

Evaluation and Pharmacokinetics of the POM-L-BH DU-MP Prodrug

Against Varicella Zoster Virus and Herpes Simplex Virus 1 in vivo



Jennifer Moffat, Megan Lloyd



Uma Singh, David CK Chu, Y Kothapalli, V Annavarapu



Mihyung Kim

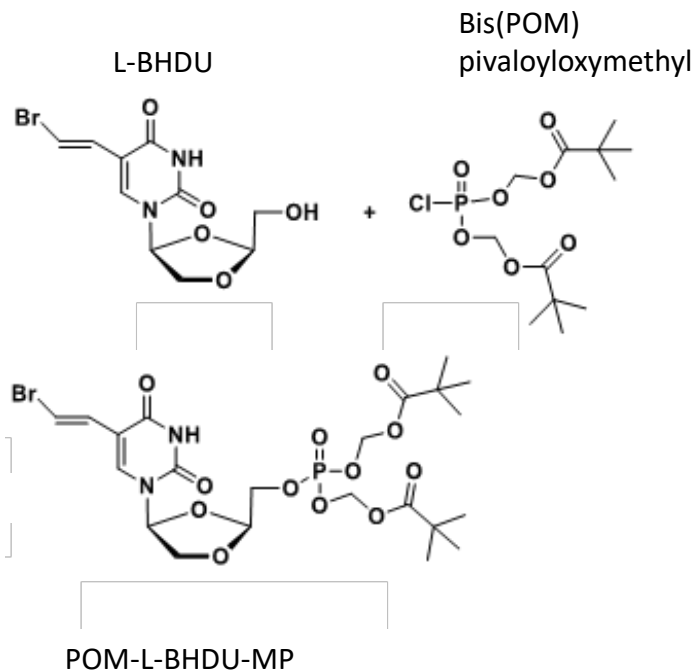
Topical therapies are needed for VZV & HSV

- Cold sores, genital lesions, and shingles are skin lesions
- Acyclovir & penciclovir are effective if given early
 - Tablets are common
 - Intravenous formulations are used in hospital
 - Topical acyclovir is less effective



POM-L-BHDU-MP

Lead Compound For topical and oral uses



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Article

Prodrug Strategies for the Development of β -L-5-((E)-2-Bromovinyl)-1-((2S,4S)-2-(hydroxymethyl)-1,3-(dioxolane-4-yl))uracil (L-BHDU) against Varicella Zoster Virus (VZV)

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Uma S. Singh,* Ananda K. Konreddy, Yugandhar Kothapalli, Dongmei Liu, Megan G. Lloyd, Vidya Annavarapu, Catherine A. White, Michael G. Bartlett, Jennifer F. Moffat, and Chung K. Chu*

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POM-L-BH DU-MP is highly potent in cells

