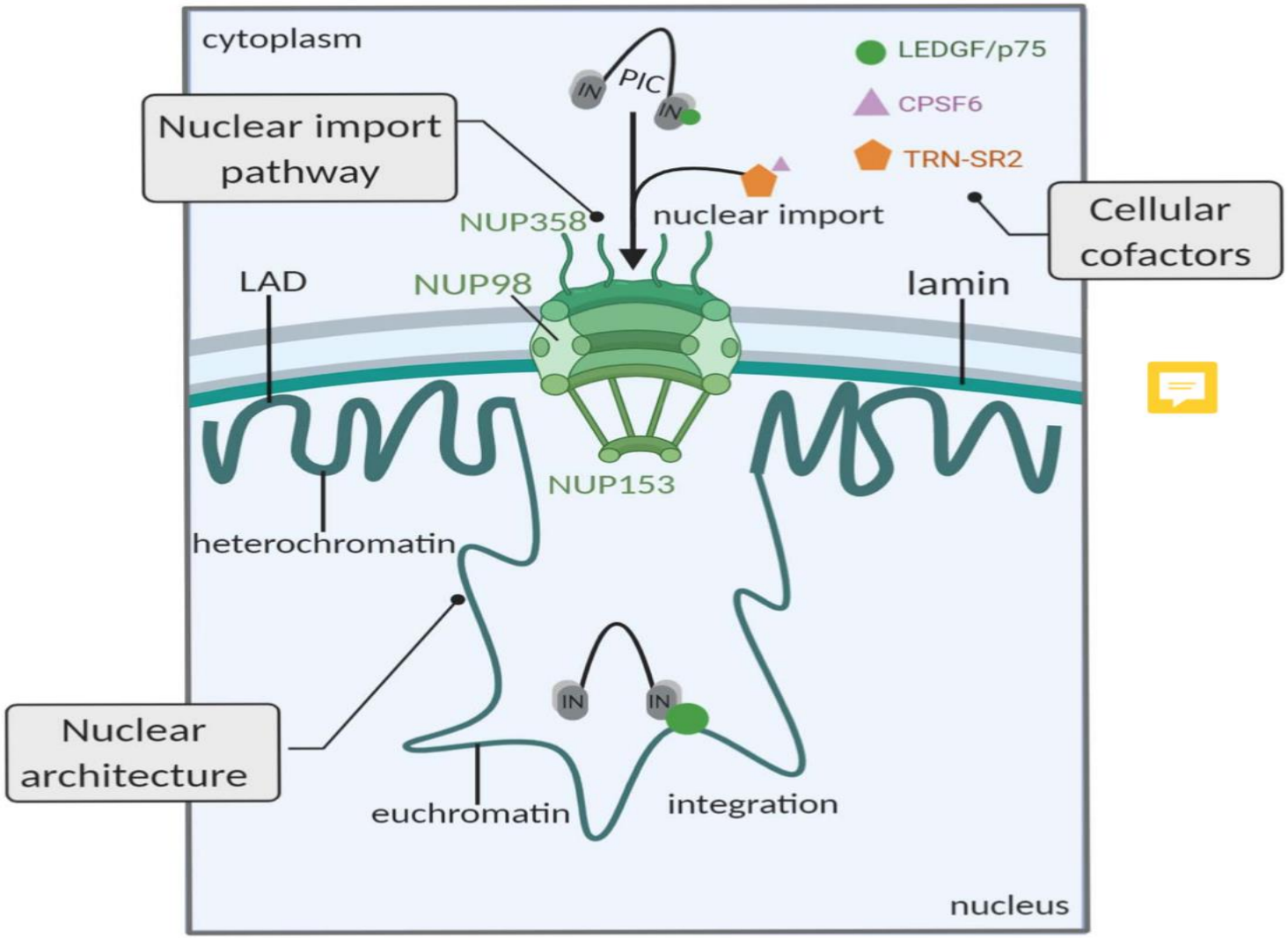
Latentlik

- ✓ **Pre-integrasyon**
- ✓ **Transkripsiyon**

  epigenetik
- ✓ **Post-transkripsiyon**

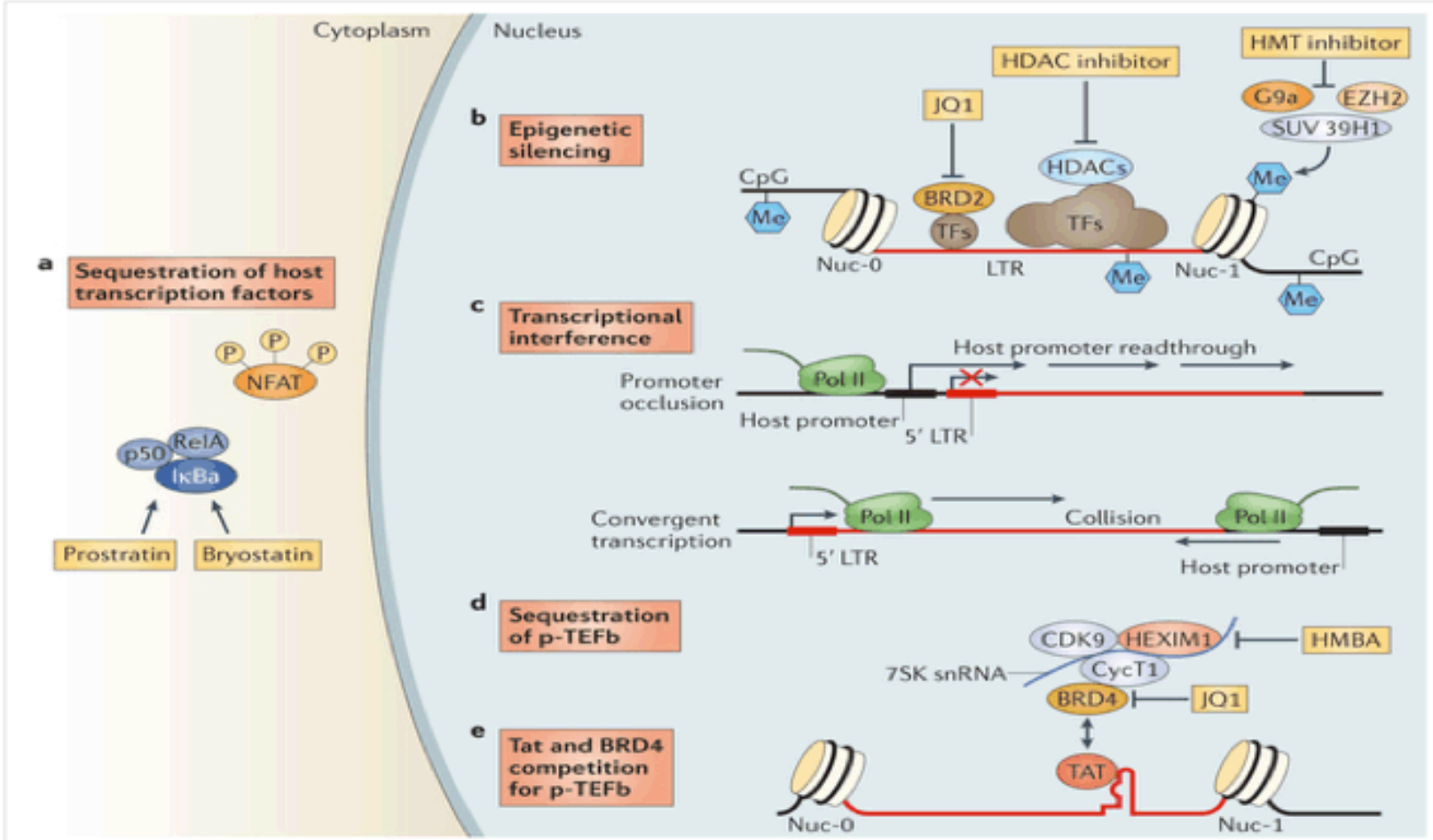
  m-RNA taşınması, kesilmesi, translasyon

Pre-integrasyon

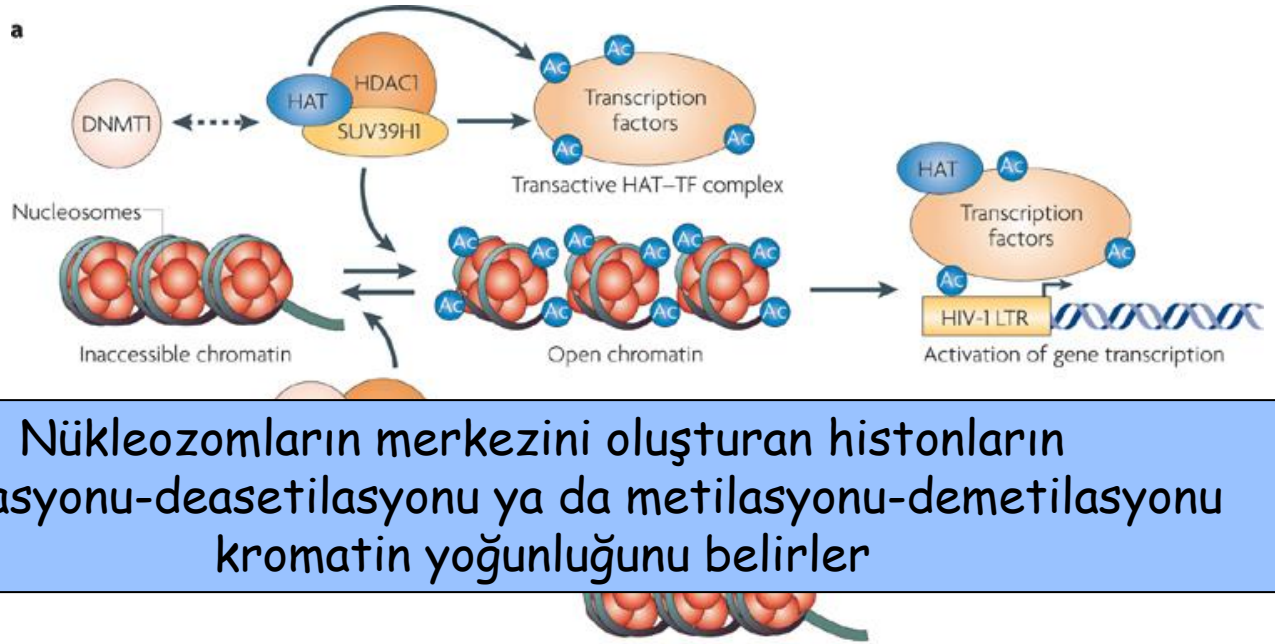


Transkripsiyon

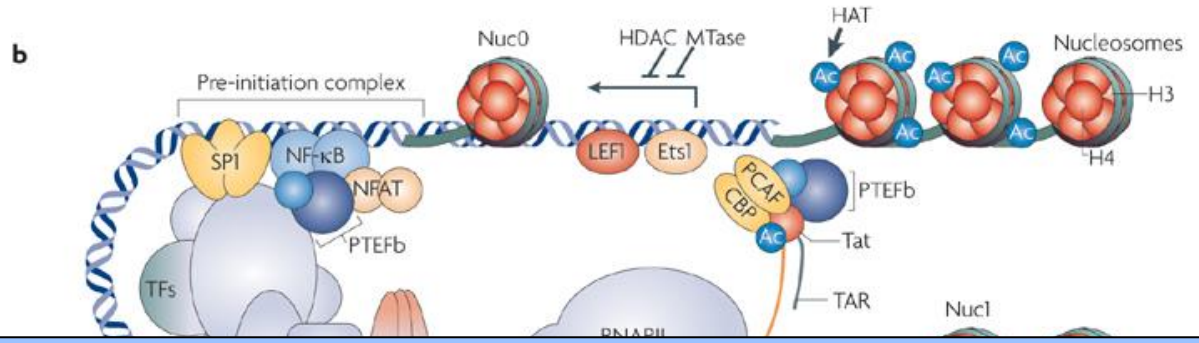
Figure 1: Mechanisms involved in the maintenance of HIV-1 latency and strategies to disrupt latency.



