中国科学技术大学 University of Western Ontario

HIV序列的极端多样性及防治对策

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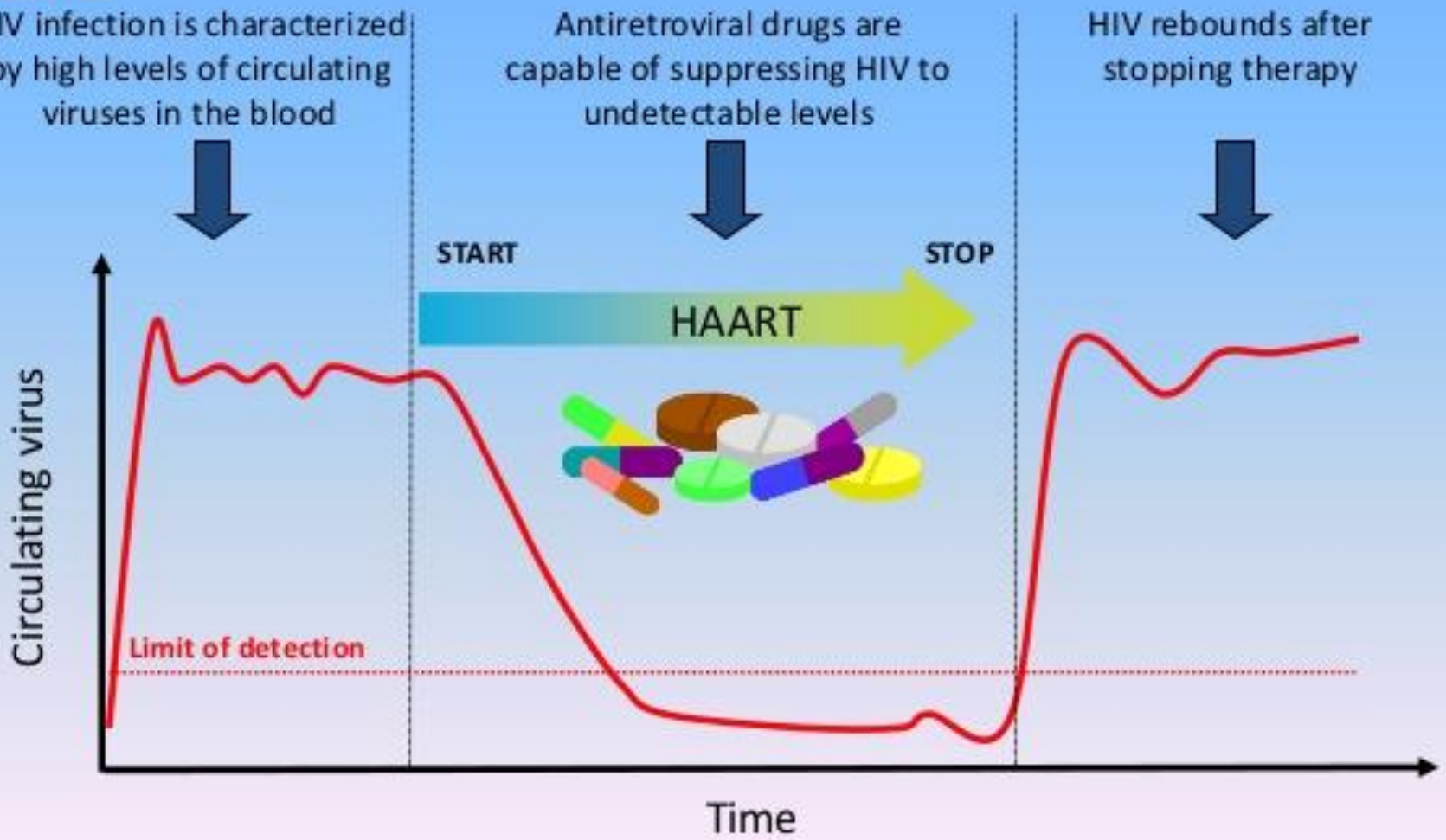
抗HIV药物一览

治疗艾滋病的抗病毒药物近年来研究进展迅速，目前共有大类、超过30种药物。这些药物都是针对HIV生命周期的某一点阻止病毒的制而发挥作用，联合高效抗病毒疗法可以将病毒复制水平压制到检测水平以下（<50拷贝/ml）。这些药物的使用极大地改善HIV患者生活质量，使HIV患者的寿命和正常人相差无几。

停止抗病毒治疗后病毒复制水平反跳



这些药物中没有一种能够治愈HIV感染。在停止抗病毒治疗后，病毒复制水平可以迅速反跳。

Recent Ongoing HIV vaccine Clinical trials

Trial ID	Vaccine description	Category	Phase	Duration
RV305	ALVAC-HIV (vCP1521) and/or AIDSVAX B/E late boost	RV144-related	II	2012.04-2017.05
RV306	ALVAC-HIV (vCP1521) prime, ALVAC-HIV/ AIDSVAX B/E boost	RV144-related	II	2013.09-2017.11
RV328	AIDSVAX B/E prime and boost	RV144-related	II	2014.07-2018.12
HVTN100	ALVAC-HIV (vCP2438) prime, ALVAC-HIV (vCP2438)/bivalent clade C gp120/MF59 boost	RV144-related	I/II	2015.01-2017.01
HVTN702	ALVAC-HIV (vCP2438) prime, ALVAC-HIV (vCP2438)/bivalent clade C gp120/MF59 boost	RV144-related	IIb/III	2016.10-2021.07
X001	CN54gp140 with GLA-AF	Env immunogens	I	2013.10-2015.11
CR104488/ HIV-V-A003/ IPCAVD008	Trimeric gp140 with/without aluminium phosphate	Env immunogens	I	2014.12-2016.04
FLSC-001	Full length single chain gp120-CD4 complex vaccine	Env immunogens	I	2015.11-2018.07
CR100965/ HIV-V-A002/ IPCAVD006	MVA Mosaic HIV	Mosaic vaccine	I	2014.09-2015.11
CR106152/ HIV-V-A004/ IPCAVD009	Ad26 Mosaic HIV prime, Ad26 Mosaic HIV or MVA Mosaic and/or clade C gp140/aluminum phosphate boost	Mosaic vaccine	I/II	2014.12-2019.04
CR108152/ VAC89220HPX2004	Ad26 Mosaic HIV or Ad26 Mosaic4 HIV prime, clade C gp140/aluminum phosphate and Ad26 Mosaic HIV or Ad26 Mosaic4 HIV boost	Mosaic vaccine	II	2016.07-2018.09
CR108068/ VAC89220HPX1002	Ad26 Mosaic HIV with clade C gp140/ aluminum phosphate prime and boost		I	2016.03-2019.01
HVTN 090	VSV-Indiana HIV gag vaccine	Replicating vectors	I	2011.10-2013.01
NCT01989533	Ad4-mgag and Ad4-EnvC150	Replicating vectors	I	2013.11-2020.02
HVTN 110	Ad4-mgag and/or Ad4-EnvC150 prime, AIDSVAX B/E/aluminum hydroxide boost	Replicating vectors	I	2015.03-2017.02
rcAd001/IAVI R001	RcAd26.Mosaic1.HIV-Env	Replicating vectors	I	2015.01-2016.06
HVTN076	VRC-HIVDNA-016-00-VP prime, VRC-HIVADV014-00-VP boost	DNA based	I	2011.05-2013.09
HVTN 087	HIV-MAG vaccine with/without IL-12 pDNA adjuvant electroporation prime, VSV HIV gag boost	DNA based	I	2012.05-2014.09
CRO2059	HIV DNA (CN54ENV/ZM6GPN) prime, MVA-C/ CN54rgp140/GLA-AF adjuvant boost	DNA based	I	2014-2016
HVTN 092	DNA-HIV-PT123 prime with/without NYVAC-HIV-PT1 and NYVAC-HIV-PT4 boost	DNA based	I	2013.04-2014.09
HIV-CORE 004/ IAVI N004	Ad35-GRIN/MVA.HIVconsv with/without pSG2. HIVconsv DNA with/without electroporation	DNA based	I/II	2014.03-2015.08
HVTN 106	DNA Nat-B env or DNA CON-S env or DNA Mosaic env prime, MVA-CMDR boost	DNA based	I	2015.01-2020.09
HVTN 098	PENNVAX⊠-GP HIV-1 DNA vaccine with electroporation with/without IL-12 DNA adjuvant	DNA based	I	2015.04-2016.08
CUTHIVAC002	HIV DNA-C CN54ENV prime with and without electroporation, CN54gp140 boost	DNA based	I	2015.11-2017.04
VRI01	LIPO-5 or MVA HIV-B or GTU-Multi HIV B prime and LIPO-5 or MVA HIV-B boost	Lipopeptides	I/II	2014.03-2016.03

Gao Y, McKay PF, Mann JFS. Viruses. 2018 Apr 1;10(4).

RV-144: Evidence that an AIDS Vaccine Can Prevent HIV-1 Infection in Humans

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

ABSTRACT

subjects (with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline), the vaccine efficacy was 31.2% (95% CI, 1.1 to 51.2; P=0.04). Vaccination did not affect the degree of viremia or the CD4+ T-cell count in subjects in whom HIV-1 infection was subsequently diagnosed.

CONCLUSIONS

This ALVAC-HIV and AIDSVAX B/E vaccine regimen may reduce the risk of HIV infection in a community-based population with largely heterosexual risk. Vaccination did not affect the viral load or CD4+ count in subjects with HIV infection. Although the results show only a modest benefit, they offer insight for future research. (ClinicalTrials.gov number, NCT00223080.)

requests to Dr. Kim at the U.S. Military HIV Research Program, Walter Reed Army Institute of Research, 1600 E. Gude Dr., Rockville, MD 20850, or at jkim@hivresearch.org.

*The names and affiliations of the Ministry of Public Health–Thai AIDS Vaccine Evaluation Group (MOPH–TAVEG) investigators are listed in the Appendix.

This article (10.1056/NEJMoa0908492) was published on October 20, 2009, at NEJM.org.

N Engl J Med 2009;361.

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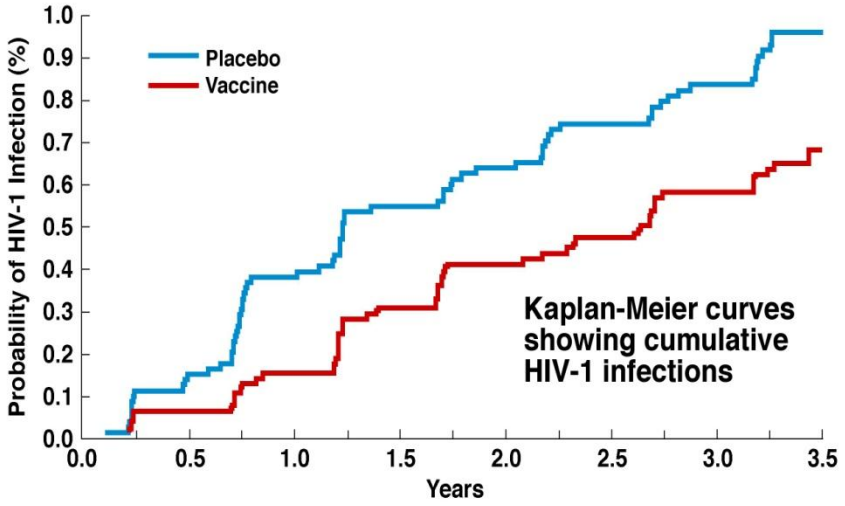
***N Engl J Med.*, 2009 Dec 3;361(23):2209-20.**

