Pipeline of Long-Acting agents for HIV treatment and prevention: The LEAP experience

Charles Flexner, MD

Johns Hopkins University

Dr. Flexner is disclosing the following potential conflicts as required by the organizers:

- Research grants and contracts: none to report
- Consulting: Gilead, Janssen, Merck, ViiV Healthcare
- Stockholder and equity: none to report
- Patents and intellectual property: Co-inventor on two issued patents related to the development of long-acting formulations for delivery of antiretroviral drugs

What is LEAP?

The Long-Acting/Extended Release Antiretroviral Research Resource Program

leap

WHAT IS LEAP?

- An R24 Research Resource Support Program funded by the Division of AIDS, NIH, since May 01, 2015.

- SPECIFIC AIMS:

1. To support scientific innovation related to the development of LA/ER antiretroviral drugs through investigator access to broad-based scientific expertise, including the pharmaceutical industry.
2. To develop a communications and data hub to support investigators in this field.
3. To provide a Modeling and Simulation Core Service that helps investigators identify the most promising approaches to the development of new products.

leap

WHAT IS LEAP?

- An “honest broker” to connect key stakeholders from academia, industry, regulatory agencies, funding agencies, and community representatives to promote development, approval, and implementation of LA/ER formulations for HIV and related infections.
- A catalyst for innovation and problem solving to help make such products reality.
- An engine to encourage and promote novel solutions to scientific, regulatory and logistical barriers to the effective uptake of LA/ER formulations, in order to optimize their impact on the treatment and prevention of HIV and related infectious diseases.

leap

WHAT IS LEAP?

- An “ho
  regulat
  represe
  and im
  and rel
- A catal
  make s
- An eng
  to scie
  effecti
  optimiz
  preven

leap»

The LEAP Process

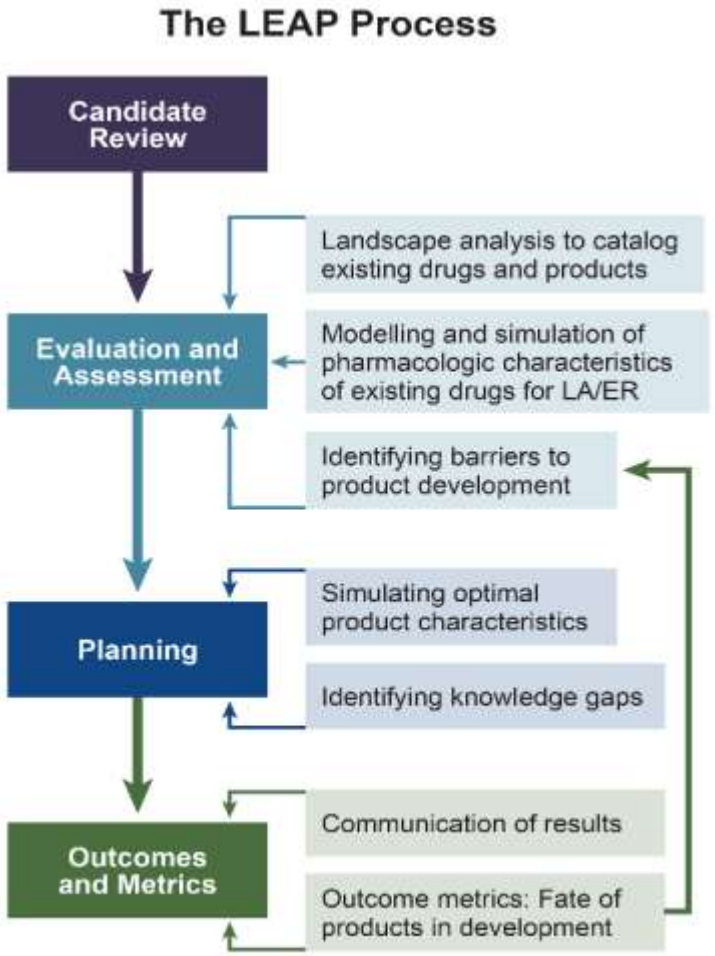


Figure 2. The LEAP process to facilitate drug and formulation development.

With thanks to A. Owen and M. Siccardi, Univ. of Liverpool

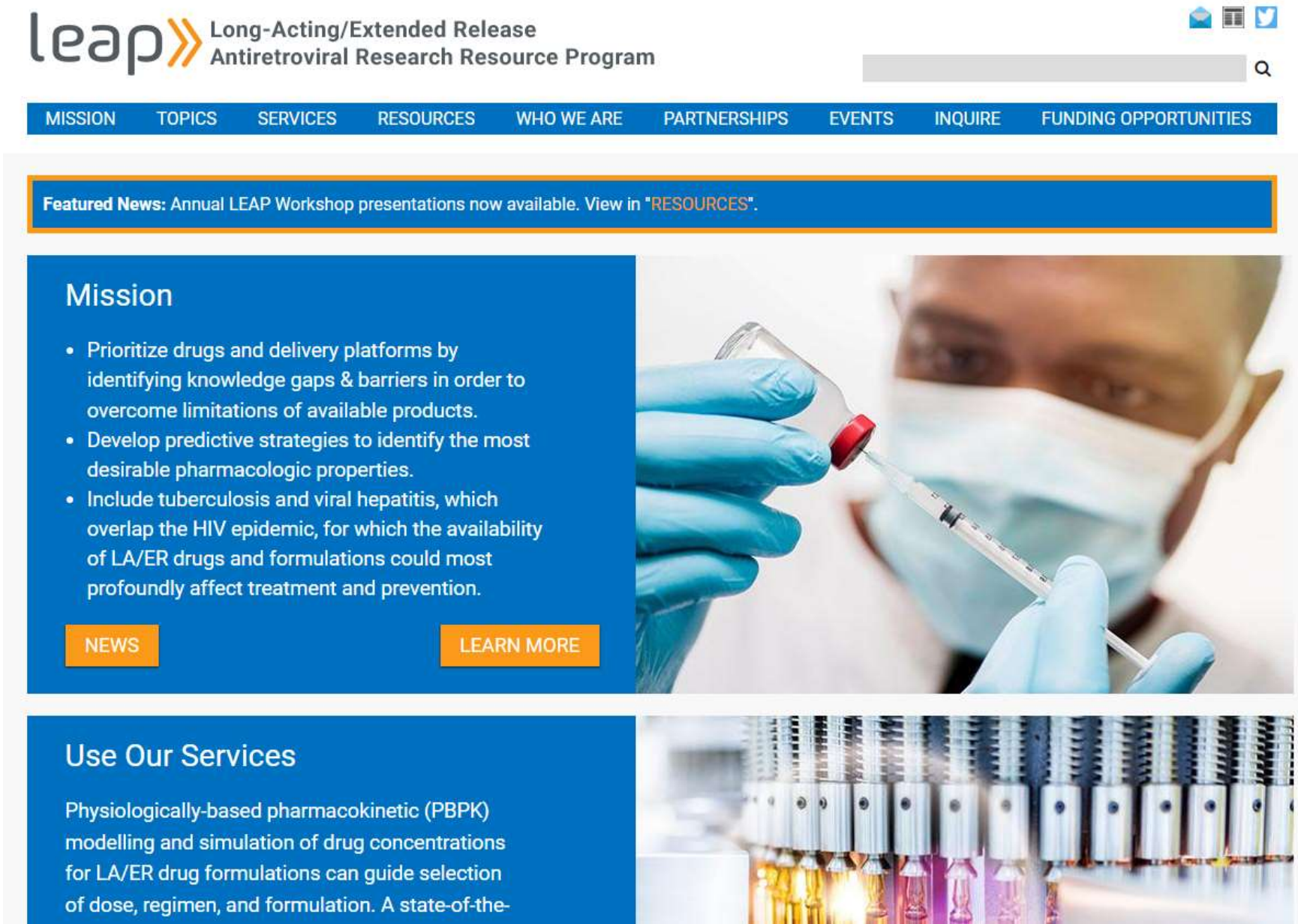
The LEAP Process

- Conduct landscape analyses
  - Systematic reviews of the literature
  - Searchable databases
- Perform modelling and simulation
  - Existing products that meet PK/PD targets
  - Explore performance characteristics of model formulations
- Identify knowledge gaps and potential solutions
- Partner with academia, industry, and NGO's to support development of the most promising candidate drugs and formulations
- Communicate results
- Track outcomes of products in development

leap

OUR WEBSITE:

