
Setbacks in the Clinical Development of TRPV1 Antagonists: What Next?

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Abstract: TRPV1 antagonists have been considered as potential treatments for pain associated with inflammatory diseases and cancer. During Phase I clinical trials with AMG 517, a highly selective TRPV1 antagonist, we found that TRPV1 blockade elicits marked, but reversible, and generally plasma concentration-dependent hyperthermia. Furthermore, in a Phase Ib study, AMG 517 administered after molar extraction (a surgical cause of acute pain) elicited long-lasting hyperthermia with maximal body temperature surpassing 40 °C, suggesting that TRPV1 blockade elicits undesirable hyperthermia in susceptible individuals.

Since TRPV1 blockade elicited hyperthermia is a major hurdle, we investigated the possibility of eliminating hyperthermia while maintaining antihyperalgesia by two approaches: i) peripheral restriction of TRPV1 antagonists, ii) characterization of TRPV1 modulators that exhibit differential pharmacology. Results from the preclinical studies of both approaches will be discussed.

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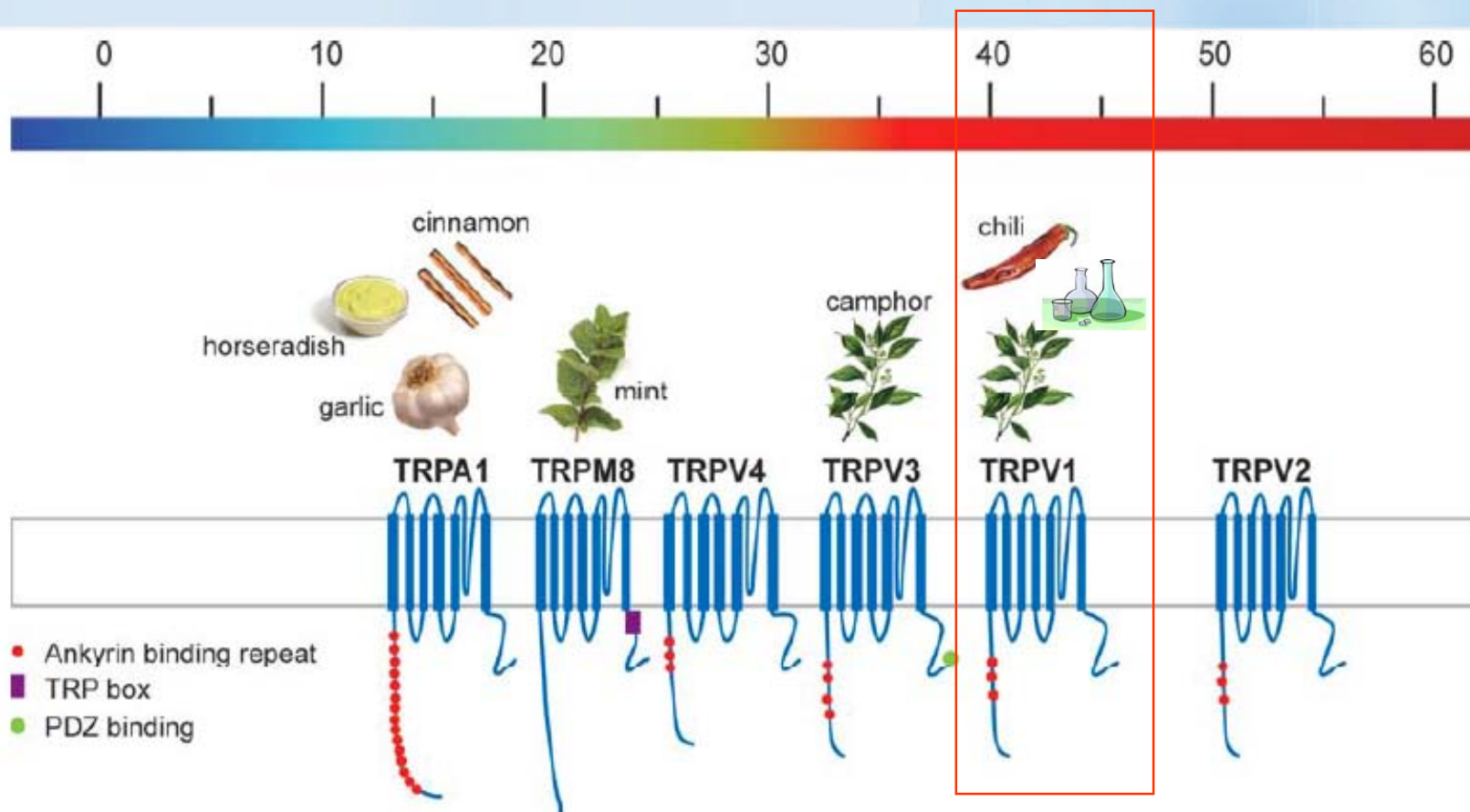


AMGEN

Outline

- Introduction
- Functional assays
- AMG 517 preclinical studies
- TRPV1 antagonism - hyperthermia
- Mechanisms of hyperthermia
- AMG 517 clinical trial results
- Peripherally restricted antagonists – hyperthermia
- Differential pharmacology of antagonists – no hyperthermia
- Conclusions

TRP channels are integrators of multiple noxious stimuli

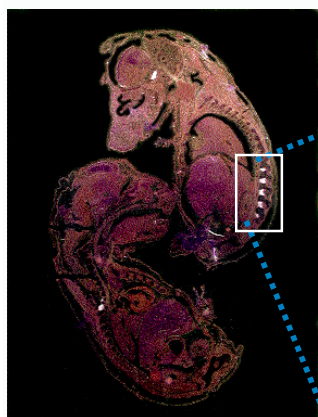


Dhaka et al (2006) *Annu Rev Neurosci.* 29:135-61

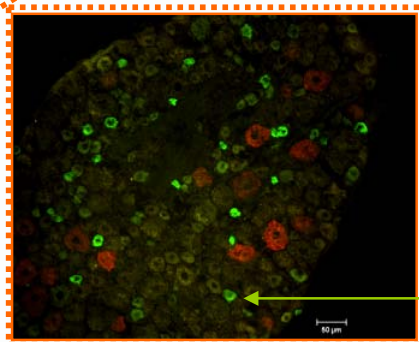
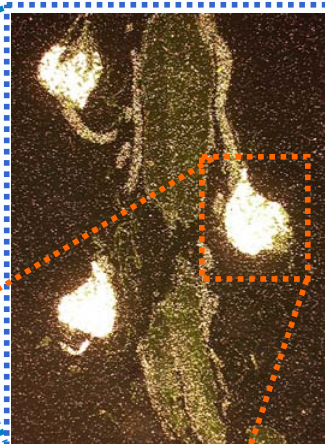
- **Agonists of TRPA1 and TRPV1 cause pain in humans and pain behavior in rodents**

TRPV1: A polymodal detector of painful stimuli

TRPV1 Expression
in E19 Rat



White Areas Show
Expression In DRG
Neurons in Rats

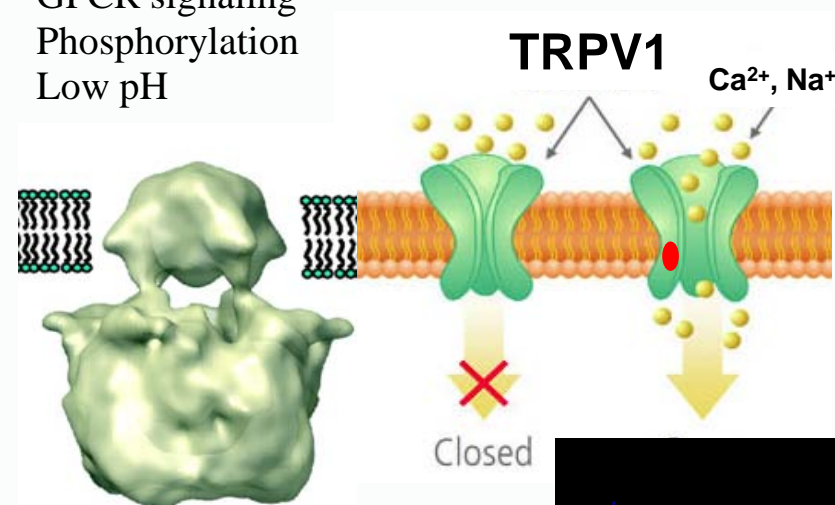


TRPV1
positive DRG
neurons

Narender Gavva

TRPV1 is activated by:

- Chemical ligands (capsaicin, RTX etc)
- Heat
- GPCR signaling
- Phosphorylation
- Low pH

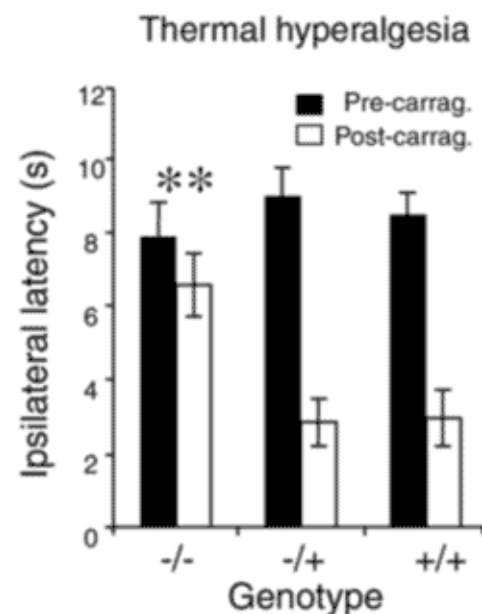
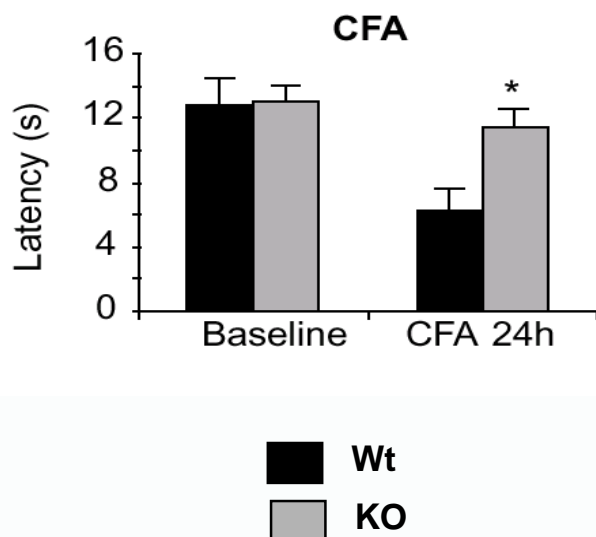