Cumulative Infection Rates in RV144 ("Thai Trial") – modified ITT Analysis



- Modest 31% reduction in infection
- limited duration

Proof of concept for a protective vaccine

- HIV序列的极端多样性
- HIV自体多价治疗性疫苗的研究
- bnAb及免疫调节在HIV中的研究

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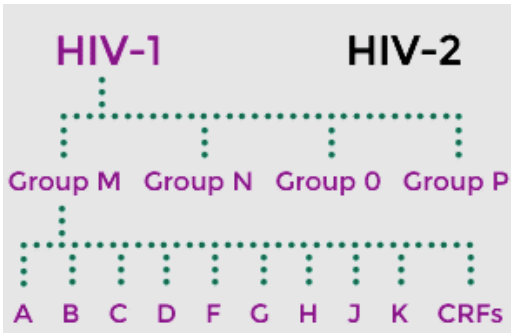
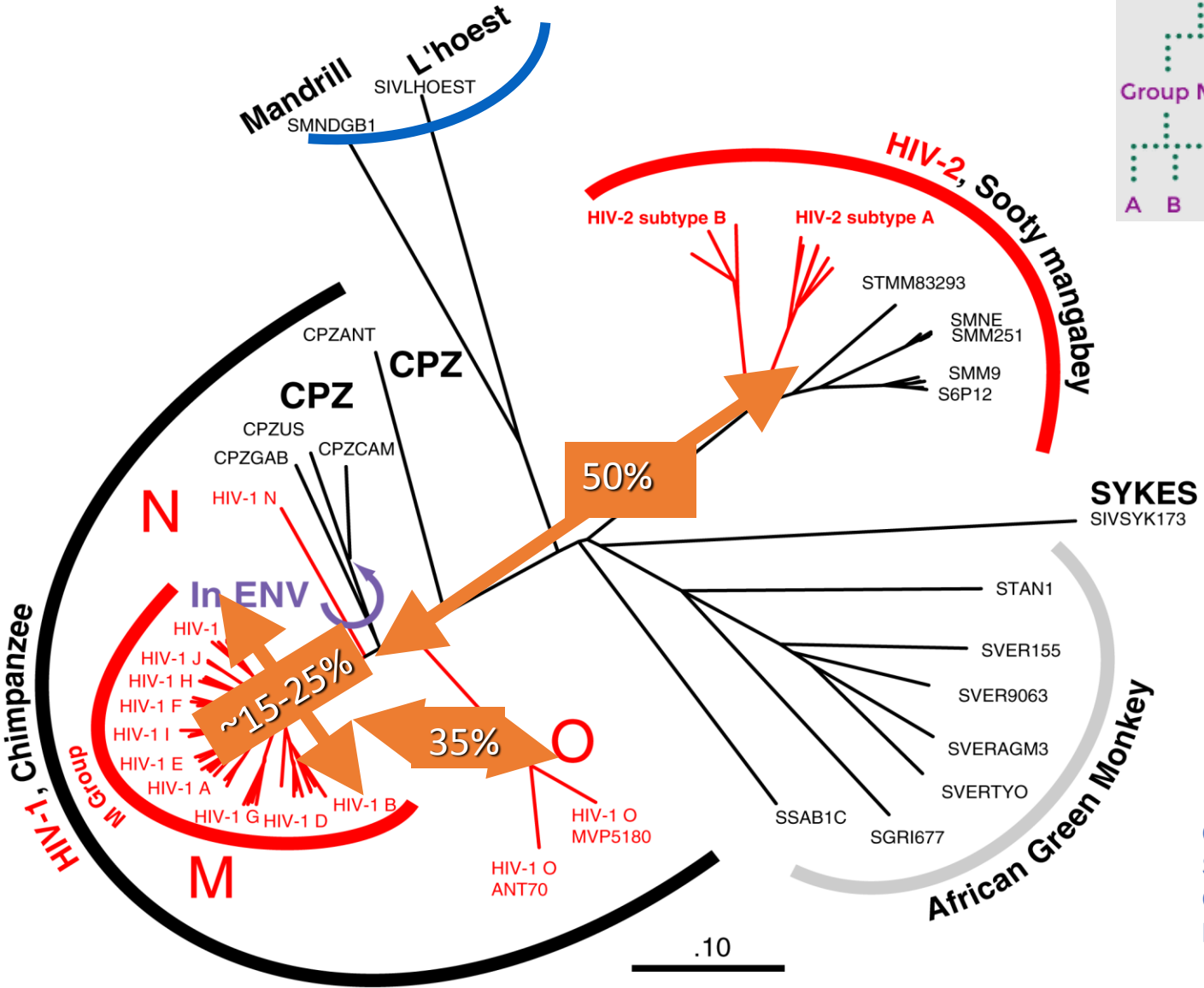
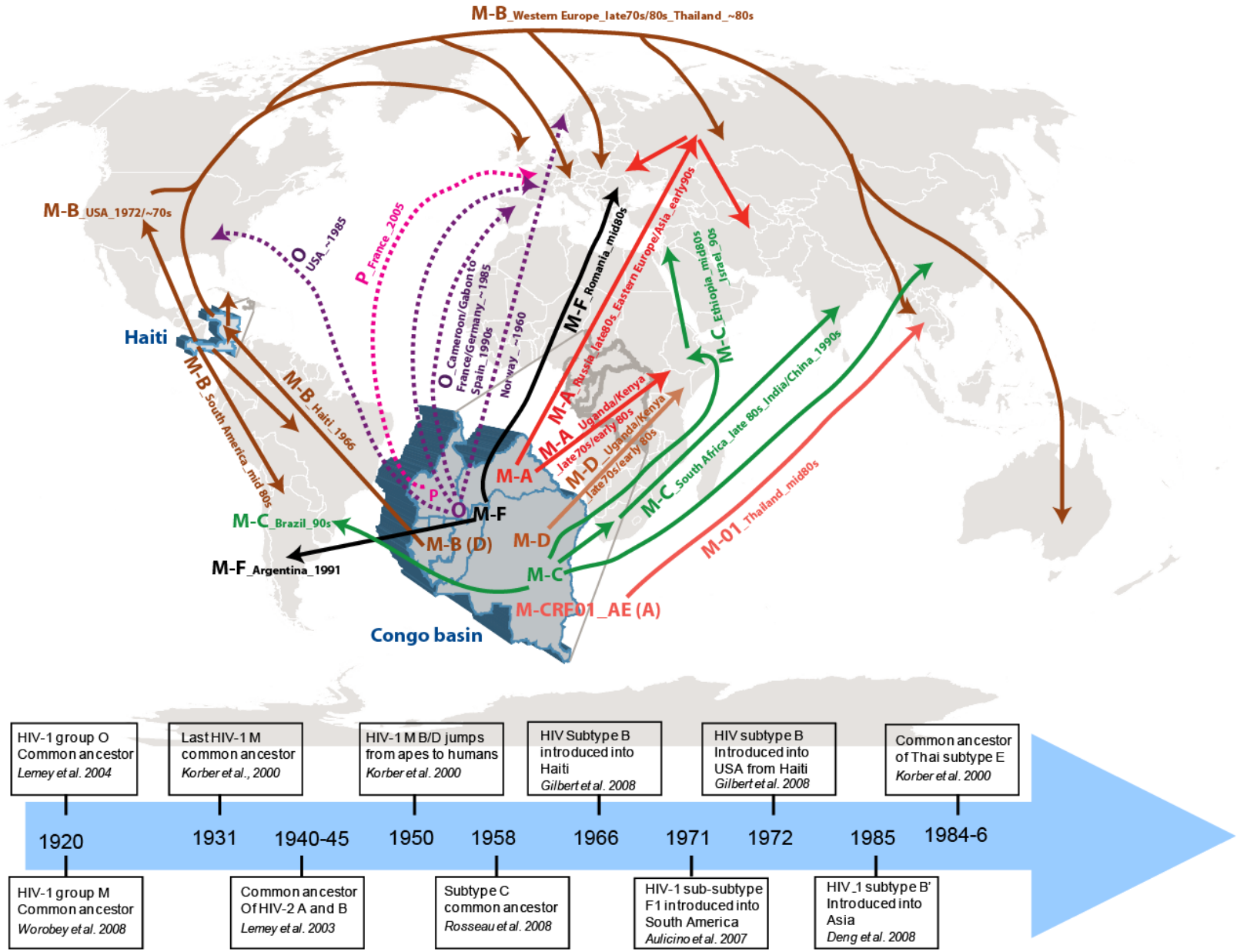
Diversity of primate lentiviruses





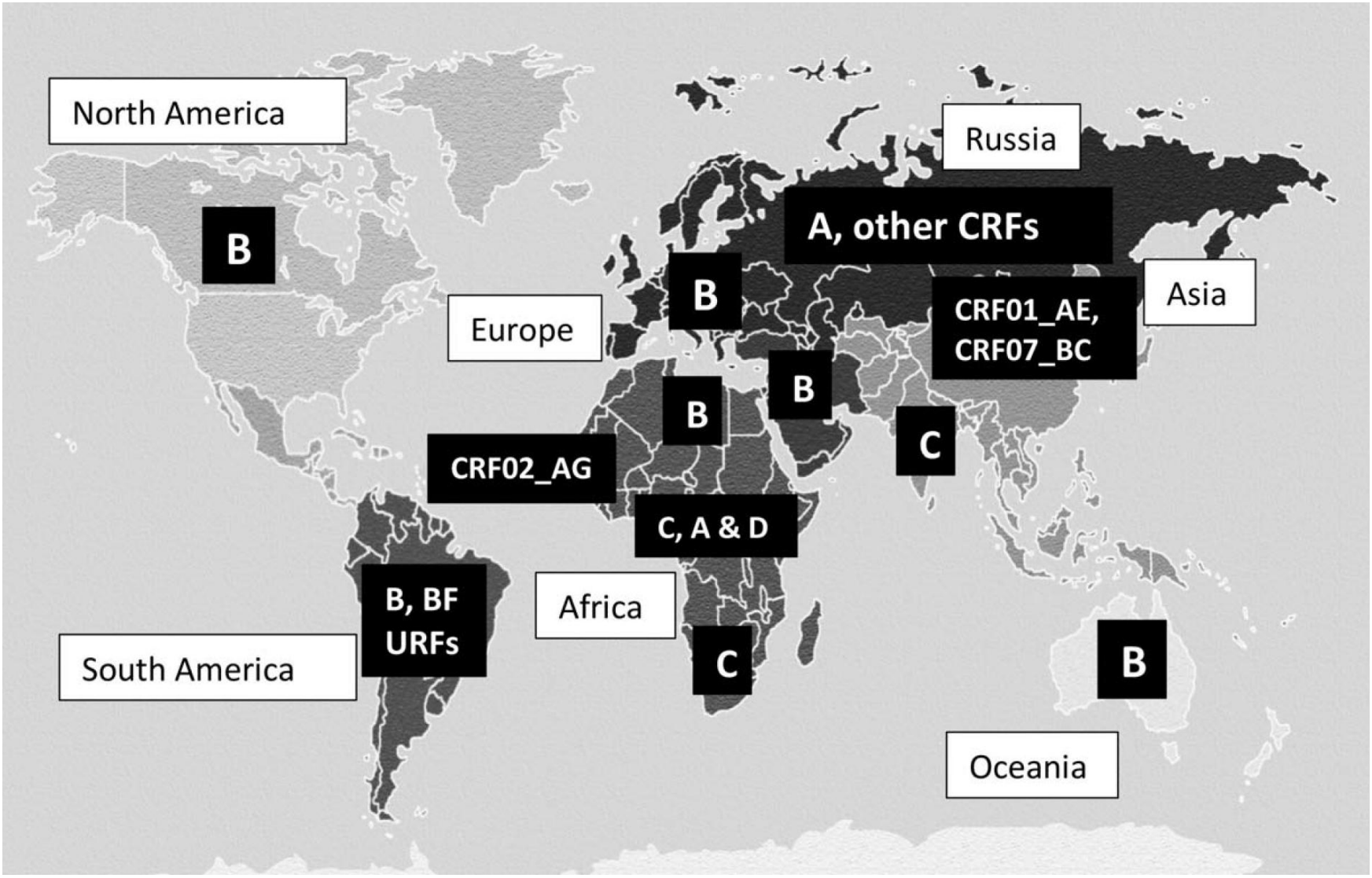
Gao et al., *Nature*, 1999
Santiago et al., *Science*, 2002
Corbet, *J Virol*, 2000
Foley & Korber
HIV Database, LANL

HIV spread pattern worldwide



Tebit and Arts, Lancet Infectious Dis. 2010

Global distribution of major HIV subtypes



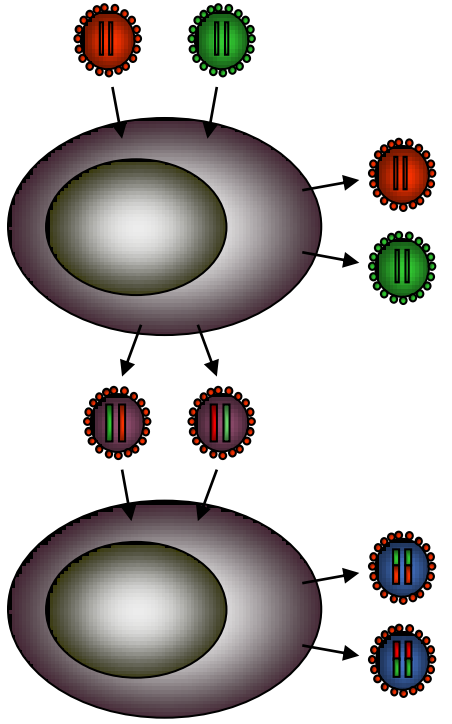
Curr Opin HIV AIDS 2019, 14:153–160

Mechanism of HIV diversity

- Error-prone reverse transcriptase, a high propensity for recombination, and an extremely rapid turnover in vivo, HIV's capacity for mutation and adaptation is enormous.

- Retrovial recombination was first described in 1970 by Dr. Temin.

  Prior to a recombination event, heterodiploid virus must be produced from cells co-infected with two different viruses. Following de novo infection with a heterodiploid retrovirus, recombinant or chimeric genome are created by reverse transcriptase jumping between the two (+) RNA or (-) DNA templates during proviral DNA synthesis.



