Modeling and Simulation for Determination of the Therapeutic Window of MK-2295: a TRPV1 Antagonist

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Outline

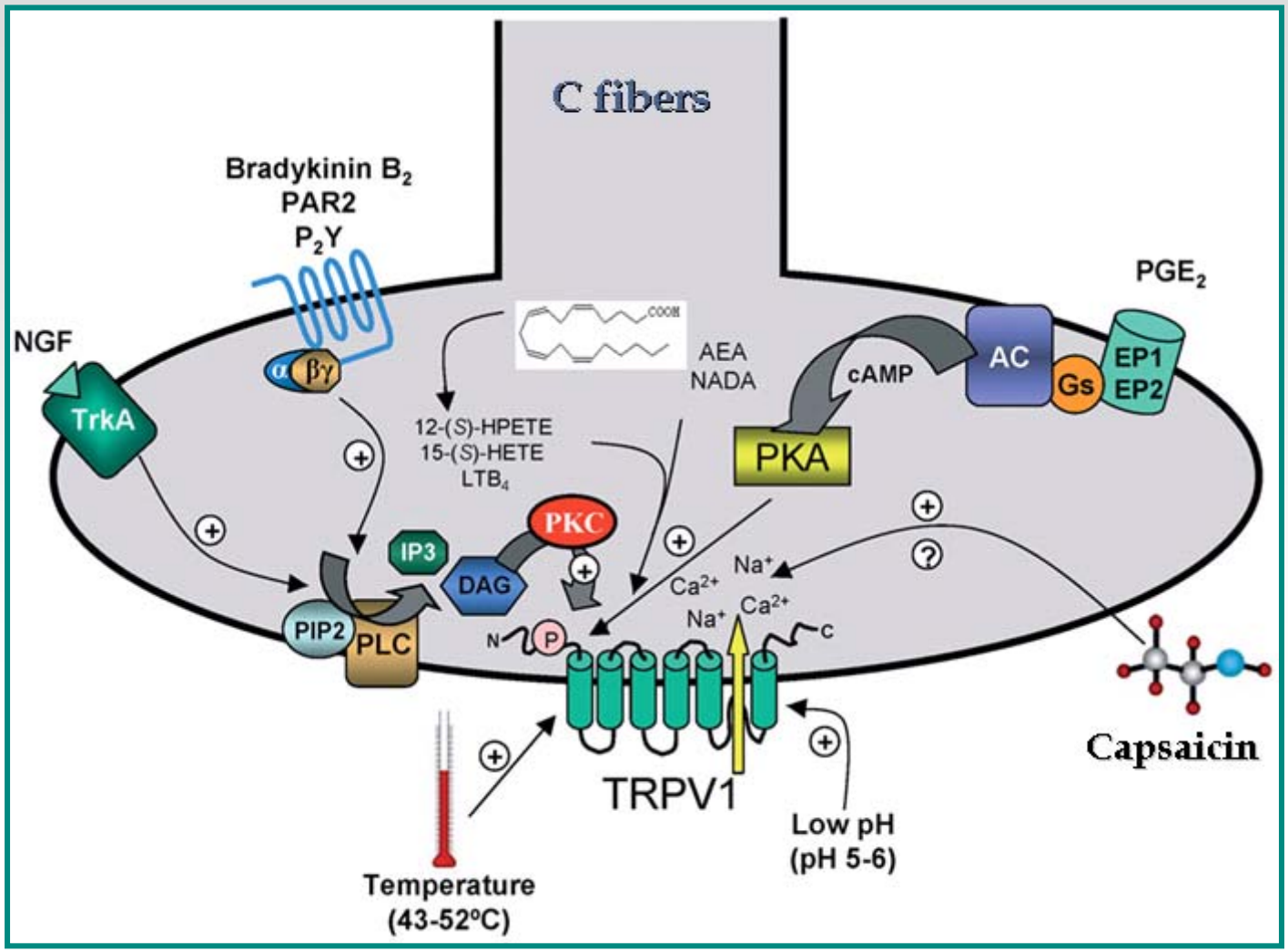
The Mechanism of TRPV1 Antagonism

One molecule, many models

Consolidation of understanding

Summary

TRPV1 is a Polymodal Nociceptor



