



KÜR NE ZAMAN? ÇALIŞMALAR NE AŞAMADA?

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

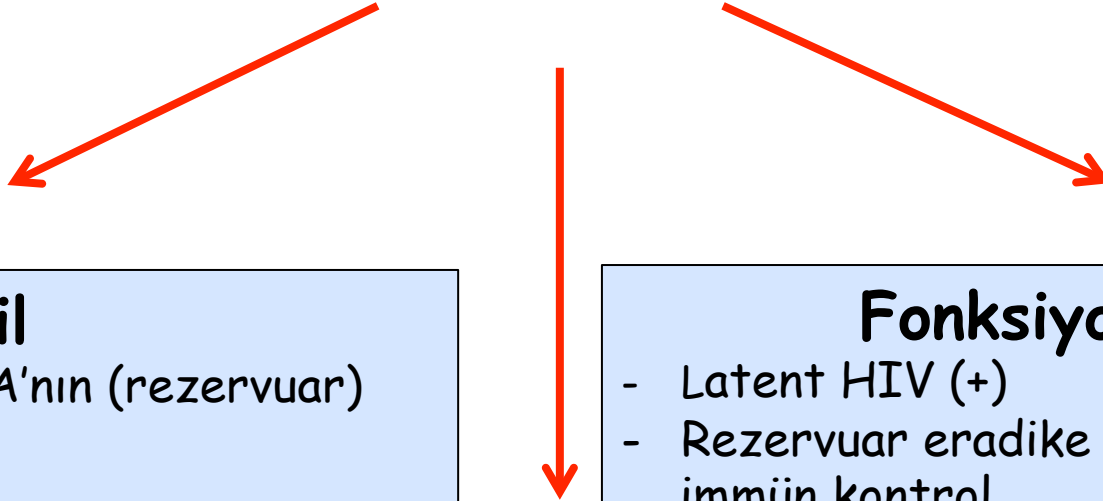


KÜR

- ✓ Yakın vadede beklenmiyor...
- ✓ Çalışmalar devam ediyor....



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



Steril/fonksiyonel kür

TABLE 1 | Differences between the Berlin and London Patients and other Patients.

Patients	Malignancy types	ART regimen	Conditioning regimen	HSC donor	Viral load after HSCT	ART interruption	Viral remission	Viral rebound
Berlin Patient	Acute myeloid leukemia	EFV, FTC, TDF	HSCT #1: FLAMSA, CTX, ATG, TBI; HSCT #2: Ara-C, GO, TBI	10/10 HLA match; homozygous for CCR5 delta32	Undetectable	Day of HSCT	Over 12 years	No
London Patient	Hodgkin lymphoma	EFV, FTC, TDF, RAL,RPV, 3TC, DTG	LACE, anti-CD52	9/10 HLA match; homozygous for CCR5 delta32	Undetectable	16 months after HSCT	Over 3 years	No
Düsseldorf Patient	Acute myeloid leukemia	FTC, TDF, DRV, RAL, ABC, 3TC, DTG	Flu, Treo	10/10 HLA match; CCR5 delta32	Undetectable	4 years after HSCT	NA	No
Minnesota Patient	Acute lymphoblastic leukemia	AZT/3TC IDV/riv AZT/LAM, TDF/FTC, ATV/riv, RAL, efavirenz	RIC (Flu/Mel)	8/8 HLA-matched, ABO-matched; wild-type CCR5	Detectable at 56 days after HSCT. Undetectable at 91 days after HSCT	2 years after HSCT	288 days	Yes
Boston Patients	A: Hodgkin lymphoma	A: EFV, FTC, TDF, RAL, DRV/r	A: RIC chemotherapy (busulfan, Flu)	A: 7/8 HLA match; without CCR5 delta32	A: Undetectable	A: 4.3 years after HSCT	A: 84 days	A: Yes
	B: Diffuse large B-cell lymphoma	B: EFV, FTC, TDF, NFV, ABC, RAL	B: RIC chemotherapy (busulfan, Flu)	B: 8/8 HLA match; without CCR5 delta32	B: Undetectable	B: 2.6 years after HSCT	B: 225 days	B: Yes
Essen Patient	Anaplastic large-cell lymphoma	LPV/r, TDF, FTC, 3TC, ABC, RAL	ATG, CSA, MTX	10/10 HLA match; homozygous for CCR5 delta32	Undetectable	7 days before HSCT	20 days	Yes
Mississippi baby		AZT, 3TC, NVP, LPV/r; began receiving ART 90 hours after birth				18 and 23 months of age	27 months	Yes

EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; RAL, raltegravir; RPV, rilpivirine; 3TC, lamivudine; DTG, dolutegravir; DRV/r, darunavir; ABC, abacavir; LPV/r, ritonavir-boosted lopinavir; NFV, nelfinavir; AZT, zidovudine; LAM, lamivudine; NVP, nevirapine; IDV, didanosine; r, raltegravir; ATV, atazanavir; Flu/Mel, fludarabine/melphalan; FLAMSA, fludarabine, Ara-C, and amsacrine; CTX, cyclophosphamide; ATG, anti-thymocyte globulin; TBI, total-body irradiation; Ara-C, cytarabine; GO, gemtuzumab oxogamicin; LACE, lomustine; Ara-C, cyclophosphamide, etoposide; Flu, fludarabine; Treo, treosulfan; RIC, reduced-intensity conditioning; CSA, cyclosporine-A; MTX, methotrexate; NA, not available.



Post-Treatment Controllers: Role in HIV “Cure” Research

Leslie R. Cockerham¹ · Hiroyu Hatano² · Steven G. Deeks²

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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 controllers:
 - erken tedavi:%13
 - kronik enfeksiyon:%4
- ✓ **5 yıl remisyon (HIV RNA<400 kopya/ml): %22**
- ✓ Erken tedavi başlanan grupta az oranda **10 yıllık remisyon**



The Journal of Clinical Investigation

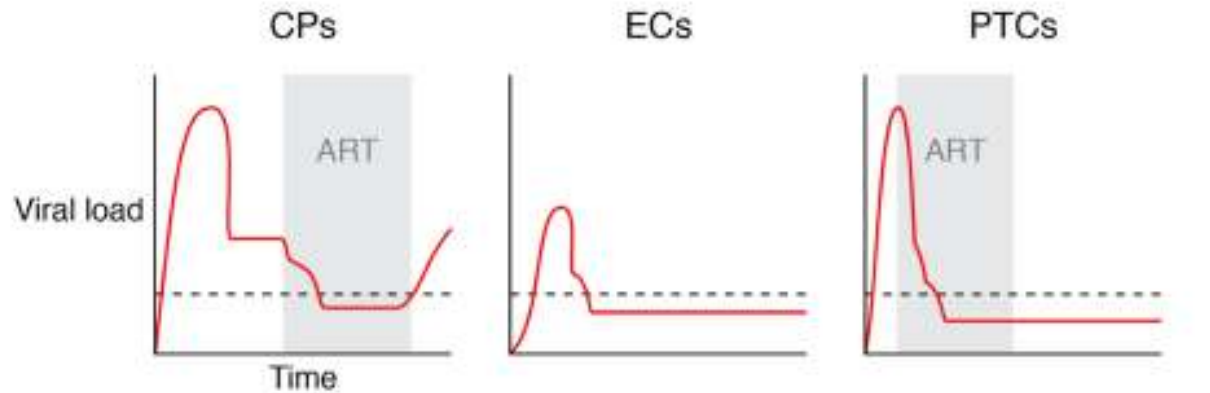
REVIEW

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

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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-naïve 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.



The Buenos Aires patient Argentinian woman controls HIV for at least 12 years after stopping treatment

- ✓ 1996 yılında 37 yaşında ilk tanı
serebral toksoplazmoz, HIV ilişkili demans
- ✓ 1998 yılından beri viral yük < 50 kopya/ml (2001'de blip)
- ✓ Birçok kez ART değişimi
- ✓ 2007'de lipodistrofiye bağlı ART'yi kesmiş
- ✓ 12 yıl boyunca viral yük saptanamaz düzeyde
CD4 >500 h/mm³
- ✓ **Anti HIV (-), HIV DNA (-)**

Uruena A et al.

[Prolonged posttreatment virologic control and complete seroreversion after advanced human immunodeficiency virus-1 infection.](#) Open Forum Infectious Diseases 8: ofaa613, 2021



NIH (National Institutes of Health)'te yapılan arařtırmalarda

- ✓ HIV RNA $<0,2$ kopya/ml, Anti HIV (-)
- ✓ Lenf doku örneklerinde HIV RNA (-), çok düşük düzeyde HIV DNA
- ✓ Kolon dokusunda ve periferik mononükleer hücrelerde HIV DNA (-)
- ✓ CD4+ T hücrelerinde çok düşük düzeyde replikasyon yeteneğinde olan HIV (+)
- ✓ HIV (-) kontrol grubuyla kıyaslandığında yüksek düzeyde HIV'e özgü CD4 hücre yanıtı düşük düzeyde CD8+T hücre yanıtı



- ✓ **Dr Asier Saez-Cirion, VISCONTI's principal investigator, told aidsmap.com: "Each post-treatment controller is unique. This Buenos Aires case is interesting because of the very complete clinical, immunological and virological evaluation.**
- ✓ **"We have so far identified 27 post-treatment controllers in the VISCONTI study. The median time off ART is now 10.5 years and we have a few cases who have maintained post-treatment remission for over 20 years. We also observed different degrees of loss of antibodies to HIV in some.**



Neden K r Saęlanamıyor?





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



Latent hücre



Replikasyon yeteneđi olan
stabil provirüs taşıır
Transkripsiyon aşamasında
sesiz

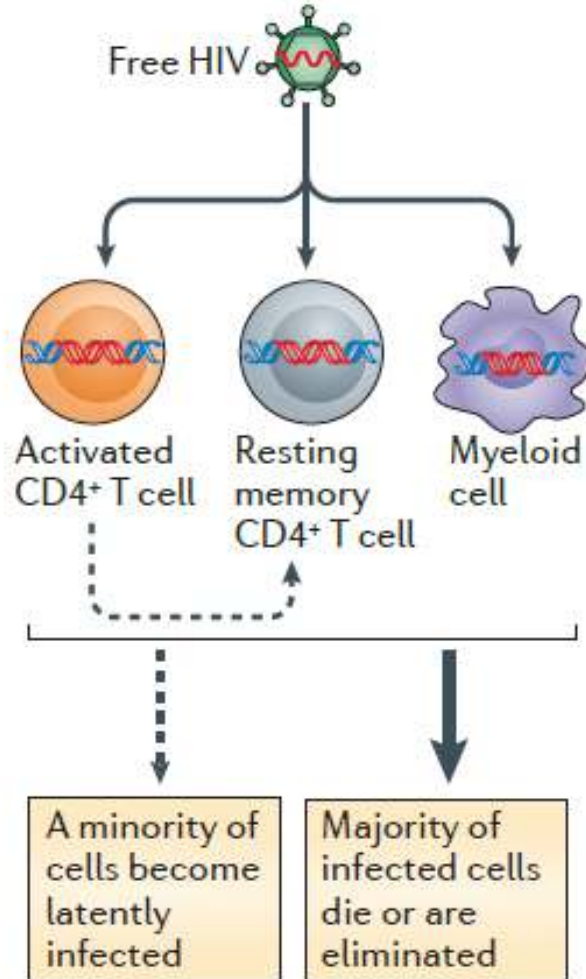
(viral transkript ya da viriyon
üretimi yok)