HIV Recombinants

HIV-1 CRF

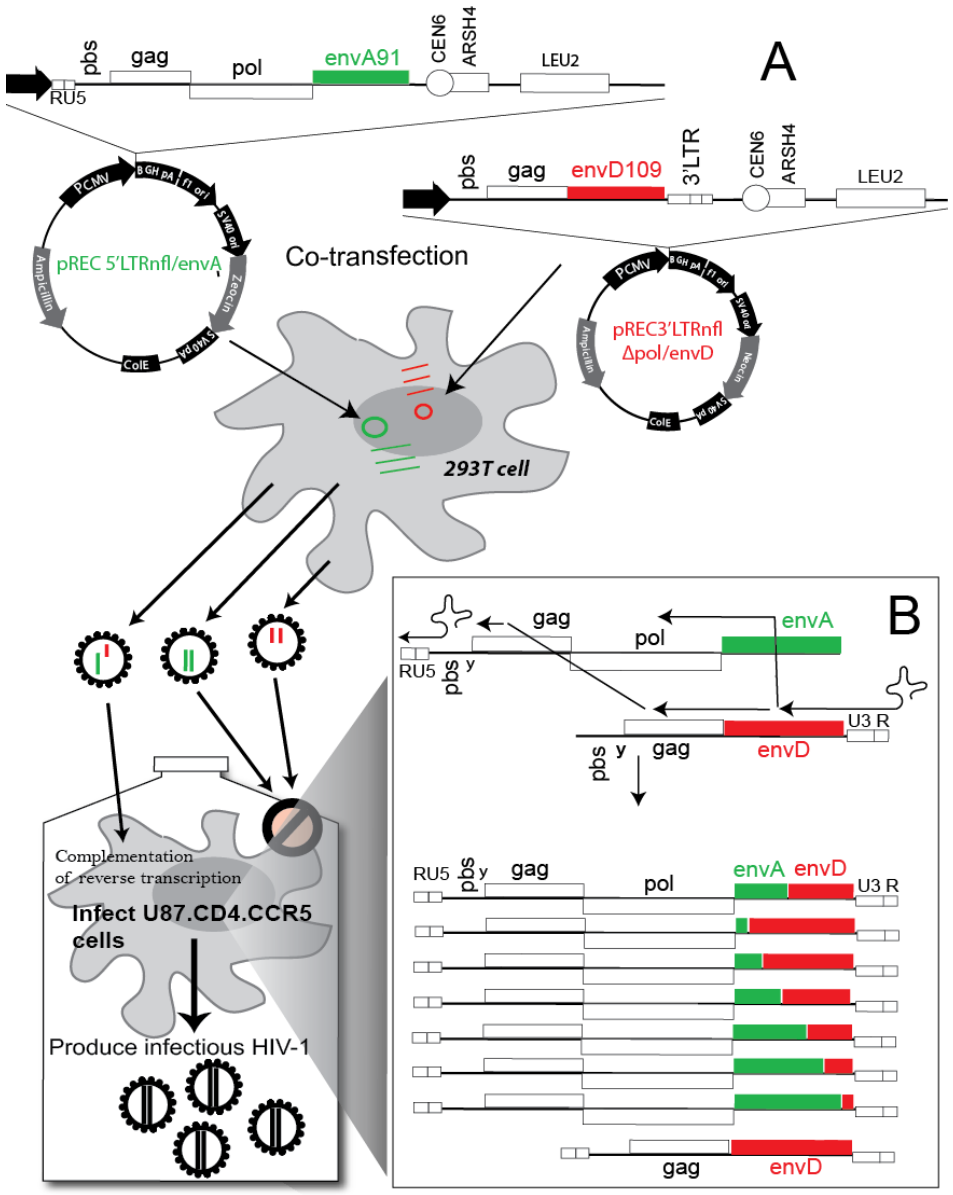
Name	Reference strain	Subtypes
CRF01_AE	CM240	A, E
CRF02_AG	IbNG	A, G
CRF03_AB	Kal153	A, B
CRF04_cpx	94CY032	A, G, H, K, U
CRF05_DF	VI1310	D, F
CRF06_cpx	BFP90	A, G, J, K
CRF07_BC	97CN54	B', C
CRF08_BC	97CNGX-6F	B', C
CRF09_cpx	96GH2911	A, G, U
CRF10_CD	TZBF061	C, D
CRF11_cpx	GR17	A, E, G, J, U
CRF12_BF	ARMA159	B, F1
CRF13_cpx	96CM-1849	CRF01, A, G, J, U
CRF14_BG	X397	B, G
CRF15_01B	99TH.MU2079	CRF01, B
CRF16_A2D	97KR004	A2, D
CRF17_BF	ARMA038	B, F1
CRF18_cpx	CU76	A1, F, G, H, K, U
CRF19_cpx	CU7	A1, D, G
CRF20_BG	Cu103	B, G
CRF21_A2D	99KE_KER2003	A2, D
CRF22_01A1	02CMLT72	CRF01, A1
CRF23_BG	CB118	B, G
CRF24_BG	CB378	B, G
CRF25_cpx	02CM_1918LE	A, G, U
CRF26_A5U	02CD_MBTB047	A, U
CRF27_cpx	04FR-KZS	A, E, G, H, J, K, U
CRF28_BF	BREPM12609	B, F1
CRF29_BF	BREPM16704	B, F1
CRF30_0206	00NE36	CRF02, CRF06
CRF31_BC	04BR142	B, C
CRF32_06A6	EE0369	CRF06, A6
CRF33_01B	05MYKL007	CRF01, B
CRF34_01B	OUR2275P	CRF01, B
CRF35_AD	AF095	A, D
CRF36_cpx	NYU830	CRF01, CRF02, A, G
CRF37_cpx	NYU926	CRF01, CRF02, A, G, U
CRF38_BF	UY03_3389	B, F1
CRF39_BF	03BRRJ103	B, F1
CRF40_BF	05BRRJ055	B, F1
CRF41_CD	CO6650V1	C, D
CRF42_BF	luBF_13_05	B, F1
CRF43_02G	J11223	CRF02, G
CRF44_BF	CH80	B, F1
CRF45_cpx	04FR.AKU	A, K, U
CRF46_BF	01BR087	B, F1
CRF47_BF	P1942	B, F1
CRF48_01B	07MYKT014	CRF01, B
CRF49_cpx	N28353	A1, C, J, K, U
CRF50_A1D	8179	A1, D
CRF51_01B	HM021	CRF01, B
CRF52_01B	M043	CRF01, B
CRF53_01B	11FIR164	CRF01, B
CRF54_01B	09MYSB023	CRF01, B
CRF55_01B	HNCS102056	CRF01, B
CRF56_cpx	URF5	CRF02, B, G
CRF57_BC	1439	B, C
CRF58_01B	09MYPR37	CRF01, B
CRF59_01B	09LNA423	CRF01, B
CRF60_BC	BAV499	B, C
CRF61_BC	JL100010	B, C
CRF62_BC	YNFL13	B, C
CRF63_02A	10RU6637	CRF02, A6
CRF64_BC	YNFL31	B, C
CRF65_cpx	YNFL05	CRF01, B, C
CRF66		
CRF67_01B	MAS59	CRF01, B
CRF68_01B	XC46	CRF01, B
CRF69_01B	10JP-5091N200	CRF01, B
CRF70_BF	PE004	B, F1
CRF71_BF	PE008	B, F1
CRF72_BF	MG002	B, F1
CRF73_BG	9196_01	B, G
CRF74_01B	10MYPR268	CRF01, B
CRF75		
CRF76_01B	N628	CRF01, B
CRF77_cpx	14MYNBB090	CRF01, B, C
CRF78_cpx	YNTC19	CRF01, B, C
CRF79_0107	SX15DT013	CRF01, CRF07
CRF80_0107	YA285	CRF01, CRF07
CRF81		
CRF82_cpx	mSSDU12	CRF01, B, C
CRF83_cpx	mSSDU94	CRF01, B, C
CRF84		
CRF85_BC	SCYB2	B, C
CRF86_BC	15YNHS18	B, C
CRF87_cpx	DH32	CRF01, B, C
CRF88_BC	05YNRL25	B, C
CRF89		
CRF90_BF1	BRGO6043	B, F1
CRF91		
CRF92_C2U	DRC699	C, U
CRF93_cpx	DRC817	A1, A5, C, CRF02, U
CRF94_cpx	32FR0916	CRF02, B, F2
CRF95		
CRF96_cpx	JL.RF01	CRF01, B, C
CRF98_06B	A-Bordeaux	CRF06_cpx, B

HIV-2 CRF

Name	Reference strain	Subtypes
HIV2-CRF01_AB	7312A	HIV2-A, HIV2-B

https://www.hiv.lanl.gov/content/sequence/HIV/CRFs/CRFs.html

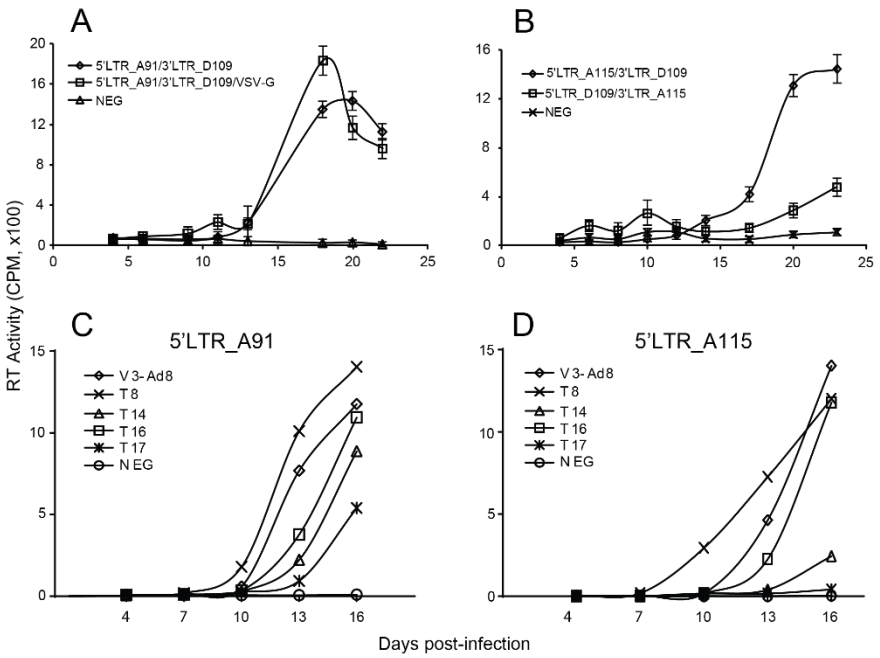
Study on HIV recombination



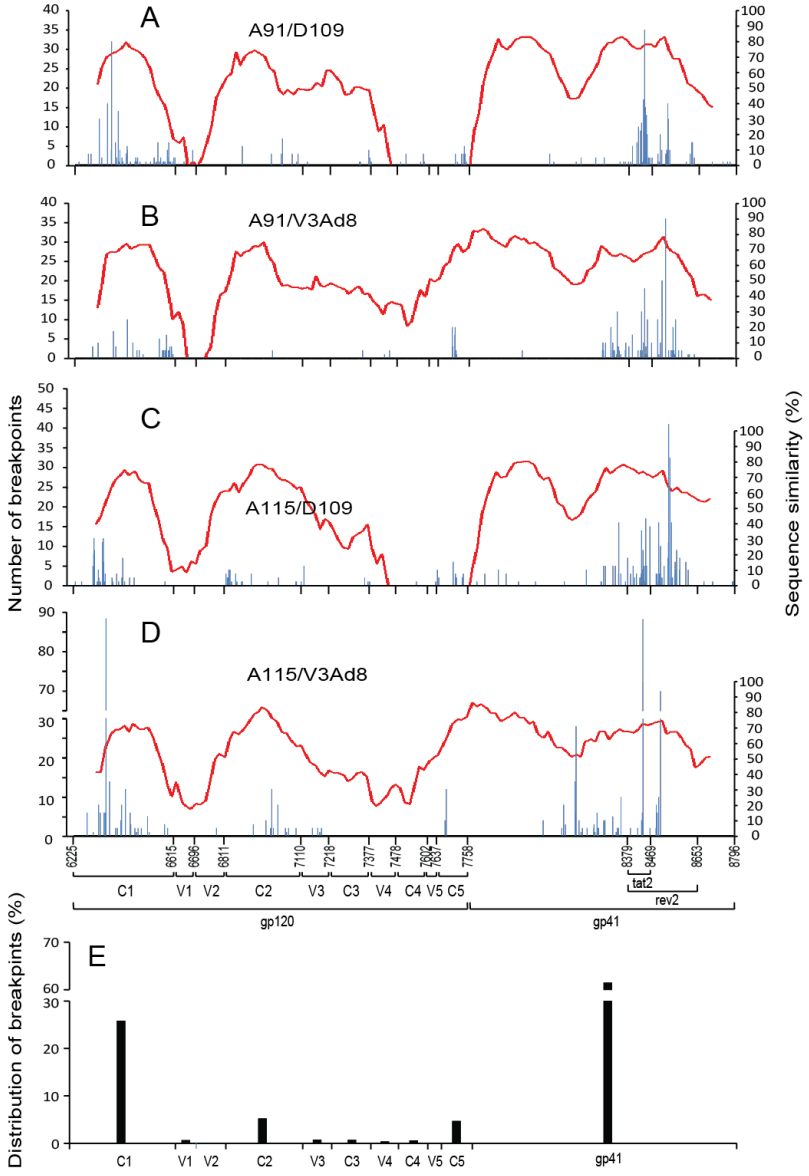
Schematic for HIV-1 Env FRP system. (A) pREC_5′ LTR_nfl_envA (aka 5′ LTR_envA) is the major plasmid containing all genes except the 3′ LTR sequence and expresses all of the viral proteins. The pREC__nfl_Δ pol_3′ LTR_envD (aka 3′ LTR_envD) is a helper plasmid containing a truncated HIV-1 genome devoid of the 5′ LTR and pol sequences. The HIV-1 strain NL4-3 env genes in the two plasmids have been replaced by subtype A and D env sequences, respectively. (B and C) Illustration of how intersubtype recombination occurs using the HIV-1 Env FRP system. The two defective HIV-1 genomes, if co-packaged, can complement each other to initiate and complete reverse transcription; however, (B) infectious complete genomes will only result when recombination occurs within the env region, while (C) recombination in gag region will result in defective viral genome and noninfectious viruses.

J Mol Biol. 2017 May 1; 2836 (17):30192-4

Study on HIV recombination



Production of infectious HIV-1 viruses through the HIV-1 Env FRP system.



Distribution of recombination breakpoints from early infection culture of FRP detected by 454 pyrosequencing.