Moiseenkova-Bell et al 2008
PNAS. 105:7451-5

Rat sensory neurons
responding to capsaicin
(calcium imaging)

TRPV1 – Target validation

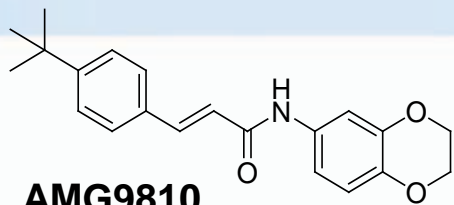
TRPV1 knockout mice show reduced thermal hyperalgesia



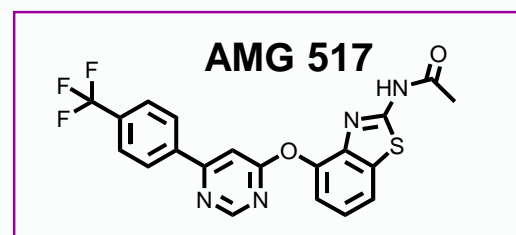
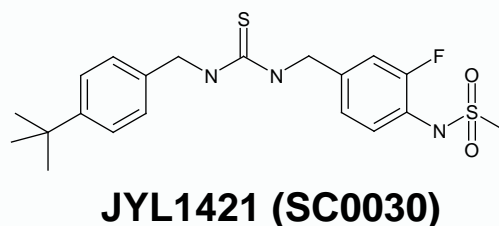
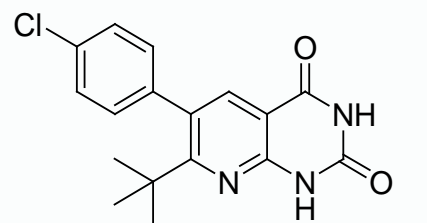
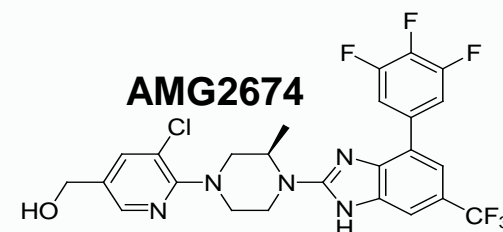
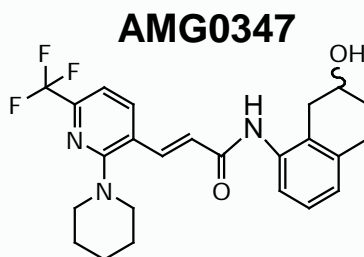
Davis et al (2000) *Nature* 405:183-7; Caterina et al (2000) *Science*, 288, 306-13

- TRPV1 expression in the spinal cord is up-regulated after SCI – Zhou et al (2002) *J Surg Res.* **107**:140-4
- TRPV1 expression increased in inflamed human oesophagus – Mathews et al (2004) *Eur J Gastroenterol Hepatol.* **16**:897-902

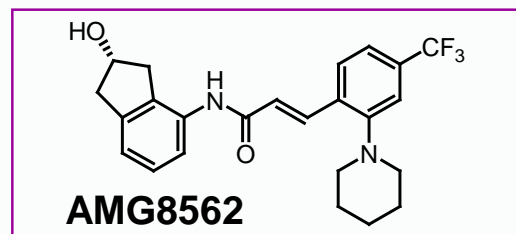
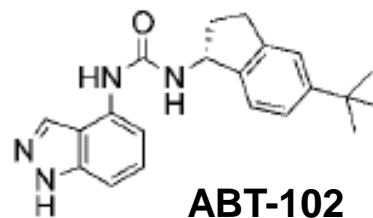
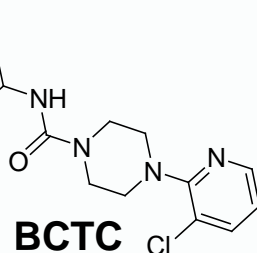
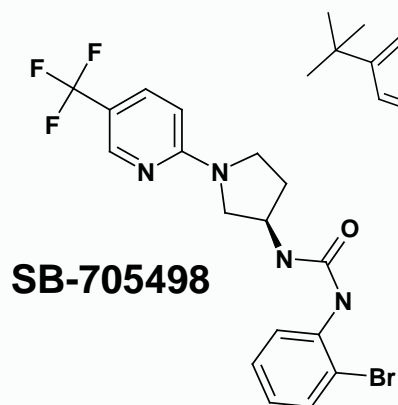
Various distinct chemical scaffolds act as TRPV1 antagonists



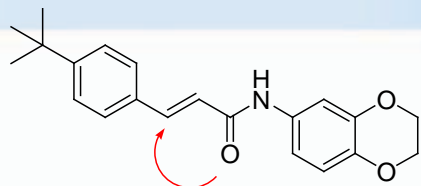
Gavva et al 2005 JPET, 313:474-484



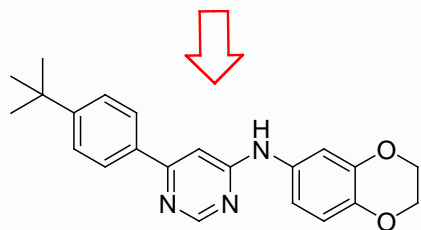
Doherty et al., 2007 JMC 50:3515-27
Gavva et al., 2007 JPET 323:128-137



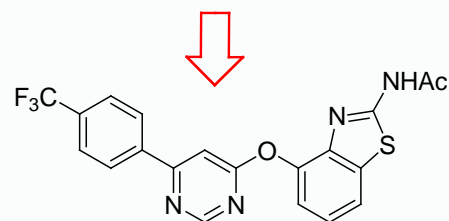
Strategy for SAR development



rTRPV1 (Cap) IC₅₀ = 79 nM
rTRPV1 (pH) IC₅₀ = 350 nM



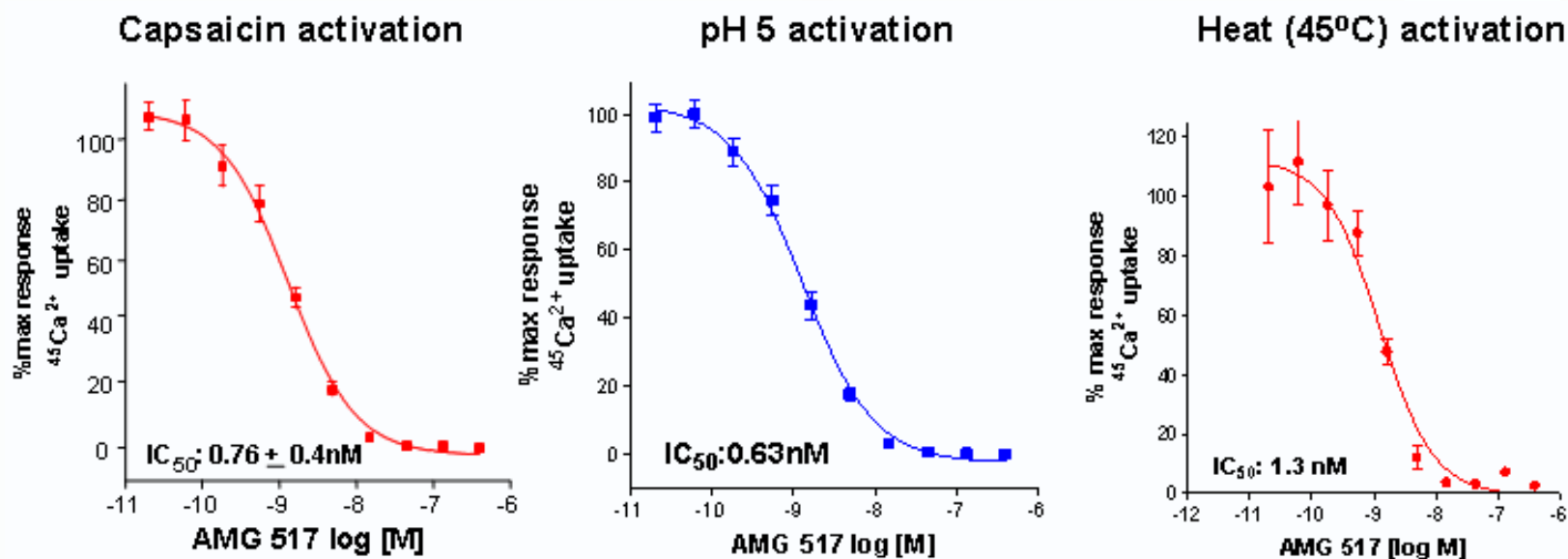
rTRPV1 (Cap) IC₅₀ = 120 nM
rTRPV1 (pH) IC₅₀ = 680 nM



rTRPV1 (Cap) IC₅₀ = 0.9 nM
rTRPV1 (pH) IC₅₀ = 0.5 nM

- High-throughput screening of our corporate database identified several *N*-aryl cinnamides as TRPV1 antagonists
- Constrained analogs of *s*-cis cinnamides provided an entry into a novel chemical series of TRPV1 antagonists
- Further optimization lead to the clinical candidate AMG 517