Hücreşel uyarı



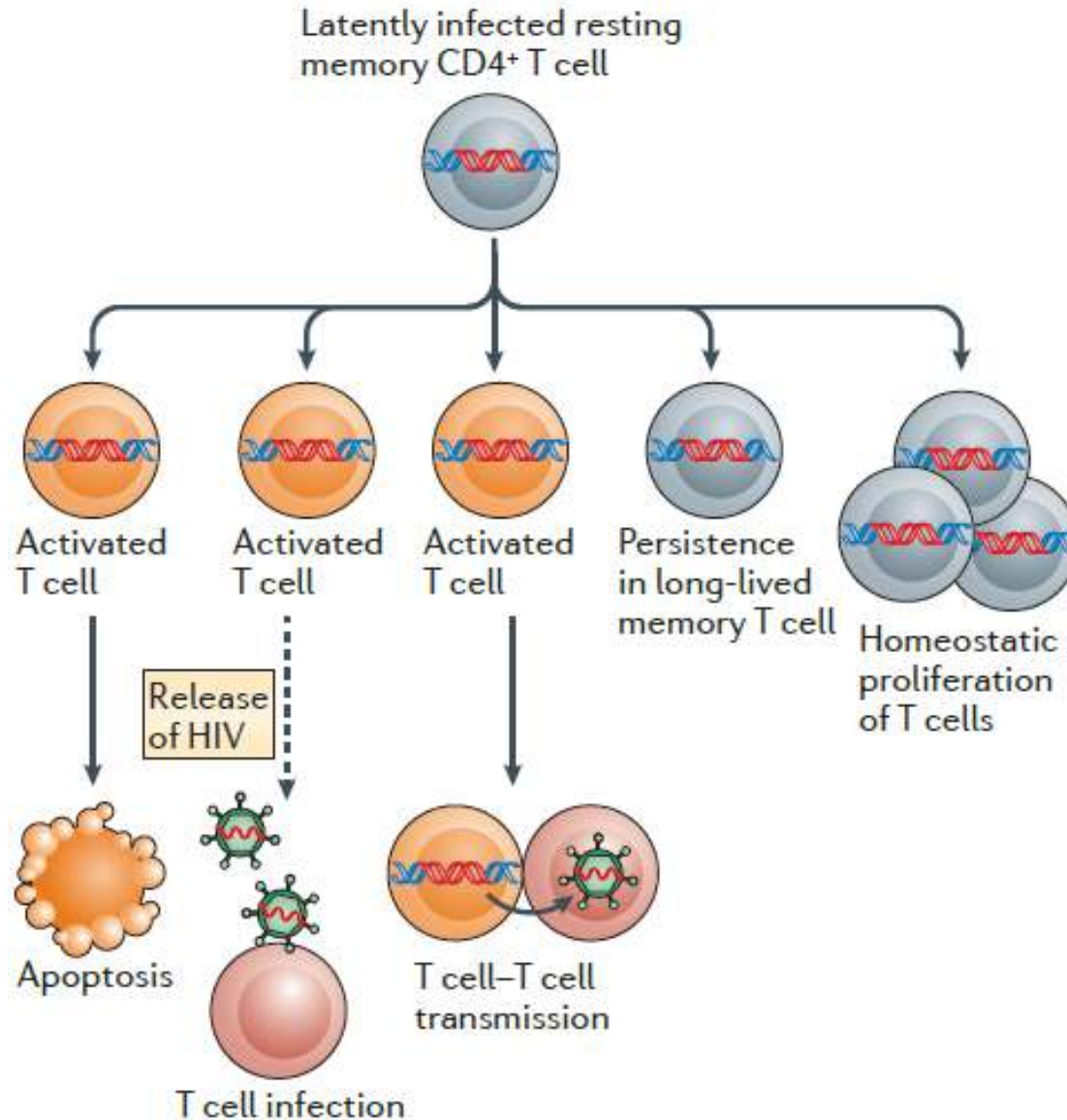
Viriyon üretimi

Establishment of latency



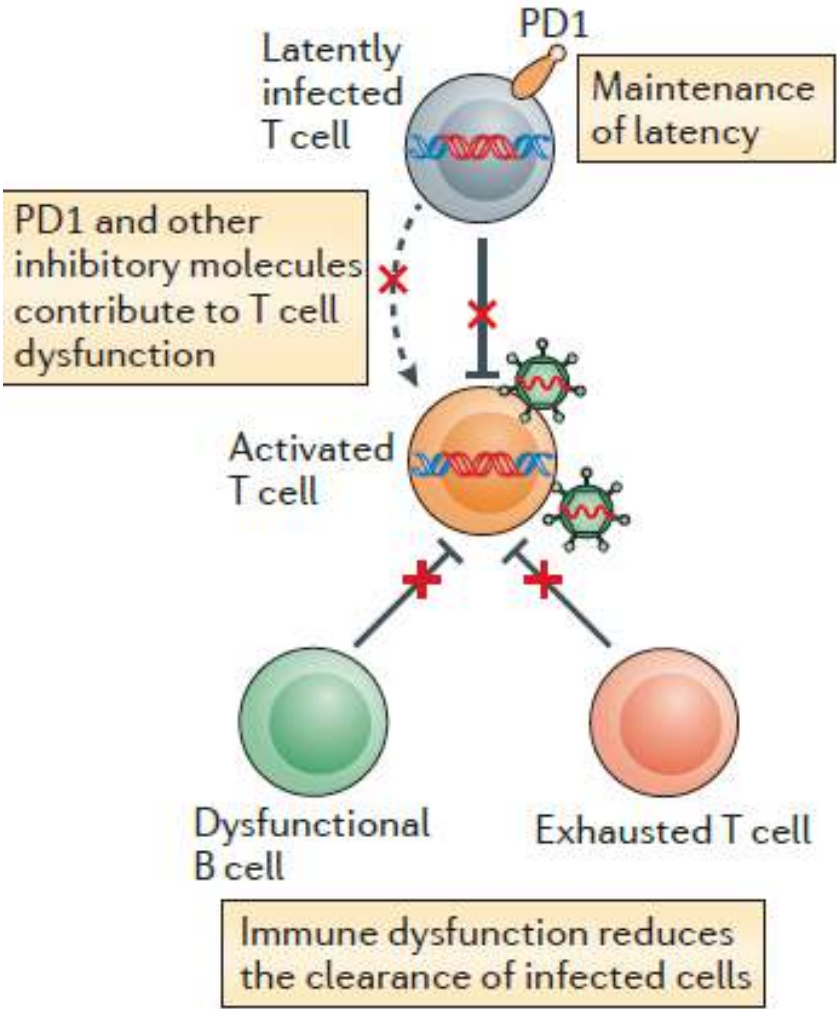


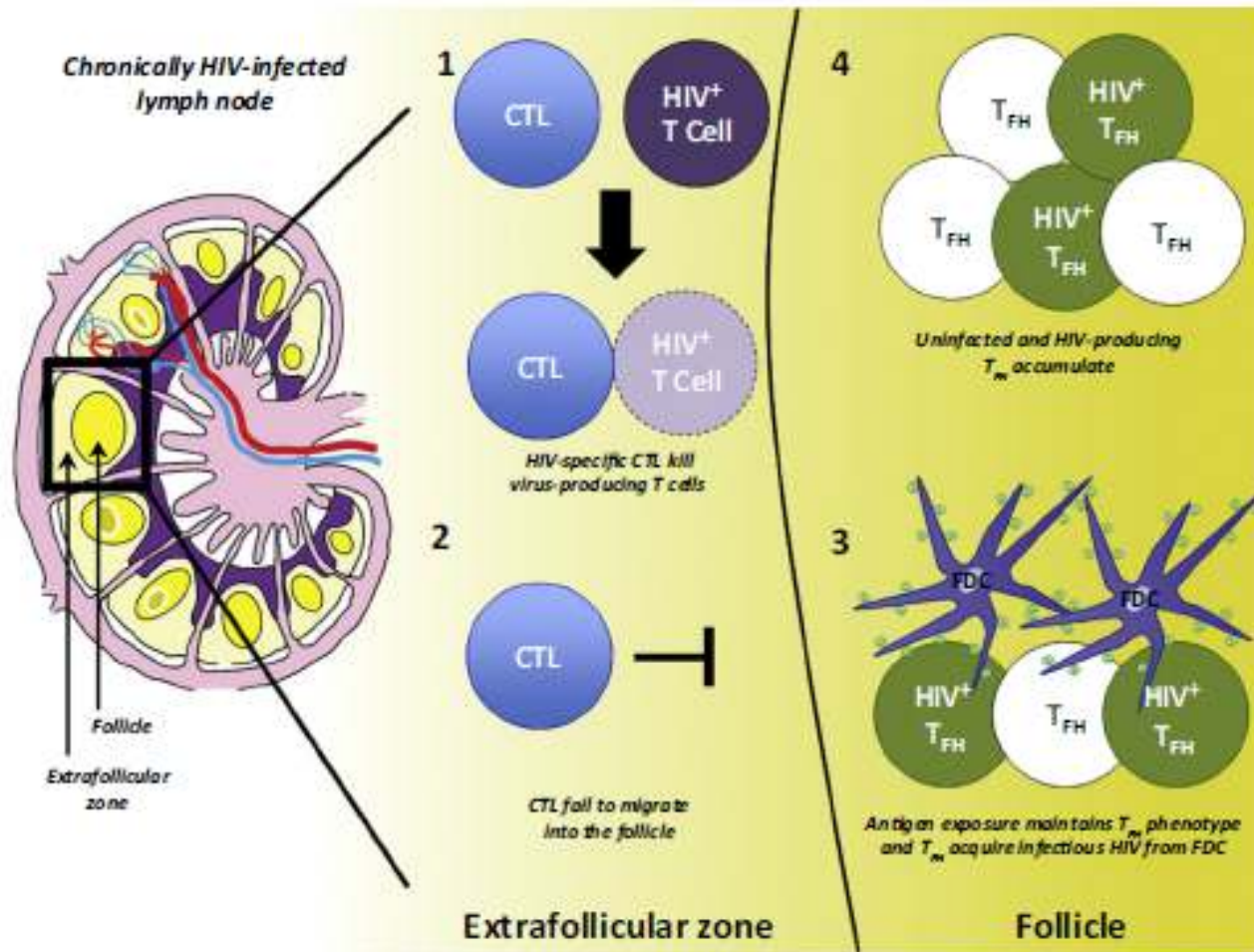
Fate of latently infected cells





Immune dysfunction prevents clearance of infected cells





Trends in Microbiology

Figure 1. Model of T Follicular Helper Cells (T_{FH}) Accumulation in Chronic, Untreated HIV Infection. HIV-specific cytotoxic T lymphocytes (CTLs) recognize and kill virus-producing T cells (HIV⁺ T cell) in the extrafollicular zone (1), but are found in low numbers within the follicle due to low CXCR5 expression (2). Within the follicle, T_{FH} receive both activation signals and infectious HIV from interactions with follicular dendritic cells (FDCs) (3). T_{FH}, including HIV-producing T_{FH} (HIV⁺), accumulate within the follicle (4).

Miles B, et al. TFH in HIV Latency and as Sources of Replication-Competent Virus. Trends in Microbiology 2016.