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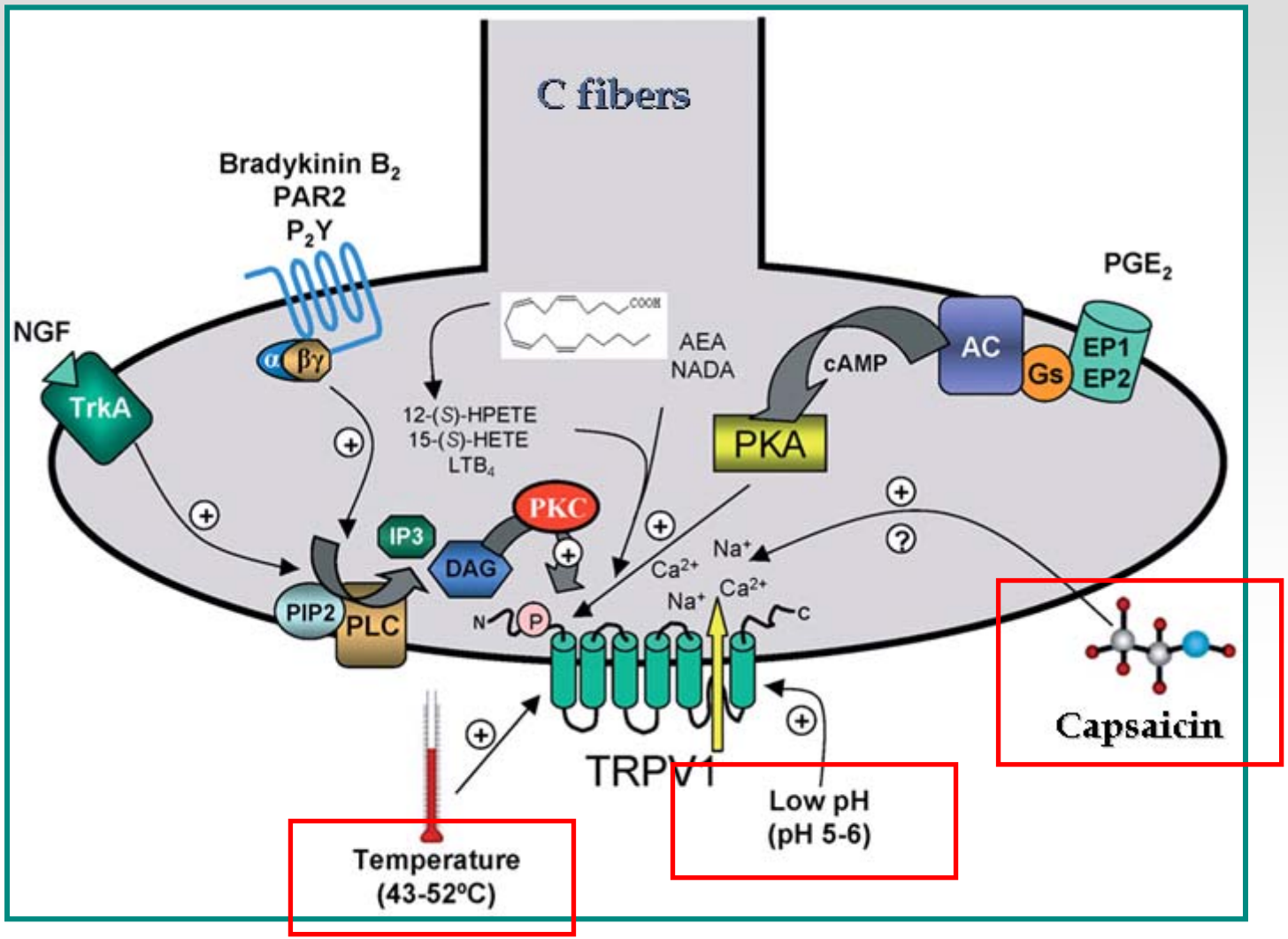


One Molecule, Many Models

Capsaicin induced dermal vasodilation (CIDV)

Core Body Temperature

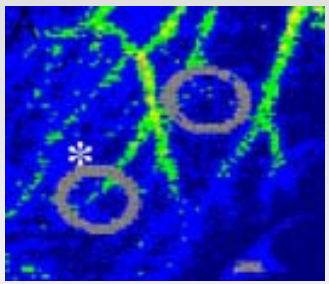
Warmth Sensation

Hand Withdrawal Time

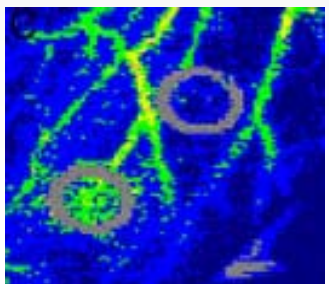
Hot Water Sipping

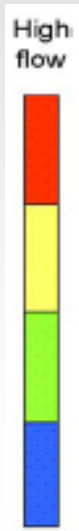
Capsaicin-Induced Dermal Vasodilation (CIDV) Model

