PBPK Modeling of Locally Acting Drug Products: Identifying and Addressing Factors Affecting Extrapolation

Dr. Jessica Spires

May 20, 2024

Active Scientific Collaborations Between Simulations Plus and FDA

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy,[1] Ming-Liang Tan,[1] Andrew Babiskin,[1,2] and Liang Zhao[1]

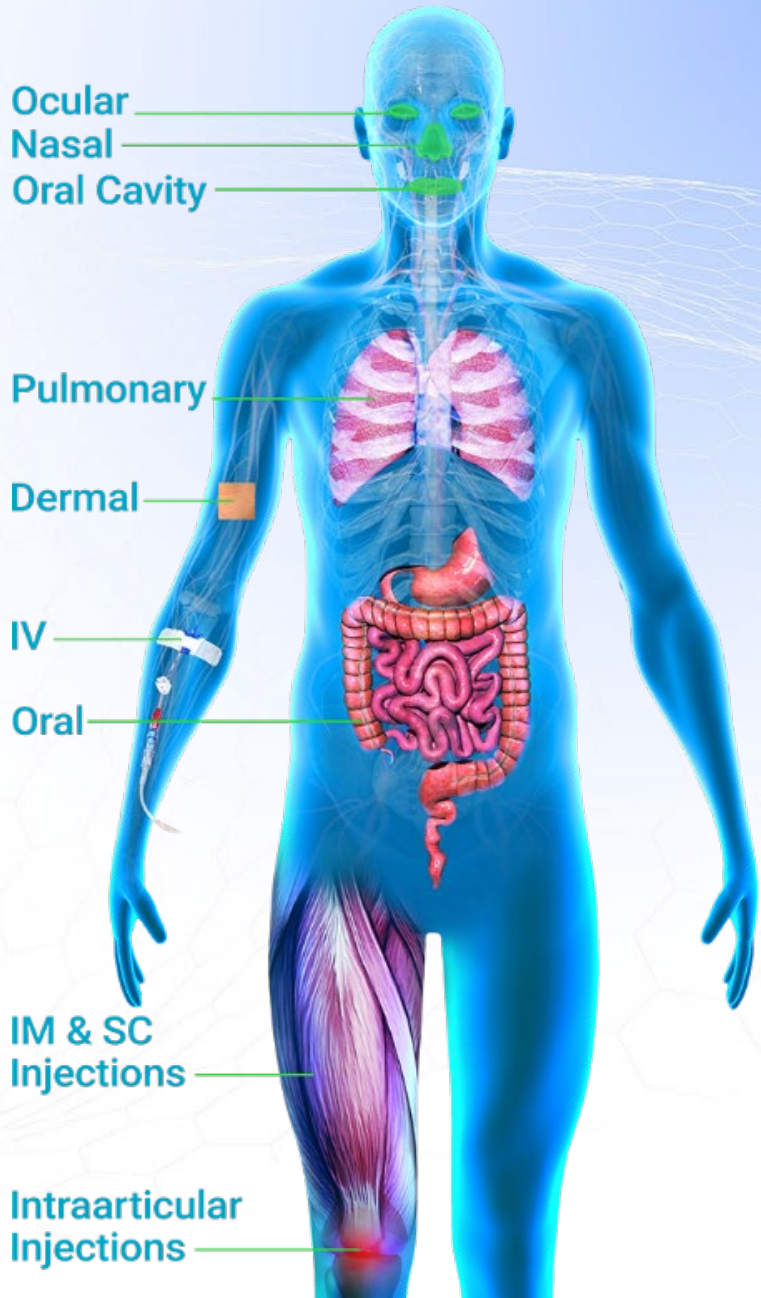
Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation

Maxime Le Merdy[1] · Farah AlQaraghuli[1] · Ming-Liang Tan[2] · Ross Walenga[2] · Andrew Babiskin[2] · Liang Zhao[2] · Viera Lukacova[1]

Predicting Human Dermal Drug Concentrations Using PBPK Modeling and Simulation: Clobetasol Propionate Case Study

William W. van Osdol[1] · Jasmina Novakovic[1] · Maxime Le Merdy[1] · Eleftheria Tsakalozou[2] · Priyanka Ghosh[2] · Jessica Spires[1] · Viera Lukacova[1]

- FDA: Ocular model extensions
- FDA: Oral cavity model extensions
- FDA: Pulmonary model extensions
- FDA: Dermal model extensions
- FDA: ACAT™ – GI Diseases – Local acting drugs
- FDA: ACAT™ - Modified release
- FDA: Virtual BE trial workflows
- FDA: Long-acting injection model extensions



Common Challenges in Modeling Non-Oral Routes of Administration

- Extrapolating from measurements and *in vitro* data to generate reliable *in vivo* predictions
  - What are the best *in vitro* assays to perform? What are the most important measurements to take?
  - How do parameters need to be adjusted when used *in vivo*?
  - Are there new *in vitro* assays or measurements that will be more useful?

- Extrapolating between species
  - How well do we understand differences between absorption, distribution, and clearance at local sites of application?
  - How well do we understand local PD differences between species?

- How do we know when models we have developed can be extended to new scenarios? Do we know what adjustments need to be made?