Kür için en büyük engel latent rezervuar

CD4+ T hücreleri
monosit/makrofaj
mikroglia

GIS- ilişkili lenfoid doku makrofajları
dendritik hücreler





Kürde Temel Yaklaşımlar



Temel Hedefler

- ✓ Viral rezervuarın eradikasyonu
- ✓ Viral rezervuarın baskılanması

İmmünoterapi

konağın bağışıklık sistemini HIV'e karşı güçlendirmek

Gen terapileri

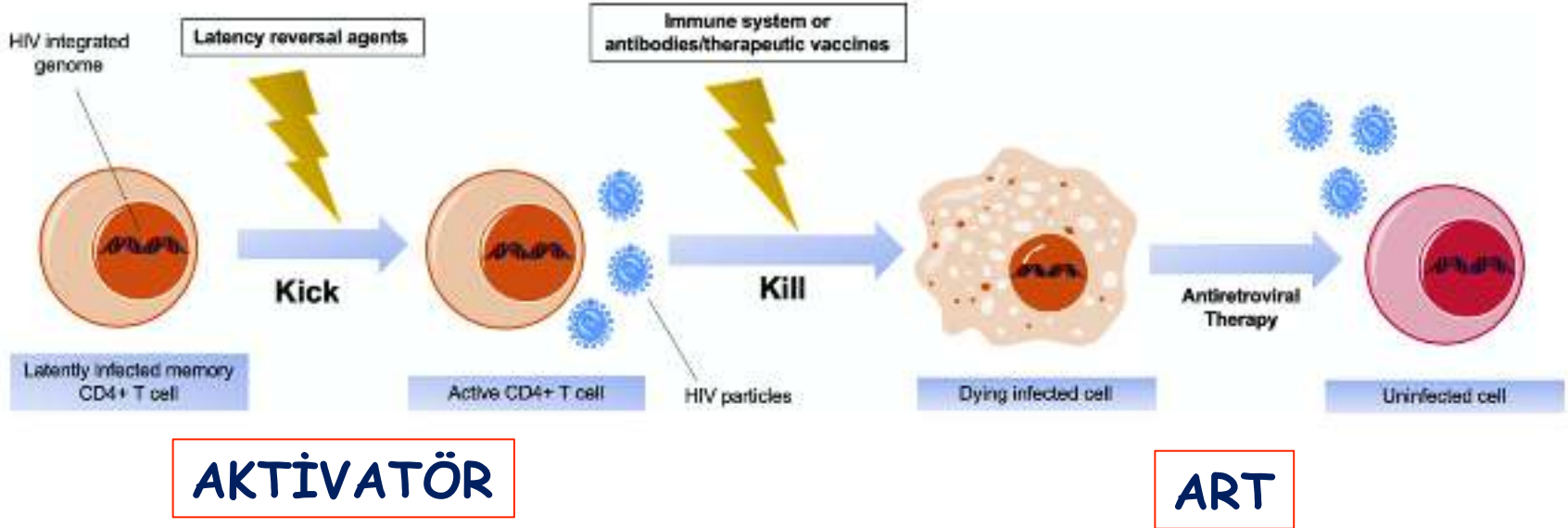
CD4 + T hücrelerini virüse dirençli hale getirebilmek



Viral Rezervuarın Eradikasyonu



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

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

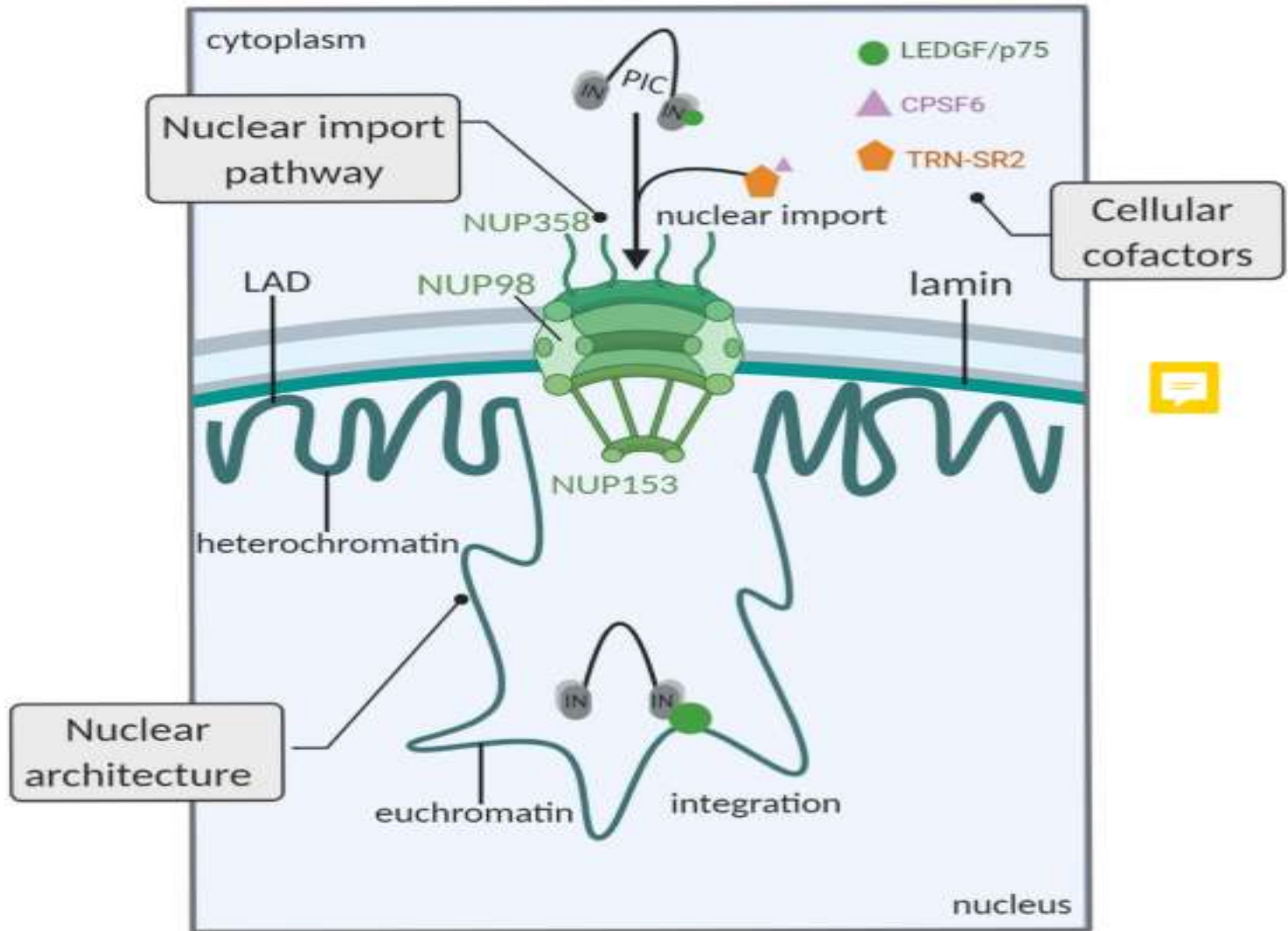


Latentlik

- ✓ **Pre-integrasyon**
- ✓ **Transkripsiyon**
epigenetik
- ✓ **Post-transkripsiyon**
m-RNA taşınması, kesilmesi, translasyon



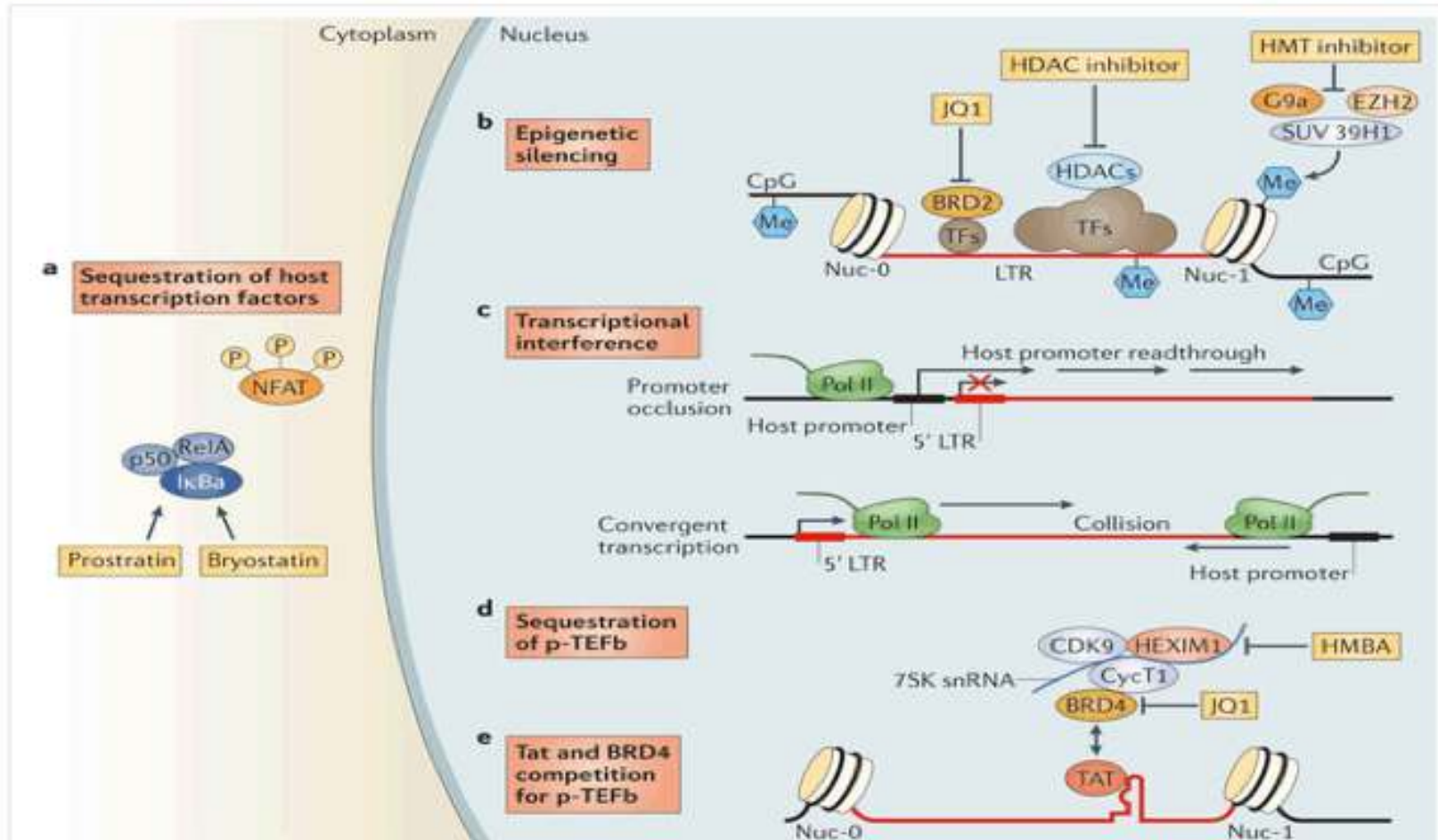
Pre-integrasyon

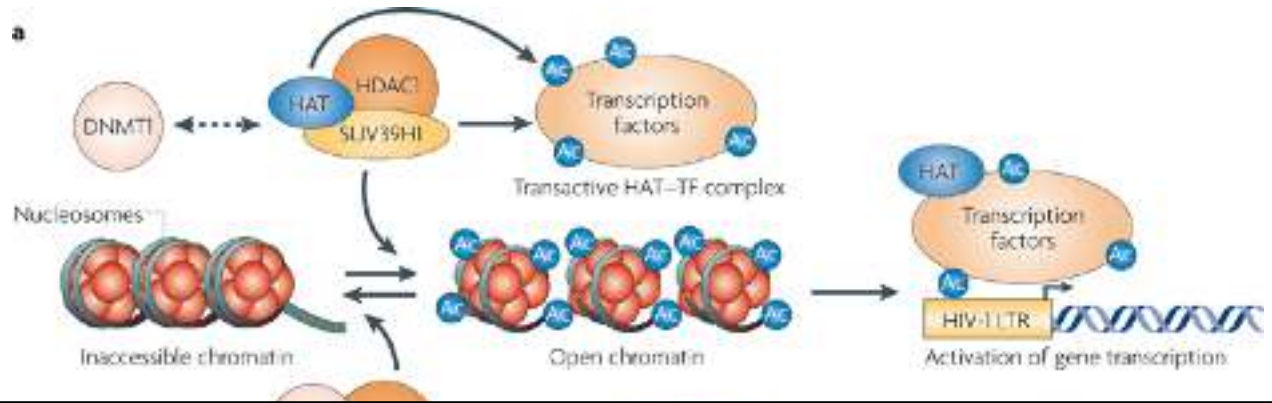




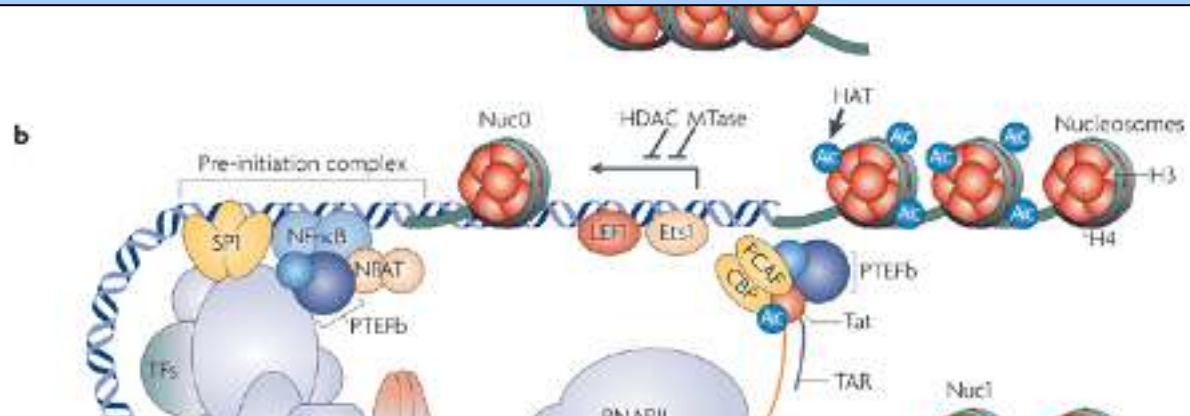
Transkripsiyon

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





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
- ✓ İnterlökinler (2,7,15)