	EC ₅₀ μM*	CC ₅₀ μM	SI
VZV	0.04	>100	>2500
HSV1	0.03		>3333
HSV2	7.0		>14

*Average of >5 assays

Performed by Dr. Megan Lloyd

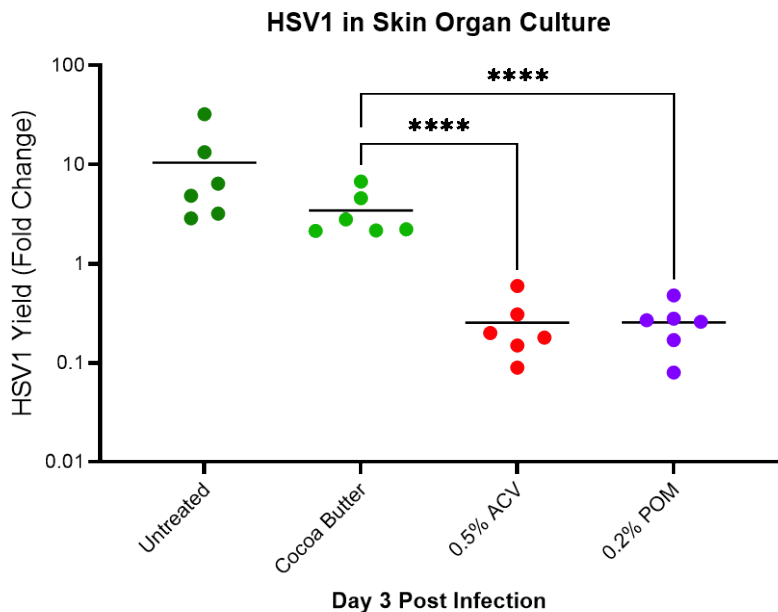
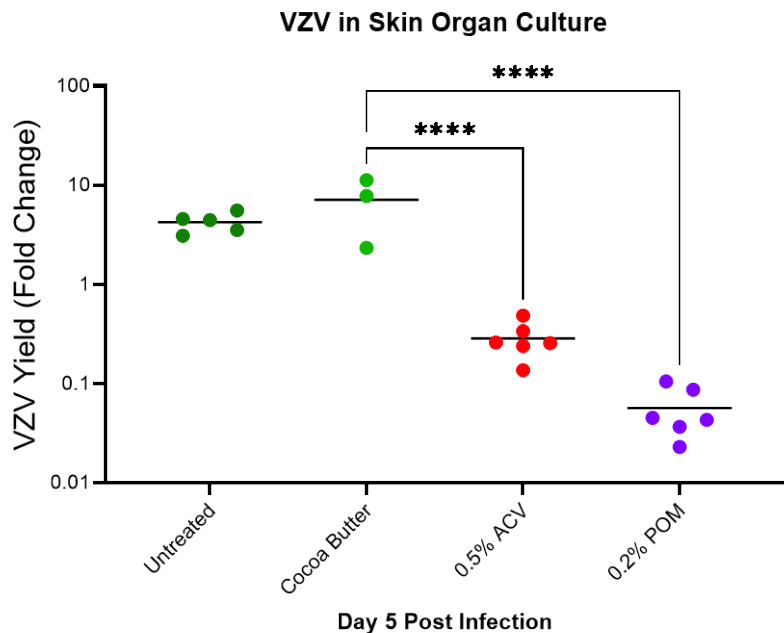
- **Evaluation in cell-based assays**

- Viruses express firefly luciferase reporter genes
- Confluent ARPE-19 cells in 96-well format
- IVIS scan 72 HPI (VZV) or 24 HPI (HSV) to measure virus yield

- **Cytotoxicity assays**

- Neutral Red Dye Uptake
- Concentration range 0-100 μM
- Absorbance (550 nm) after 72 HPI

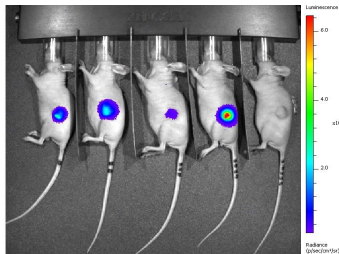
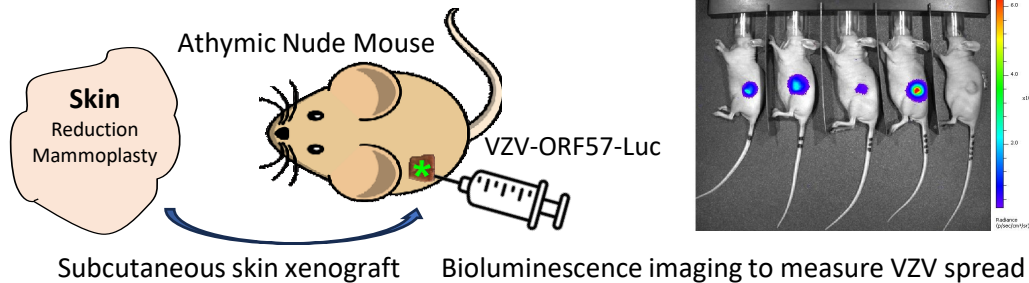
POM-L-BH DU-MP is effective topically in skin



