



Lenacapavir (GS-6207): The First Clinically Active Long-Acting Inhibitor of HIV Capsid

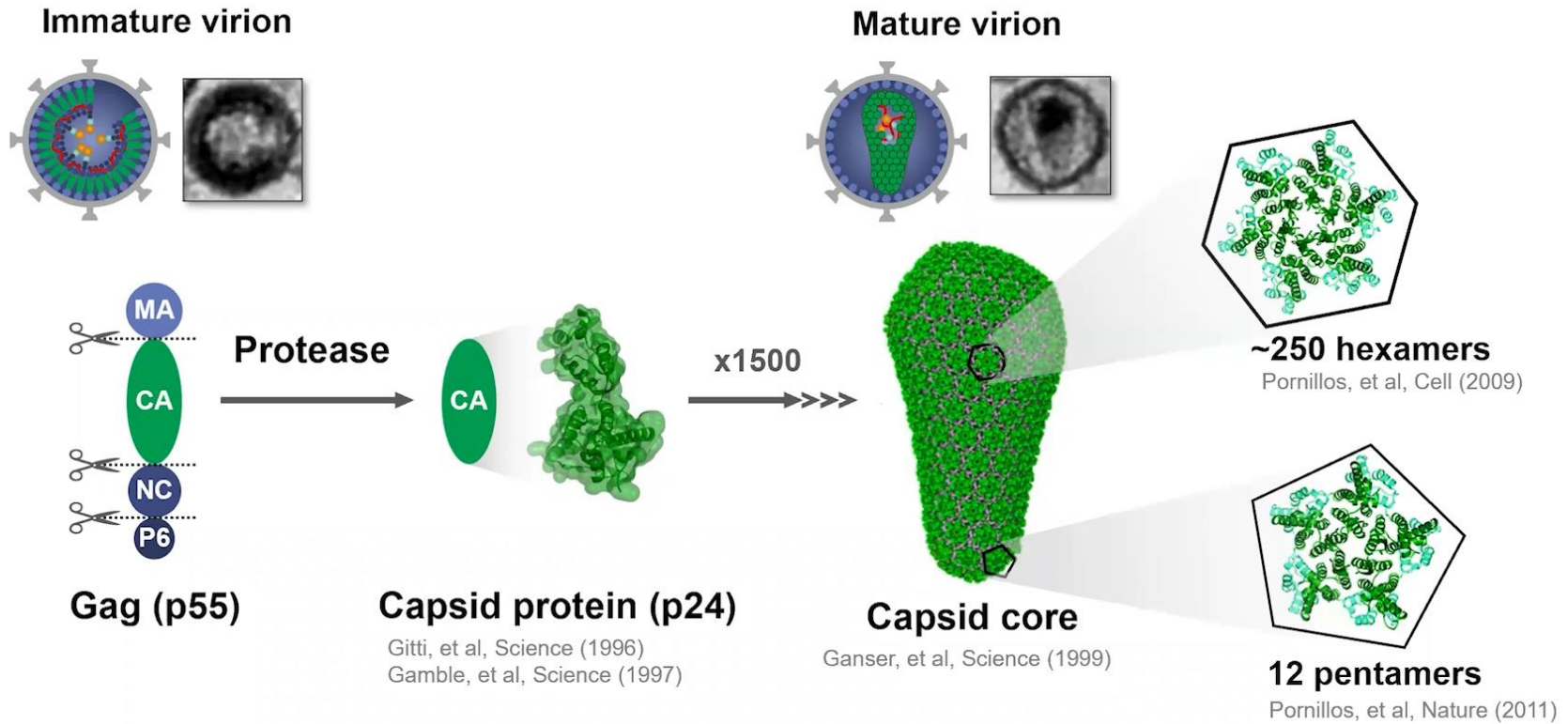
Tomas Cihlar

*Gilead Sciences, Inc.
Foster City, CA, USA*

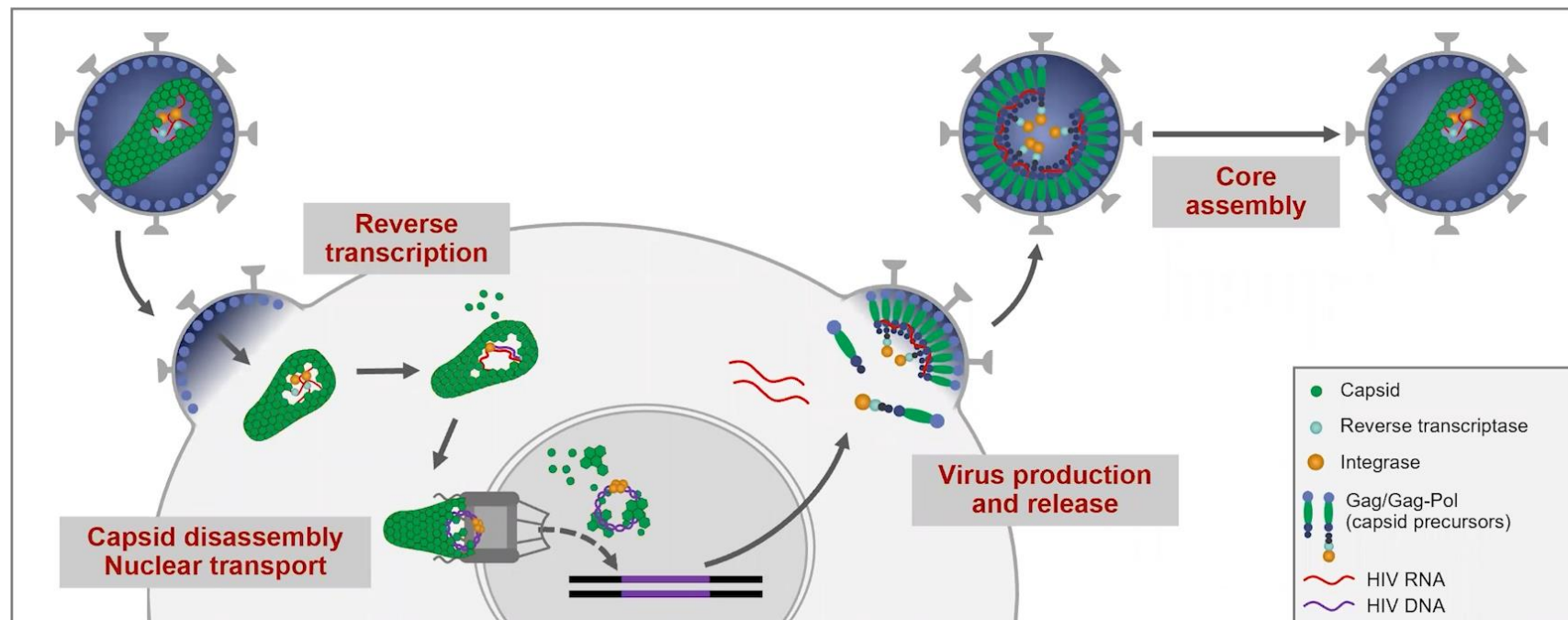
Disclosure: Employee of Gilead and owner of company stock

↓ **CROI** 2021

HIV Capsid

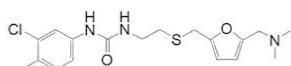


Capsid is Critical at Multiple Stages of HIV Replication Cycle



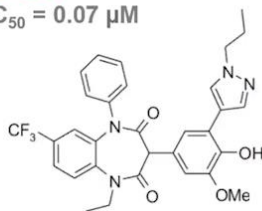
Search for Compounds Targeting HIV Capsid

CAP-1
EC₅₀ ~ 75 μM



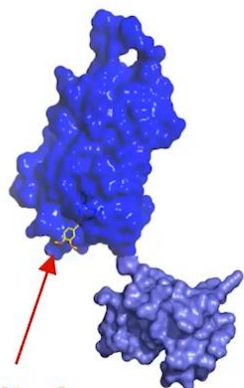
Tang, et al, J Mol Biol (2003)
Kelly, et al, J Mol Biol (2007)

BI-257
EC₅₀ = 0.07 μM



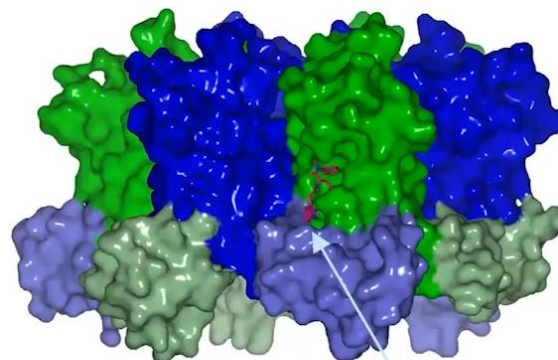
Titolo, et al, CROI (2010)
Fader et al, BMCL (2013)

CA Monomer



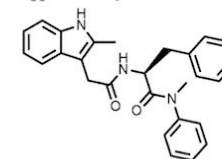
Site I

CA Hexamer



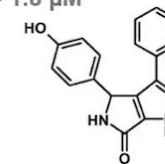
Site II

PF-74
EC₅₀ = 0.6 μM



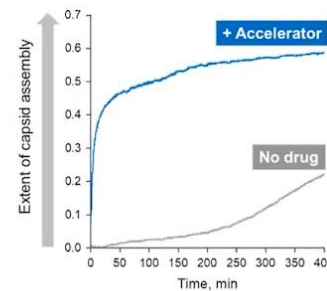
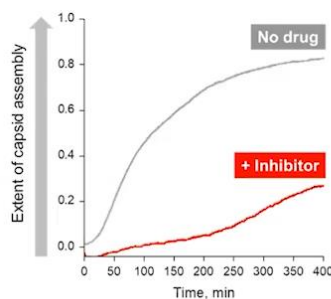
Blair, et al, PLOS Path (2010)
Shi, et al, J Virol (2011)

BI-2
EC₅₀ = 1.8 μM



Lamorte, et al, AAC (2013)

- **Inhibitors** bind CA monomer
- Capsid assembly **inhibited**



- **Accelerators** bind interface
- Capsid assembly **activated**

Our Long Term Commitment to Targeting HIV Capsid

1. Capsid structure

Gitti, et al, Science (1996)
Ganser, et al, Science (1999)

2. In vitro assembly assay

Lanman, et al, J Virol (2002)

3. Molecular validation of the target

von Schwedler, et al, J Virol (2003)