AMG 517 blocks all modes of TRPV1 activation

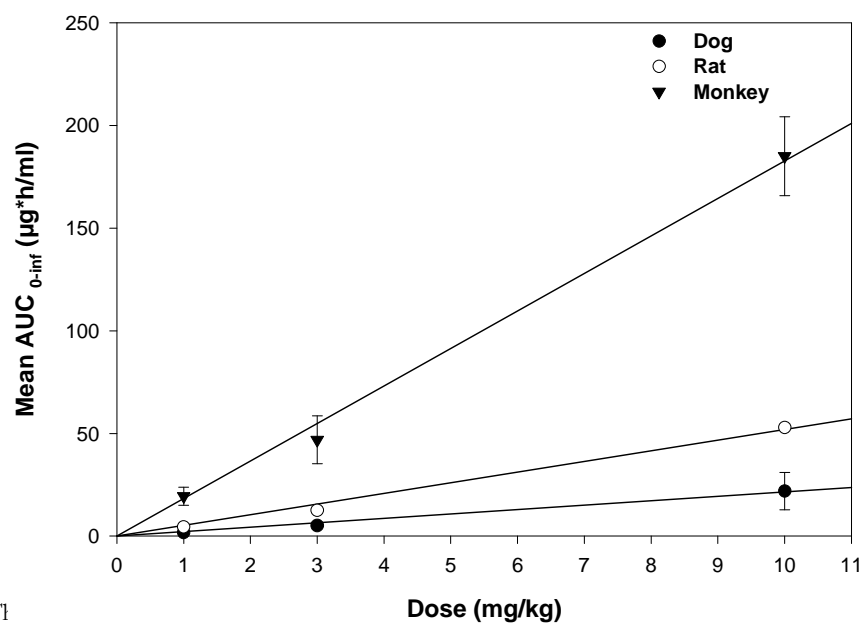


- AMG 517 is a potent antagonist of rodent, dog, monkey and human TRPV1
- AMG 517 does not block TRPA1, TRPV2, TRPV3, TRPV4, and TRPM8

AMG 517: Pharmacokinetic profile

Species	Intravenous dosing				Oral dosing
	AUC _{0-inf} (ng.hr/mL)	CL (mL/hr/kg)	V _{ss} (mL/kg)	t _{1/2} (h)	F (%)
Rat	8800	120	4000	31	51
Dog	7400	140	7000	41	23
Monkey	37000	30	2300	62	52
Human (projected)		50	4500	60-120	

- Good Oral Bioavailability
- Low Clearance
- Long Half-life
- Linear PK (1-10 mg/kg)



AMG 517 blocks capsaicin-induced flinching in rats

Dose
AMG 517 p.o.

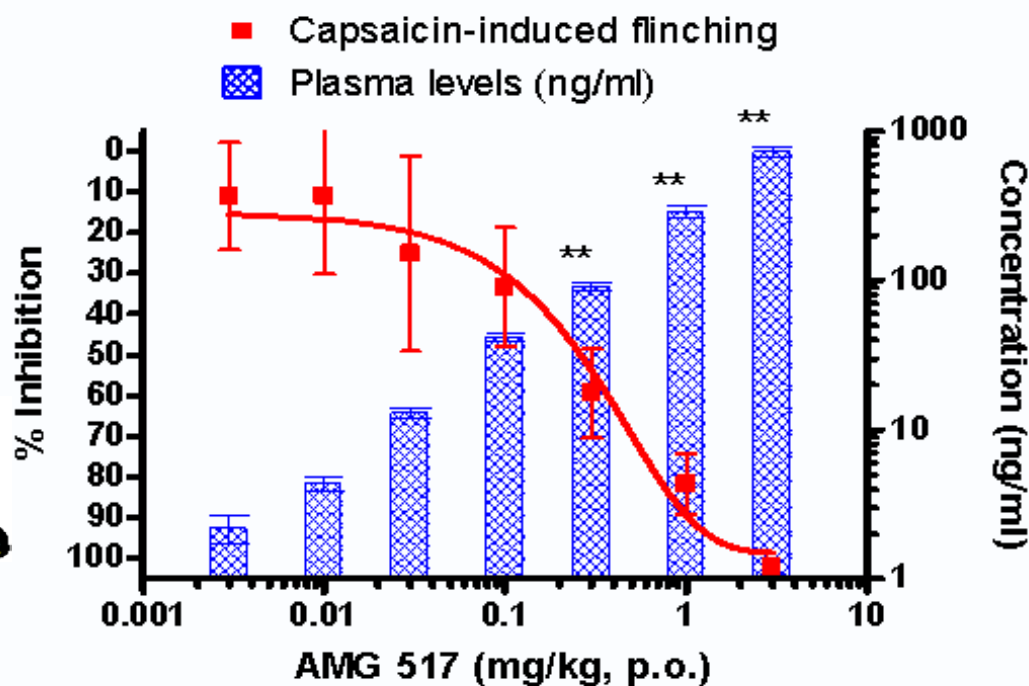


60 min

Inject Capsaicin
Into the Paw



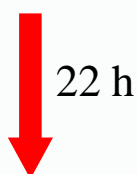
Count # of
Paw Flinches
in 1 min



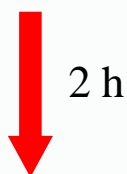
Gava et al., 2007 JPET 323:128-137

AMG 517 blocks inflammation-induced thermal hyperalgesia

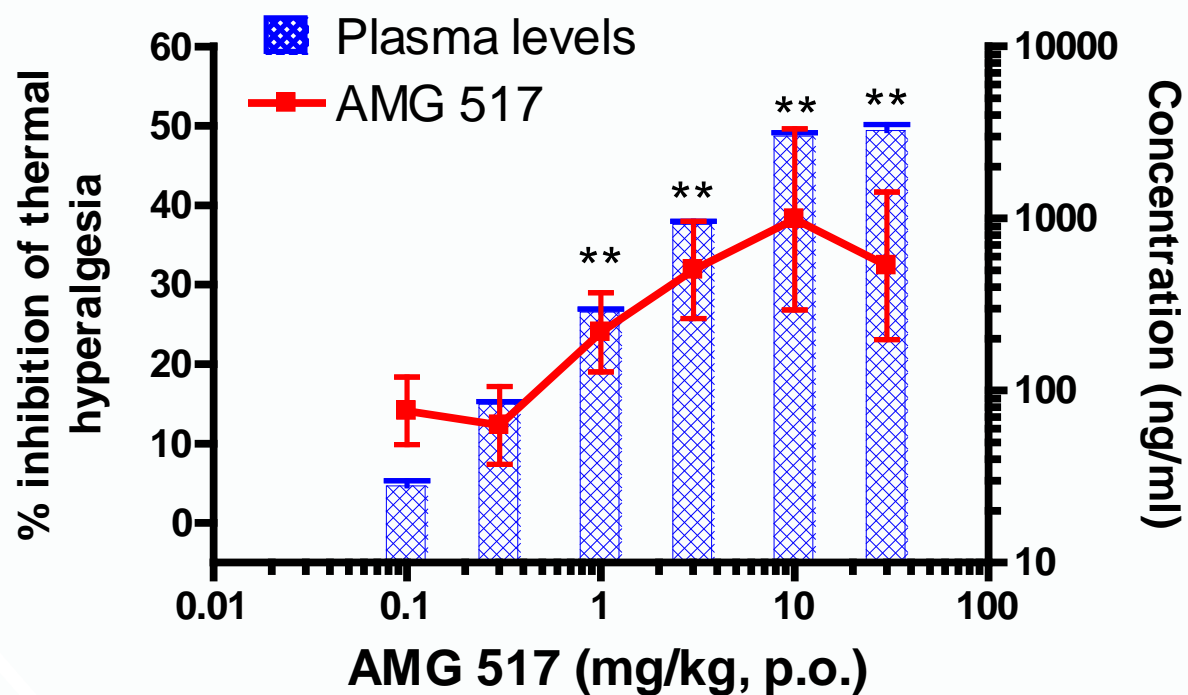
Inject CFA
into the paw



Dose
AMG 517, p.o.



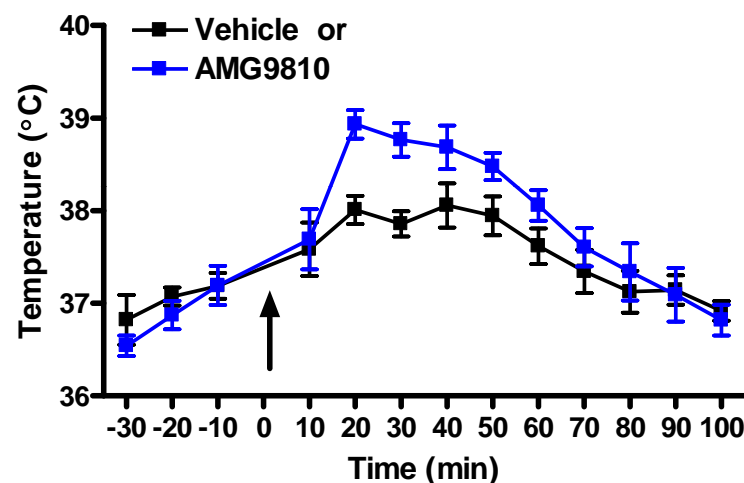
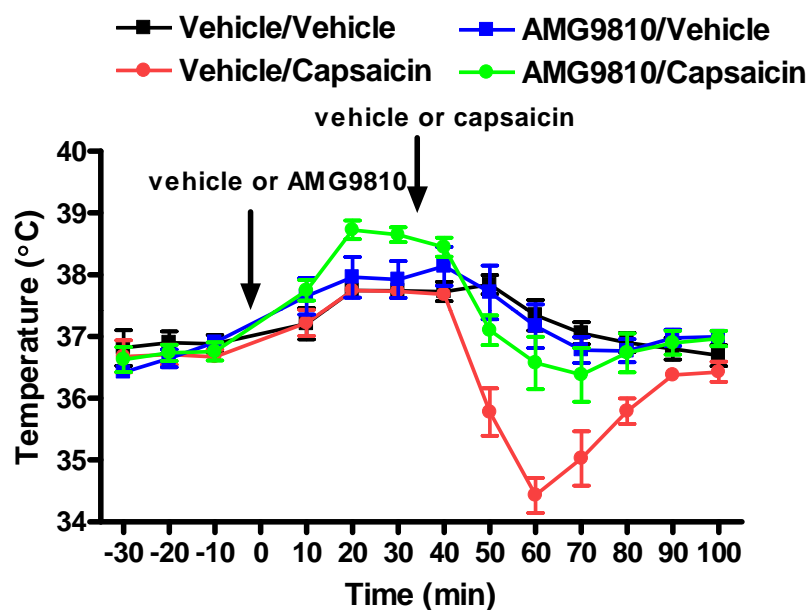
Record thermal
sensitivity