Rhesus monkeys

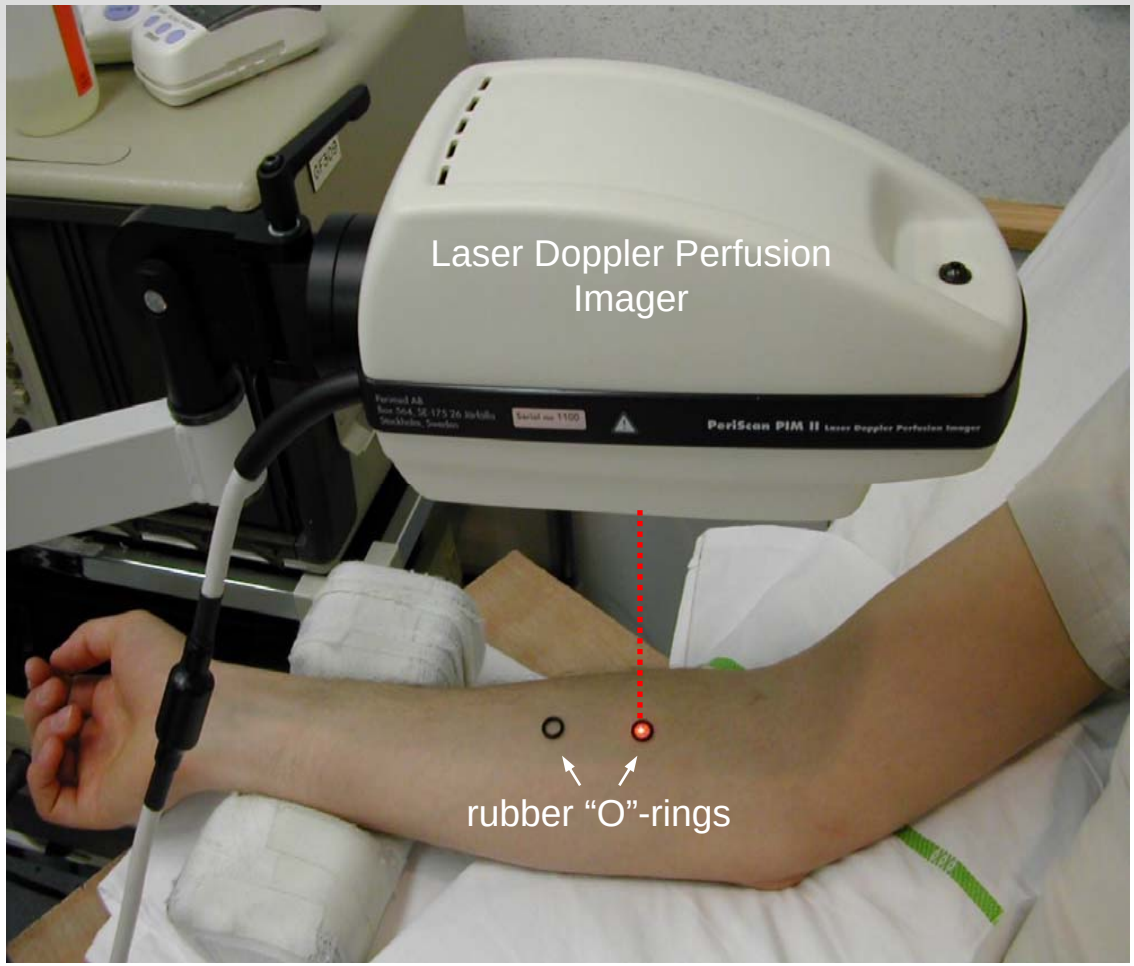


Capsaicin

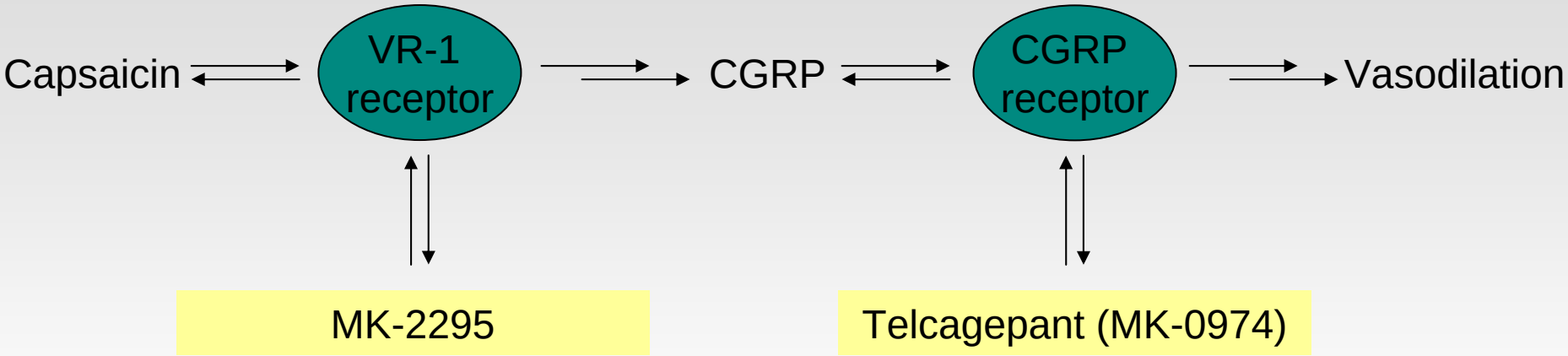




Hershey et al., 2005



Capsaicin-Induced Dermal Vasodilation (CIDV) Model



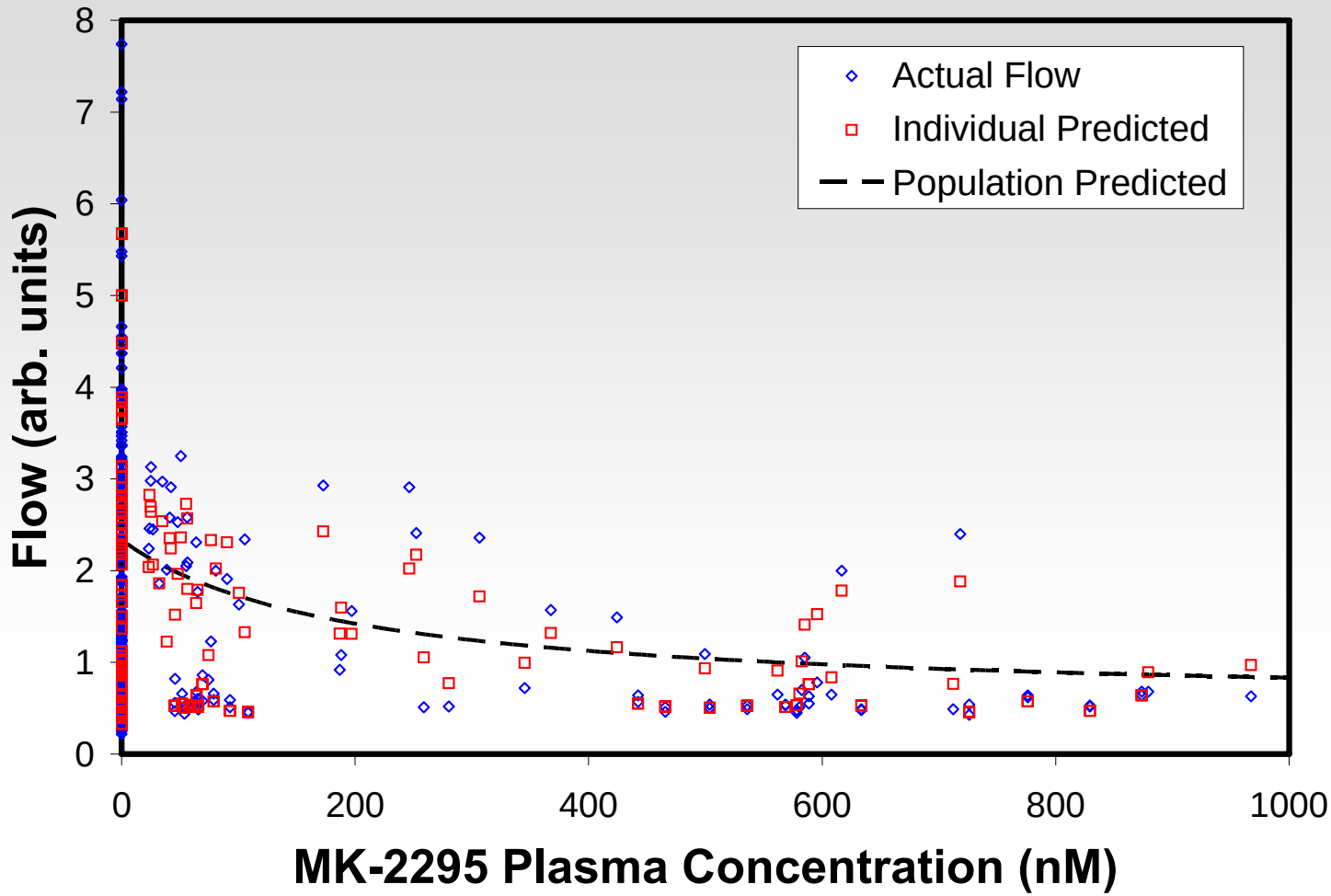
- The mechanisms of drugs/receptors are competitive inhibition.
- Double right arrows indicate the multiple steps between VR-1 binding capsaicin and CGRP release and also multiple steps between CGRP binding its receptor and vasodilation.

