KÜR ALANINDA YENİLİKLER

Dr. Birgül Mete
İUC-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/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/rtv AZT/LAM, TDF/FTC, ATV/rtv, RAL, etravirine	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 30 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, indinavir; rtv, ritonavir; 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 ozogamicin; LACE, lomustine, Ara-C, cyclophosphamide, etoposide; Flu, fludarabine; Treo, treosulfan; RIC, reduced-intensity conditioning; CSA, cyclosporine-A; MTX, methotrexate; NA, not available.

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

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

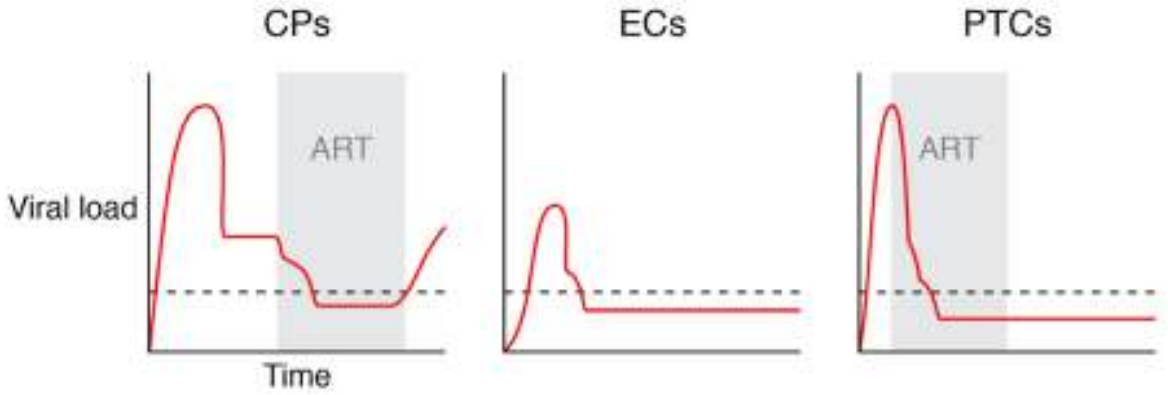
REVIEW

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.

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/mm^3
- ✓ **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 araştırmalarda

- ✓ HIV RNA< 0,2 kopya/ml
- ✓ Lenf doku örneklerinde HIV RNA (-), çok düşük düzeyde HIV DNA
- ✓ Kolon dokusunda ve periferik mononükleer hücrelerde HIV DNA (-)
- ✓ Anti HIV (-)
- ✓ 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**

Uruena A et al.
Prolonged posttreatment virologic control and complete seroreversion after advanced human mmunodeficiency virus-1 infection. Open Forum Infectious Diseases 8: ofaa613, 2021

- ✓ **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**.

