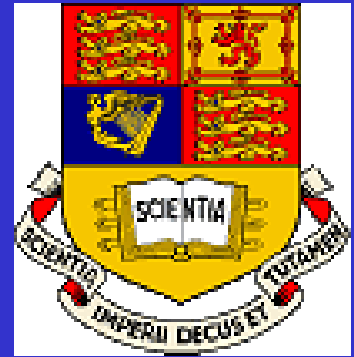


Imperial College London



Translational PD Studies in Early Stage CNS Drug Development: AHPPI conference

October 2013, London

Meeting translational needs for novel
neuropathic pain drug development

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Too many potential targets ?

Need validation for successful Clinical Trials

Novel pain targets in human neuropathic pain states:

Nav 1.8, 1.9 (SNS1,2) (Coward et al, 2000, Shembalkar et al, 2001, Bucknill et al, 2002)

Nav 1.7 (PNI), Brain III (Coward et al, 2001)

$\beta 1$, $\beta 2$ and $\beta 3$ subunits (Coward et al 2001, Casula et al, 2002)

P2X3 (Yiangou et al, 2001)

ASIC3 (Yiangou et al, 2001)

NaG (Coward et al, 2001)

Vanilloid-like receptor, TRPV1 (Chan et al, 2003)

Vanilloid-like receptor, TRPV4 (Delany et al, 2001)

Vanilloid-like receptor, TRPV3 (Smith et al, 2002)

Calcium-activated potassium channels (Boettger et al, 2002)

P2X7 (Chessell et al, 2004)

R-type calcium channels (Green et al, 2002)

B1 receptor (Casula et al, 2002)

Cox-2, EP1, CB2, TRPM8, TRPA1, EP1, SNSR, p38MAPK, TrkA, AT2R

Translational pain medicine needs

Validation of novel drug targets in common human pain states

In vitro human surrogates : “clinical trial in a dish”

Biomarkers / surrogates for pain : pathophysiological and imaging

New volunteer / patient clinical models for designer drugs

Aim to deliver:

Pre-clinical to POC / Phase II success

Rational mechanistic trials with homogenous patient sub-groups
 (“Matchmaking”)

Meeting translational needs

illustrated with target TRPV1, the heat and capsaicin receptor and CHEPS, for new pain medicines

Validated novel targets (TRPV1) in common human clinical states

In vitro (hDRG), physiological (CHEPS) and fMRI human surrogates

New volunteer / patient clinical models for novel drugs (PBS, IBS)

Aim to deliver:

Pre-clinical to POC / Phase II success (PD in Phase I / IIa)

Rational mechanistic trials with homogenous patient sub-groups

TRP agonists



Capsaicin

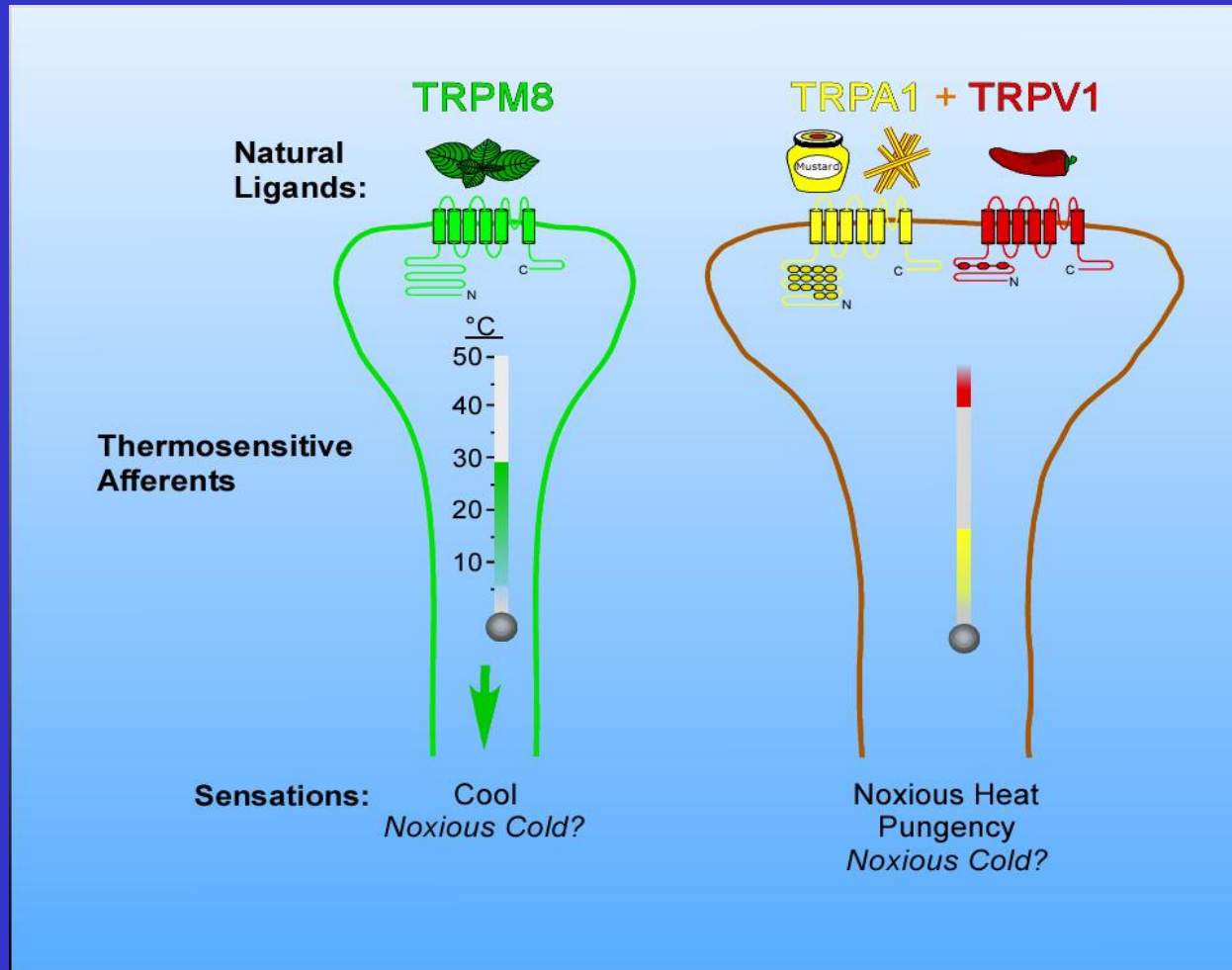
Activates TRPV1, causes a burning sensation



