



WorldPharma2010

16th World Congress on Basic and Clinical Pharmacology.
July 17-23, 2010, Copenhagen, Denmark

WorldPharma2010 will include a
congress workshop on

Targeting TRP channels for
pain relief (and more)

18 July 2010

12.45 - 16.15

**TRPV1 antagonists for pain relief,
cough and incontinence**

Marcello Trevisani, Ph.D.

PharmEste, Italy

PharmEste

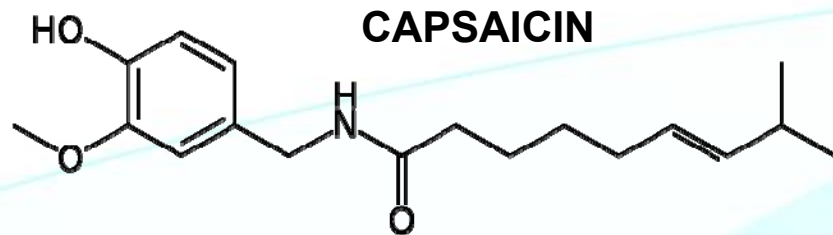
CAPSAICIN



Spicy Food



Medisterpølse



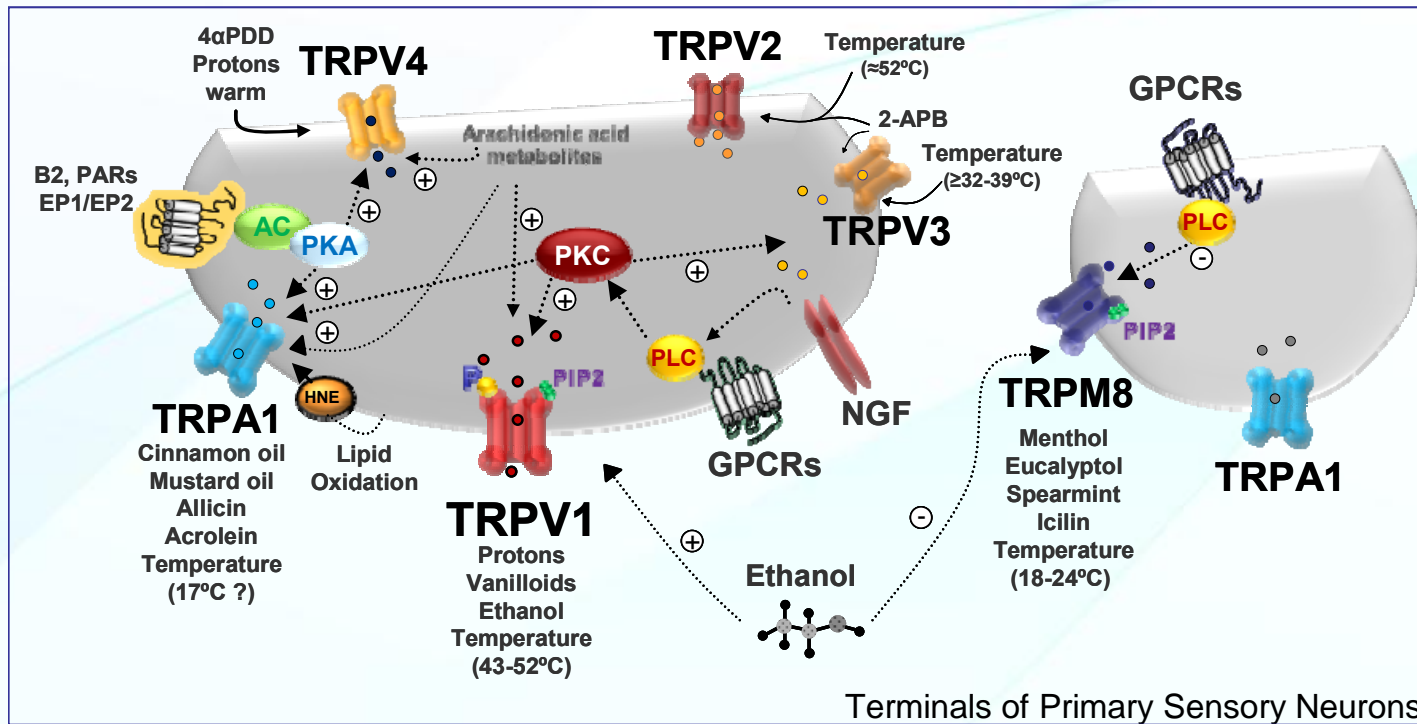
Hotness

Pungency

Vasodilatation

Redness

Specialized Sensors of a variety of Noxious Stimuli



CNS

Burning Pain
Cough

SYNAPTIC
TRANSMISSION

SP, NKA, CGRP
glutamate, aspartate

neuropeptide
synthesis

SENSORY
GANGLION

CAPSAICIN SENSITIVE PRIMARY
SENSORY NEURONS

Neurogenic
Inflammation

LOCAL EFFECTOR
FUNCTION

TRPV1

SP, NKA, CGRP

PNS

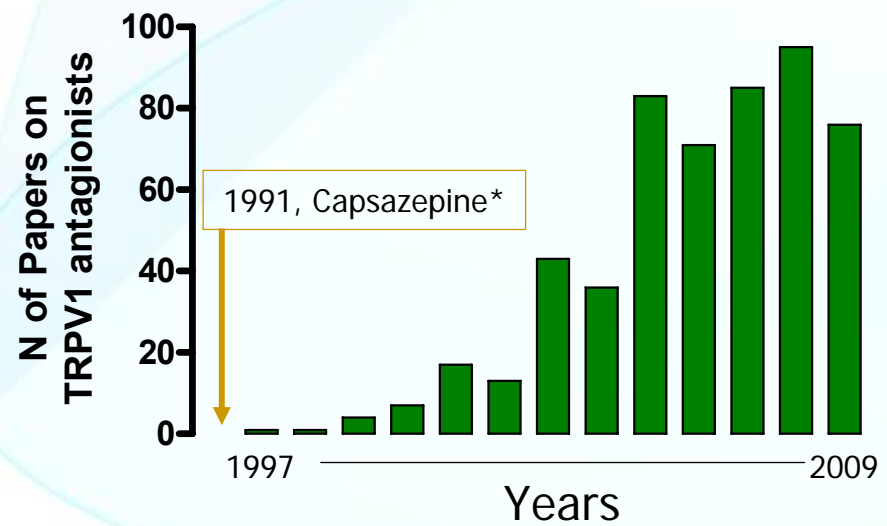
articles

The capsaicin receptor: a heat-activated ion channel in the pain pathway

Michael J. Caterina*, Mark A. Schumacher†‡, Makoto Tominaga*‡, Tobias A. Rosen*, Jon D. Levine‡ & David Julius*

Departments of* Cellular and Molecular Pharmacology, † Anesthesia, and ‡ Medicine, University of California, San Francisco, California 94143-0450, USA
‡ These authors contributed equally to this study.