Project start

HTS campaign

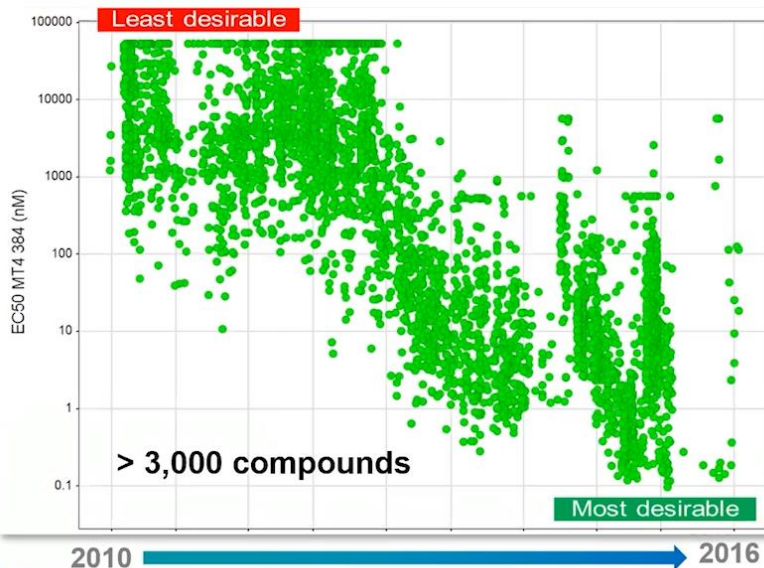
1st gen lead



2nd gen lead

Optimization:

Potency, stability, PK, off-target profile



2006

2008

2010

2012

2014

2016

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HTS campaign

1st gen lead



2nd gen lead

Optimization:

Potency, stability, PK, off-target profile

Clinical candidate

2006

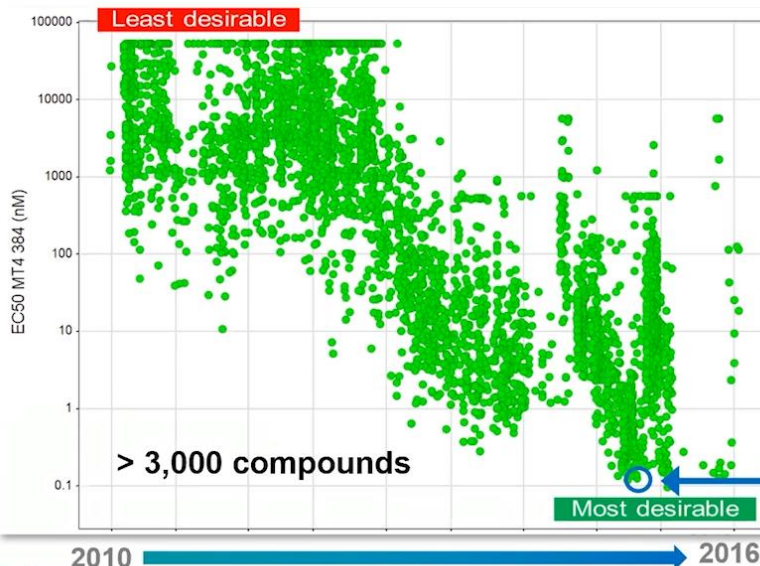
2008

2010

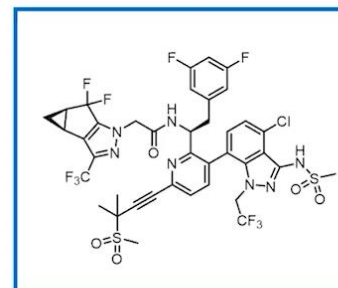
2012

2014

2016



> 3,000 compounds



GS-6207
Lenacapavir (LEN)

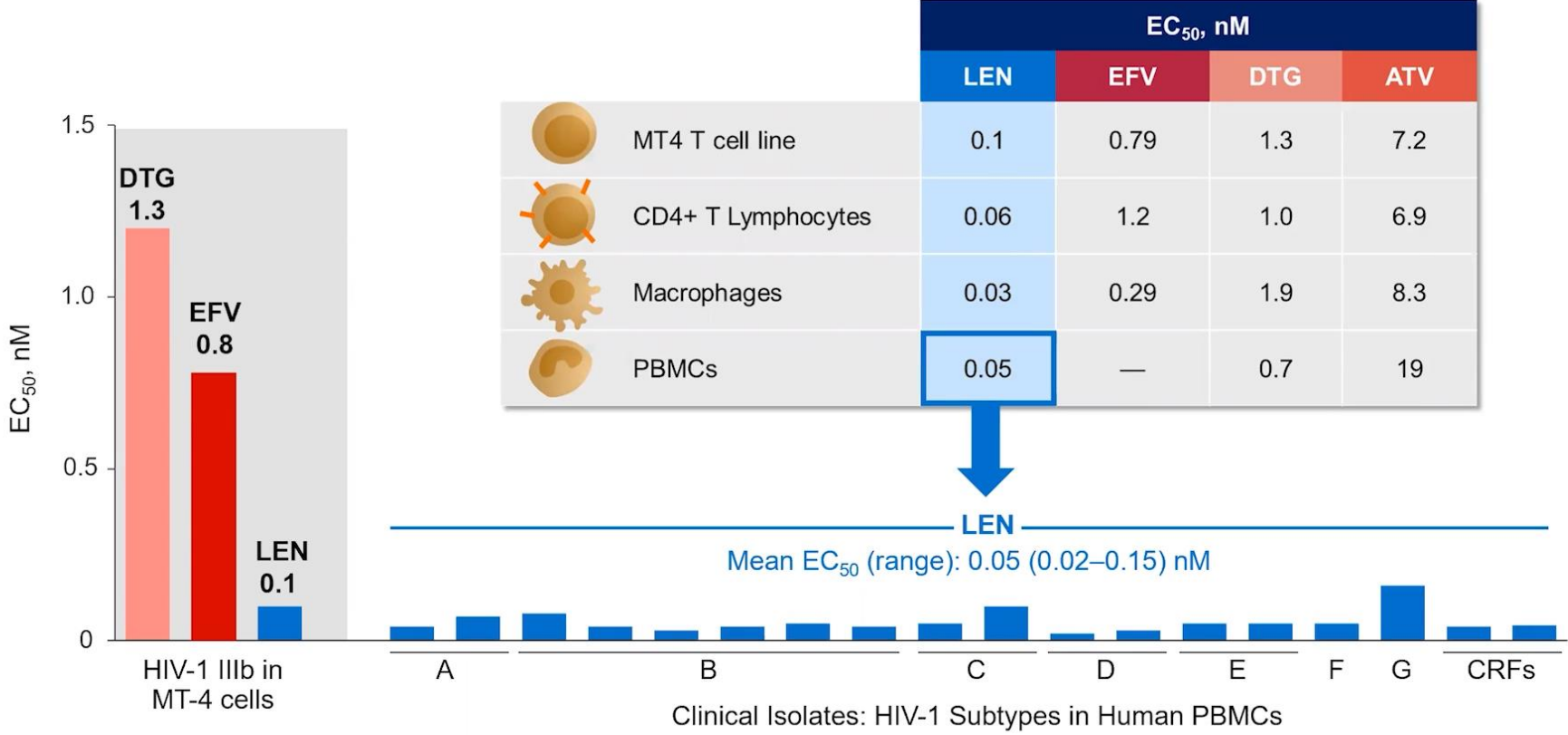
LEN Exhibits Exceptionally Potent Anti-HIV Activity In Vitro

	Antiviral activity		Cytotoxicity CC ₅₀ (nM)	Selectivity CC ₅₀ / EC ₅₀
	EC ₅₀ (nM)	paEC ₉₅ (nM)		
Lenacapavir	0.10	4.0	26,600	266,000
Rilpivirine	0.57	45	6,800	11,900
Cabotegravir	1.3	310	10,120	7,780
Dolutegravir	1.3	156	15,300	11,770
Atazanavir	7.2	150	50,500	7,000

- EC₅₀ and EC₉₅ determined in MT-4 T-cells with HIV-1 IIIB
- paEC₉₅, protein adjusted EC₉₅

Link, et al, *Nature* (2020)

LEN Exhibits Exceptionally Potent Anti-HIV Activity In Vitro



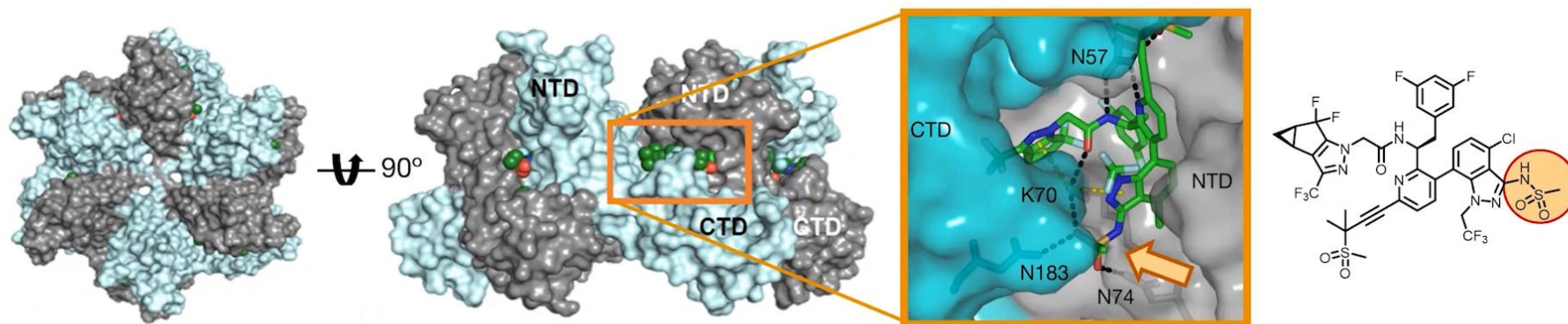
Link, et al, *Nature* (2020)