Latent CD4 hücreleri aktivatörleri

- ✓ **Histon deasetilaz inhibitörleri (HDACi)**
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- ✓ İnterlökinler (2,7,15)



✓ HDACi

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

✓ PKC agonistleri

SUW133 (bryostatin-1 analogu) >
panobinostat, vorinostat, bryostatin-1
Gnidimacrin > romidepsin



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

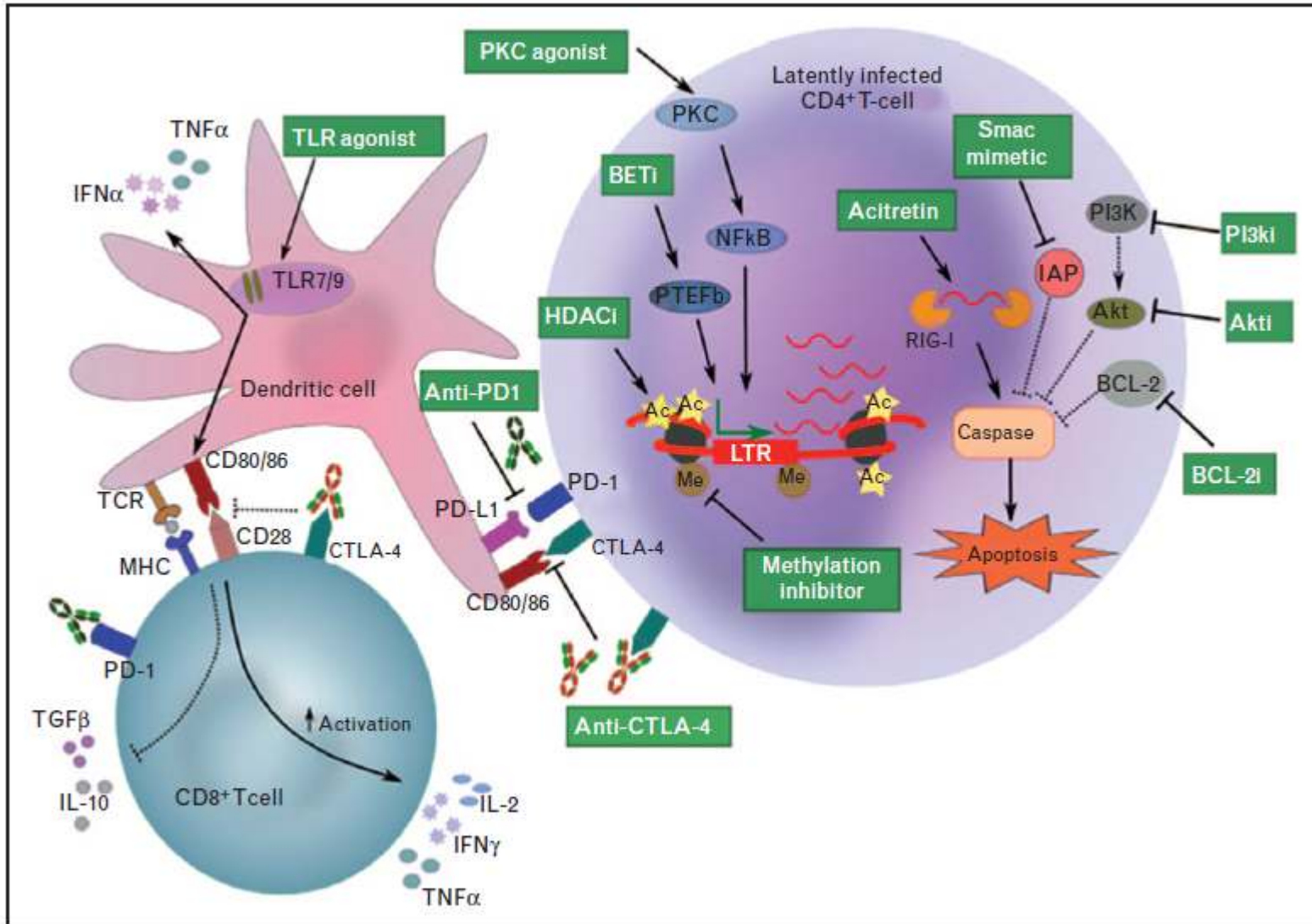
Table 1. Cancer therapies investigated in HIV cure research

Drug class	Promising compounds in HIV research	Phase	Mechanism of action	Used in clinical 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 methylation that represses HIV transcription	Yes, refs [14–16]
PKC agonists	Bryostatın-1, prostratin	Phase 1/2	Reversing HIV latency by promoting recruitment of P-TEFb to the HIV LTR	Yes, refs [17–19]

Klinik çalışmalarda
bryostatın güvenli
ancak latent rezervuarı
aktif edici dozlar toksik



Apoptozu indükleyici ve immünmodulatuvar ilaçlar





Latent CD4 hücreleri aktivatörleri

- ✓ Histon deasetilaz inhibitörleri (HDACi)
- ✓ DNA metiltransferaz inhibitörleri
- ✓ Protein kinaz C agonistleri
- ✓ **Bromodomain ekstraterminal motif inhibitörleri**
klinik çalışmalara ihtiyaç var
- ✓ Apoptoz protein inhibitörlerinin inhibitörleri
- ✓ **İmmün checkpoint inhibitörleri**
- ✓ **Toll-like reseptör agonistleri**
- ✓ İnterlökinler (2,7,15)



(ii) Apoptosis promoting compounds

BCL-2 antagonists	Venetoclax	Licensed (CLL), phases 1-3	Inhibits antiapoptotic BCL-2, sensitizing cells to apoptosis. When combined with IRA	No
RIG-I inducers	Acitretin			No
PI3k/Akt inhibitors	Perifosine, a			No
SMAC mimetics	Birinapant, SBI-06371 LCL1			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

İmmünmodülatuvar aktivatörlerin avantajı: şok ve öldürme aşamalarında etkililer

(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]



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

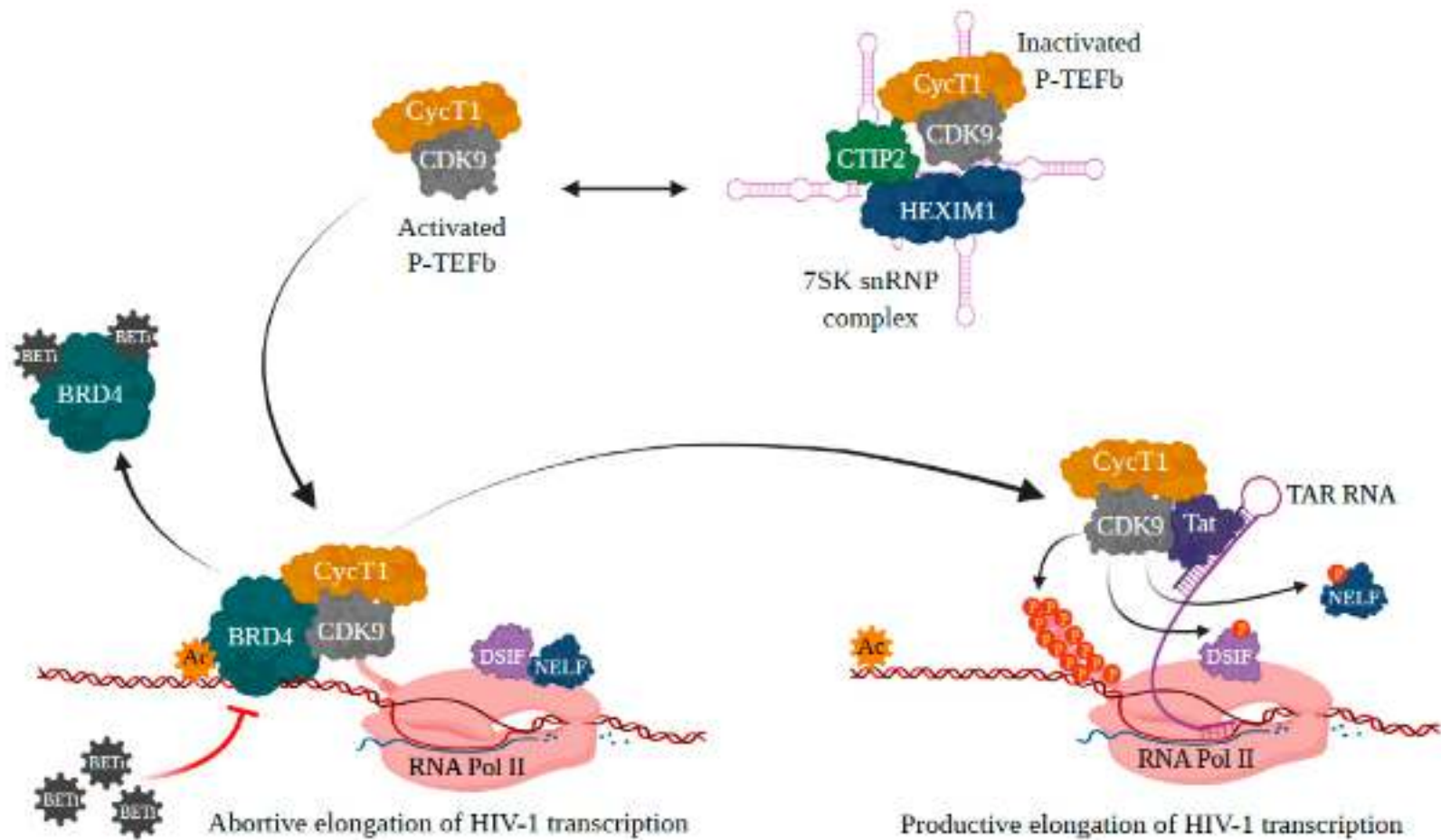


Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-dependent manner.