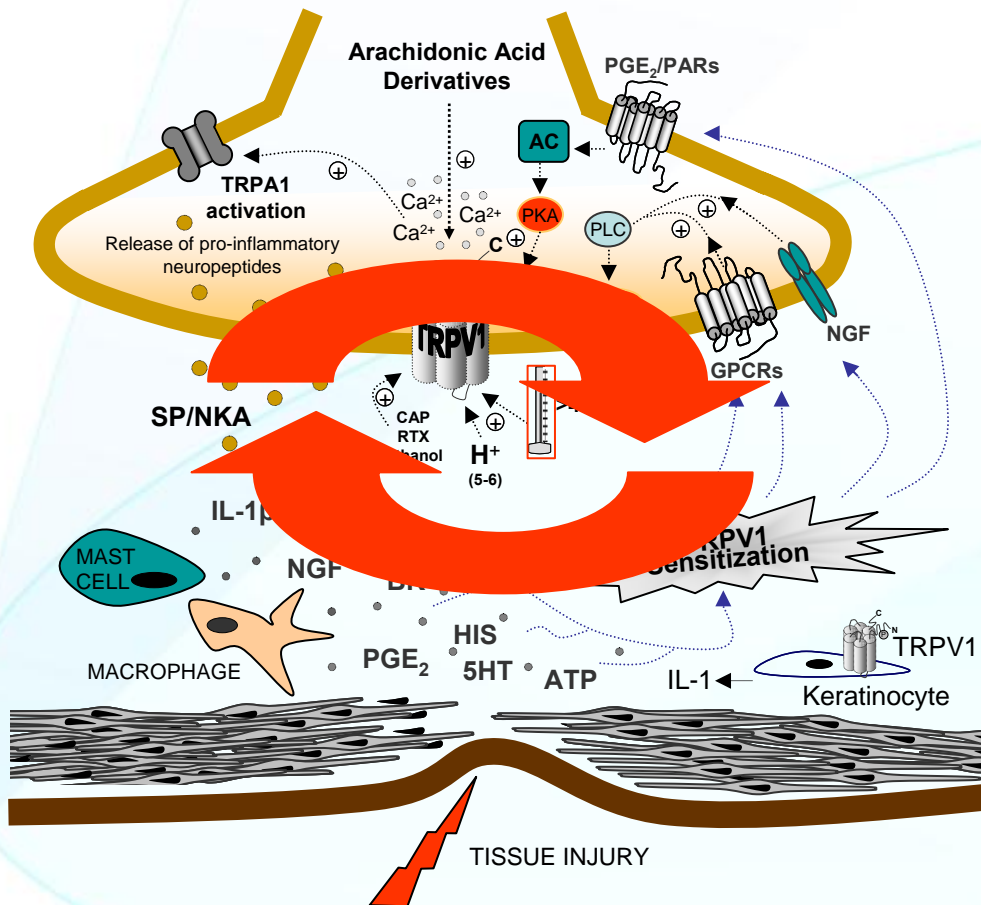
NATURE | VOL 389 | 23 OCTOBER 1997



To date, tens TRPV1 selective small molecule antagonists have been disclosed.

*, Bevan et al., Br. J. Pharmacol., 102, 77P & Dray et al., Br. J. Pharmacol., 102, 78P.

“The Strange Case of Dr. Jekyll and Mr. Hyde”



Elevated TRPV1 sensitivity / functionality.

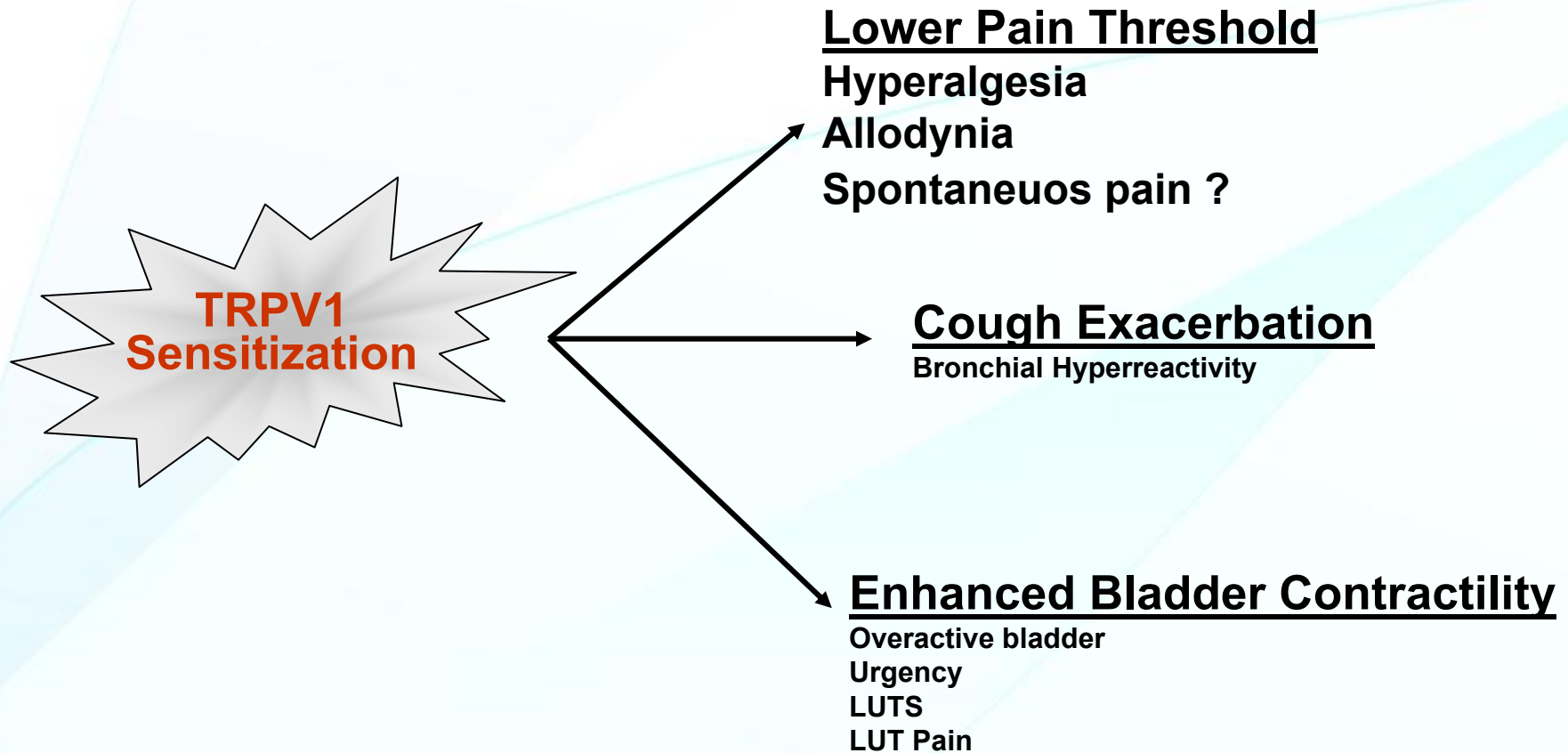
Lowered dynamic threshold of activation;

Pivotal role in Peripheral Sensitisation;

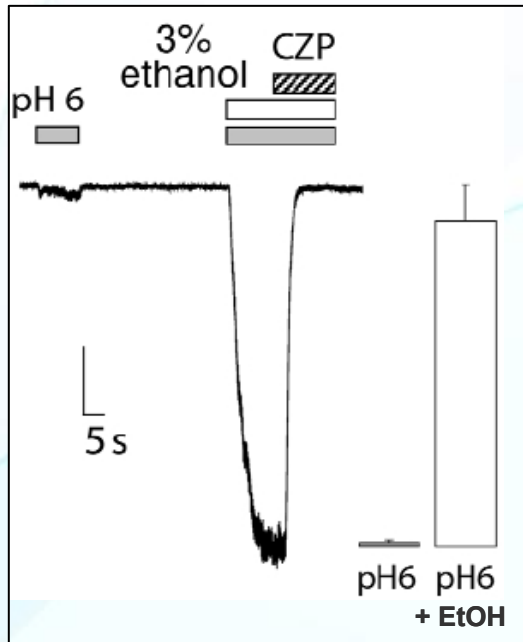
Modulation by intra and extracellular mediators (Inflammatory Soup);

