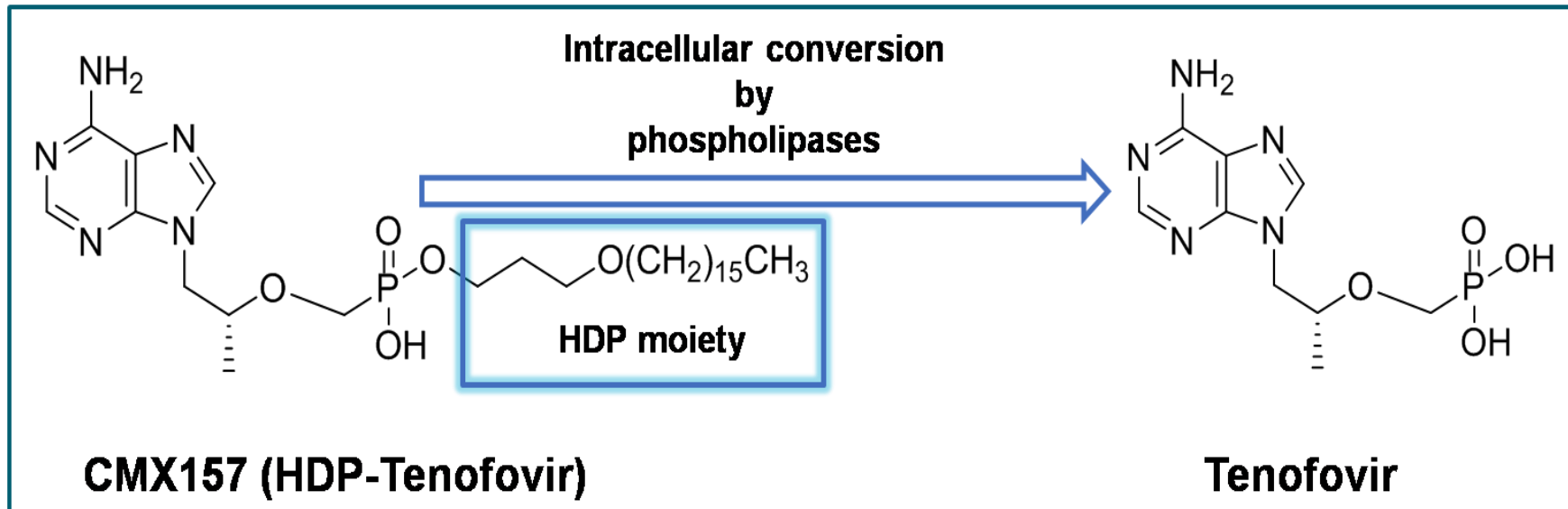




Hexadecyloxypropyl Tenofovir
(CMX157) Has Enhanced Potency *in*
Vitro against NRTI Resistant HIV
Relative to Tenofovir and a
Favorable Preclinical Profile

Randall Lanier, PhD

CMX157 structure and reasons for interest



Goals

- Increase efficacy by boosting intracellular levels of active drug
- Decrease nephrotoxicity by reducing circulating TFV
- Explore once weekly dosing (PK)

Genotypes associated with reduced virologic response to TDF and median fold change in IC₅₀

Genotype	Virologic Response	Median FC in IC₅₀ for Genotype (MBS)
Wild-type ¹	-1.5 log ₁₀	1.0
K65R ²	-0.01 log ₁₀	1.9
K65R/M184V ³	0?	1.4
>2 TAMs with 210 or 41 ²	-0.21	2.0