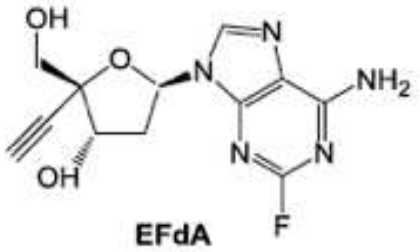
http://longactinghiv.org



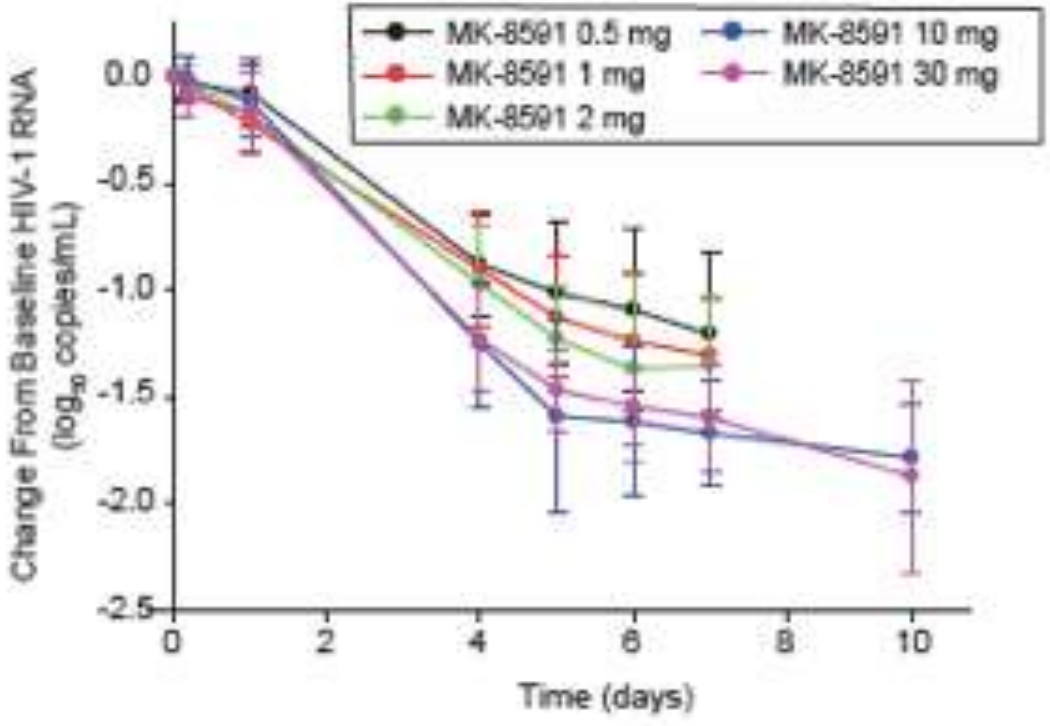
leap

Novel delivery:
Long-acting Oral ARV's

Islatravir (ISL)

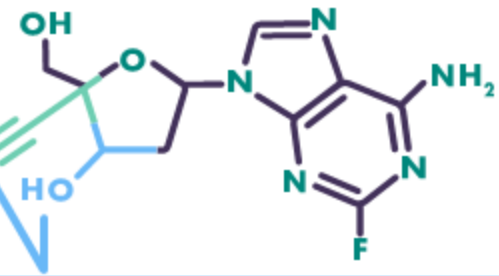


- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; MK-8591; EFdA
- DNA chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Half-life = 50-60 hours in plasma
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Low-dose and parenteral formulations
- Phase 1b: single oral dose



Schurmann et al. Lancet HIV 2020;7:e164-e172

Islatravir (ISL, MK-8591), a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) with multiple mechanisms of action

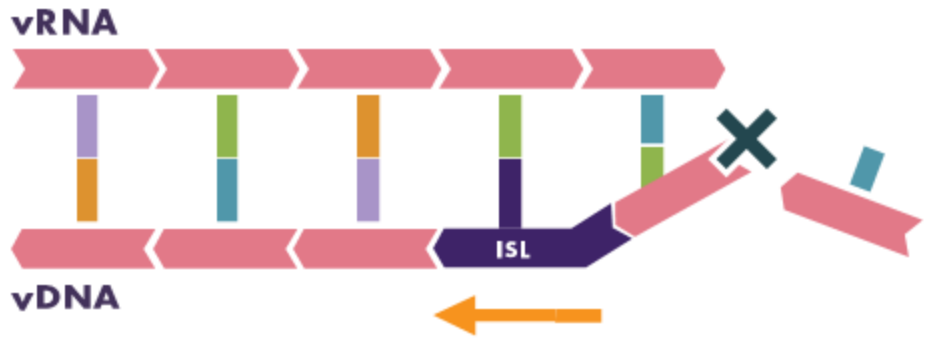


Translocation inhibition
due to the 4'-ethynyl group

- Translocation inhibition prevents the opening of the nucleotide binding site
- Additional nucleotides cannot bind or be incorporated into the viral DNA
- Viral replication is inhibited

ISL is in clinical development for the treatment and prevention of HIV-1 infection.

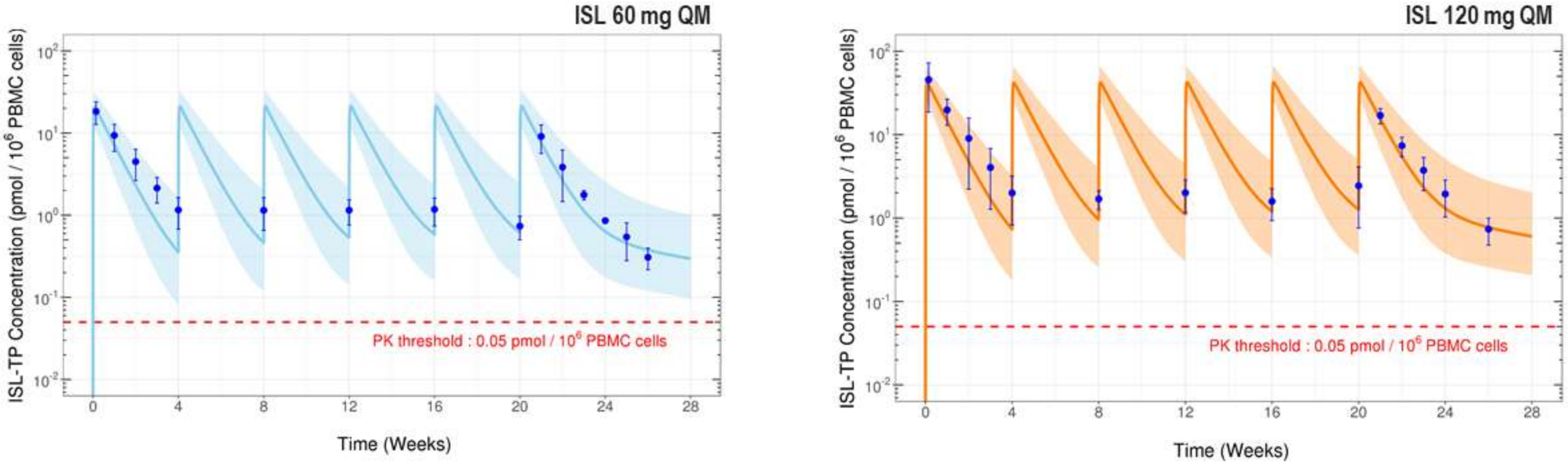
Delayed chain termination
due to the 4'-ethynyl and 3'-hydroxyl groups



- ISL incorporation changes the vDNA structure
- If translocation occurs and a nucleotide is added, the structural change prevents further nucleotide incorporation
- Viral replication is inhibited
- As such, ISL is not in the reverse transcriptase (RT) active site and is no longer susceptible to resistance-conferring mutations

ISL-TP PK exhibited approximately linear dose proportionality

Mean (SD) ISL-TP concentration-time profile in PBMCs overlaid on population PK model-simulated median (95% PI) ISL-TP concentrations in PBMCs



Population PK simulations assessed the interim observed plasma and PBMC PK data[1]