Many intra and extracellular inputs converge on TRPV1;

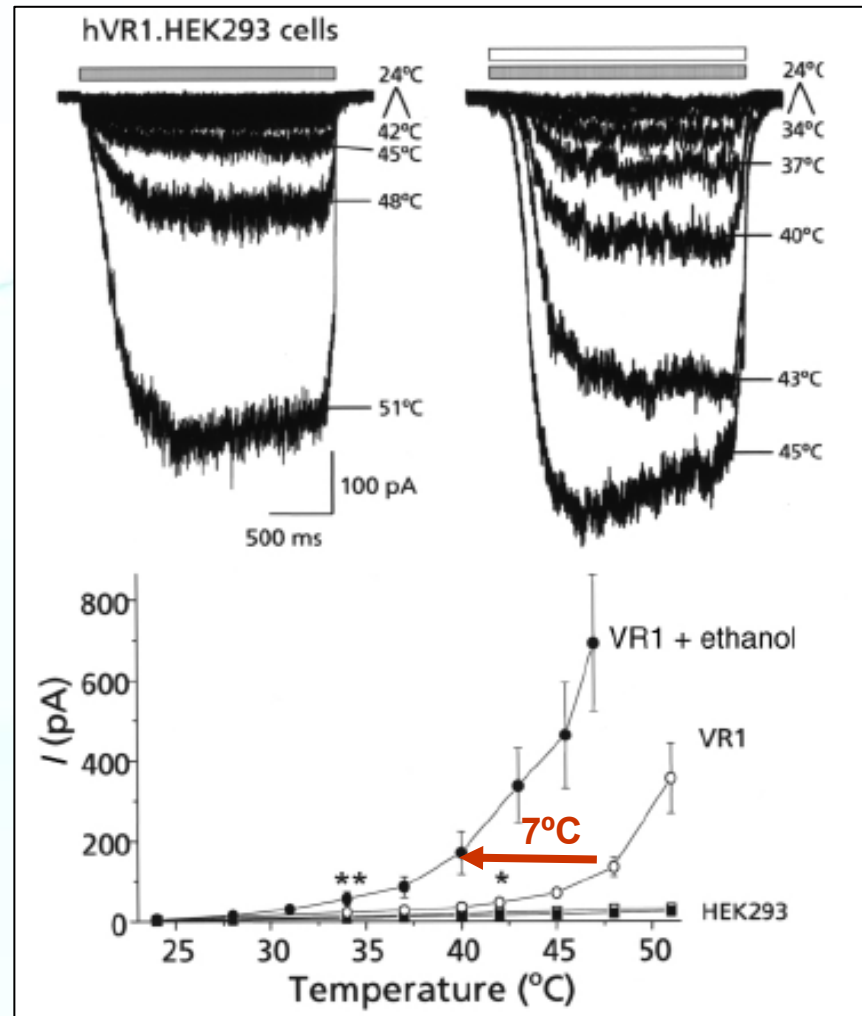
Trevisani M and Szallasi A, The Open Drug Discovery Journal, 2010, 2, 37-48



TRPV1 THRESHOLD OF ACTIVATION

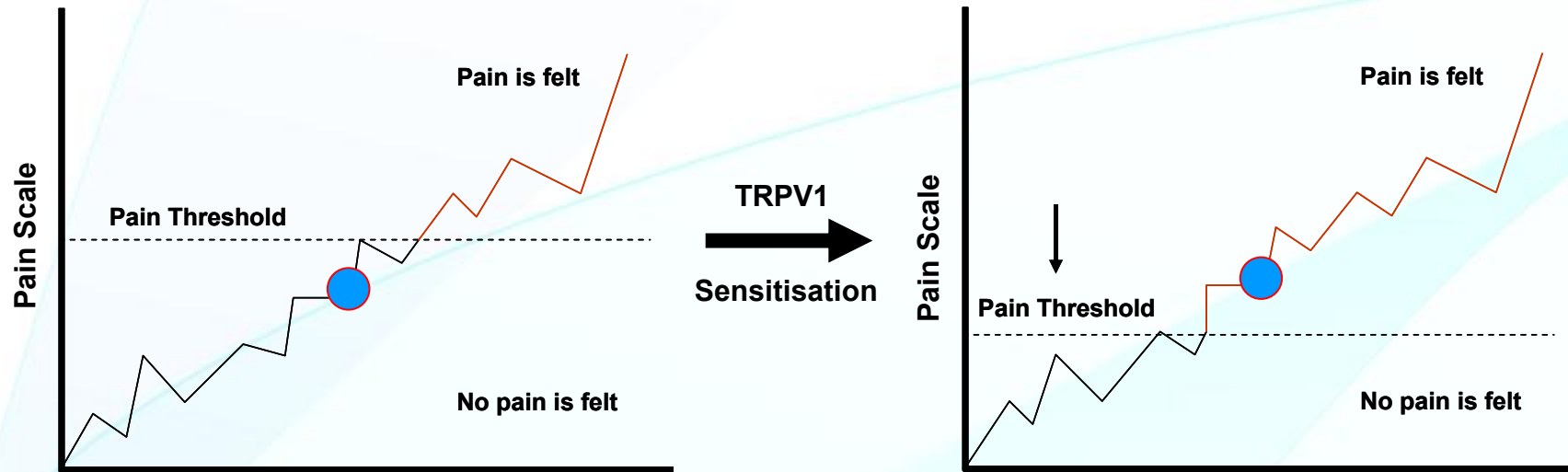


Trevisani et al., Nature Neurosc. 2002



Trevisani et al., Nature Neurosc. 2002

TRPV1 and PAIN THRESHOLD



**HYPERALGESIA / ALLODYNIA
NEUROPATHIC PAIN STATES**

TRPV1 antagonists: efficacy in **PAIN** MODELS



Acute nociception

- Hotplate and tail flick
- CAP & AA-induced nocifensive response

Inflammatory pain

- Formalin test (weak)
- Acute thermal hyperalgesia
- Chronic thermal hyperalgesia (CFA)

Neuropathic pain

- Chronic constriction injury (*Bennett and Xie, 1988*)
- L5/L6 nerve ligation (SNL, Kim and *Chung, 1992*)
- PSNL (*Seltzer et al. 1990*)
- Painful Diabetic Neuropathy