Inter-species differences in drug effects on intra-ocular pressure

- Glaucoma elevates the intra-ocular pressure (IOP), leading to vision loss
- Compounds such as latanoprost can be used to modify the aqueous humour (AH) dynamic to slow or prevent this vision loss
- Rabbits are the typical preclinical model to study ocular pharmacokinetics, but may not be sensitive to a drug's effect, limiting PD extrapolation
- Therefore, scaling of PK and PD may require multiple species for these drug products

Latanoprost effects differ between species

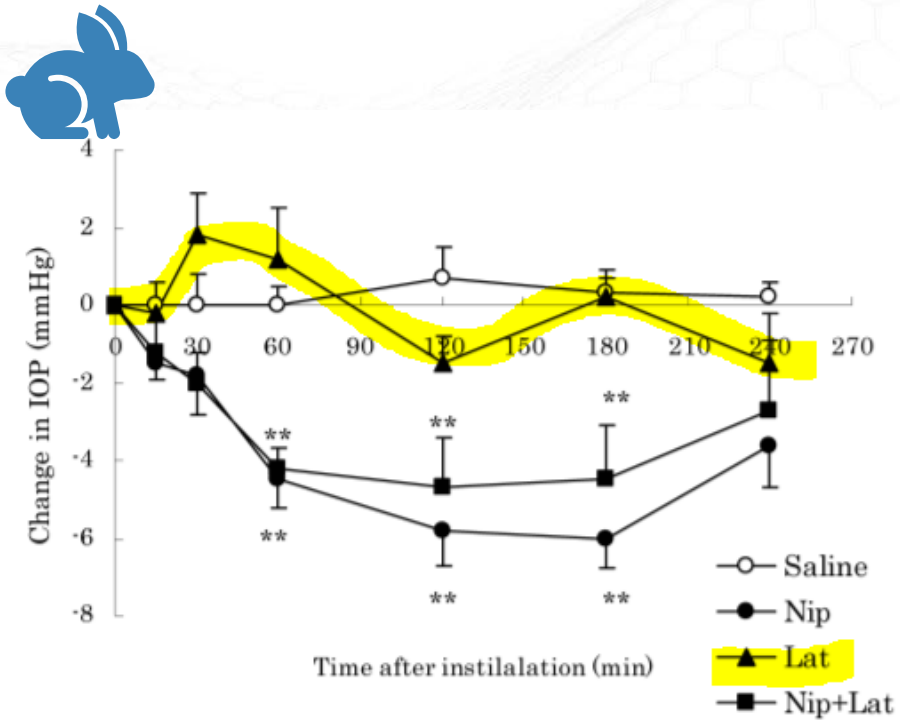
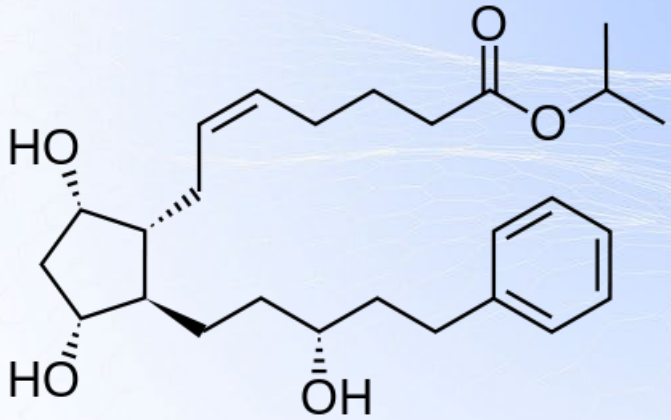


Fig. 1. Effects of Nipradilol, Latanoprost, and Their Combination in Ocular Normotensive Rabbits