Aidsmap,2020

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

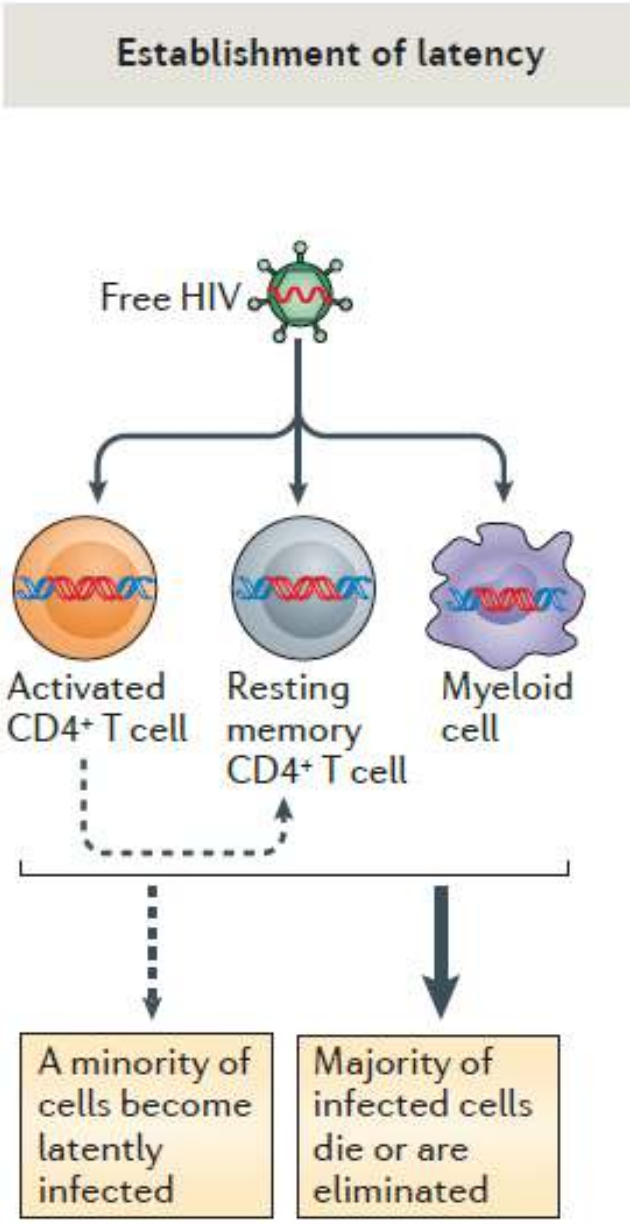
⇩

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

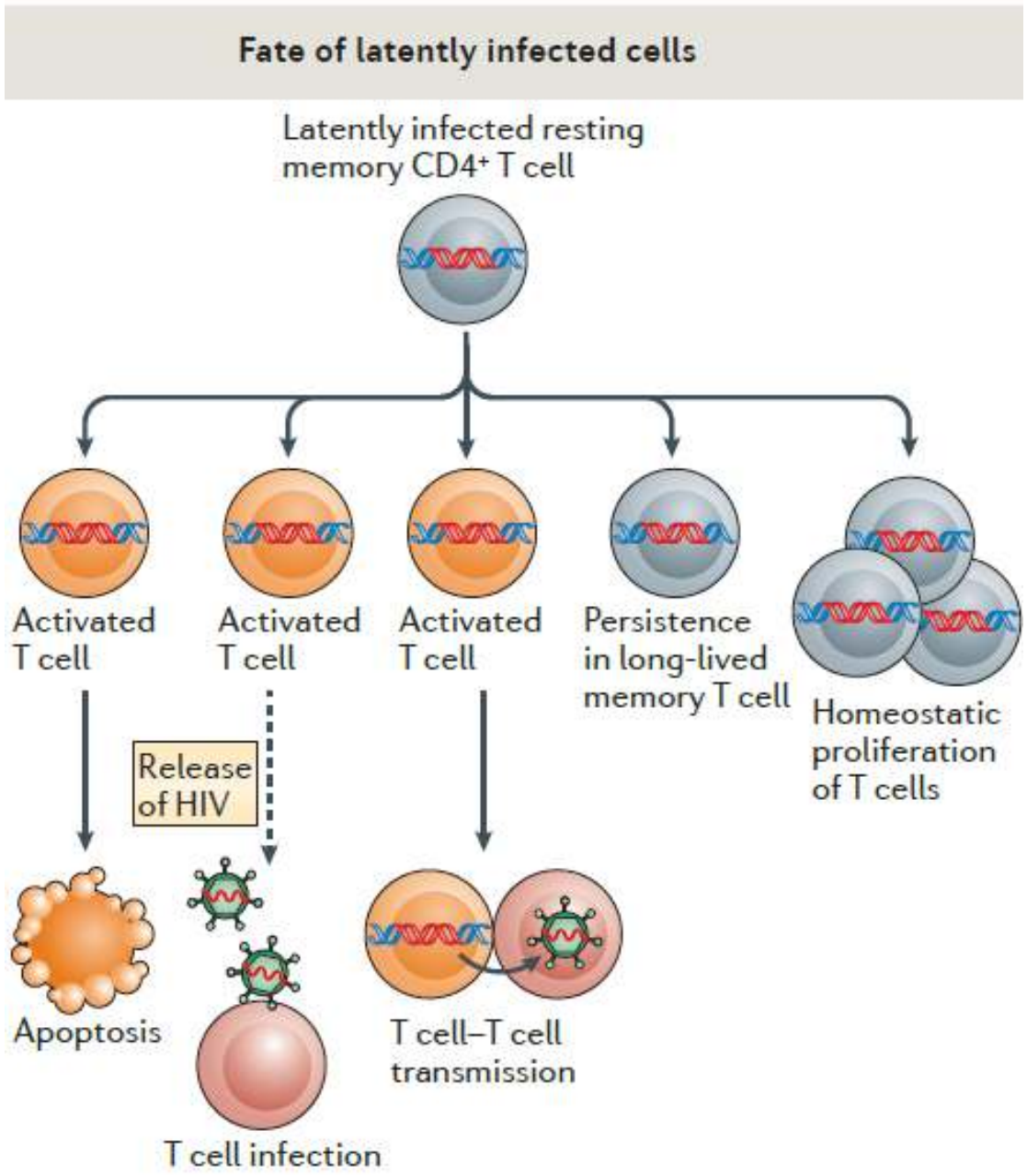
Hücresel uyarı

⇩

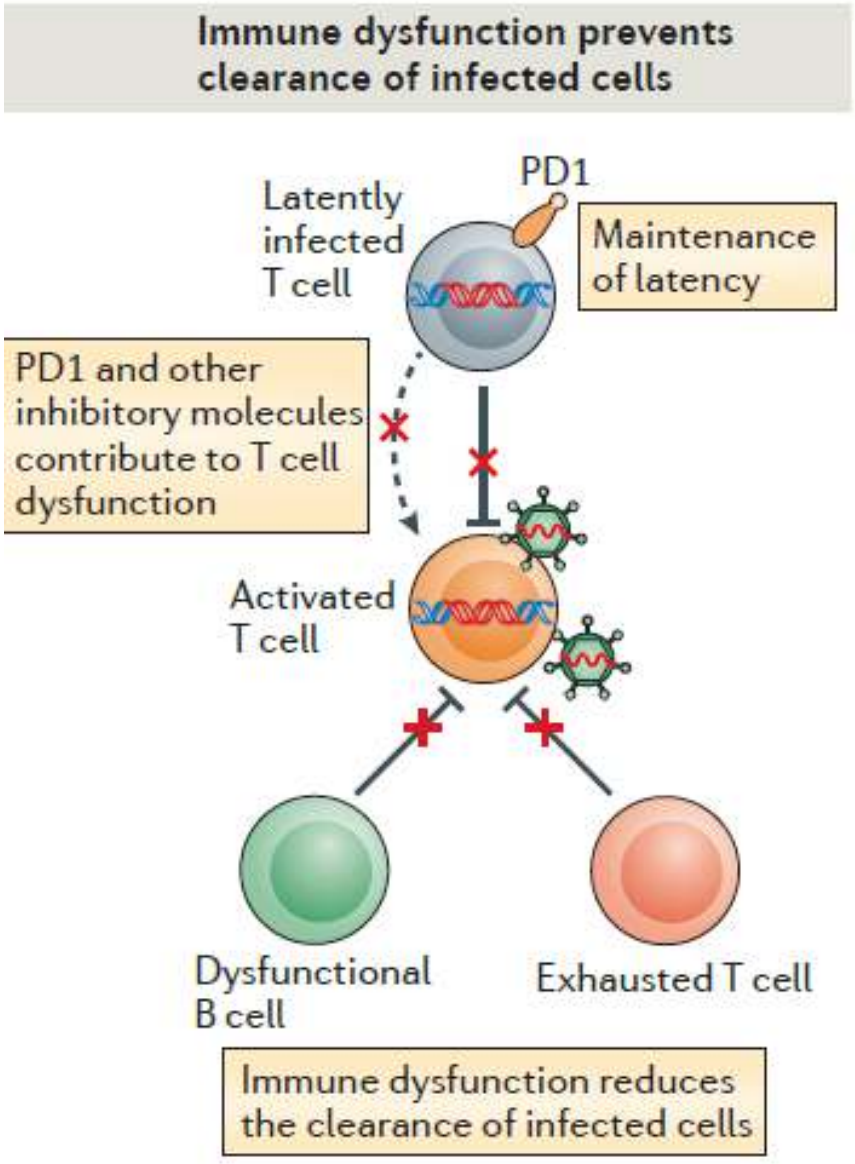
Viriyon üretimi



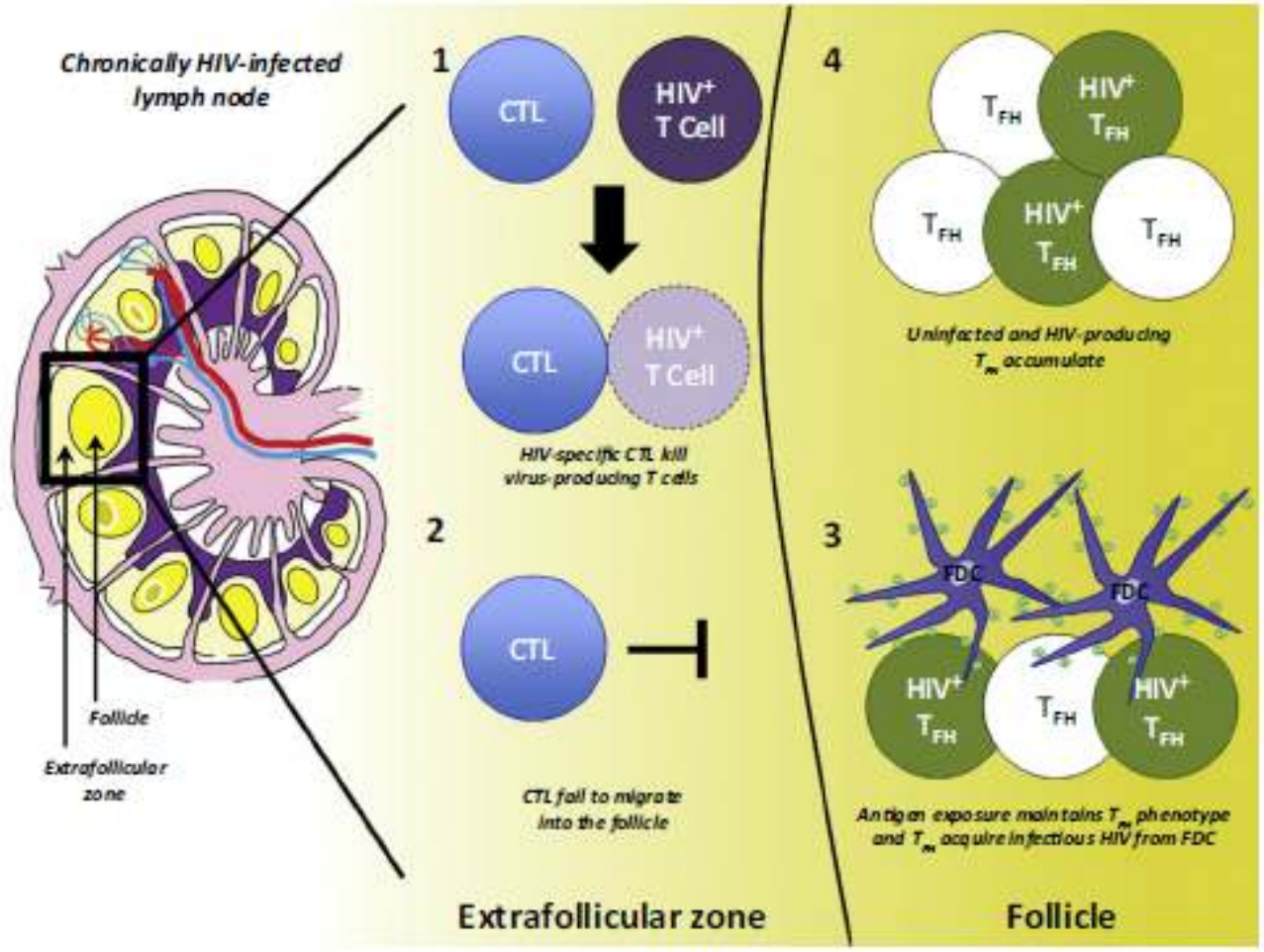
Towards an HIV cure: a global scientific strategy.
Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Kumar A, et al. Clin Epigenetics 2015 Sep 24;7(1):103.



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



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



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
GİS- ilişkili lenfoid doku makrofajları
dendritik hücreler

Kürde Temel Yaklaşımlar

Temel Hedefler

- ✓**Viral rezervuarın eradikasyonu**
- ✓**Viral rezervuarın baskılanması**

İmmünoterapi

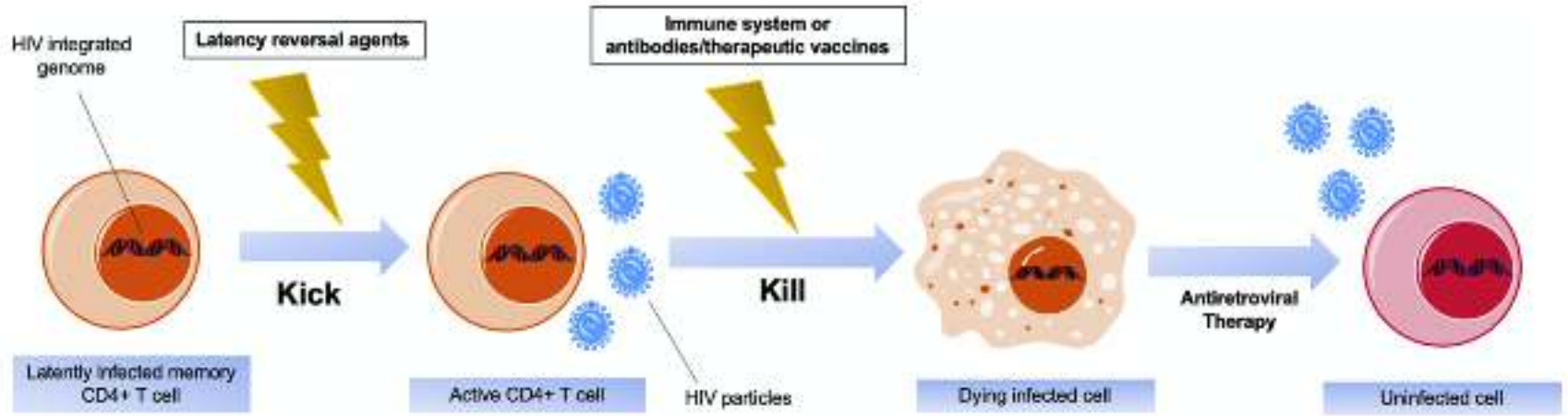
konağın bağışıklık sistemini HIV'e karşı güçlendirmek

