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# Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway

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**TRPV1 is a noxious heat, capsaicin (vanilloid) and acid receptor for which the development of antagonists represents a novel therapeutic approach for the treatment of pain. TRPV1 antagonists have entered early clinical development and initial reports indicate that they have demonstrated pharmacodynamic effects consistent with TRPV1 antagonist activity and anti-hyperalgesic action in humans. Should these effects extend to the relief of symptoms experienced by patients with chronic pain then this class of compounds may offer one of the first novel mechanisms of action for the treatment for pain for many years. In this article we will discuss recent progress and challenges in the field in this highly competitive area of drug discovery.**

## Introduction

The unmistakable pungency of capsaicin, a component of chilli peppers, and other natural products that act at the 'vanilloid receptor' has led to much basic research into TRPV1 function and an appreciation that this ion channel acts as a key signalling complex in the pain pathway [1]. TRPV1 is primarily found on small diameter primary afferents, particularly unmyelinated C-fibres and thinly myelinated A-δ fibres but is also expressed, albeit at apparently lower levels, in upstream parts of the pain pathway such as the spinal cord and brain [2–4]. Besides being activated by capsaicin (Fig. 1), TRPV1 also responds to a wide range of exogenous and endogenous chemical ligands (e.g. 'endovanilloids' such as anandamide) as well as changes in more diverse activators such as protons (acid, pH $< 6$) and physical stimuli such as heat ($>42^{\circ}C$) [5–7]. TRPV1 is also subject to regulation by changes in membrane potential and this intrinsic voltage-dependence is thought to underlie the gating mechanism of this non-selective cation channel [8] which leads to the influx of $Na^+$ and $Ca^{2+}$ ions into cells. Importantly, TRPV1 activity is also subject to regulation by a host of intracellular signalling cascades that are implicated in the response to algogenic agents, inflammatory mediators and injury (Fig. 2). Overall, this points towards a role of TRPV1 as a key integrator of a diverse array of activators and downstream regulatory pathways that can act in concert to recruit or enhance TRPV1 activity in parts of the peripheral and central nervous system resulting in ongoing or 'inappropriate' neuronal activity that may ultimately be perceived as chronic pain.

Characterisation of TRPV1 knockout (KO) mice, which were engineered to lack both copies of the TRPV1 gene, provided pivotal evidence for the key role of TRPV1 in pain. Although phenotypically normal, and virtually inseparable from their littermates in terms of behaviour, these animals show a clear attenuation of the thermal hyperalgesia associated with inflammation [9,10]. These findings provided a strong rationale for the development of selective TRPV1 antagonists as a novel pain therapy with the potential for an improved side effect profile compared to current agents [11,12]. In the period of extensive research that has followed, many novel selective and chemically diverse TRPV1 antagonists have been identified and assessed in preclinical models of pain. For example, BCTC, AMG9810, A425619 and SB-705498 all show good activity in the Freund's complete adjuvant (FCA) model of inflammatory pain [13–16]. Such agents appear to be able to reduce thermal and mechanical hyperalgesia as well as tactile allodynia. Furthermore, TRPV1 antagonists also show efficacy in models of neuropathic pain [15], postoperative pain, cancer pain [17] and the mono-iodoacetate model of osteoarthritis [18]. These data therefore extend the findings of the TRPV1 KO studies and provide a robust pre-clinical rationale for exploring the potential of TRPV1