Gavva et al., 2007 JPET 323:128-137

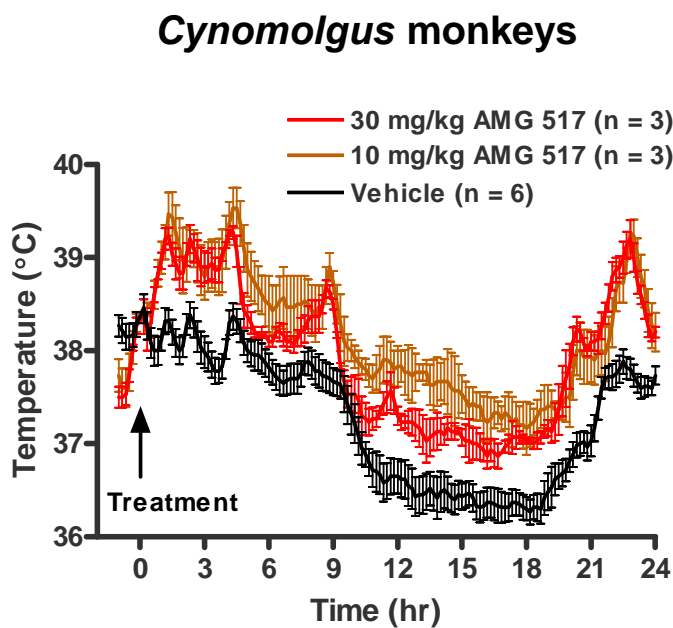
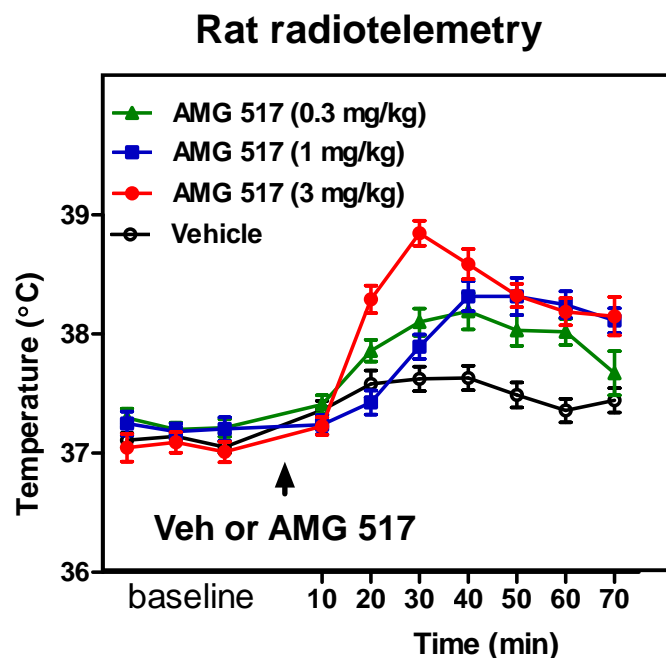
TRPV1 antagonists block capsaicin-induced hypothermia and cause hyperthermia by themselves

- On-target challenge model
 - Capsaicin, a TRPV1 agonist produces an “on-target” decrease in body temperature
 - Pretreatment with a TRPV1 antagonist should block capsaicin-induced hypothermia



Gavva et al., *J Neurosci.* 2007 Mar 28;27(13):3366-3374

AMG 517 causes hyperthermia in multiple species

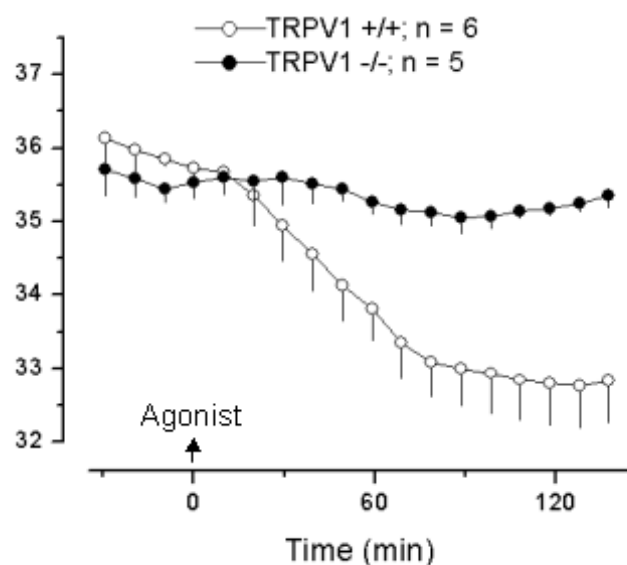


Gavva et al., *JPET* 2007 [323](#):128-137

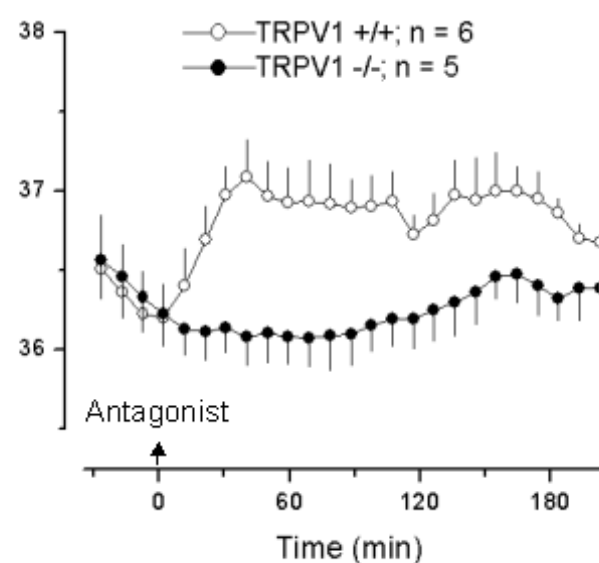
- TRPV1 antagonists caused hyperthermia in rodents, dogs, monkeys

Agonists and antagonists do not cause body temperature changes in TRPV1 knockout mice

Agonist-induced hypothermia



Antagonist-induced hyperthermia

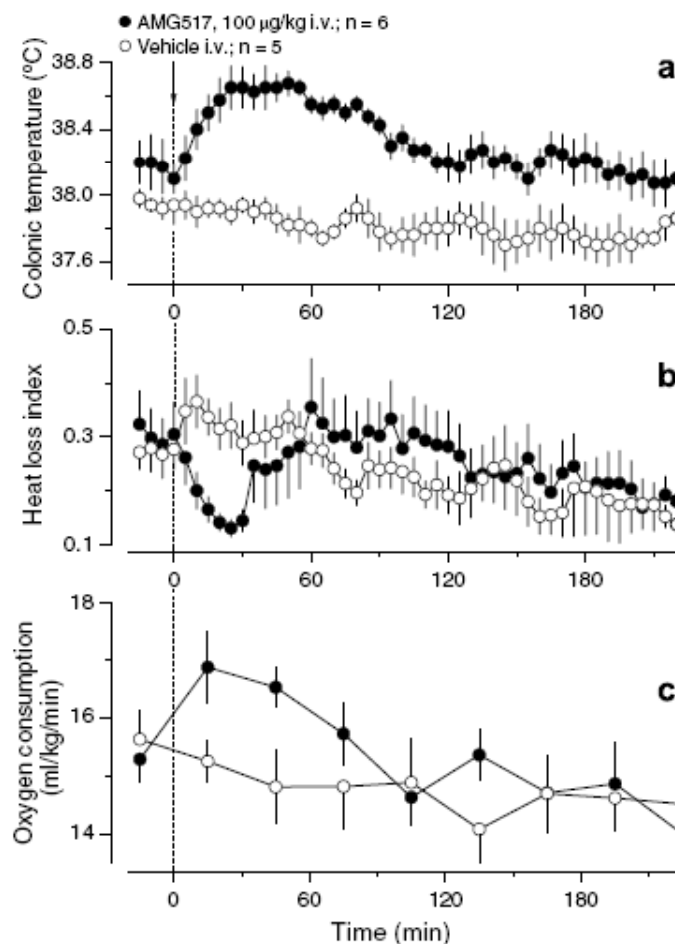
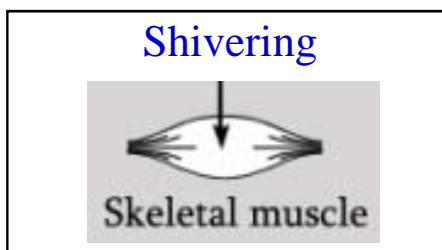
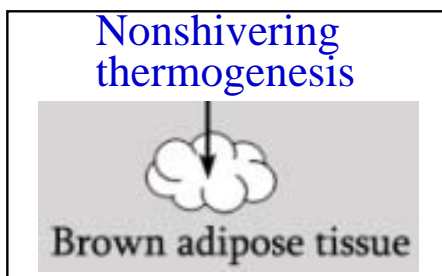
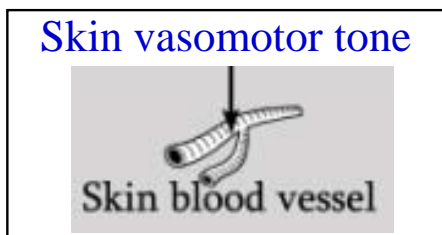


