Rational Design of Nucleoside Phosphonates for Intracellular Delivery Using Lipid Conjugation

International Conference on Antiviral Research

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CHIMERIX, INC.

Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," and other similar expressions are intended to identify forward looking statements. All of these forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. Forward-looking statements involve risks and uncertainties, including, but not limited to, economic, competitive, governmental and technological factors outside of our control, that may cause our business, industry, strategy or actual results to differ materially from the forward-looking statements. These statements are also subject to a number of material risks and uncertainties that are described more fully in our filings with the Securities and Exchange Commission, including without limitation our Registration Statement on Form S-1 that was originally filed with the Securities and Exchange Commission on March 8, 2013, and the amendments thereto. Any forward-looking statement speaks only as of its date. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Disclosures

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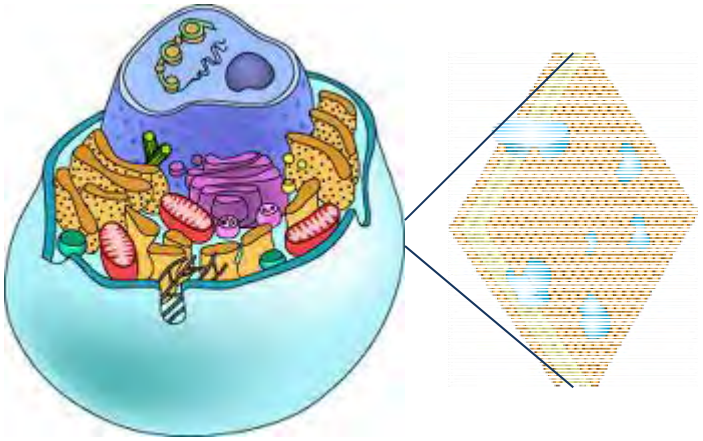
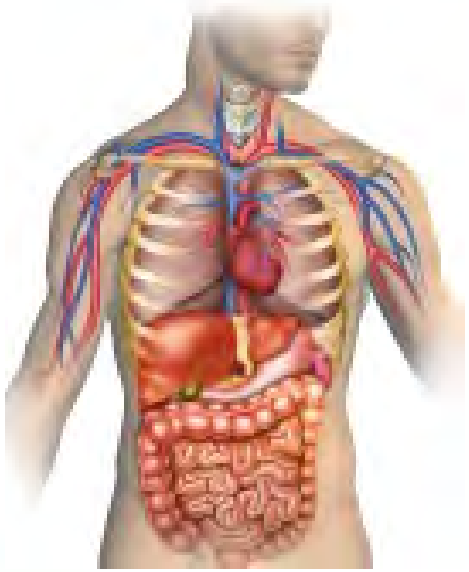
Acyclic Nucleoside Phosphonates (ANPs)

- **Major advantage: phosphonate bypasses 1st phosphorylation (kinase bypass)**
- **Limited cell penetration and oral bioavailability**
- **Cidofovir and tenofovir are concentrated in the kidney by organic anion transporters, leading to nephrotoxicity; CDV administered i.v.**
- **Oral tenofovir disoproxil fumarate rapidly cleaved and circulates as TFV**
- **Lipid conjugation of ANPs provides alternative approach which eliminates nephrotoxicity and may favorably alter other ADME properties**

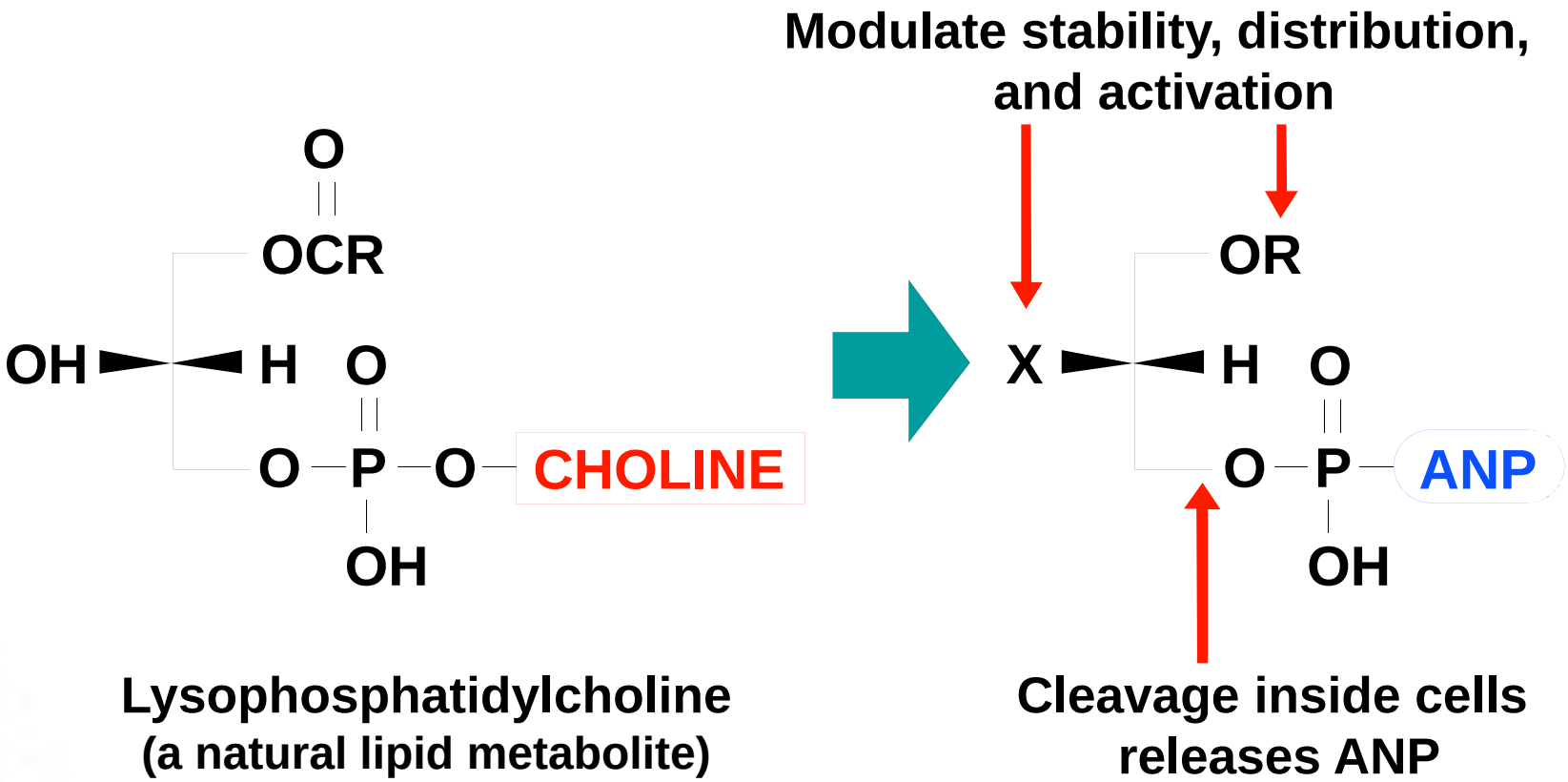
Efficient Drug Delivery to Cells Requires Variable Stability





- Lipid bilayers that define cells are major barriers to delivering antivirals to sites of viral replication
- Lipid-ANPs cross lipid bilayers much more readily than parent ANPs
- Oral lipid-ANPs should be stable saliva, stomach and intestines
- Ideally, should circulate as the lipid-ANP
- Circulating lipid-ANPs must be taken up and anabolized to active antivirals by target cells
- Desired outcome is enhanced clinical efficacy and safety

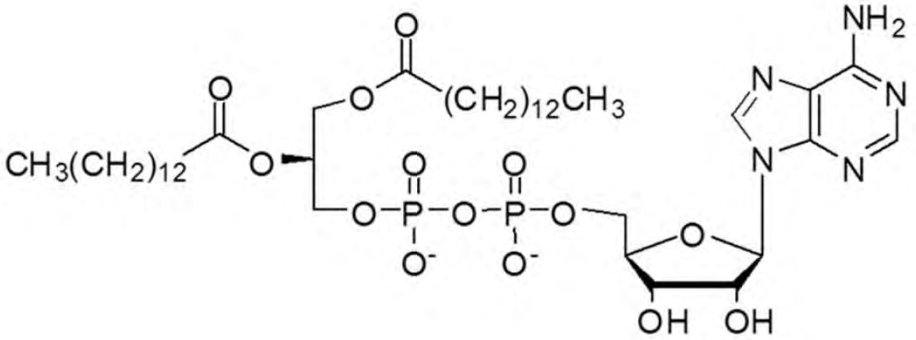
Drug Design Paradigm: Lipid Derivatives of Acyclic Nucleoside Phosphonates (ANPs)



Source: Hostetler Antiviral Research (2009): A84-A98.