Capsaicin-Induced Dermal Vasodilation (CIDV) Model

$$F = E_0 + \frac{E_{\max,caps} D_{caps}}{D_{caps} + ED_{50,caps} + \frac{ED_{50,caps}}{EC_{50,MK-2295}} C_{MK-2295}} \left(1 - \frac{E_{\max,CGRP} C_{MK-0974}}{C_{MK-0974} + EC_{50,MK-0974}}\right)$$

Parameter	Parameter Estimate	% RSE for Parameter	ω Estimate	% RSE for ω Estimate
E_0 (arb)	0.544	4.17	0.0190	41.2
$E_{max,caps}$ (arb)	2.56	18.4	0.257	49.8
$E_{max,CGRP}$ (fraction)	0.921	2.76	NA	NA
$ED_{50,\ caps}$	430	46.5	3.57	44.5
$EC_{50,\ MK\text{-}2295}$	57.9	35.2	NA	NA
$EC_{50,\ MK\text{-}0974}$	101	37.3	NA	NA
$\Delta E_{0,\ pilot}$	0.416	11.2	NA	NA
$\Delta E_{0,\ 0974}$	-0.115	21.8	NA	NA
Proportional residual Error	0.0678	10.5		

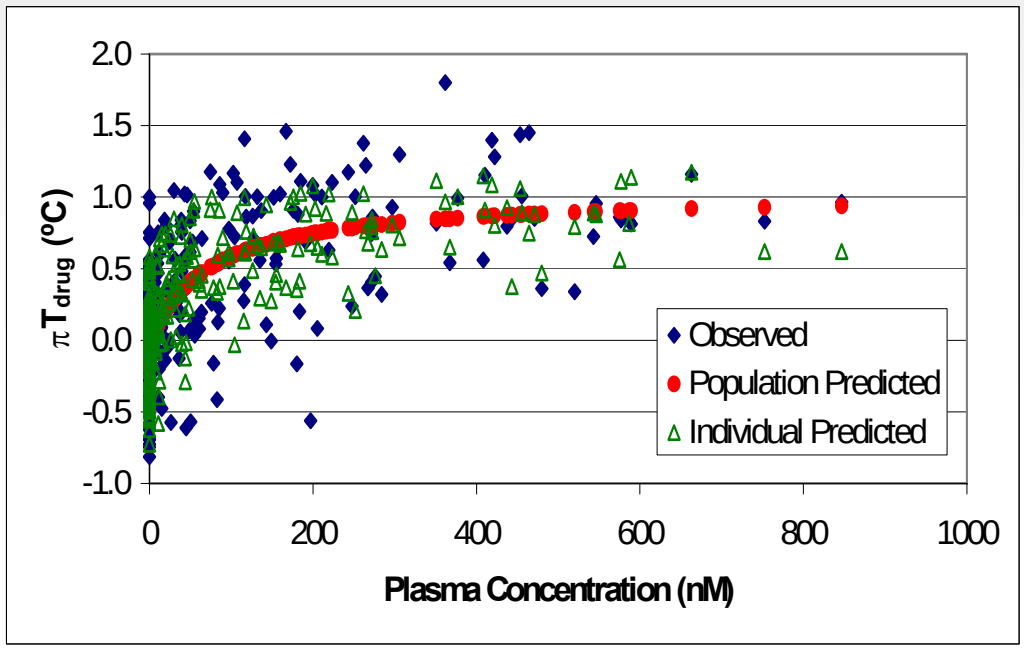
Capsaicin-Induced Dermal Vasodilation (CIDV) Model



Core Body Temperature Model

Variable	Estimate	Description
T_{obs}	-	Observed temperature (°C)
T_0	36.4	Baseline temperature (°C)
A	0.623	Diurnal variation in temperature
ω	-	Diurnal period set to π/24 hr^{-1}
t	-	Time of day (hr)
E_{max}	1.06	Maximum drug-induced temperature change (°C)
C	-	Concentration of MK-2295 (nM)
EC_{50}	69.9	Concentration of MK-2295 required to cause half-maximal temperature increase.