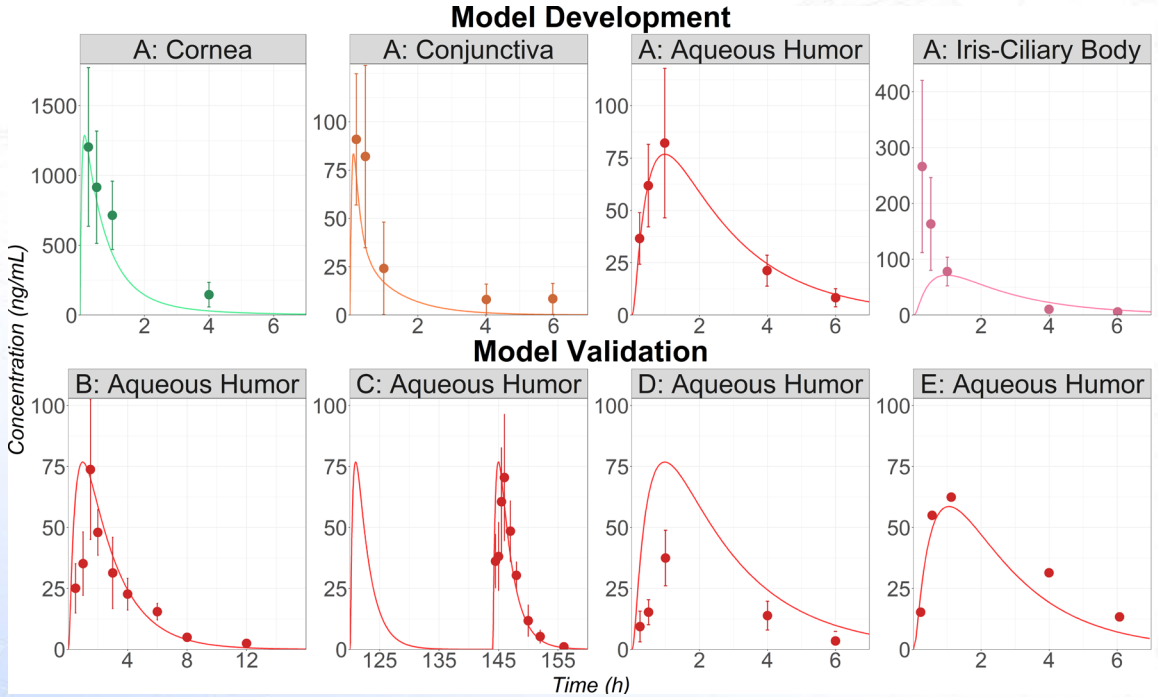


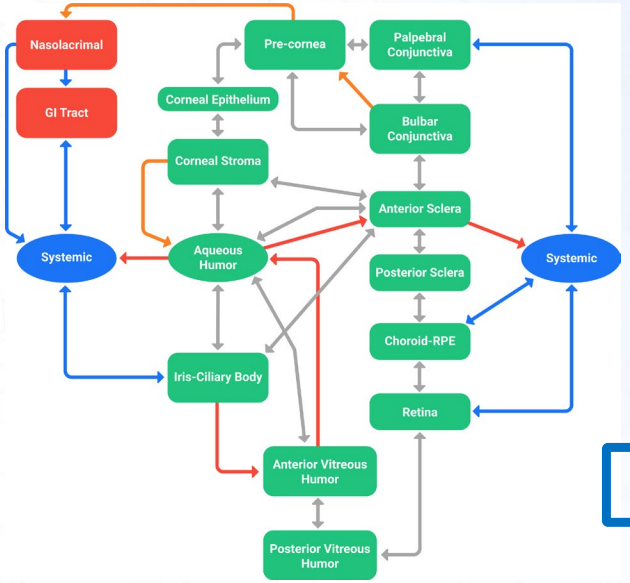
Animal Pharmacodynamics

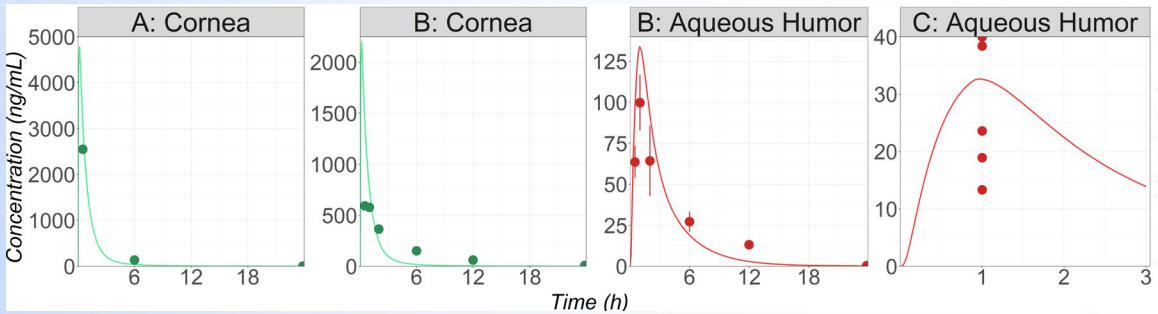
Latanoprost has been shown to lower IOP in primates, with minimal acute irritation of the eye. Results from studies show large species differences in pharmacologic responses which probably depend on the variation in prostaglandin receptor distribution between species.

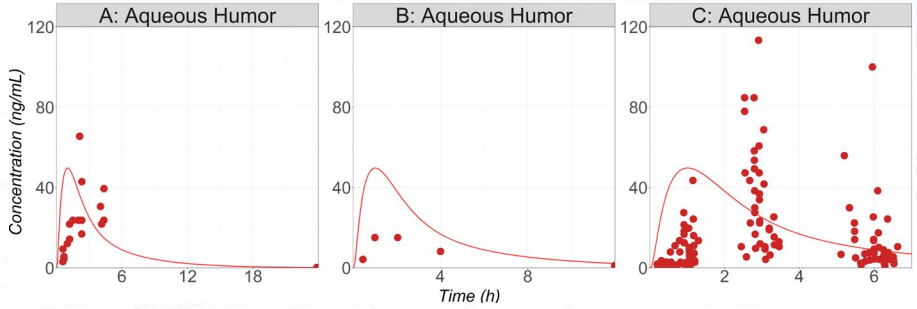
Monkey is the species of choice to investigate latanoprost mediated IOP reduction