Early Research by Karl Hostetler in Laurens van Deenen's Lab (1970-1973)

Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism
Volume 431, Jun 22 (3) 1976; Pages 408-15.
Studies on nucleotide diphosphate diacylglycerol specificity of acidic phospholipid biosynthesis in rat liver subcellular fractions.
BJHM Poorthuis, KY Hostetler



Adenosine diphosphate diglyceride

Glycerol-3-P + ADP-DG
CDP-DG
GDP-DG
UDP-DG
→ PG-3-P + Nuc-MP → Phosphatidylglycerol

Source: Poorthuis and Hostetler. BBA 1976;431(3):408-15.

Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 11835–11839, December 1993
Medical Sciences

Acyclovir diphosphate dimyristoylglycerol: A phospholipid prodrug with activity against acyclovir-resistant herpes simplex virus

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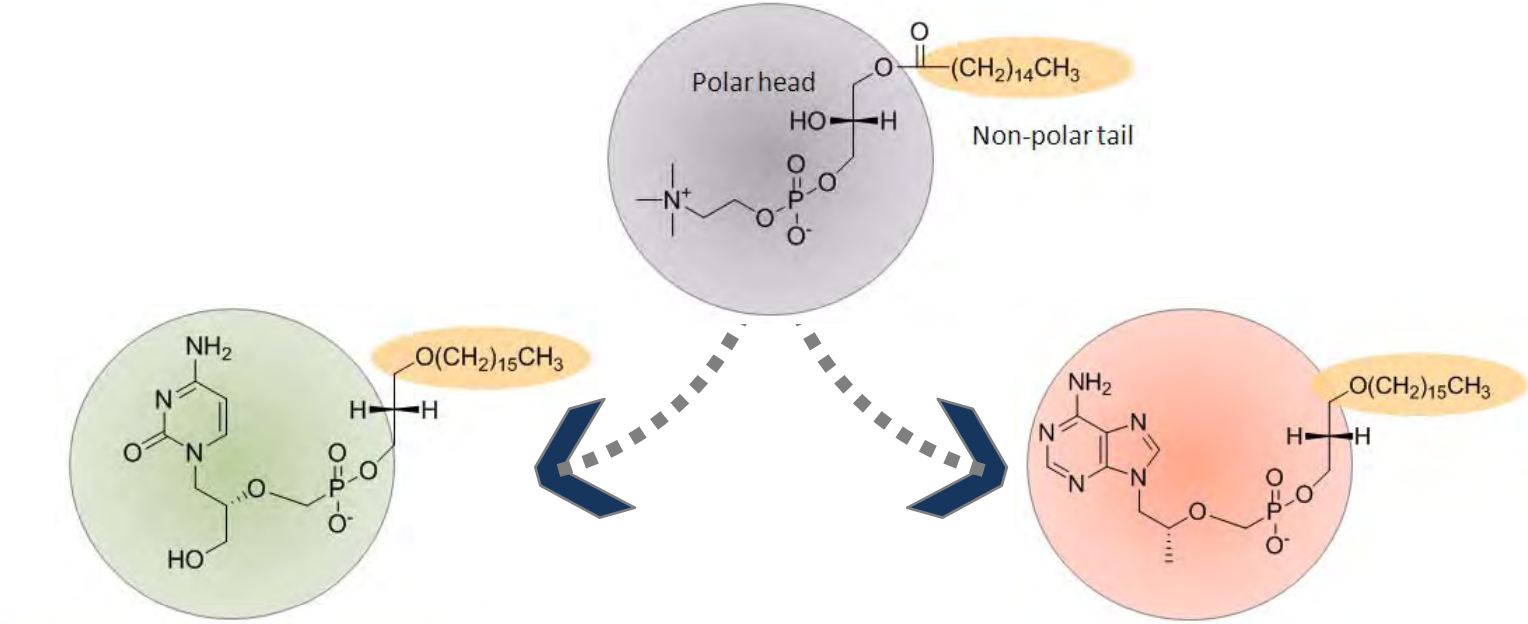
- **Tested against resistant HSV-1 which lacks thymidine kinase activity**
  - ACV EC_{50} >100 μM
- **ACV-DP-DMG EC_{50} was 0.25 μM**
- **Early demonstration of kinase bypass**
- **ACV-DP-DMG was not orally bioavailable; unsuitable for development**