Menthol

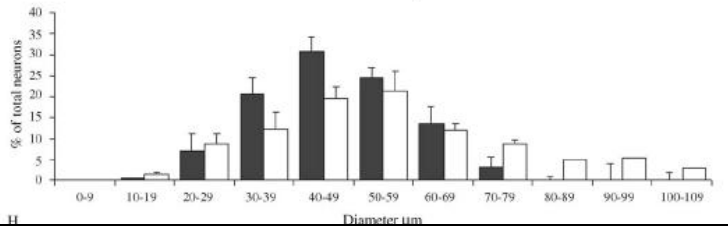
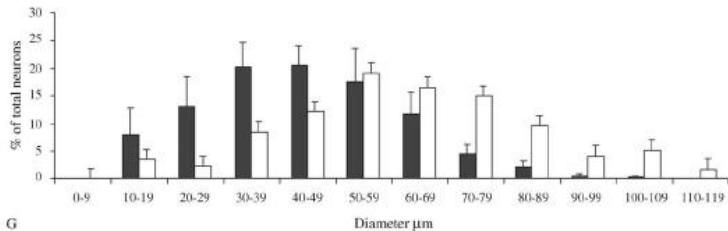
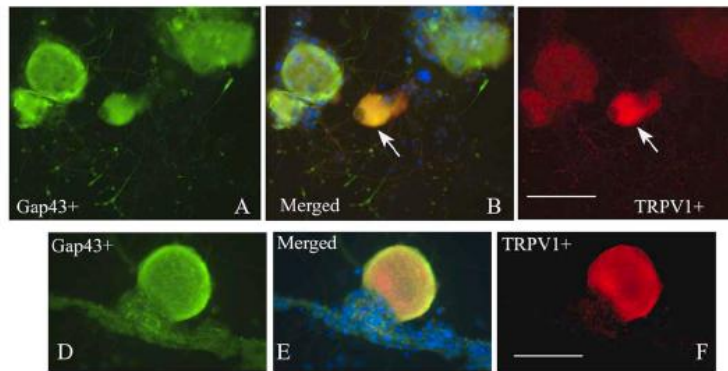
Activates TRPM8,
produces a cool sensation

TRP agonist activation of sensory neurons



Co-localisation and paradoxical sensation

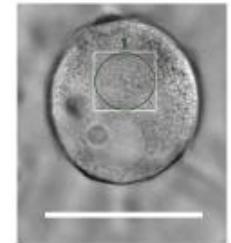
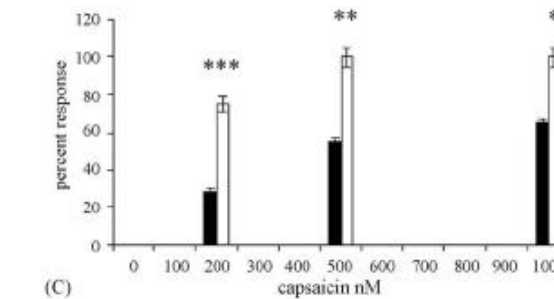
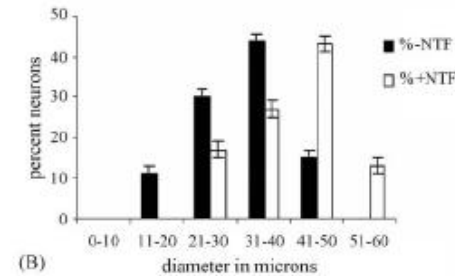
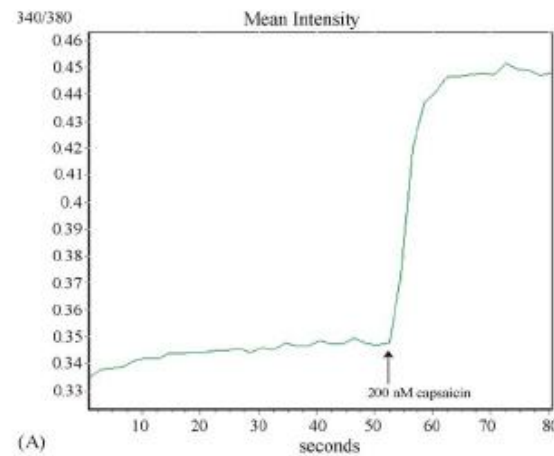
TRPV1 expression in human DRG neurons, in vitro model – “clinical trial in a dish”



TRPV1 (red) and Gap43 (green)

Gap43 neurons with NTFs (clear bars) and without NTFs (solid bars).