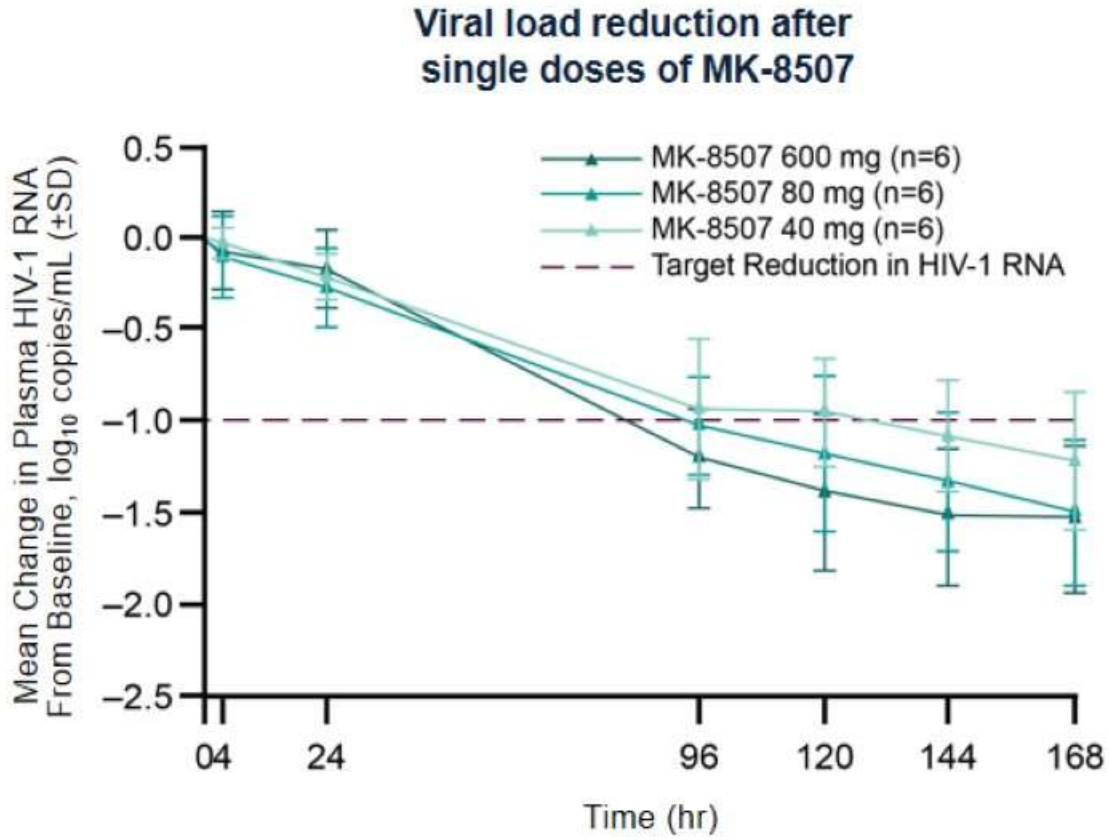
ISL-TP trough concentrations following 60 mg or 120 mg QM doses were all above the prespecified PK threshold of 0.05 pmol/10^6 PBMCs

ISL, islatravir; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; PI, prediction interval; QM, once monthly; SD, standard deviation; TP, triphosphate.
1. Rudd DJ, et al. CROI 2020 (poster).
Hillier et al. HIVR4P (2021).

Patel M et al., CROI 2021; Abstract 87

MK-8507, a once-weekly NNRTI for HIV-1 treatment

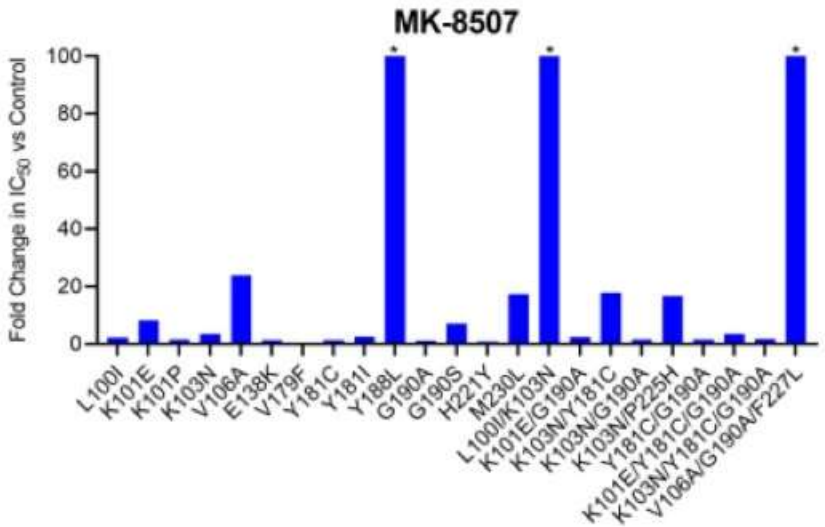
- In vitro IC_{50} (100% NHS)=51.3nM
- Mean plasma $t_{1/2}$ ~70 hours in humans supports once-weekly dosing
- Generally well tolerated with single doses up to 1200 mg and 3x weekly doses up to 400 mg
- Single oral doses of MK-8507 as low as 40 mg reduced mean plasma HIV-1 RNA levels >1 log for up to 7 days in treatment-naïve PLWH
- Phase 2 study of MK-8507 in combination with islatravir is planned (NCT04564547)

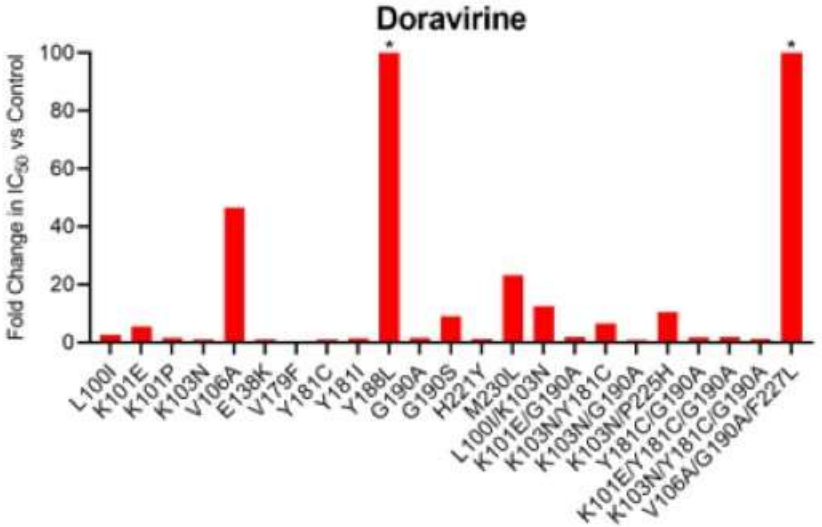


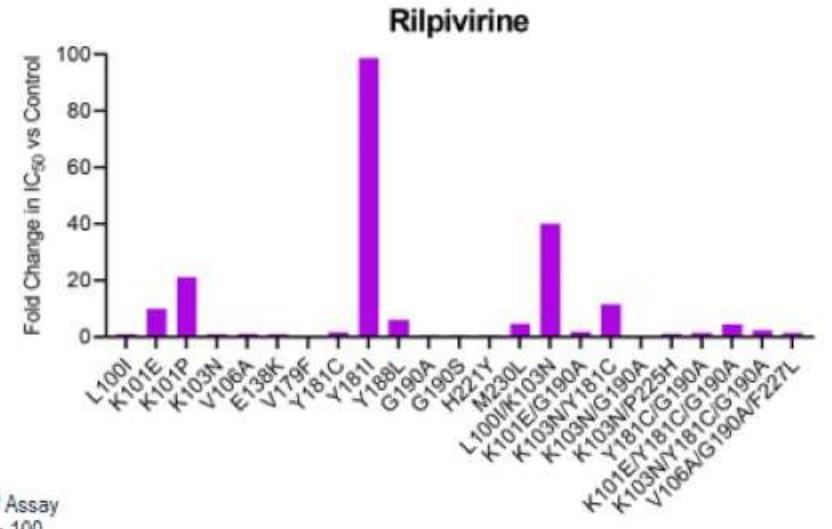
Diamond T et al. CROI 2021

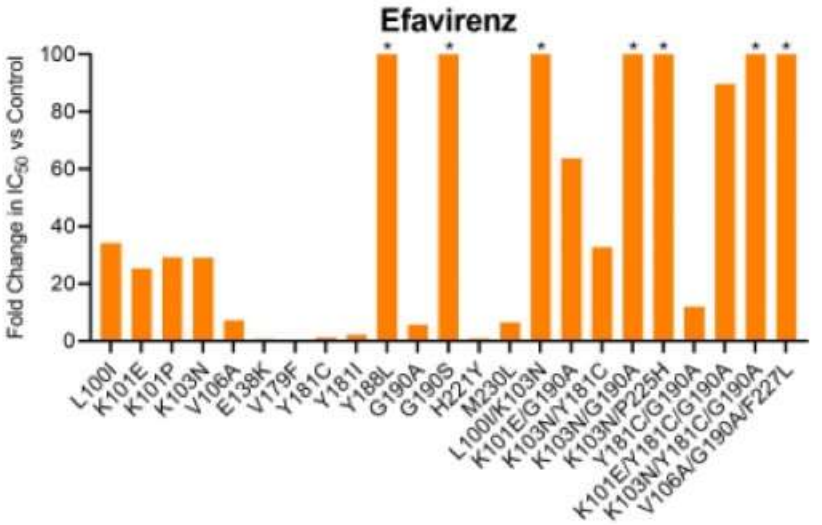
IC_{50}, half-maximal inhibitory concentration; NHS, normal human serum; PLWH, people living with HIV

MK-8507 has a similar resistance profile to doravirine and is superior to efavirenz against NNRTI resistance-associated clinical variants









PhenoSense® Assay
*Fold change >100
IC_{50}, half-maximal inhibitory concentration

Diamond T et al. CROI 2021

https://www.fiercebiotech.com/biotech/merck-pauses-very-important-hiv-program-after-seeing-red-flag-phase-2-trial-once-weekly; see also https://www.biopharmadive.com/news/merck-isltravir-hiv-safety-signal-combination/610348/

Biotech

Merck pauses 'very important' HIV program after seeing red flag in phase 2 trial of once-weekly combo

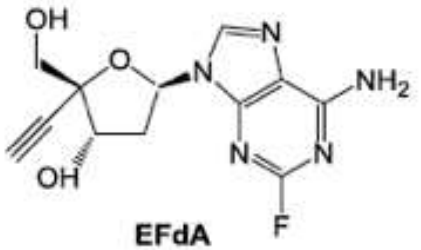
by Nick Paul Taylor |
Nov 19, 2021 7:15am

In response to MK-8507 combination data, Merck went over the results from other clinical trials of islatravir. (Merck & Co.)