Archin NM, et al. Nat Rev Microbiol. 2014 Nov;12(11):750-64



Nükleozomların merkezini oluşturan histonların asetilasyonu-deasetilasyonu ya da metilasyonu-demetilasyonu kromatin yoğunluğunu belirler



Histon deasetilaz (HDAC)
kromatin yapıda kondansasyona yol açar ve transkripsiyon inhibe olur

Latent CD4 hücre aktivatörleri

- ✓ Histon deasetilaz inhibitörleri (HDACi)
- ✓ DNA metiltransferaz inhibitörleri
- ✓ Protein kinaz C agonistleri
- ✓ Bromodomain ekstraterminal motif inhibitörleri
  - ❑ Apoptoz indükleyicileri
  - ❑ BCL-2 inhibitörleri
  - ❑ Retinoik asit-indükleyici gen 1 inhibitörleri
- ✓ Apoptoz protein inhibitörlerinin inhibitörleri
- ✓ İmmün checkpoint inhibitörleri
- ✓ Toll-like reseptör agonistleri
- ✓ STING (İnterferon gen stimulatorü) agonistleri
- ✓ İnterlökinler (2,7,15)

Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104
Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (2021)
Acchioni C, et al. Fighting HIV-1 Persistence: At the Crossroads of “Shoc-K and B-Lock” Pathogens 2021,

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✓HDACi

etinostat > panobinostat > romidepsin=
givinostat =belinostat > vorinostat….

✓PKC agonistleri

SUW133 (bryostatin-1 analoğu) >
panobinostat, vorinostat, bryostatin-1

Gnidimacrin > romidepsin

Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (202)

Klinik çalışmalarda
vorinostat etkin/değil
panobinostat-kombinasyon gerekli
romidepsin çok etkin değil

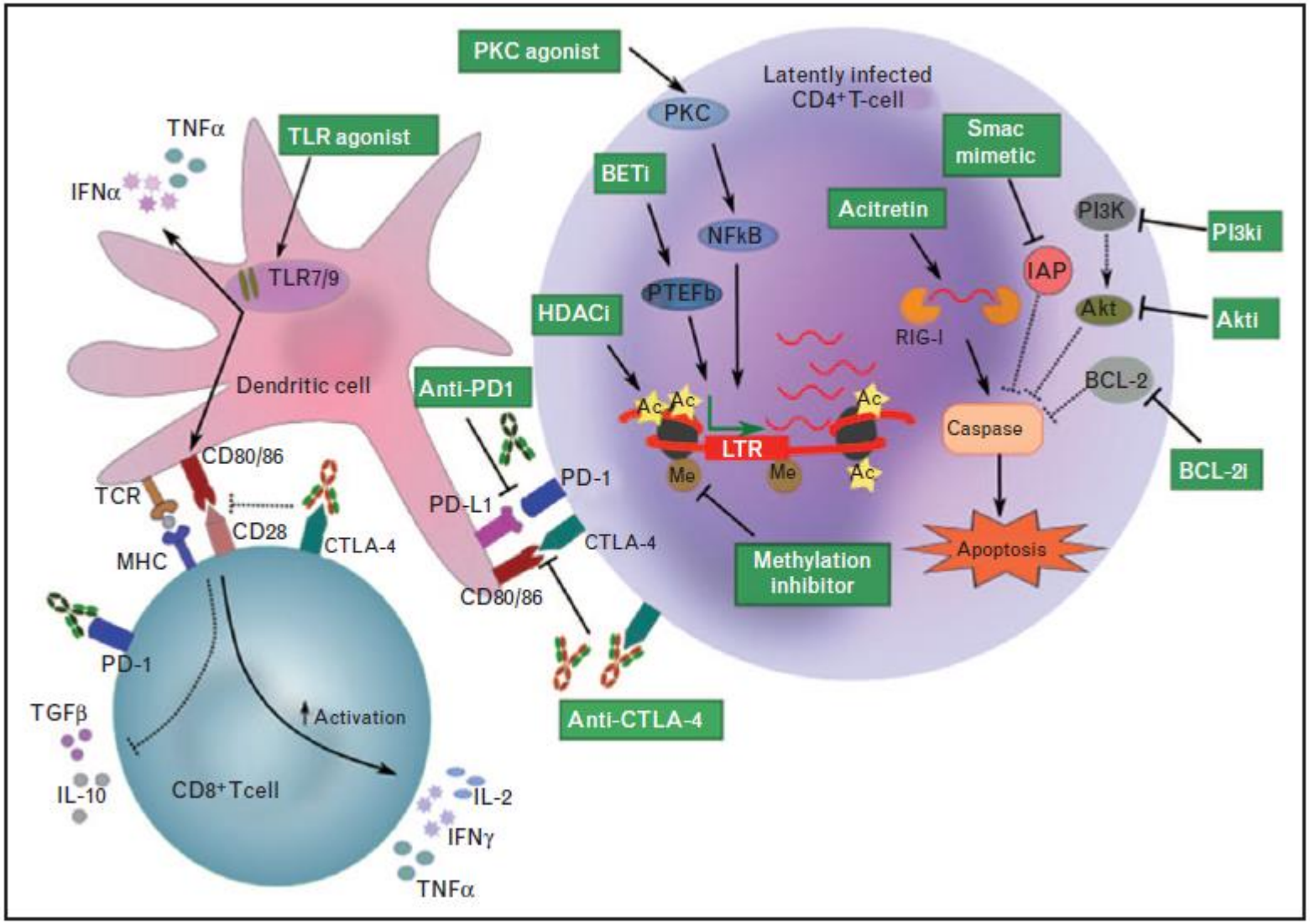
Table 1. Cancer therapies invest

Drug class	Promising compounds in HIV research	ph…		…al studies in HIV
(i) Latency reversing agents				
HDAC inhibitors	Vorinostat, romidepsin, panobinostat	Licensed (CTCL, MM)	Reversing HIV latency by chromatin remodelling	Yes, refs [9–13]
BET inhibitors	OTX015, JQ1	Phase 1/2	Reversing HIV latency by promoting recruitment of P-TEFb to the HIV LTR	No
Histone methyltransferase inhibitors	Low doses only of chaetocin, BIX-01294 or DNZep	Not safe at doses tested/preclinical	Prevents histone 3 methylation that represses HIV transcription, thereby reactivating latent HIV	No
DNA methyltransferase inhibitors	Azacitidine, decitabine	Licensed (MDS)	Prevents CpG methyl…	
PKC agonists	Bryostatin-1, prostratin	Phase…		

Klinik çalışmalarda
bryostatin güvenli
ancak latent rezervuarı
aktive edici dozlar toksik

Rasmussen AT, et al. Cancer therapies in HIV cure reser…
Ding J, et al. Knowledge From London and Berlin: Finding Th… …ontiers in Immunology 1 May 2021 | Volume 12 |

Apoptozu indükleyici ve immünmodulatuvar ilaçlar



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  - ❑ Retinoik asit-indükleyici gen 1 inhibitörleri

klinik çalışmalara ihtiyaç var

- ✓ Apoptoz protein inhibitörlerinin inhibitörleri
- ✓ İmmün checkpoint inhibitörleri
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Acchioni C, et al. Fighting HIV-1 Persistence: At the Crossroads of “Shoc-K and B-Lock” Pathogens 2021,

(ii) Apoptosis promoting compounds				
BCL-2 antagonists	Venetoclax	Licensed (CLL), phases 1–3	Inhibits antiapoptotic BCL-2, sensitizing cells to apoptosis. When combined with LRA	No
RIG-I inducers	Acitretin		ion and	No
PI3k/Akt inhibitors	Perifosine, a		HIV- osis	No
SMAC mimetics	Birinapant, SBI-06371 LCL1		osis ing HIV- osis,	No
Tyrosine kinase inhibitors	Ibrutinib	Licensed	Impairs Bruton's tyrosine kinase on the surface of HIV-infected cells, inducing selective depletion of HIV-infected cells	No
(iii) Immune modulation				
Immune checkpoint inhibitors	Ipilimumab, pembrolizumab, nivolumab	Licensed (melanoma, NSCLC)	Enhancing HIV-specific T cell responses; reversing HIV latency	Yes, ref [60]
TLR agonists	GS-9620, MGN1703	Phase 1, 2	Activating DCs and NK cells; reversing HIV latency	Yes, refs [76,78]

İmmünmodülatuvar aktivatörlerin avantajı:

şok ve öldürme aşamalarında etkililer

Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104

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Pembrolizumab induces HIV latency reversal in people living with HIV and cancer on antiretroviral therapy

Thomas S. Uldrick[1,2,3,*], **Scott V. Adams**[1], **Remi Fromentin**[4], **Michael Roche**[5,6], **Steven P. Fling**[1], **Priscila H. Gonçalves**[3], **Kathryn Lurain**[3], **Ramya Ramaswami**[3], **Chia-ching Jackie Wang**[7], **Robert J. Gorelick**[8], **Jorden L. Welker**[8], **Liz O'Donoghue**[1], **Harleen Choudhary**[1], **Jeffrey D. Lifson**[8], **Thomas A. Rasmussen**[6,9], **Ajantha Rhodes**[6], **Carolin Tumpach**[6], **Robert Yarchoan**[3], **Frank Maldarelli**[3], **Martin A. Cheever**[1,†], **Rafick Sékaly**[10], **Nicolas Chomont**[4], **Steven G. Deeks**[7], **Sharon R. Lewin**[6,11,12,*]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.