TRPV1+neurons with NTFs (clear bars) and without NTFs (solid bars).

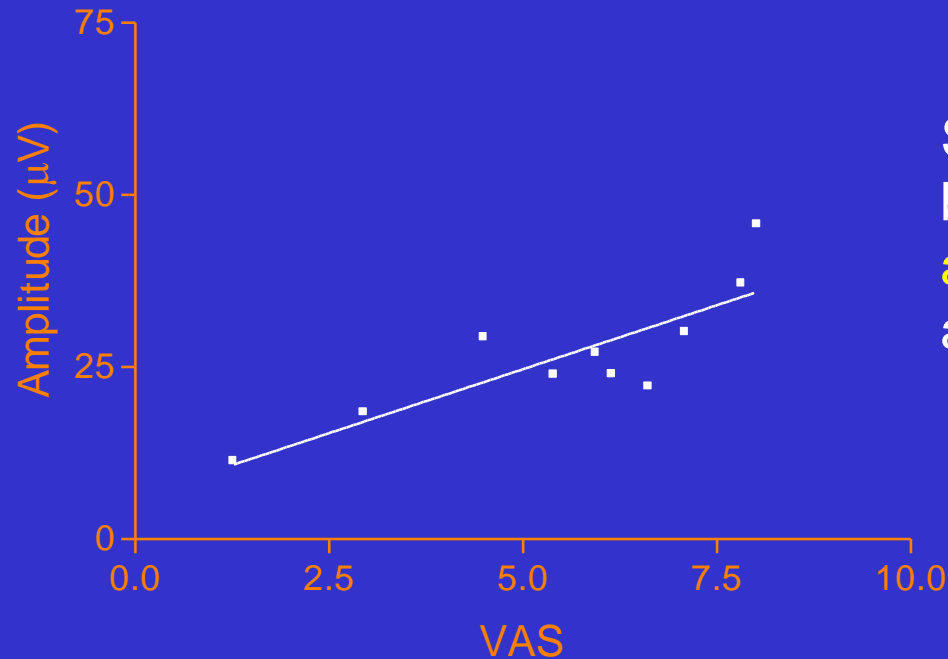


Baseline intracellular 340/380 (bound/unbound Ca) ratio, and increase due to influx by capsaicin stimulation (top).

Capsaicin responses are significantly enhanced after culturing with NTFs (clear bars) than without NTFs (solid bars)

Anand et al 2006

CHEPS – Correlation with pain



Significant positive correlation between **average VAS** and **average amplitude** (baseline 1 and 2 + fMRI 1 and 2 data) ($r_s = 0.7939$ $p = 0.0044$ **)

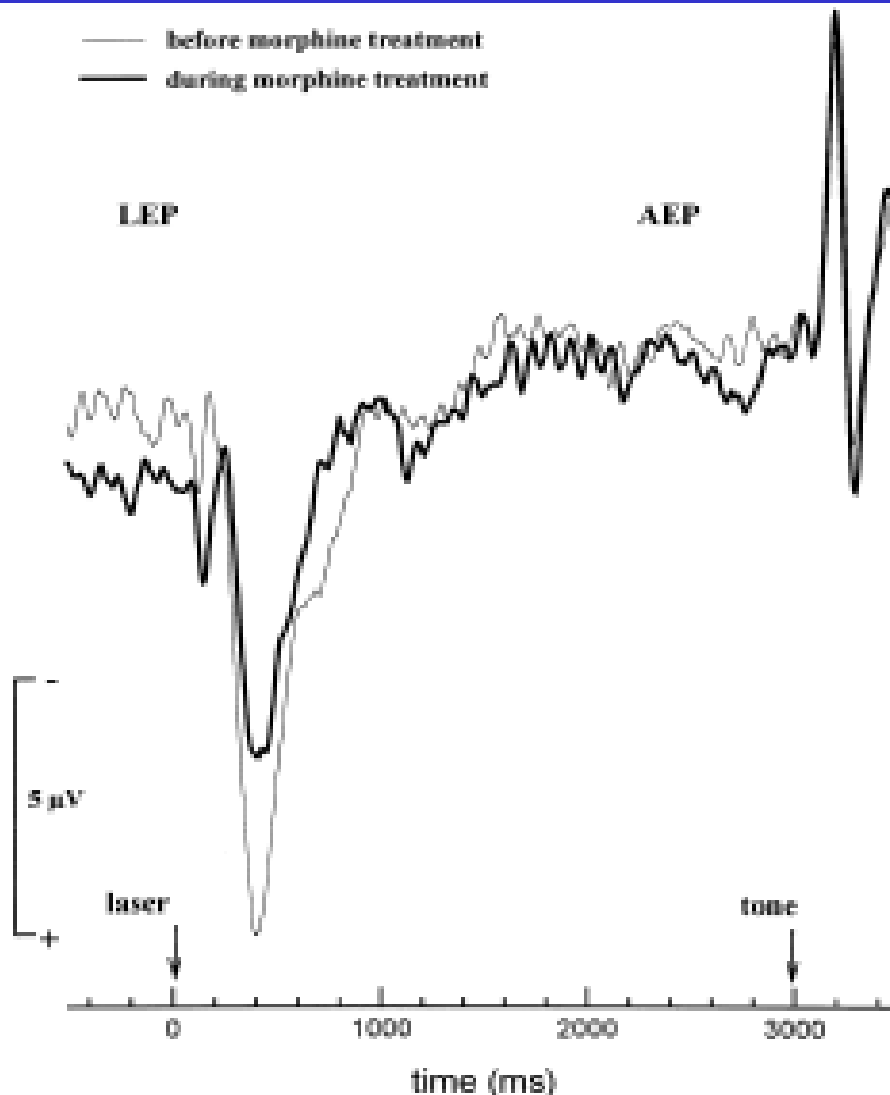
■ Contact heat evoked potentials have been shown to linearly correlate with VAS pain scores