Postoperative somatic pain – Skin incision

- Thermal and mechanical

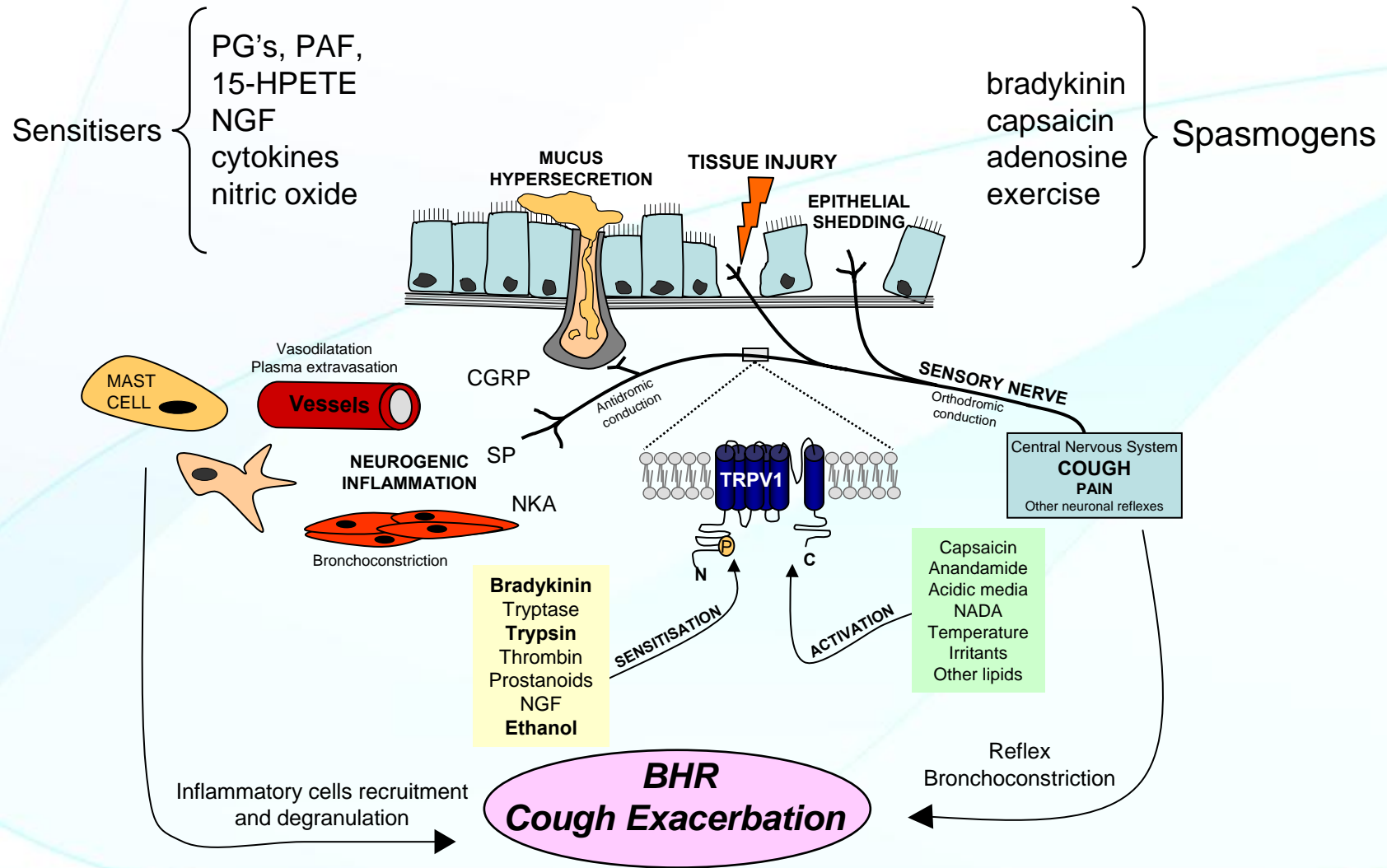
Osteoarthritic pain (MIA)

- Weight-bearing difference

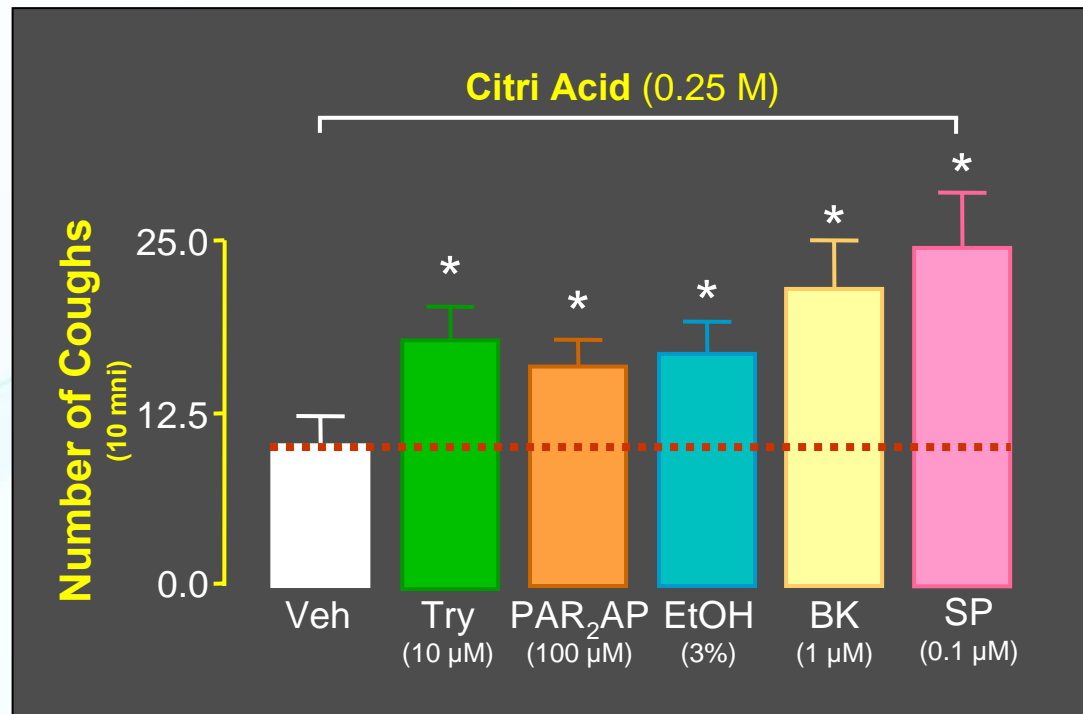
Cancer pain

- Bone cancer

TRPV1 and Bronchial Hyperactivity

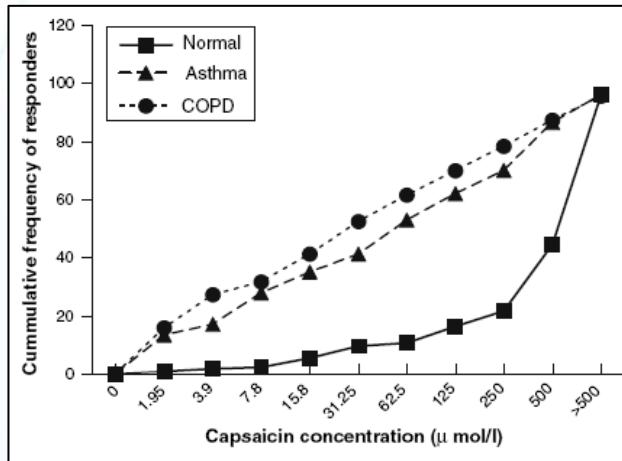


Exacerbation of TRPV1-mediated cough in the guinea pig

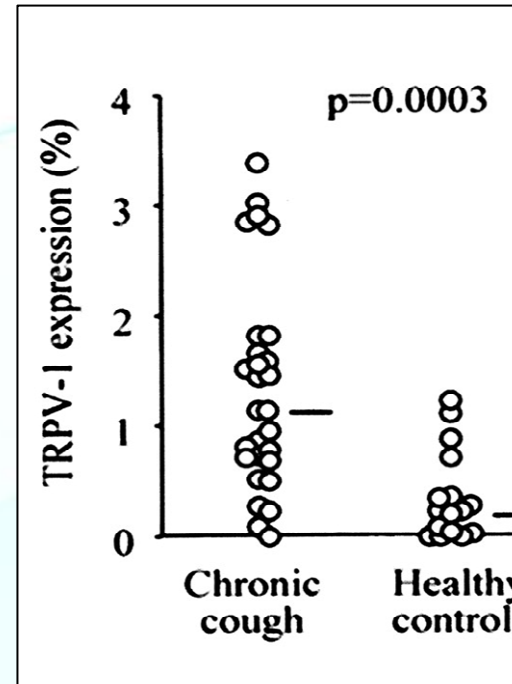


Trevisani et al., Thorax. 2004 Sep;59(9):769-72.
Gatti et al., J Appl Physiol. 2006 Aug;101(2):506-11.
Gatti et al., Pulm Pharmacol Ther. 2009 Feb;22(1):33-6.
Unpublished data