LEN Maintains Activity Against Mutants Resistant to Other ARVs

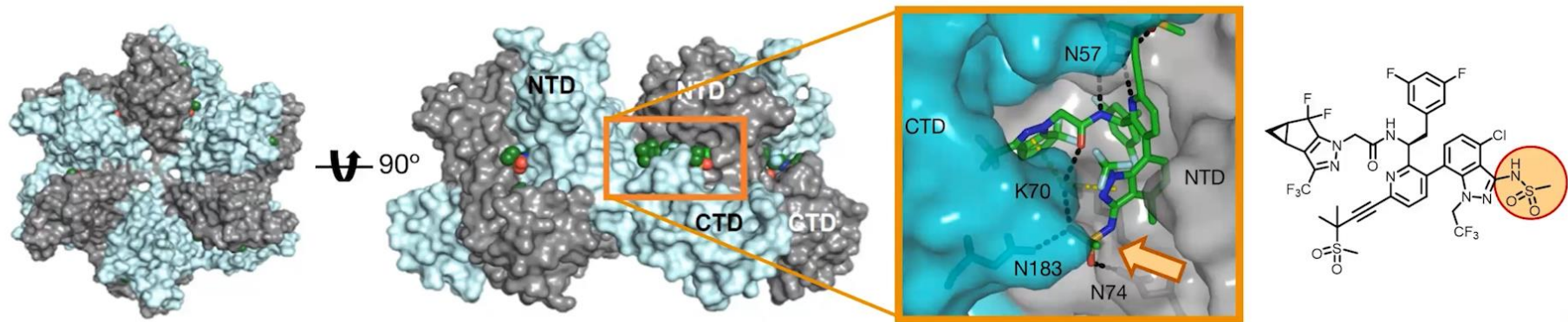
Drug Class	Potency fold change relative to wild-type virus										
	MI		PI		NRTI		NNRTI		INSTI		
Resistance Associated Mutation(s)	V230I	V7A	I84V L90M	G48V V82A L90M	K65R	M184V	Y188L	K103N Y181C	G140S Q148R	Q148R N155H	M50I R263K
Lenacapavir	0.7	0.8	0.3	0.4	0.6	0.5	0.5	0.5	0.9	1.3	0.9
Bevirimat (MI)	>68	>68									
Atazanavir (PI)			33	33							
FTC (NRTI)					13	>42					
Efavirenz (NNRTI)							>23	>23			
EVG (INSTI)									>53	>53	5.1

Link, et al, *Nature* (2020)

Interaction of LEN with HIV Capsid



Interaction of LEN with HIV Capsid



	Immature capsid	Mature capsid			
	Gag polyprotein	CA monomer	CA pentamer	CA hexamer	CA hexamer_M66I
K_D (pM)	$1,100 \pm 900$	$2,500 \pm 500$	220 ± 160	240 ± 90	$60,000 \pm 20,000$
k_{on} ($M^{-1}s^{-1}$)	ND	ND	$2 \pm 1 \times 10^5$	$6.5 \pm 0.3 \times 10^4$	$6 \pm 4 \times 10^4$
k_{off} (s^{-1})	ND	ND	$2.7 \pm 0.4 \times 10^{-5}$	$1.4 \pm 0.4 \times 10^{-5}$	$2.6 \pm 0.3 \times 10^{-3}$

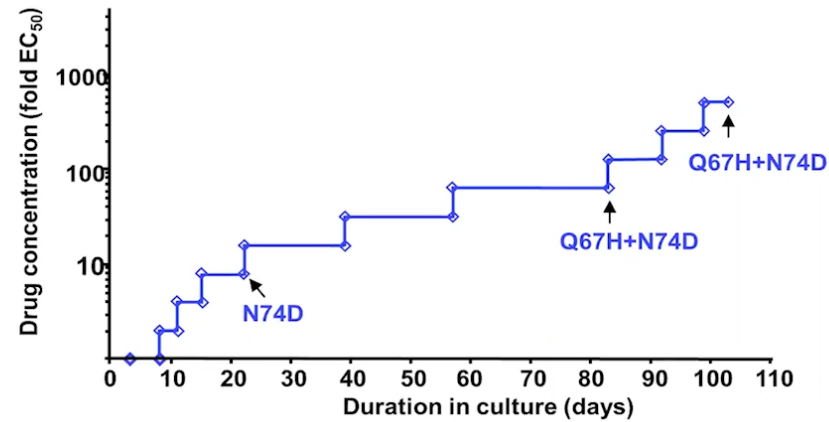
Link, et al, Nature (2020)

LEN In Vitro Resistance Maps to Capsid

Increasing drug concentrations

HIV-1 IIIb in MT-2 cells

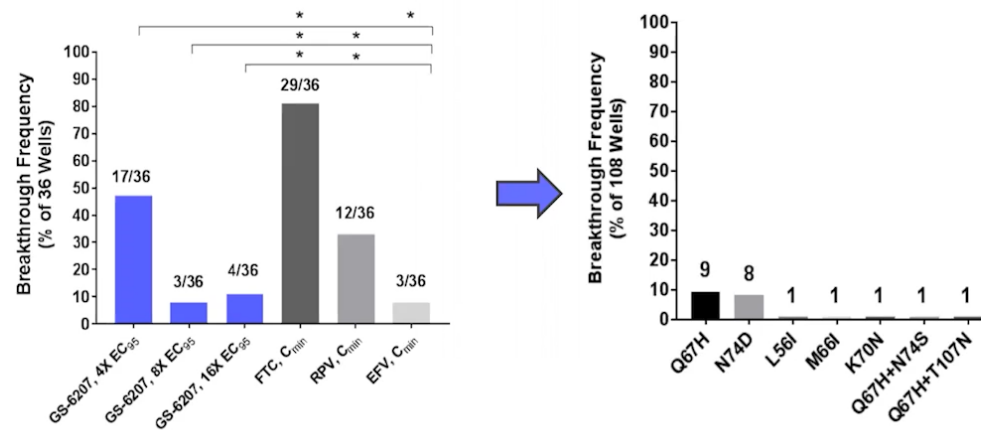
Link, et al, Nature (2020)



Fixed drug concentrations

HIV-1 clinical isolates in PBMCs

Yant, et al., IAS (2019)

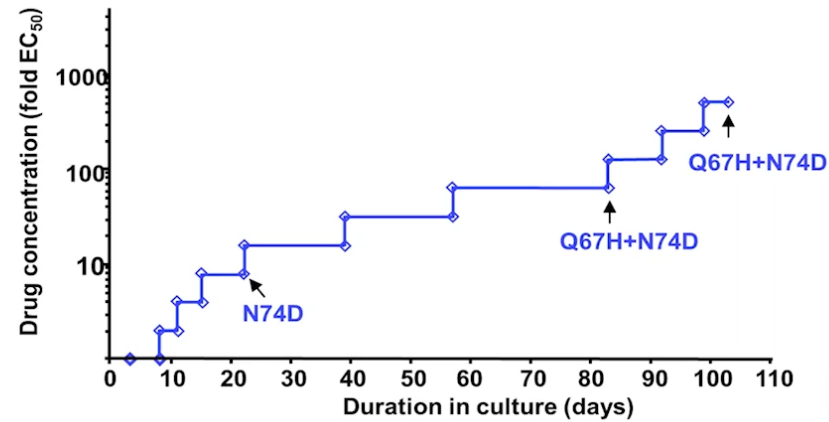


LEN In Vitro Resistance Maps to Capsid

Increasing drug concentrations

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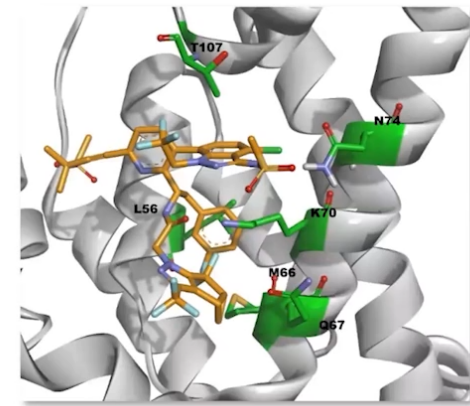
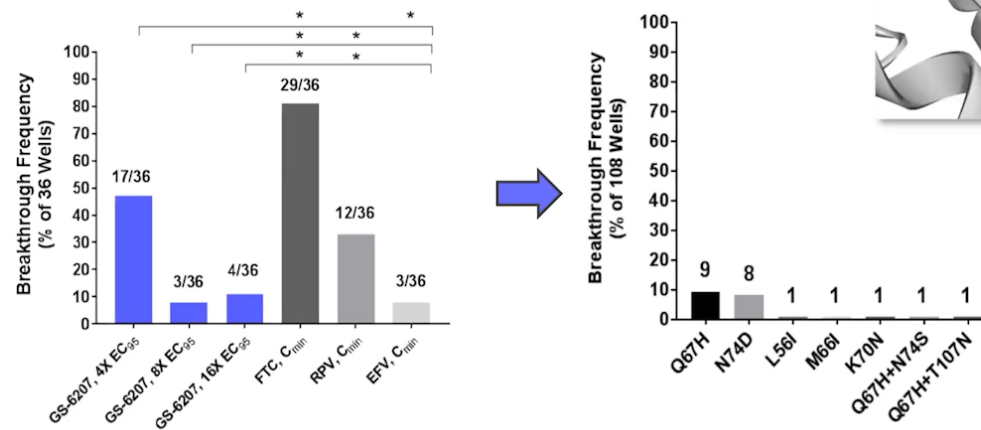
Link, et al, Nature (2020)



Fixed drug concentrations

HIV-1 clinical isolates in PBMCs

Yant, et al., IAS (2019)



Phenotype of LEN-resistant HIV-1 Variants

HIV-1 capsid mutant	WT	Q67H	N74D	K70N	Q67H N74S	Q67H T107N	L56I	Q67H N74D	M66I
Fold resistance to LEN (relative to WT) ^a	1	6	22	24	32	62	239	1,099	>3,200
Infectivity in MT-2 cells (% WT) ^b	100	95	48	7	34	41	9	29	6
Peak replication in primary CD4+ T-cells (% WT) ^c	100	100	1	1	69	28	3	<1	<1

^a Ratio of mutant/WT mean EC₅₀ values determined 2 days post-infection with single-cycle reporter HIV-1 (NL4.3 strain)

^b Luminescence values (percentage of WT) in MT-2 cells 2 days post-infection with p24-normalized inputs of single-cycle reporter HIV-1

^c Primary human CD4+ T-cells infected with a replication-competent reporter HIV-1 (NL4.3)

Yant, et al., IAS (2019)
Link, et al, Nature (2020)