[2]University of Washington, Seattle, WA 98109, USA.

[3]HIV and AIDS Malignancy Branch, National Cancer Institute, Bethesda, MD 20892, USA.

Abstract

In people living with HIV (PLWH) on antiretroviral therapy (ART), virus persists in a latent form where there is minimal transcription or protein expression. Latently infected cells are a major barrier to curing HIV. Increasing HIV transcription and viral production in latently infected cells could facilitate immune recognition and reduce the pool of infected cells that persist on ART. Given that programmed cell death protein 1 (PD-1) expressing $CD4^+$ T cells are preferentially infected with HIV in PLWH on ART, we aimed to determine whether administration of antibodies targeting PD-1 would reverse HIV latency in vivo. We therefore evaluated the impact of intravenous administration of pembrolizumab every 3 weeks on HIV latency in 32 PLWH and cancer on ART. After the first infusion of anti–PD-1, we observed a median 1.32-fold increase in unspliced HIV RNA and 1.61-fold increase in unspliced RNA:DNA ratio in sorted blood $CD4^+$ T cells compared to baseline. We also observed a 1.65-fold increase in plasma HIV RNA. The frequency of $CD4^+$ T cells with inducible virus evaluated using the *tat/rev* limiting dilution assay was higher after 6 cycles compared to baseline. Phylogenetic analyses of HIV *env* sequences in a participant who developed low concentrations of HIV viremia after 6 cycles of pembrolizumab did not demonstrate clonal expansion of HIV-infected cells. These data are consistent with anti–PD-1 being able to reverse HIV latency in vivo and support the rationale for combining anti–PD-1 with other interventions to reduce the HIV reservoir.

Toll-like reseptör agonistleri

TLR-1,2,7,8,9 agonistleri

- ✓Leftolimod, TLR-9 agonisti, faz 2 aşamasında
- ✓Vesatolimod, TLR-7 agonisti
  - ekstrasellüler HIV RNA artıyor, NK,T ve B hücre aktivasyonu
  - 2/13 rhesus makak, 2 yıl boyunca ART'siz aviremik
  - Klinik çalışmalarda istenen başarı sağlanamadı

Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (2021)

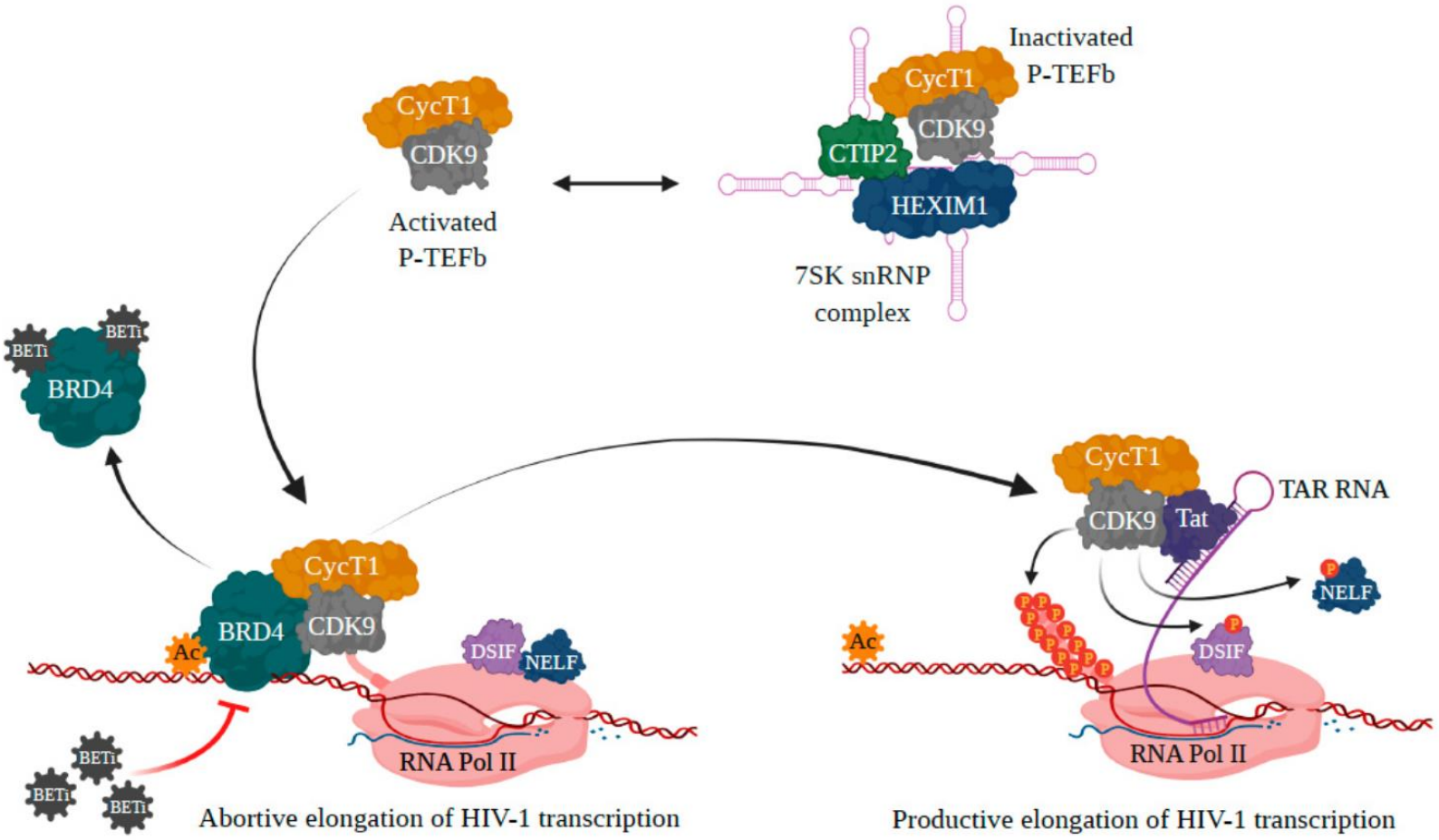

Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-dependent manner.

Salahong T, et al. Are BET Inhibitors yet Promising Latency-Reversing Agents for HIV-1 Reactivation in AIDS Therapy? *Viruses* 2021, *13*, 1026

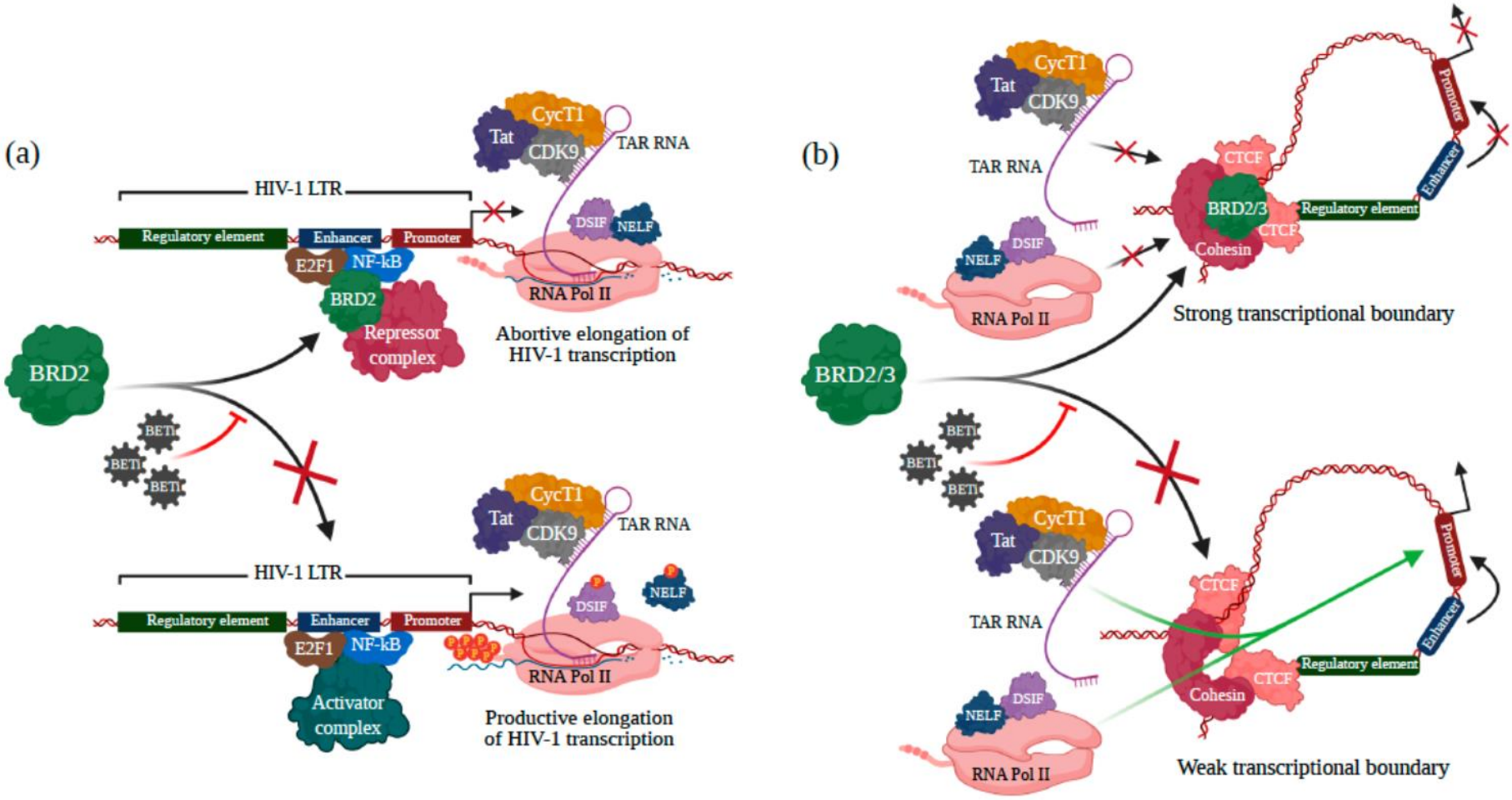

Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-independent manner.

Salahong T, et al. Are BET Inhibitors yet Promising Latency-Reversing Agents for HIV-1 Reactivation in AIDS Therapy? *Viruses* 2021, *13*, 1026

EClinicalMedicine 42 (2021) 101225

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journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Single center, open label dose escalating trial evaluating once weekly oral ixazomib in ART-suppressed, HIV positive adults and effects on HIV reservoir size in vivo.