J Mol Biol. 2017 May 1; 2836 (17):30192-4

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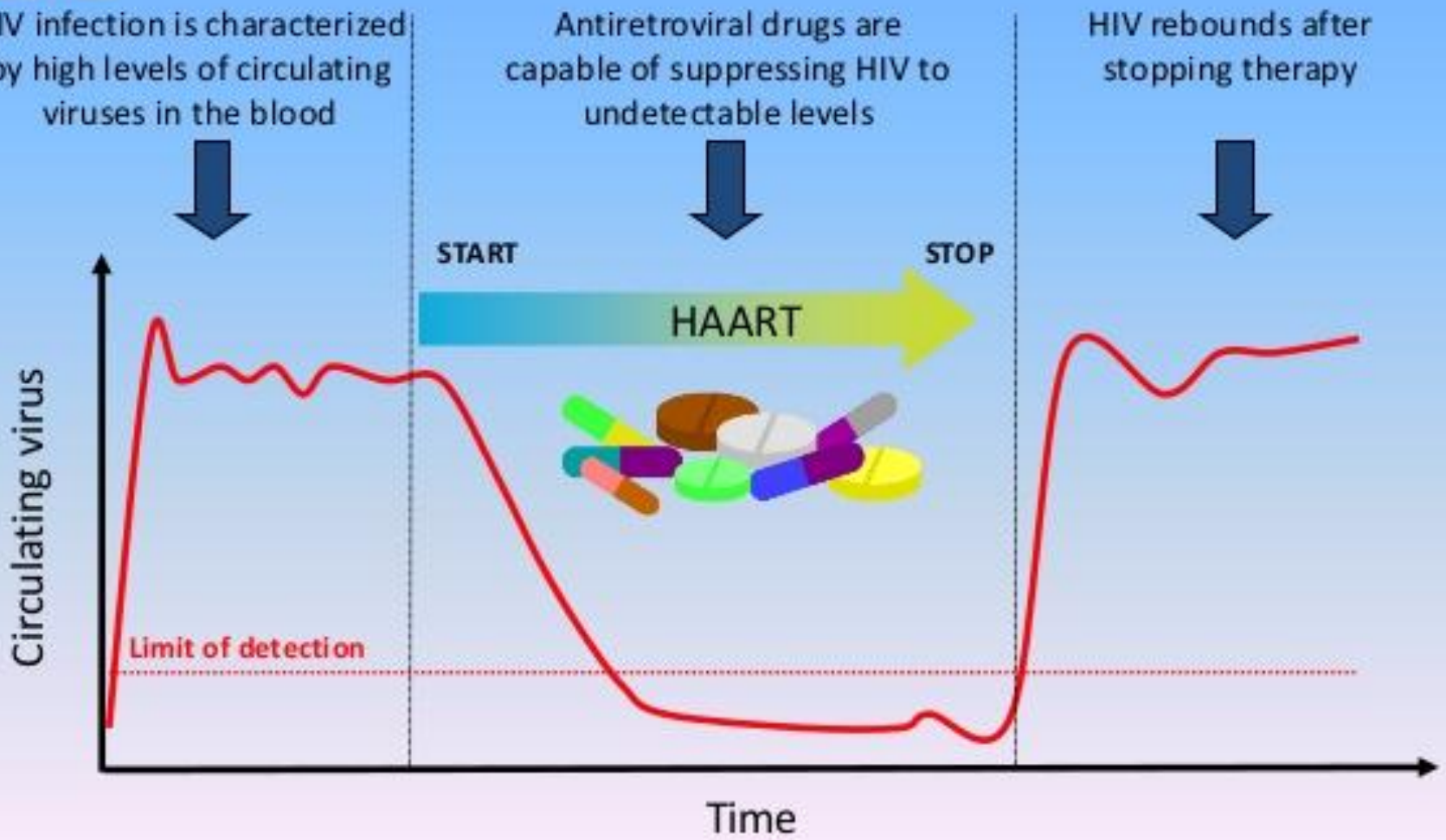
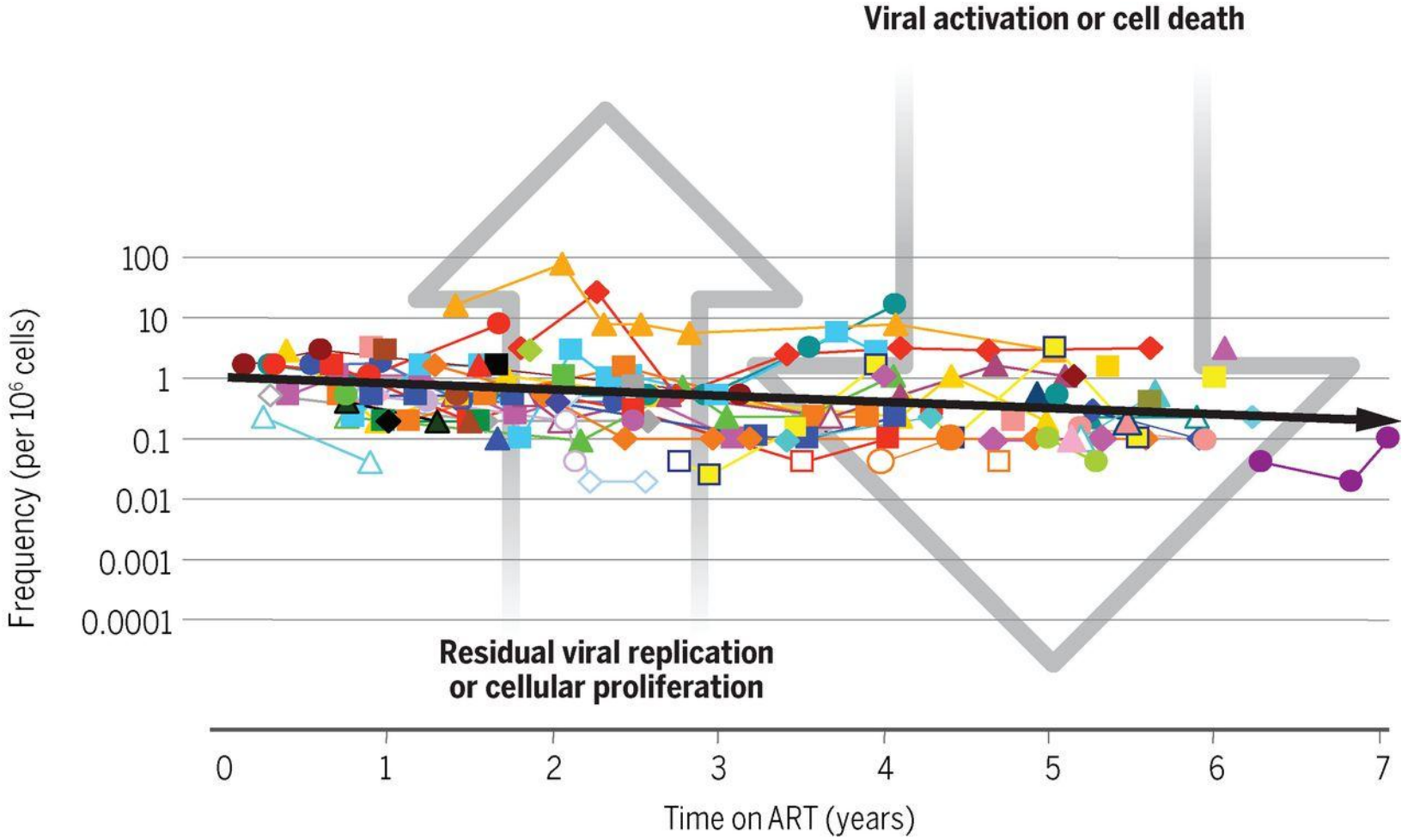
停止抗病毒治疗后病毒复制水平反跳



这些药物中没有一种能够治愈HIV感染。在停止抗病毒治疗后，病毒复制水平可以迅速反跳。

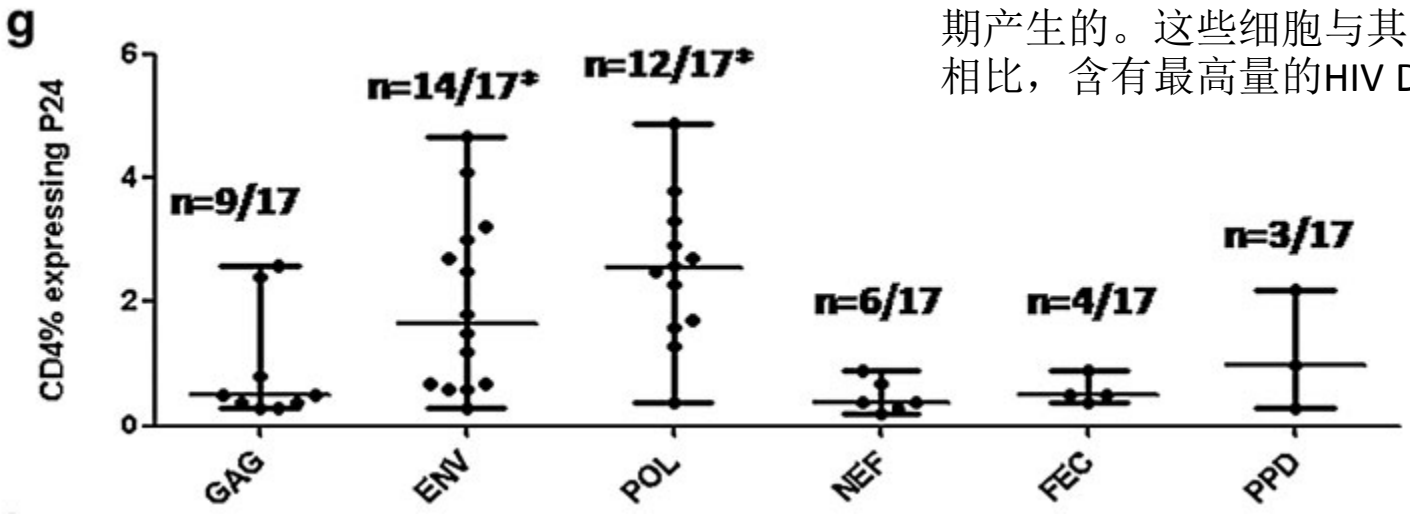
Persistent, latent infection of memory CD4 cells decays slowly over time.



David M. Margolis et al. Science 2016;353:aaf6517

HIV-1 latency reversal can be achieved more readily using HIV-1 antigens

研究显示大多数活化的感染有HIV的记忆性T细胞都是特异性针对HIV抗原。HIV特异性的CD4记忆性T细胞主要于急性感染期产生的。这些细胞与其它特异性细胞相比，含有最高量的HIV DNA。



Ashwini Shete, Madhuri Thakar, Dharmesh P. Singh, Raman Gangakhedkar, Asmita Gaikwad, Jyoti Pawar, and Ramesh Paranjape

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 28, Number 8, 2012

DOI: 10.1089/aid.2010.0363

自体同源多价治疗性疫苗的研究

假说

特定HIV患者体内的被HIV潜伏感染的静息性CD4记忆性T细胞亚群可能会被自体同源性疫苗最大程度地激活。

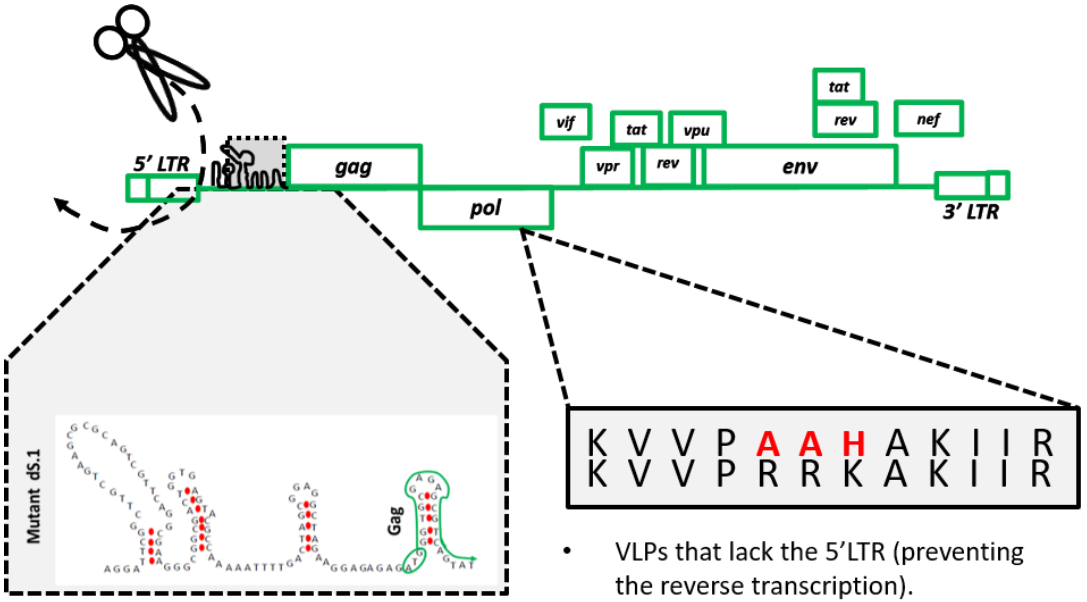
目标

研发自体同源多价治疗性疫苗（即个体化治疗性疫苗），特异性激活、清除潜伏感染的病毒贮库。

HIV治疗性疫苗系统

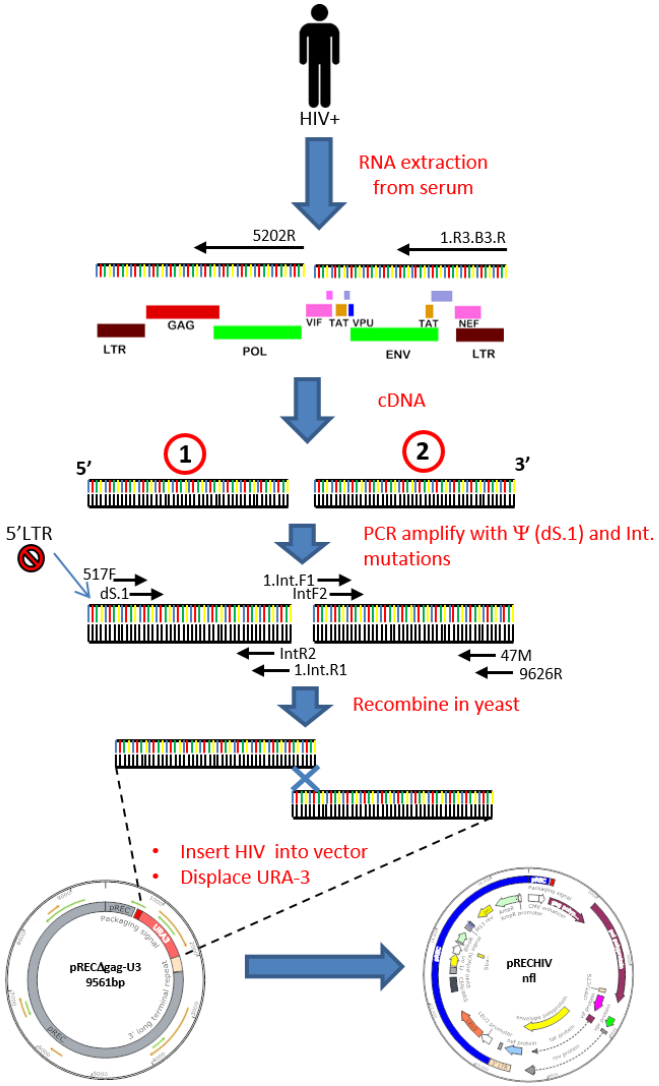
ACT-VEC cloning strategy

(A fully native but “dead” virus particle)