Ocular PK models of latanoprost

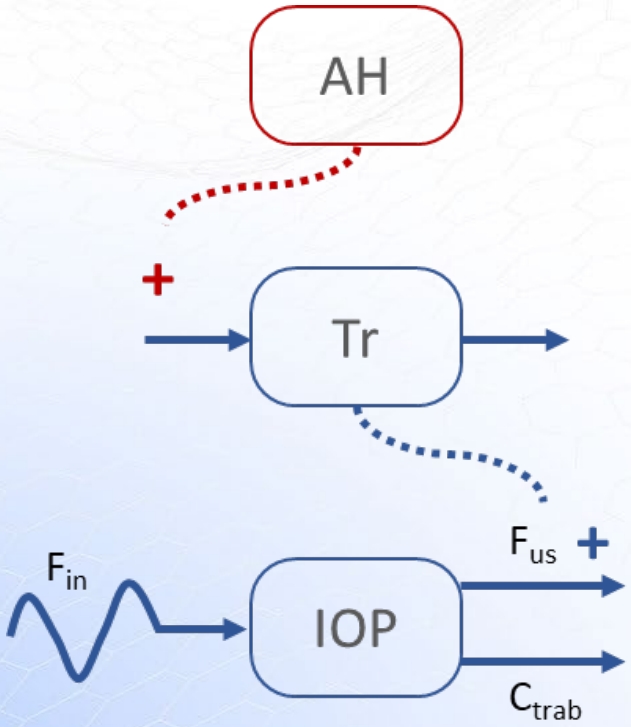


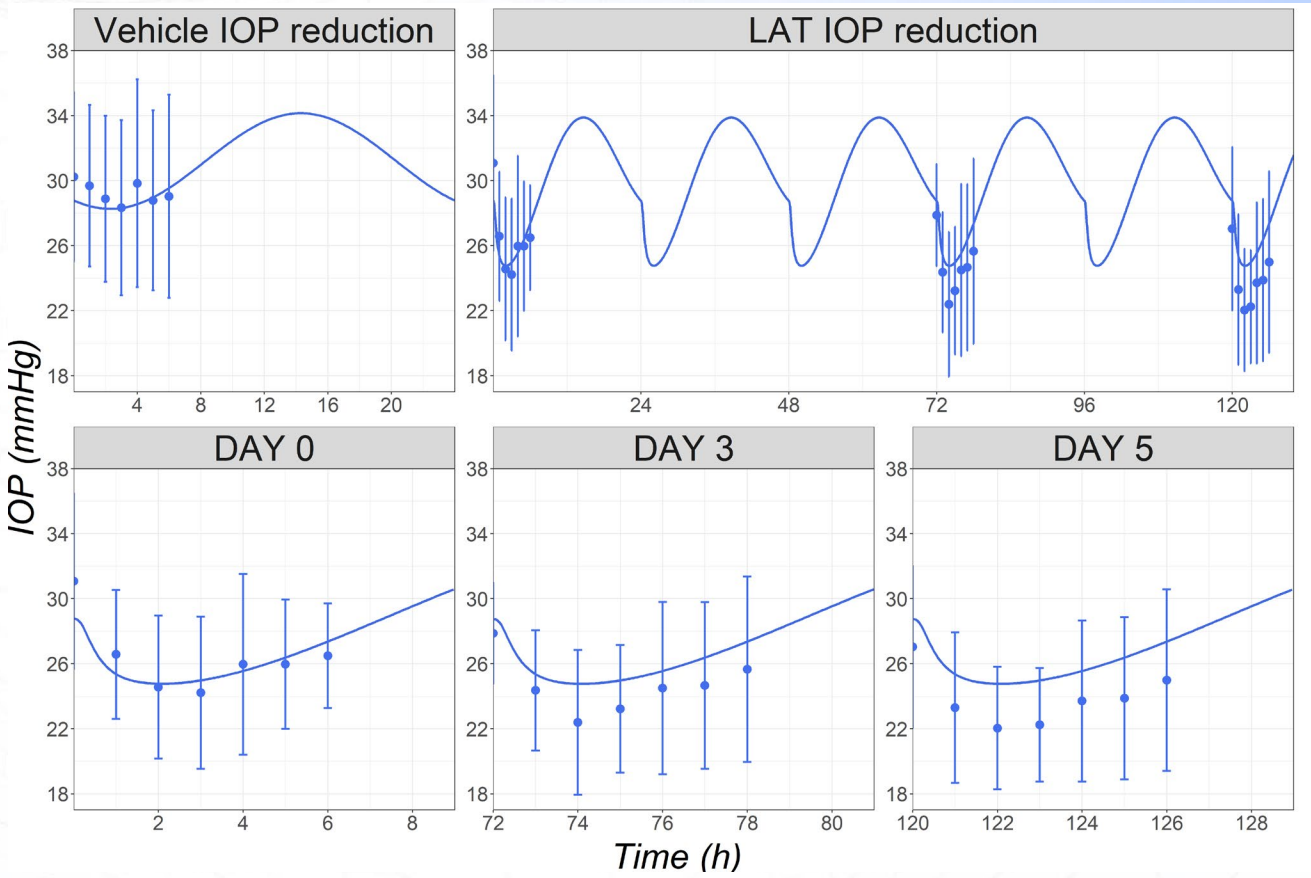






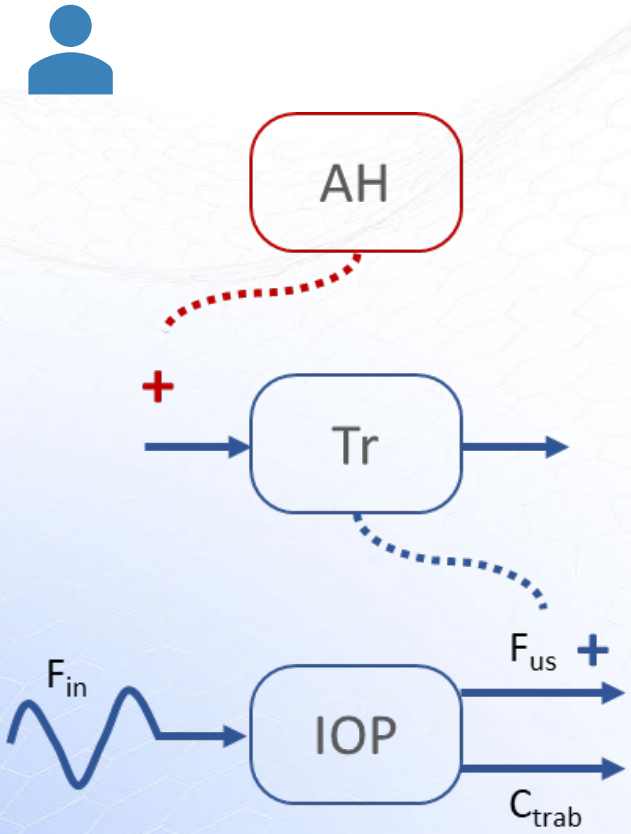
Monkey IOP model of latanoprost

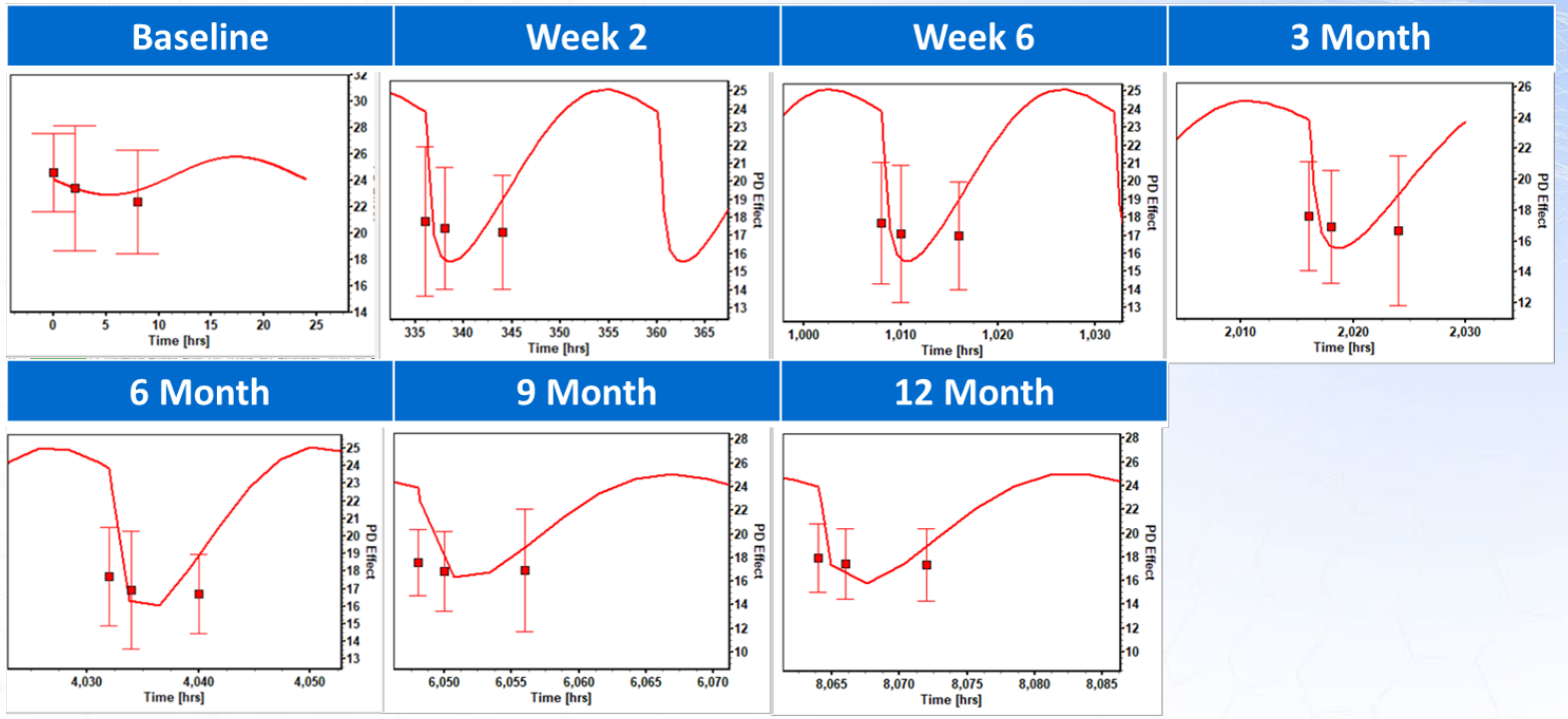




Emax	EC50
2	0.01 ng/mL

Human IOP model of latanoprost





Emax	EC50
6	0.01 ng/mL

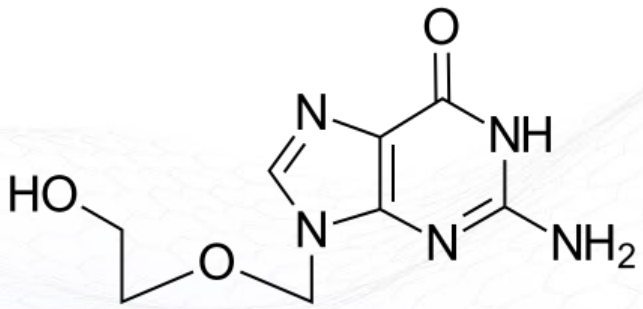
General concerns for modeling of locally acting drug products

- What is the best pre-clinical species for modeling PK for my compound at my site of action?
- What is the best pre-clinical species for modeling PD for my compound at my site of action?
- Is any further adjustment in PK or PD needed when moving from pre-clinical species to human? How do we know whether it is needed?

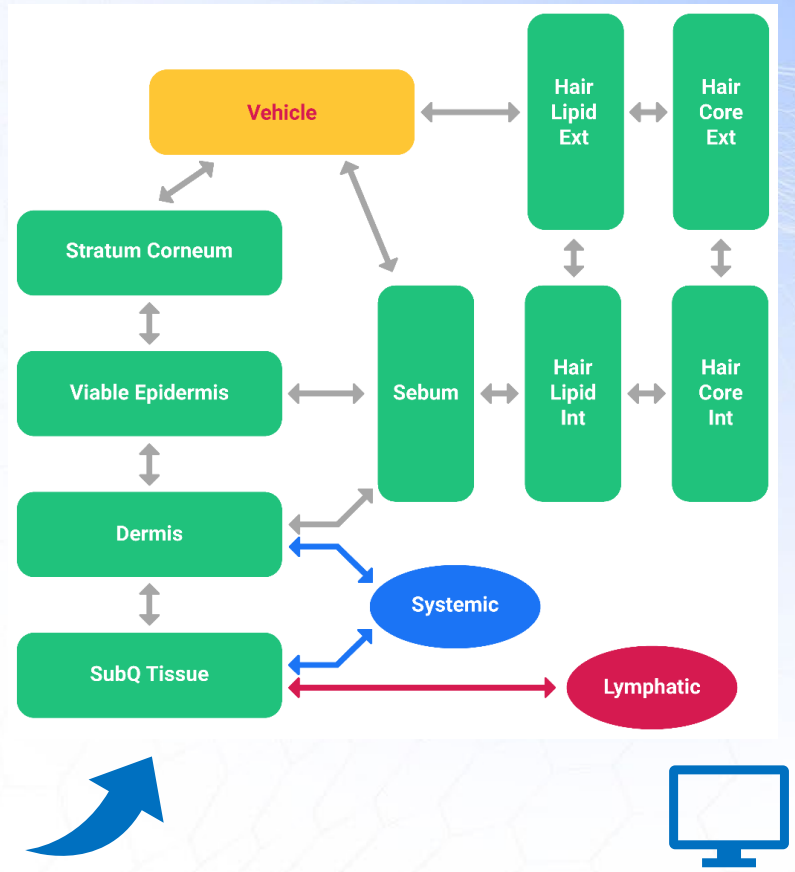
Modeling of topical drug products

- Topically applied drug products are often very complex, and poorly characterized
- Permeation through the skin is affected by many different factors