Background: Achieving a functional or sterilizing cure for HIV will require identification of therapeutic interventions that reduce HIV reservoir size in infected individuals. Proteasome inhibitors, such as ixazomib, impact multiple aspects of HIV biology including latency, transcription initiation, viral replication, and infected cell killing through the HIV protease – Casp8p41 pathway, resulting in latency reversal and reduced measures of HIV reservoir size ex vivo.

Methods: We conducted a phase 1b/2a dose escalating, open label trial of weekly oral ixazomib for 24 weeks in antiretroviral (ART)-suppressed, HIV positive adults (NCT02946047). The study was conducted from March 2017 to August 2019 at two tertiary referral centers in the United States. The primary outcomes were safety and tolerability of oral ixazomib. Secondary outcomes included changes in immunologic markers and estimates of HIV reservoir size after ixazomib treatment.

Findings: Sixteen participants completed the study. Ixazomib up to 4mg weekly was safe and well-tolerated, yielding no treatment-emergent events above grade 1. In exploratory analyses, ixazomib treatment was associated with detectable viremia that was below the lower limit of quantification (LLQ) in 9 participants,

Interpretation: Our study successfully met its primary endpoint of demonstrating the safety of ixazomib for 24 weeks in HIV infected persons. Exploratory analyses suggest that the effects observed ex vivo of latency reversal and reductions in HIV reservoir size, also occur in vivo. Future controlled studies of ixazomib are warranted.

Latent rezervuarı indükleyen ilaçlar in vitro ve klinik çalışmalarda **etkin olarak görülse de rezervuarın boyutunu (~%5) azaltamamaktadır**:

- doz düşüklüğü, tekrarlayan dozlarda etkinin azalması
- toksik etkiler
- istenmeyen sistemik inflamasyon ve otoimmün yan etkiler
- latentlik mekanizması heterojen (bireysel, hücresel düzey)

Kombinasyon tedavi gerekliliği

Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104
Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (2021)

- ✓ PKC agonist + HDACi
- ✓ TLR agonistleri + BETi
- ✓ DNA metiltransferaz inhibitörleri + HDACi

Lopes RJ, et al. HIV latency reversal agents: A potential path for functional cure? European Journal of Medicinal Chemistry 213. (2021)

- ✓ Reaktive olan hücreler tarafından salınan **HIV- 1 antijen düzeyleri yetersiz**
- ✓ **Latent rezervuar CD8+T hücrelerine karşı dirençli**
- ✓ Reaktivasyon sonrası **virüs güdümlü hücre ölümü** gerçekleşmeyebilir.
- ✓ Elit kontrollülerde gözlenen etkili **CD8+T hücre yanıtı** normal konakta gözlenmiyor.

Passaes CP, et al. Virology. 2014 Apr;454-455:340-52
Velu V, et al. 2009.Nature 458, 206–210.Amancha P.K, at al. 2013.
J. Immunol.191,6060–6070.

- ✓ Reaktive olan hücreler **B hücre folliküllerinde** korunuyor.
- ✓ **HDAC inhibitörleri**
  - **sitotoksik T lenfositleri (CTL)'nin HIV enfekte hücreleri öldürme yeteneğini baskılayabilir**
  - **CD4 ve CD8 +T hücrelerine karşı sitotoksik,** NK hücrelerinde apoptoza neden olabilir
  - sitokin salınımını engeller

Passaes CP, et al. Virology. 2014 Apr;454-455:340-52
Velu V, et al. 2009.Nature 458, 206–210.Amancha P.K, at al. 2013.
J. Immunol.191,6060–6070.

İmmünoterapi

İmmünoterapi

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

  Anti-HIV immünitesinin işlev ve yaygınlığını arttıracak aşılar

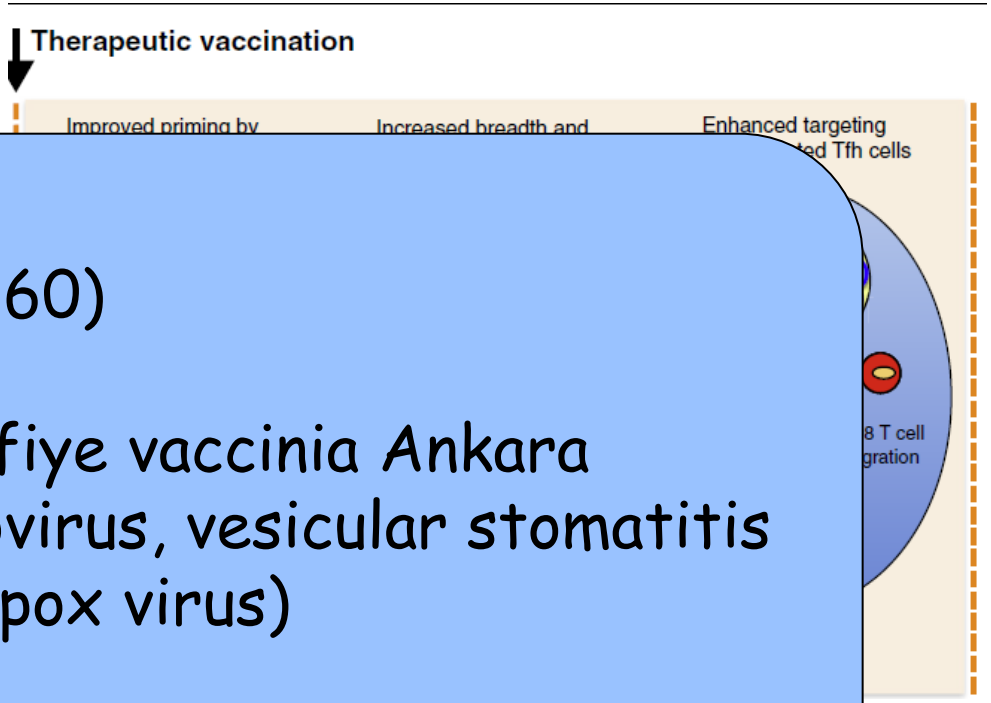
- ✓**Pasif bağışıklama**

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

Terapötik aşılar

Terapötik aşı hedefleri:

- ✓ Anti-viral CD8+ T hücreleri (CTL)
- ✓ CD4+ T h
- ✓ Nötralizo
- ✓ multi-fon üretimi
- ✓ CD8 T hü folikülleri hücreleri hedef alacak üretimi



- ➢ İnaktif
- ➢ Subunit (rgp160)
- ➢ DNA
- ➢ Vektör (modifiye vaccinia Ankara [MVA], adenovirus, vesicular stomatitis virus, canary pox virus)
- ➢ RNA
- ➢ Dendritik hücre

Mylvaganam GH, et al. Curr Opin Immunol. 2015 Aug;35:1-8.
Li MJ, et al. Immunotherapeutic approaches to HIV cure and remission. Curr Opin Infect Dis 2022

Pasif bağışıklama

- ✓ **Monoklonal HIV'e özgül nötralizan antikorlar** (gp120 ve gp41)

---Hücreler arası HIV yayılımını engellemek

---Antikor bağımlı hücre aracılıklı sitotoksiste ve/veya viral inhibisyon ile enfekte hücreleri eradike etmek

Chun TW, et al. Nat Med 1999; 5: 651–55.

Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

Marina Caskey[1]*, Florian Klein[1]*, Julio C. C. Lorenzi[1], Michael S. Seaman[2], Anthony P. West Jr[3], Noreen Buckley[1], Gisela Kremer[4,5], Lilian Nogueira[1], Malte Braunschweig[1,6], Johannes F. Scheid[1], Joshua A. Horwitz[1], Irina Shimeliovich[1], Sivan Ben-Avraham[1], Maggi Witmer-Pack[1], Martin Platten[4,7], Clara Lehmann[4,7], Leah A. Burke[1,8], Thomas Hawthorne[9], Robert J. Gorelick[10], Bruce D. Walker[11], Tibor Keler[9], Roy M. Gulick[8], Gerd Fätkenheuer[4,7], Sarah J. Schlesinger[1] & Michel C. Nussenzweig[1,12]

Açık etiketli, faz-1 çalışma
Viremik kontrollülerden klonlanan anti-CD4 bağlanma bölgesi antikoru (3BNC117)

12 HIV (-), 17 HIV(+) hasta (2'si ART altında)
1, 3,10,30 mg IV infüzyon
güvenli ve iyi tolere edildi

30 mg tek doz infüzyon ile viral yükte 0.8–2.5 $\log_{10}$ azalma ve 28 gün boyunca sebat
Direnç gelişimi sorunu

3BNC117 monoterapisi etkili değil
3BNC117+ART veya antikor etkili olabilir
Latent rezervuar aktivasyonu+ 3BNC117 ile kür?

Geniş ölçüde nötralize edici antikorlar

- ✓ **3BNC117**
- ✓ **VRC01**
- ✓ **10 – 1074**
- ✓ **Bisepsifik (V3 ve V4 glikan)**

- ✓ Monoterapiler etkisiz
- ✓ Kombine tedavilerle uzun süreli viral supresyon
  - ➢ insanlarda 30 ay, makaklarda 4 yıl supresyon

Mendoza P, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature 2018
Nishimura Y, et al. Immunotherapy during the acute SHIV infection of macaques confers long-term suppression of viremia. J Exp Med 2021