Lipid Conjugates Mimic Natural Phospholipids

Allows utilization of endogenous lipid uptake pathways

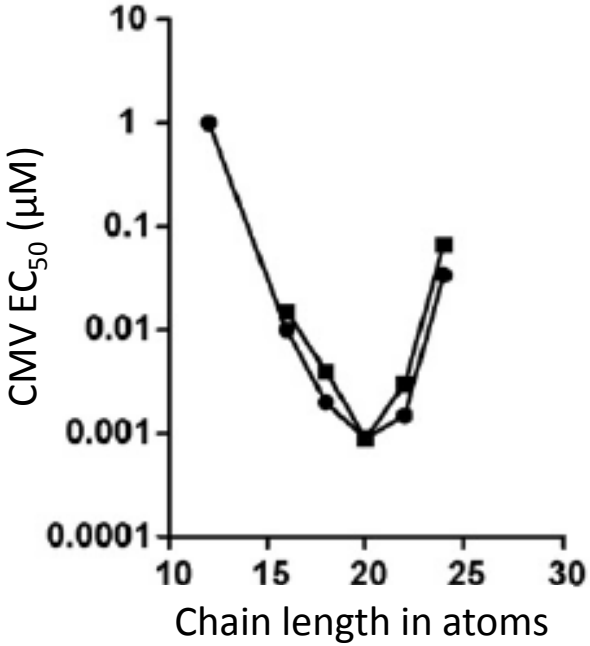
Lysolecithin

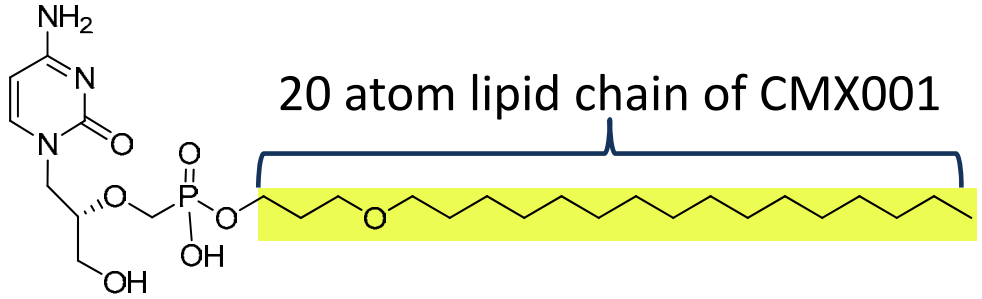


CMX001
Cidofovir Conjugate

CMX157
Tenofovir Conjugate

Lipid Linker in CMX001 Optimized for Antiviral Activity

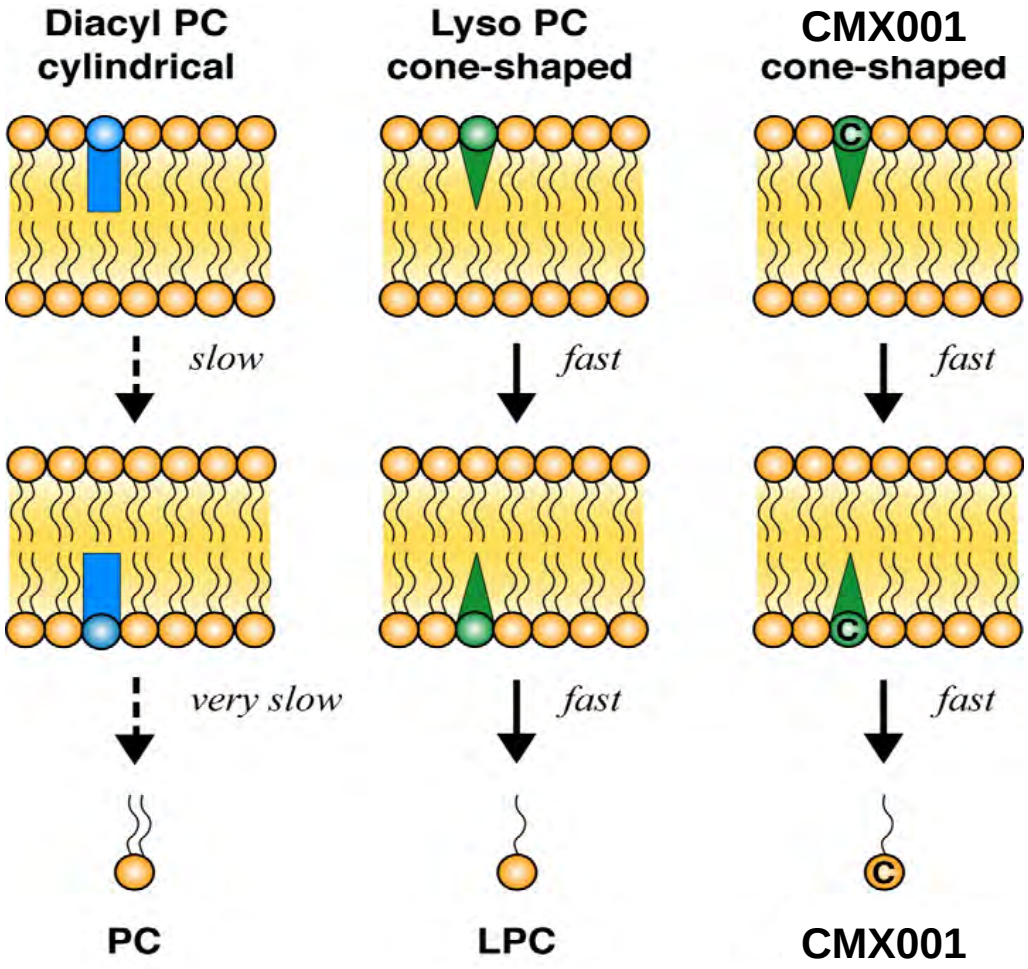




- **Alkoxyproyl (lipid) chain length affects antiviral activity against CMV**
- **Two wild-type CMV isolates were most sensitive to the 20 atom lipid side chain**

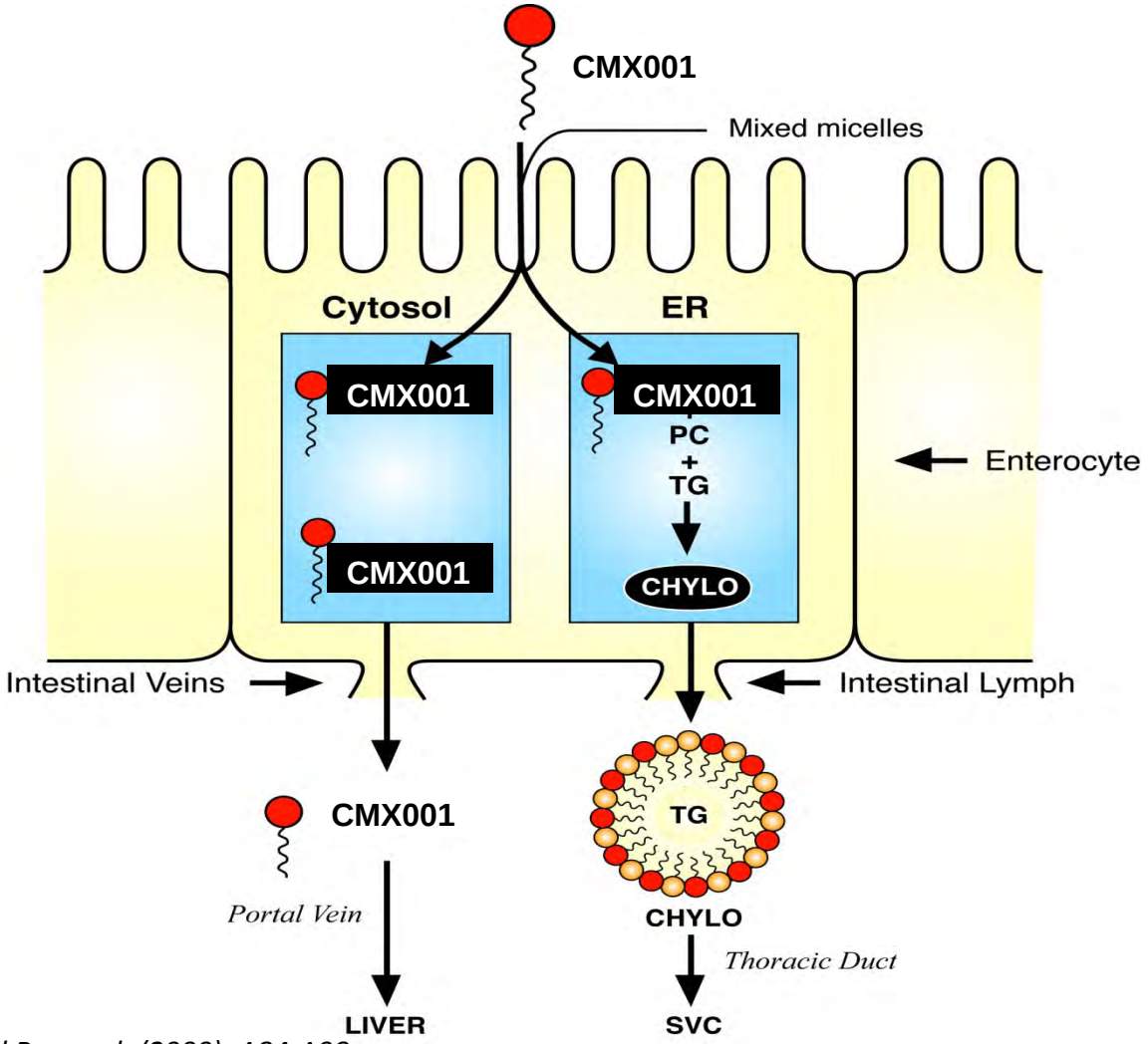
Sources: Williams-Aziz et al. AAC 49 (2005):3724-3733. Wan et al. AAC 49 (2005): 656-662. Hostetler Antiviral Research (2009): A84-A98.