  - Both *in vitro* and *in vivo* permeation can vary significantly according to experimental conditions
- Critical vehicle properties may impact absorption into the skin: solubility in the product, viscosity, volatility, excipient effects, etc.
- Acyclovir is an antiviral drug used topically to treat symptoms of chickenpox, herpes, and similar infections
- We use IVPT data to characterize permeation of acyclovir from Zovirax cream, and *in vivo* tape stripping data to characterize the *in vivo* absorption

Developing a dermal model of acyclovir



Parameter	Value	Units	Source / Derivation
ACY content	50	mg/g cream	Zovirax US prescribing information (2014)
φ^{disp}	0.282		Calculated from the composition[A]
Cont phase solubility	2.88	mg/mL	Diez-Sales et al. J Pharm Sci 94, 1039–1047 (2005).
Cont phase/water partition coeff, $K^{cont,w}$	2.62		Ratio of continuous phase and water solubilities
Disp phase/water partition coeff, $K^{disp,w}$	3.98E-02		Calculated from ADMET Predictor 10.3 Log $K_{o,w}$*
Effective diffusivity in continuous phase, D^{eff}	3.41E-08	cm^2/s	Higuchi analysis of SN Murthy's in vitro release data[B,C]
Diffusivity in the dispersed phase, D^{disp}	1.11E-08	"	Extrapolated from ferrocene cyclic voltammetry data[D]
Dispersed phase droplet radius, r^{disp}	1	µm	A nominal value for emulsions
ACY particle radius	1.88	µm	One half d_{50} from SN Murthy's particle size data (d_{10} = 2.07 mm, d_{90} = 19 mm)[B]
SC permeability, P^{SC}	5.37E-09	cm/s	Robinson model (Wilschut et al, Chemosphere 30, 1275–1296 (1995).
VE permeability, P^{VE}	2.48E-04	"	Kretsos et al. Int J Pharm 346, 64–79 (2008).
Dermis permeability, P^{De}	2.85E-05	"	"
Sebum / hair permeability, p^{Sebum}	8.865e-10	"	$D^{Sebum} = D^{disp}$, $K^{Sebum,w}$ = 1.04e-2[H] with P^{Sebum} calculated via GastroPlus 9.8.3
Fraction bound in SC	0.215		Equilibrium keratin binding model[E,F,G]
Fraction bound to protein and lipid in VE & dermis	0.145		Bound fraction in skin (1 - $f_{u,skin}$), Lukačova Method, GastroPlus 9.8.3