Pharmaceutical Applications and Clinical trials

Pain EPs produced by **CHEPS** may be used in the assessment of pain relieving agents: similar to laser literature

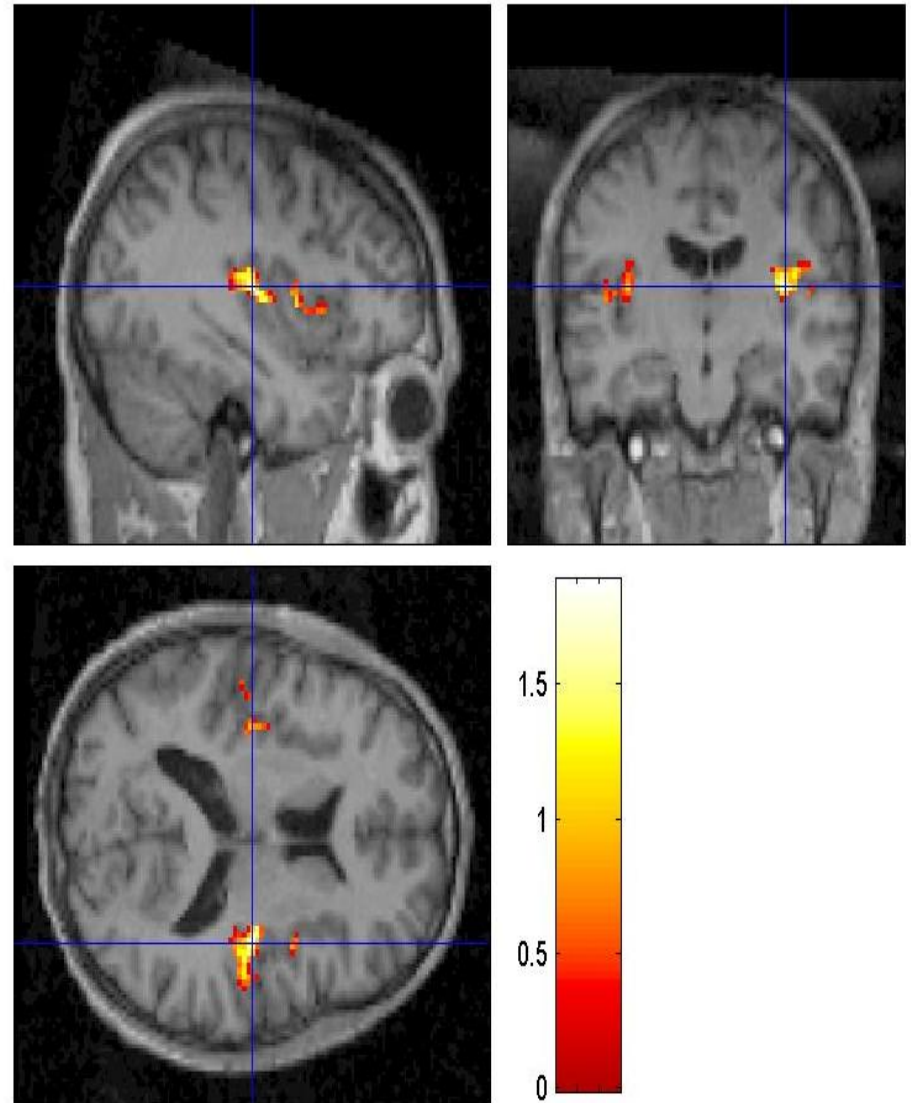
For Example Oral morphine reduces A delta amplitude but doesn't influence the AEP

(Lorenz et al., 1997)



EP and fMRI co-registration studies in clinical chronic pain states

**CHEPS with fMRI –
a powerful sensitive
non-invasive tool
to investigate neuropathic
pain mechanisms
and drug development
(PK-PD, single dose)**



TRPV1 antagonist in human volunteer studies

- Elevate heat pain threshold in volunteers (GSK)
- Reduce skin flare area spread in volunteer models (GSK)
- **Transient increase of body temperature**
(1 – 2 deg C for 24 – 48 hours) (Amgen)

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Recent successful clinical translation to Phase II
for neuropathic pain medicines