Gen terapileri

CD4 + T hücrelerini virüse dirençli hale getirebilmek

Viral Rezervuarın Eradikasyonu

Viral rezervuarın eradikasyonu --şok et ve öldür--



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)

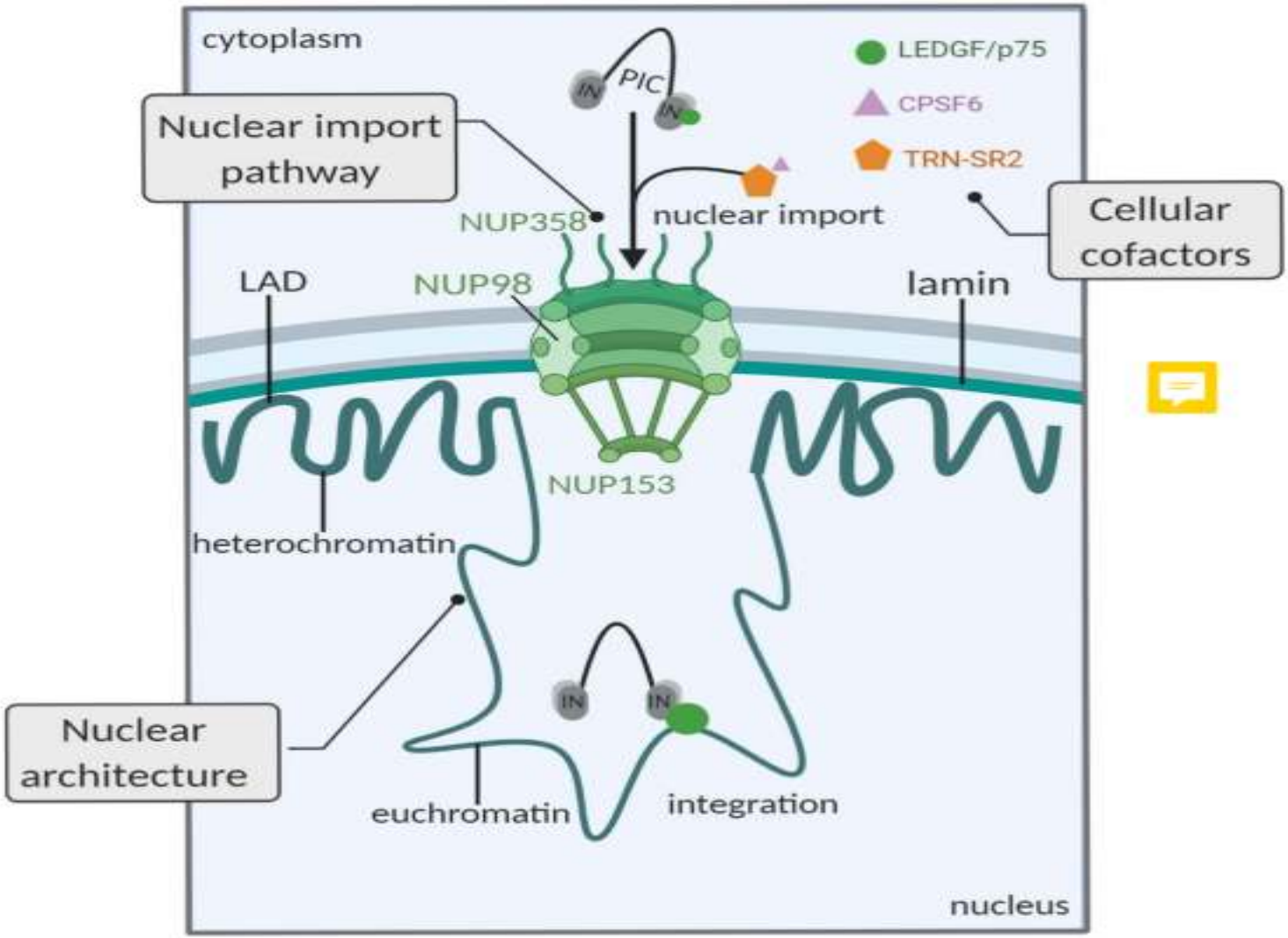
Latentlik

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

  epigenetik
- ✓ **Post-transkripsiyon**

  m-RNA taşınması, kesilmesi, translasyon

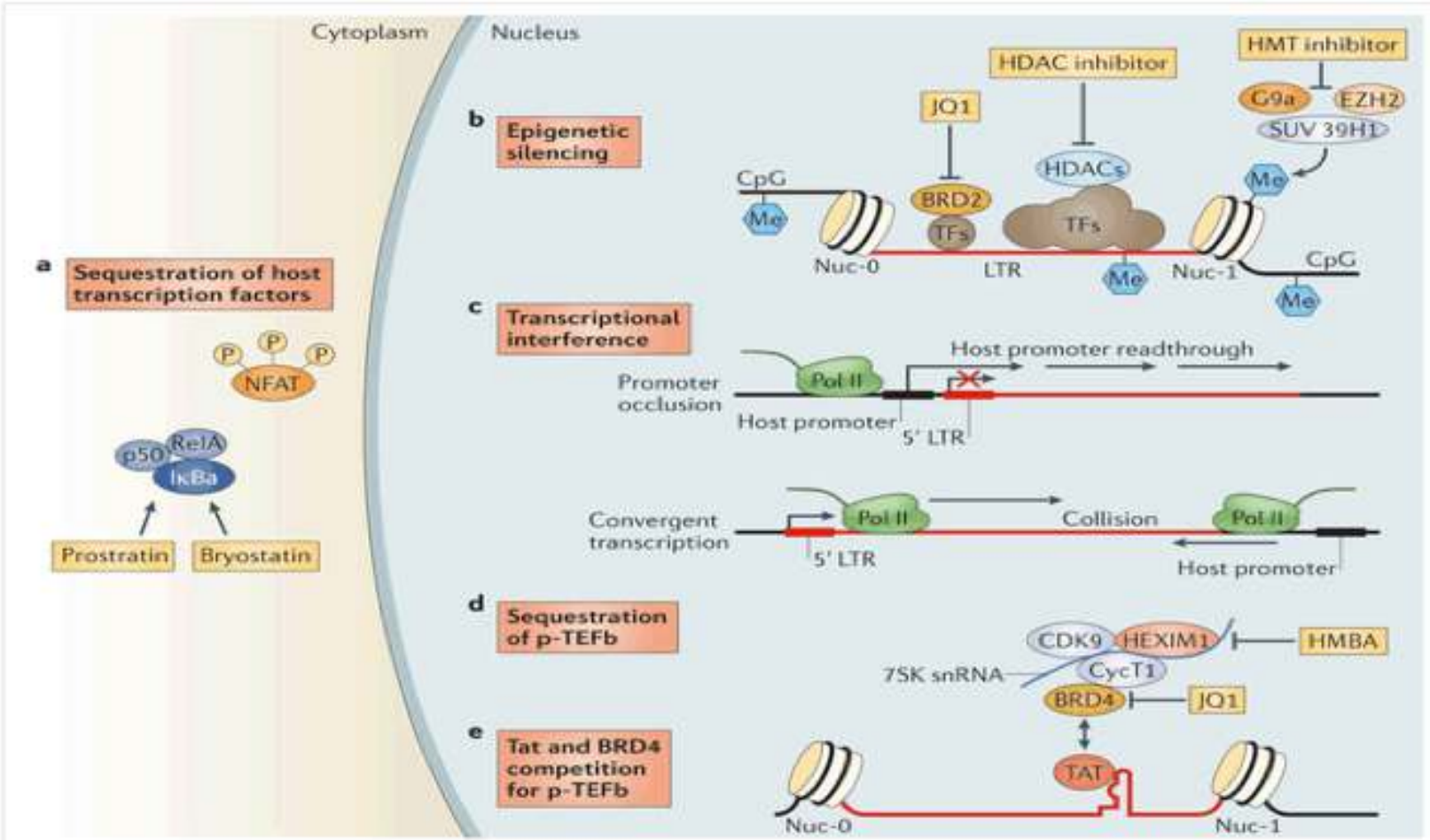
Pre-integrasyon



Janssens et al. Towards a Functional Cure of HIV-1. Frontiers in Microbiology | www.frontiersin.org **1** March 2021 | Volume 12