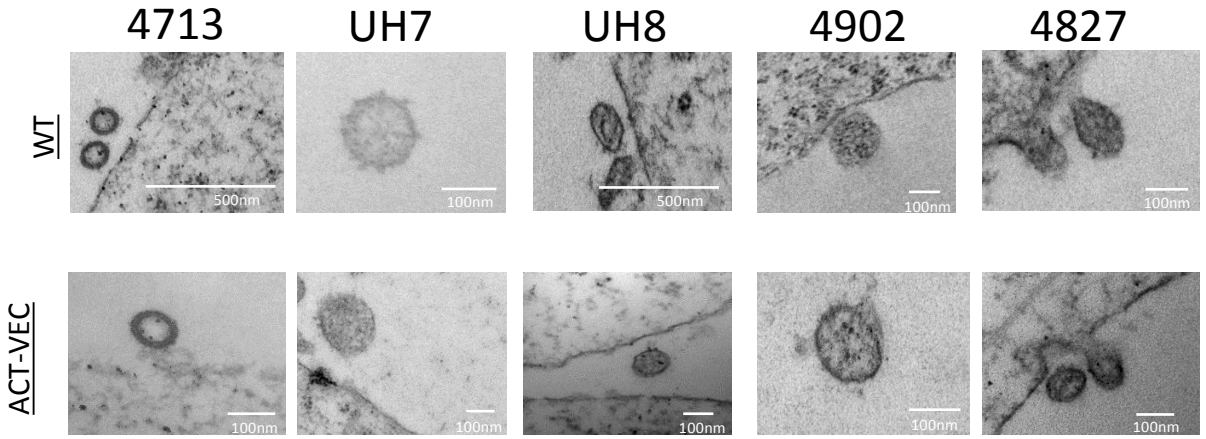


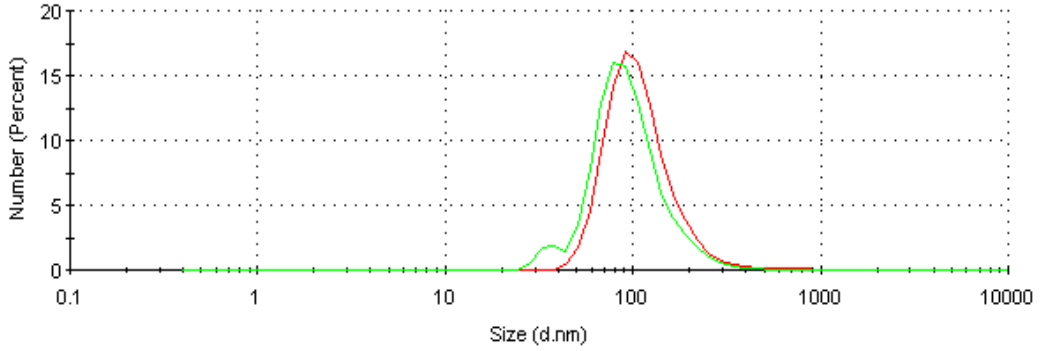
K V V P **A A H** A K I I R
K V V P R R K A K I I R

- VLPs that lack the 5′LTR (preventing the reverse transcription).
- mutated AAH>RRK to inactivate Integrase.
- Harbor extensive Ψ mutations to prevent viral genomic RNA packaging.

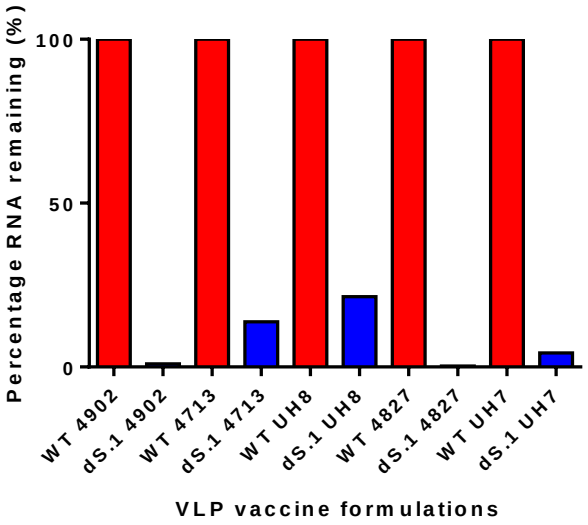


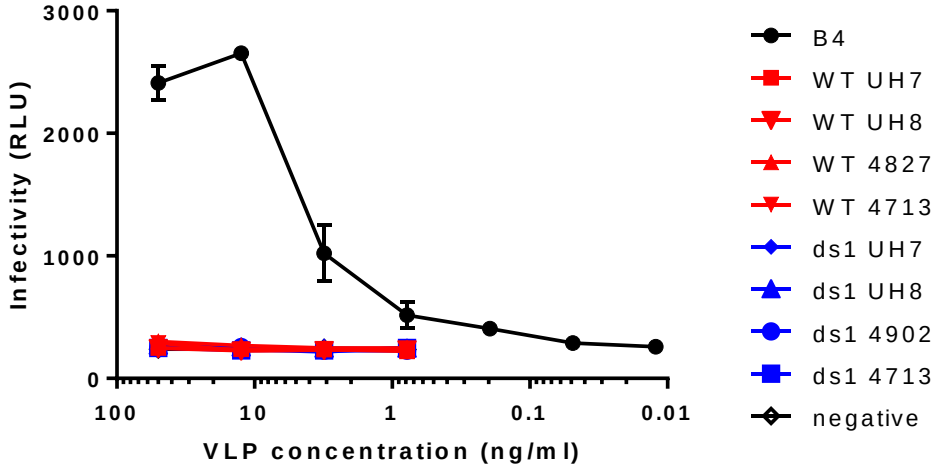
ACT-VEC are morphologically similar to HIV-1