P38 MAPK inhibitor Dilmapimod
GlaxoSmithKline

AT2 Type 2 inhibitor EMA401
Spinifex

TrkA inhibitor CT327 for itch
Creabilis

High dose 8% capsaicin patch Qutenza (novel application)
Astellas

Background – p38 MAP kinase

- p38 α mitogen-activated protein kinase is a serine/threonine-directed protein kinase
- p38 MAPK activation is involved in a cytokine amplification loop
- Inhibitors of this kinase are expected to be effective in diseases where the pro-inflammatory mechanisms are cytokine-dependent

p38 MAP kinase inhibitor for neuropathic pain

Successful translation from lab to clinical trial

Collaboration with industry: GlaxoSmithKline



Clinical trial of the p38 MAP kinase inhibitor dilmapimod in neuropathic pain following nerve injury

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^a Peripheral Neuropathy Unit, Hammersmith Hospital, Imperial College, London, UK

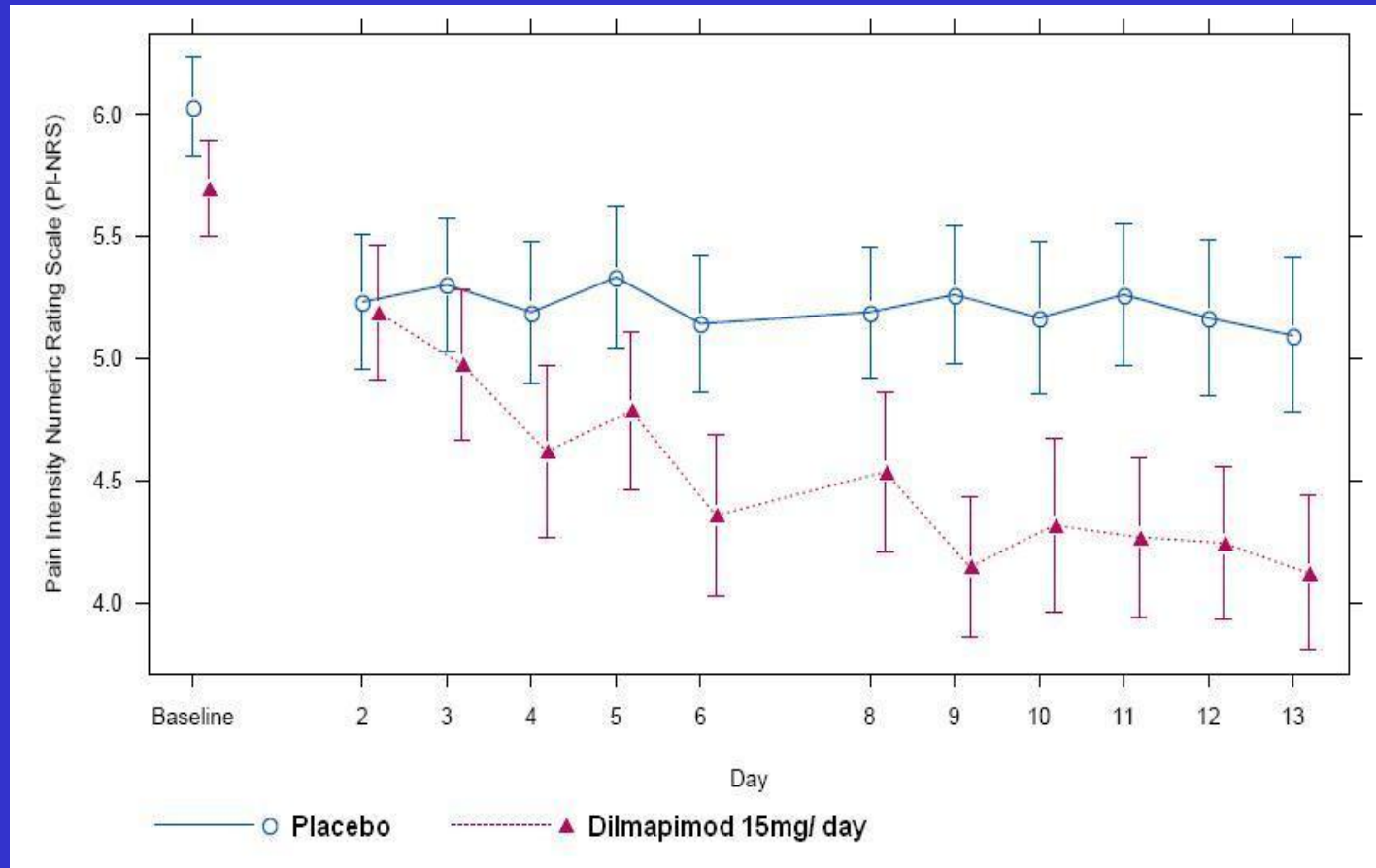
^b Clinical Pharmacology and Discovery Medicine, GlaxoSmithKline R&D, Cambridge, UK

^c Neurosciences Discovery Medicine, GlaxoSmithKline R&D, Harlow, UK

^d Neurosciences Discovery Biometrics, GlaxoSmithKline R&D, Harlow, UK

p38 inhibitor Dilmapimod clinical trial for chronic neuropathic pain (nerve injury)

Pain intensity scores



PAIN

MAPK inhibitor shows promise in clinical trial for neuropathic pain

Dilmapimod, a p38 mitogen-activated protein kinase (MAPK) inhibitor, could be beneficial in neuropathic pain, according to a double-blind, placebo-controlled, two-period crossover trial involving 43 patients.

“...treatment with dilmapimod was associated with attenuated neuropathic pain...”