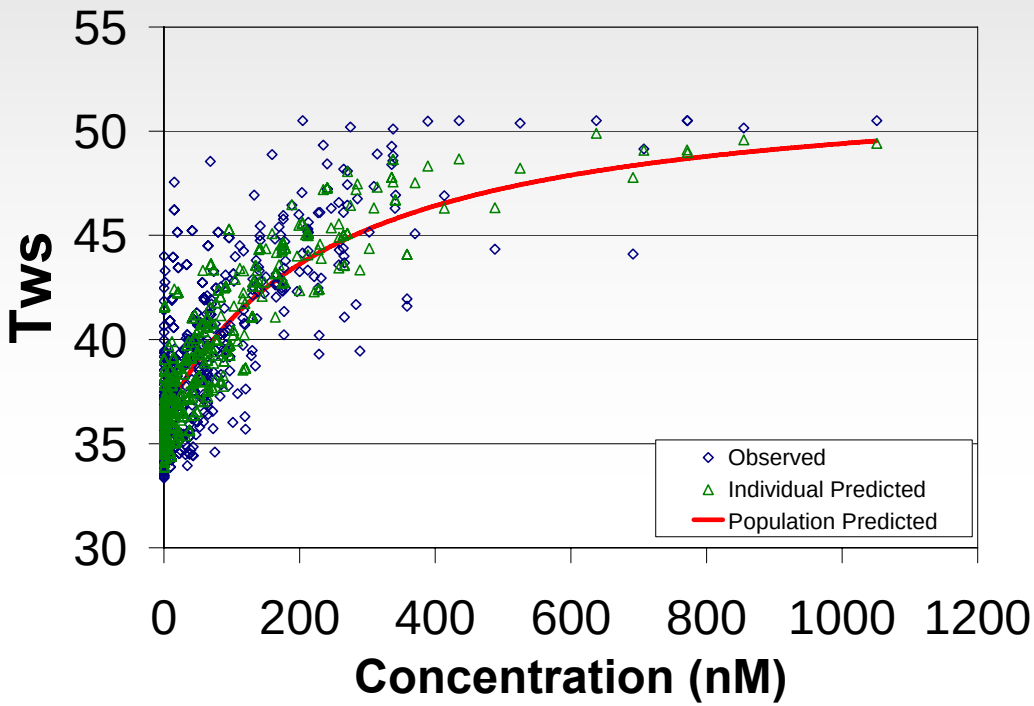
$$T_{obs} = T_0 + A\left|\sin(\omega t)\right| + \frac{E_{max} C}{C + EC_{50}}$$