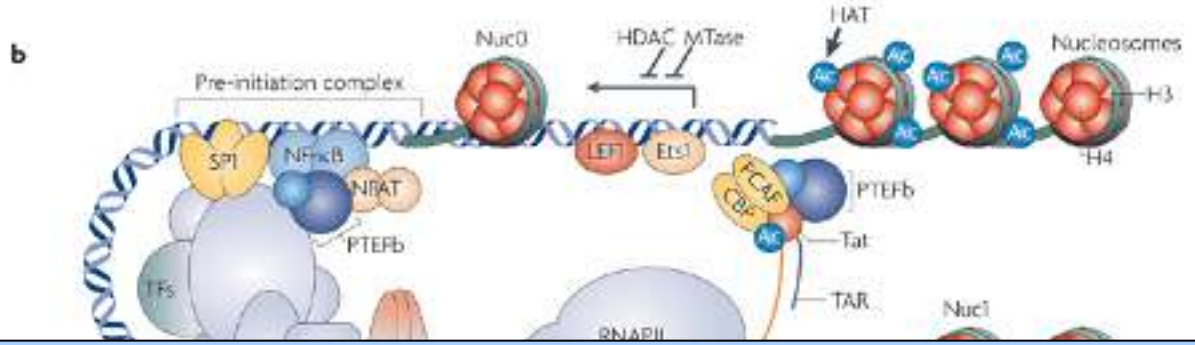
Transkripsiyon

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
- ✓ 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)

Latent CD4 hücreleri 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)

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)

- ✓ **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

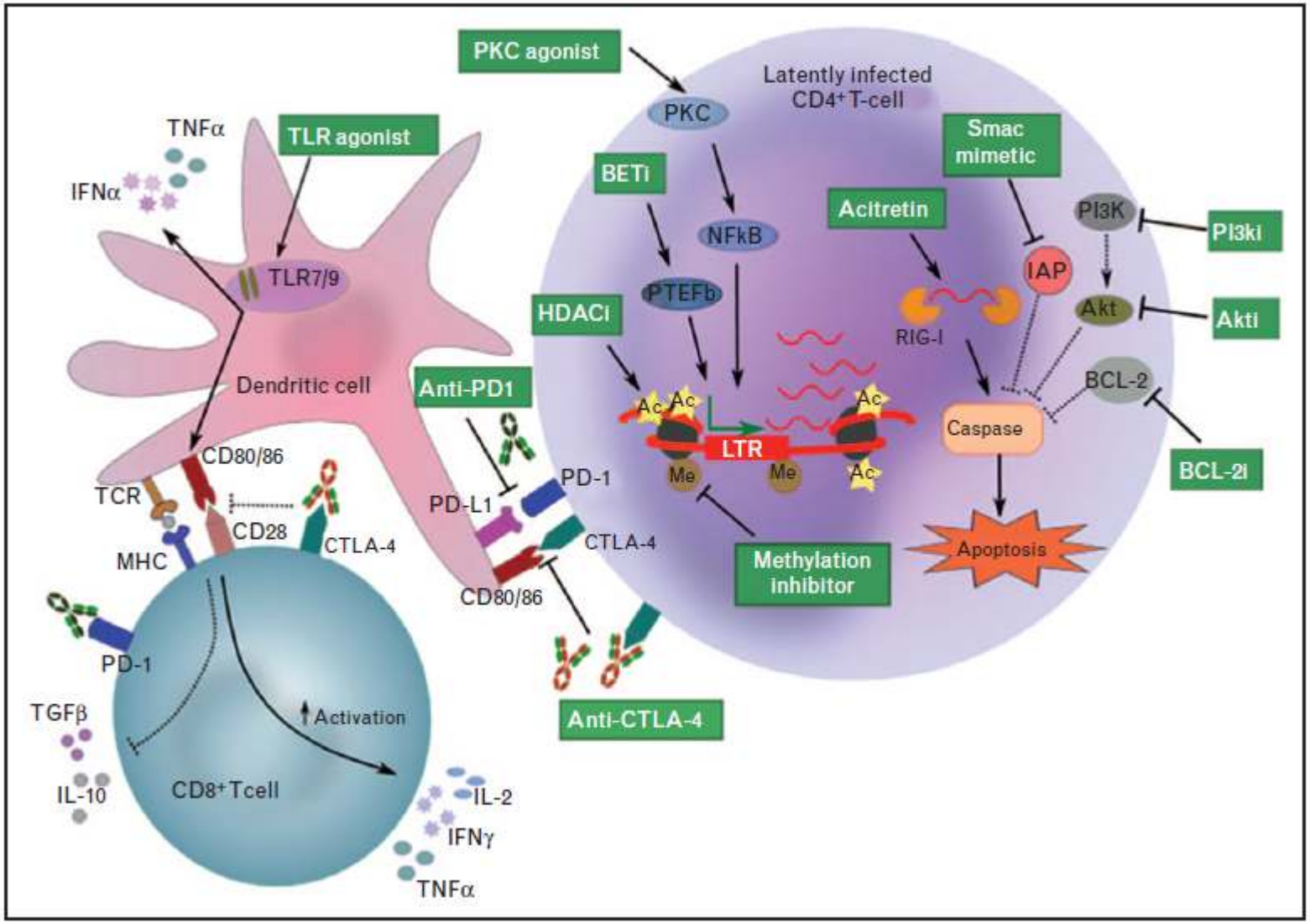
Table 1. Cancer therapies invest

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 rese…
Ding J, et al. Knowledge From London and Berlin: Finding … …ontiers in Immunology 1 May 2021 | Volume 12 |

Apoptozu indükleyici ve immünmodulatuvar ilaçlar



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

Latent CD4 hücreleri aktivatörleri

- ✓ Histon deasetilaz inhibitörleri (HDACi)
- ✓ DNA metiltransferaz inhibitörleri
- ✓ Protein kinaz C agonistleri
- ✓ **Bromodomain ekstraterminal motif inhibitörleri**

  klinik çalışmlara ihtiyaç var
- ✓ Apoptoz protein inhibitörlerinin inhibitörleri
- ✓ **İmmün checkpoint inhibitörleri**
- ✓ **Toll-like reseptör 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)

(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

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)

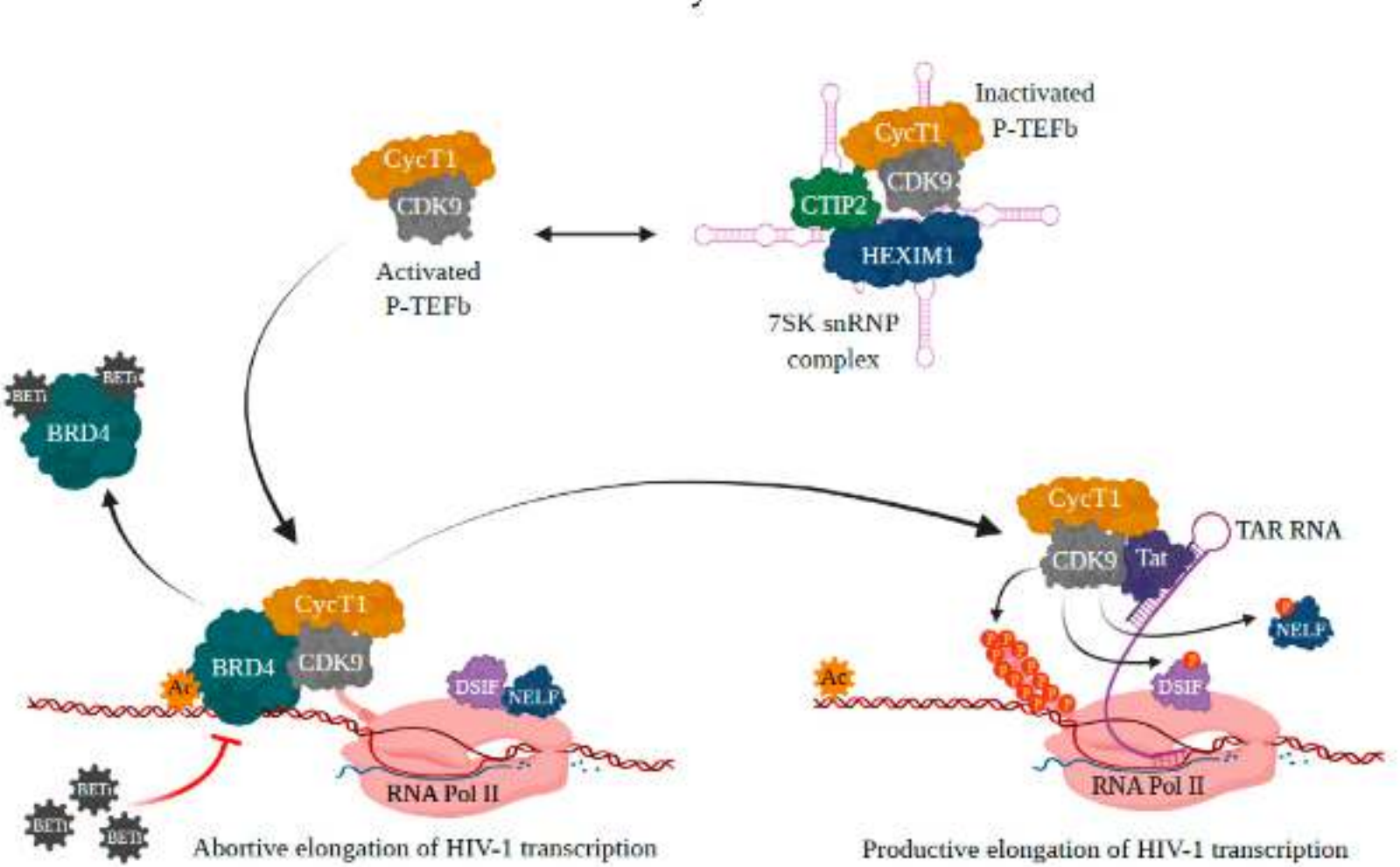


Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-dependent manner.