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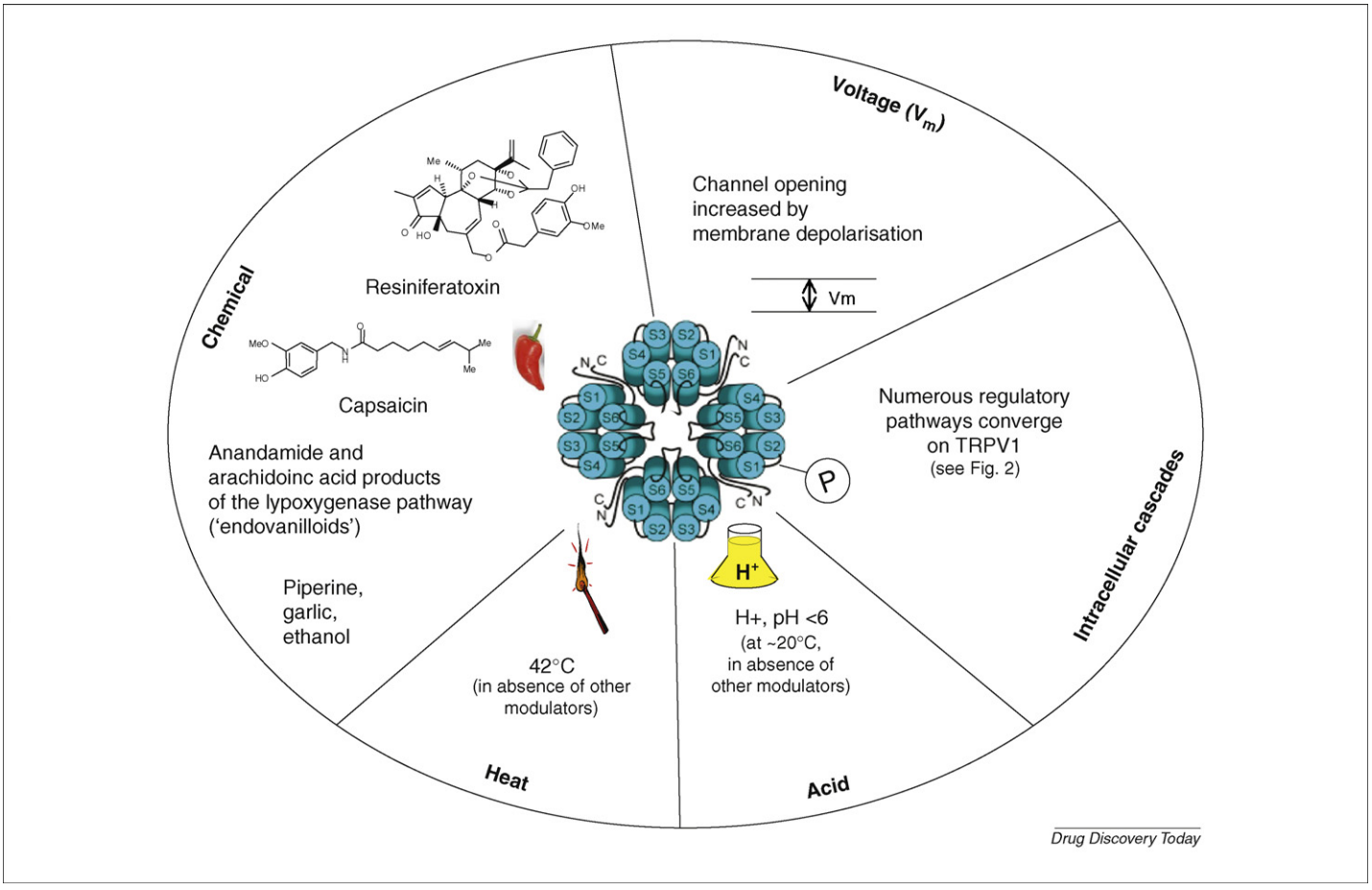