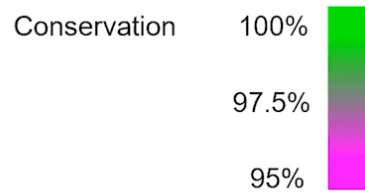
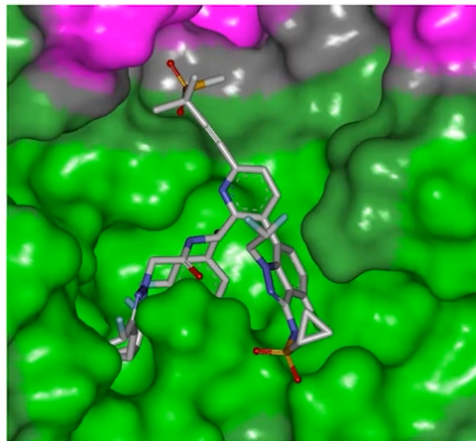
- Capsid mutants maintain full sensitivity to other antiretroviral classes including PIs

VanderVeen et al. (Oral Abstr. 1781, Tue 3/9/21)

Activity and Resistance Characterization of the HIV Capsid Inhibitor Lenacapavir

LEN Binding Site Is Conserved Across HIV-1 Subtypes

Total of 10,512 sequences analyzed
www.hiv.lanl.gov

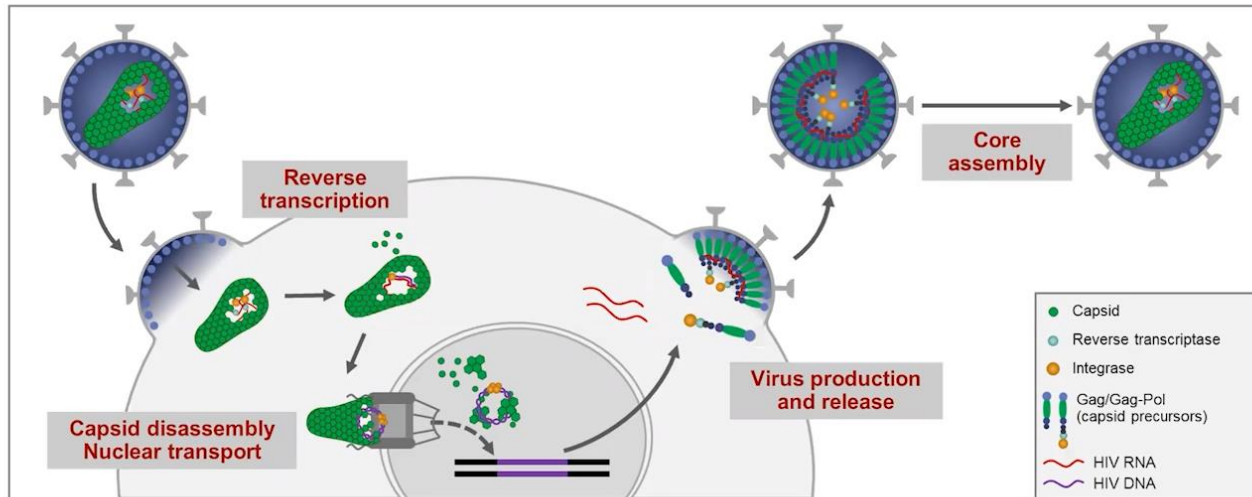


HIV-1 Subtype (N)	LEN Binding Site Conservation (% of WT residue)						
	L56	N57	M66	Q67	K70	N74	T107*
A1 (756)	100	100	100	100	100	100	99
B (4,410)	100	100	100	100	100	100	99
C (2,662)	100	100	100	100	100	100	98
D (287)	100	98	100	100	100	100	99
F1 (148)	100	100	100	100	100	100	96
G (117)	100	100	100	100	100	100	94
AE (1,794)	100	100	100	99	100	100	99
AG (338)	100	100	100	100	100	100	98
Variant(s)	none	H	none	H	none	none	S/A/V

* T107 variants alone do not confer resistance to LEN but increases the resistance in combination with Q67H

Yant, et al., IAS (2019)
 Yant, et al., Nature Med (2019)

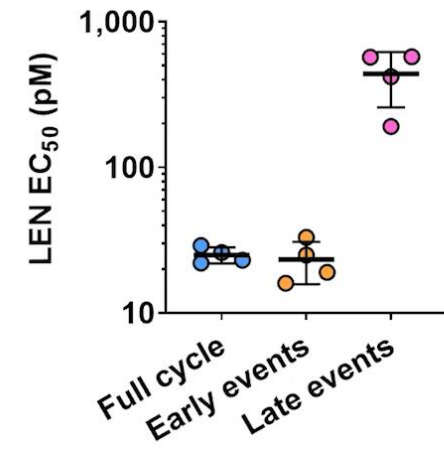
LEN Affects Both Early and Late Stages of HIV Replication



Early events (target cells)
 $EC_{50} = 23 \text{ pM}$

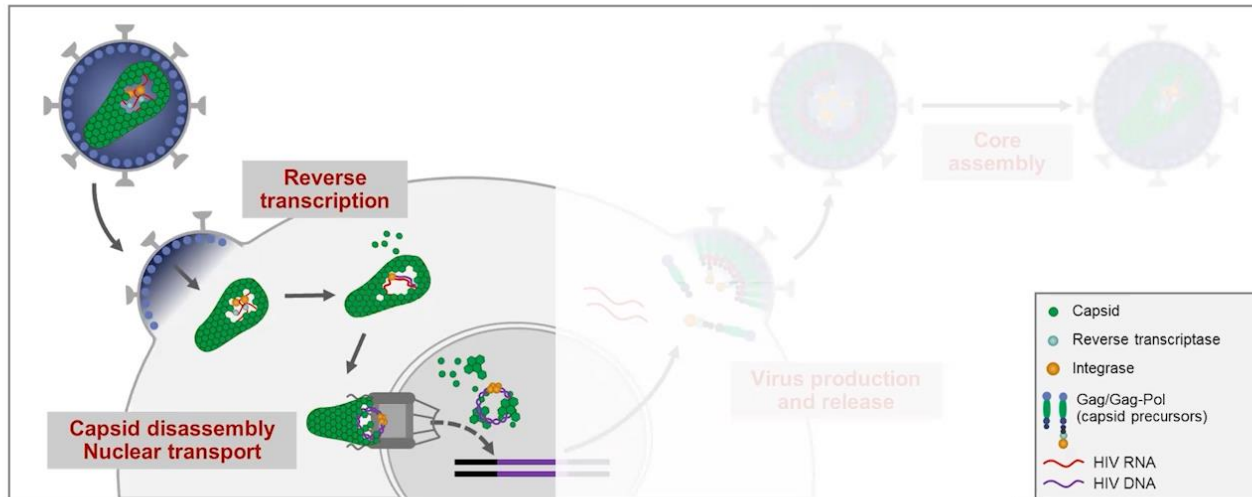
Late events (producer cells)
 $EC_{50} = 430 \text{ pM}$

Full cycle
 $EC_{50} = 25 \text{ pM}$

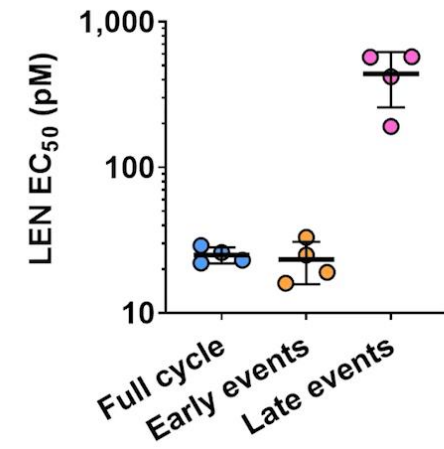


Link, et al, Nature (2020)

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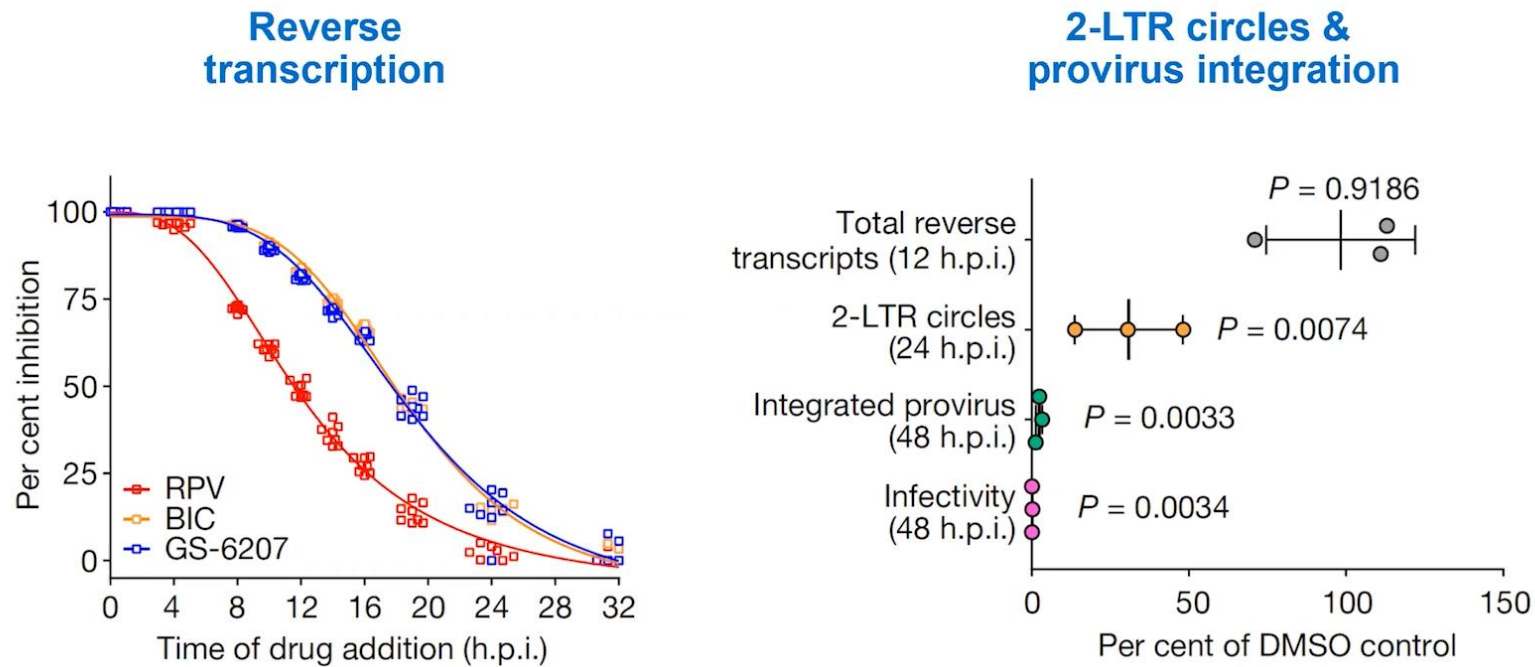