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

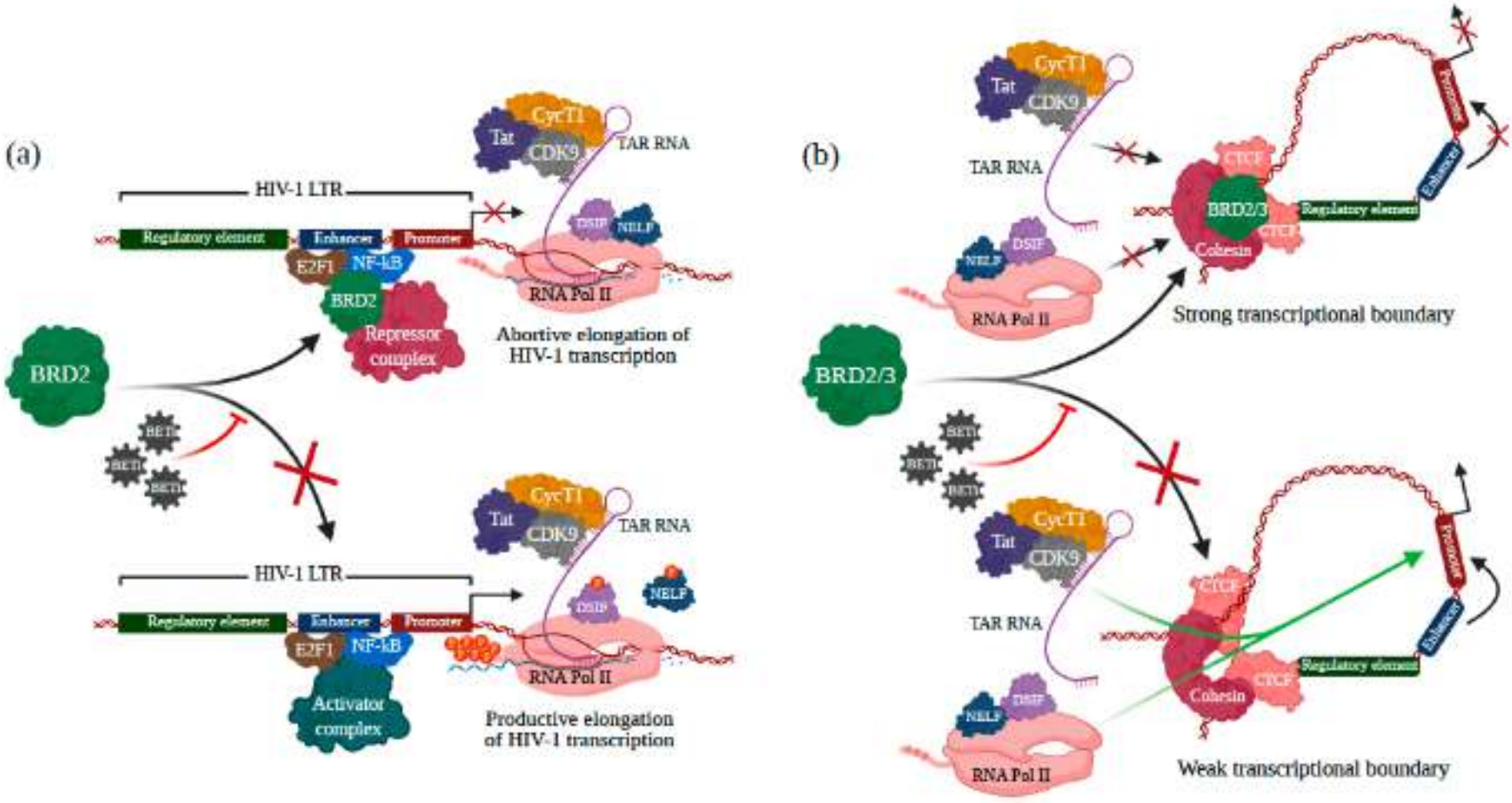


Figure 2. Roles of BET proteins and BETis in HIV-1 latency through the Tat-independent manner.

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

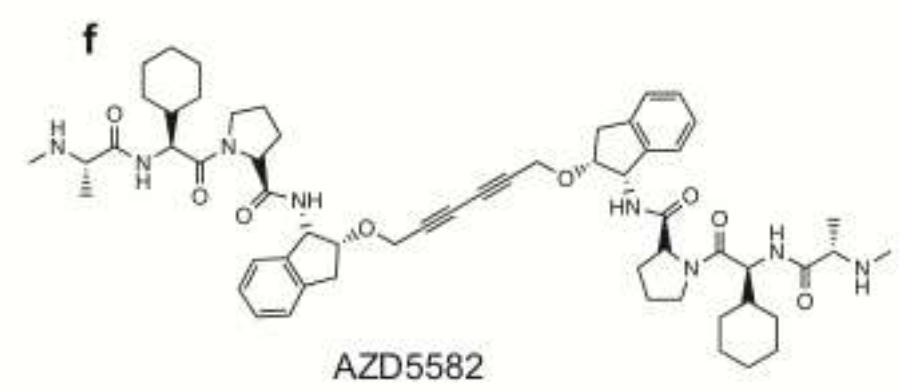
Yeni moleküller

Molecular Therapy
Nucleic Acids
Review

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

Saikat Boliar[1] and David G. Russell[1]

[1]Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA



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

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 hücre'lerine 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.

Published in final edited form as:
Immunity. 2012 March 23; 36(3): 491–501. doi:10.1016/j.immuni.2012.01.014.

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

AR
(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 aşılar**

  Anti-HIV immünitesinin işlev ve yaygınlığını arttıracak aşılar

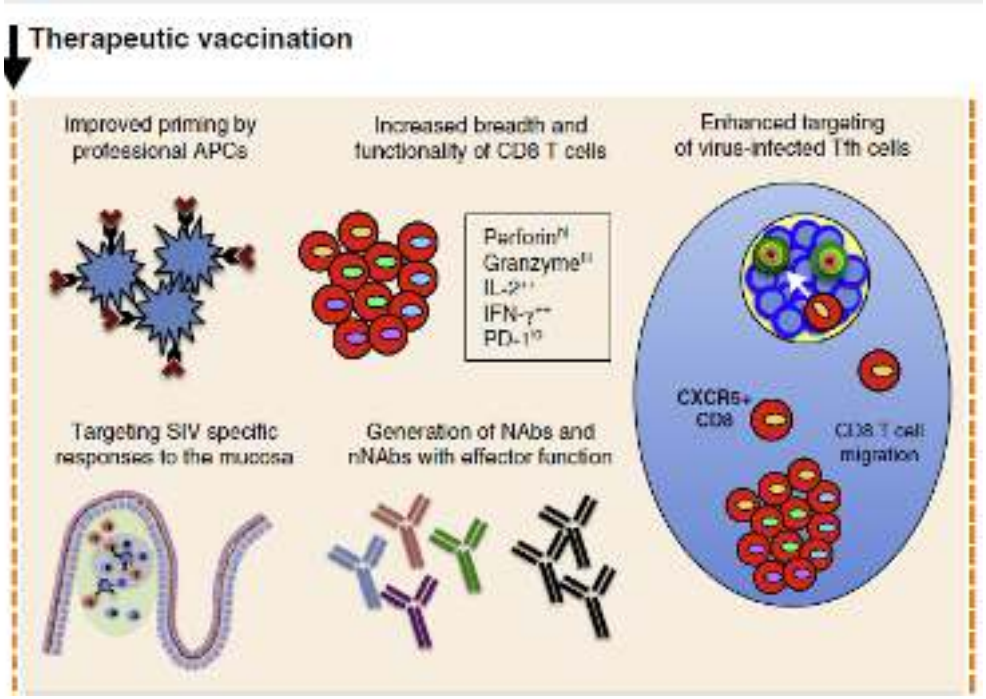
- ✓**Pasif bağışıklama**

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 hücreleri
- ✓ Nötralizan antikorlar
- ✓ multi-fonksiyonel T hücre (uzun süreli progresse olmayanlarla ilişkili) üretimi
- ✓ CD8 T hücre (B hücre foliküllerindeki foliküler T hücreleri hedef alacak) üretimi



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

Klinik çalışmalar

Var olan immüniteyi güçlendiren

- DNA ± adjuvan
- Virüs ± adjuvan
- Dendritik hücre kökenli aşı çalışmaları

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

Klinik yarar belirsiz

Latent rezervuar üzerine minimal etki

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

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

Hafıza T hücrelerini hedef alan aşı +/- antikor temelli yaklaşım ile HIV enfeksiyonunda kür??

future management of millions of HIV-infected individuals. We recently reported that ~50% of

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

of measurable plasma or tissue-associated virus using ultrasensitive assays, and loss of T cell reactivity to SIV determinants not in the vaccine. Extensive ultrasensitive RT-PCR and PCR analysis of tissues from RhCMV/SIV vector-protected RM necropsied 69–172 weeks after challenge did not detect SIV RNA or DNA over background, and replication-competent SIV was not detected in these RM by extensive co-culture analysis of tissues or by adoptive transfer of 60 million hematolymphoid cells to naïve RM. These data provide compelling evidence for progressive clearance of a pathogenic lentiviral infection, and suggest that some lentiviral

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?