Chronic neuropathic pain arises following damage to the nervous system and is a feature of numerous diseases, including diabetic neuropathy and postherpetic neuralgia. Current therapies offer only partial pain relief and are associated with adverse effects. “There is a high unmet clinical need for effective treatment of chronic neuropathic pain,” says Praveen Anand, Professor of Clinical Neurology at Imperial College London and lead author of the study, which was an academia–industry partnership with GlaxoSmithKline. “p38 MAPK has been identified as the target of a novel class of cytokine-suppressive anti-inflammatory drugs (CSAIDs), and its inhibition has been shown to reduce neuropathic pain in animal models.”

Patients enrolled in the study had focal neuropathic pain related to nerve injury, lumbosacral radiculopathy or carpal tunnel syndrome. The study protocol involved 2 weeks of twice-daily oral

doses of either 7.5 mg dilmapimod or placebo, followed by a washout period of 2–4 weeks before crossover to the drug or placebo for 2 weeks. Patients recorded daily pain intensities on the 11-point pain intensity numerical rating scale (PI-NRS). Some concomitant medications for pain relief, such as opioids, were permitted, whereas others, such as nerve blocks and anti-inflammatory drugs, were not.

After 2 weeks of dosing, treatment with dilmapimod was associated with attenuated neuropathic pain: the drug produced a statistically significant reduction in the mean daily PI-NRS score compared with placebo ($P=0.0034$) and the proportion of patients with a 50% response rate was significantly higher after 2 weeks of treatment with dilmapimod than with placebo. In addition, the drug was well-tolerated.

“The study provides the first demonstration that this novel class of CSAIDs has the potential to be developed as a treatment for clinical neuropathic pain,” explains Anand. Larger, parallel-group trials are currently underway for the use of another p38 MAPK inhibitor to treat peripheral nerve injury and lumbosacral radiculopathy.

Katie Kingwell

Original article Anand, P. et al. Clinical trial of the p38 MAP kinase inhibitor dilmapimod in neuropathic pain following nerve injury. *Eur. J. Pain* doi:10.1016/j.ejpain.2011.04.005

“CSAID” Cytokine Suppressive Anti-inflam Drug

Novel First-in-class for Neuropathic pain

TrkA inhibitor CT327 for itch

- In vitro studies of CT327 showed inhibition of capsaicin responses (70%) at dose which did not affect neurite outgrowth
- Placebo-controlled study of topical CT327 administered to 160 patients with psoriasis for up to 8 weeks.
- There was a statistically significant and clinically meaningful reduction of VAS for pruritus (60% reduction for lowest dose CT327, versus 20.4% for placebo, $p < 0.05$).
- These findings indicate the prospect of effective and safe TrkA inhibitor topical treatment for cutaneous hypersensitivity in clinical disorders. First in class.