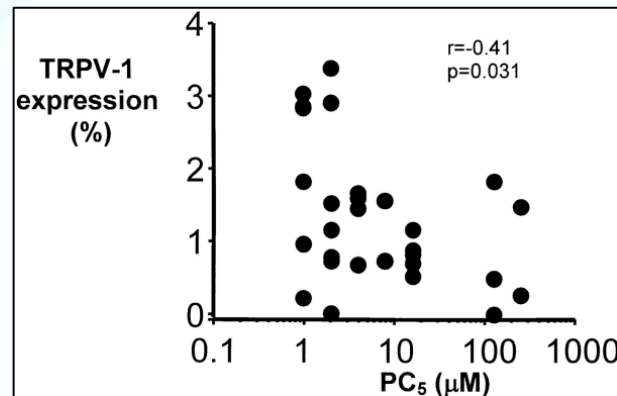
TRPV1 and chronic cough in humans



McLeod RL, Correll CC, Jia Y, Anthes JC. Lung. 2008;186 Suppl 1:S59-65.

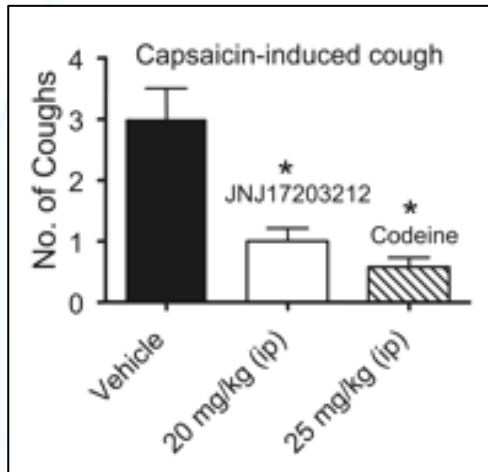


Groneberg et al., Am J Respir Crit Care Med. 2004.

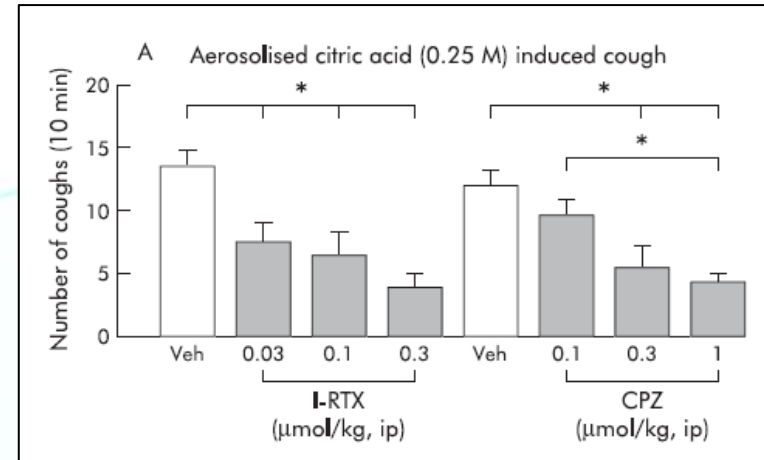


Groneberg et al., Am J Respir Crit Care Med. 2004.

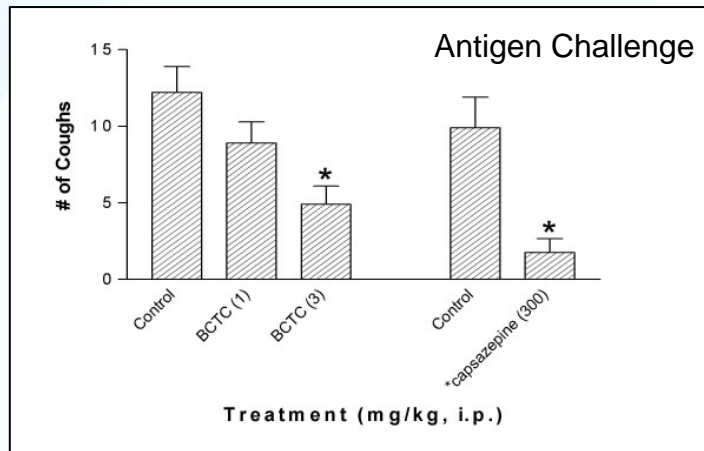
TRPV1 antagonists: efficacy in **COUGH** MODELS



Bhattacharya A, J Pharmacol Exp Ther. 2007 Nov;323(2):665-74.

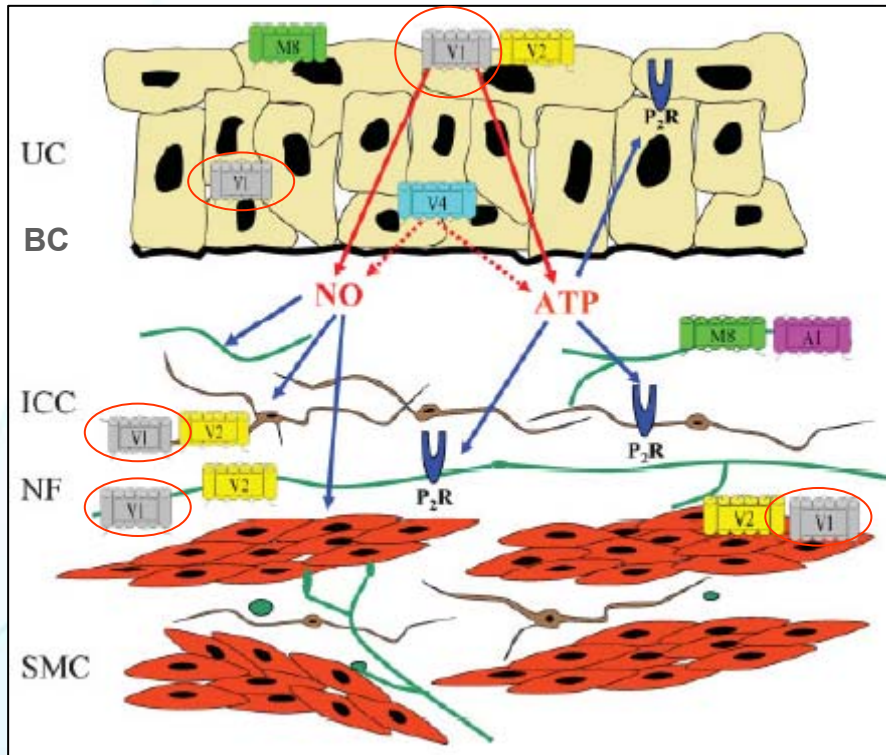


Trevisani et al., Thorax. 2004 Sep;59(9):769-72.