Aşı+ İmmünstimülan + Antikor kombinasyonu

51 rhesus makak maymunun yapay insan/maymun virus-SHIV ile enfeksiyonu + 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 infüzyonun son dozundan 3 ay sonra ART kesildi

A **PLACEBO-CONTROLLED ATI 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, Bonaventura Clotet2, Christian Brander2, Jose Molto1, Beatriz Mothe2, for the AELIX-002 Trial Group 1Fundacioì·Lluita Contra la Sida, Badalona, Spain, 2IrsiCaixa Institute for AIDS Research, Badalona, Spain, 3Projecte dels NOMS Hispanosida, PCN Checkpoint, Barcelona, Spain, 4AELIX Therapeutics S.L., Barcelona, Spain, 5Unive

Backgrou viral control.

Methods: immunog reated people li ting of DDDMM as monitore

w nd

Results: 26) or PPP (n= recipients encies of HTI-sp IV-1 T-cell respo nees and 1 (8%) L being observed in 5 a itively correlated with time was similar between vaccine and placebo arms.

Conclusion: HTI vaccines were safe and highly immunogenic in early-treated PLWH with a prolonged time off ART seen in vaccinees with non-beneficial HLA class I alleles. Time off ART positively correlated with vaccine-induced HTI-specific T cell responses at ATI start. Multivariate analysis for other correlates of response is ongoing. These encouraging data strongly support the use of HTI- based vaccines as the backbone of combination cure regimens such as with the TLR7 agonist vesatolimod, which is currently being evaluated in the AELIX-003 study (NCT04364035).

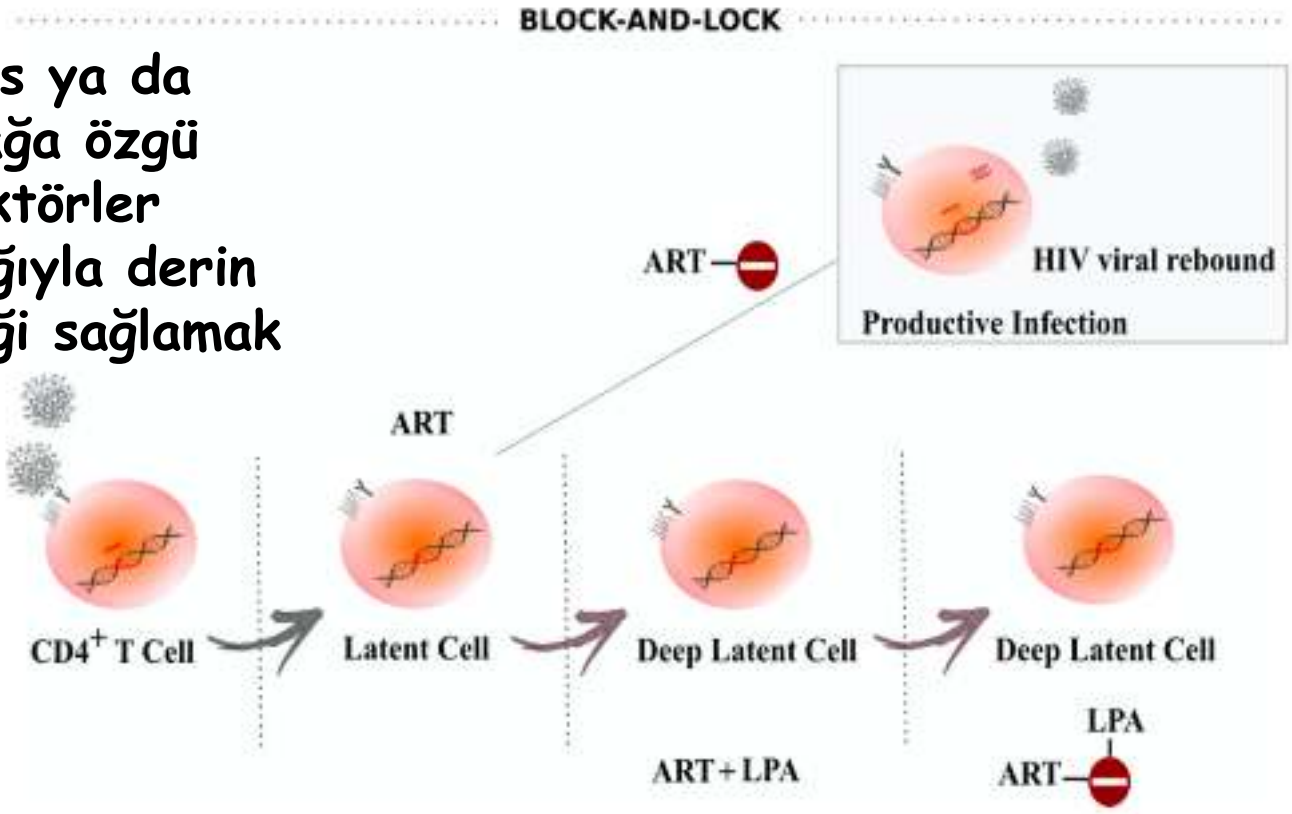
For participants **without any potentially beneficial HLA class I alleles**
8 (40%) of the vaccinees
1 (8%) of the placebo recipients
were able to remain off ART for 22 weeks

"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.

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 çalışması:NCT02990312 ve NCT0244)

- ✓ BRD4 inhibitörleri
- ✓ Isı şok proteini 90 (HSP90) inhibitörleri
- ✓ 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

Gen terapileri

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

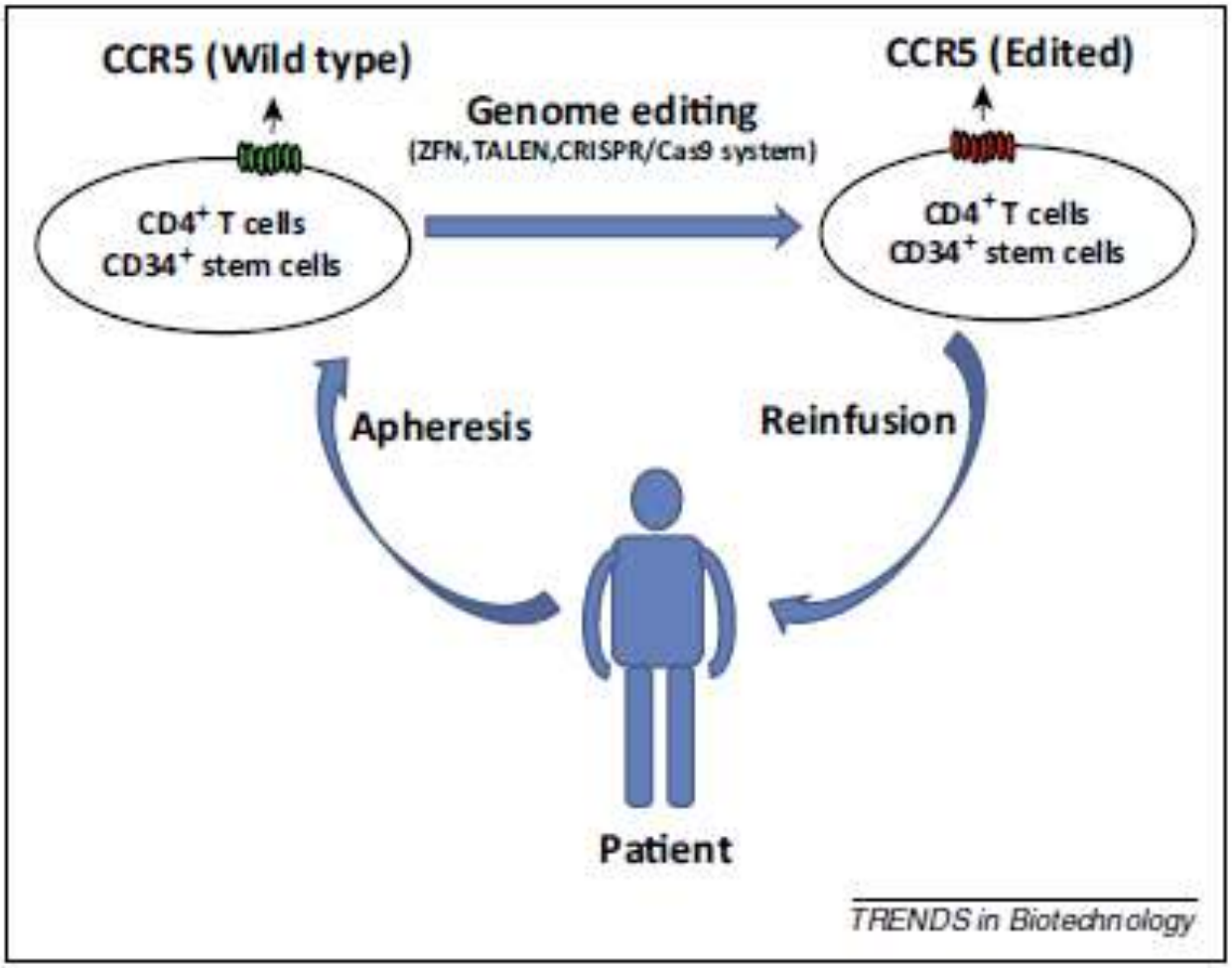
Nükleazlar, rekombinazlar, RNAiler….