¹ Louie et al., AIDS 2003: 17

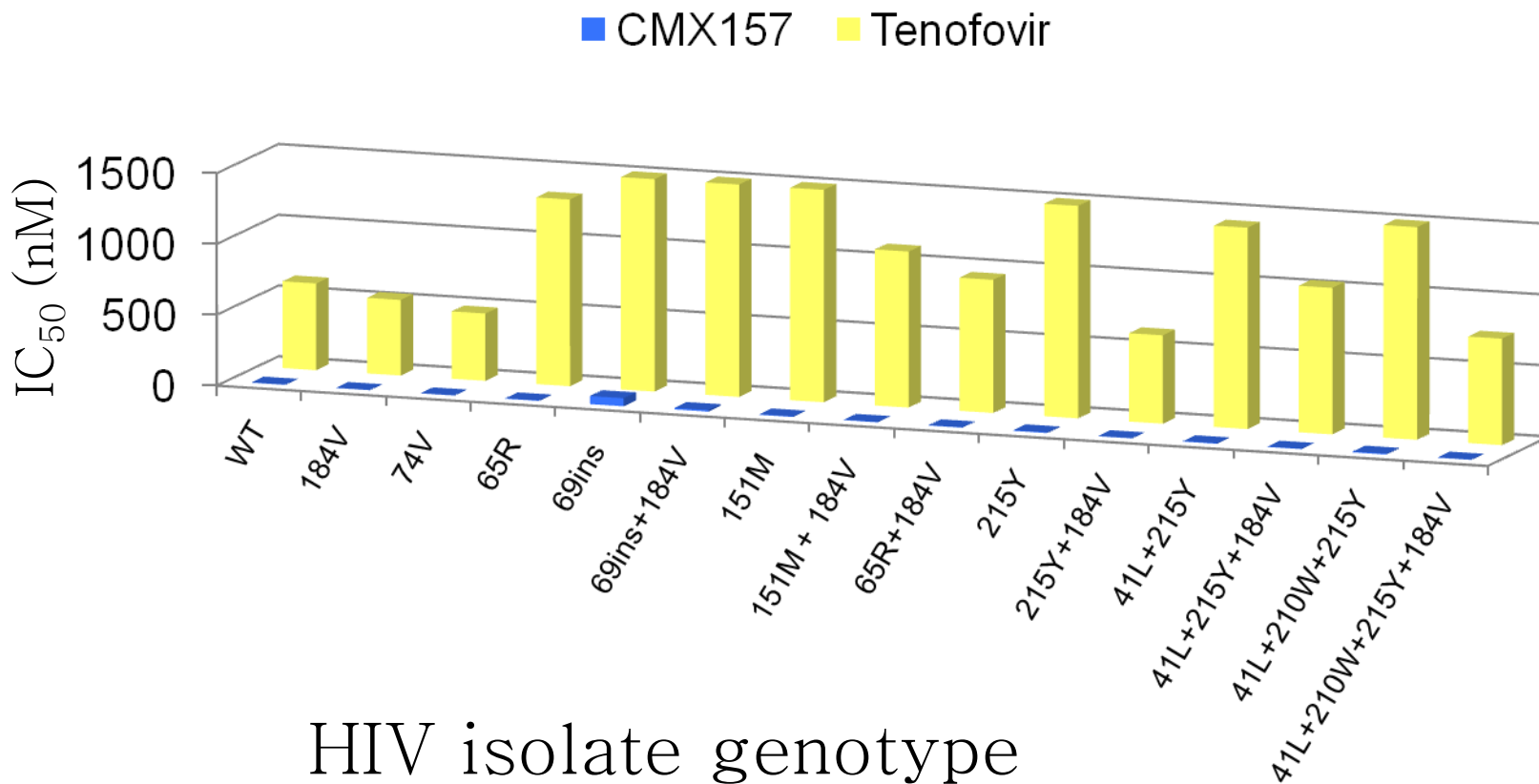
² Miller et al., JID 2004: 189

³ Hsu et al., DRW 2007

Activity of CMX157 against HIV

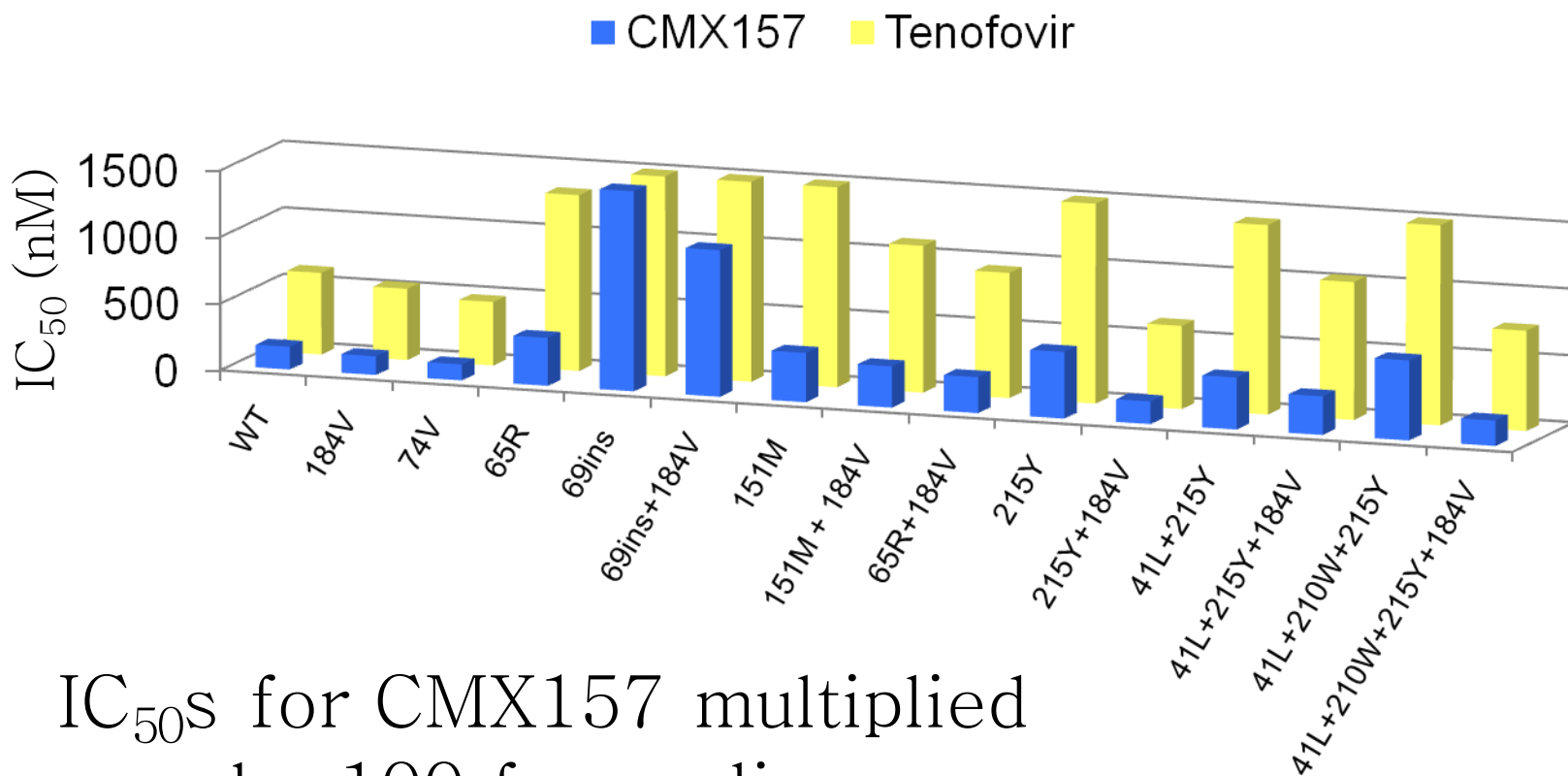
- ▶ CMX157 IC₅₀s against HIV-1 subtypes (A-G,O) ranged from <1 to 7 nM
 - TFV IC₅₀s against HIV-1 subtypes (A-G,O) ranged from 1600 to 4900 nM¹
- ▶ IC₅₀s against NRTI resistant HIV ranged from <1-57 nM
 - median of 359-fold more potent than TFV (range 295-472)