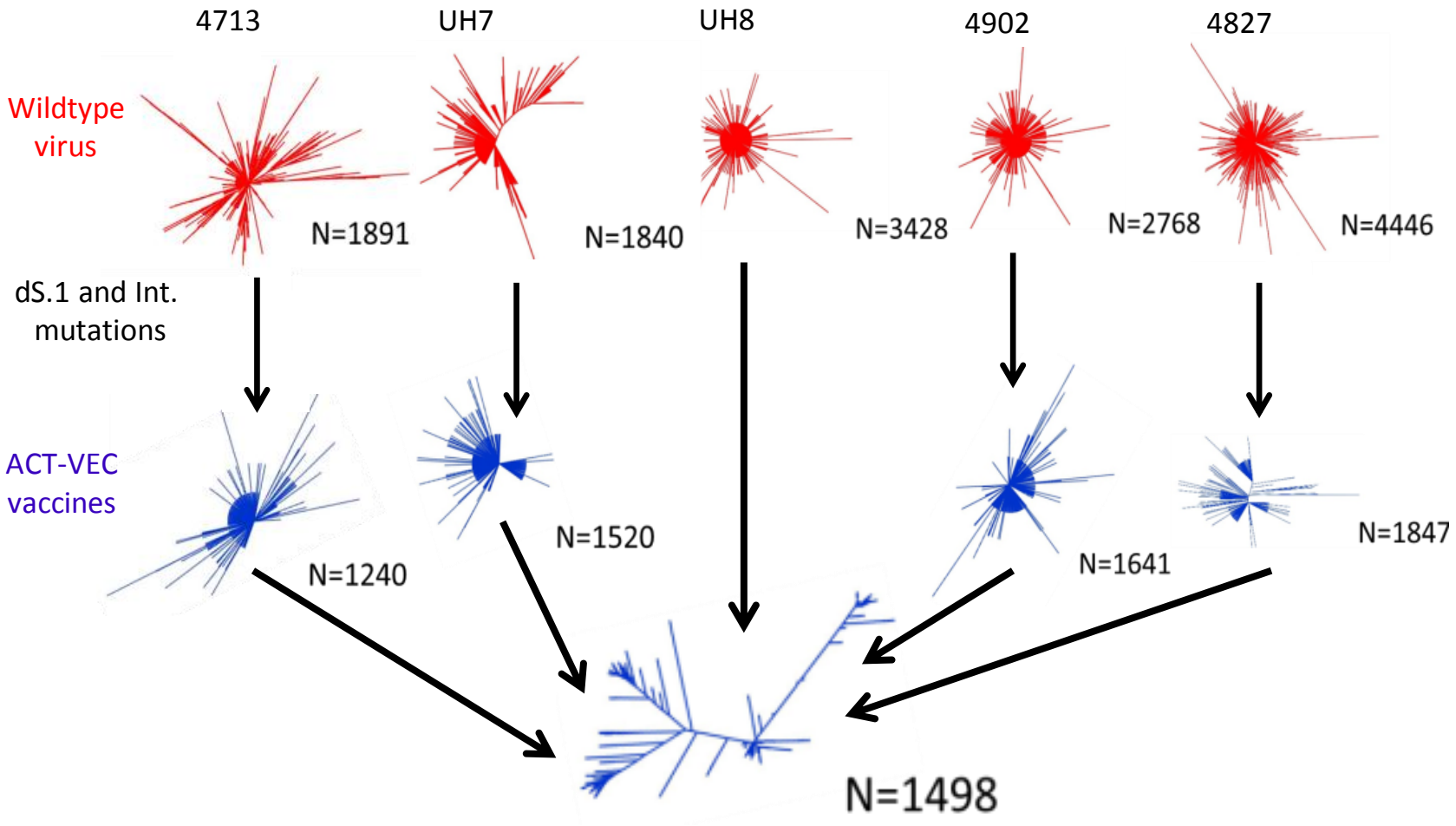


ACT-VEC contain no viral RNA and are non-infectious

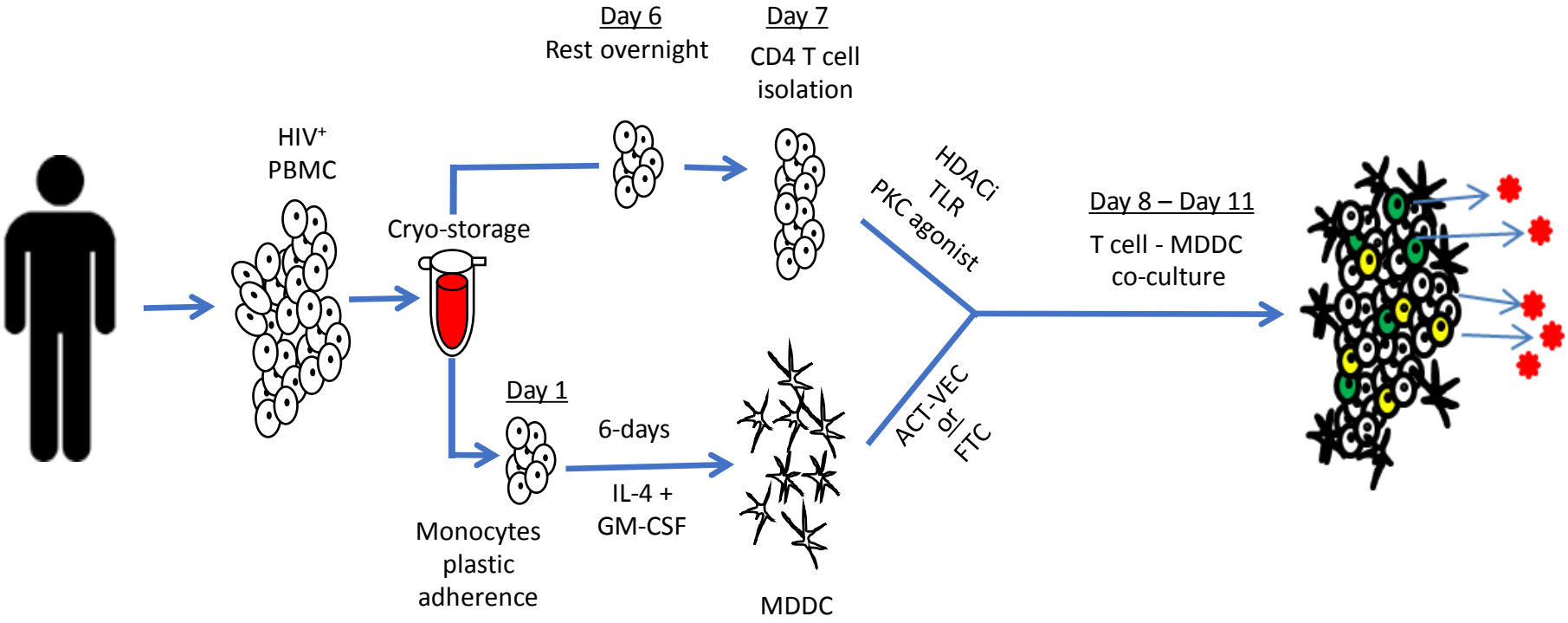




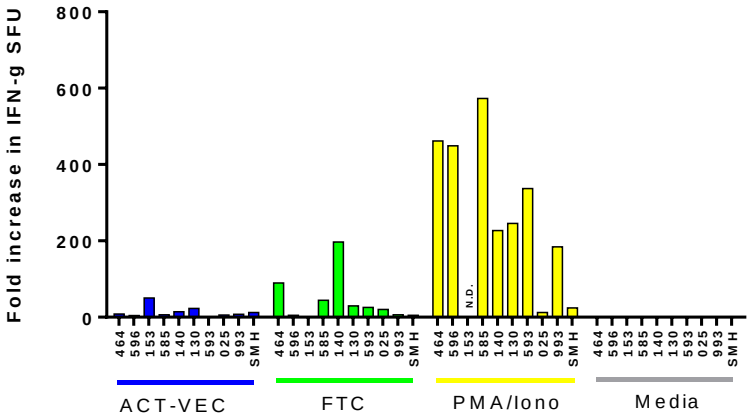
ACT-VEC are a polyvalent quasi-species

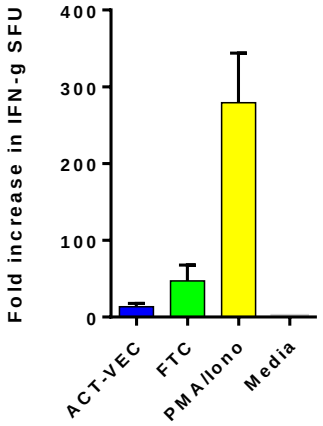


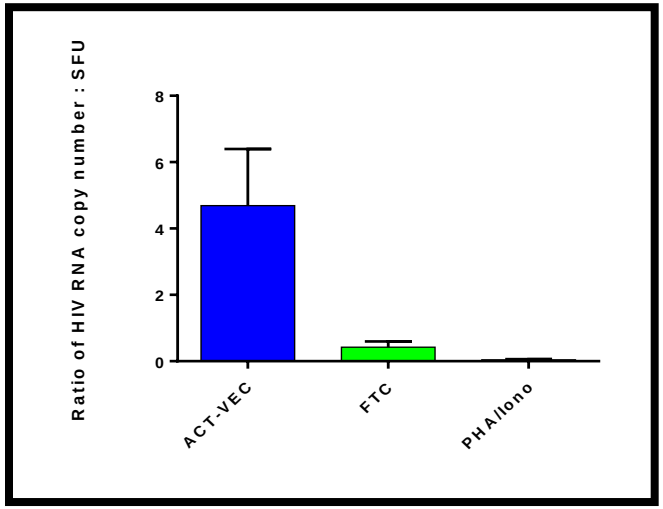
Experimental process

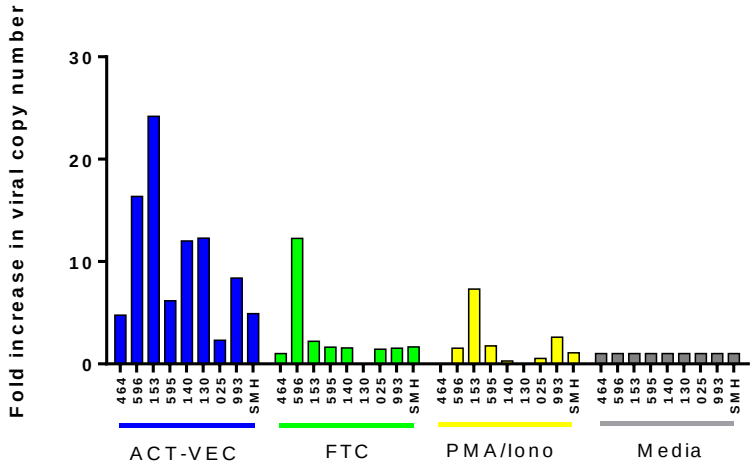


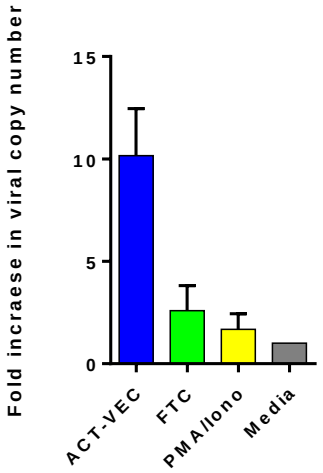
UH8 ACT-VEC causes HIV-1 latency reversal



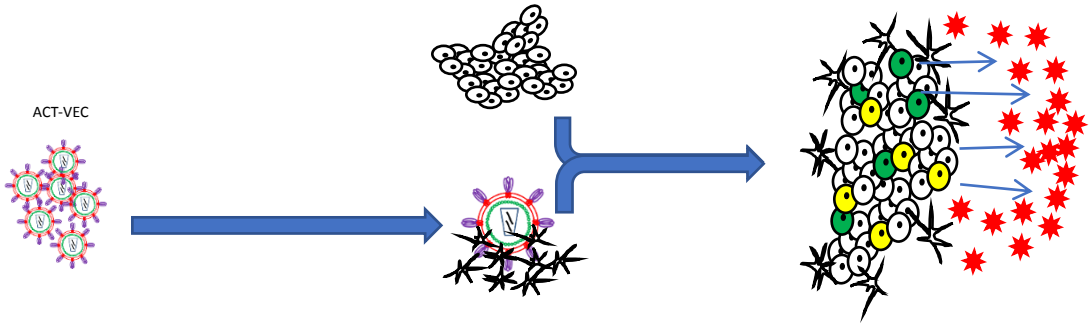


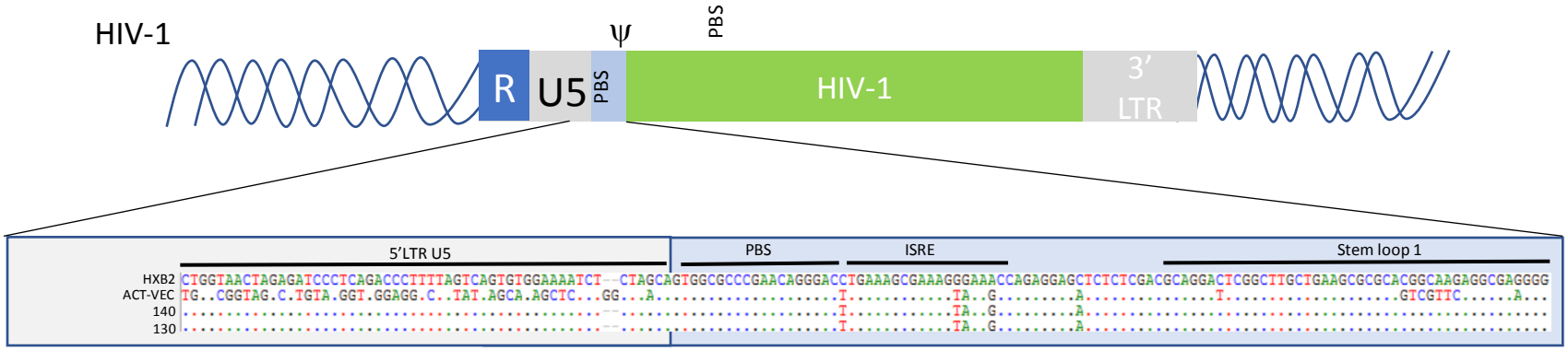


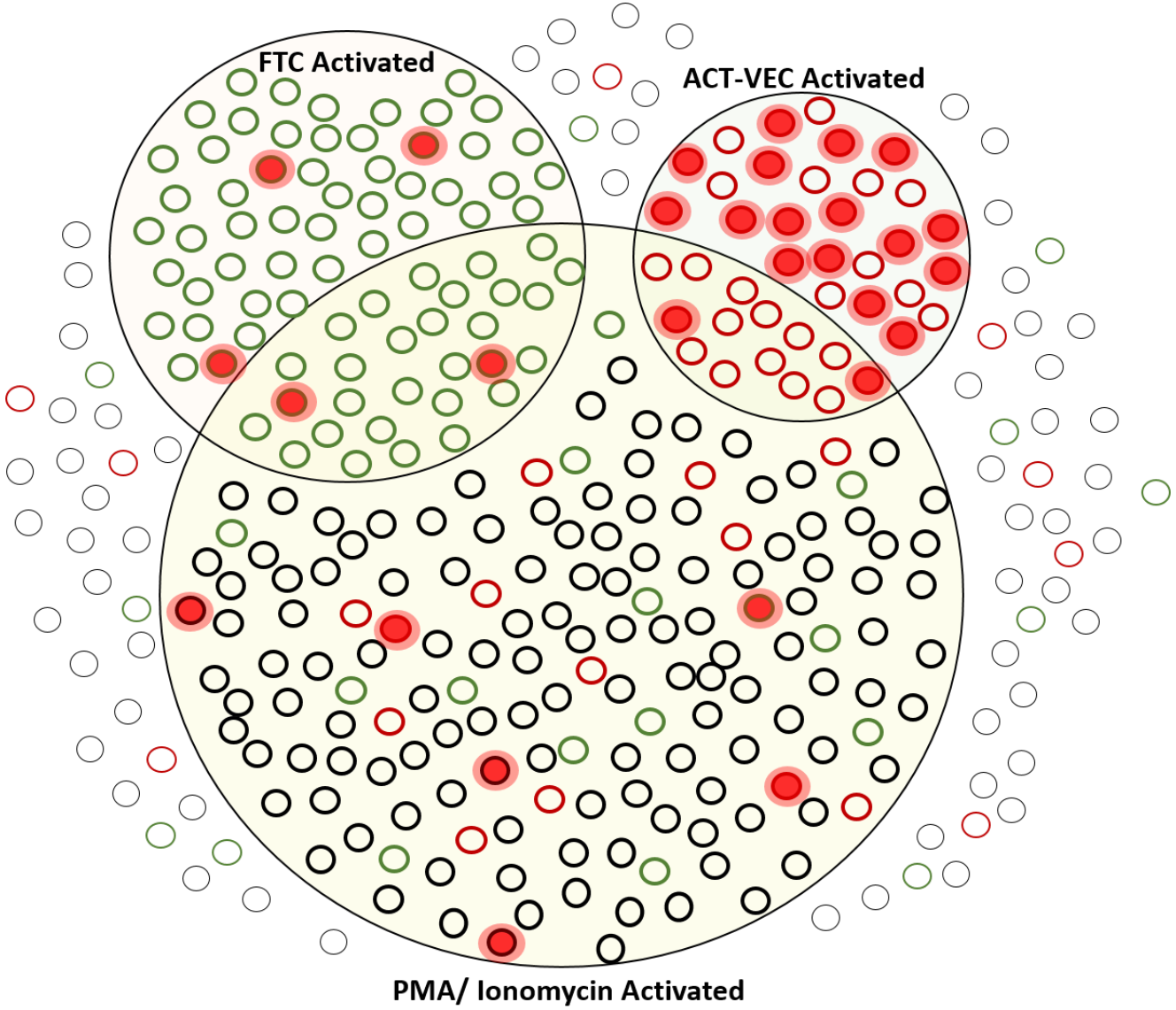




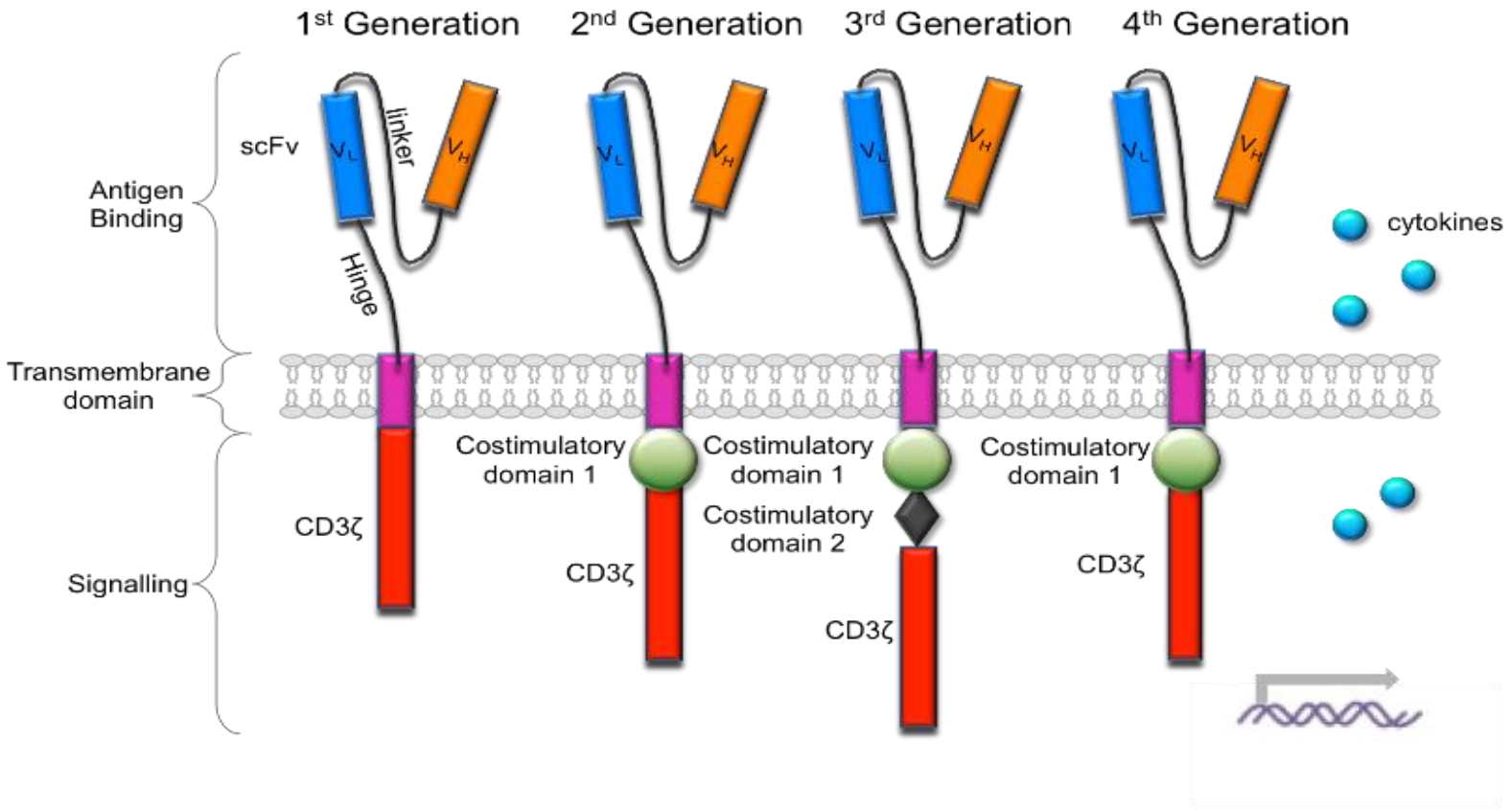
Induced virus has the 5'LTR and wild type sequence for Ψ <u>but</u>
ACT-VEC lack the 5'LTR and has mutated Ψ (DS.1 mutations)