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

Genetik materyalde

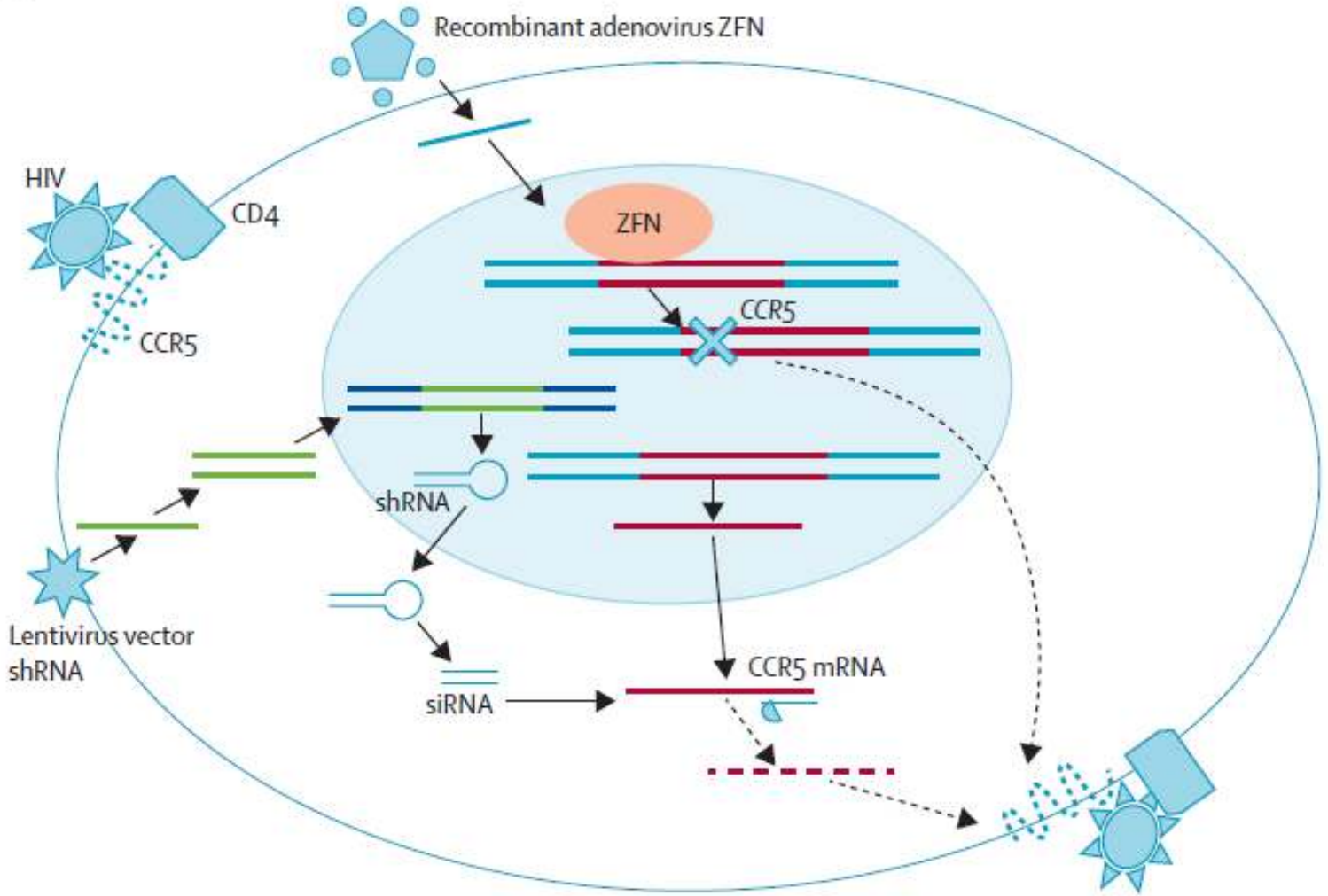
- modifikasyon
- parçalanma
- eklemeler..

HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi

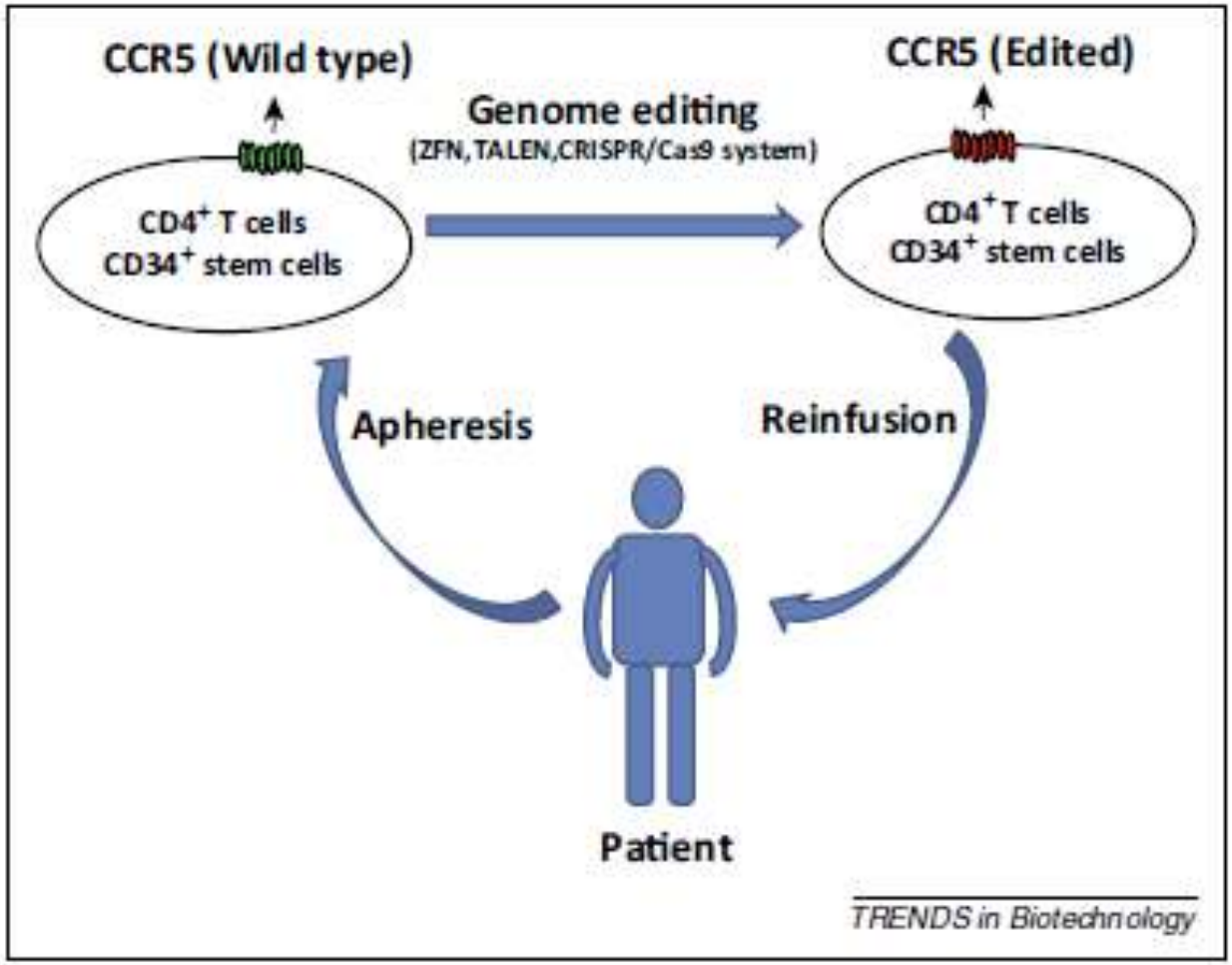


Gu WG.Trends Biotechnol 2015 Mar;33(3):172-9.