*In vitro efficacy of tenofovir (TFV) versus HDP-TFV (CMX157)**



*Monogram BioSciences PhenoSense™⁵ assay

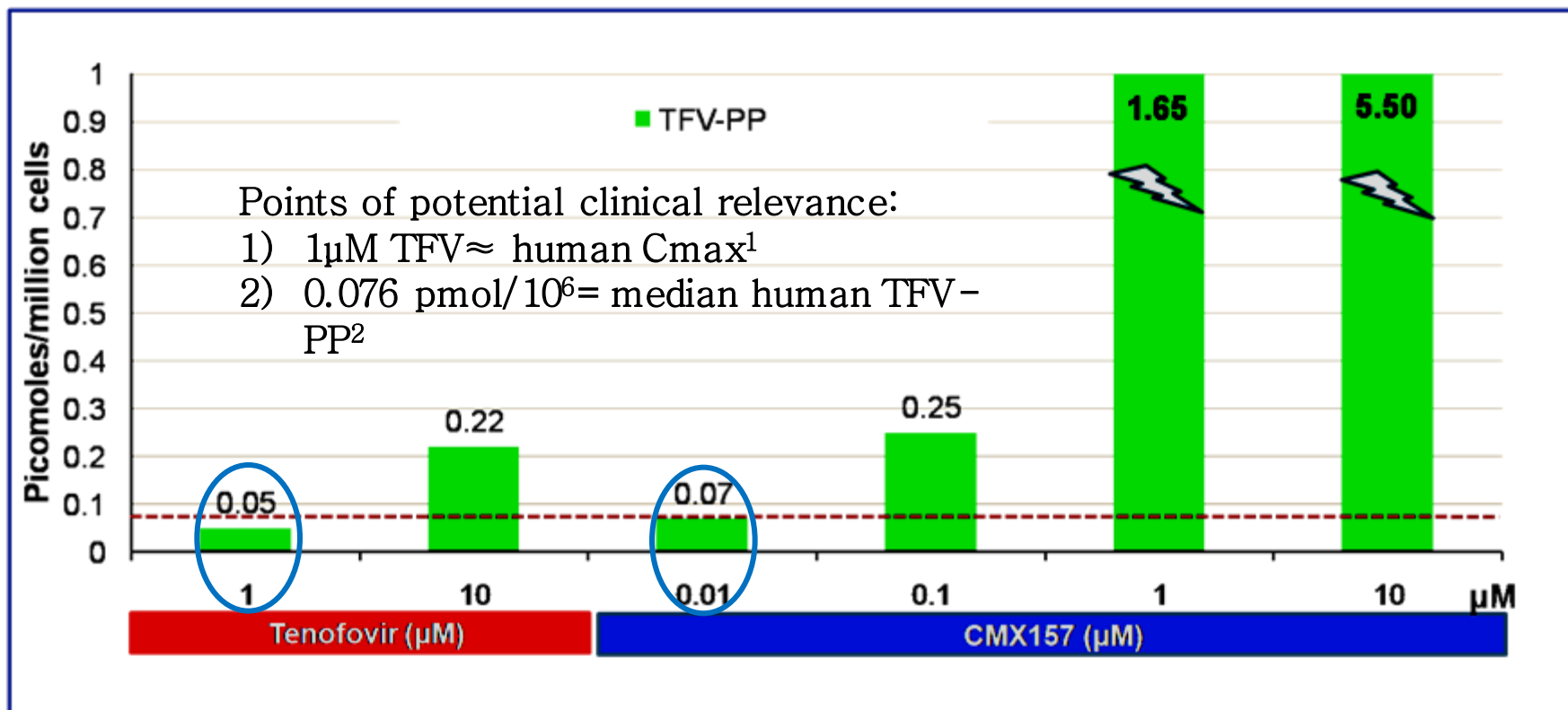
*In vitro efficacy of tenofovir (TFV) versus HDP-TFV (CMX157)**



IC₅₀s for CMX157 multiplied by 100 for scaling

*Monogram BioSciences PhenoSense™⁶ assay

Higher active drug levels in activated human PBMCs following exposure to CMX157 versus TFV in vitro