Steiner et al., *J Neurosci.* 2007 Jul 11;27(28):7459-68

- Agonist-induced hypothermia & antagonist-induced hyperthermia are entirely TRPV1 mediated

AMG 517 causes hyperthermia by vasoconstriction and increased thermogenesis

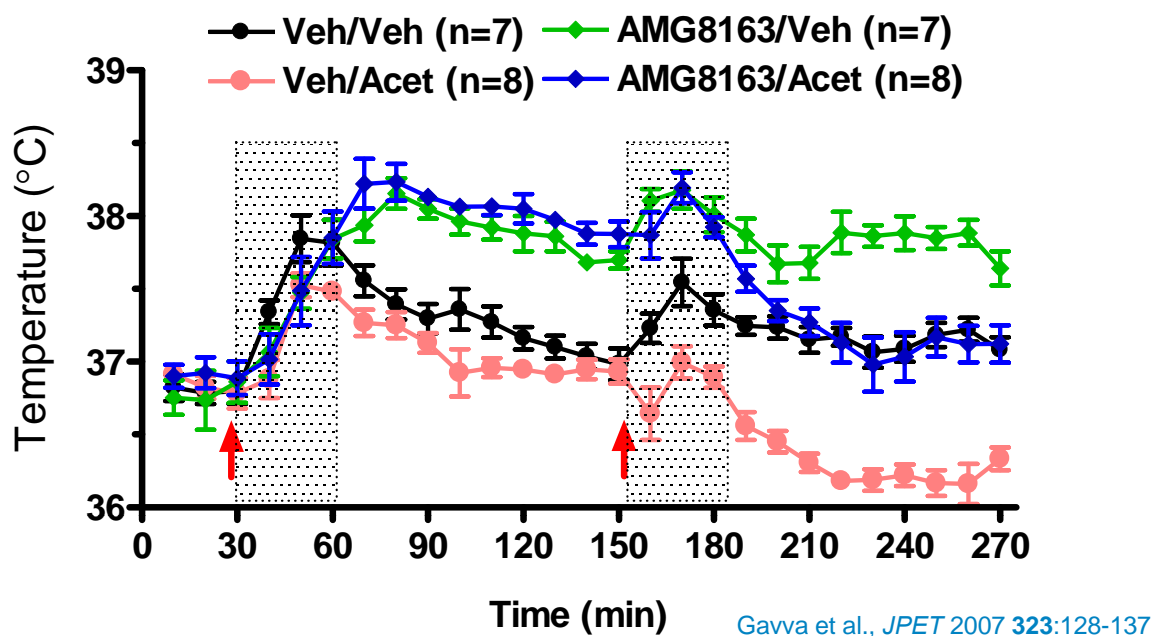
Individual effectors



Gavva et al., 2008 *Pain* 136:202-210

Antipyretic acetaminophen suppresses TRPV1 antagonist-induced hyperthermia

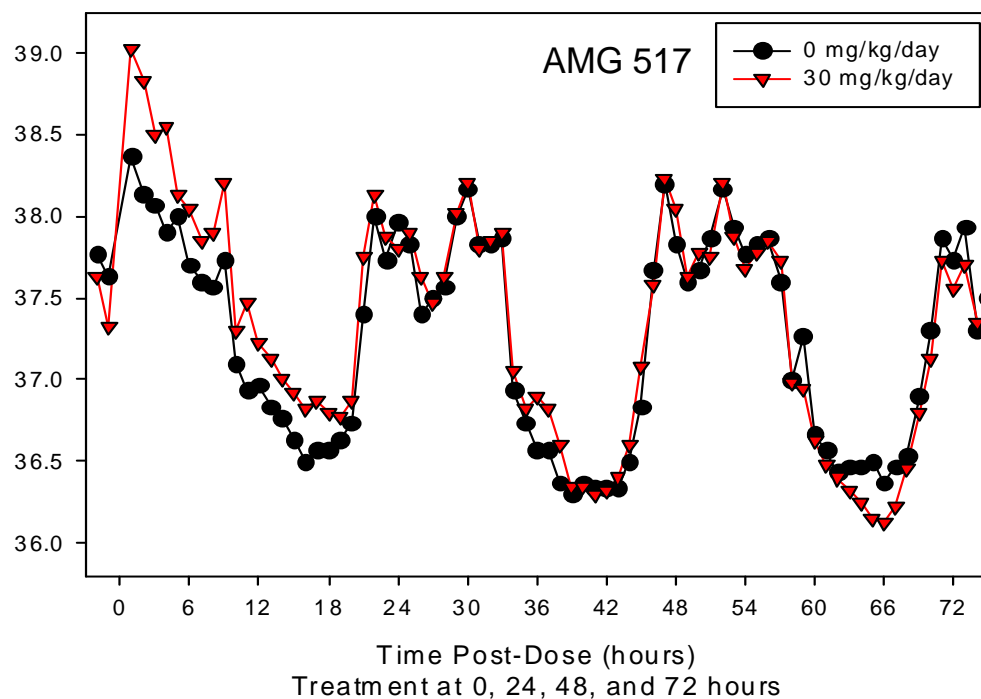
Rat radiotelemetry



- AMG8163 is a 'boc' analogue of AMG 517
- Similar to AMG 517, AMG8163 blocks all modes of TRPV1 activation

Repeated administration of AMG 517 attenuates hyperthermia

Monkey radiotelemetry



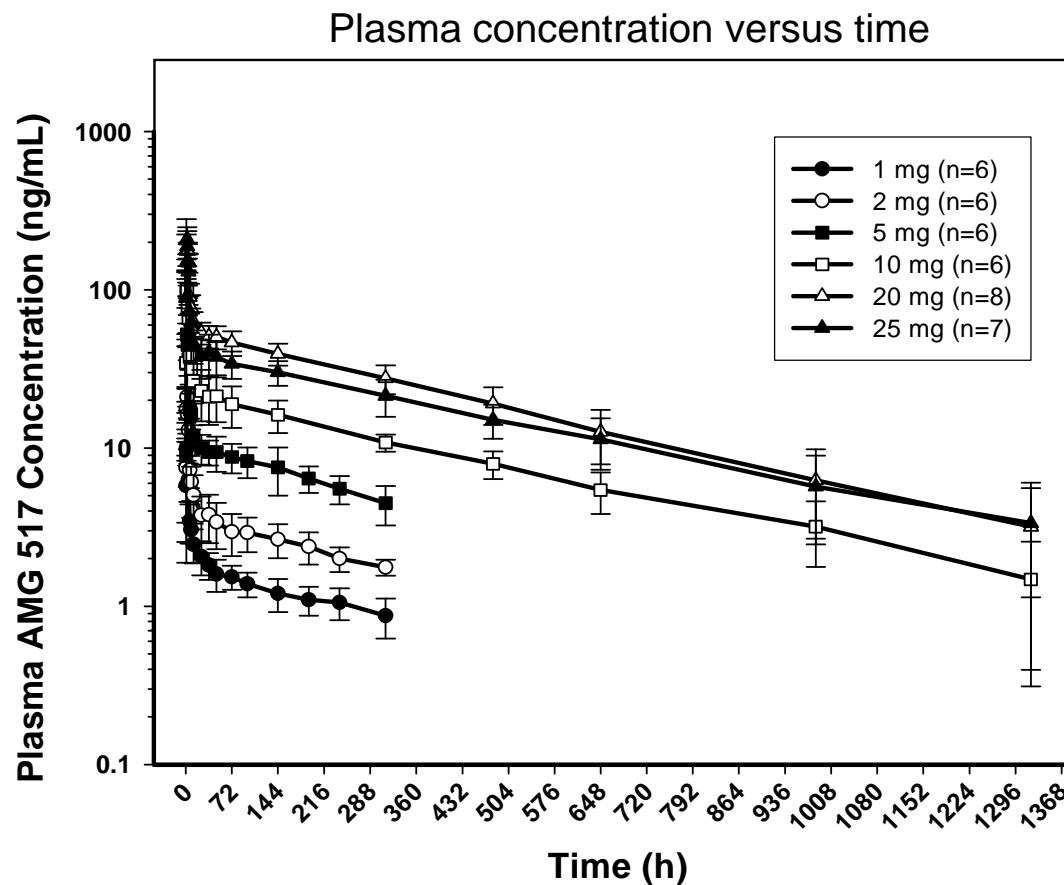
- TRPV1 is tonically activated and plays a role in body temperature regulation
- Role of TRPV1 in thermoregulation can be compensated

Clinical trial design

- **Vehicle of all studies:** A suspension in a 100 ml of 2% Pluronic 108 in OraPlus® followed by two 75 ml water washes
- **1st Phase I – single dose safety & pharmacokinetic study**
 - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
 - Healthy subjects received 1, 2, 5, 10, 20, or 25 mg AMG 517
 - End points: number and incidence of treatment emergent-events, oral and tympanic body temperature measurements
- **2nd Phase I – Repeated dose study**
 - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
 - Placebo, 2, 5, or 10 mg of AMG 517
 - treatment emergent-events, difference in max body temperature on day 1 versus subsequent days, through day 7
- **Phase Ib – Dental pain study**
 - Double-blind, placebo-controlled, randomized, Parallel group, multi-center study
 - Inclusion criteria: moderate to severe post-operative pain
 - Single doses of placebo, 2, 8, or 15 mg of AMG 517