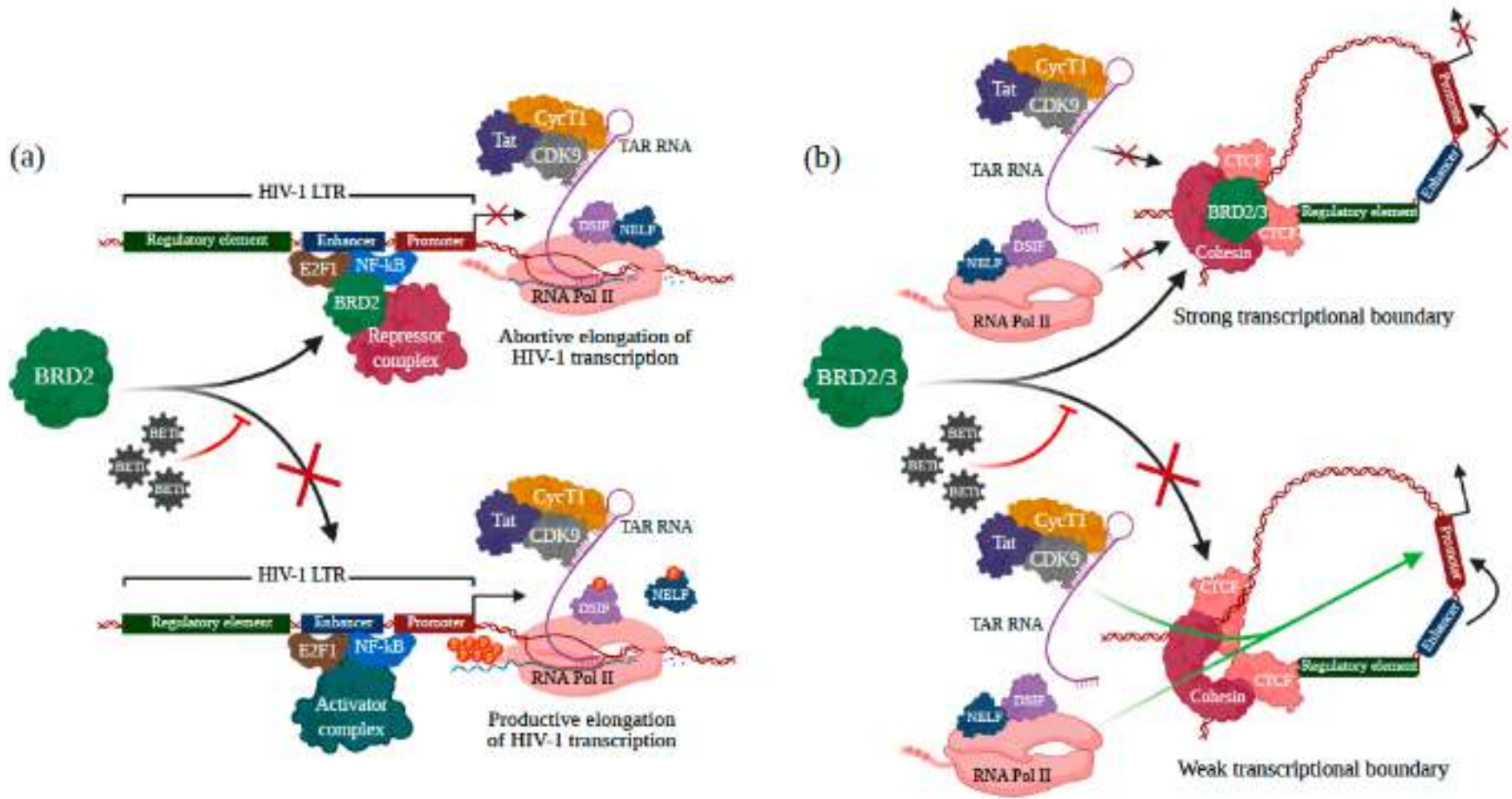


Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-independent manner.



Yeni moleküller

Molecular Therapy
Nucleic Acids

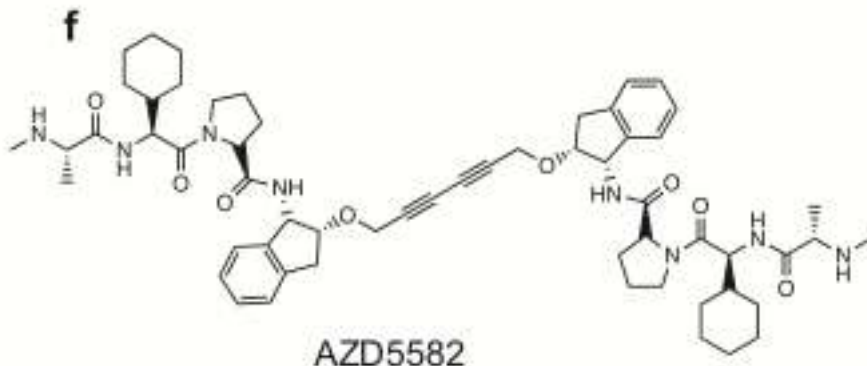
Review



Lnc(ing)RNAs to the “shock and kill” strategy for HIV-1 cure

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**NIH-Supported Scientists Reverse HIV
and SIV Latency in Two Animal Models**

Findings Represent Progress Toward an
HIV Cure

January 22, 2020



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



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



- ✓ Reaktif 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.**



- ✓ 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



NIH Public Access

Author Manuscript

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NIH-P

**Latent rezervuarın reaktivasyonu öncesi
sitotoksik hücrelerin terapötik aşılama
ile güçlendirilmesi eradikasyon için
gerekli olabilir**

ART
(HI

erle
uarı

stimulating HIV-1-specific CTLs prior to reactivating latent HIV-1 may be essential for successful eradication efforts and should be considered in future clinical trials.



İmmünoterapi



İmmünoterapi

✓ **Latent rezervuarı eradike edecek ya da baskılayacak terapötik aşular**

Anti-HIV immünotesinin işlev ve yaygınlığını arttıracak aşular

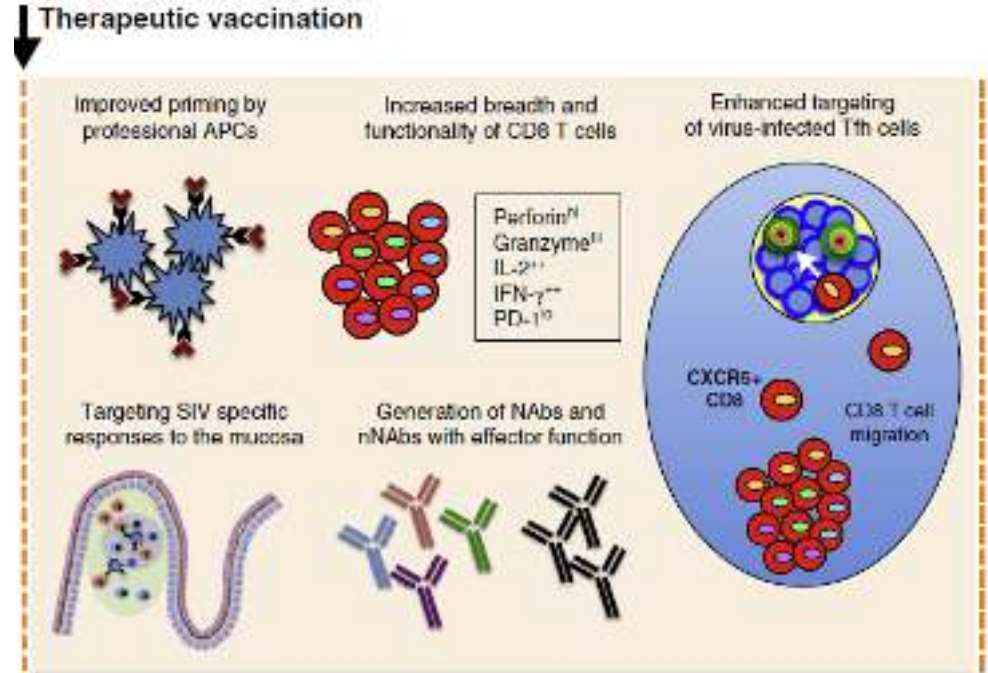
✓ **Pasif bağışıklama**



Terapötik aşular

Terapötik aşı hedefleri:

- ✓ Anti-viral CD8+ T hücreleri (CTL)
- ✓ CD4+ T hücreleri
- ✓ Nötralizan antikorlar
- ✓ multi-fonksiyonel T hücre üretimi
- ✓ CD8+ T hücre (B hücre foliküllerindeki foliküler T hücreleri hedef alacak) üretimi

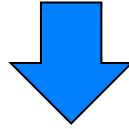




Klinik alıřmalar

Var olan immüniteyi güçlendiren

- DNA ± adjuvan
- Virüs ± adjuvan
- Dendritik hücre kökenli aşı alıřmaları



ART kesilmesi sonrası viral geri tepmede
gecikme, viral yükte 0,5-1 log düşüş

Klinik yarar belirsiz

Latent rezervuar üzerine minimal etki



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Immune clearance of highly pathogenic SIV infection

Scott G. Hansen^{1,*}, Michael Piatak Jr.^{2,*}, Abigail B. Ventura¹, Colette M. Hughes¹, Roxanne M. Gilbride¹, Julia C. Ford¹, Kelli Oswald², Rebecca Shoemaker², Yuan Li², Matthew S. Lewis¹, Awbrey N. Gilliam¹, Guangwu Xu¹, Nathan Whizin¹, Benjamin J. Burwitz¹, Shannon

SIV-protein ekspresse eden RhCMV vektör kökenli aşı ile aşılanan rhesus makaklar SIVmac239 ile (intrarektal, intravajinal, IV) enfekte ediliyor

Abstract

Makakların ~%50'sinde süregelen, aviremik kontrol
Zamanla SIV enfeksiyon bulgularının kaybı

Aşıya özgü ve otolog SIV enfekte CD4 T hücrelerini tanıyan
CD8T hücre düzeyi stabil kaldı

69-172 hafta sonra yapılan nekropsilerde perifer ya da dokuda
SIV RNA veya SIV DNA saptanamadı (ultrasensitif PZR)



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



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

Marina Caskey^{1*}, Florian Klein^{1*}, Julio C. C. Lorenzi¹, Michael S. Seaman², Anthony P. West Jr³, Noreen Buckley¹, Gisela Kremer^{4,5}, Lilian Nogueira¹, Malte Braunschweig^{1,6}, Johannes F. Scheid¹, Joshua A. Horwitz¹, Irina Shimeliovich¹, Sivan Ben-Avraham¹, Maggi Witmer-Pack¹, Martin Platten^{4,7}, Clara Lehmann^{4,7}, Leah A. Burke^{1,8}, Thomas Hawthorne⁹, Robert J. Gorelick¹⁰, Bruce D. Walker¹¹, Tibor Keler⁹, Roy M. Gulick⁸, Gerd Fätkenheuer^{4,7}, Sarah J. Schlesinger¹ & 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 log₁₀
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?



Aşı+ İmmünstimülan + Antikor
kombinasyonu



51 rhesus makak maymun
yapay insan/maymun virus-SHIV ile enfeksiyon
+ 9. gün ART

↓ 6 ay ART

n=24
Ad26 ve MVA vektörleri aracılığıyla
4 doz SHIV geni içeren terapötik aşı

↓ 6 ay sonra

10 doz vesatolimod

↓ 3 ay sonra

5 doz bNAb PGT121



HIV cure at CROI: new data on antibodies, vaccines and genetically engineered T-cells

Pre-conference Community HIV Cure Research Workshop outlines the results
Gus Cairns-24 March 2020

n=15	plasebo	Viral yük ↑
n=12	vesatolimod+PGT121	n=8, viral yük~2000 k/ml n=4, viral yük 12 haftaya kadar yükselmedi
n=12	vesatolimod+ ad26/MVA aşısı	Viral yük ↑ (genellikle 200 k/ml, <2000 k/ml) n=3, 12 hafta boyunca saptanamaz düzeyde
n=12	vesatolimod+ PGT121 + ad26/MVA aşısı	n=4, viral yük~1000 k/ml n=2, viral yük artsa da 12. haftaya kadar baskılandı n=4, viral yük 12 haftaya kadar yükselmedi

Vesatolimodun ve antikor infüzyonunun son dozundan
3 ay sonra ART kesildi



A PLACEBO-CONTROLLED TRIAL OF HTI VACCINES IN EARLY TREATED HIV INFECTION

CROI 2021 March 6-10 Reported by Jules Levin

Lucia Bailon¹, Anuska Llano², Samandhy Cedeno², Miriam B. Lopez¹, Yovaninna Alarcon¹, Pep Coll², Angel Rivero³, Anne R. Leselbaum⁴, Ian McGowan⁵, Devi SenGupta⁶, Borja Lopez¹, and the AELIX-003 Study Group. ¹Centro de Investigación Biomédica en Red sobre Enfermedades Infecciosas (CIBERESP), ²IRSI-Caixa Investigación Biomédica, ³IRSI-Caixa Investigación Biomédica, ⁴University of Melbourne, ⁵University of Melbourne, ⁶University of Melbourne, Spain, ⁵University of Melbourne, Australia.