**FIGURE 1**

Multiple modes of TRPV1 receptor activation. TRPV1 receptors are formed by the assembly of four subunits with a six transmembrane topology (S1–S6, as pictured) around a central ion channel pore that is permeable to cations such as $Na^+$ and $Ca^{2+}$. TRPV1 is activated by a wide range of diverse chemical and physical stimuli (different modes of activation) as pictured. Chemical activation incorporates small molecule endogenous and exogenous agonists many of which bind to the capsaicin binding site; acidification, effectively involving protonation of the receptor by $H^+$ binding is typically considered as a specific mode of chemical activation and probably involves multiple extracellular binding sites on the receptor. Physical stimuli include the effects of heat, with a threshold of ~42°C in the absence of other activators at physiological pH, and membrane potential ($V_m$) where depolarisation favours channel opening. TRPV1 is also subject to intense regulation by intracellular cascades many of which lead to post-translational modification and TRPV1 activation. TRPV1 is therefore described as a multimodal receptor and effectively acts as a molecular integrator summing (or *'sensing'*) the contributions of all activators to set the overall level of ion channel activity.

antagonists for the treatment of a broad range of acute and chronic pain conditions in humans. It is noteworthy that there is also renewed excitement regarding the development of TRPV1 agonist therapies for which recent clinical data have defined the efficacy of injectable and dermal (topical) patch formulations of relatively high concentrations of capsaicin in the treatment of osteoarthritic pain of the knee and in HIV-induced neuropathy. Such approaches capitalise on the desensitising properties of capsaicin but are limited to topical application owing to the issues of systemic side effects associated with capsaicin administration (Table 1). The progress in this field has been reviewed extensively elsewhere [19].

In this article, we will discuss recent progress defining the therapeutic potential of small molecule TRPV1 antagonists as novel analgesic agents and review the current clinical candidates and emerging clinical data for this highly competitive area of drug discovery. The broad therapeutic potential of TRPV1 antagonists for a range of additional indications has been reviewed recently [20–22] and alternative biological strategies such as the use of antibodies or RNA inhibition to reduce TRPV1 function are also now showing promise (Table 1), but will not be discussed further here.

## Mechanistic insight into the contribution of TRPV1 to the pain pathway

Following the identification of several selective TRPV1 antagonists that serve as valuable research tools, a recent work regarding the role of TRPV1 in pain has focused on understanding the site and biological mechanism(s) of action. A recent study by Cui *et al.*, using potent TRPV1 antagonists with either high (A-784168) or low CNS penetration (A-795614) delivered either systemically (orally) or intrathecally or intracerebroventricularly provided evidence for peripheral, spinal and supraspinal sites of action through which TRPV1 antagonists mediate their efficacy in models of inflammatory pain [23]. The contributions of TRPV1 receptor activity to the pain state and the resultant effects of TRPV1 antagonists on the body to generate efficacy are therefore complex and go beyond the initial simplistic model in which TRPV1 was considered as a 'peripheral nociceptor'.