A “very important” part of Merck’s HIV strategy has come off the rails. Just months after talking up the importance of MK-8507, Merck has **paused** development of the asset in response to mid-phase data that also raised questions about the backbone of all the company’s planned HIV regimens.

Merck paused development of MK-8507 after seeing decreases in white blood cells in HIV patients who took the non-nucleoside reverse transcriptase inhibitor in combination with backbone therapy islatravir in a phase 2 clinical trial. The external data monitoring committee concluded the

Islatravir-associated lymphopenia



EFdA

- Can a “safe” dose of islatravir be identified?
- Should the focus of development shift to prevention (HIV seronegative recipients) rather than treatment (HIV seropositive recipients)?
- What should happen to MK-8507?
- What other partners exist for subcutaneous lenacapavir?
  - Broadly-neutralizing antibodies?
  - Cabotegravir?
  - Tenofovir prodrugs?
  - Something else?

Novel delivery: Implantable ARV’s

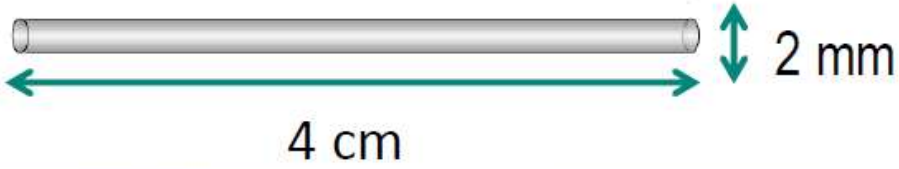
ISL Implant Design Similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