Warmth Sensation Model

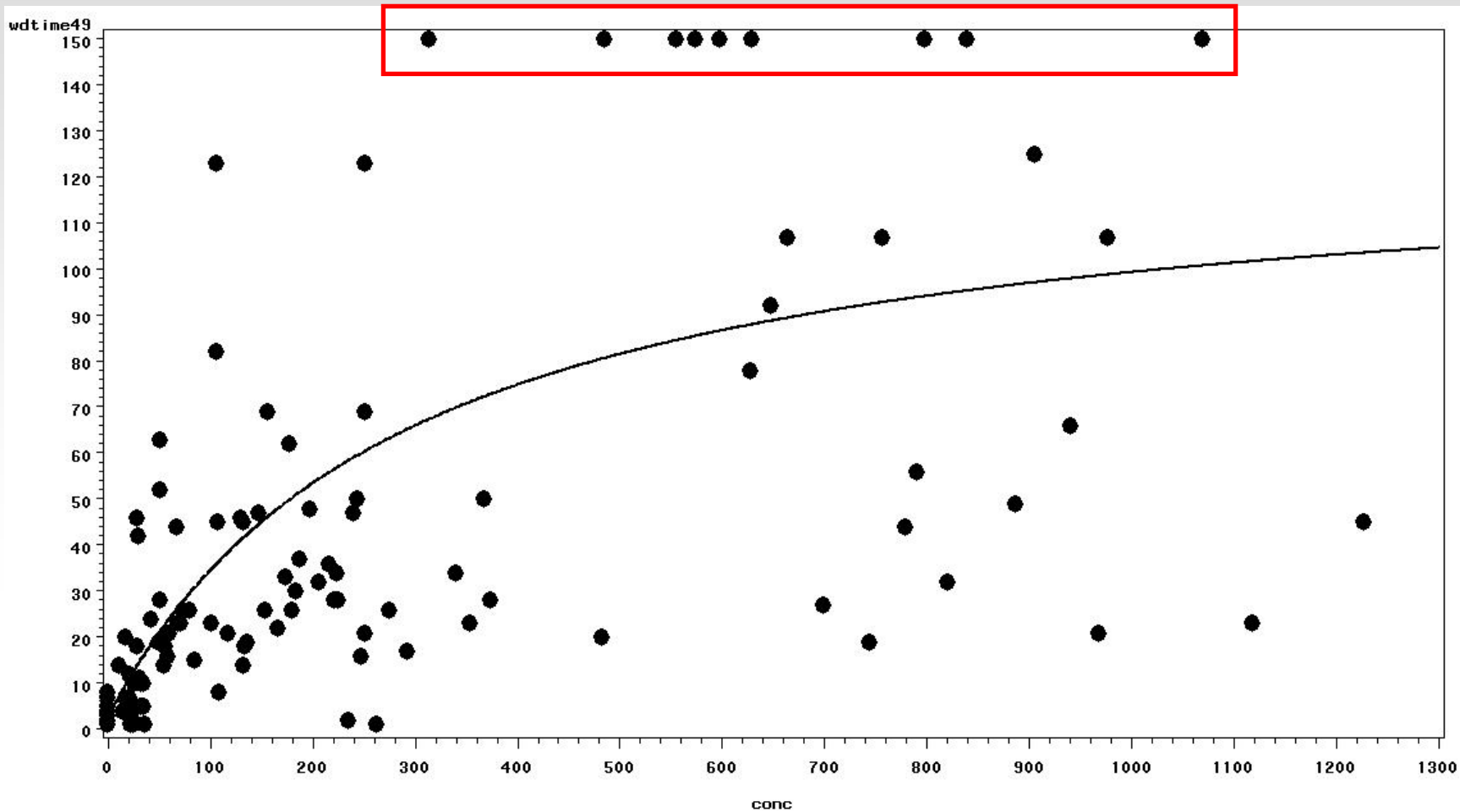
Variable	Estimate	Description
T_{ws}	-	minimum temperature at which warm sensation is detected on the right hand following an oral dose of MK-2295 (°C)
C	-	MK-2295 plasma concentration (nM)
E_0	36.2	Minimum temp. at which warm sensation is detected at C = 0 (°C)
E_{max}	52.6	The temp. at which warm sensation would be detected at C = ∞ (°C)
EC_{50}	242	Concentration of MK-2295 required to cause half-maximal increase in T_{ws}. (nM)

$$T_{WS} = E_0 + \frac{(E_{max} - E_0)C}{C + EC_{50}}$$



Hand Withdrawal Time Model

Data was censored due to the fact that subjects were instructed to remove their hands at 150 sec.



Hand Withdrawal Time Model

$$f(t;\beta,\eta)=\begin{cases}\frac{\beta}{\eta}\left(\frac{t}{\eta}\right)^{\beta-1}\exp\left(-\left(\frac{t}{\eta}\right)^{\beta}\right), & t\geq 0\\ 0, & t<0\end{cases}$$

Weibull distribution survival model.
Scale parameter was fit as an Emax function.

$$\eta = E_0 + \frac{E_{\max} C}{EC_{50} + C}$$

PDF for censored data was the integral of PDF above 150 sec.

Intra- and inter-individual data variability only allowed naïve pooled fitting.

Fit using SAS 9.1 NLMIXED procedure

Parameter	Estimate	SE	p
Shape (β)	1.39	0.0896	<0.0001
E_0 (sec)	2.89	0.293	<0.0001
EC_{50} (nM)	292	107	0.0069
E_{max} (sec)	137	32.4	<0.0001