More details can be found in: Gavva et al., 2008 Pain 136:202-210

AMG 517 has a long half-life in healthy subjects

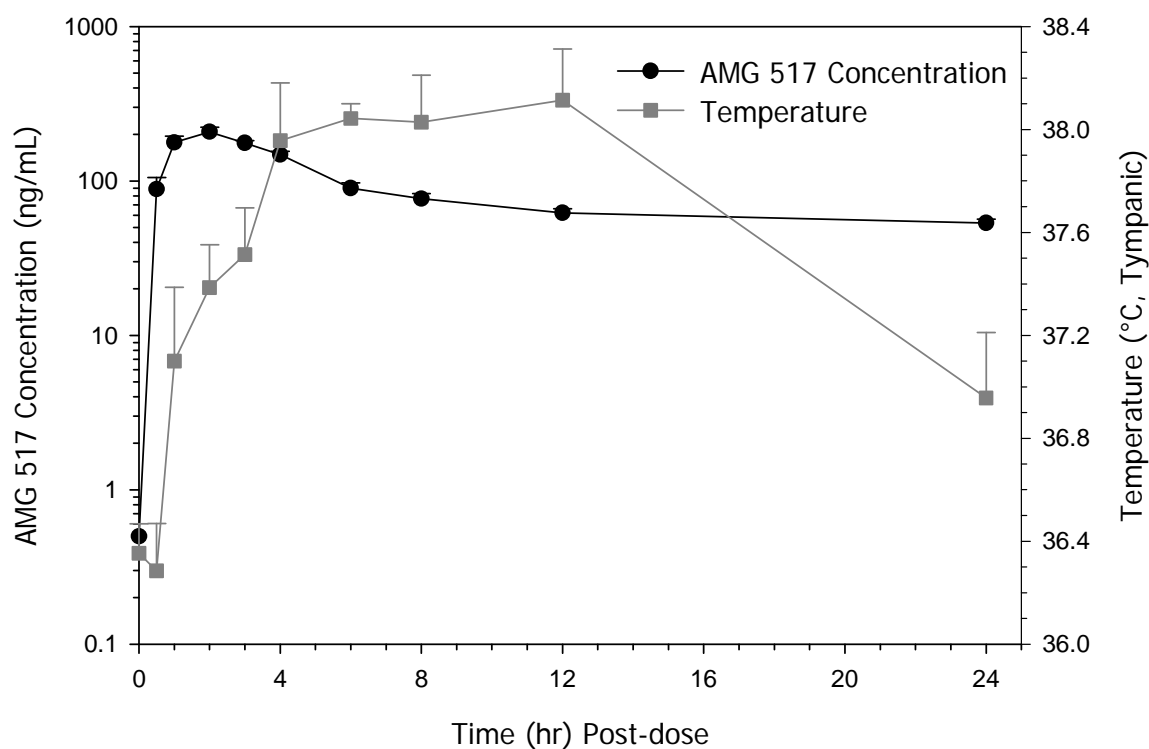


- Plasma half life: ~ 300 hrs

Gavva et al., 2008 *Pain* 136:202-210

AMG 517 elicits transient hyperthermia in humans

Body temperature & C_{max} versus time

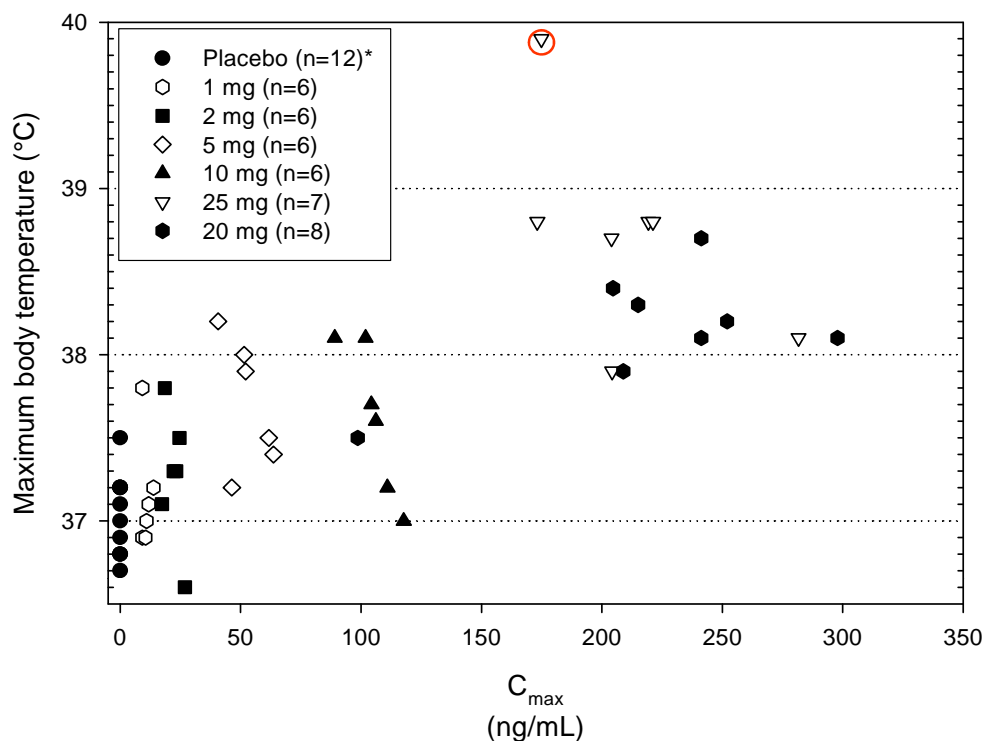


(mean ± SD of the max body temperature [tympanic] presented)

Gavva et al., 2008 Pain 136:202-210

AMG 517 caused plasma concentration-dependent hyperthermia in healthy subjects

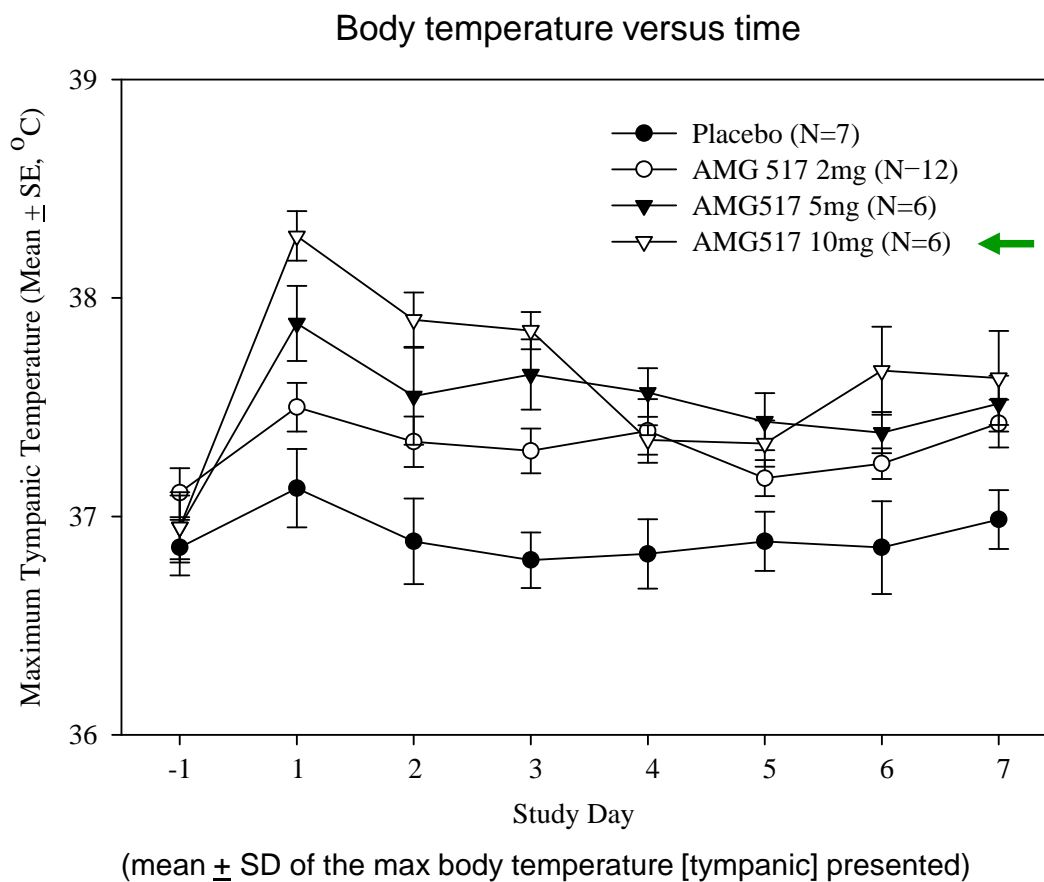
Body temperature versus C_{max}



Gavva et al., 2008 *Pain* 136:202-210

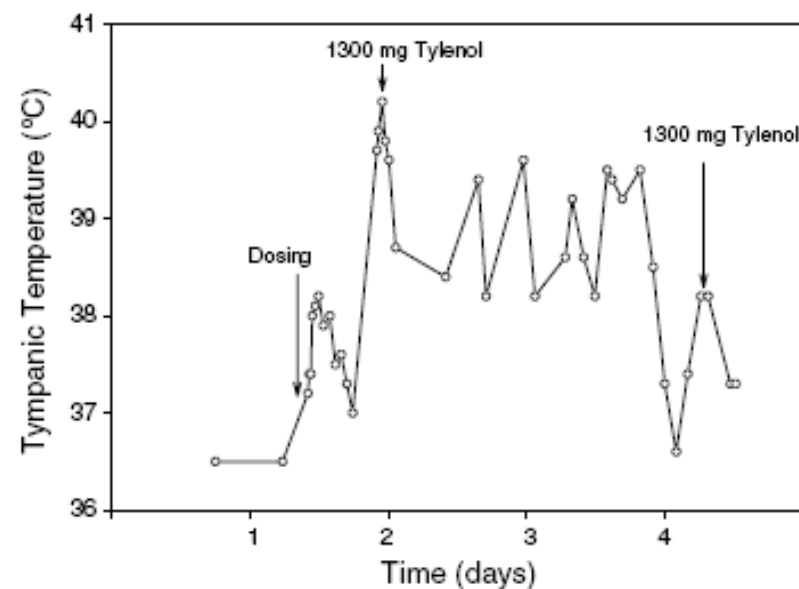
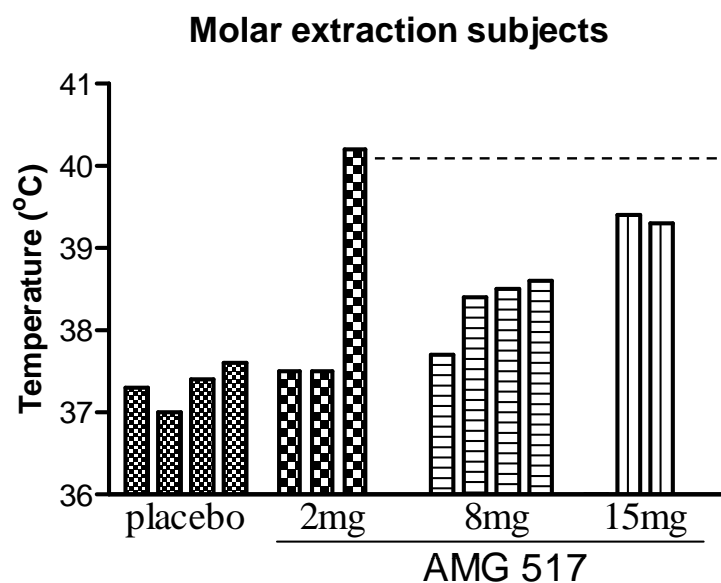
- Single dose, oral suspension in a 100 mL of 2% Pluronic 108 in OraPlus®
- Plasma half life of AMG 517 in humans: ~ 300 hrs