Aşı+ İmmünstimülan

+

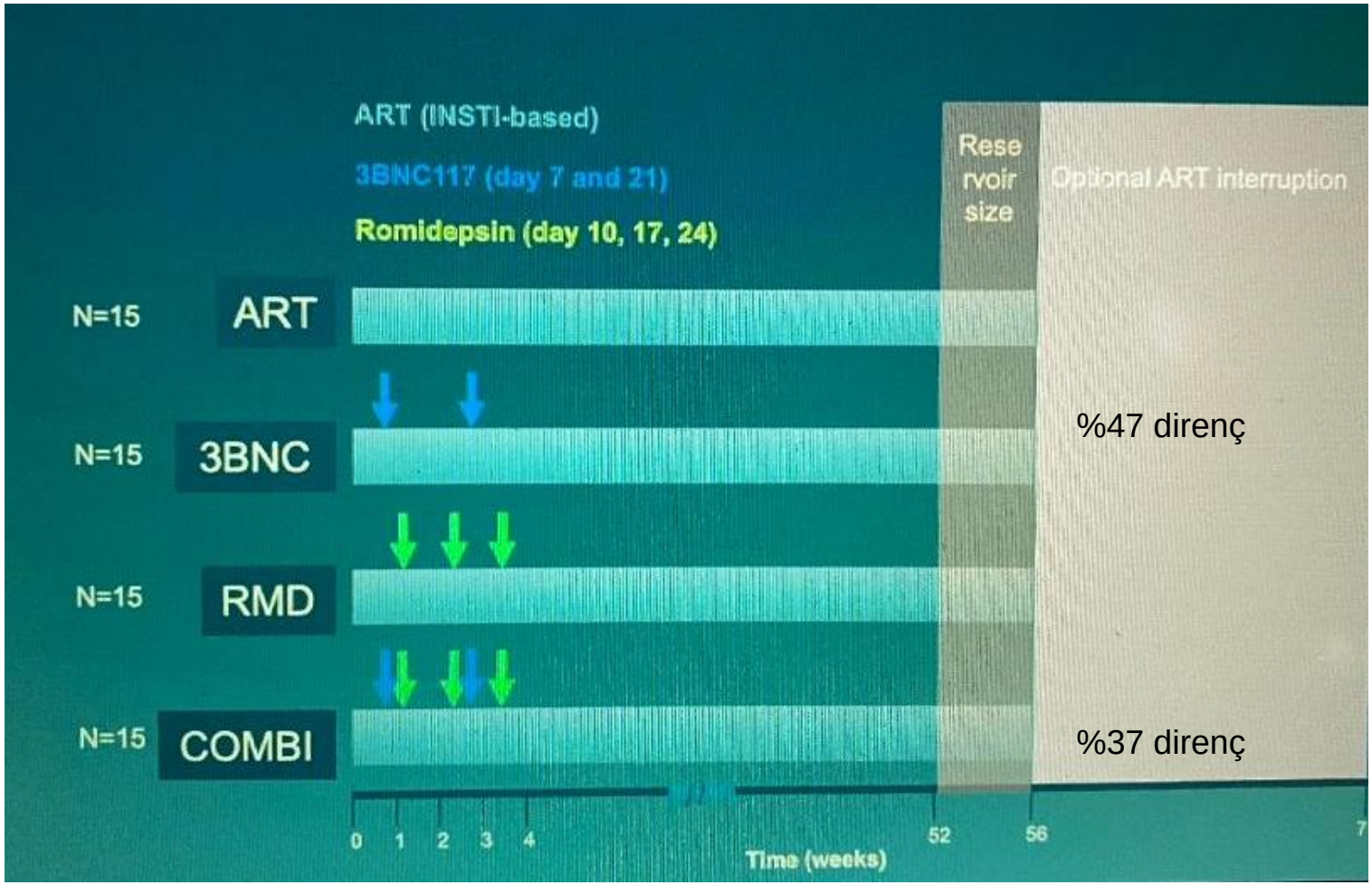
Antikor kombinasyonu

eCLEAR

- ✓ Danimarka'da 5, İngiltere'de 2 merkez
- ✓ ART naif 59 kişi (29'u primer HIV enfeksiyonu)
  - ➢ %92 erkek
  - ➢ CD4 sayısı ortalama: 500/mm^3
  - ➢ HIV RNA: 49.000 kopya/ml (740- 24.000.000)
  - ➢ 400 gün sonra, katılımcılara ART'ye ara verilmesi teklif edildi----20 hastada ART kesildi.
  - ➢ HIV RNA > 5000 kopya/ml veya CD4 sayısı<350/mm^3 --- yeniden tedavi

Rosás-Umbert M et al. *Administration of 3BNC117 at ART initiation induces long-term HIV CD8 T-cell immunity.* Conference on Retroviruses and Opportunistic Infections, abstract 122, 2022.

eCLEAR


ART (INSTI-based)
3BNC117 (day 7 and 21)
Romidepsin (day 10, 17, 24)
Reservoir size
Optional ART interruption
N=15
ART
N=15
3BNC
N=15
RMD
N=15
COMBI
%47 direnç
%37 direnç
0
1
2
3
4
52
56
Time (weeks)

- ✓ **Antikor ya da romidepsin alan grupta viral yükte düşüş daha hızlı**
  - ➢ ART--10 kopya/gün
  - ➢ Romidepsin-- 18 kopya/gün
  - ➢ 3BNC117'ye duyarlı--- 18 kopya/gün
  - ➢ 3BNC117'ye dirençli--- 15 kopya/gün
  - ➢ Romidepsin+ 3BNC117--artış yok
- ✓ 3BNC117 antikoruna duyarlı olanlarda, enfekte CD4 hücrelerinin sayısında kabaca %80'lik düşüş
- ✓ **İlk romidepsin dozu sonrası enfekte olmuş hücrelerde kabaca iki kat artış, 2. dozda etki yok**

Rosás-Umbert M et al. *Administration of 3BNC117 at ART initiation induces long-term HIV CD8 T-cell immunity.* Conference on Retroviruses and Opportunistic Infections, abstract 122, 2022.

- ✓ **Çalışmanın en önemli laboratuvar bulgusu**, 3BNC117'ye duyarlı kişilerde HIV'in gag proteinine duyarlı **CD8 hücrelerinin sayısının büyük ölçüde artması**
- ✓ **Tedaviye başladıktan bir yıl sonra CD8 hücrelerinin HIV'e karşı immün reaktivite oranı**:
  - Kontrol grubu---%0,1
  - 3BNC117---%2,9
  - Romidepsin+ 3BNC117---%1

Rosás-Umbert M et al. *Administration of 3BNC117 at ART initiation induces long-term HIV CD8 T-cell immunity.* Conference on Retroviruses and Opportunistic Infections, abstract 122, 2022.

- ✓20 hastada ART kesildi:
  - ➢7 hasta---12 hafta tedavisiz

ART+romidepsin+ 3BNC117 grubundan 1 kişi ART'yi bıraktıktan sonra 3.7 yıl boyunca viral yük baskılanmış durumda

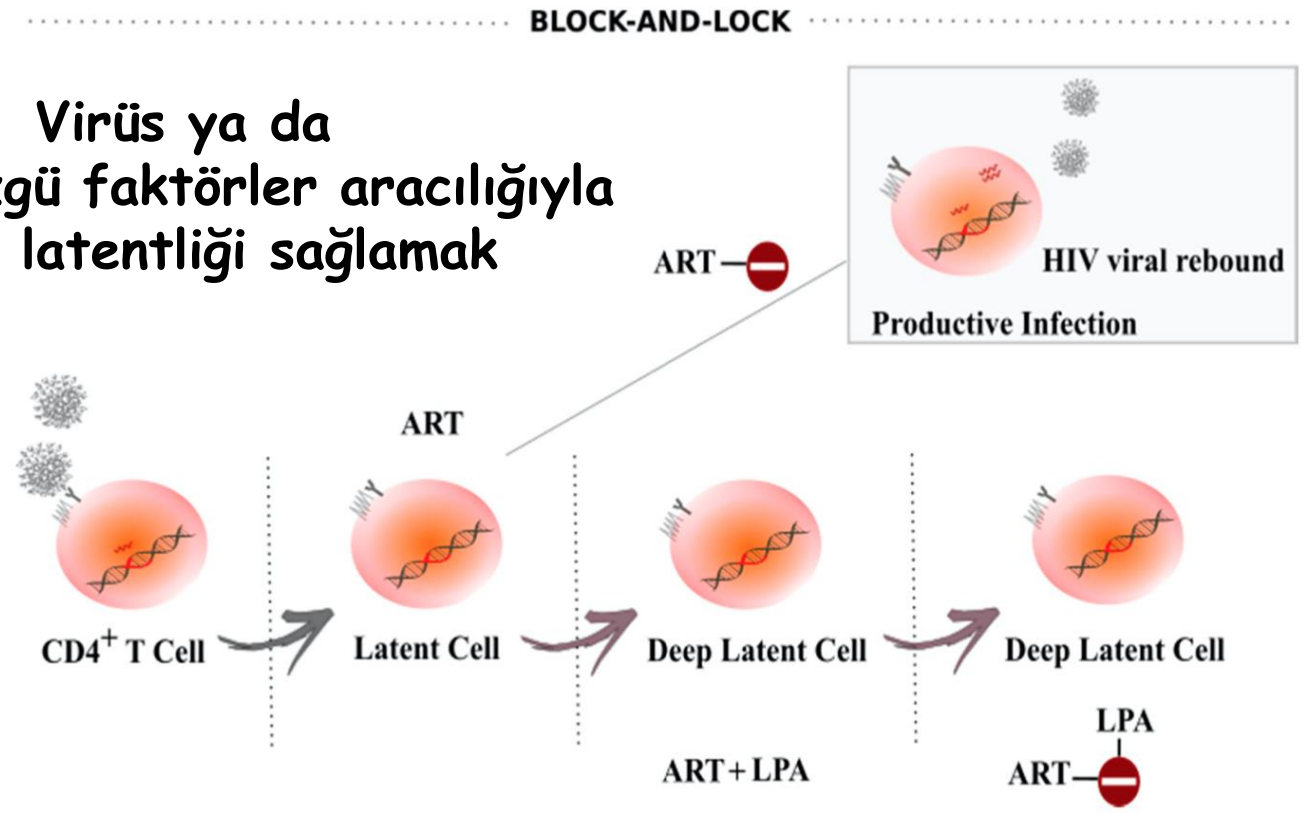
  - ➢3---ART+romidepsin+3BNC117
  - ➢5/7-- yüksek düzeyde IFN-gama

Rosás-Umbert M et al. *Administration of 3BNC117 at ART initiation induces long-term HIV CD8 T-cell immunity.* Conference on Retroviruses and Opportunistic Infections, abstract 122, 2022.