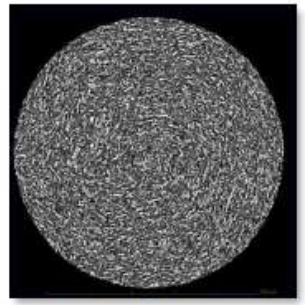
- Initial trial uses prototype implant

Polymer + **ISL**

- Matthews R et al. *IAS* 2019

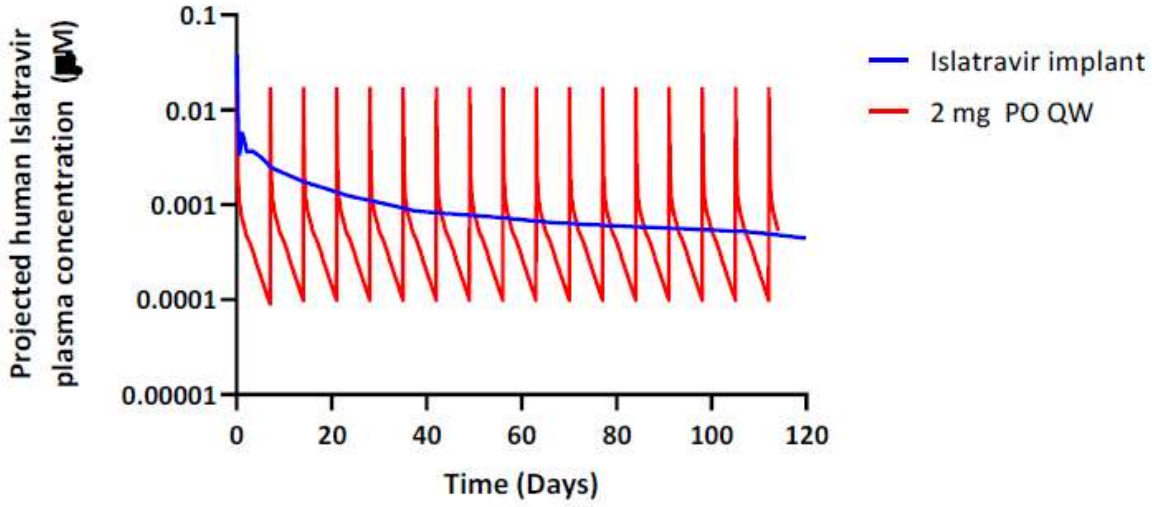


Nexplanon®

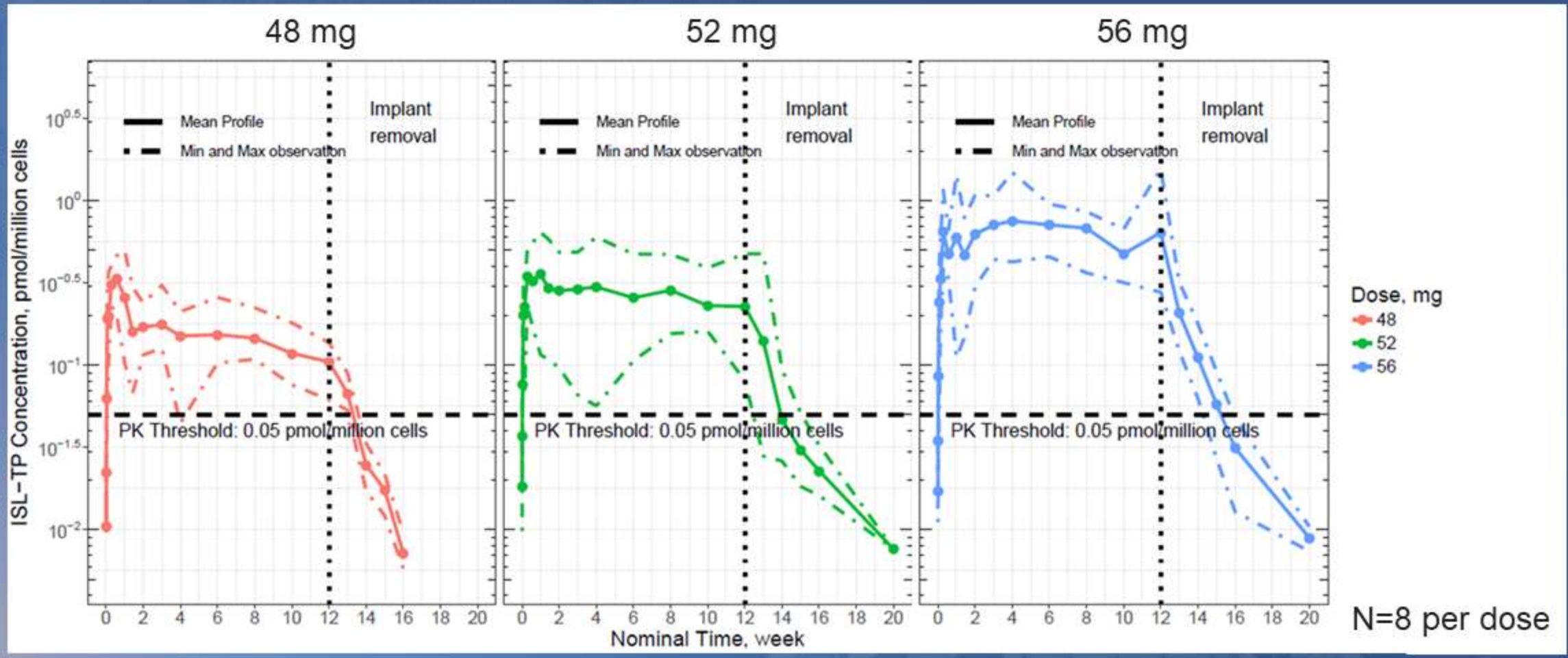


XRCT of ISL implant

Simulated Human PK Profiles



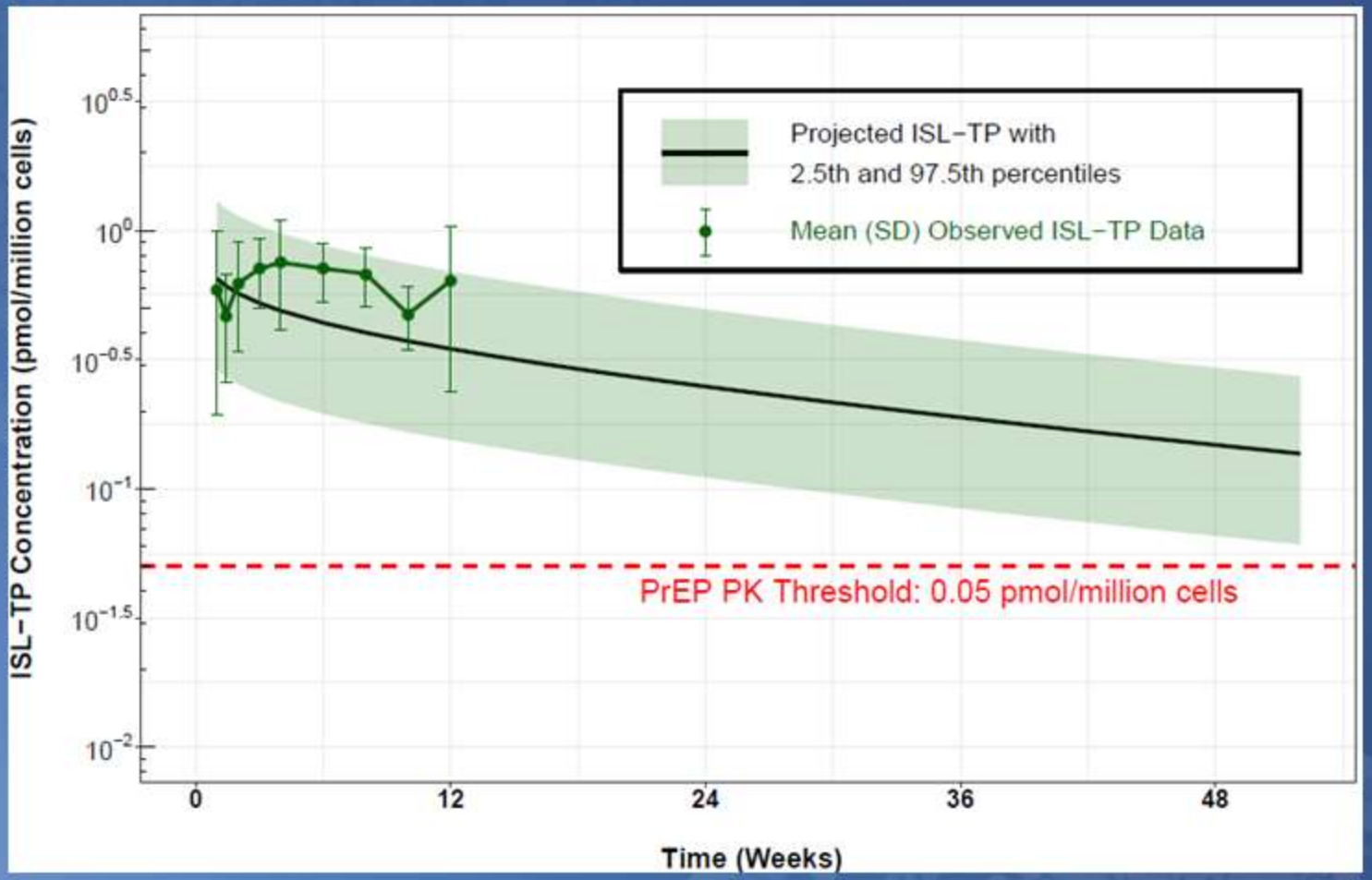
Intracellular ISL-TP PK threshold of 0.05 pmol/10^6 cells maintained throughout placement for two highest doses



- 56 mg implant ISL-TP concentrations comparable to 62 mg from previous study
- Half-life after removal of implant similar to half-life of orally dosed ISL ($t_{1/2}$ for 56 mg is ~198 hr)

R Matthews et al., CROI 2021.

56 mg implant projected to lead to concentrations above threshold for 52 weeks

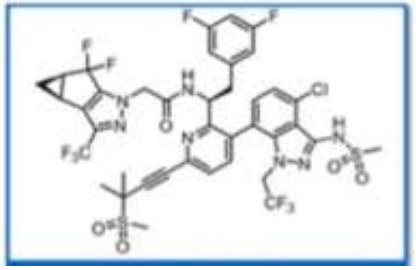


- 56 mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for >52 weeks

R Matthews et al., CROI 2021.

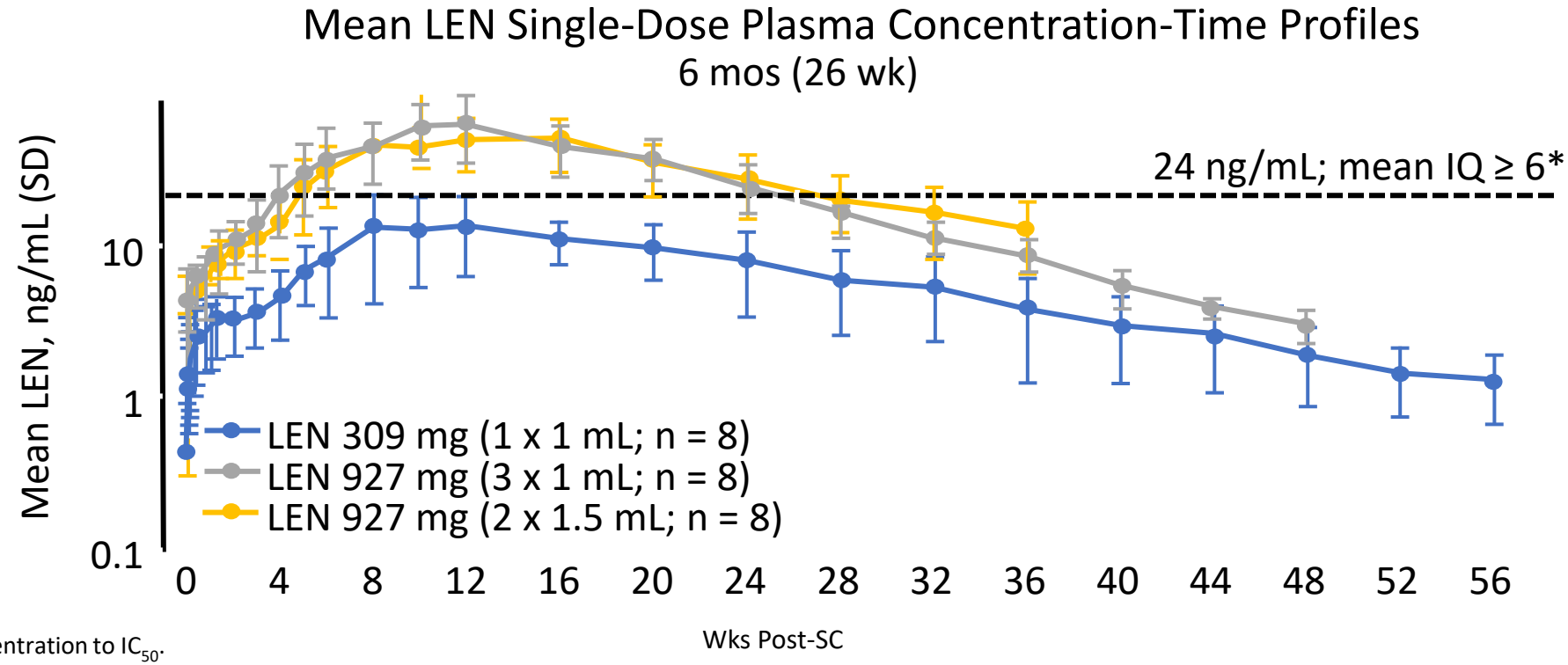
Novel delivery: Subcutaneous ARV's

Lenacapavir (GS-6207) PK Profile



- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor / oral and SC long-acting formulations
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants
- Supports 6 monthly dosing , maintained target concentrations for 26 weeks

N= 30



*IQ: ratio of LEN plasma concentration to IC_{50}.