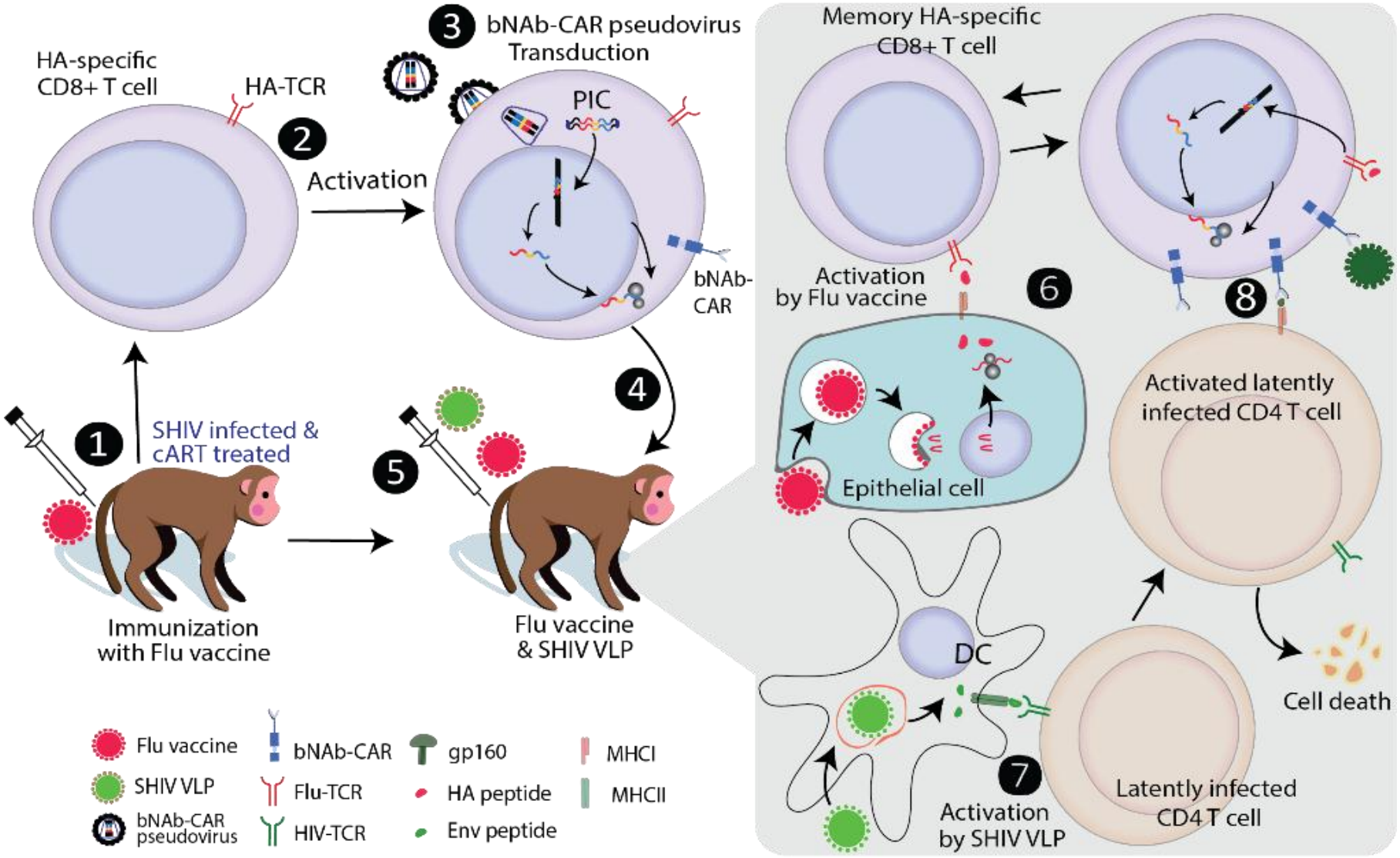

FTC Activated
ACT-VEC Activated
PMA/ Ionomycin Activated

Evolution of CARs design



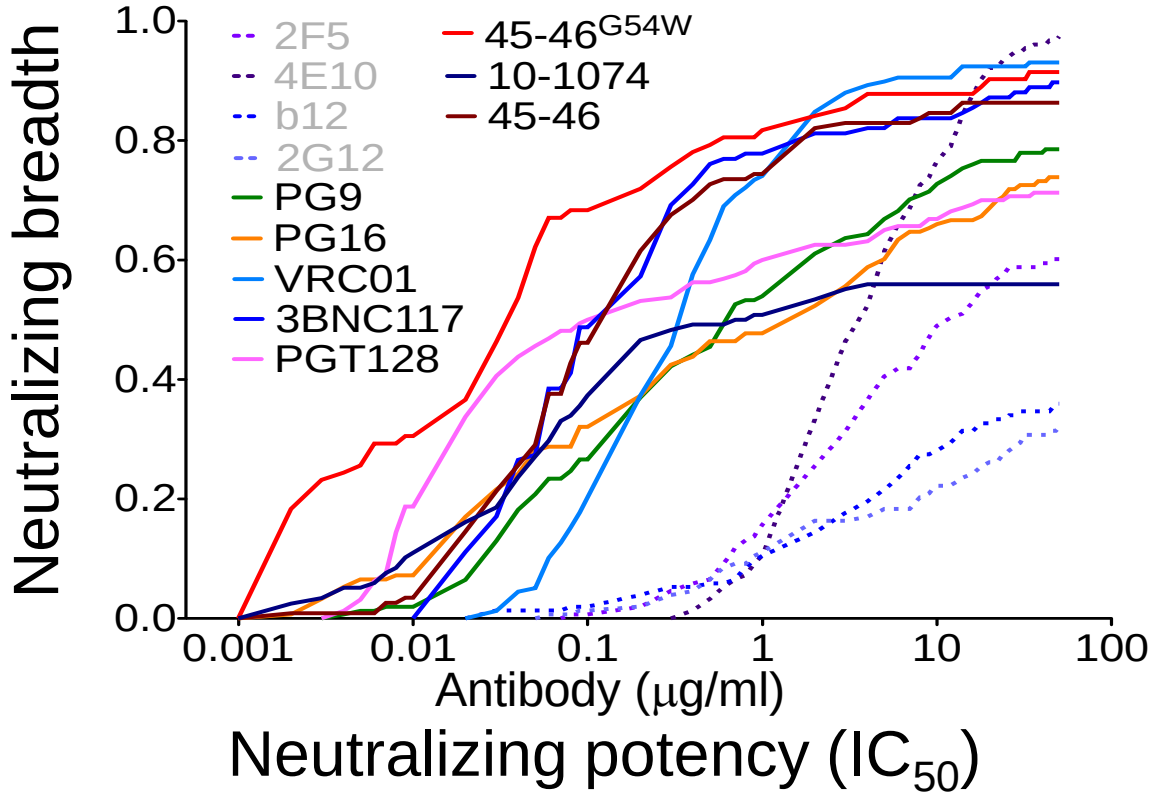
The CAR is composed of 3 components: 1) Extracellular antigen-binding domain derived from a monoclonal antibody single chain variable fragment (scFv); 2) A transmembrane domain anchoring the CAR to the T cell; 3) An intracellular T cell activation domain of CD3ζ with or without costimulatory molecules. The transmembrane domain connects the scFv, which specifies the T cell binding to an antigen, and the intracellular CD3ζ domain responsible for T cell activation. CARs can recognize cell surface antigens in an MHC-independent manner. When the CAR binds to a tumor antigen on the surface of a target cell, the CAR T cell will induce apoptosis using the same mechanism as normal T cells.

Combination vaccination with Flu and HIV vaccine to maximally expand bNAb-CAR T cells in vivo



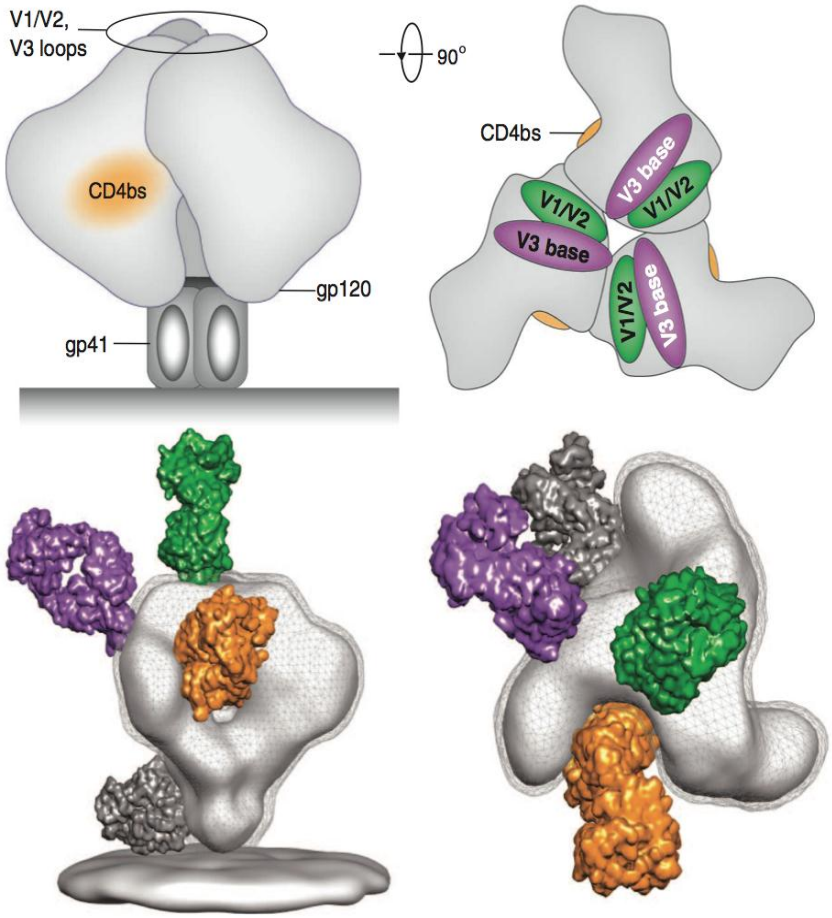
- HIV序列的极端多样性
- HIV自体多价治疗性疫苗的研究
- bnAb及免疫调节在HIV中的研究

Broadly neutralizing antibodies against HIV-1



Mouquet *et al*., PNAS 2012
Scheid *et al*., Science 2011
Diskin *et al*., Science 2011
Walker *et al*., Nature 2011
Wu *et al*., Science 2010
Walker *et al*., Science 2009

The sites recognized by best in class antibodies



From Klein et al. Science 2013

CD4 binding site

b12	1NC9
HJ16	12A12, 12A21
NIH45-46, 45-46^{G54W}	8ANC131, 8ANC134
VRC01-03, VRC06	CH30-CH34
3BNC117, 3BNC60	VRC23
VRC-PG04	CH103

Glycan-V3

PGT121-PGT123
10-1074
PGT125-128,130,131
PGT135-137
VRC24

Trimer (gp120/41)

8ANC195
PGT151
35022

V1/V2 loop

PG9/PG16
PGT141–145
CH01-CH04

PGDM1400
CAP256-VRC26

gp41

4E10
2F5
10E8
HK20
Z13

Others

8ANC195
2G12
3BC176/
3BC315

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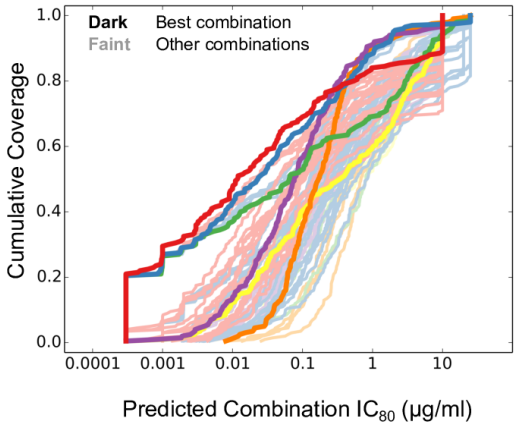
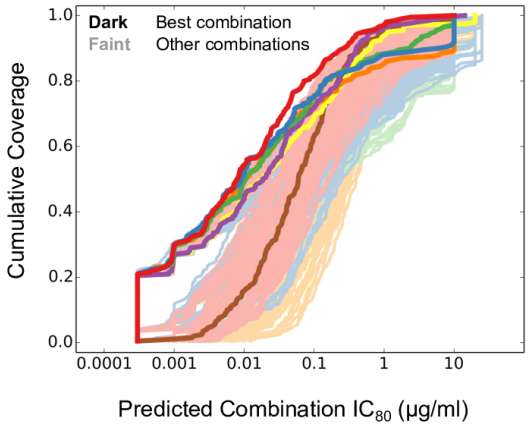
Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection

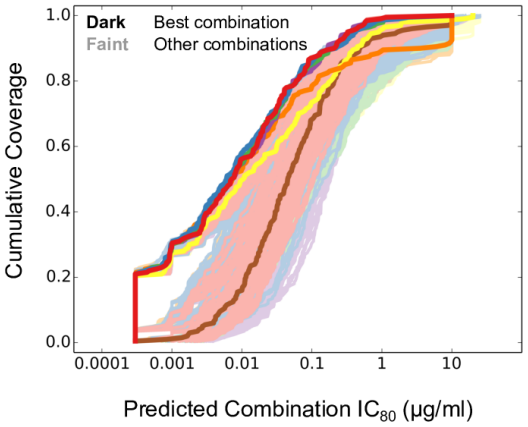
A **2 bnAb combinations**



B **3 bnAb combinations**



C **4 bnAb combinations**



No. of bnAb types in combinations:

	CD4bs	V2g	V3g	MPER	Best Combo
		1	1		bc
	1	1			ab
	1		1		ac
		1		1	bd
	1			1	ad
			1	1	cd

	CD4bs	V2g	V3g	MPER	Best Combo
	1	1	1		abc
	0/1	2	0/1	0/1	bb_2c
		1	1	1	bcd
	1	1		1	abd
	0/1	0/1	2	0/1	bcc_2
	2	0/1	0/1	0/1	aa_2b
	1		1	1	acd

	CD4bs	V2g	V3g	MPER	Best Combo
	1	1	1	1	abcd
	0/1	2	0/1	0/1	abb_2c
	0/1	0/1	2	0/1	$abcc_2$
	2	0/1	0/1	0/1	aa_2bc
		2	2		bb_2cc_2
	2	2			aa_2bb_2
	2		2		aa_2cc_2

bnAbs:

CD4bs:
a VRC07-523
a_2 3BNC117
a_3 VRC07
a_4 VRC01
a_5 VRC13

V2g:
b CAP256-VRC26.25
b_2 PGDM1400
b_3 CAP256-VRC26.08
b_4 PGT145
b_5 PG9

V3g:
c 10-1074V
c_2 PGT128
c_3 10-1074
c_4 PGT121

MPER
d 10E8

Combination of two bnAbs offers >98% coverage.