Early events (target cells)
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Link, et al, Nature (2020)

Inhibition of Early Stage Events in HIV Replication Cycle

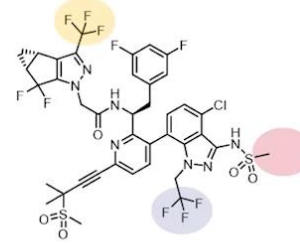
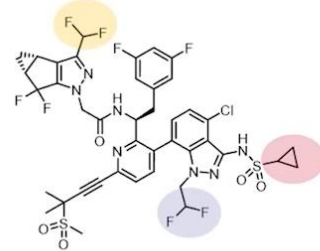


Link, et al, *Nature* (2020)

LEN Analog Blocks Nuclear Import of Viral DNA

GS-CA1

EC₅₀ (early) = 87 pM
EC₅₀ (late) = 240 pM



Lenacapavir

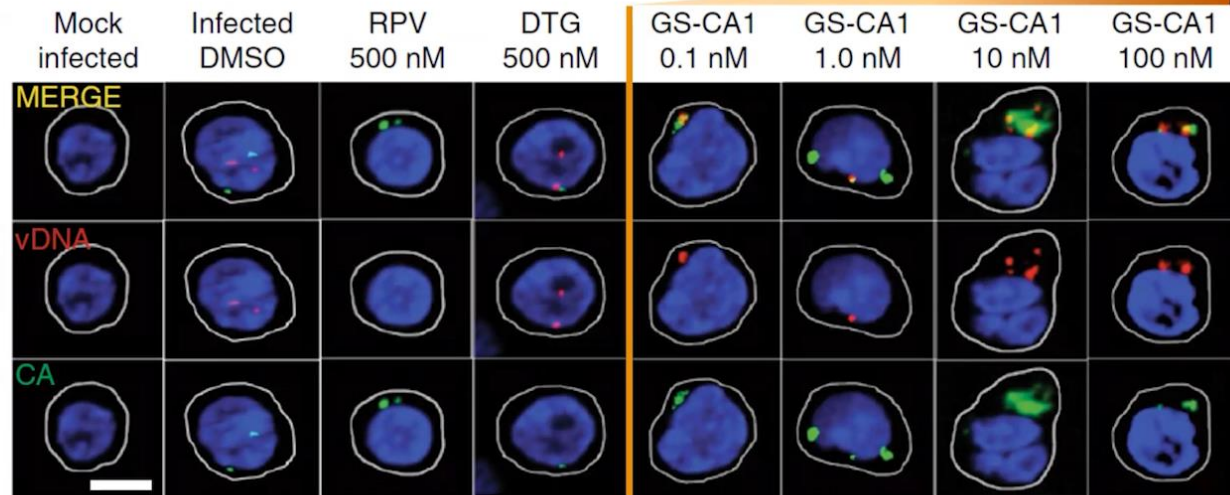
EC₅₀ (early) = 46 pM
EC₅₀ (late) = 318 pM

HIV-1 infected primary human CD4+ T cells

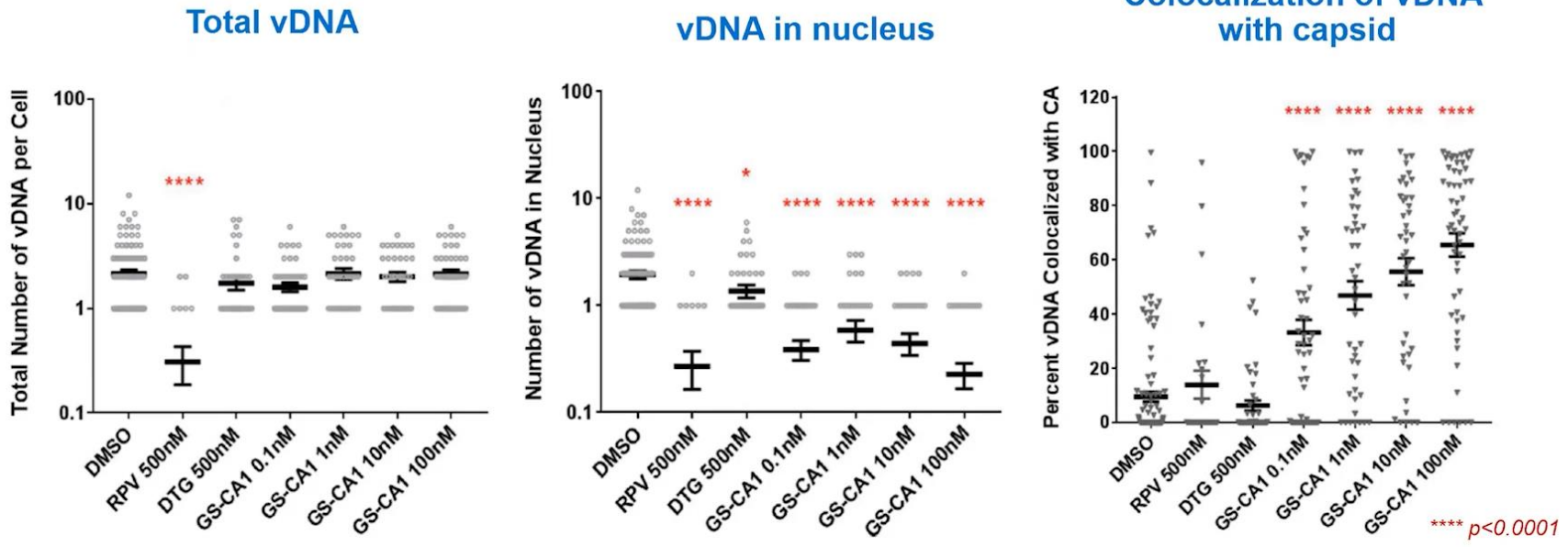
ViewHIV platform

Chin, et al, *Cell Rep* (2015)

Yant, et al, *Nature Med* (2019)



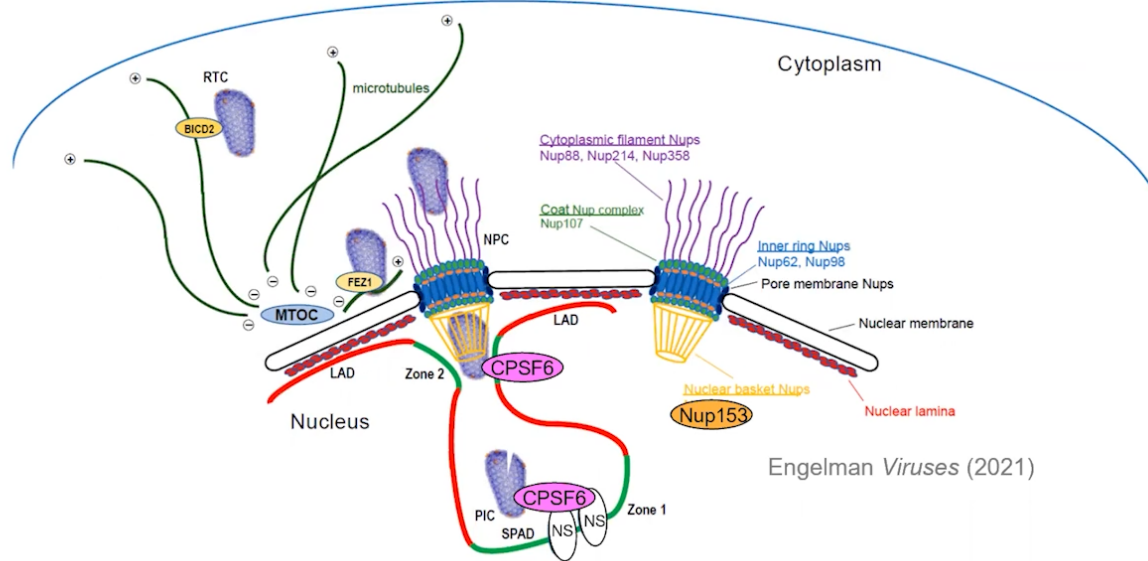
LEN Analog Blocks Nuclear Import of Viral DNA



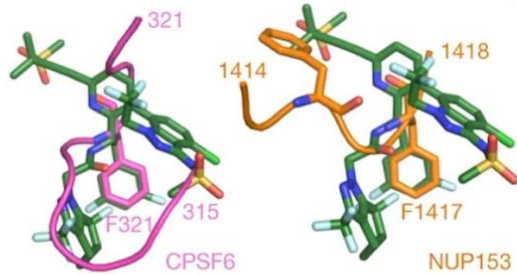
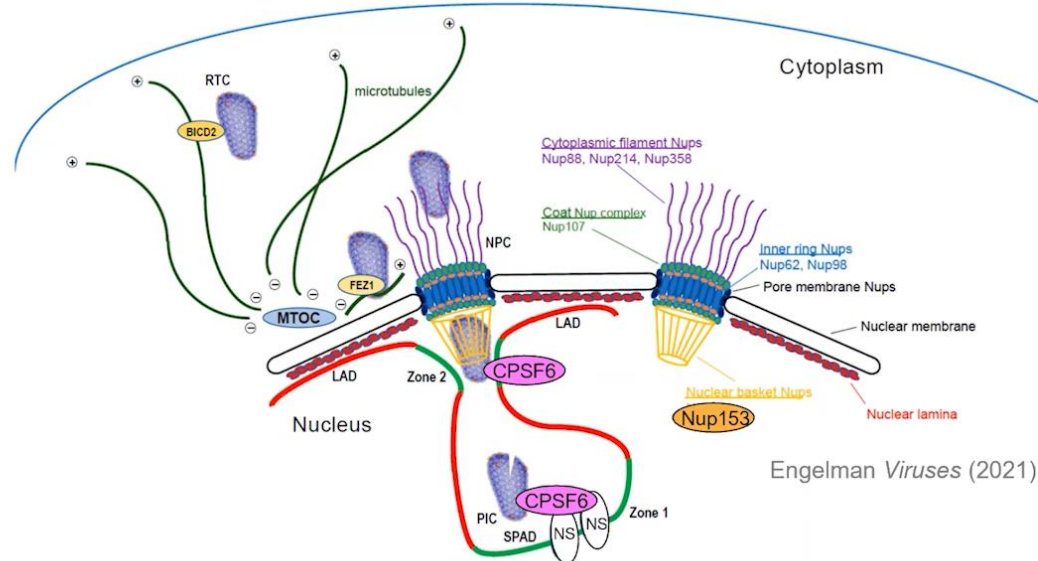
- In the presence of GS-CA1:**
- Viral DNA does not enter nucleus
 - Capsid accumulates in cytoplasm
 - Co-localization of viral DNA with CA increases