Hot Water Sipping Model

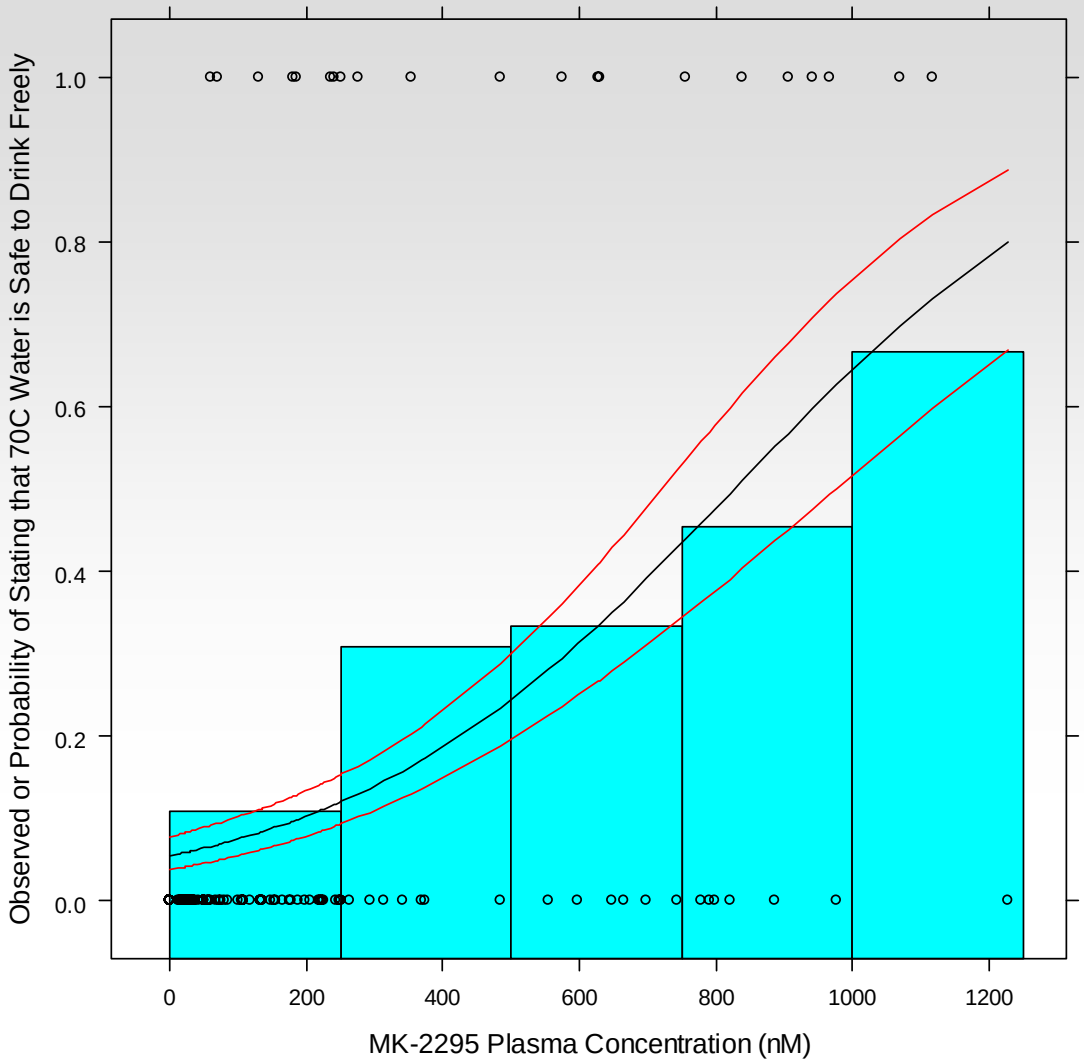
Subjects given 70°C water to sip and then asked if it was safe to drink freely.

Graph shows individual and binned responses along with model predictions ± SE.

Logistic regression:

$$P(Safe) = \frac{\exp(a + b \times Conc)}{1 + \exp(a + b \times Conc)}$$

Parameter	Estimate	Rel. Std. Err (%)
a	-2.85	13.4
b (nM^{-1})	0.00345	21.3



Consolidation of Understanding

	Steady State TID Dose (mg)		1	2	4	6	8
PK	C_{max} (nM)	**Actual**		**75**	**130**	**210**	**290**
		Predicted	**38**	**75**	**150**	**230**	**300**
	C_{trough} (nM)	**Actual**		**9.5**	**15**	**30**	**39**
		Predicted	**7.5**	**15**	**30**	**45**	**60**
Target Engagement at Steady State C_{max}	Competitive CIDV (%) **(Max effect=2.56†, EC50=57.9 nM)**		40	56	69-72	78-80	83-84
	Core Body Temperature (%) **(Max effect§=1.06ºC, EC50=69.9 nM)**		35	52	66	75	81
	Warm sensation (%) **(Max effect=52.6ºC, EC50=242 nM)**		**14**	**24**	**36-38**	**46-48**	**55**
	Pct. of Max Hand Withdrawal Time¶ (%) **(EC50=292 nM)**		**12**	**21**	**30-33**	**40-42**	**47-48**
	Hot Water Sipping P(Safe to drink at 70°)		**6**	**7**	**8-9**	**11**	**14**

*Based on a 2-compartment PK model (not shown) † arbitrary units
§ Circadian rhythm accounted for an additional 0.623ºC ¶ population mean response

Represents on-target effects | **Represents undesired effects**

Summary

Models were developed that described both on-target and undesired effects.

Simulations suggest that it is not possible to decouple the loss of temperature sensitivity from the on-target effects.

These models taken as a combined set can help inform decision making through the understanding of the therapeutic window for the compound.

Acknowledgments

Dick Simpson (currently with United Phosphorous)