“Single Lipid Tail” of CMX001 Facilitates Transfer Across Membranes



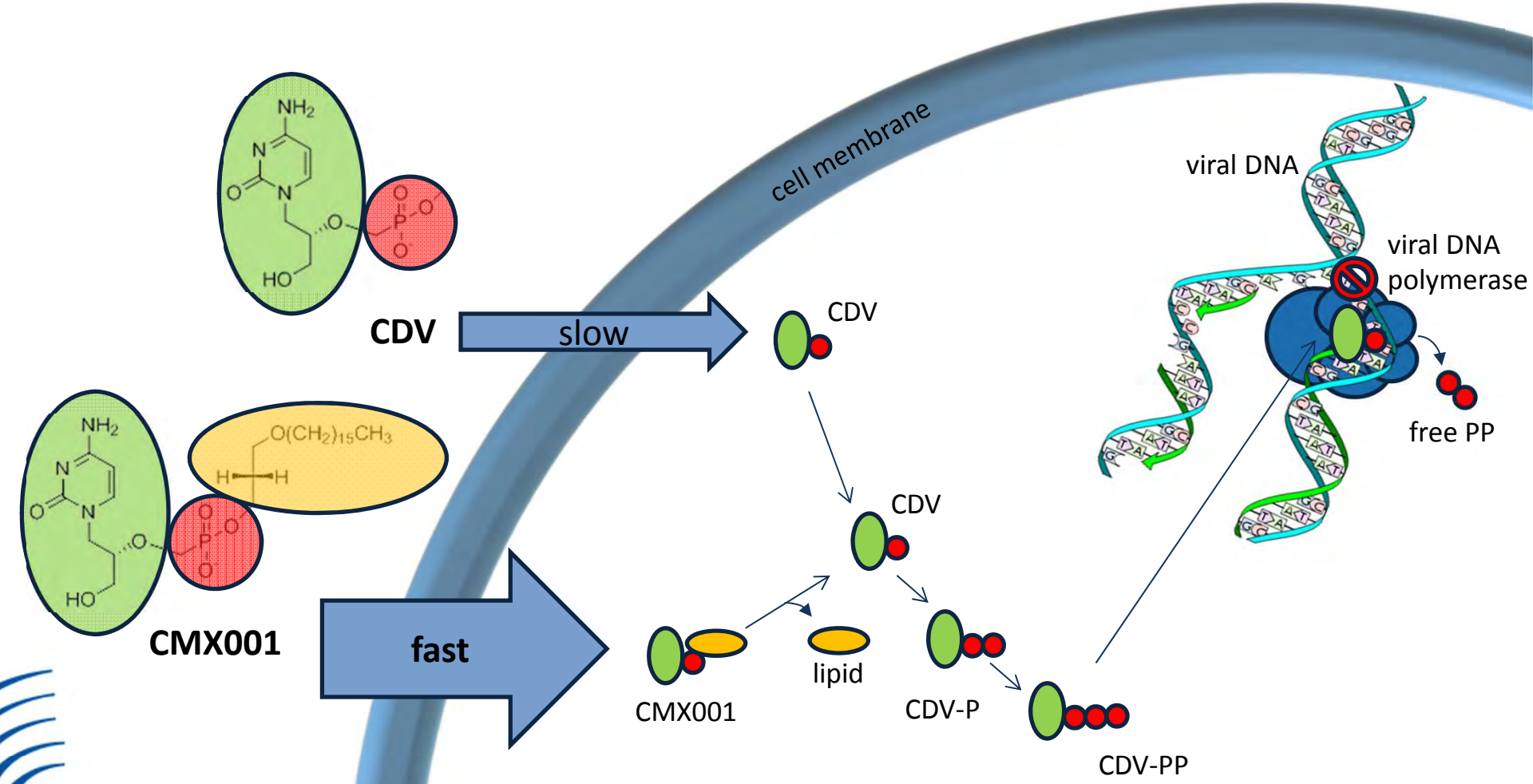
Source: Hostetler Antiviral Research (2009): A84-A98.

Proposed Pathways of Intestinal Absorption for CMX001



Source: Hostetler Antiviral Research (2009): A84-A98.

Mechanism of Inhibition of CMV Viral Replication by CMX001



Potent & Broad Spectrum Activity Against dsDNA Viruses

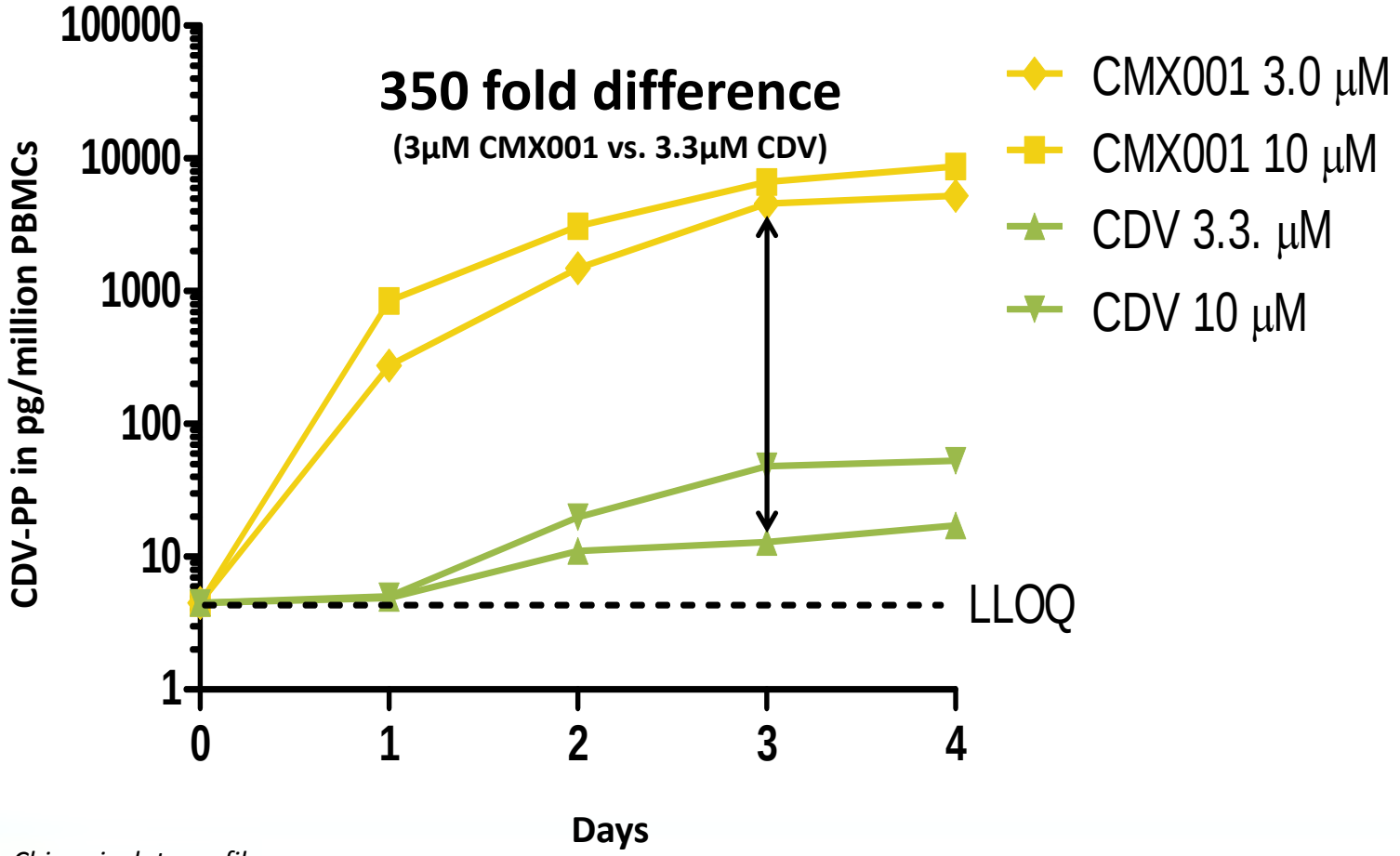
Viral Family	Virus	CMX001	Cidofovir	Ganciclovir*	Foscarnet	Acyclovir	Maribavir	Letermovir
Herpes	Cytomegalovirus (CMV)	0.001	0.4	3.8	50-800	>200	0.31	0.0051
	Epstein-Barr Virus (EBV)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6A (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	No data
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus 7 (AdV 7)	0.02	1.3	4.5-33	Inactive (AdV2)	>100	No data	>10 (AdV2)
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	No data	No data
	JC Virus (JCV)	0.045	>0.1	No data	Inactive	No data	No data	No data
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	No data	Inactive	No data	No data
Pox	Variola	0.1	27	No data	No data	No data	No data	No data
	Vaccinia	0.8	46	>392	Inactive	>144	No data	No data

EC_{50} = concentration in µM required to reduce viral replication by 50% *in vitro*.