Begley. AIDS 2020. Abstr PEB0265

Novel delivery: Intravenous ARV’s

Broadly Neutralizing mAbs in Development

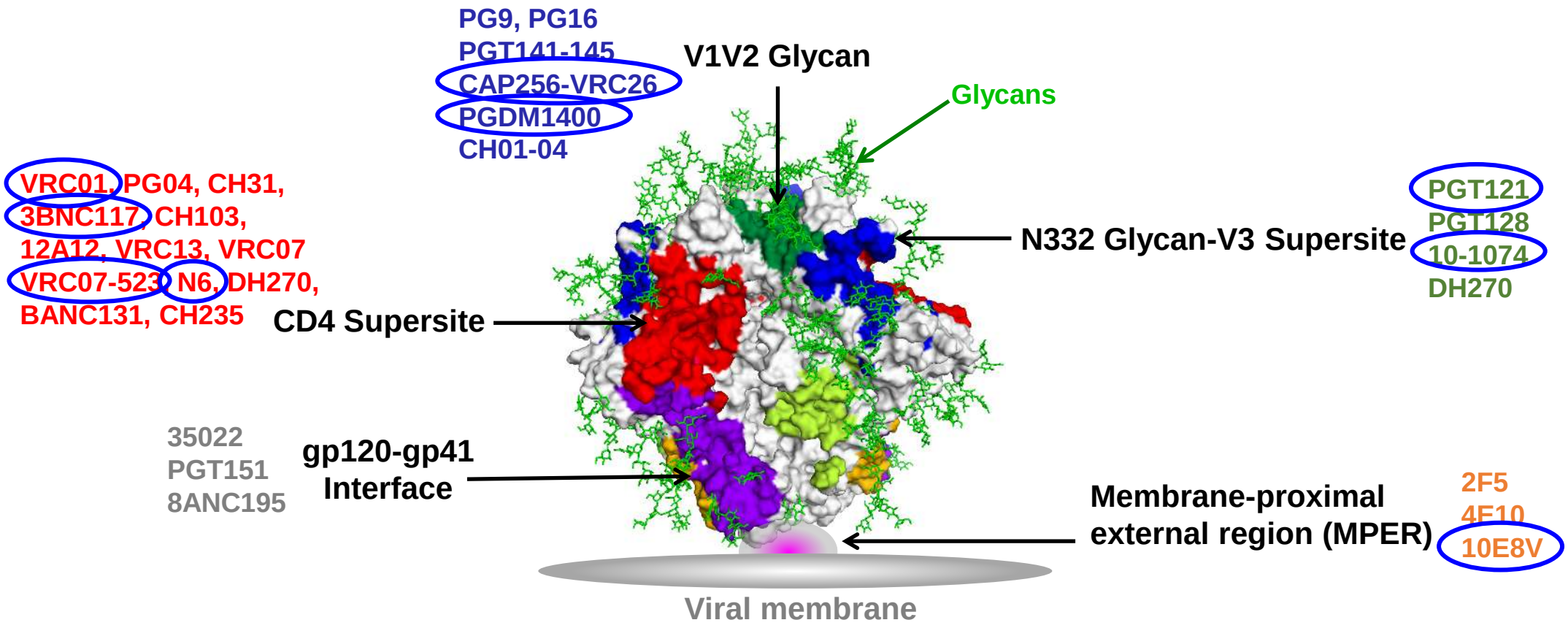
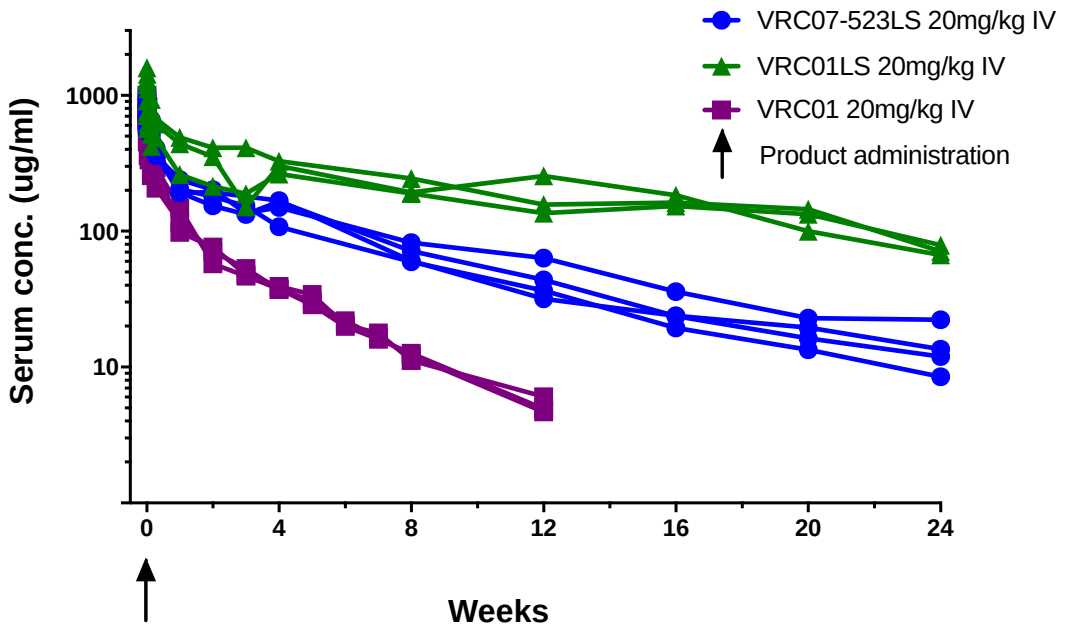


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

VRC07-523LS and VRC01LS serum conc.



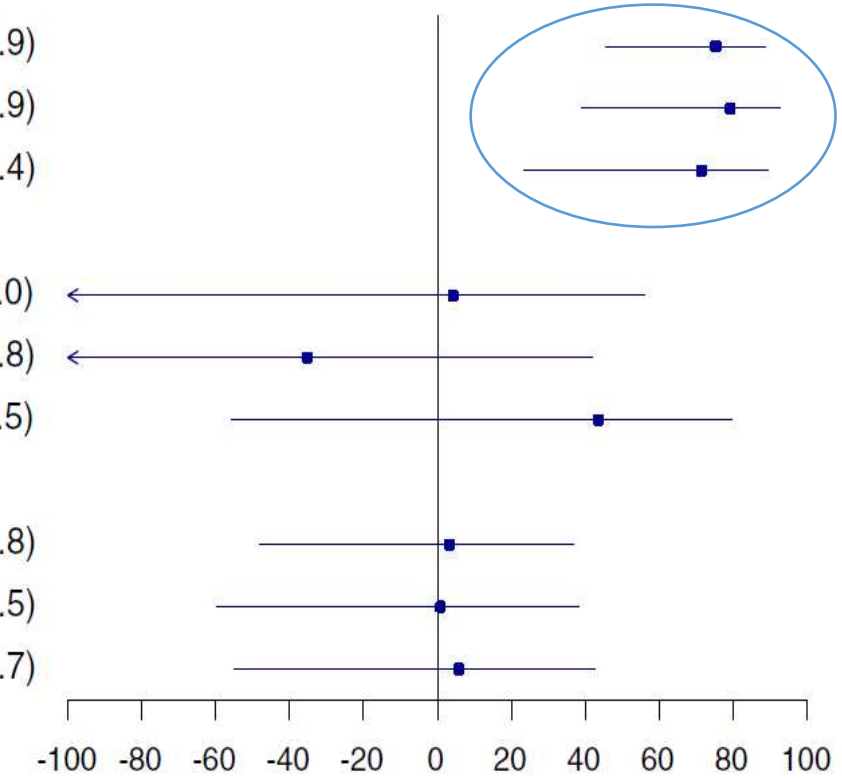
Trough at 12 weeks is 3-fold lower
Trough at 16 to 24 weeks is 5-fold lower

But overall, serum neut is better for VRC07-523LS vs VRC01LS

Gaudinski, Ledgerwood et al. Lancet HIV (2019)

Prevention with VRC01: The AMP Studies (Pooled Trials)

Neutralization Resistance Level	Treatment arm	No. of HIV-1 Infections	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)
<1 µg/ml	Control	19	2203	0.86	
	VRC01 Pooled	9	4427	0.20	75.4 (45.5, 88.9)
	VRC01 10 mg/kg	4	2210	0.18	79.2 (39.1, 92.9)
	VRC01 30 mg/kg	5	2217	0.23	71.5 (23.3, 89.4)
1-3 µg/ml	Control	10	2203	0.45	
	VRC01 Pooled	19	4427	0.43	4.2 (–108.7, 56.0)
	VRC01 10 mg/kg	13	2210	0.59	–35.2 (–214.3, 41.8)
	VRC01 30 mg/kg	6	2217	0.27	43.5 (–55.8, 79.5)
>3 µg/ml	Control	35	2203	1.59	
	VRC01 Pooled	70	4427	1.58	3.3 (–48.0, 36.8)
	VRC01 10 mg/kg	37	2210	1.67	0.9 (–59.7, 38.5)
	VRC01 30 mg/kg	33	2217	1.49	5.8 (–55.1, 42.7)

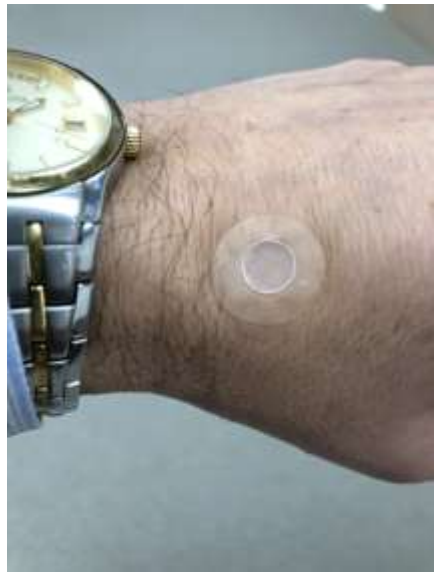


Corey L et al., *N Engl J Med*. 2021; 384: 1003-1014.