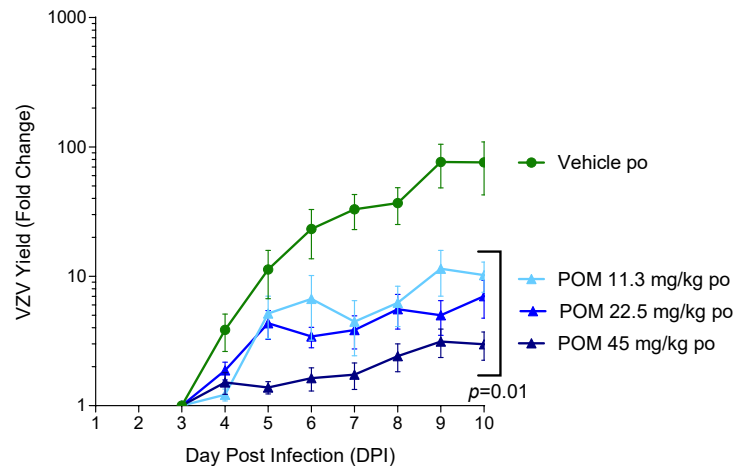
**** $p < 0.001$ by 1-way ANOVA. See PMID: 32878893 for methods. Performed by Dr. Megan Lloyd.

POM-L-BH DU-MP is effective orally in mice

NuSkin Mouse Model for VZV



POM-L-BH DU-MP prevents VZV spread in NuSkin mice



POM-L-BH DU-MP was effective via the oral route. Antiviral effects were dose-dependent. The mice tolerated the compound well (not shown).

POM-L-BH DU-MP NuSkin Mouse Assay

N	Compound	Dose (mg/kg)	Tx Schedule Days 3-9 QD
10	Vehicle Cremophor-DMSO-Saline (CDS)	0	Oral
10	L-BH DU-POM	45	
10		22.5	
10		11.3	

Murine Cutaneous Flank Model for HSV1

Evaluation of POM-L-BH DU-MP in vivo



BALB/c Mouse
male and female



Pluck fur
Prick skin
Inoculate HSV1
Treat with antivirals

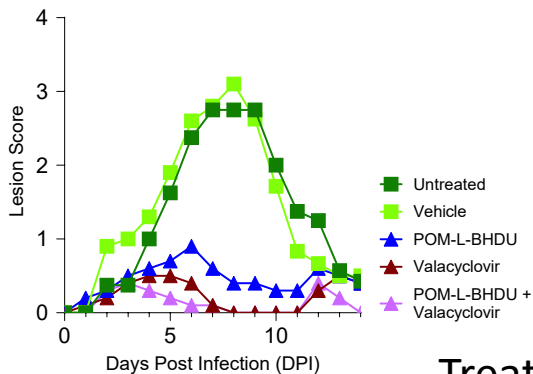


Lesion score
Body weight
Mortality

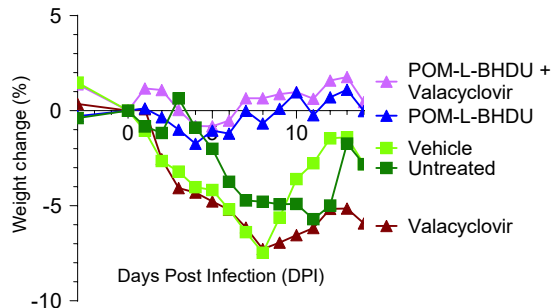
N	HSV 1	Group	Treatment	Tx route	Tx Schedule
3	No	Treatment control	Vehicle	sc	BID Days 0-7
3		POM control	22.5 mg/kg/dose	sc	BID Days 0-7
10	Yes	Virus control	None		
10		Vehicle (CDS)	Vehicle	sc	BID Days 0-7
10		VACV	1 mg/mL	Drinking water	Ad libidum
10		POM	22.5 mg/kg/dose	sc	BID Days 0-7
10		VACV + POM	1 mg/mL + 22.5 mg/kg/dose	Drinking water and sc	Ad libidum and BID Days 0-7