*Valganciclovir is rapidly converted to ganciclovir *in vivo*. Therefore, ganciclovir is the relevant compound for cell activity studies.

Source: Data are compiled from multiple sources and include multiple materials and methodologies.

Higher Levels of Active Antiviral Inside PBMCs (CMX001 vs. CCDV)

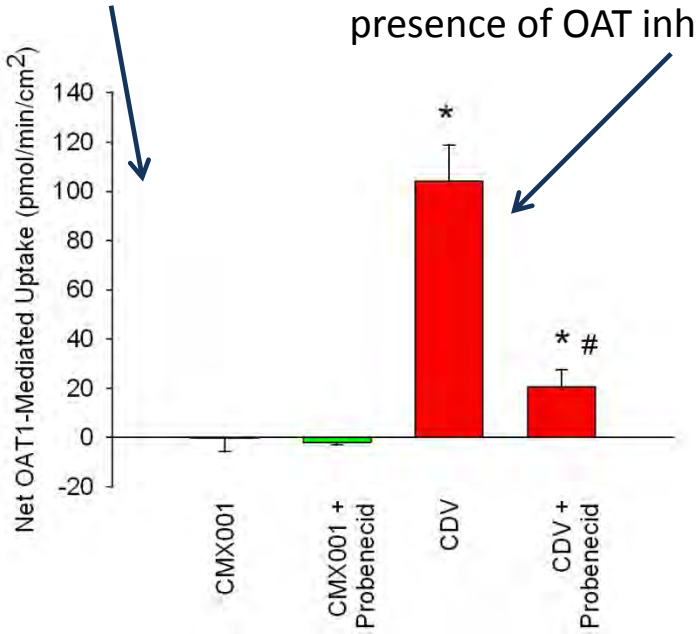


Source: Chimerix data on file.

CMX001 is Not A Substrate of Human Organic Anion Transporter 1 (hOAT1)

Net uptake of CMX001 not enhanced in hOAT1 expressing cells

Net uptake of cidofovir enhanced in hOAT1 expressing cells, and decreased in presence of OAT inhibitor probenecid

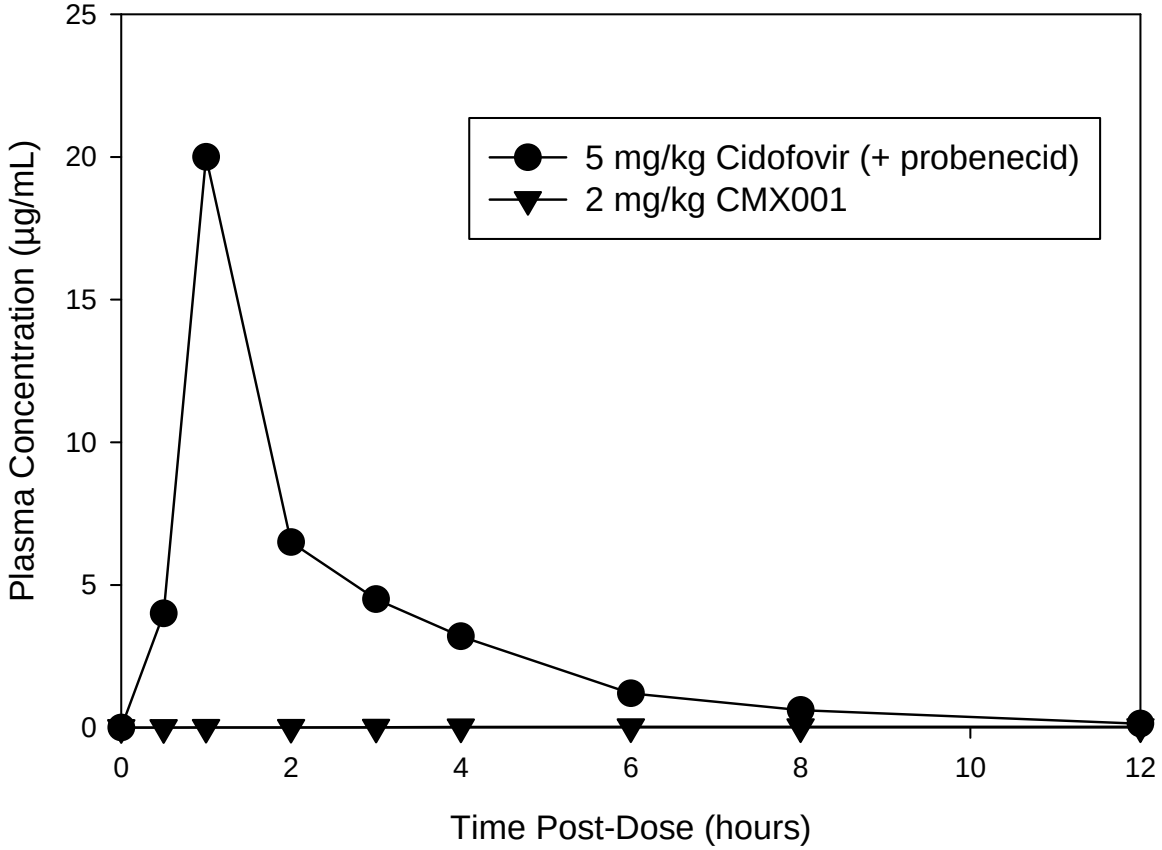


Data provide mechanistic explanation for lack of nephrotoxicity observed in animals and humans following administration of CMX001

Source: Data presented at International Pharmaceutical Federation Pharmaceutical Sciences World Congress and American Association of Pharmaceutical Sciences (AAPS) Annual Meeting 2010.

Peripheral Exposure to CDV Dramatically Lower with Oral CMX001 Versus I.V. CDV

Estimated CDV Plasma Concentrations in Patients Given a Single I.V. Dose of 5 mg/kg CDV with Probenecid[1] Compared with Single Dose of 2 mg/kg CMX001 in Healthy Subjects[2]



Sources: (1) Cundy Clin Pharmacokinet 1999 Feb; 36 (2): 127-143. (2) Chimerix data on file.

CMX001 Development Program Advancing in 3 Indications

- **Adenovirus (AdV): Preemptive Therapy in Pediatric and Adult Hematopoietic Stem Cell Transplant (HSCT) Recipients**
  - Enrollment complete in Phase 2 trial
  - Underscores CMX001's broad spectrum activity for lethal indication

- **Cytomegalovirus (CMV): Prevention in HSCT Recipients**
  - Completed Phase 2 Study in 230 adult subjects post-HSCT
  - Initiating Phase 3 SUPPRESS trial

- **Smallpox: Medical Countermeasure for Treatment**
  - Development program focused on animal efficacy and human safety data
  - Extensive CMC package accelerated by government funding

CMX001 Expanded Access Protocol: Study 350 (n=210)

- **Part of CMX001 Expanded Access Program to treat life-threatening dsDNA viral infections in patients who had exhausted all available therapies or for whom there were no therapeutic options available**

Baseline Demographics

- **N = 210**
  - 68 pediatric, 142 adult
- **CMX001 Exposure**
  - Mean 9.5 weeks (1-43 weeks)
  - 68% > 4 weeks
  - 30% > 12 weeks
- **Immunodeficiency**
  - 153 HSCT (73%)
  - 33 SOT (16%)
  - Congenital, HIV, other (11%)