Viral Rezervuarın Baskılanması

Viral rezervuarın baskılanması --bloke et ve kilitle--

Virüs ya da konağa özgü faktörler aracılığıyla derin latentliği sağlamak



Moranguinho I, et al. Block-And-Lock: New Horizons for a Cure for HIV-1. *Viruses* 2020, *12*, 1443

Latentliği sağlayan ajanlar

- ✓ **Didehidro-kortistatin A** (dCA)-potent Tat inhibitörü
- ✓ Tat'ın TAR bağlanma bölgesine bağlanarak HIV-1'in transkripsyonel elongasyonunu inhibe eder
- ✓ İn-vivo çalışmalarda dCA dokularda viral RNA'nın azalmasına ve ART'nin kesilmesi ile viral reboundda gecikmeye yol açıyor.
- ✓ Çalışmalar devam ediyor

Moranguinho I, et al. Block-And-Lock: New Horizons for a Cure for HIV-1. *Viruses* 2020, *12*, 1443

Latentliği sağlayan ajanlar

- ✓ Levosimandan, spironalakton
- ✓ **LDGF/p75 inhibitörleri**
- ✓ mTOR kompleks inhibitörleri

  Rapamisinin, 2019'da başlayan 2 klinik çalışma:NCT02990312 ve NCT0244
- ✓ BRD4 inhibitörleri
- ✓ Jak inhibitörü

  Roksolitinib, klinik çalışma: NCT02475655
- ✓ Isı şok proteini 90 (HSP90) inhibitörleri

  Tanespimisin
- ✓ Çalışmalara ihtiyaç var

Moranguinho I, et al. Block-And-Lock: New Horizons for a Cure for HIV-1. *Viruses* 2020, *12*, 1443.
Janssens et al. Towards a Functional Cure of HIV-1. Frontiers in Microbiology | www.frontiersin.org **1** March 2021 | Volume 12
Acchioni C, et al. Fighting HIV-1 Persistence: At the Crossroads of "Shoc-K and B-Lock" Pathogens 2021,

Gen Terapileri ile Hücrelerde Değişim

Gen terapileri

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

Hedef: Steril ya da fonksiyonel kür

- ✓ **Entegre olan provirüsün eksizyonu**

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

Gen terapileri

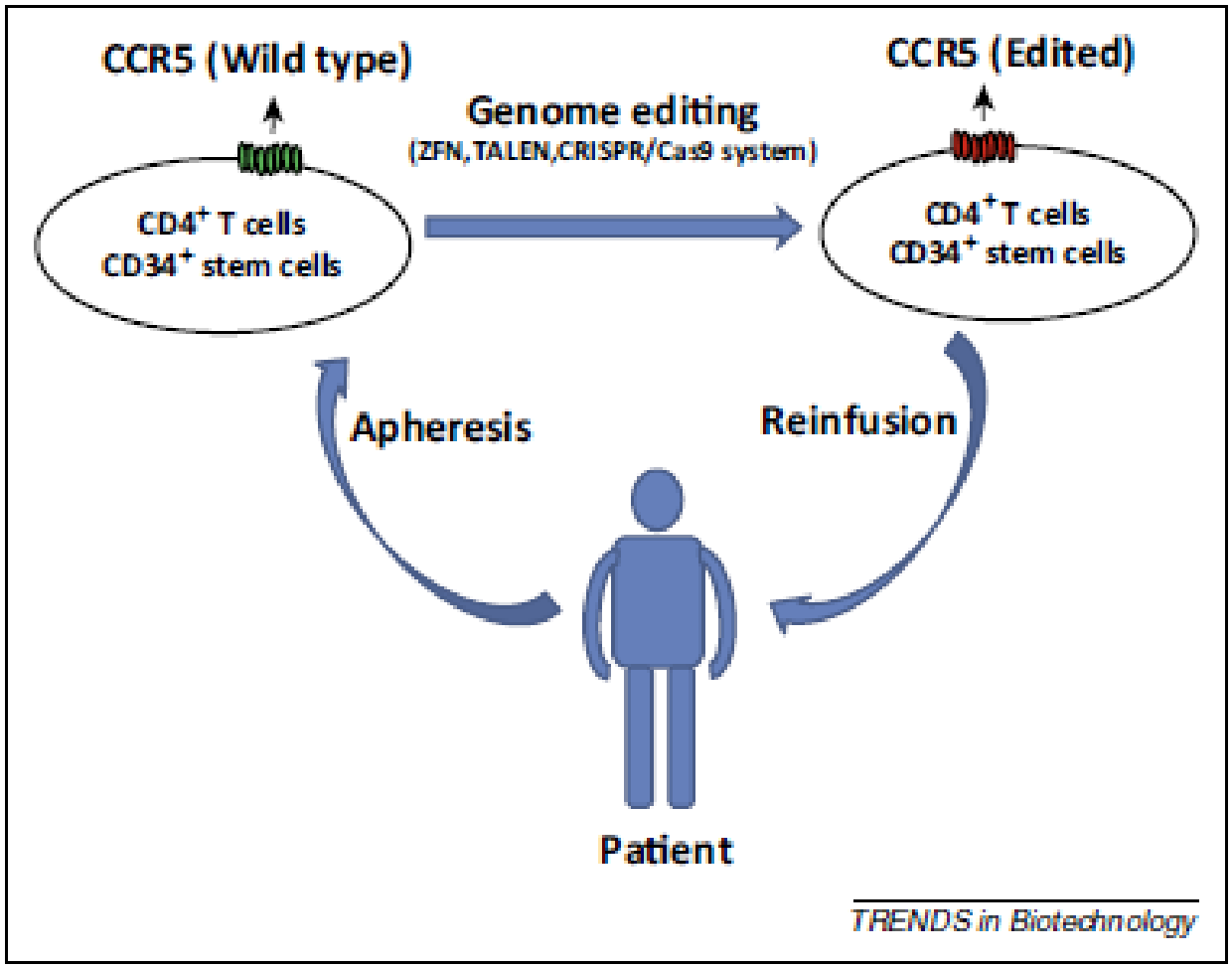
Nükleazlar, rekombinazlar, RNAiler….

Zinc-finger nucleases (ZFNs)
Transcription activator-like effector nucleases (TALENs)
Clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)

Genetik materyalde

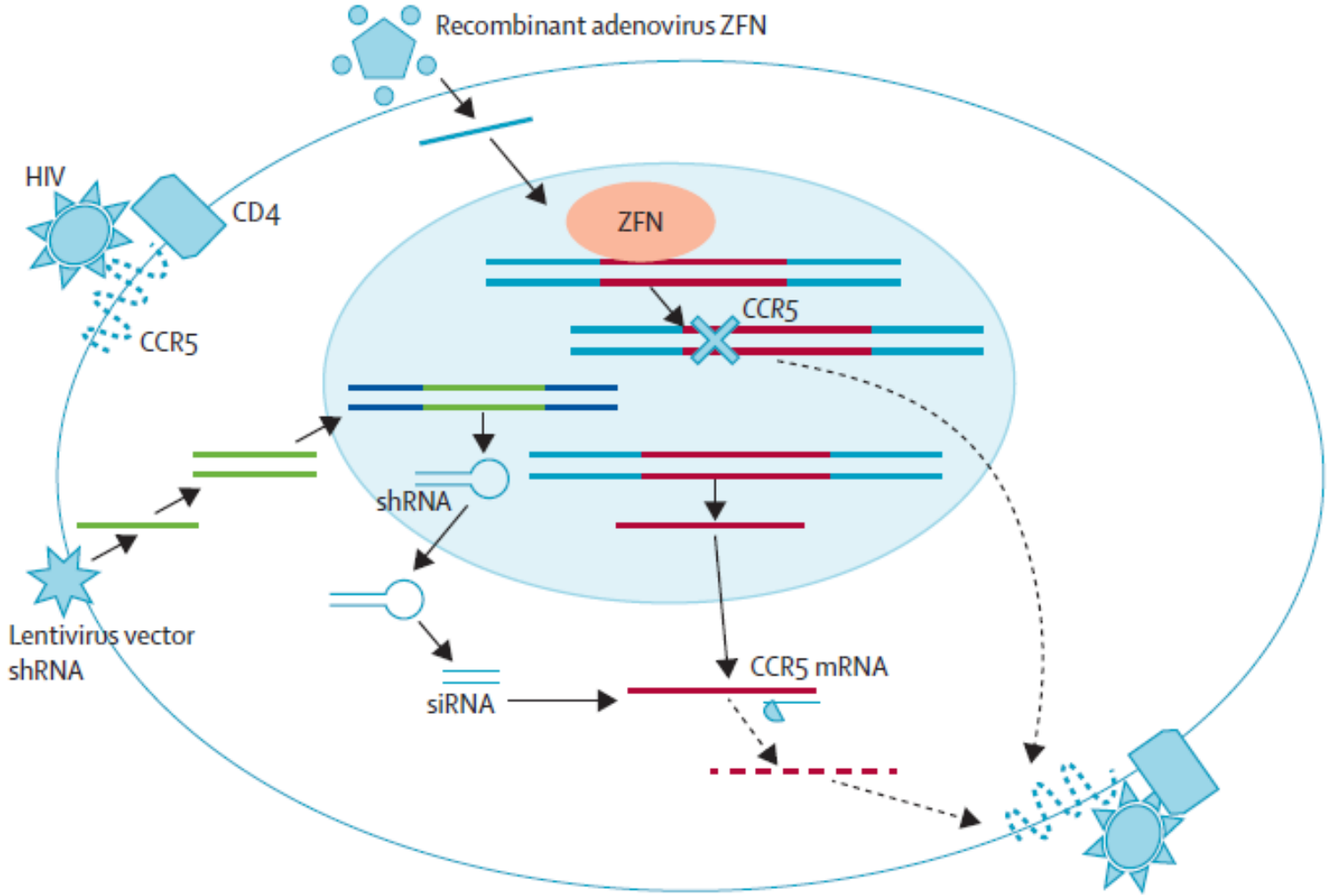
- modifikasyon
- parçalanma
- eklemeler..

HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi

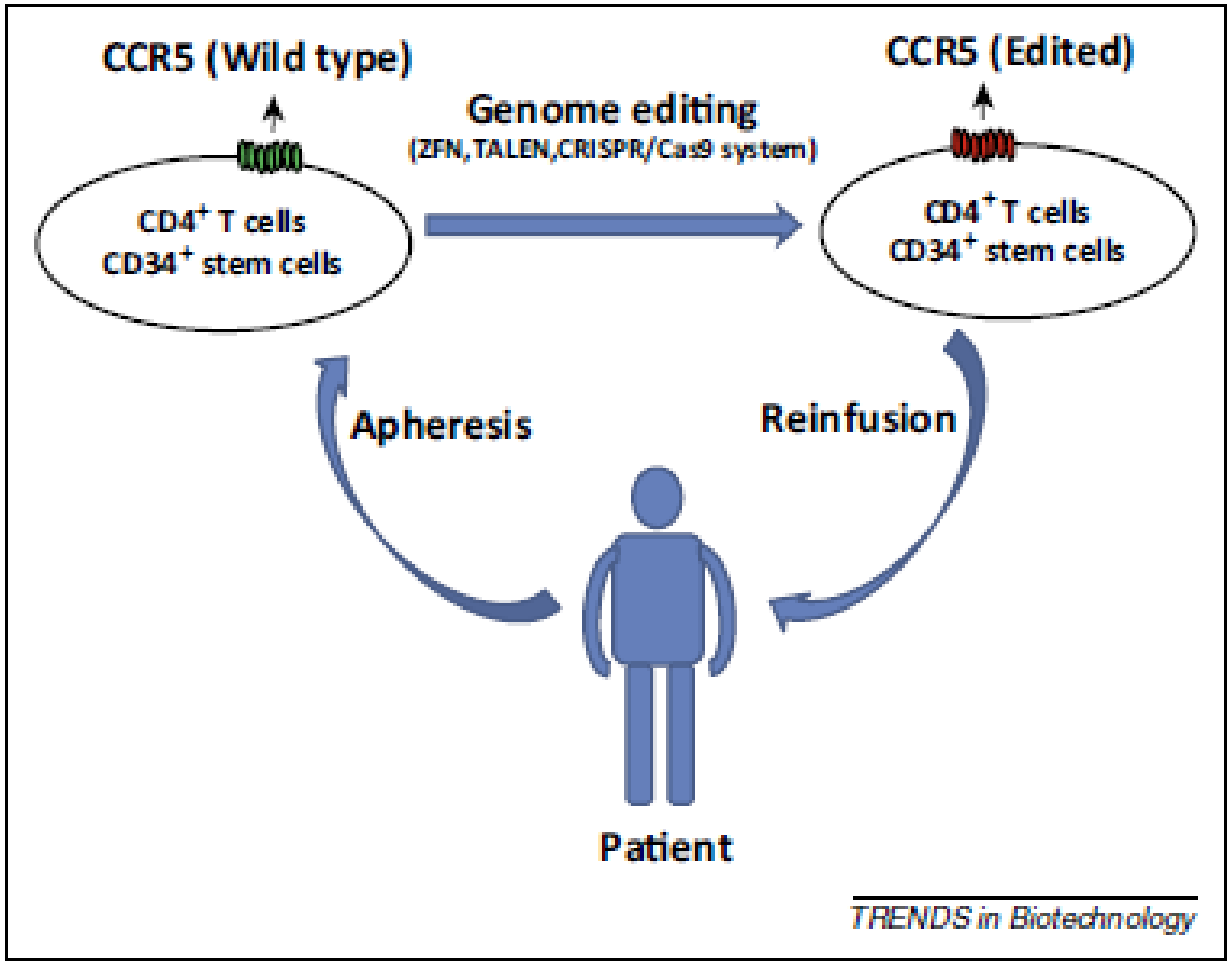


Gu WG.Trends Biotechnol 2015 Mar;33(3):172-9.

A



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



Orijinal HIV'e duyarlı hücrelerin eradikasyonu için kemoterapi gerekli olabilir

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

ART altındaki aviremik 12 hastaya ZFN ile CCR5 modifiye otolog CD4 hücre infüzyonu (%11-28'i ZFN ile modifiye)

tigated whether site-specific modification of the gene ("gene editing") — in this case, the infusion of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN) — is safe.

ART kesilmesinden sonra HIV DNA ⇩
CD4 hücre sayısı ⇧
1 hastada HIV RNA saptanamadı
Transfüzyon sırasında ciddi reaksiyon gelişen 1 olgu

During treatment interruption and the resultant viremia, the decline in circulating *CCR5*-modified cells (–1.81 cells per day) was significantly less than the decline in unmodified cells (–7.25 cells per day) ($P=0.02$). HIV RNA became undetectable in one of four patients who could be evaluated. The blood level of HIV DNA decreased in most patients.

CONCLUSIONS

CCR5-modified autologous CD4 T-cell infusions are safe within the limits of this study. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00842634.)

Gen terapilerinde asıl hedeflenen molekül CCR5

- ✓ CCR5 δ32 HIV enfeksiyonuna direnç sağlar ve kök hücre transplantasyonu ile kür olgusu mevcut
- ✓ HLA uyumlu CCR5 δ32 homozigot donör bulma olasılığı (1/100), transplant zorluğu
- ✓ Yapay CCR5 mutasyonu ve hücrelerin hastaya reinfüzyonu ile HIV direnci sağlanabiliyor

- ✓ **Uzun vadede etkinlik ve güvenlik kaygısı??**
- ✓ **Seçilecek genetik teknoloji, hücre tipi, veriliş şekli??**
- ✓ **Hücre topluluğunda CXCR4 varlığında CCR5 mutasyonu yeterli olabilir mi?**
- ✓ **CXCR4 hematopoietik, immün ve sinir hücrelerinin fonksiyonu için gerekli- inhibitör moleküller seçenek olabilir**

CRISPR/Cas9 ile modifiye edilmiş CCR5 geni taşıyan HSPC transplantasyonu-klinik çalışma (NCT03164135)

- ✓ ALL+HIV enfekte bireylere, siklofosfamid +tüm vücut radyoterapi sonrasına CCR5 modifiye edilen HSPC transplantasyonu yapıldı
- ✓ Transplantasyon öncesi gen modifikasyon etkinliği %17,8
- ✓ Transplantasyon sonrası oran %5,20 ile %8,28 arasında
- ✓ **Gen modifikasyon oranı çok düşük: periferik kandaki CD4+ hücrelerinin yaklaşık %2'si ve CD8+ hücrelerinin yaklaşık %1'i**

Xu L, et al. Crispr-Edited Stem Cells in a Patient With HIV and Acute Lymphocytic Leukemia. N Engl J Med (2019) 381(13):1240–7.

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

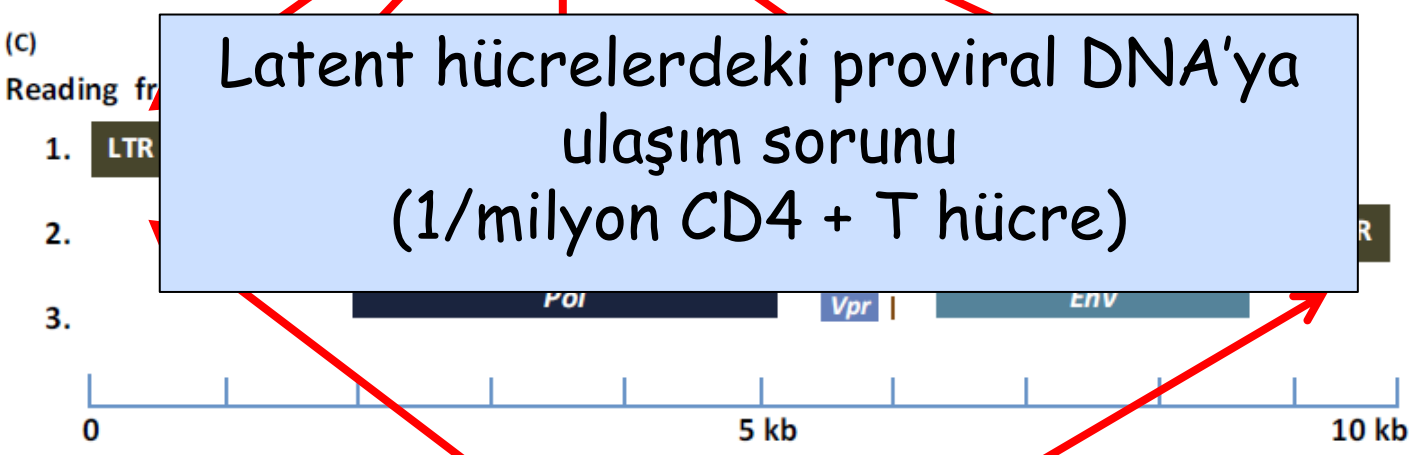
TABLE 2 | Clinical experiments of *CCR5*-based stem/progenitor cell or T cell therapy for HIV-1 infection.

Trial Number	Study Title	Tool	Date	Interventions	Status
NCT04201782	Long-Term Follow-up of HIV-Infected Subjects Treated With Autologous T-Cells Genetically Modified at the *CCR5* Gene by Zinc Finger Nucleases (SB-728-T or SB-728mR-T)	ZFN	2011–2031	Infusion of *CCR5*-disrupted SB-728-T or SB-728mR-T	Enrolling by invitation
NCT03617198	A Pilot Study of T Cells Genetically Modified by Zinc Finger Nucleases SB-728mR and CD4 Chimeric Antigen Receptor in HIV-infected Subjects	ZFN	2019–2025	Infusion of autologous T cells genetically modified to express a CD4 chimeric antigen receptor while also having ZFN-mediated disruption of the *CCR5* gene	Active, not recruiting
NCT02140944	Cord Blood Transplantation With *CCR5Δ32* Donor Cells in HIV-1 Infected Subjects Who Require Bone Marrow Transplantation for Any Indication and Its Observed Effects on HIV-1 Persistence		2015–2023	Transplantation with *CCR5Δ32* cord blood stem cells	Active, not recruiting
NCT02500849	A Pilot Study to Evaluate the Feasibility, Safety and Engraftment of Zinc Finger Nuclease (ZFN) *CCR5* Modified CD34+ Hematopoietic Stem/Progenitor Cells (SB-728mR-HSPC) in HIV-1 (R5) Infected Patients	ZFN	2015–2022	Infusion of *CCR5*-disrupted SB-728mR-HSPC after conditioning with busulfan	Active, not recruiting
NCT03164135	Safety and Feasibility Study of Allotransplantation of CRISPR/Cas9 *CCR5* Gene Modified CD34+ Hematopoietic Stem/Progenitor Cells in HIV-infected Subjects With Hematological Malignancies	CRISPR/Cas9	2017–2021	Transplantation of CD34+ hematopoietic stem/progenitor cells genetically modified at the CCR5 gene by CRISPR/Cas9	Recruiting
NCT02732457	Allogeneic Hematopoietic Stem Cell Transplantation in HIV-1 Infected Patients		2014–2024	Infusion of *CCR5Δ32* allogeneic HSCT in HIV-infected patients	Recruiting
NCT03666871	T-Cell Reinfusion After Interfering With Lymphocyte Binding Location of AIDS Virus Through Zinc-finger-nuclease Elimination of *CCR5* Receptors: The TRAILBLAZER Study	ZFN	2019–2024	Transplantation of autologous CD4+ T cells genetically modified at the *CCR5* gene by ZNF SB-728 versus	Recruiting
NCT00842634	A Phase I Study of Autologous T-Cells Genetically Modified at the *CCR5* Gene by Zinc Finger Nucleases SB-728 in HIV-Infected Patients	ZFN	2009–2013	Infusion of *CCR5*-disrupted CD4+ T Cells	Completed
NCT01252641	A Phase 1/2, Open Label, Single Infusion Study of Autologous T-Cells Genetically Modified at the *CCR5* Gene by Zinc Finger Nucleases (SB-728-T) in HIV-Infected Subjects	ZFN	2010–2015	Infusion of *CCR5*-disrupted SB-728-T	Completed
NCT01044654	A Phase 1 Dose Escalation, Single Dose Study of Autologous T-Cells Genetically Modified at the *CCR5* Gene by Zinc Finger Nucleases SB-278 in HIV-Infected Patients Who Have Exhibited Suboptimal CD4+ T-Cell Gains During Long-Term Antiretroviral Therapy	ZFN	2009–2014	Infusion of *CCR5*-disrupted SB-728-T	Completed
NCT01543152	A Phase I, Open-Label Study to Assess the Effect of Escalating Doses of Cyclophosphamide on the Engraftment of SB-728-T in Aviremic HIV-Infected Subjects on HAART	ZFN	2011–2017	Infusion of *CCR5*-disrupted SB-728-T after conditioning with cyclophosphamide	Completed
NCT02225665	A Phase 1/2, Open-Label Study to Assess the Safety and Tolerability of Repeat Doses of Autologous T-Cells Genetically Modified at the *CCR5* Gene by zinc finger Nucleases in HIV-Infected Subjects Following Cyclophosphamide Conditioning	ZFN	2014–2018	Infusion of *CCR5*-disrupted SB-728mR-T after conditioning with cyclophosphamide	Completed
NCT02388594	A Phase I Study of T-Cells Genetically Modified the *CCR5* Gene by Zinc Finger Nucleases SB-728mR in HIV-Infected Patients, with or without the *CCR5* Delta-32 Mutation, Pretreated With Cyclophosphamide	ZFN	2015–2019	Infusion of autologous CD4+ T cells genetically modified at the *CCR5* gene by ZFN SB-728mR with or without cyclophosphamide	Completed