Novel delivery: Topical ARV’s

Dapivirine Vaginal Ring – Prevention only!

- Less effective than other prevention strategies in clinical trials
- Removable
  - Susceptible to nonadherence
  - Removal associated with reduced efficacy in clinical trials
- In development as a combination technology
  - Combined with topical hormonal contraception
  - May improve adherence
- Unconventional implementation strategy
  - Developed strictly in a not-for-profit setting
  - Regulated as both a drug and a device



Novel delivery: Transdermal ARV's

Microarray Patches – Possible application to ART

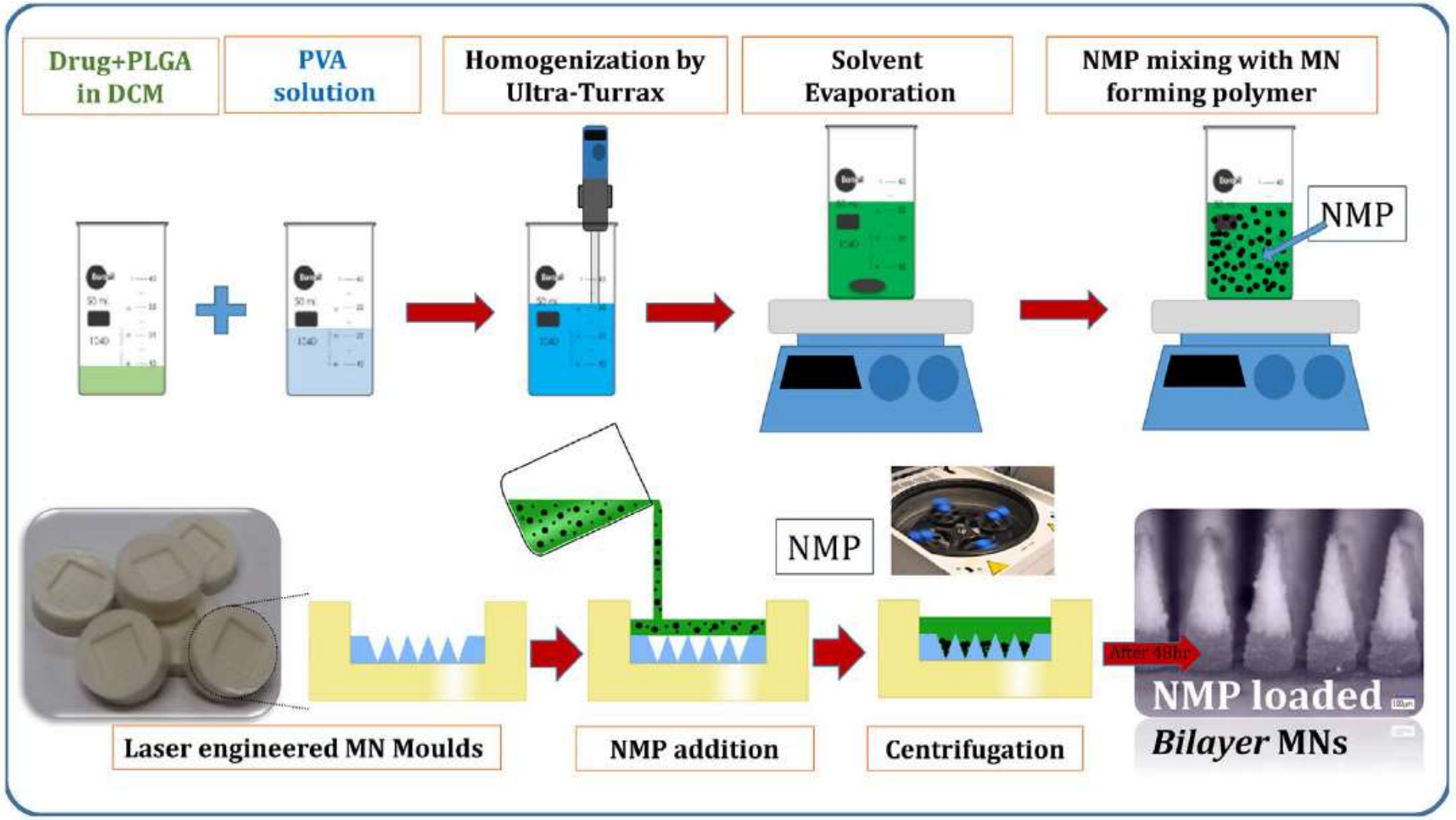


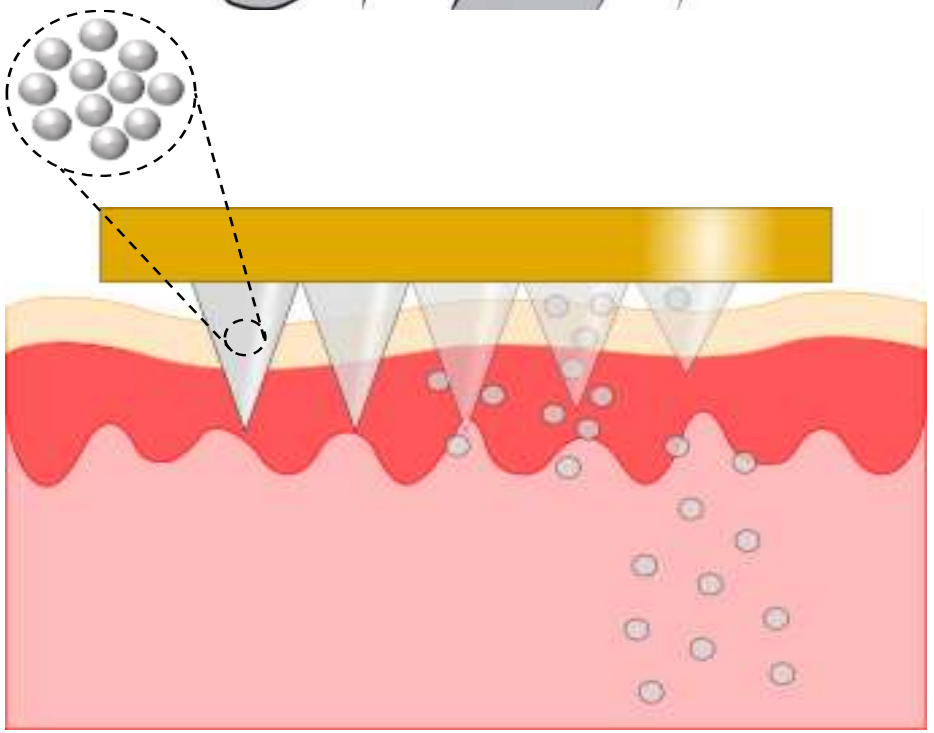
Fig. 1. Schematic representation of fabrication of PLGA nano-microparticle-loaded bilayer microneedle arrays.

- Vora et al. *J Contr Release* 2017

Formulation and Application of LA ART

Microarray Patches

- **Load nanoformulated drugs at high concentration into aqueous gels**
- **Cast into mould**
- **Dry and add border adhesive and occlusive backing layer to form microarray patch (MAP)**
- **Baseplate should readily detach upon microneedle dissolution in skin**
- **Nanoformulated drugs deposited in viable skin layers for sustained release and absorption by rich dermal microcirculation**