Background: HIV-1 infection is a global health problem. ART has reduced HIV-1 related mortality and morbidity, but does not eliminate the virus. HTI vaccines are being developed to generate immune control, which is a state of low viral load and high CD4+ T-cell counts. This study evaluated the safety and immunogenicity of HTI vaccines in early treated HIV-1 infection.

Methods: A phase 1, placebo-controlled, randomised trial of HTI vaccines in early treated HIV-1 infection. The study included 12 participants in the vaccine group and 12 in the placebo group. All participants were on ART. The primary endpoint was the proportion of participants with viral load <2,000 copies/mL at 22 weeks without ART. Secondary endpoints included immunogenicity and safety.

Results: All participants were on ART. The primary endpoint was met in 5 (41.7%) participants in the vaccine group and 1 (8.3%) in the placebo group. Immunogenicity was similar between groups. Safety was acceptable.

Conclusion: HTI vaccines are safe and immunogenic in early treated HIV-1 infection. They should be considered as a backbone for future HIV cure eradication trials. HTI vaccines should be considered as a backbone for future HIV cure eradication trials. HTI vaccines should be considered as a backbone for future HIV cure eradication trials.

8 (40%) aşıllı, 1 (8%) plasebo



ART'siz 22 hafta

Viral yük <2,000 kopya/mL → 5 aşıllı/1 plasebo

"I think the study has convincingly shown that the HTI vaccines can generate immune control; it is clear that they should be considered as a backbone for future HIV cure eradication trials," said Professor Sharon Lewin, director of the Peter Doherty Institute for Infection and Immunity and professor of medicine at the University of Melbourne.

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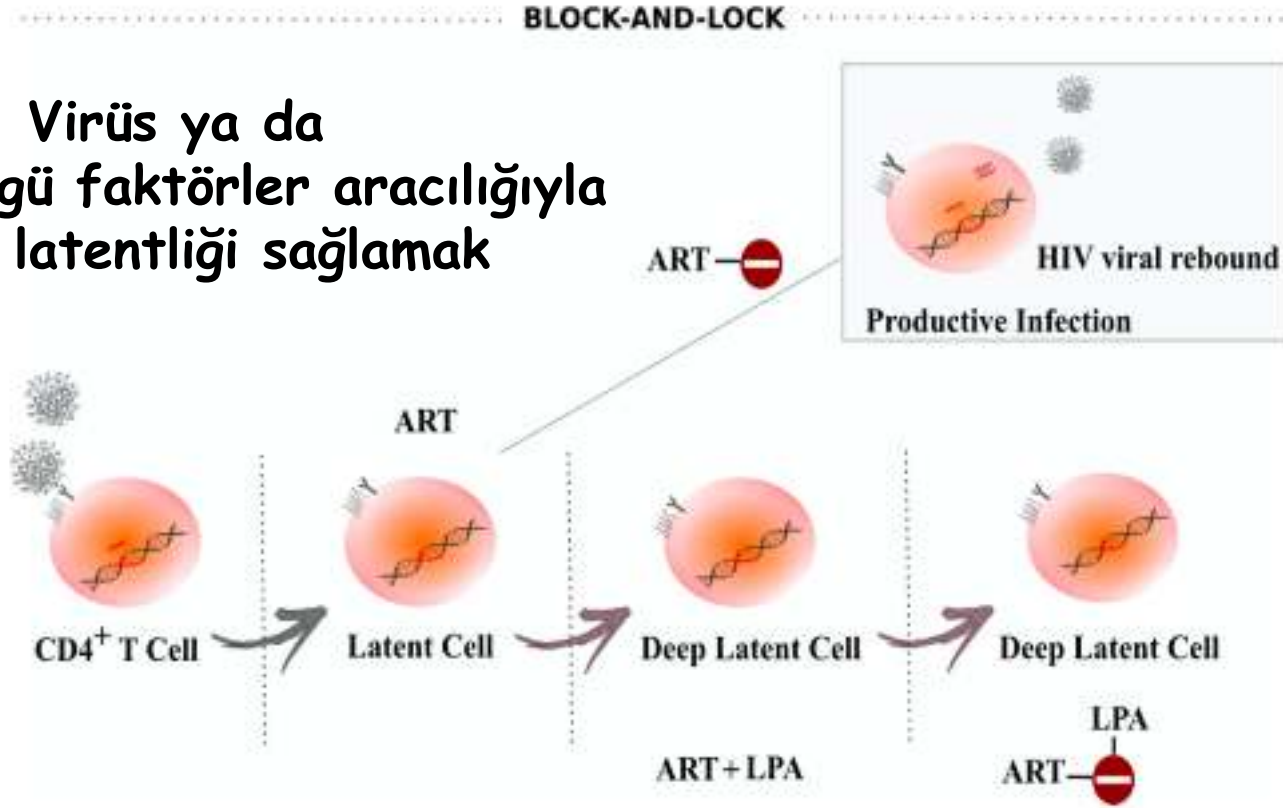


Viral Rezervuarın Baskılanması



Viral rezervuarın baskılanması --bloke et ve kilitle--

Virüs ya da
konağa özgü faktörler aracılığıyla
derin latentliği sağlamak





Latentliđi sađlayan ajanlar

- ✓ Didehidro-kortistatin A (dCA)-potent Tat inhibit6r6
- ✓ Tat'ın TAR bađlanma b6lgesine bađlanarak HIV-1'in transkripsiyonel elongasyonunu inhibe eder
- ✓ İn-vivo alıřmalarda dCA dokularda viral RNA'nın azalmasına ve ART'nin kesilmesi ile viral reboundda gecikmeye yol aıyor.
- ✓ alıřmalar devam ediyor



Latentliđi sađlayan ajanlar

- ✓ Levosimandan, spironalakton
- ✓ **LDGF/p75 inhibitörleri**
- ✓ mTOR kompleks inhibitörleri
(rapamisinin 2019'da başlayan 2 klinik çalışması:NCT02990312 ve NCT0244)
- ✓ BRD4 inhibitörleri
- ✓ Isı şok proteini 90 (HSP90) inhibitörleri
- ✓ Çalışmalara ihtiyaç var



Gen terapileri



Gen terapileri

- ✓ Enfeksiyon ilişkili özgül genleri modifiye ederek hücreleri HIV'e

Hedef: Steril ya da fonksiyonel kür

- ✓ Entegre olan provirüsün eksizyonu



Gen terapileri

Nükleazlar, rekombinazlar, RNAiler...

Zinc-finger nucleases (ZFNs)

Transcription activator-like effector nucleases (TALENs)

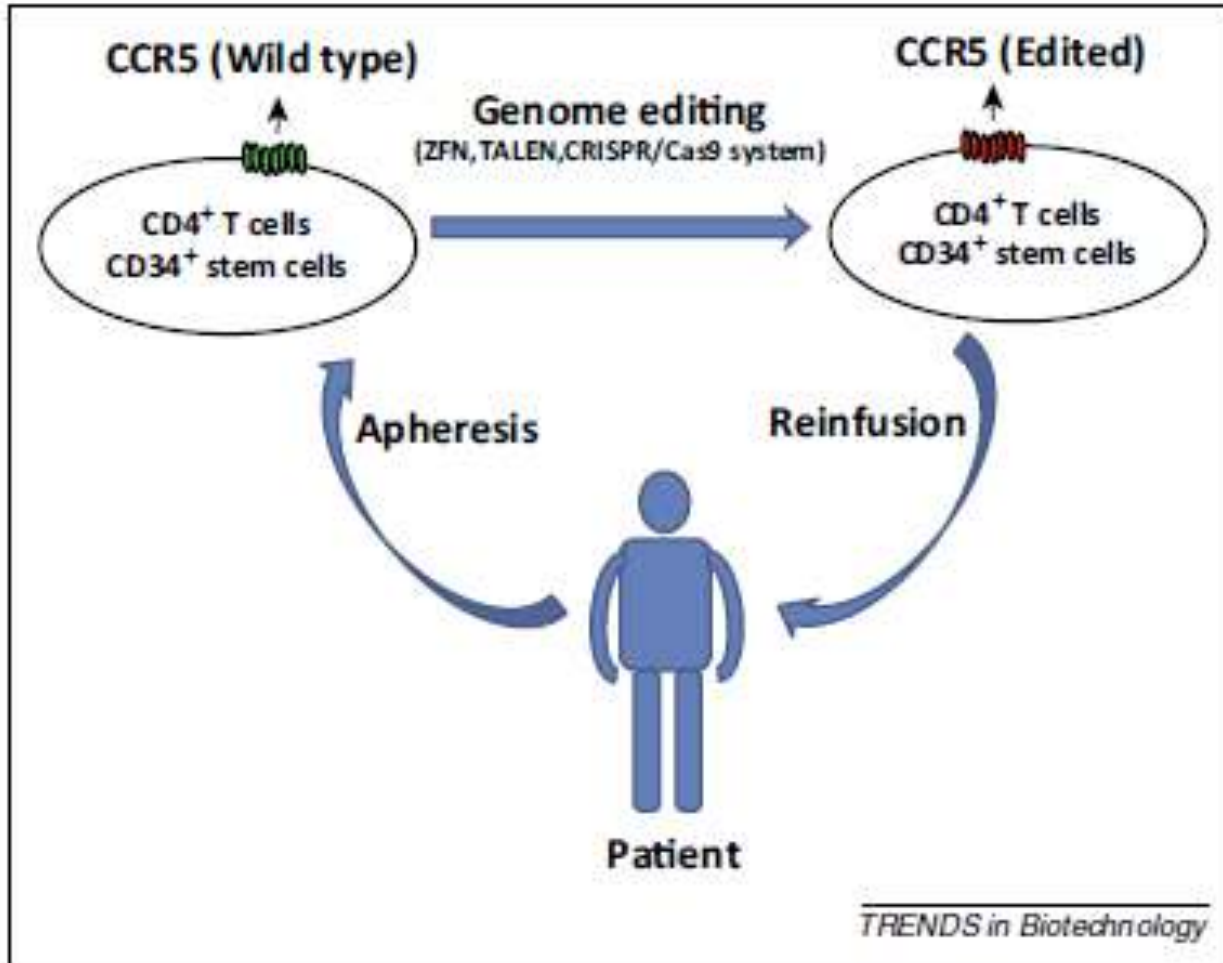
Clustered regularly interspaced palindromic repeats (CRISPR)/
CRISPR-associated protein 9 (Cas9)

Genetik materyalde

- modifikasyon
- parçalanma
- eklemeler..