Zovirax Cream US	
Hydrophilic (% w/w)	**Lipo- / Amphiphilic (% w/w)**
Water (29%)	Mineral oil (5%)
Propylene Glycol (40%)	White Petrolatum (12.5%)
Acyclovir (5%)	Cetostearyl OH (6.75%)
	Na·Dodecyl Sulfate (0.75%)
	PEG-PPG-PEG (1%)

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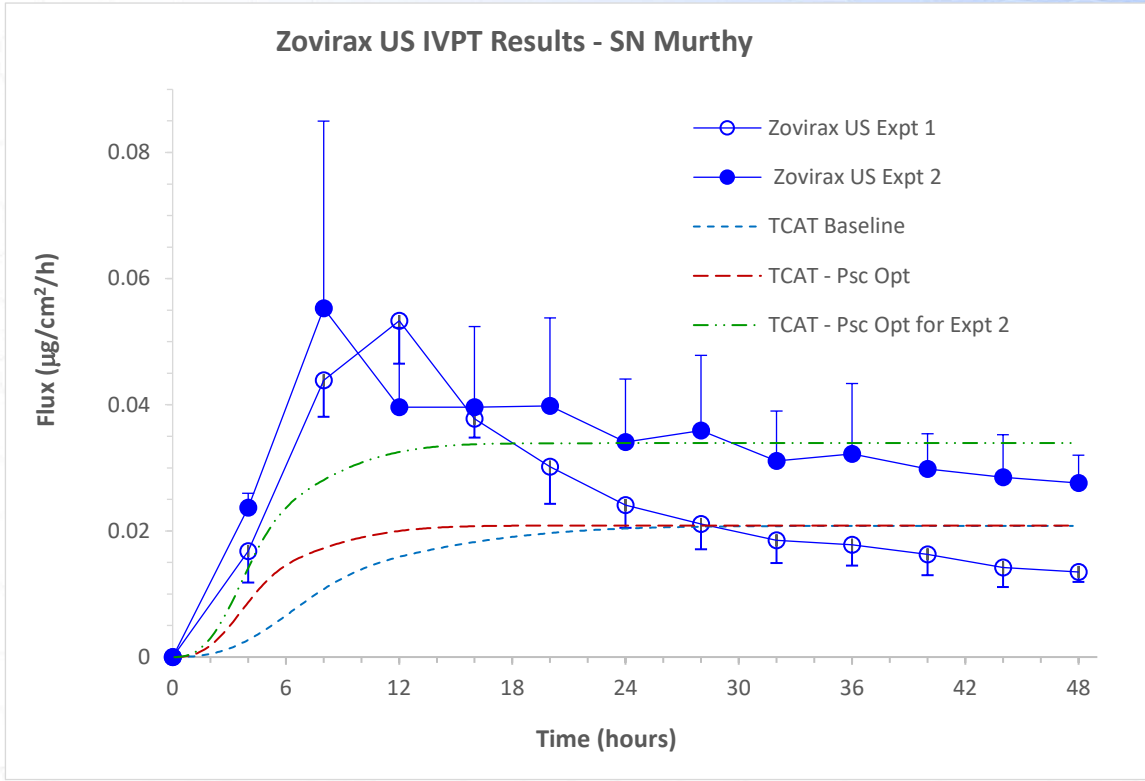
Modeling *in vitro* permeation of acyclovir

- We used published IVPT data for Zovirax cream to adjust stratum corneum permeability (P^{SC}) through the diffusivity (D^{SC}) and partition coefficient ($K^{SC/w}$)

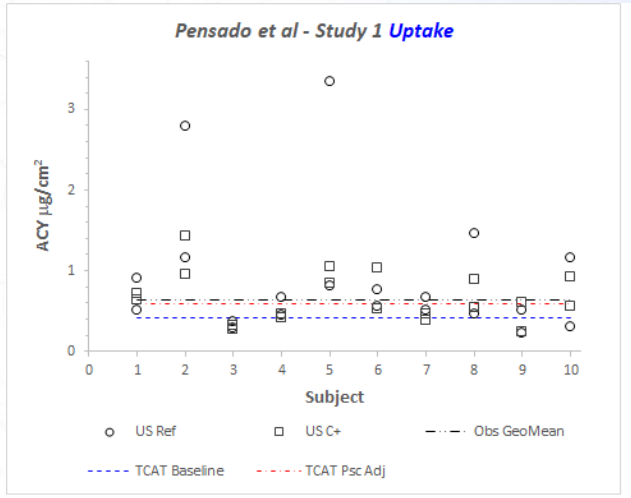
Model	D^{SC} (cm^2/s)	$K^{SC/w}$	P^{SC}(cm^2/s)
TCAT Baseline	1.01e-11	0.658	5.1e-9
TCAT – Psc Opt	1.82e-11	0.366	5.1e-9
TCAT – PSC Opt for Expt 2	1.82e-11	0.585	8.2e-9