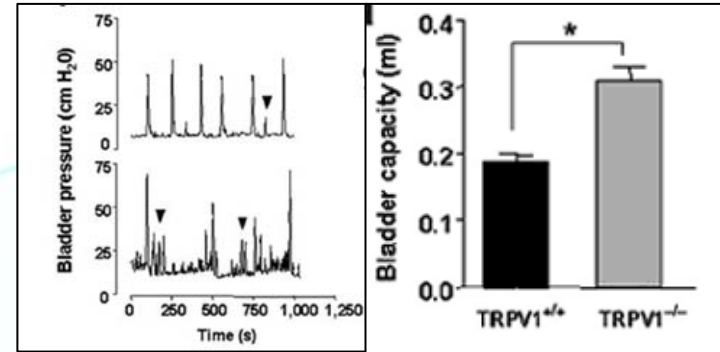
McLeod RL, Cough. 2006 Dec 15;2:10.

TRPV1 and Urinary Bladder

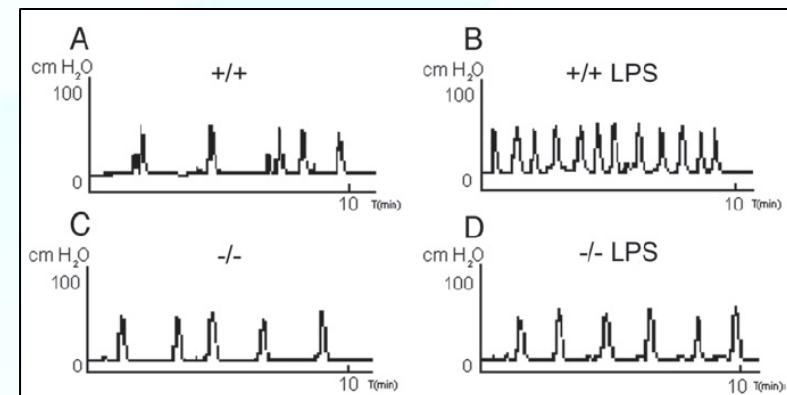


Everaerts et al., *Neurourol Urodyn.* 2008;27(4):264-73.

- on small unmyelinated (C-type) afferent
- myelinated (A-type) nerve fibers
- on interstitial cells in the suburothelium
- smooth muscle cell
- urothelium

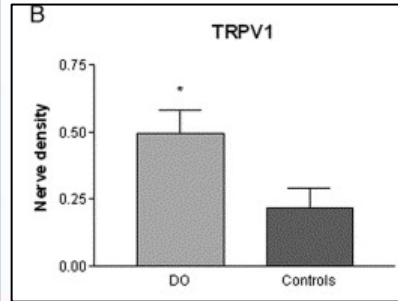
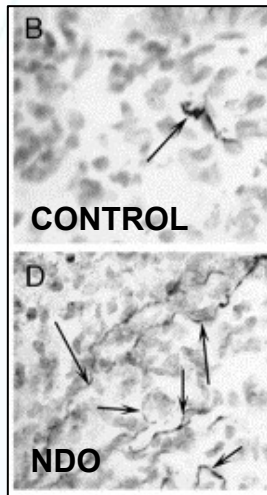


Birder *LA Nat Neurosci.* 2002 Sep;5(9):856-60.

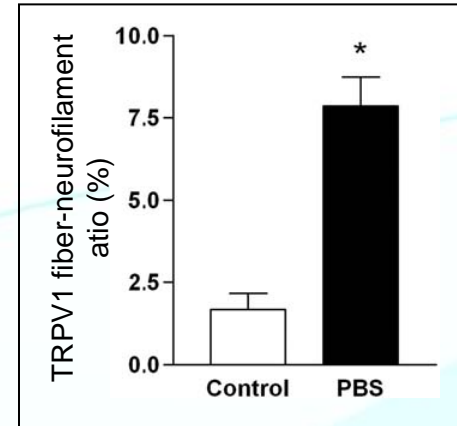


Charrua et al., *The Journal of Urology*, 177, 1537-1541, 2007

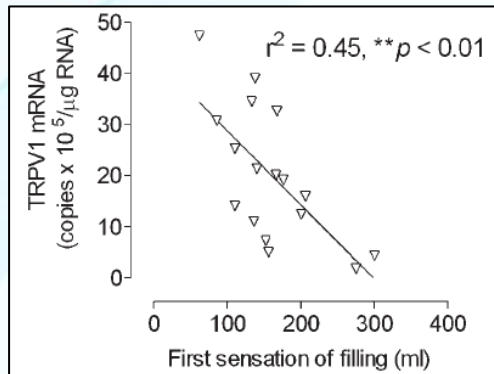
TRPV1 EXPRESSION IN HUMAN DISEASE (1)



Apostolidis A, J Urol. 2005
174(3):977-82; 2005



Mukerji, G, THE JOURNAL OF UROLOGY 176, 2006



Liu L, NeuroUrol Urodyn. 2007;26(3):433-8;

TABLE II. The Amount of TRPV1 mRNA ($10^5 \times$ Copies/ μ g Total RNA) Expressed in Human Bladder Biopsies, Determined by QC-RT-PCR

	Control	SU	IDO
Body mucosa	14.2 (8.2–20.7), n = 35	8.2 (4.2–20.3), n = 17	11.4 (6.7–16.1), n = 10
Trigonal mucosa	4.1 (0.77–26.2), n = 6	17.5 (10.9–28.0)*, n = 20	10.9 (8.5–15.7), n = 12

Data are expressed as median (IQR).

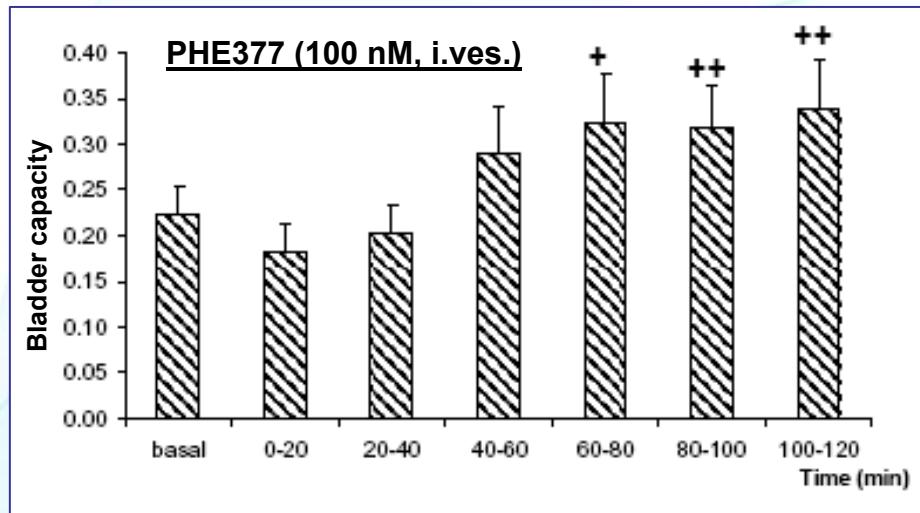
* $p < 0.05$ compared to trigonal mucosa of control biopsies (Kruskal–Wallis non-parametric one-way ANOVA test followed by Dunn’s multiple comparison).

The TRPV1 mRNA expression level in trigonal mucosa of SU patients correlated inversely with the bladder volume at first sensation of filling.