PLoS Pathog 12(3): e1005520

Challenges associated with bNAb application

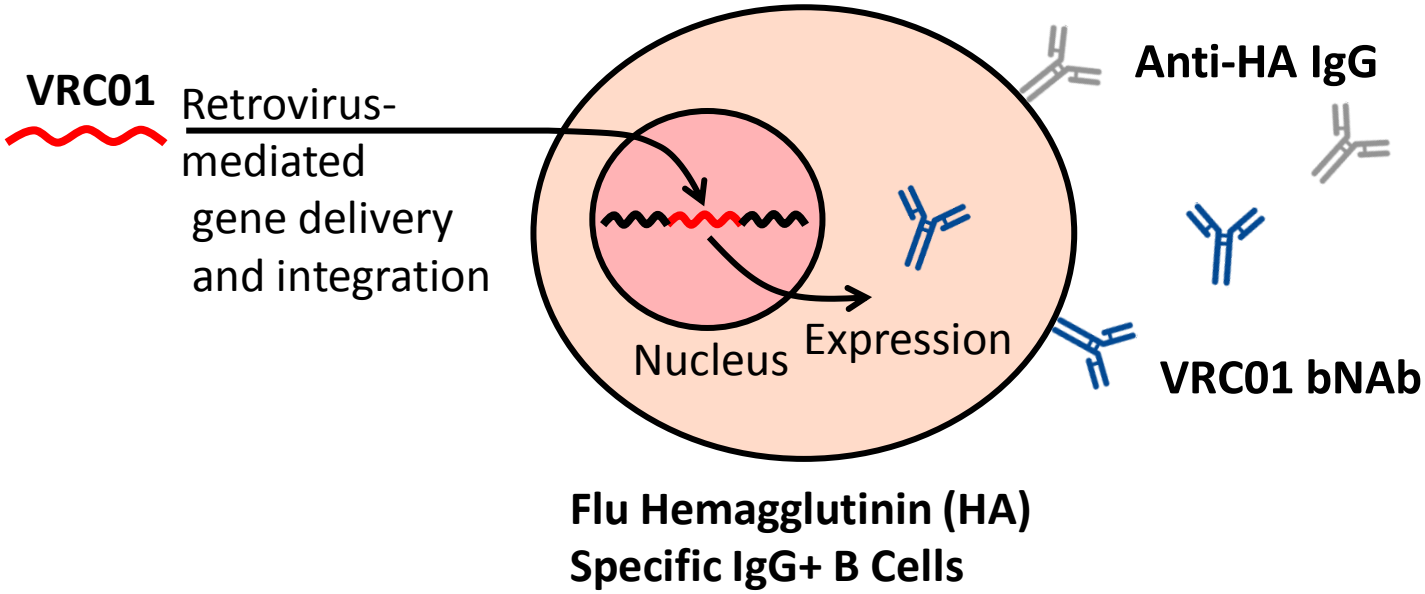
in HIV prevention/treatment

Passive Immunization	Gene Transfer
• Short half life requires repeated injections	• Autoimmunity from sustained bNAb production • Efficient antibody expression and yield

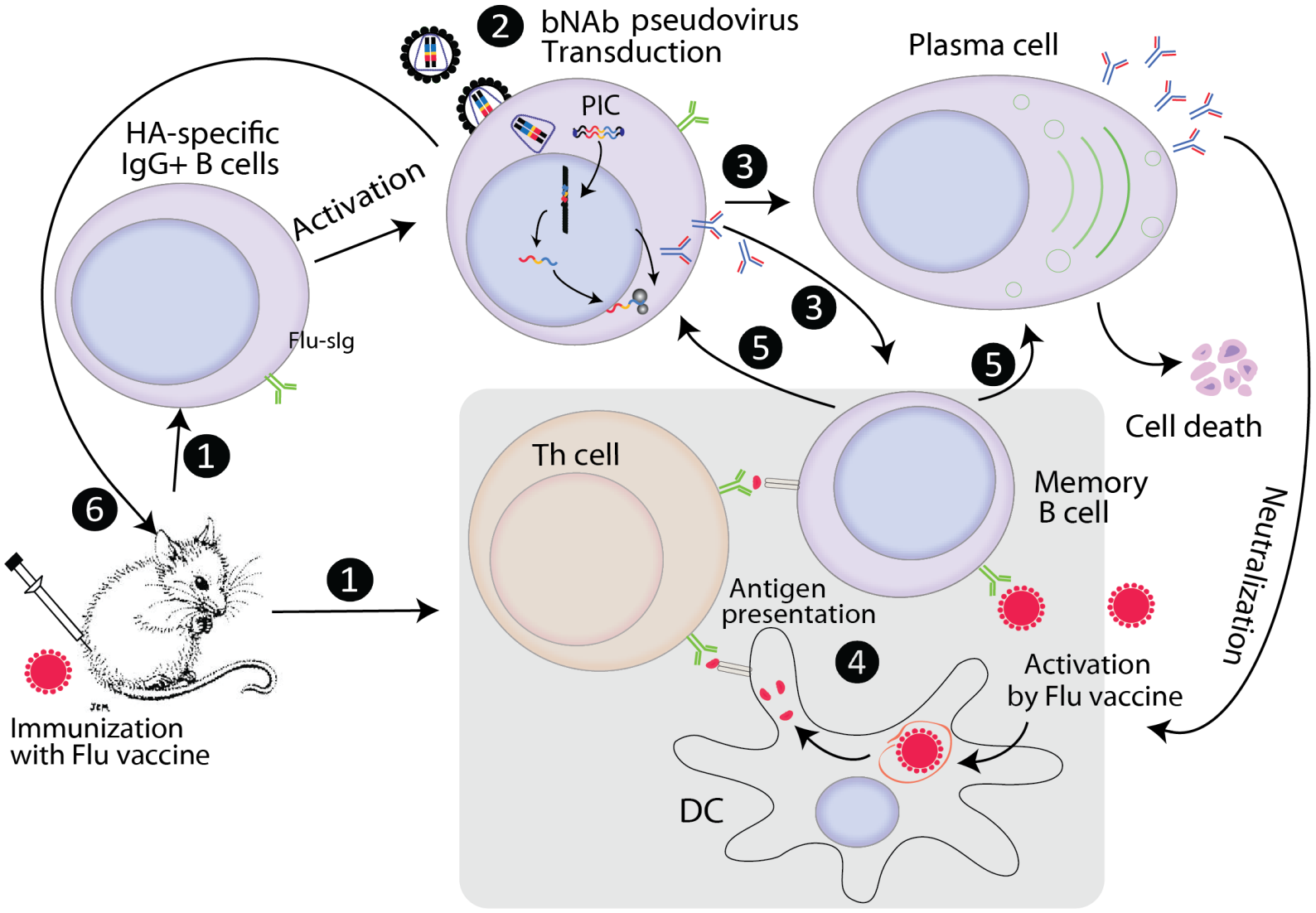
- Auto-reactive bNAbs with the long-term antibody expression achieved by gene therapy creates a potential for autoimmunity
- How to achieve a protective bNAb level while minimizing the side effects caused by long-term bNAb expression. i.e. Controlled expression of bNAb?

Hypothesis

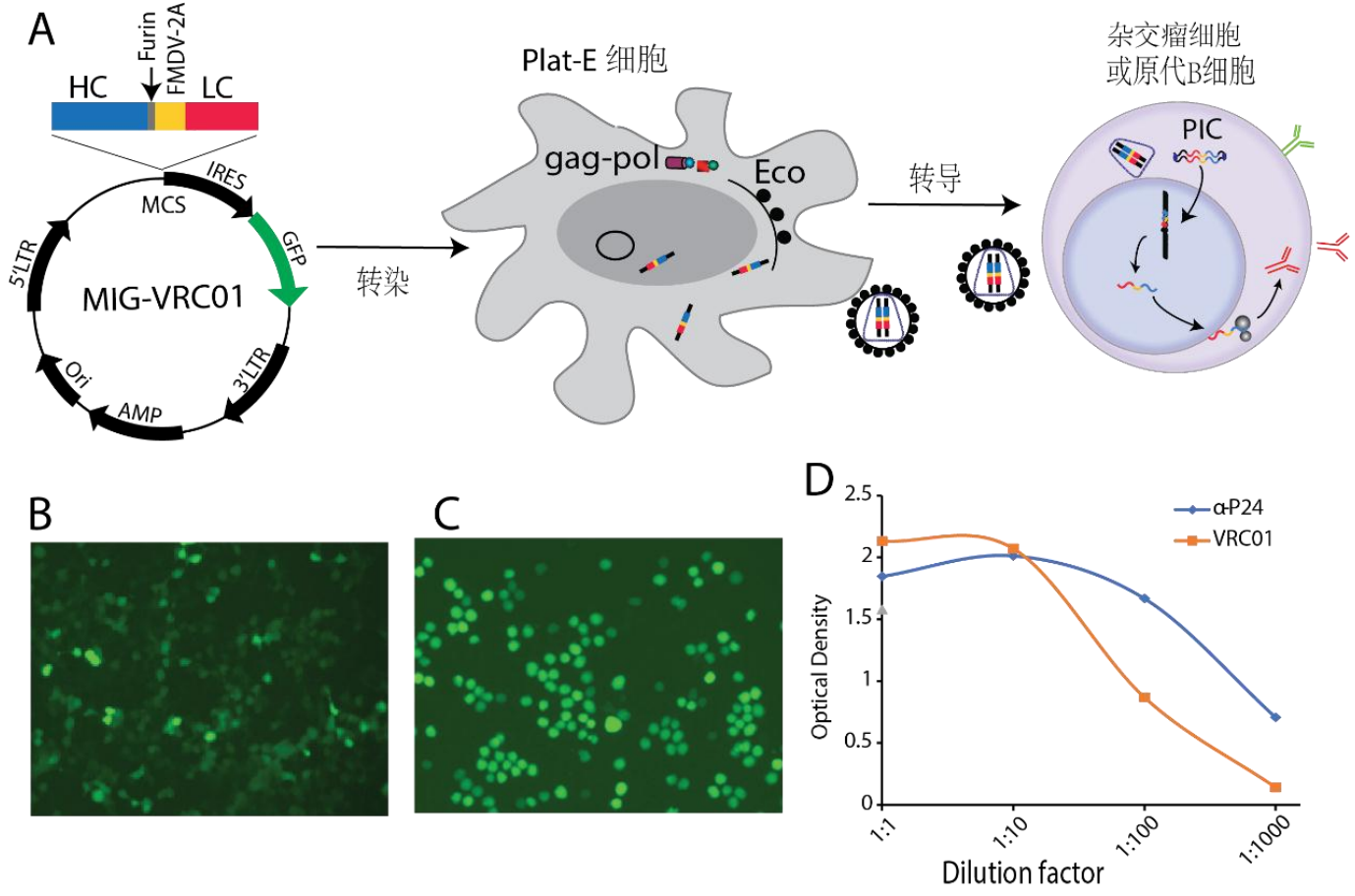
Based on memory response dynamics, bNAb expression from the transduced antigen-specific B cells can be activated and modulated by the same immunogen (i.e. Flu vaccine) in the preimmunized animal.



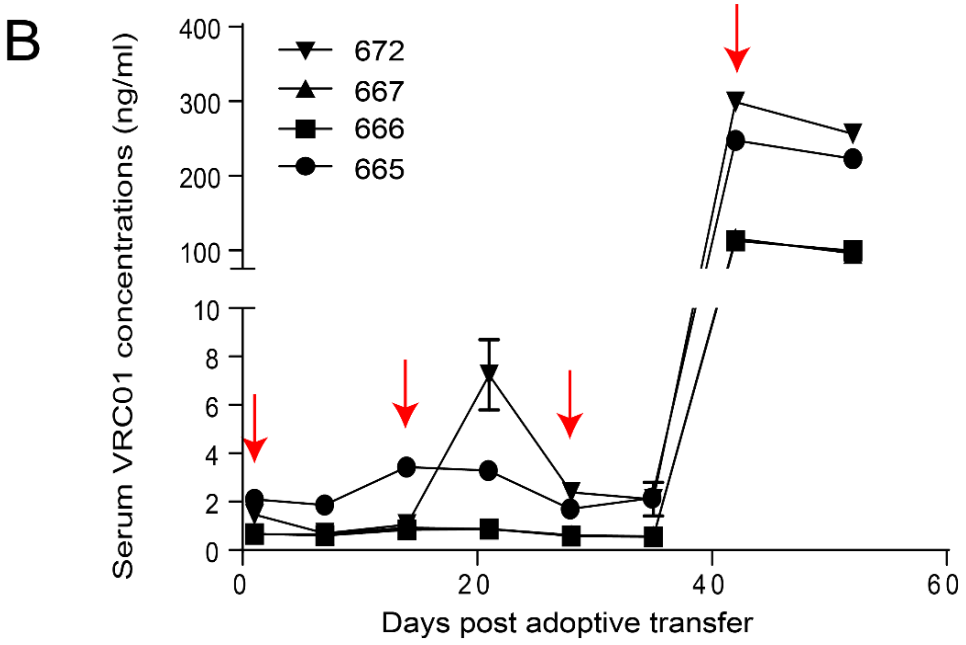
Schematics of Project



MIG-VRC01的构建、转染、转导及VRC01的表达



流感免疫对VRC01体内调控的初步实验结果



结　语

- HIV尚无有效的预防性或治疗性疫苗，HIV病毒序列的极端多样性是疫苗研发的主要障碍之一；
- 多价疫苗和个体化疫苗为HIV根治策略提供了新的思路和希望；
- 广谱中和性抗体的发现和运用为HIV防治提供了很好的工具；免疫调节以及CAR T 的研究为彻底根治HIV感染开辟了一个新的路径。

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