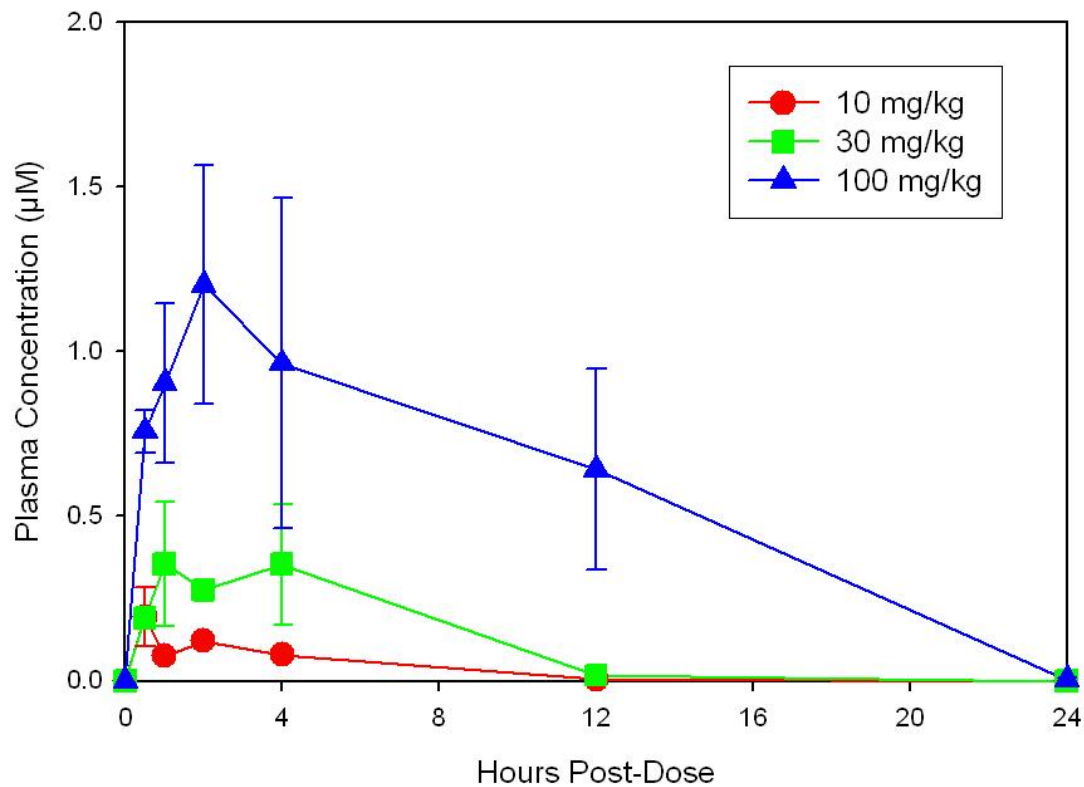
¹VIREAD® package insert 2007

²Kiser et al. JAIDS 2008: 47

CMX157 Toxicology

- **IND-enabling studies support a FTIH dose of 50 mg (0.8 mg/kg)**
 - **Genetic Toxicology Studies**
 - All negative for mutagenicity/clastogenicity
 - **Safety Pharmacology Studies**
 - Examine effects on heart, brain, lungs, GI, and renal systems
 - Slight effects at 200 and 1000 mg/kg, NOAEL will be 40 or 200 mg/kg
 - **28 Day Tox/TK Studies in Rats and Monkeys**
 - Doses of 50 and 200 mg/kg/day well tolerated with good systemic exposure
 - High doses (600/800 mg/kg/day) caused GI toxicity (apparently reversible)
 - In-life complete, pathology remaining, NOAEL expected to be 50 or 200 mg/kg/day

Plasma concentrations of HDP-TFV on day 7 in rats given HDP-TFV p.o.



Summary/Conclusions

- ▶ CMX157 is >300 fold more potent than TFV *in vitro* against wt and clinically relevant HIV mutants
- ▶ The amount of active drug produced in human PBMCs is much higher following exposure to CMX157 vs TFV
- ▶ Toxicology and TK data reveal high exposure to CMX157 in plasma with minimal toxicity

Gratitude Slide

Chimerix

- ▶ Lars Trost
- ▶ Bernhard Lampert
- ▶ Merrick Almond
- ▶ George Painter
- ▶ Alice Robertson
- ▶ Neil Frazer
- ▶ Susan Godkin
- ▶ Rose O'Mahony
- ▶ Roy Ware

Not Chimerix

- ▶ Roger Ptak (SRI)
- ▶ Clay Osterling (SRI)
- ▶ Monogram BioSciences

- ▶ Karl Hostetler (UCSD)
- ▶ Doug Richman (UCSD)