TRPV1 antagonists: efficacy in **BLADDER OVERACTIVITY MODELS**

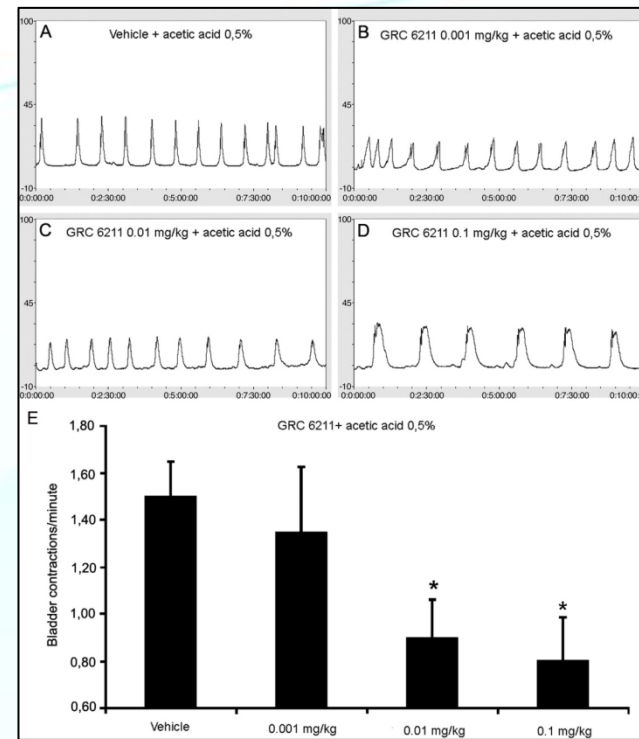


Cyclophosphamide Induced Bladder Overactivity

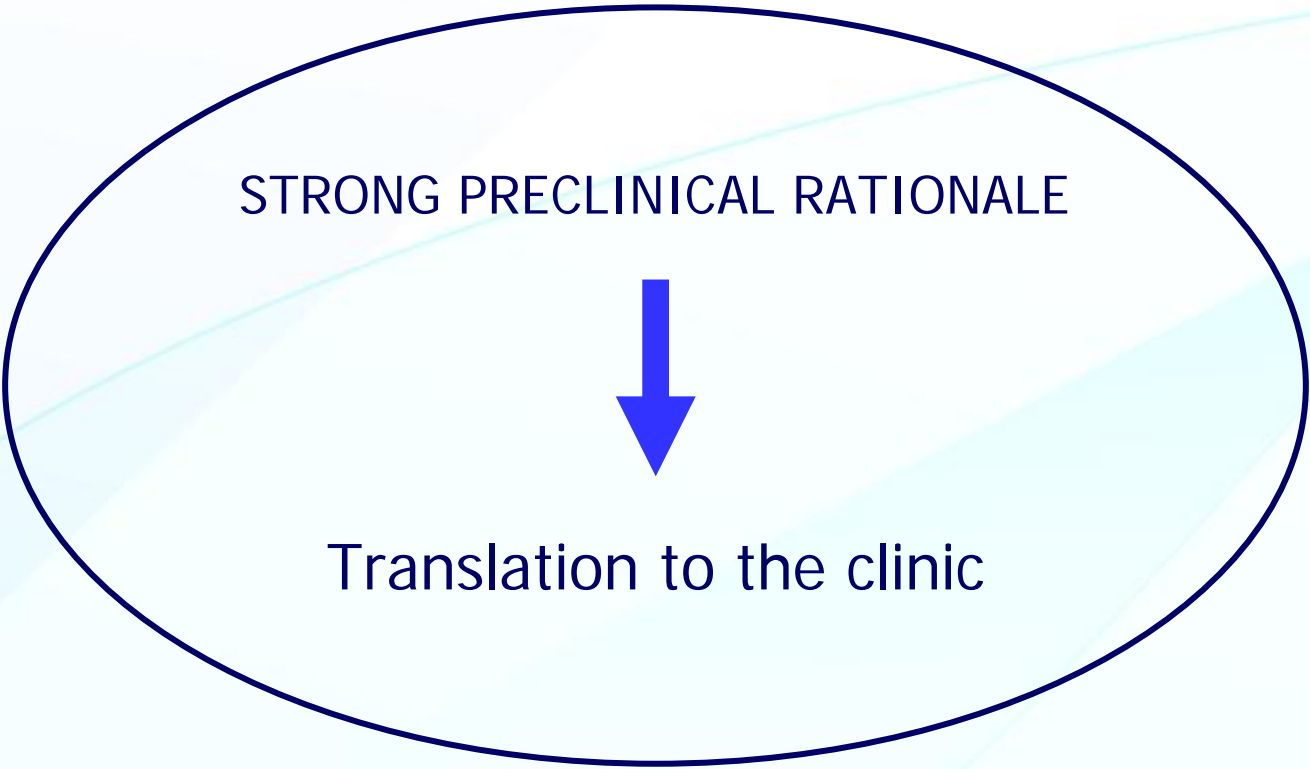


PharmEste, Unpublished Data

Acetic acid-induced bladder contractions



Charrua A et al., The Journal of Urology, 181, 1, 2009, Pages 379-386



SB-705498 (GSK)

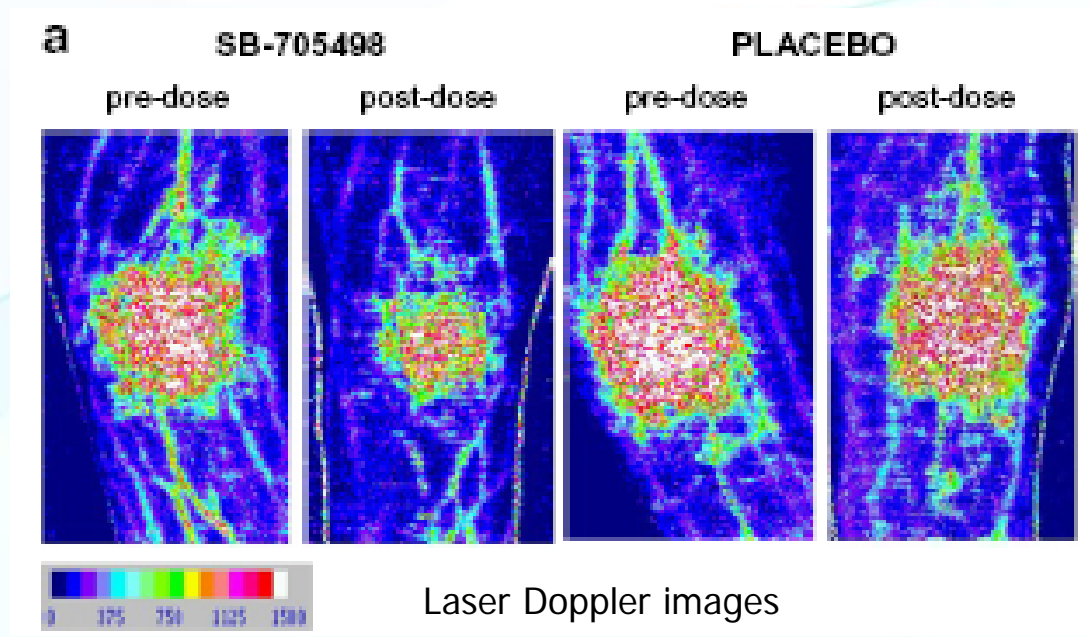
- **Part 1**: Placebo-controlled escalating dose in 24 healthy volunteers
(Characterise the safety, tolerability and PKs)