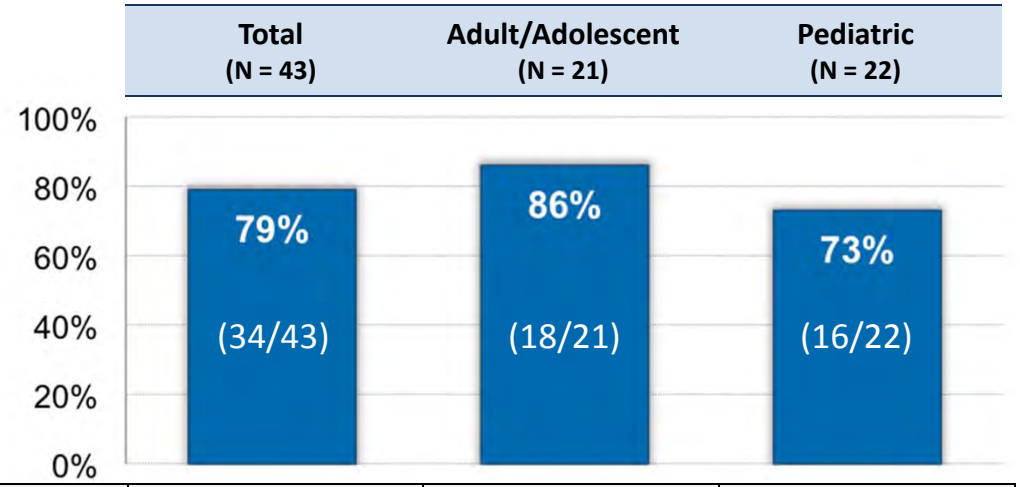
dsDNA Viral Infection(s)

- **28% had two or more viral infections**
- **Breakdown by virus:**
  - 107 – CMV
  - 61 – AdV
  - 7 – BKV
  - 35 – Other

GCV = ganciclovir; FOS = foscarnet

Substantially Reduced AdV Viral Burden in Both Children and Adults

Percent of Responders (>1 log Viral Load Decrease or ≤ LLOQ) at End of Treatment

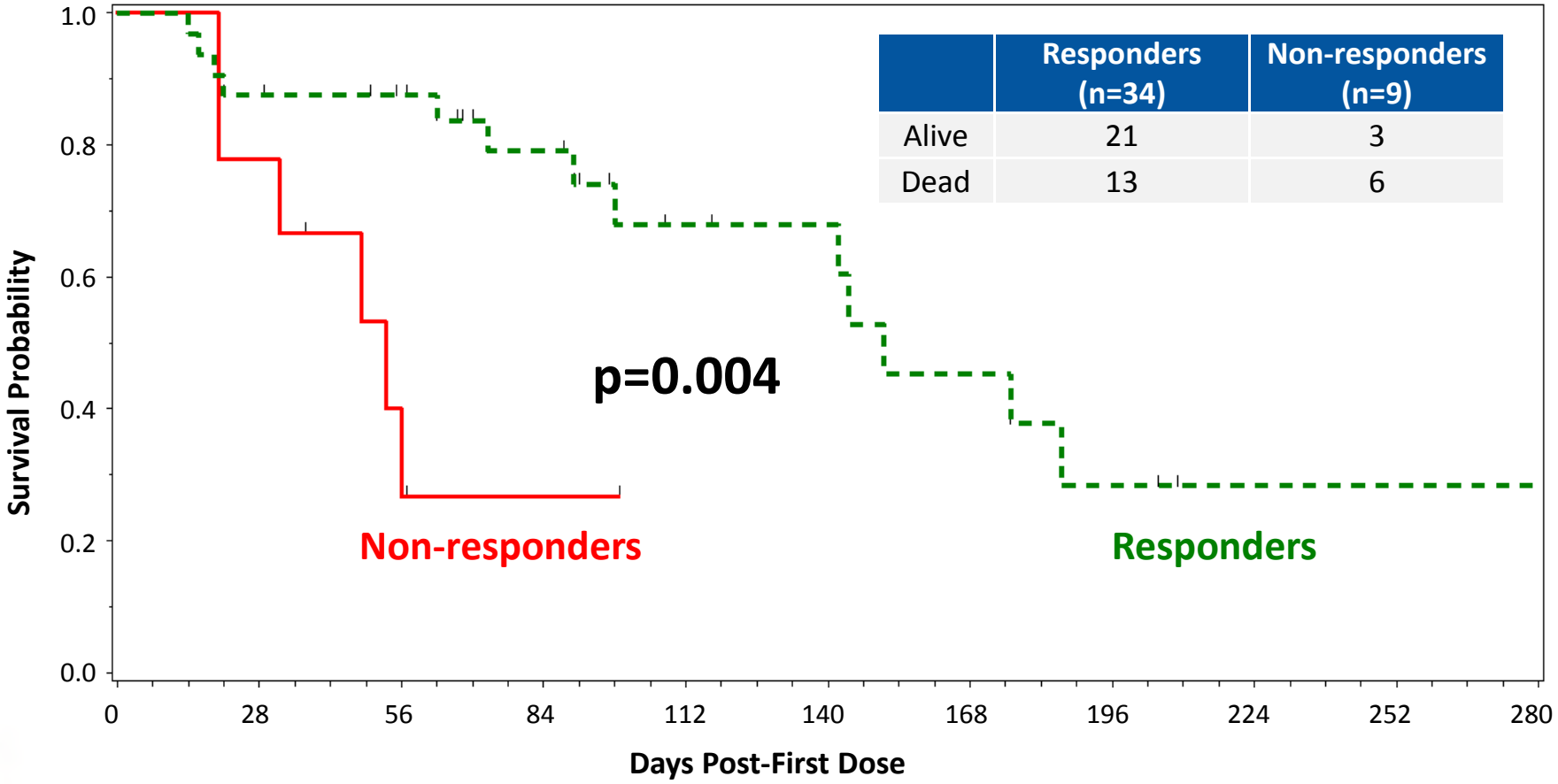


	Total (N = 43)	Adult/Adolescent (N = 21)	Pediatric (N = 22)
Percent of Patients with AdV Viremia ≤ LLOQ	**51% (22/43)**	**48% (10/21)**	**55% (12/22)**
Median Viral Load Drop (log c/mL)	1.6	2.2	1.2

End of treatment was defined as last viral load sample up to 7 days following last dose of CMX001, or last viral load sample if last dose of CMX001 is unknown. Includes Chimerix Study 350 subjects with AdV identified as primary virus. Patients were excluded due to viral load at baseline ≤ 100 c/mL (LLOQ). Data through June 2012.

Source: *Data from Chimerix Study 350 presented at EBMT Annual Meeting, April 2013.*

AdV Viral Response Correlates with Survival



	Responders (n=34)	Non-responders (n=9)
Alive	21	3
Dead	13	6

Figure presents preliminary results from adult and pediatric patients treated with CMX001 under EIND or through Open-Label Study 350. Responders defined as > 1 log reduction from Baseline or undetectable at Week 2. Non-responder (depicted as solid red line) outcome is consistent with natural history of adenovirus disease. Non-responders may have failed due to previous treatment with cidofovir.