Yant, et al, *Nature Med* (2019)

Proposed Mechanism of the Nuclear Import Inhibition



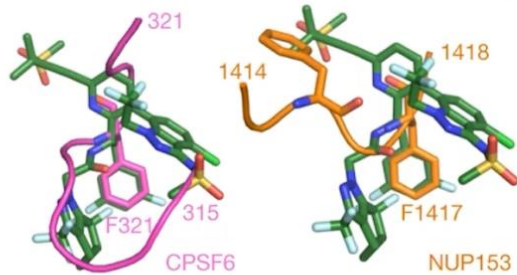
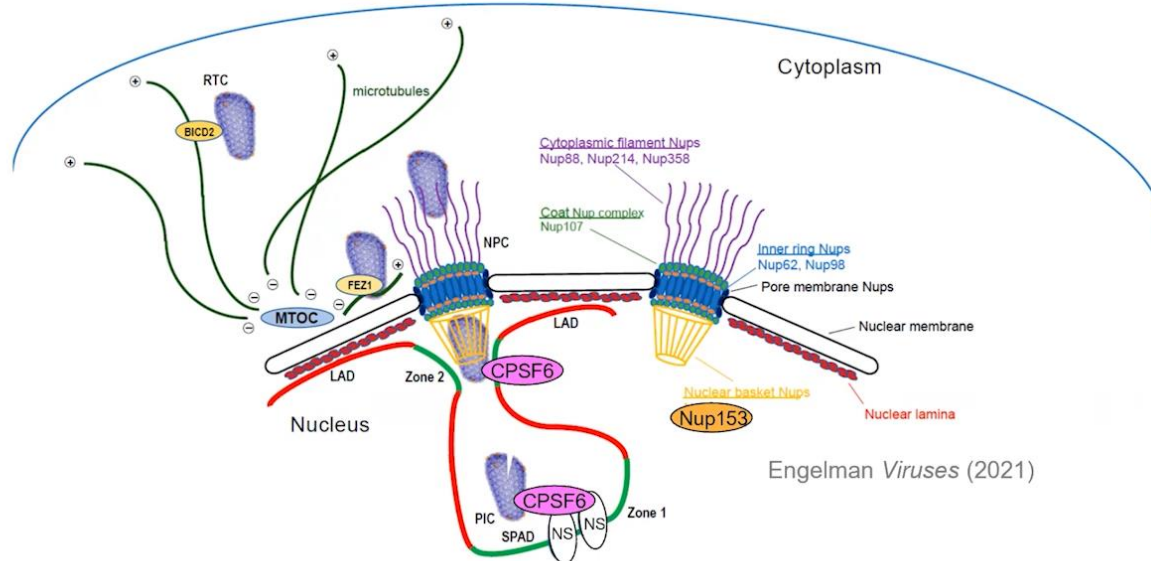
Proposed Mechanism of the Nuclear Import Inhibition



LEN shares capsid binding site with CPSF6 and NUP153

Link, et al, *Nature* (2020)

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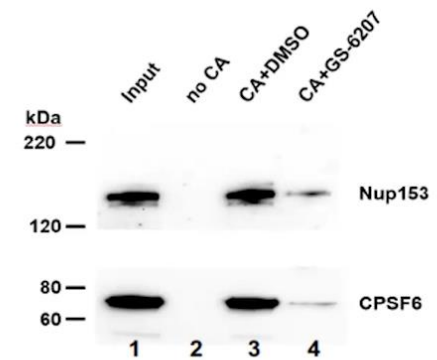


LEN shares capsid binding site with CPSF6 and NUP153

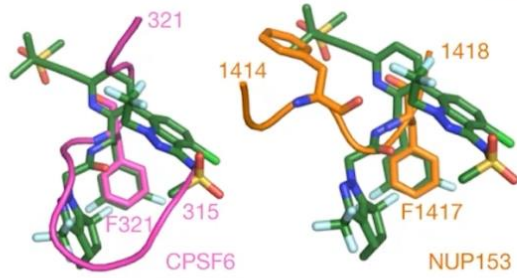
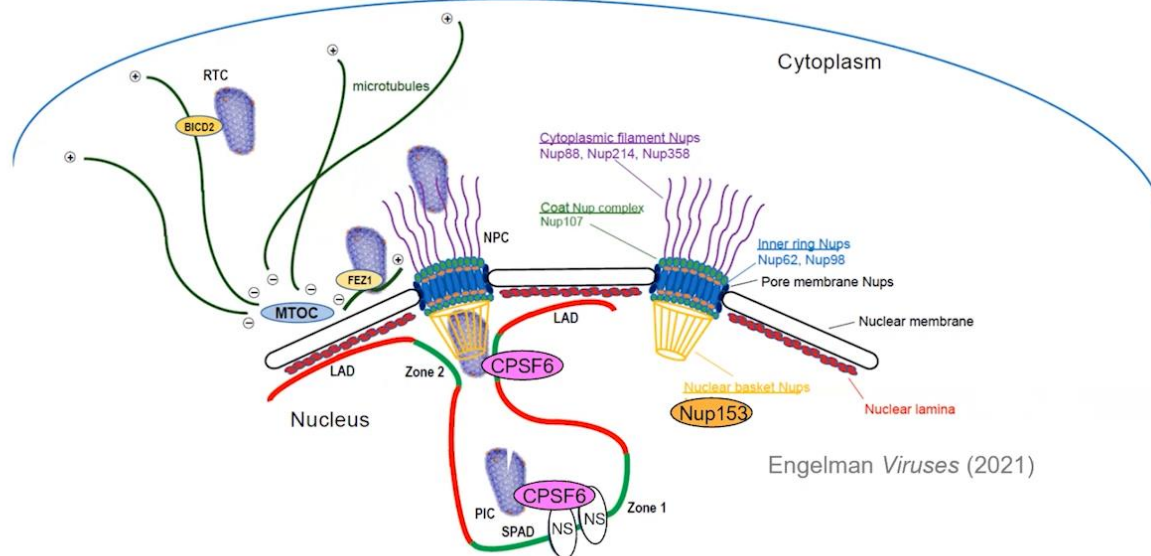
Link, et al, *Nature* (2020)

LEN inhibits Nup153 and CPSF6 binding to CA tubes

Bester, et al. *Science* (2020)



Proposed Mechanism of the Nuclear Import Inhibition

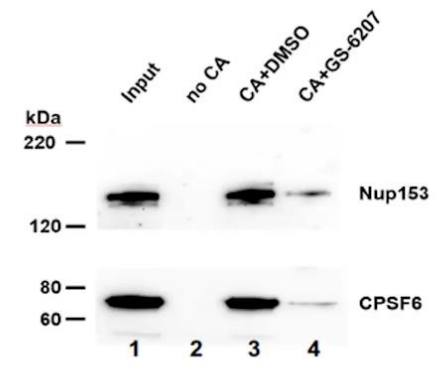
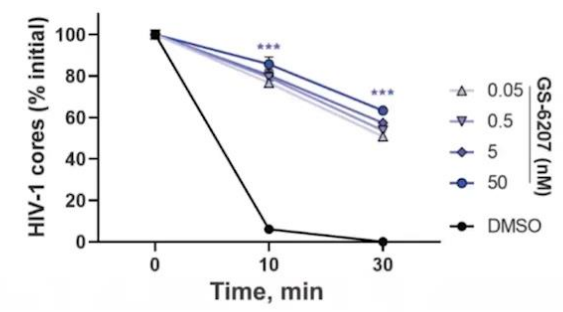


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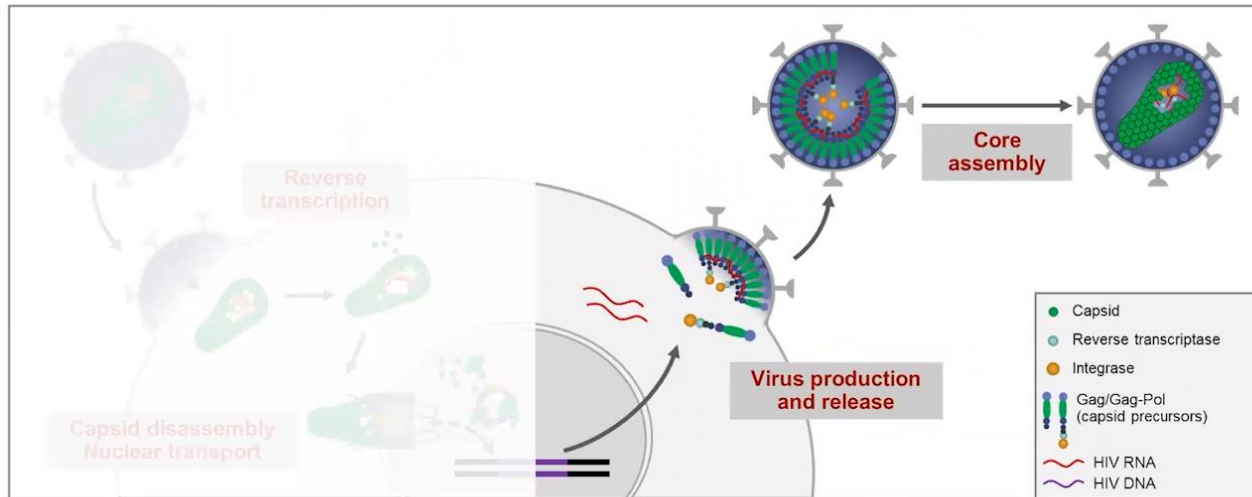
LEN inhibits Nup153 and CPSF6 binding to CA tubes
 Bester, et al. *Science* (2020)