SB-705498 appeared safe, well tolerated
with minor adverse events not related with the treatment

- **Part 2**: Randomized single-blind (400 mg)
(PD assessment)

- Capsaicin-Induced Flare

Flare evoked by topical application of capsaicin cream



- **Part 1**: Single dose safety and pharmacokinetics

a single oral dose of placebo, or 1, 2, 5, 10, 20, or 25 mg AMG 517
(primary endpoints: treatment-emergent adverse events)

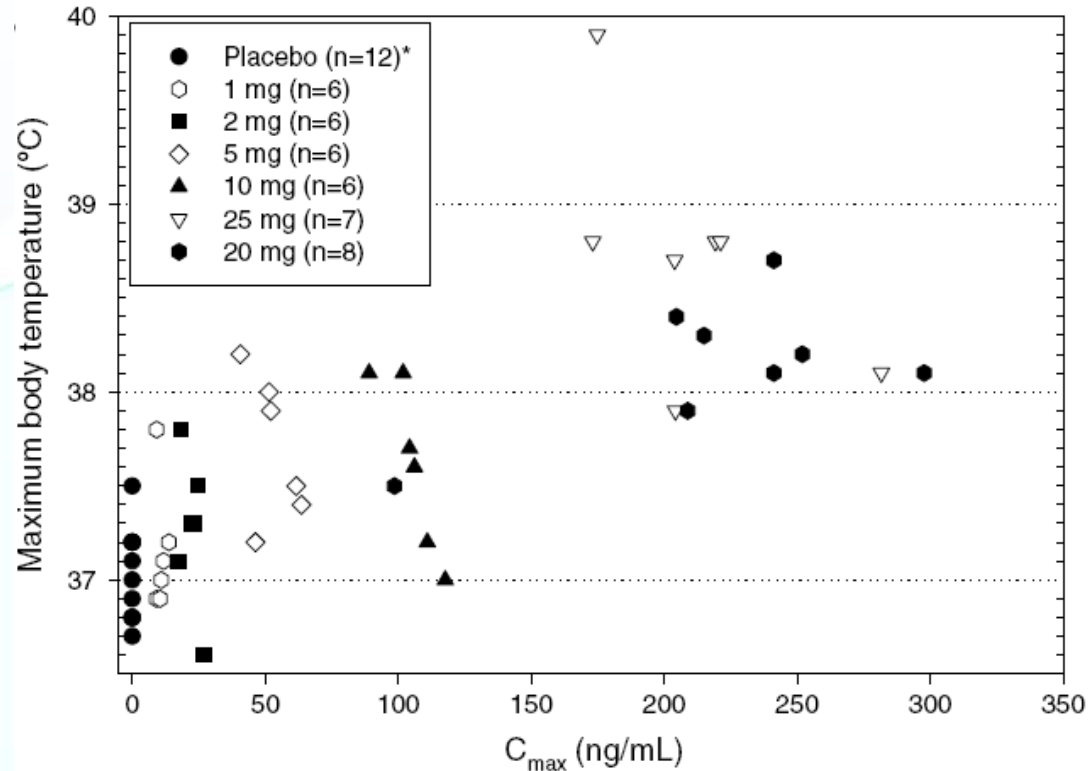
- **Part 2**: Multiple dose-temperature

7 days of either placebo or 2, 5 or 10 mg AMG 517
(primary endpoints: treatment-emergent adverse events and difference in max body temperature)

Phase Ib: Molar extraction study

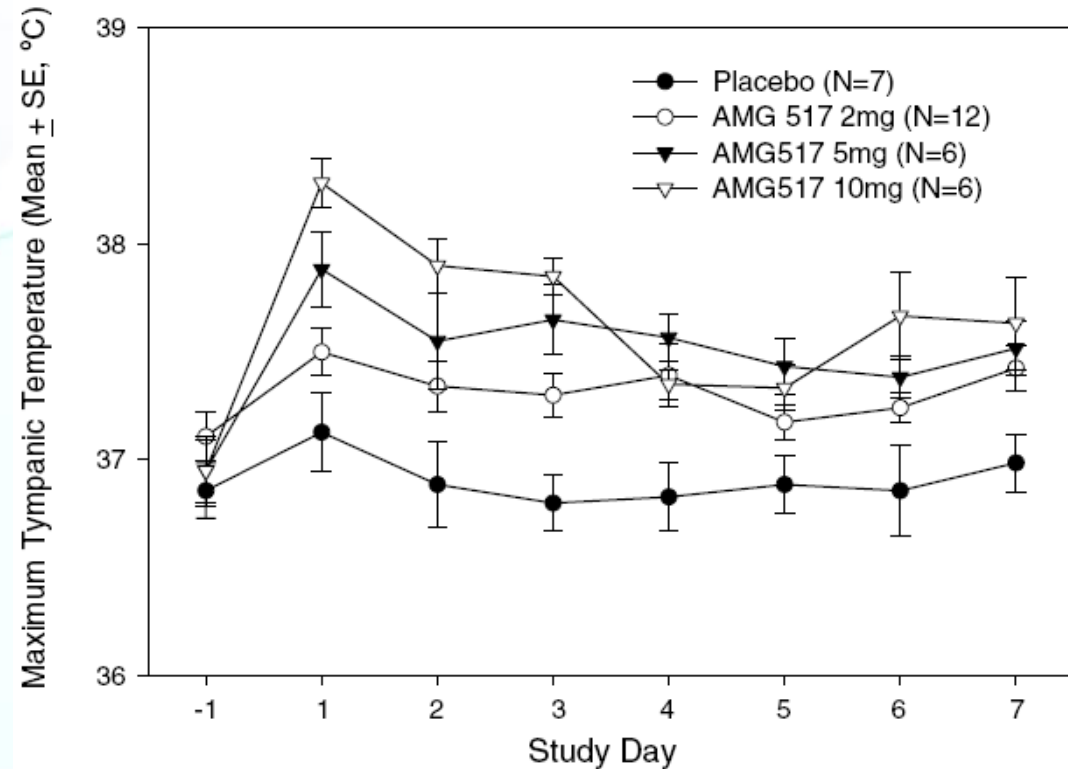
Single doses of 2, 8 or 15 mg of AMG 517, 400 mg of ibuprofen, or placebo
(primary endpoints: treatment-emergent adverse events and relief from pain during an 8-h period after administration)

AMG 517 elicited a generally plasma concentration-dependent hyperthermia in humans



Body temperature typically increased between 1 and 4 h after AMG 517 administration and returned to baseline values within 24 h, suggesting the transient nature of hyperthermia induced by AMG 517.

AMG 517-induced hyperthermia was attenuated after repeated (at the highest dose tested)



AMG 517 for 7 days: hyperthermia was attenuated after repeated dosing of the 10 mg dose, but not the 2 or 5 mg doses of AMG 517, suggesting that attenuation of hyperthermia is dose-dependent.

PHE-377 is a **potent, competitive** and **selective** TRPV1 antagonist.

It is orally available and shows good efficacy in variety of **pain models** (acute and chronic and neuropathic pain)

High safety profile both in rats and dogs

Appropriate **systemic exposure**

No effect on body temperature

No adverse effect in 28 day Tox

No effect on **motor activity** and **memory/learning**

Phase I: ONGOING

A class of compounds that may offer one of the first novel mechanistic treatments for a wide range of acute and chronic pain disorders for many years

?

We are still waiting for a “REAL” PoC in Humans