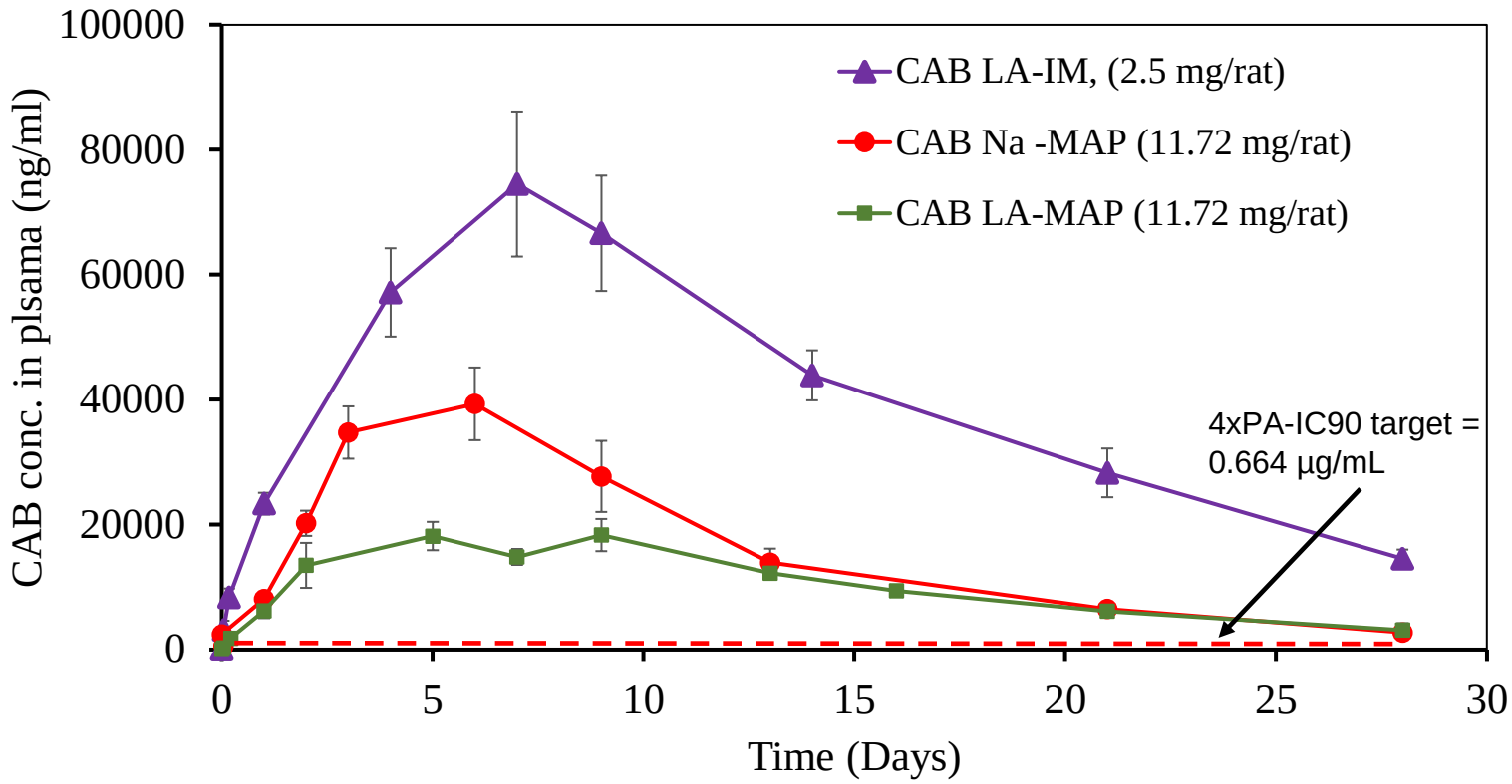


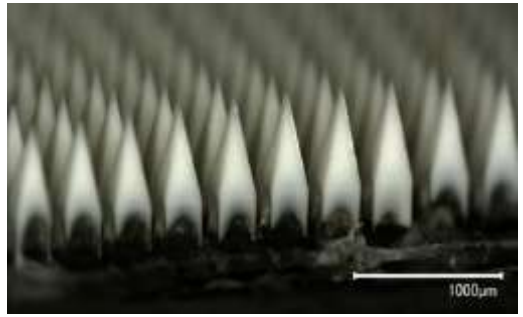
PEPFAR U.S. President's Emergency Plan for AIDS Relief

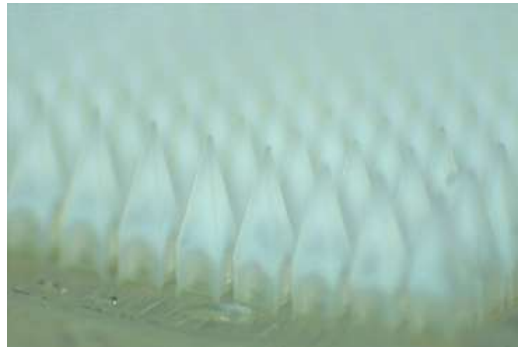
USAID FROM THE AMERICAN PEOPLE

PATH

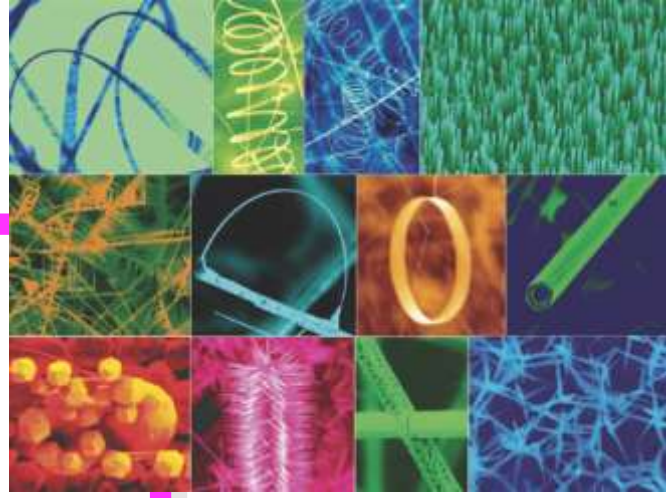
Cabotegravir Microarray Patch – PK profile comparison



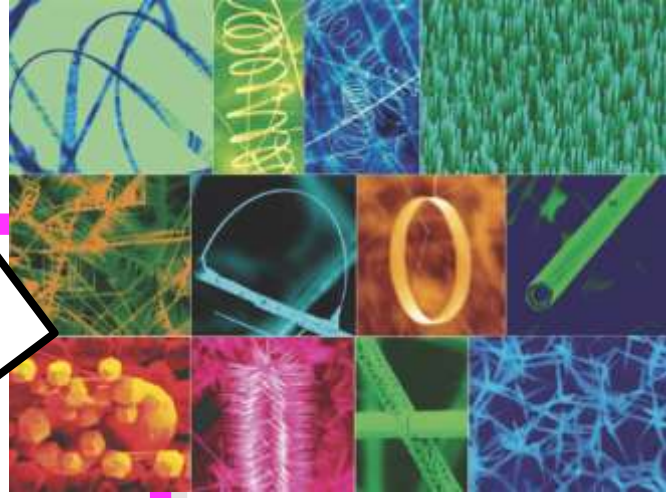




- Courtesy Prof. Ryan Donnelly



Novel delivery: What will the future hold???



Novel deli
Wh
the f e hold???

THE FUTURE IS NOW!!!

Acknowledgements

Johns Hopkins University

Jane McKenzie-White

Melissa Davey-Rothwell

David Thomas

Ana Cervantes

Vaccine Research Center

Richard Koup

UNC

Myron Cohen

Queen's University, Belfast

Ryan Donnelly

Merck

Jay Grobler

Randy Matthews

Tracy Diamond

Bhargava Kandala

Gilead

Martin Rhee

James Rooney

FUNDING SOURCES

Bill and Melinda Gates Foundation

NIAID, R24 AI-118397 (LEAP)

NIAID, R01 AI-114405

leap

longactinghiv.org

LEAP EXECUTIVE COMMITTEE

- Charles Flexner, MD, Principal Investigator and Executive Committee Chair, Johns Hopkins University
- Terrance Blaschke, MD, Senior Program Officer, Global Health Discovery & Translational Sciences, Bill and Melinda Gates Foundation
- Polly Clayden, iBase, London, UK
- Simon Collins, iBase, London, UK
- Paul L. Domanico, PhD, Senior Director of Research & Development, Clinton Health Access Initiative
- Rodney Ho, PhD, Professor of Pharmaceutics, University of Washington
- Jeffrey Jacobson, MD, Director, Division of Infectious Diseases, Drexel University
- Andy Kaytes, Community Representative, University of California, San Diego
- Mark Mirochnick, MD, Professor of Pediatrics and Director, Division of Neonatology, Boston University School of Medicine
- Andrew Owen, PhD, Professor of Molecular and Clinical Pharmacology, University of Liverpool
- Patrick Sinko, PhD, Associate Vice President for Research, Ernest Mario School of Pharmacy, Rutgers
- Susan Swindells, MBBS, Professor and Medical Director, HIV Clinic, University of Nebraska Medical Center
- Bob Bollinger, MD, MPH, Director JHU CCGHE, Johns Hopkins University
- Jane McKenzie-White, MAS, MSEd, Senior Program Officer, Johns Hopkins University

leap

LEAP Pharmaceutical Advisory Board

- Elliot Ehrich, MD, Chief Medical Officer and Senior Vice President, Research and Development, Alkermes Pharmaceuticals
- Daria Hazuda, PhD, Vice President, Infectious Diseases Drug Discovery & Development, Merck Laboratories
- Magali Hickey, PhD, Director, Pharmaceutical Research and Development, Alkermes Pharmaceuticals
- James Rooney, MD, Vice President, Medical Affairs, Gilead Sciences
- Kimberly Smith, MD, PhD, Vice President, Global Medical Strategy, ViiV Healthcare
- William Spreen, PhD, Director & Medicines Development Leader, Infectious Diseases, GlaxoSmithKline Pharmaceuticals
- Manoli Vourvahis, PharmD, Director, Clinical Pharmacology-HIV/Infectious Diseases, Pfizer Pharmaceuticals
- Peter Williams, MBBS, Compound Development Team Leader, Janssen Global Public Health

leap