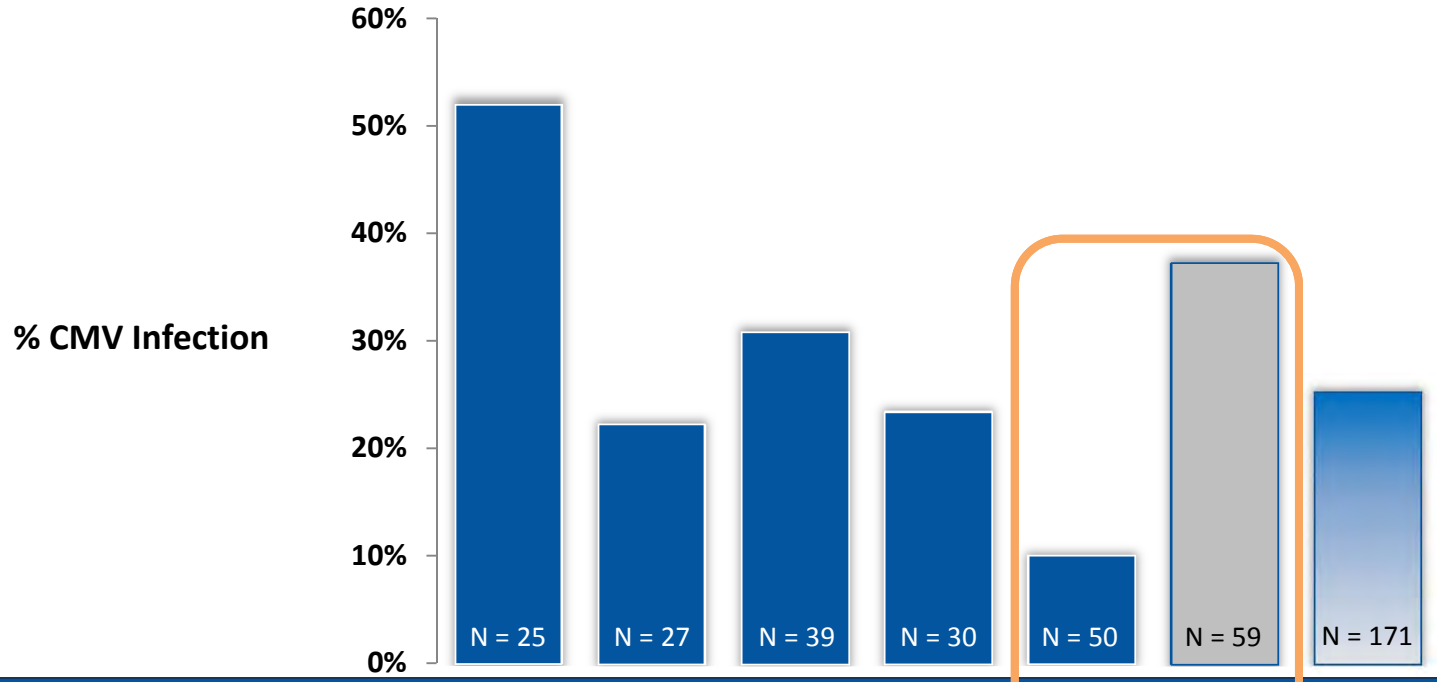
Source: Data from Chimerix Study 350 presented at EBMT Annual Meeting, April 2013.

CMX001: Early Evidence of CMV Prevention in Phase 2

- **Patient population:**
  - 230 allogeneic HSCT recipients
    - Included highest risk patients: cord blood or mismatched transplant
  - Recipient seropositive for CMV (R+)
- **Study 201 design:**
  - Dose-escalation: CMX001 40 – 100 – 200 mg evaluated
  - Once-weekly (QW) and twice weekly (BIW) dosing schedules
- **Primary endpoint: Failure of CMV prevention**
  - CMV disease, OR
  - CMV DNA (PCR) > 200 copies/mL at end of treatment

Study 201: > 50% Decrease in Risk of CMV Events

Primary Endpoint = CMV Disease or CMV PCR > 200 copies/mL at End of Treatment



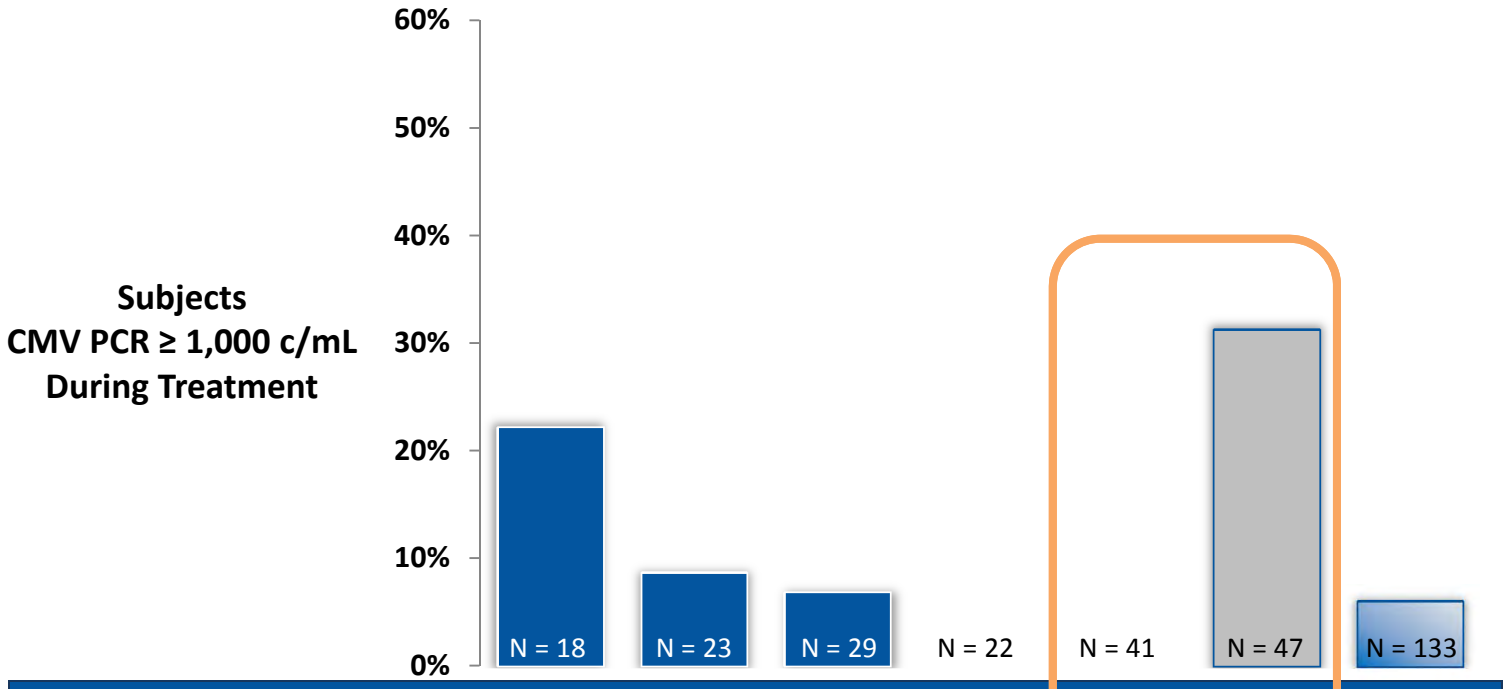
	40 mg QW	100 mg QW	200 mg QW	200 mg BIW	100 mg BIW	Placebo	All CMX001
CMV Infection	13 (52%)	6 (22%)	12 (31%)	7 (23%)	5 (10%)	22 (37%)	43 (25%)
p-value	**0.234**	**0.218**	**0.525**	**0.235**	**0.002**		**0.093**

Intent to Treat (ITT) population

Source: Data from Chimerix Study 201 presented at BMT Tandem, February 2012.

Study 201: Prevention of CMV PCR ≥ 1,000 copies/mL

Secondary Endpoint; Subjects CMV PCR- at First Day of Dosing



	40 mg QW	100 mg QW	200 mg QW	200 mg BIW	100 mg BIW	Placebo	All CMX001
Subjects CMV PCR ≥ 1,000 c/mL During Treatment	4 (22%)	2 (9%)	2 (7%)	0	0	15 (32%)	8 (6%)
p-value	**0.550**	**0.040**	**0.012**	**0.002**	**<0.001**		**<0.001**

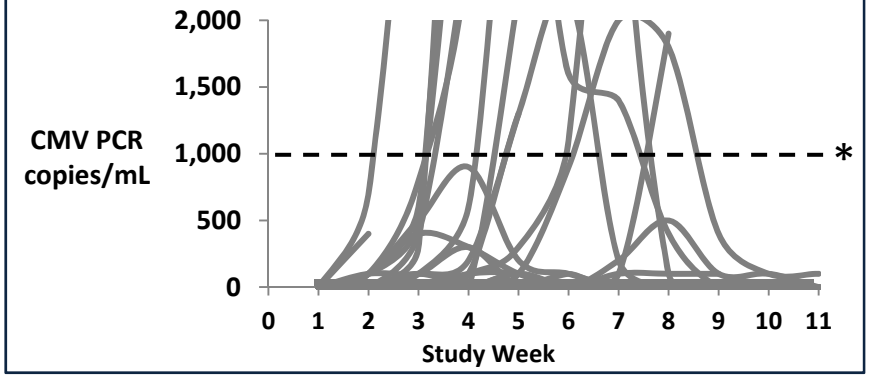
Source: Data from Chimerix Study 201 presented at BMT Tandem, February 2012.