LEN stabilizes HIV cores

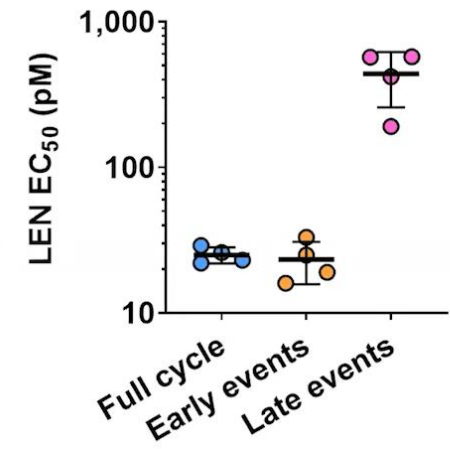
Bester, et al. *Science* (2020)



LEN Affects the Late Stages of HIV Replication

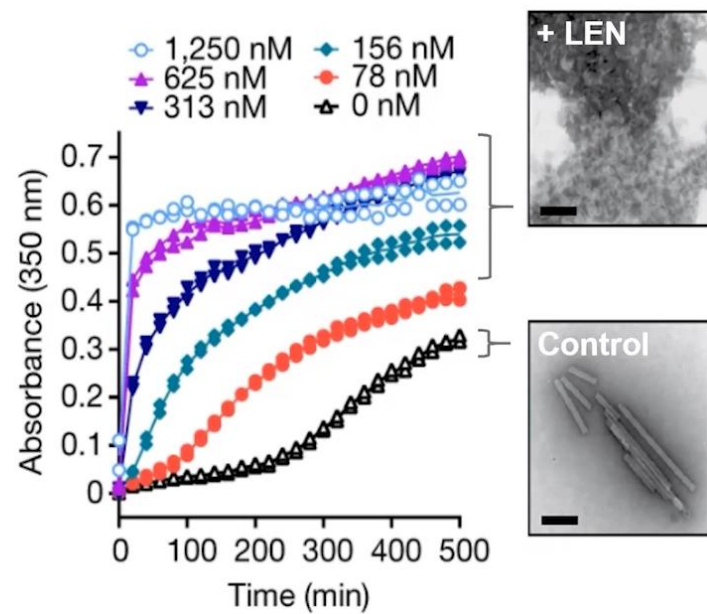


Late events (producer cells)
 $EC_{50} = 430 \text{ pM}$

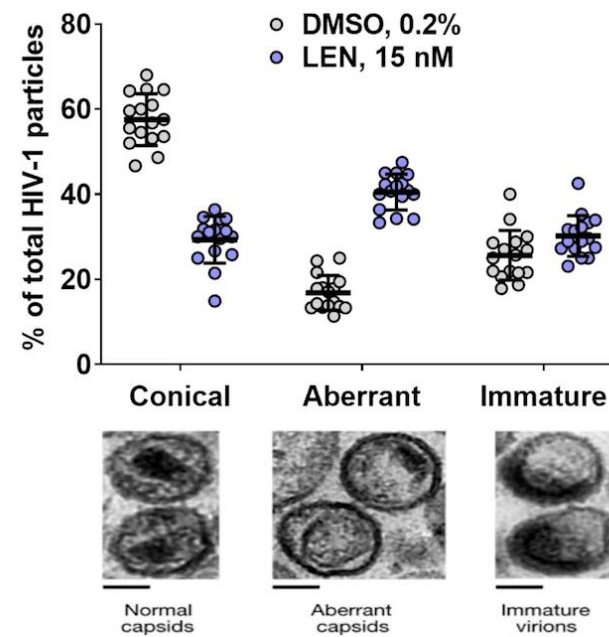


Effect of LEN on Capsid Assembly

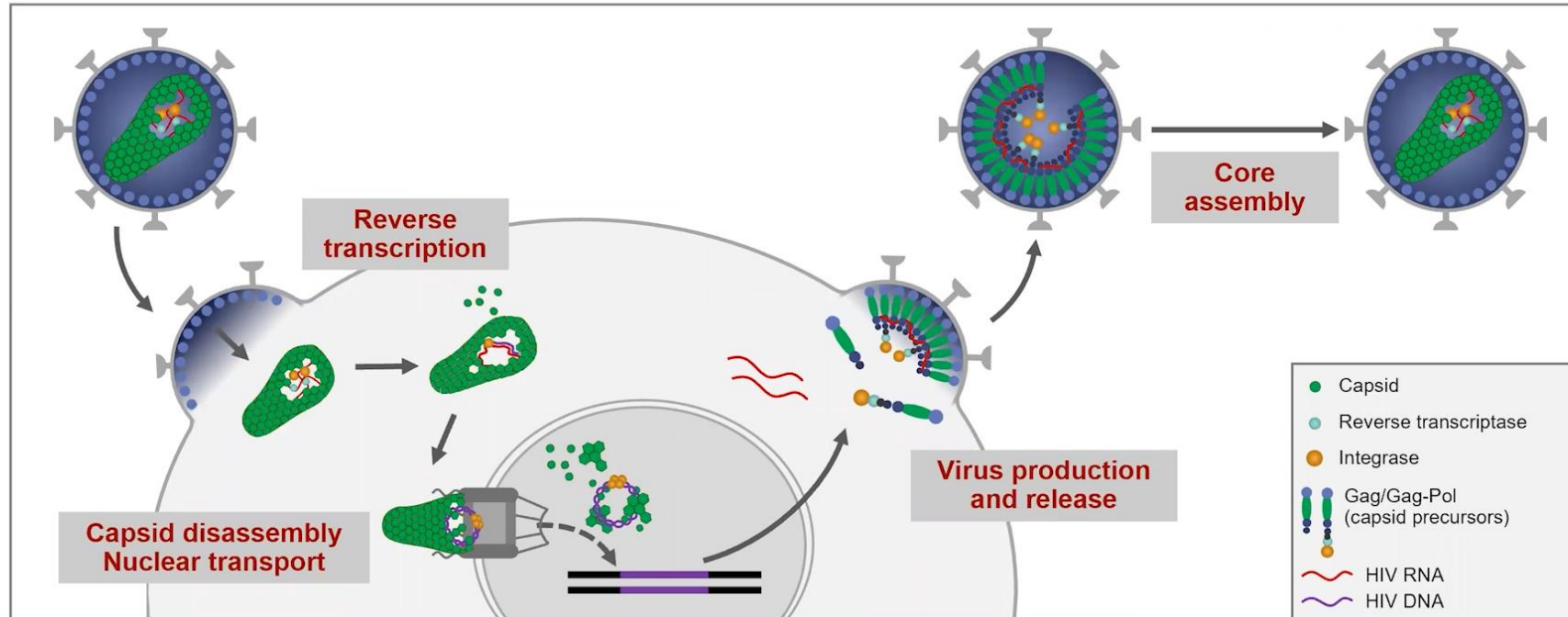
In vitro CA assembly



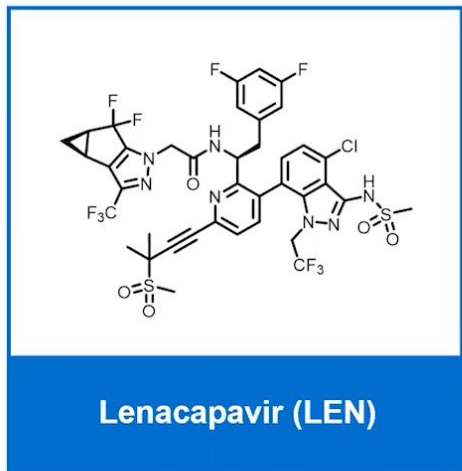
Virion morphology



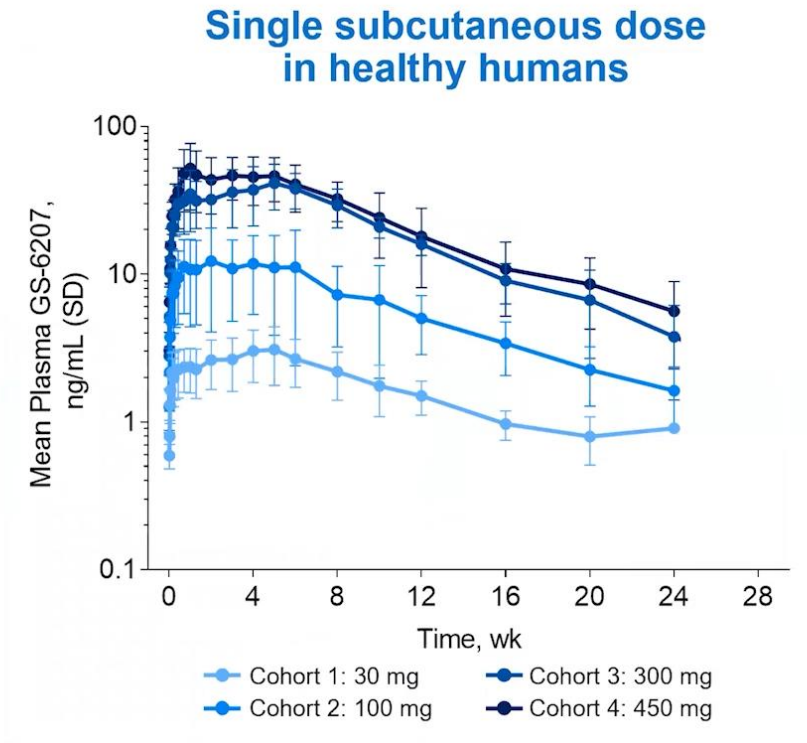
Capsid is Critical at Multiple Stages of HIV Replication Cycle