Trend of hyperthermia attenuation after repeated administration of AMG 517



Gavva et al., 2008 Pain 136:202-210

AMG 517 caused marked hyperthermia in subjects who underwent molar extraction



- TRPV1 antagonists causing hyperthermia in rodents, dogs, monkeys, and humans indicates an evolutionarily conserved role of TRPV1 in thermoregulation

Gavva et al., 2008 *Pain* **136**:202-210

First approach to address hyperthermia: Peripheral restriction of antagonists

Hypothesis

- Thermoregulation is CNS mediated
- Can we minimize hyperthermia by restricting antagonists to the periphery?

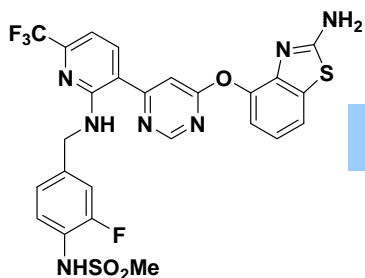
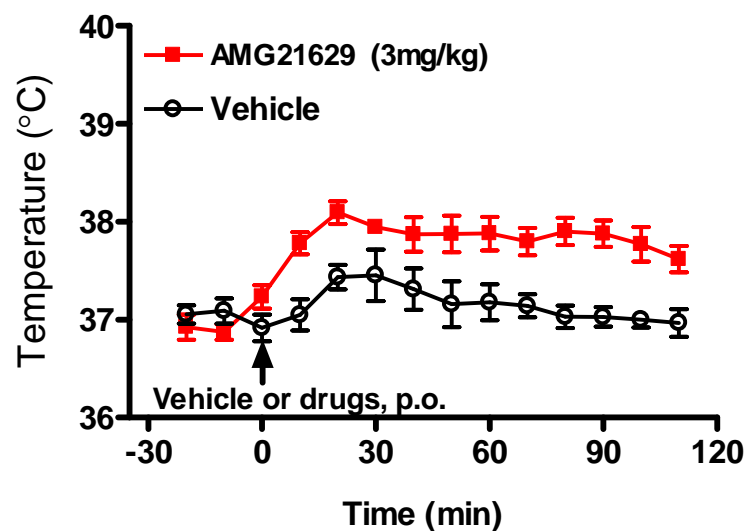
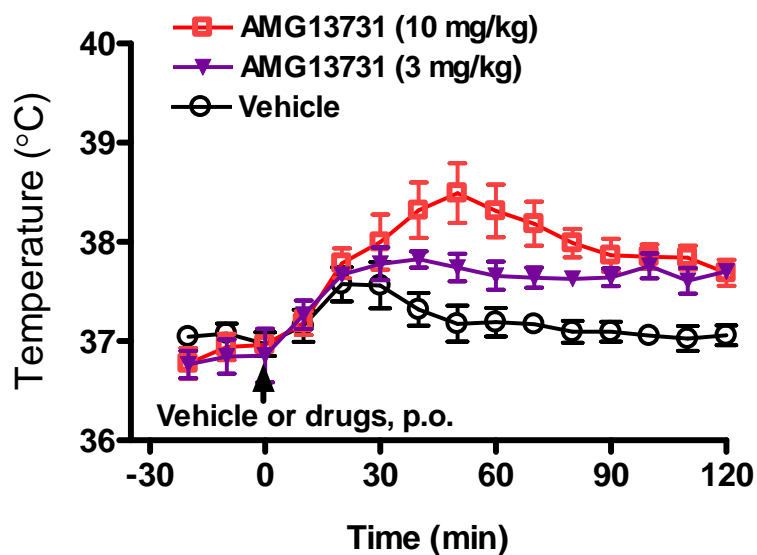
Strategy

- Reduce brain exposure: peripherally restricted TRPV1 antagonists
 - Increase polar surface area (PSA)
 - Decrease logP
 - Increase number of hydrogen-bond donors

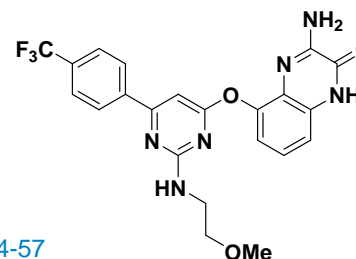
Profiles of peripherally restricted TRPV1 antagonists

Compound	PSA	clogP	Cap IC ₅₀	B/P ratio
AMG13731	145	3.9	2.9	0.02
AMG21629	128	3.5	0.5	0.05
AMG32915	141	1.9	0.2	0.04
AMG41394	132	3.9	1.3	0.04

Effect of AMG13731 and AMG21629 on rat body core temperature



AMG13731



AMG21629

Tamayo et al 2008 J Med Chem. 51:2744-57

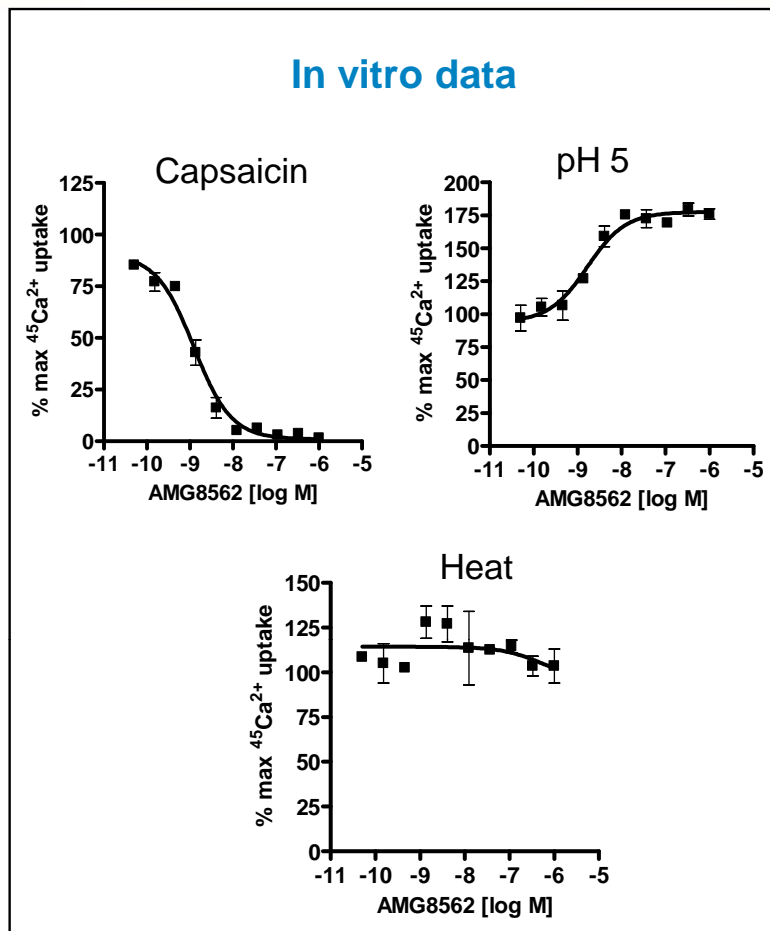
- Site of action for TRPV1 antagonist-induced hyperthermia is outside the BBB

Evaluation of compounds exhibiting differential pharmacology - 2nd Approach

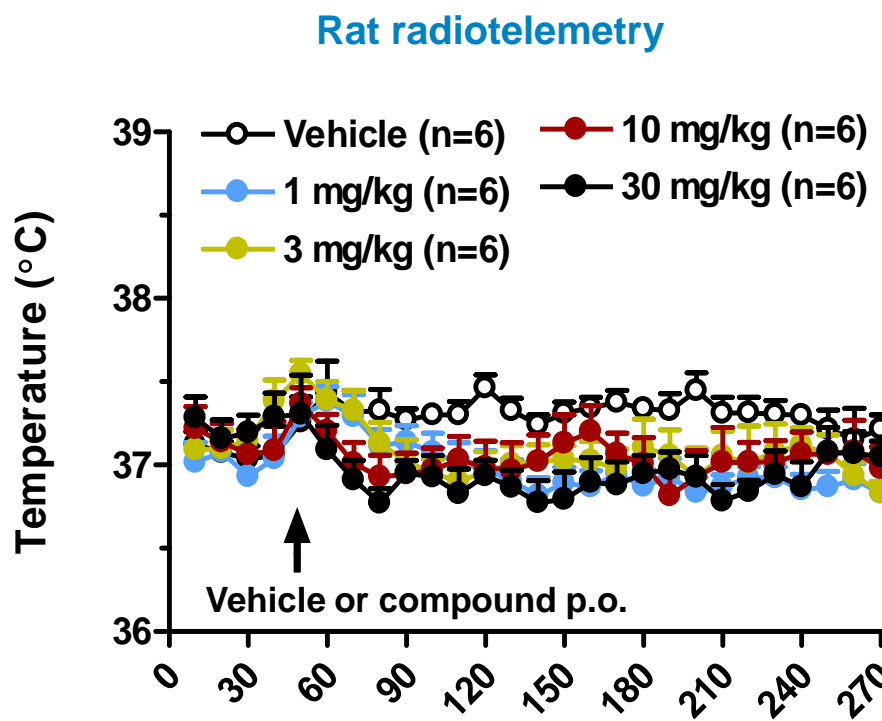
	Capsaicin	pH 5	Heat	Body temp
Profile A	Block	Block	Block	↑
Profile B	Block	Partial block	Block	↑
Profile C	Block	Potentiate	No effect	— ↓
Profile D	Block	Potentiate	Potentiate	↓