Angiotensin II receptor Type 2 (AT2R) in clinical tissues and in vitro studies

Localisation and levels of AT2 receptors in peripheral nerves

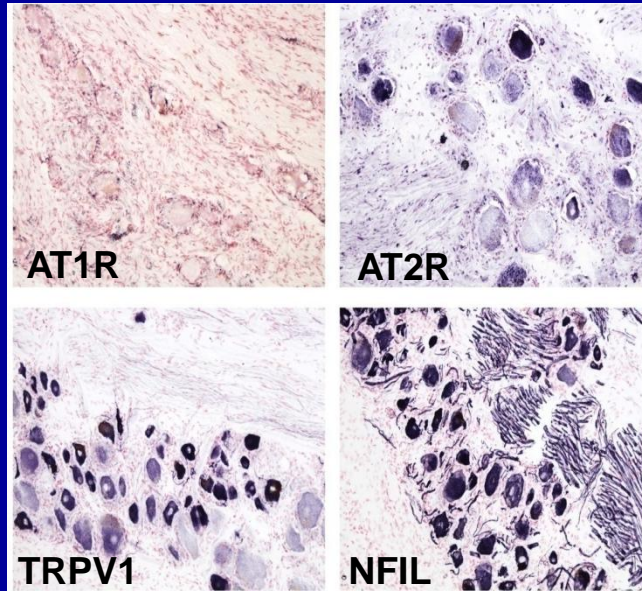
with a panel of antibodies

from patients with chronic pain and hypersensitivity disorders

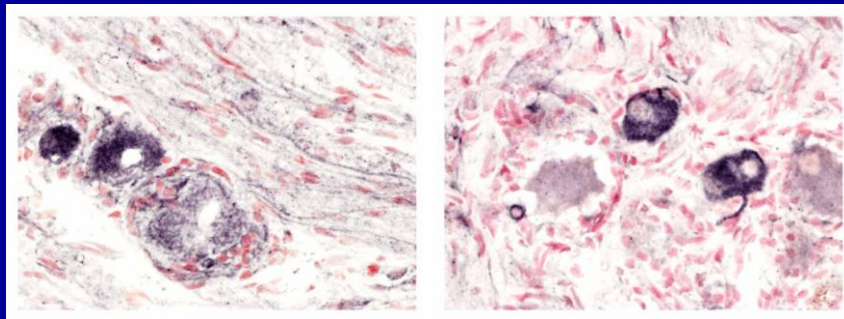
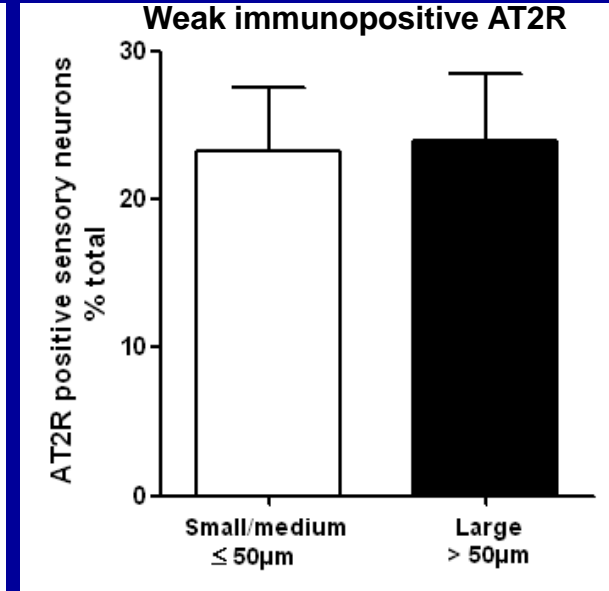
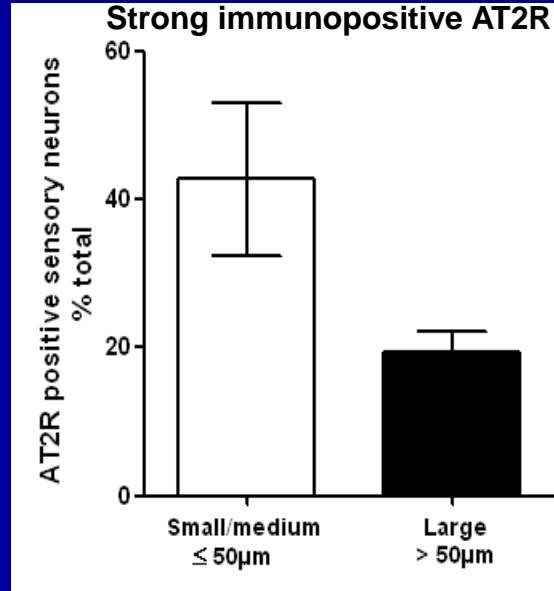
for clinical target validation

and selection of cohorts for rational clinical trials

AT2R is expressed by nociceptors in injured human dorsal root ganglia



AT2 R Ab sc 7420



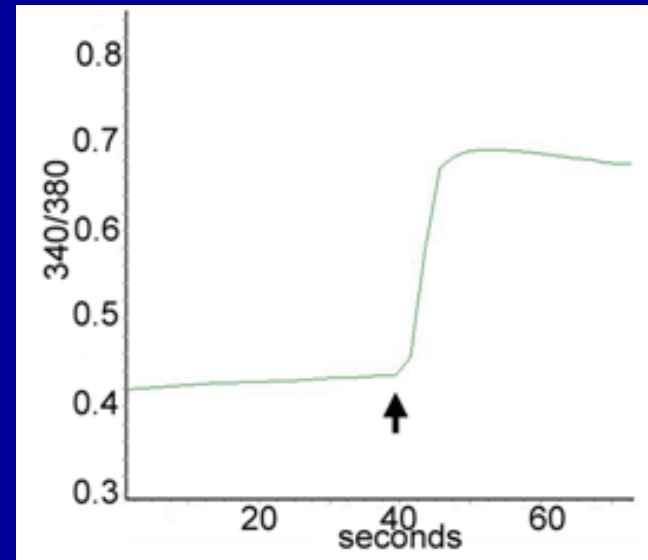
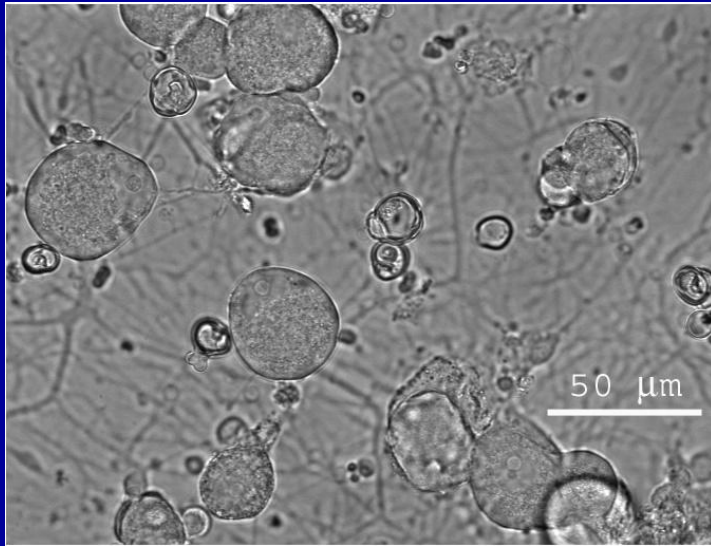
post-fixed