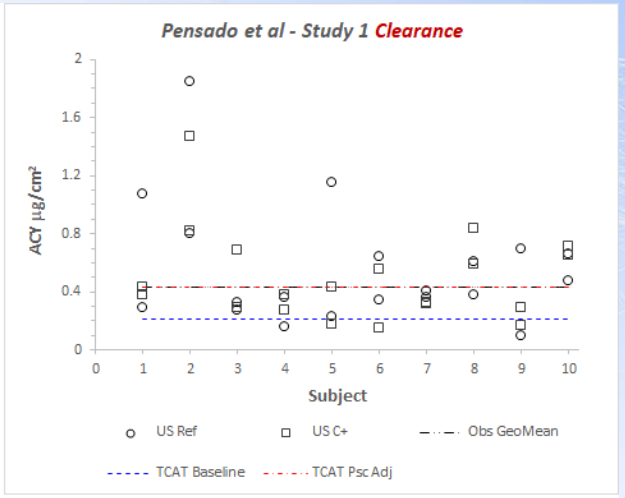


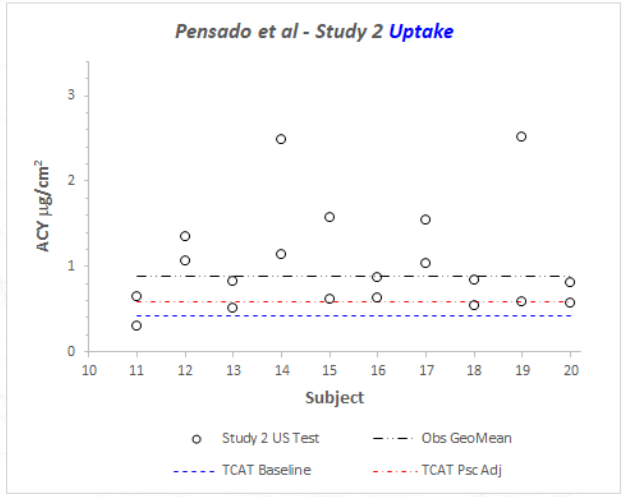
Modeling *in vivo* permeation of acyclovir

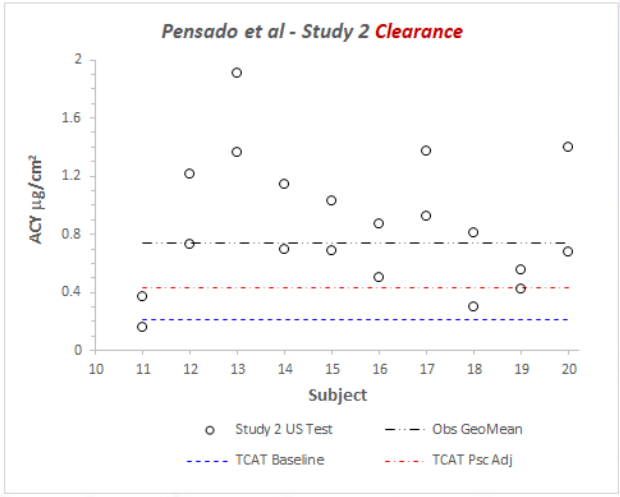
- Next, we applied the model to an *in vivo* tape stripping study
- We had to change D^{SC} and $K^{SC/w}$ in the opposite direction for the *in vivo* data

Model	D^{SC} (cm^2/s)	$K^{SC/w}$	P^{SC}(cm^2/s)
TCAT Baseline	1.01e-11	0.658	5.1e-9
TCAT – Psc Adj	5.61e-12	1.18	5.1e-9









General concerns for modeling of locally acting drug products

- How well do I understand my formulation? Do I know what its critical attributes are? Can I measure or calculate these?
- What can my *in vitro* data tell me about local PK at my site of action?
- What adjustments do I need to make when moving to models of *in vivo* PK at my site of action?

Where would we like to see improvements?

- Better understanding of inter-species differences at local sites of action
- Better understanding of what measurements and *in vitro* assays are most important in characterizing locally acting drug products and disposition at local sites of action
- Better understanding of complex dosage forms used in locally acting drug products

Ocular model citations

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Thank you!

Simulations Plus, Inc.

- Farah AlQaraghuli
- Viera Lukacova
- Maxime le Merdy
- Jasmina Novakovic
- Bill van Osdol
- Sandra Suarez-Sharp

FDA

- Priyanka Ghosh
- Andre O'Reilly
- Mingliang Tan
- Eleftheria Tsakalozou

Funding for this project was made possible, in part, by the US FDA through grants 1U01FD006927, 1U01FD006526, and 1U01FD007320. Views expressed here do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices or organizations imply endorsement by the United States Government.