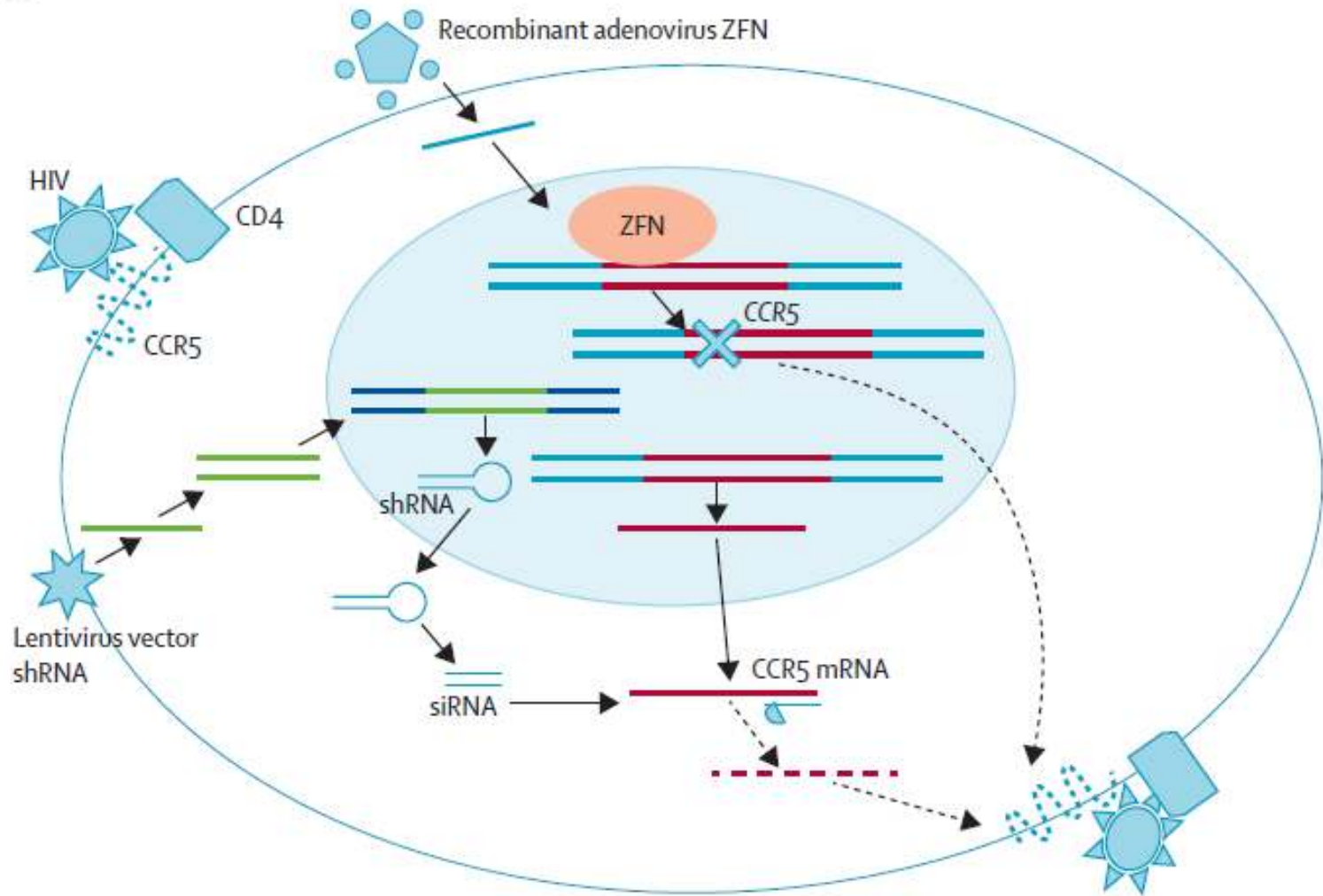


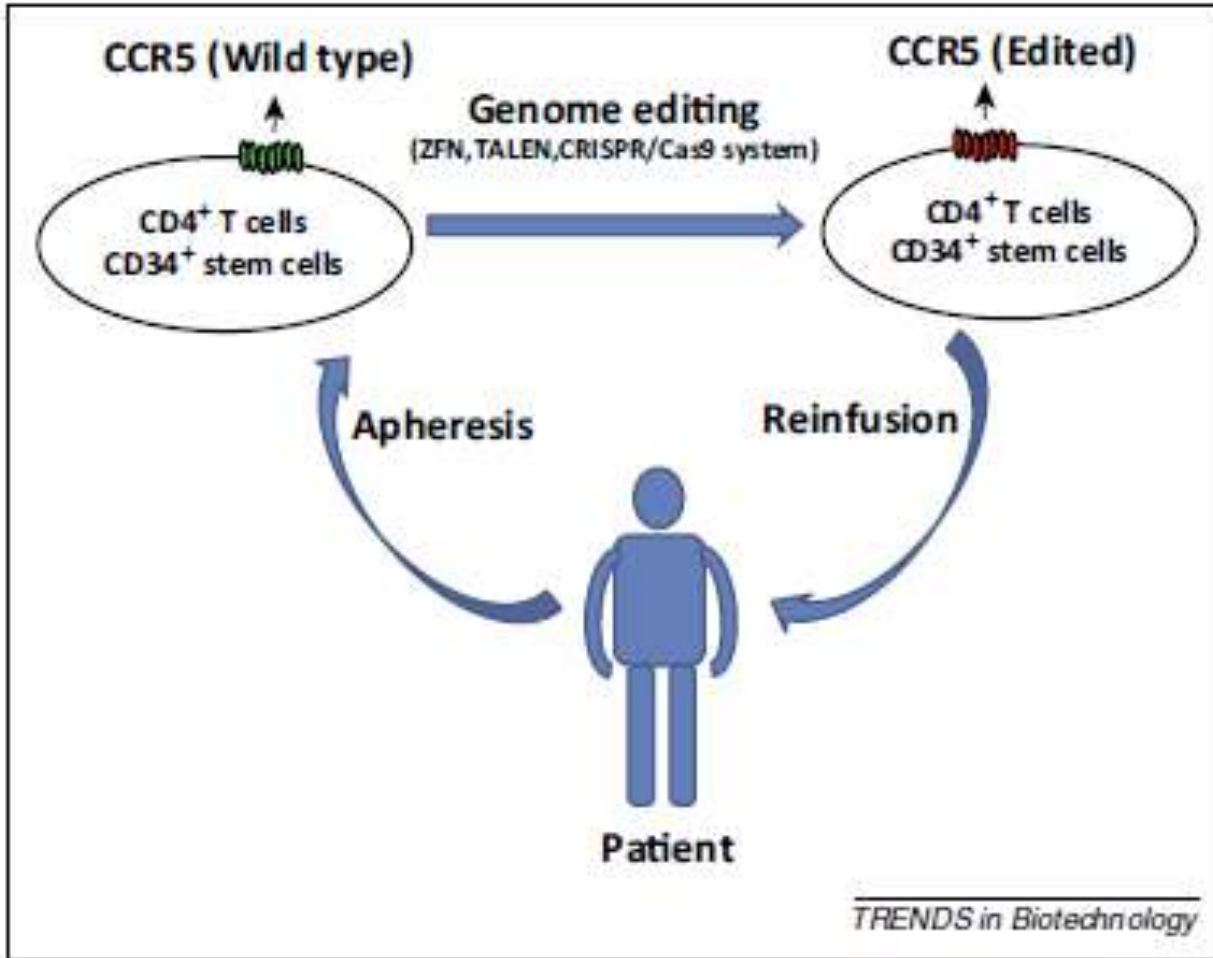
HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi





A





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

Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV

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

aviremic HIV infection while they were receiving highly active antiretroviral therapy. Six of them underwent an interruption in antiretroviral treatment 4 weeks after the infusion of 10 billion autologous CD4 T cells, 11 to 28% of which were genetically modified with the ZFN. The primary outcome was safety as assessed by treatment-related adverse events. Secondary outcomes included measures of immune recon-

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

study. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00842634.)



Gen terapilerinde asıl hedeflenen molekül CCR5

- ✓ CCR5 $\delta 32$ HIV enfeksiyonuna direnç sağlar ve kök hücre transplantasyonu ile kür olgusu mevcut
- ✓ HLA uyumlu CCR5 $\delta 32$ 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, verilmiş 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 transplantasyonunun uygulanabilirliğini ve güvenliğini değerlendiren klinik çalışma (NCT03164135)


- ✓ ALL+HIV enfekte bireyler
- ✓ Siklofosfamid +tüm vücut radyoterapi
- ✓ CCR5 modifiye edilen HSPC transplantasyonu
- ✓ 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

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 Jin³, Qiankun Wang¹, Kongxiang Yang⁴, Chenlin Li¹, Qiaoqiao Xiao¹, Panpan Hou⁴, Shuai Liu¹, Shaoshuai Wu¹, Wei Hou¹, Yong Xiong⁵, Chunyan Kong¹, Xixian Zhao¹, Li Wu², Chunmei Li^{1,6}, Guihong Sun¹ 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

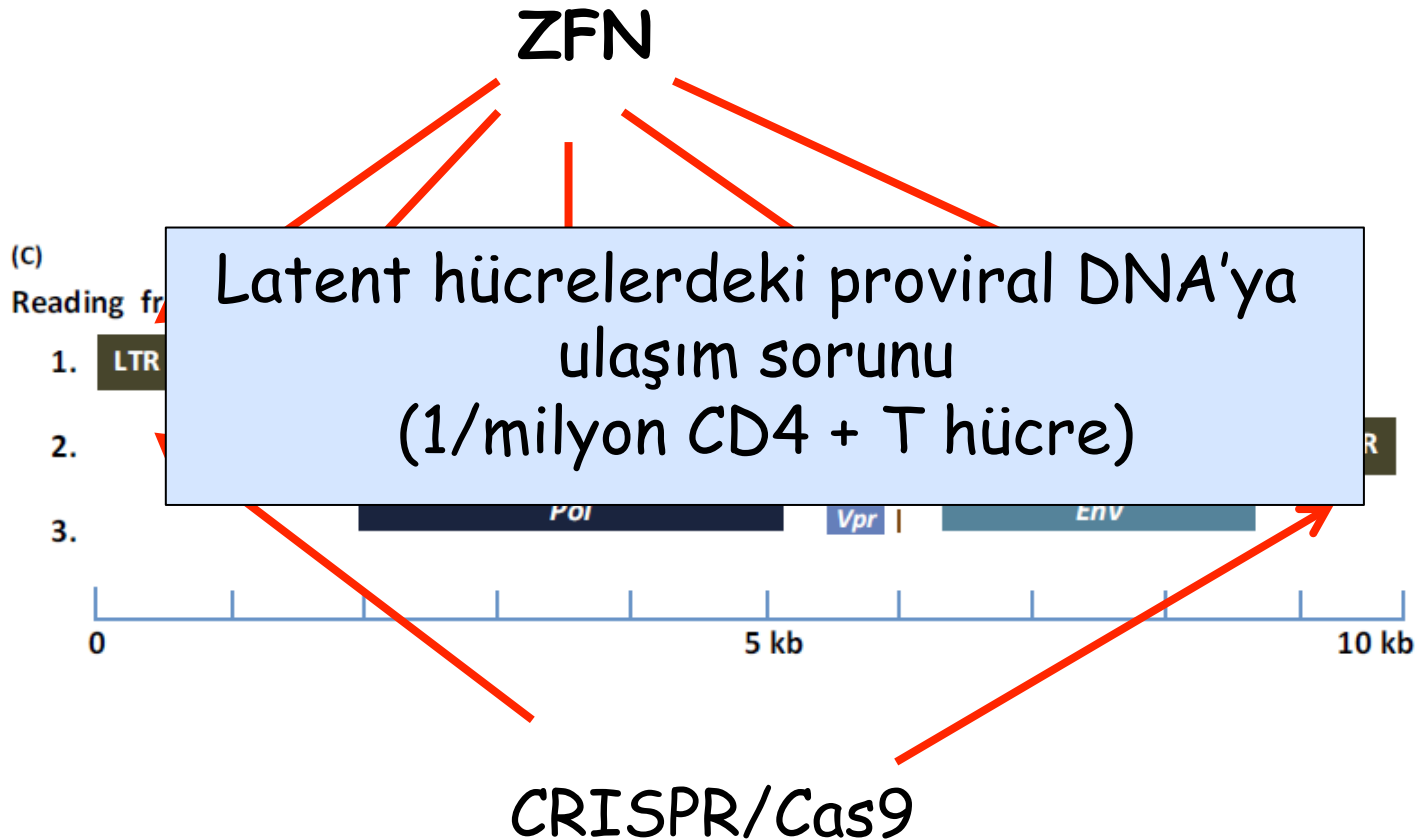


TABLE 2 | Clinical experiments of CCR5-based stem/progenitor cell or T cell therapy for HIV-1 infection.