LEN Exhibits Optimal Properties for Long-Acting Injectable Use



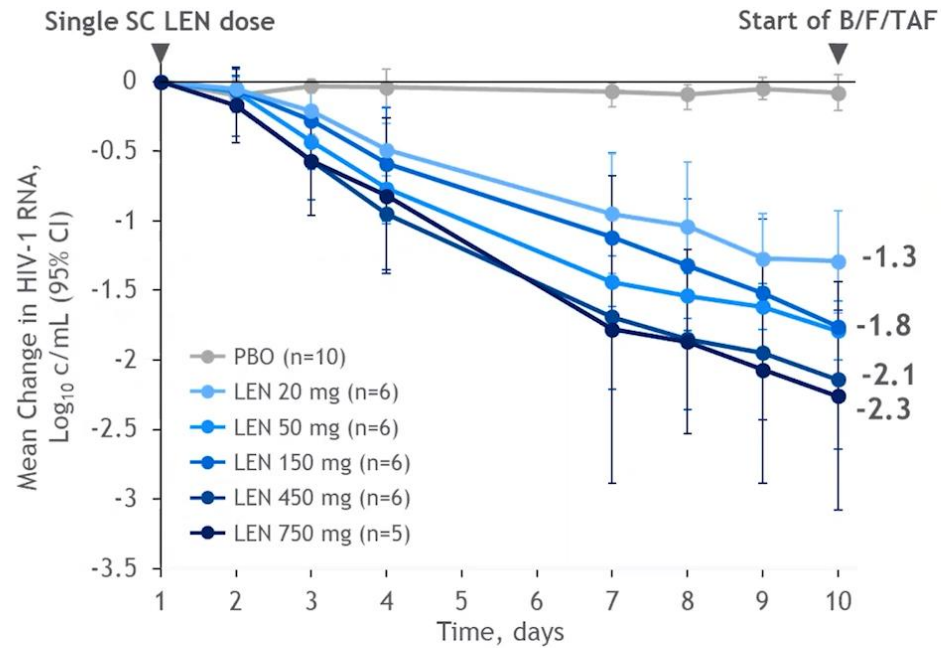
- Uniquely potent antiviral activity: $EC_{50} = 50-100$ pM
- Novel mechanism of action
- Low systemic clearance: 0.06 L/h/kg
- Low solubility: <1 μ g/mL



Sager, et al, CROI (2019)
Link, et al, Nature (2020)

Clinical HIV Efficacy of LEN Single Subcutaneous Dose

- Double-blind, randomized, placebo-controlled Phase 1b monotherapy study in treatment-naïve PWH (NCT03739866)



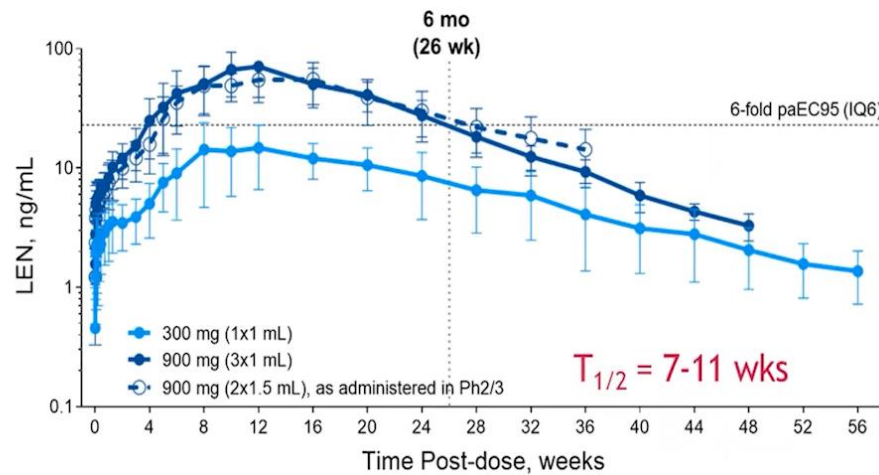
B/F/TAF: daily oral STR of bicitgravir (50mg); emtricitabine (200mg); tenofovir alafenamide (25mg)

Daar, et al, CROI (2020)
Link, et al, Nature (2020)

LEN Can Be Administered Both Subcutaneously and Orally

Single dose s.c. formulation

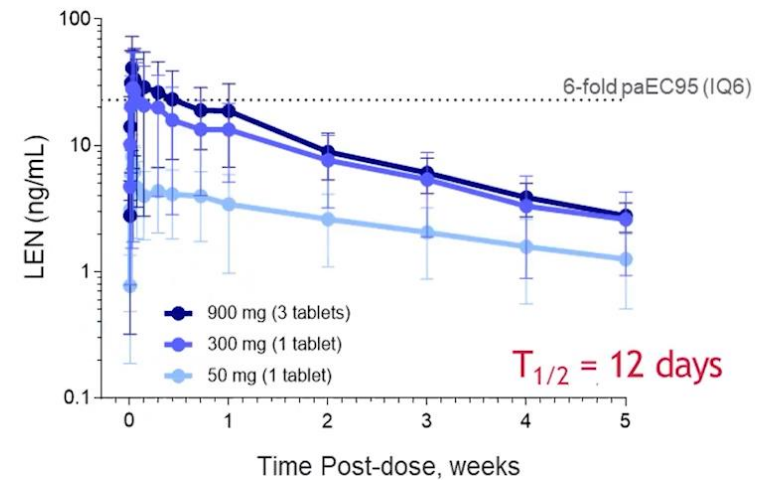
Begley R, et al., AIDS 2020



- Adjustable dosing frequency
- **Once every 6 months dosing feasible**

Single dose oral formulation

Begley R, et al., CROI 2020



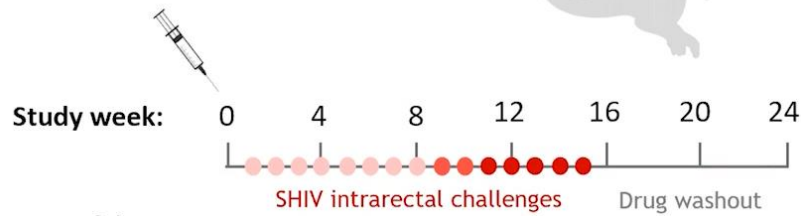
- Accumulation with repeated oral dosing
- Minimal food effect
- **Once-weekly dosing feasible**

IQ, inhibitory quotient; paEC₉₅, protein binding-adjusted 95% effective concentration.

Targeting HIV Capsid for Pre-Exposure Prophylaxis

GS-CA1
 EC_{50} (HIV) = 130 pM
 EC_{50} (SHIV) = 760 pM

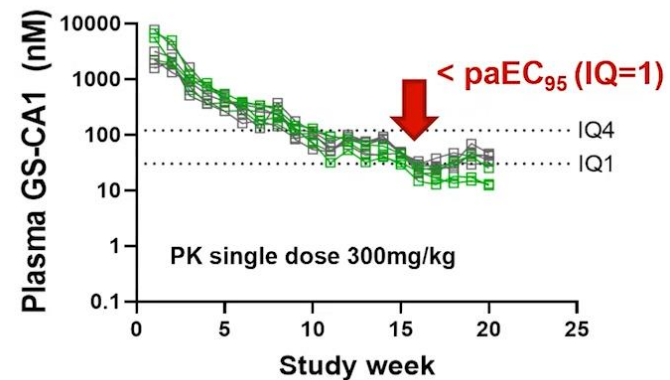
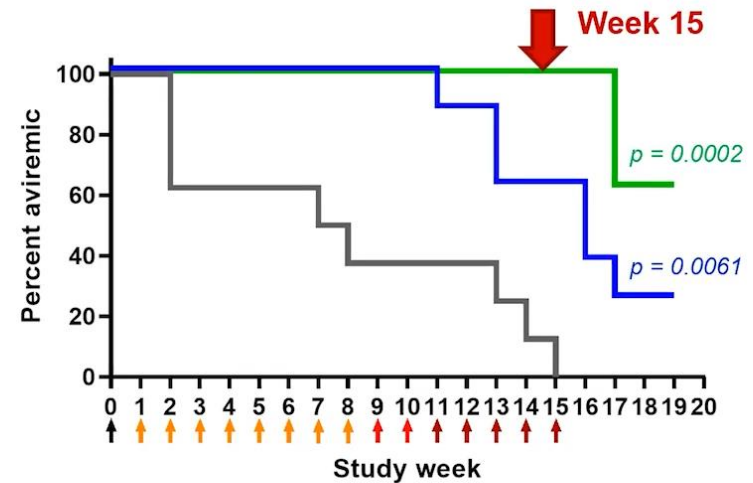
Single subcutaneous
 drug administration



n=8/group



*Bekerman et al. (Oral Science Spotlight Abstr. 2228, Sat 3/6/21)
 Long-Acting HIV Capsid Inhibitor Effective as PrEP in a SHIV
 Rhesus Macaque Model*



Ongoing and Planned Ph2/3 Clinical Studies with LEN

Treatment

CAPELLA (NCT04150068)

- Ph 2/3 study in highly treatment-experienced PWH
- Subcutaneous LEN Q6M added to an OBR

Segal-Maurer et al. (Oral Abstr. 2228, Tue 3/9/21)

Potent Antiviral Activity of Lenacapavir in Phase 2/3 in Heavily ART-Experienced PWH

CALIBRATE (NCT04143594)

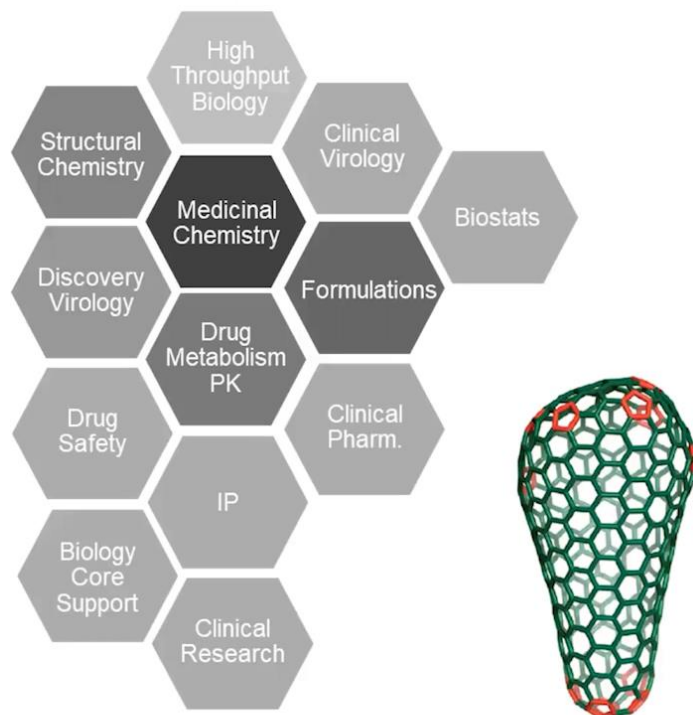
- Ph 2 study in treatment-naïve PWH
- Combination of oral or subcutaneous LEN with oral daily TAF/FTC, TAF, or bictegravir

PrEP (planned for 2021)

- Ph 3 study in cisgender adolescent girls and young women (Q6M SC LEN, TAF/FTC, and TDF/FTC)
- Ph 3 study in cisgender men, transgender women, transgender men, and gender non-binary individuals who have sex with men (Q6M SC LEN, TDF/FTC)

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