pre-fixed

AT2 R Ab sc 48452

AT2R co-localises with TRPV1, the capsaicin and heat receptor

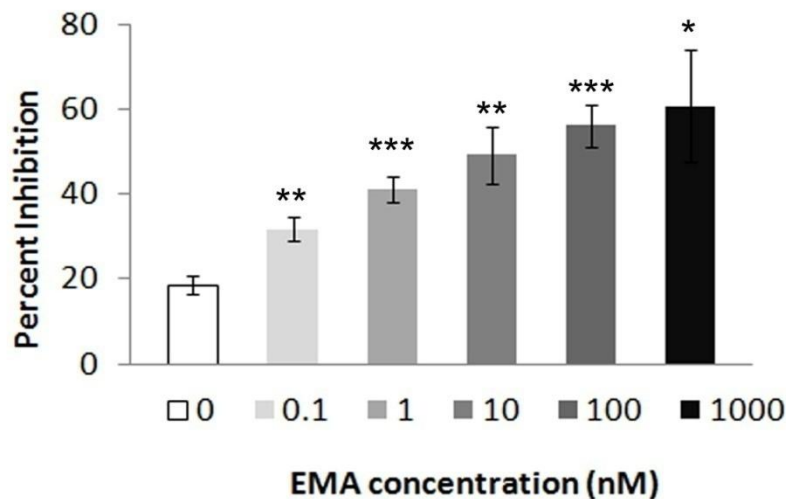
Functional effect of AT2 antagonist EMA401 - Inhibition of capsaicin responses in DRG neurons *in vitro*



Phase contrast image of DRG neurons used in Calcium imaging

Trace shows response to capsaicin with rapid rise in intracellular calcium

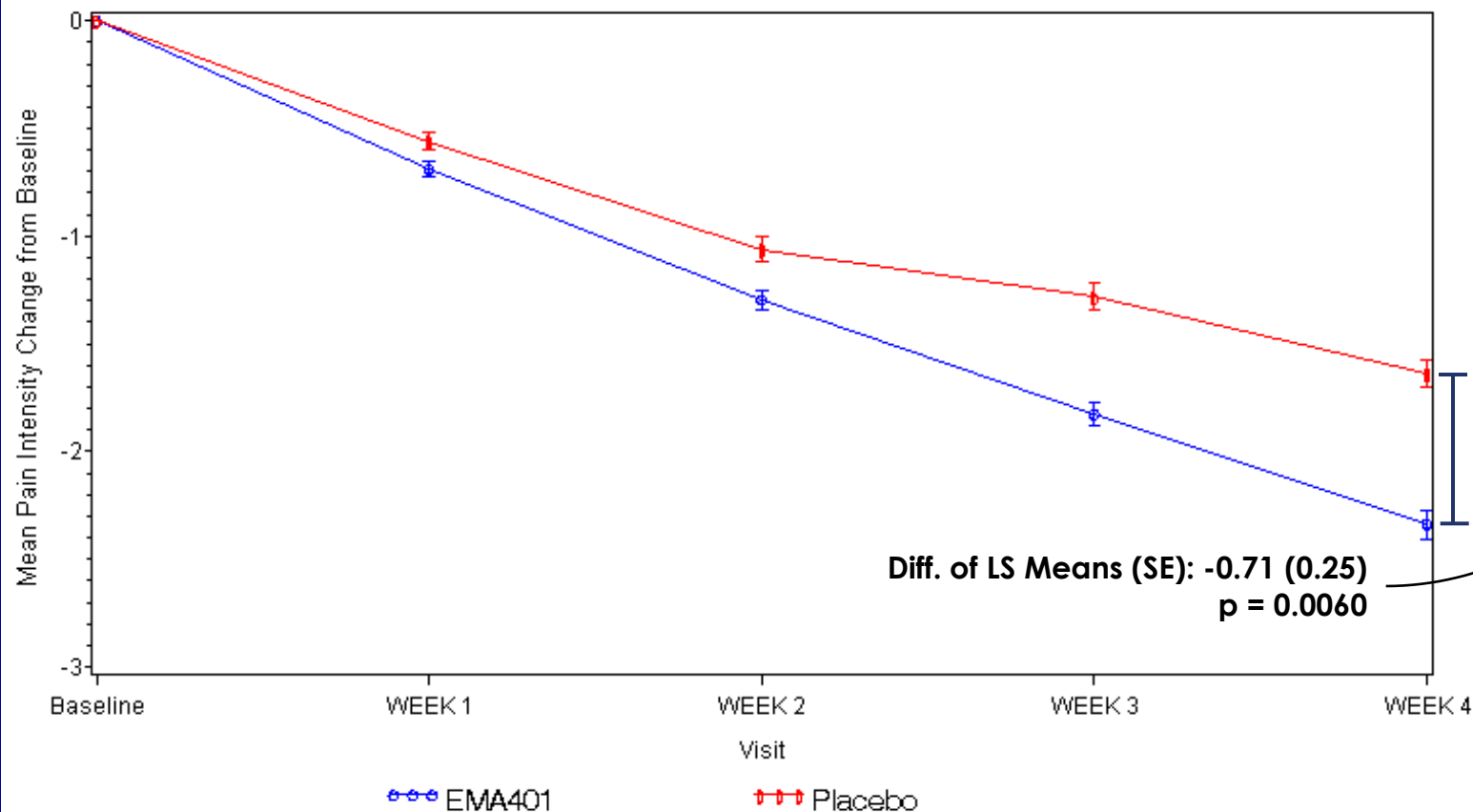
Dose dependent inhibition of Capsaicin responses in the presence of the AT2 receptor antagonist EMA401



EMA401 Clinical Trial

Change from Baseline in Mean Pain Intensity

Figure 1.2 Change Mean (+/- SE) Pain Intensity Scale from Baseline by Treatment Group and Visit (Full Analysis Set)



Conclusions

There are rapidly increasing numbers of novel mechanisms and drug targets in patients with chronic pain and hypersensitivity

The best pain models to progress novel analgesics are target validated human disease states with mechanism-based end-points