- Profiles defined by agonist-induced $^{45}\text{Ca}^{2+}$ uptake assays

AMG8562, a profile C compound that does not cause hyperthermia in rats

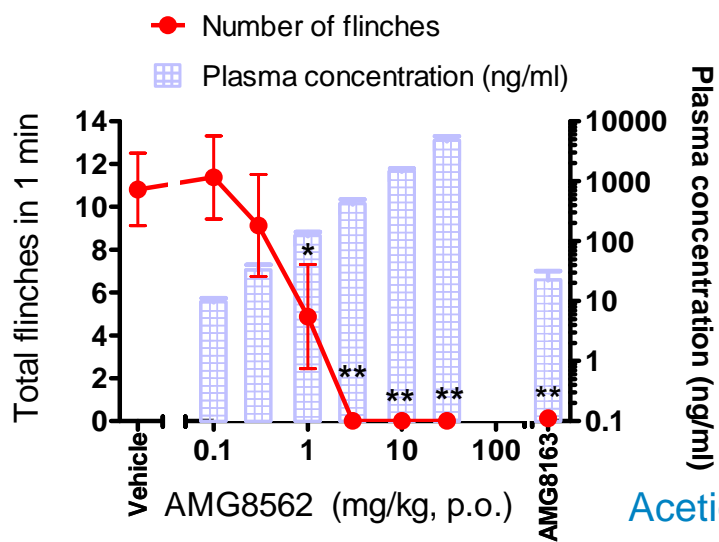


Lehto et al 2008 JPET 326:218-229

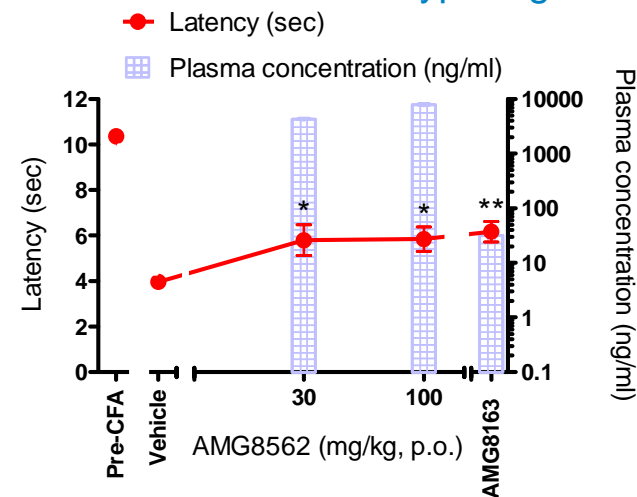


AMG8562 is modestly effective in capsaicin-challenge and pain models

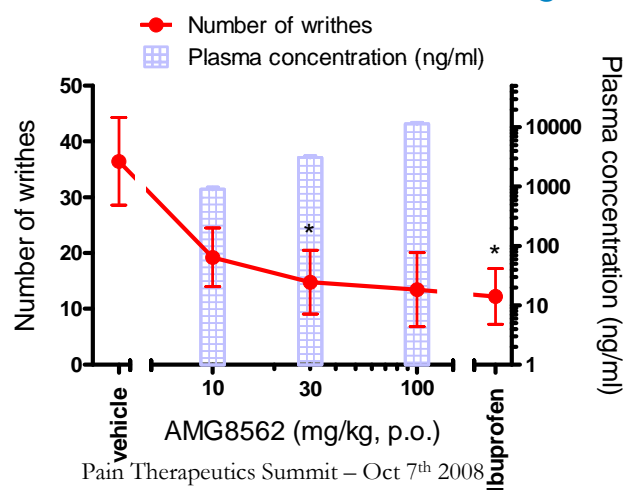
Capsaicin-induced flinch



CFA-induced thermal hyperalgesia

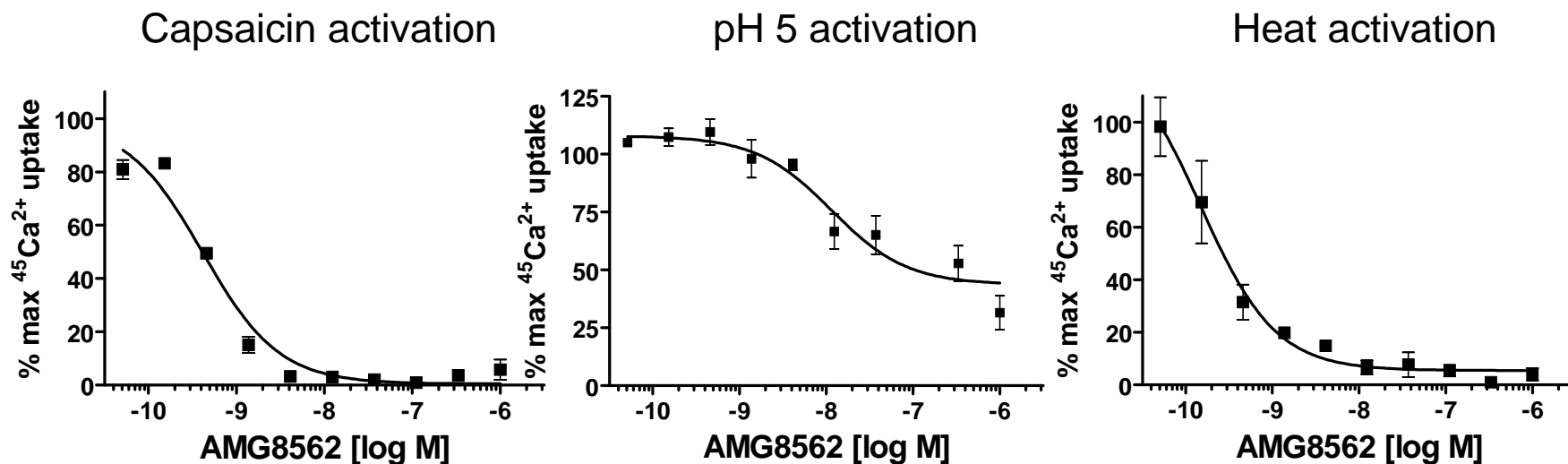


Acetic acid-induced writhing



Lehto et al 2008 JPET 326:218-229

AMG8562, exhibits profile B modulation of human TRPV1



Lehto et al 2008 JPET 326:218-229

- Profile B modulators cause hyperthermia in rats

Current status of TRPV1 antagonists in the clinic

Compound name	Company	Route of administration	Indication	Stage	Current status
ABT-102	Abbott	Oral		Phase I	Initiated ?
AMG 517	Amgen	Oral	Dental pain	Phase Ib	Terminated
AZD1386	AstraZeneca	Oral	Dental pain	Phase II	Completed
GRC 6211	Lilly/Glenmark	Oral	Dental pain	Phase II	Suspended
JTS-653	Japan Tobacco	Oral	Overactive bladder pain	Phase I	On going
MK 2295	Merck/Neurogen	Oral	Dental pain	Phase II	Completed
SB-705498	GSK	Oral	Migraine	Phase II	Terminated
			Rectal pain	Phase II	Terminated
			Dental pain	Phase II	Completed
PF-4065463	Evotec/Pfizer	unknown	unknown	unknown	unknown

Conclusions

- Genetic and pharmacological evidence suggests that TRPV1 contributes to hyperalgesia
 - TRPV1 antagonists block capsaicin-induced flinch (on-target challenge) and act as anti-hyperalgesics
- AMG 517, a selective TRPV1 antagonist caused plasma concentration dependent hyperthermia in humans
- Antagonist-induced hyperthermia showed a complete and clear attenuation after repeated dosing in preclinical species but not in humans
- Mechanisms of hyperthermia include antagonist-induced vasoconstriction and increased thermogenesis
- Peripherally restricted TRPV1 antagonists caused hyperthermia
- Profile C modulators of TRPV1 did not cause hyperthermia and demonstrated modest efficacy in pain models
- **Clinical trial results of other TRPV1 antagonists are eagerly awaited**

Outstanding questions and next steps

Preclinical

- 'Profile C' modulators of both rodent and human TRPV1
- Efficacy after repeated dosing of TRPV1 antagonists
- TRPV1 function in non-pathophysiological states (e.g., thermosensation)

Clinical

- Development by different routes of administration (e.g., topical application)
- Development of short half-life antagonists
- Development of antipyretic + TRPV1 antagonist combination
- Development of TRPV1 antagonists in primary indications (e.g., Osteoarthritis)



The Team

Departments

Neuroscience
 PKDM
 Modeling
 E-phys
 Sample Bank
 Regulatory Affairs
 Toxicology
 Pharmaceutics
 Clinical
 Analytical
 Legal
 Project Management
 Marketing

Neuroscience

Leyla Arik
 Anthony Bannon
 James Davis
 Narender Gavva
 Charles Henley
 Gal Hever
 Rongzhen Kuang
 David Immke
 Sonya Lehto
 Lana Klionsky
 Ella Magal
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