Ding J, et al. Knowledge From London and Berlin: Finding Threads to a Functional HIV Cure. Frontiers in Immunology 1 May 2021 | Volume 12 |

Proviral DNA eliminasyonu

ZFN



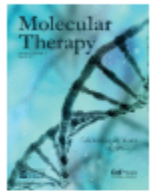
Latent hücrelerdeki proviral DNA'ya ulaşım sorunu
(1/milyon CD4 + T hücre)

CRISPR/Cas9

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

Export

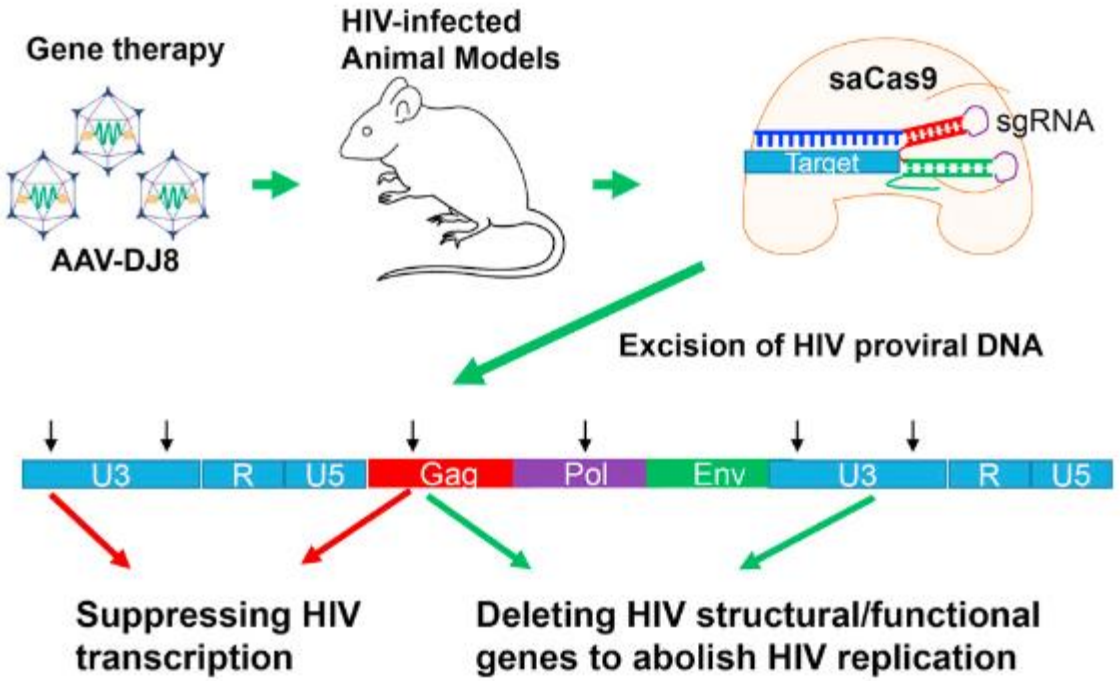
Molecular Therapy



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

Original Article

In Vivo Excision of HIV-1 Provirus by saCas9 and



- ✓ **SIV ile enfekte 3 maymun**+12 hafta sonra ART
- ✓ 8 hafta sonra kandan **immün hücreler** elde edilmesi
- ✓ Laboratuvar ortamında **gRNA/Cas9 terapisi ile SIV genetik materyalinin eksizyonu**
- ✓ 4 hafta sonra hücrelerin 2 maymuna infüzyonu (100 trilyon adenovirüs/100 dak)
- ✓ Tedavi uygulanan maymunların **dokularında DNA saptanmıyor**, kontrol maymunda saptanıyor.
- ✓ Eksize edilen ürün bir maymunun dokularının **%42'sinde diğerinin %76'sında** mevcut

Burdo TH et al. *Ex vivo and in vivo editing of the SIV genome in nonhuman primates by CRISPR-CAS9.*Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 24, 2019.

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CRISPR-Cas9 Mediated Exonic Disruption for HIV-1 Elimination

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Latent infection
CRISPR delivery

ABSTRACT

Background: A barrier to HIV-1 cure rests in the persistence of proviral DNA in infected CD4+ leukocytes. The high HIV-1 mutation rate leads to viral diversity, immune evasion, and consequent antiretroviral drug resistance. While CRISPR-spCas9 can eliminate latent proviral DNA, its efficacy is limited by HIV strain diversity and precision target cell delivery.

Methods: A library of guide RNAs (gRNAs) designed to disrupt five HIV-1 exons (tat_{1-2}/rev_{1-2}/*gp41*) was constructed. The gRNAs were derived from a conseensus sequence of the transcriptional regulator tat from 4004 HIV-1 strains. Efficacy was affirmed by gRNA cell entry through transfection, electroporation, or by lentivirus or lipid nanoparticle (LNP) delivery. Treated cells were evaluated for viral excision by monitoring HIV-1 DNA, RNA, protein, and progeny virus levels.

Findings: Virus was reduced in all transmitted founder strains by 82 and 94% after CRISPR TatDE transfection or lentivirus treatments, respectively. No recorded off-target cleavages were detected. Electroporation of TatDE ribonucleoprotein and delivery of LNP TatDE gRNA and spCas9 mRNA to latently infected cells resulted in up to 100% viral excision. Protection against HIV-1-challenge or induction of virus during latent infection, in primary or transformed CD4+ T cells or monocytes was achieved. We propose that multi-exon gRNA TatDE disruption delivered by LNPs enables translation for animal and human testing.

Interpretation: These results provide "proof of concept' for CRISPR gRNA treatments for HIV-1 elimination. The absence of full-length viral DNA by LNP delivery paired with undetectable off-target affirms the importance of payload delivery for effective viral gene editing.

Funding: The work was supported by the University of Nebraska Foundation, including donations from the Carol Swarts, M.D. Emerging Neuroscience Research Laboratory, the Margaret R. Larson Professorship, and individual donor support from the Frances and Louie Blumkin Foundation and from Harriet Singer. The research received support from National Institutes of Health grants T32 NS105594, 5R01MH121402, 1R01AI158160, R01 DA054535, PO1 DA028555, R01 NS126089, R01 NS36126, PO1 MH64570, P30 MH062261, and 2R01 NS034239.

Yeni Buluşlar ve Stratejiler

Bi-specific antibody both prevents infection and controls disease in monkeys

- ✓ Further along in development is BiIA-SG, a bi-specific antibody that **caused considerable excitement last year** when data from experiments in mice were published, especially in China, where this therapy has been developed by the University of Hong Kong.
- ✓ Bi-specific means that the **antibody both neutralises HIV viral particles and prevents them attaching to cells, thus acting as an entry inhibitor, and also attaches to HIV-infected cells, targeting them for destruction**. It can therefore be used as both treatment and as pre-exposure prophylaxis (PrEP). When BiIA-SG was given as a single dose before inoculation with SHIV, it completely protected the monkeys from infection, and when given after infection, all monkeys survived beyond three months, with the preservation of strong anti-HIV cellular responses.
- ✓ Further monkey experiments are planned before BiIA-SG is taken into human trials.

Niu MY *Tandem bispecific antibody prevents fully and induces prolonged T-cell immunity against pathogenic SHIV in monkey models.* 2019 HIV & HBV Cure Forum, Mexico City, 20 & 21 July 2019.

Enochian
BioSciences

Enochian BioSciences Announces FDA Acceptance of Pre-IND Request For Potential HIV Cure

June 14, 2021 07:00 ET | Source: Enochian Biosciences, Inc.

LOS ANGELES, June 14, 2021 (GLOBE NEWSWIRE) -- Enochian BioSciences, Inc., a company focused on gene-modified cellular and immune therapies in infectious diseases and cancer, today announced that the FDA has accepted a Pre-IND (Investigational New Drug) request for a potential functional cure or treatment of HIV. Written comments are expected this Fall.

Dr. Serhat Gumrukçu, co-founder and inventor of Enochian BioSciences, and Director of Seraph Research Institute (SRI), submitted the Pre-IND. The request was based on the results of a 54-year old man living with HIV who had failed to suppress the virus with antiviral therapy. The patient subsequently achieved viral control for 255 days with an innovative treatment of Natural Killer (NK) and Gamma Delta T-cells (GDT) collected from another person. During the entire period, no antiviral drugs were given. It is believed that the GDT cells, a small subset of immune cells that can be infected with HIV, could be a key factor in controlling the virus.

The findings were presented during the Conference of the American Society of Gene and Cell Therapy this past May. Presentations can be found at Enochianbio.com/Collaborations

Enochian BioSciences holds the exclusive license for the proprietary technology.

✓ Şok et ve öldür + bloke et ve kilitle

reaktive rezervuarın eliminasyonu

geriye kalan provirüslerin baskılanması

✓ Bloke et ve kilitle + şok et ve öldür

rezervuarın boyutunun azaltılması

geriye kalan virüslerin reaktive edilip eliminasyonu

Moranguinho I, et al. Block-And-Lock: New Horizons for a Cure for HIV-1. *Viruses* 2020, *12*, 1443
Janssens et al. Towards a Functional Cure of HIV-1. Frontiers in Microbiology | www.frontiersin.org **1** March 2021 | Volume 12

Sonuç

- ✓ **HIV enfeksiyonu akılcı ART ile yönetilebilir kronik enfeksiyon**

- ✓ **Küre yönelik çalışmalar:**

  Viral rezervuarın aktivasyonu

  İmmünoterapi — Bloke et ve kilitle

  Gen terapileri

  Kombine tedaviler

TEŞEKKÜR EDERİM