POM-L-BHDU-MP prevents HSV1 disease in mice

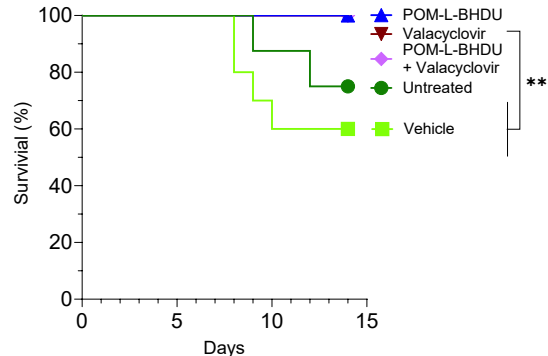
POM-L-BHDU-MP and VACV protect against lesions



POM-L-BHDU-MP protects against weight loss



POM-L-BHDU-MP and VACV protect against mortality



Treated mouse

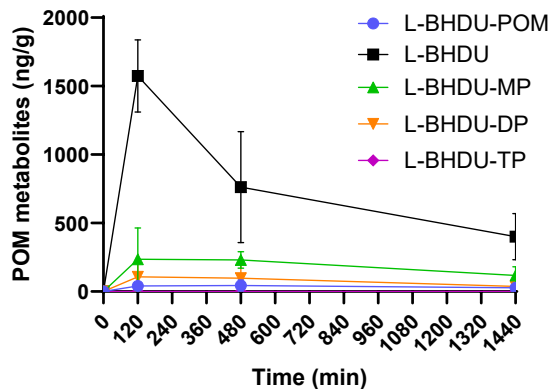


Untreated mouse

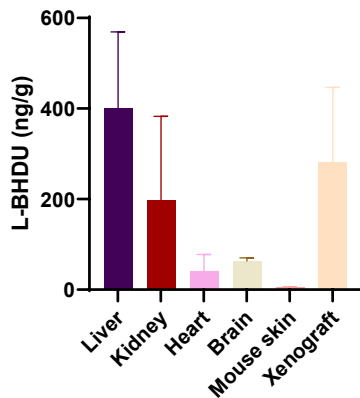


POM-L-BHDU-MP Pharmacokinetics & Distribution

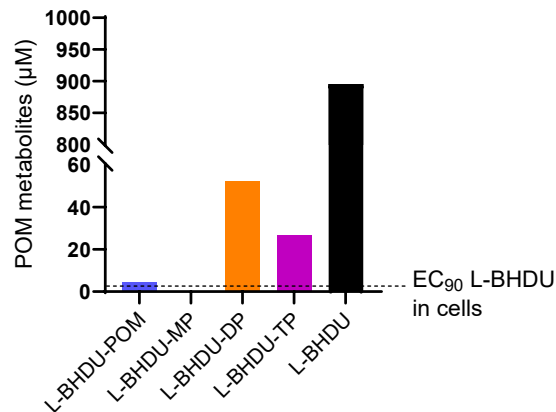
POM-L-BHDU-MP metabolites in Liver



POM-L-BHDU-MP converts to L-BHDU in vivo
Concentration at 1440 min



L-BHDU exceeds EC_{90} in skin xenografts



- NuSkin mice with VZV-infected skin xenografts, N=4
- 22.5 mg/kg POM-L-BHDU-MP po
- Blood and organs were harvested at timed intervals
- LC-MS/MS by Aragen Life Sciences (Hyderabad, India)
- Data analyzed by Dr. Mihyung Kim

POM-L-BH DU-MP Summary

- Highly potent (30-40 nM) against VZV and HSV1, not HSV2
- Effective topically in human skin at 0.2%
- Effective orally in mice
- Well tolerated in mice
- Long half-life (5.6 h) and distribution to skin and brain

POM-L-BH DU-MP prodrug is a promising lead compound for treating VZV and HSV1 skin lesions.

It wouldn't be possible without....



Megan Lloyd
Research Associate



Pradeep Dumpala
Lab Animal Resources



Gregory Baum
Syracuse Plastic
Surgery

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