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
NCT03617188	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 (RS) Infected Patients	ZFN	2015–2022	infusion of CCR5-disrupted SB-728mR-HSPC after conditioning with busulfan	Active, not recruiting
NCT03164136	Safety and Feasibility Study of Allogeneic Transplantation 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
NCT03888671	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
NCT00942034	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	2010–2016	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-728 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 Avenic 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



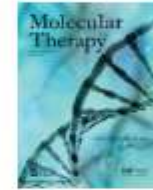
Proviral DNA eliminasyonu





Export

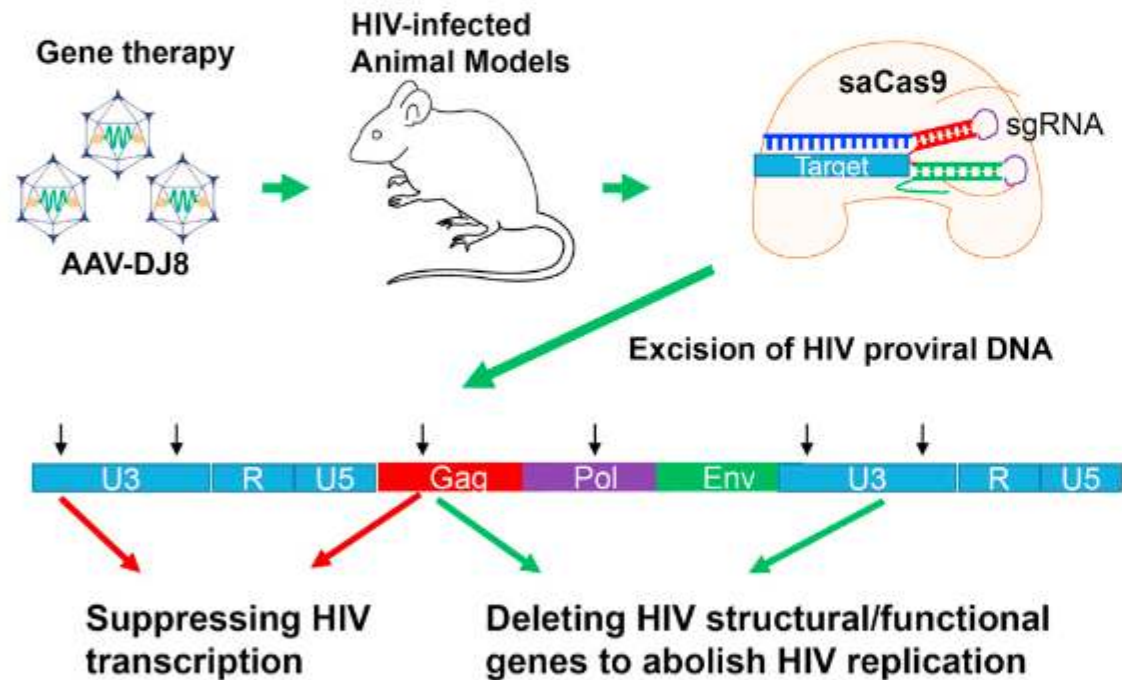
Molecular Therapy



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 dokularınınin %42'sinde diğerinin %76'sında mevcut**



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CRISPR-Cas9 Mediated Exonic Disruption for HIV-1 Elimination

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RNA loaded Lipid nanoparticles (rLNP)
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 (*tat₁₋₂/rev₁₋₂/gp41*) was constructed. The gRNAs were derived from a consensus 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.

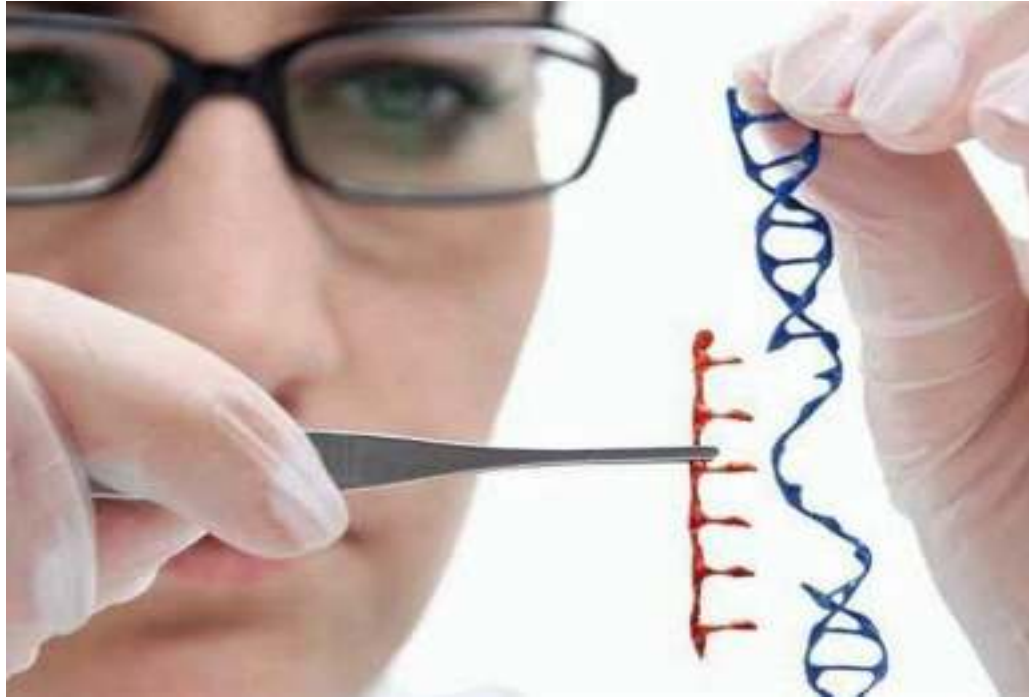
Interpretation: These results provide "proof of concept" for CRISPR gRNA treatments for HIV-1 elimination. The absence of full-length viral DNA by LNP delivery paired with undetectable off-target affirms the importance of payload delivery for effective viral gene editing.

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, 1R01A1158160, R01 DA054535, PO1 DA028555, R01 NS126089, R01 NS36126, PO1 MH64570, P30 MH062261, and 2R01 NS034239.

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Yeni Buluşlar ve Stratejiler





✓ **Heterodimerik interlökin-15 ile tedavi**

CD8+ T ve NK hücrelerin sayısının artmasına yol açarak aktive olmuş enfekte hücreler yok edilebilir

✓ **Regulatuvar T hücre (Tregs) depleksyonu + dendritik hücre temelli aşı**

Pavlakis GN, et al. Heterodimeric IL-15 induces effector cell activation and trafficking to the germinal centers of SIV infected macaques. J VirusErad 2016; 2(Suppl 2): 6. Abstract OA4-1.
He T, et al. T regulatory cell depletion in controller macaques reactivates SIV and boosts CTLs. J Virus Erad 2016; 2(Suppl 2): 16. Poster21.



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

- ✓ Further along in development is BiA-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

- ✓ B... p... a... th... W...
Giriş inhibitörü
+
HIV ile enfekte olmuş hücrelere bağlanarak onları yok etme
d... also...

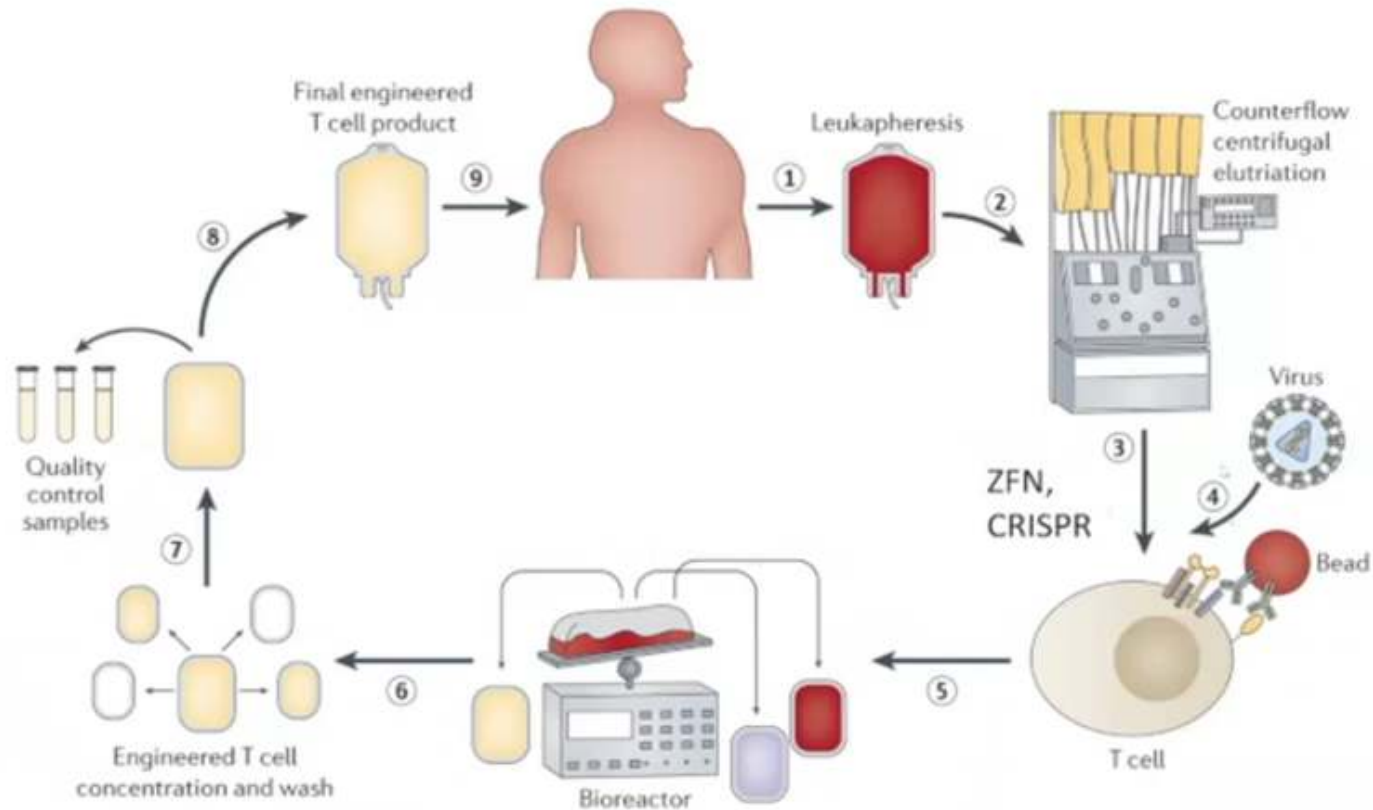
completely protected the monkeys from infection, and when given after infection, all monkeys survived beyond three months, with the preservation of strong anti-HIV cellular responses.

- ✓ Further monkey experiments are planned before BiA-SG is taken into human trials.



CROI 2020

Manufacturing CAR T cells



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.

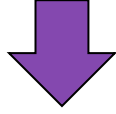
Dr. Serhat Gumrukçu, co-founder and inventor of Enochian BioSciences, and Director of Seraph Research Institute (SRI), submitted the Pre-IND. The request was based on the results of a 54-year old man living with HIV who had failed to suppress the virus with antiviral therapy. The patient subsequently 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](https://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 reaktifte edilip
eliminasyonu



Sonu

✓ HIV enfeksiyonu akılcı ART ile yönetilebilir kronik enfeksiyon

✓ Küre yönelik alıřmalar:

Viral rezervuarın aktivasyonu

İmmünoterapi

Gen terapileri

Bloke et ve kilitle

Kombine tedaviler



TEŞEKKÜR EDERİM