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 transplantasyonunun uygulanabilirliğini ve güvenliğini değerlendiren 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

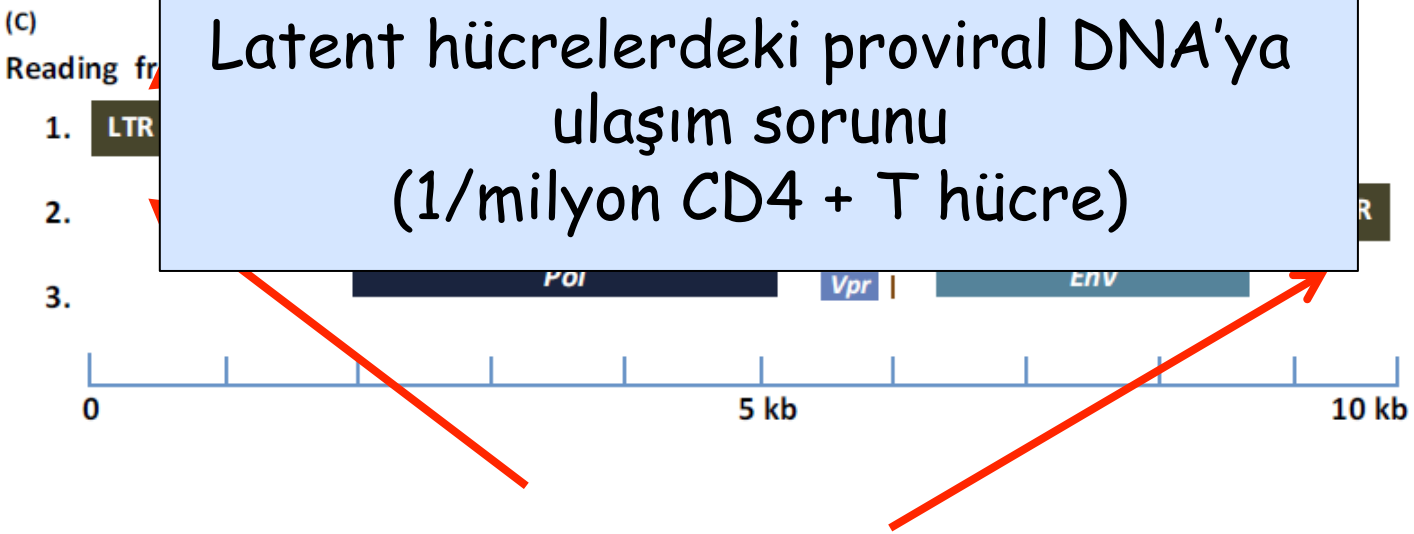
TABLE 2 | Clinical experiments of CCR5-based stem/progenitor cell or T cell therapy for HIV-1 infection.

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	2018–2025	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-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 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-1 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.

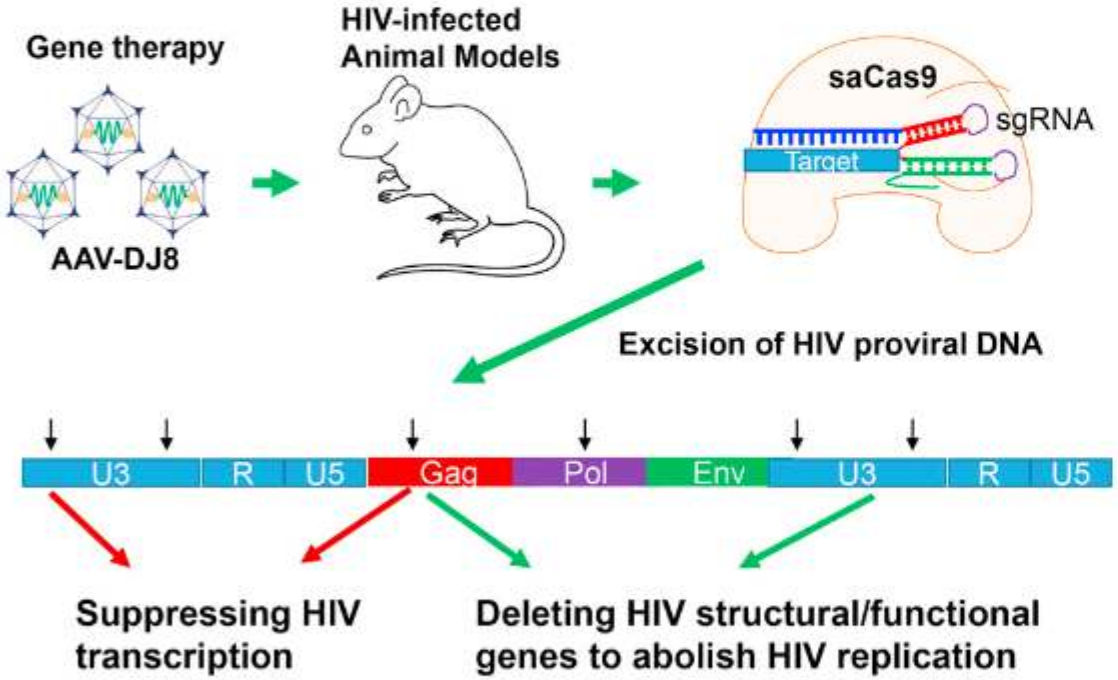
Export

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.

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) deplesyonu + 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.

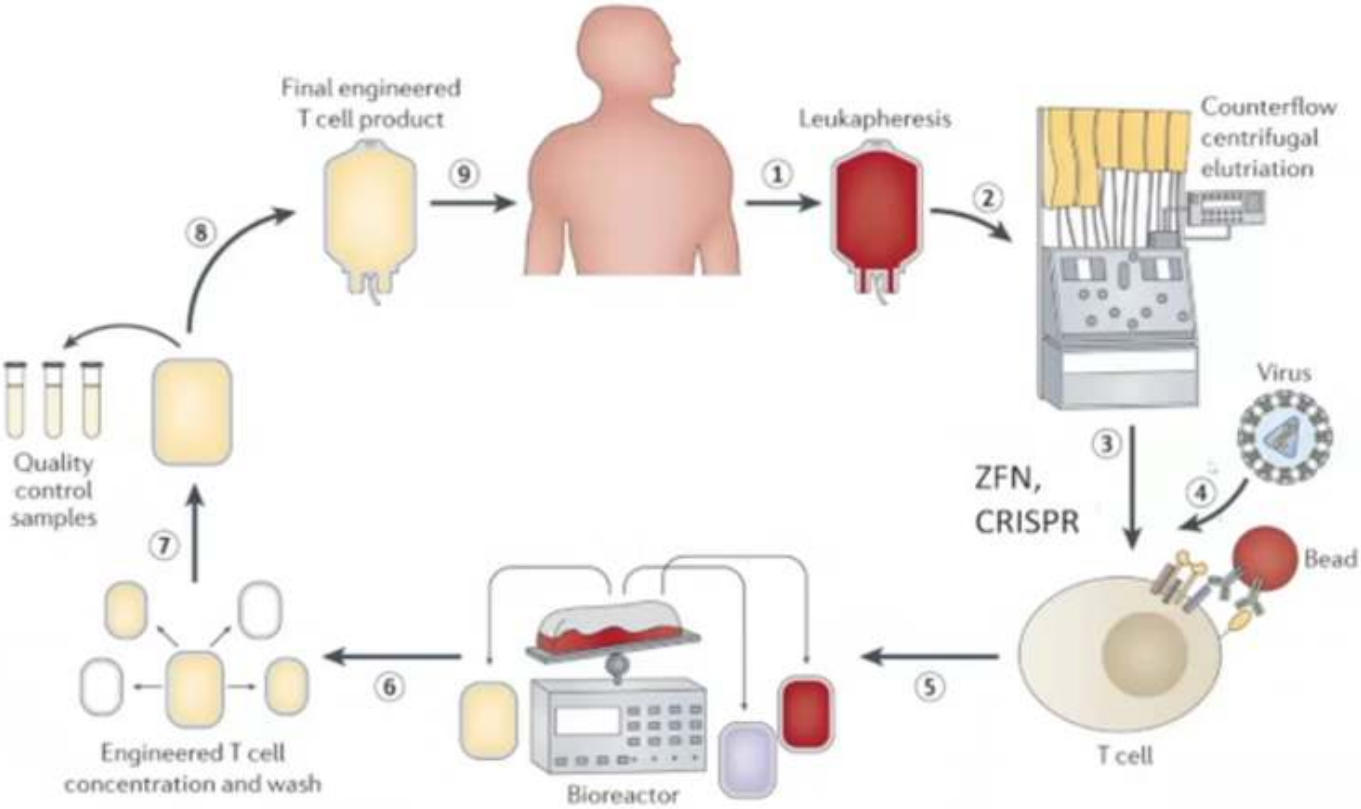
Bi-specific antibody both prevents infection and controls disease in monkeys

- ✓ Further along in development is 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.

CROI 2020

Manufacturing CAR T cells



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