Study 201: CMX001 Suppressed CMV Reactivation

Placebo

- N = 47
- 15/47 ≥ 1,000 c/mL

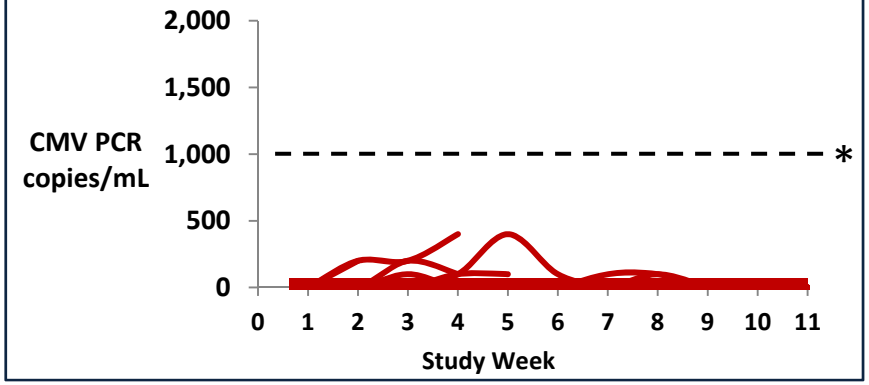
Placebo



CMX001 100 mg BIW

- N = 41
- 0/41 ≥ 1,000 c/mL
- 9/41 CMV PCR+

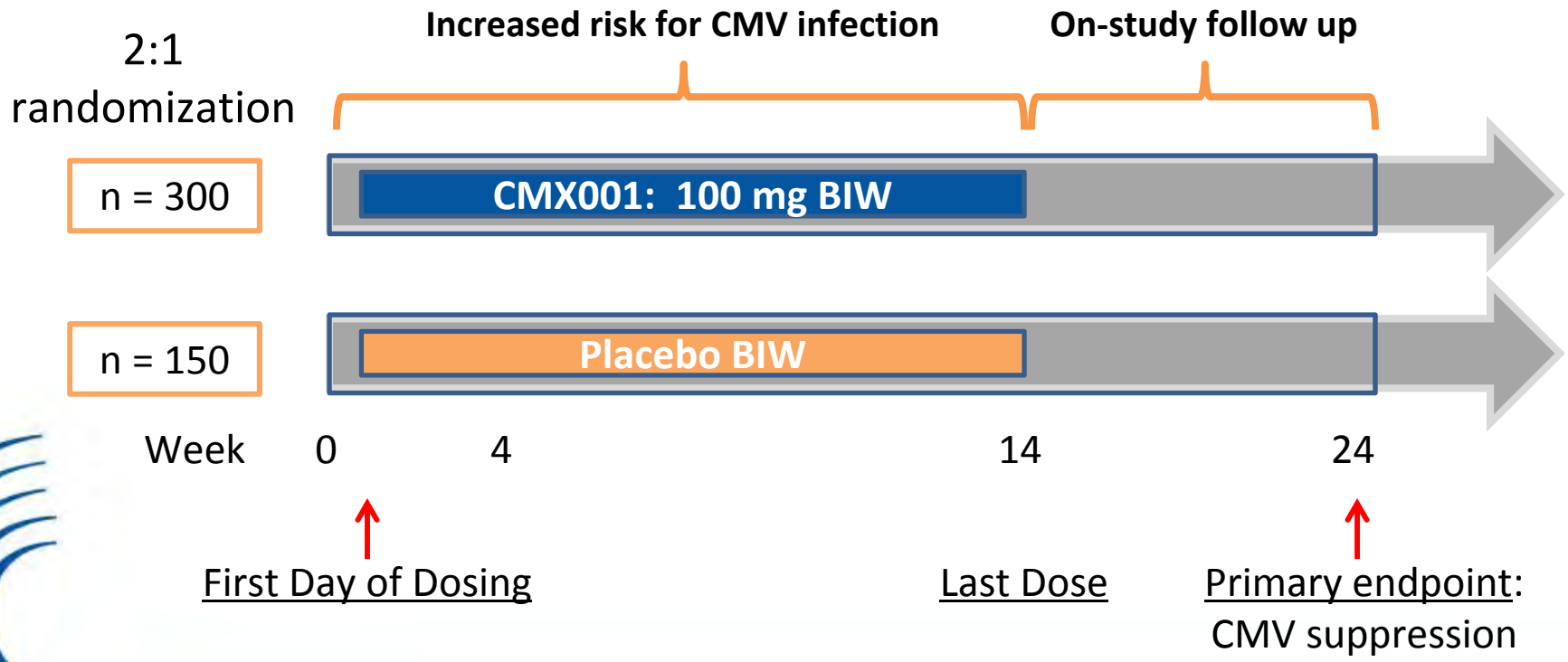
CMX001 100 mg BIW



*Represents clinically relevant threshold.
Subjects CMV negative at Baseline.
Source: Data from Chimerix Study 201 presented at BMT Tandem, February 2012.

SUPPRESS: Final Study Design

- **Population: High-risk HSCT CMV seropositive transplant recipients**
- **Primary endpoint: CMV prevention through Week 24**
- **Superiority design vs. placebo; no currently approved prevention for CMV**
- **Dosing to begin prior to engraftment**



Building a Unique Pipeline

- **Chimerix Chemical Library**
  - Purchased from the University of Michigan
  - 30+ years of work by a large group of chemists under Dr. Leroy Townsend, an internationally recognized medicinal chemist
- **~10,000 distinct compounds**
  - Heterocyclic ring systems with diverse nucleoside analogs
  - Approximately 3,500 distinct nucleoside analogs
  - Unique compound set that is different from what is found in combinatorial chemistry libraries
- **Initial screening complete for several indications**
- **Second generation phospholipid technology applicable to nucleosides and potentially other compound classes**

In Vitro HIV Activity for Lipid Derivatives of PMPG and PMPDAP

	PBMC (EC_{50}, nM)	Cytotoxicity (CC_{50}, nM)	Selectivity
HDP-(R)-PMPG	0.63 ± 0.17	>100	>159
15M-HDP-(R)-PMPG	10.33 ± 2.08	>100	>9.7
ODE-(R)-PMPG	3.5 ± 0.87	>100	>28
17M-ODE-(R)-PMPG	0.20 ± 0.07	>100	>500
HDP-(R)-PMPDAP	0.26 ± 0.13	>100	>385
15M-HDP-(R)-PMPDAP	1.27 ± 0.23	>100	>79
ODE-(R)-PMPDAP	0.27 ± 0.20	>100	>370
17M-ODE-(R)-PMPDAP	1.15 ± 0.23	>100	>87

Source: Ruiz et al. Poster #18 ICAR 2013

Conclusions

- **Alkoxyalkyl lipid ester strategy is a versatile approach to improving performance of acyclic nucleoside phosphonates**
- **Two lipid ester acyclic nucleoside phosphonate drugs are currently progressing in clinical trials (CMX001 and CMX157)**
- **Preclinical studies conducted with lipid-ANPs for other indications confirm general applicability of technology**

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