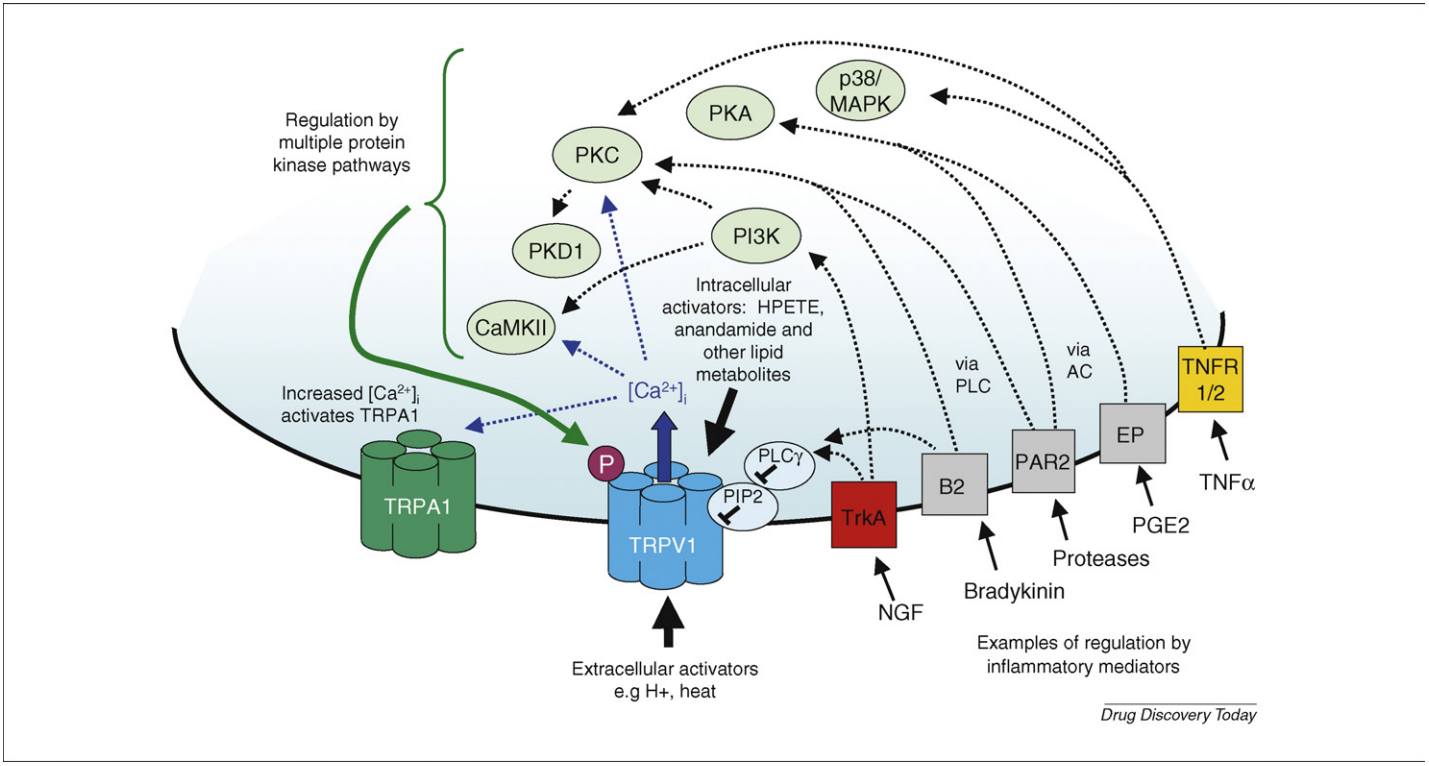


**FIGURE 2**

TRPV1, a convergent target of intracellular regulatory cascades that mediate pain sensitization. Beyond the direct chemical and physical activators of TRPV1 highlighted in Fig. 1 there are numerous second messenger systems that regulate receptor activity. A range of inflammatory mediators and growth or tumour factors are known to contribute to hyperalgesia via sensitization of TRPV1 through activation of kinase pathways that can lead to direct receptor phosphorylation (P) at multiple intracellular sites. There are also negative regulators of receptor activity, for example binding of the membrane lipid phosphatidylinositol-4,5-bisphosphate (PIP2) that can be overcome by phospholipase C (PLC)-mediated hydrolysis. This schematic is a simplified representation of the key components of the regulatory mechanisms highlighted. Other components, interactions and additional mechanisms such as transcriptional and trafficking changes are also important contributors to sensitisation and plasticity following inflammation or injury but are omitted for clarity. Key effects of TRPV1 receptor activation include changes in intracellular $Ca^{2+}$ levels that may activate other channels implicated in pain (such as TRPA1) and associated downstream post-translational and transcriptional events, the release of neuropeptides such as calcitonin gene-related peptide and substance P that can cause neurogenic inflammation and depolarisation (due mainly to $Na^{+}$ entry) that can initiate action potential generation and signalling in the nervous system. PKA, Protein kinase A; AC, adenylate cyclase; PKC, protein kinase C (particularly epsilon subunit); PKD1, protein kinase D1; PI3K, phosphatidylinositol 3-kinase; CaMKII, $Ca^{2+}$-calmodulin-dependent kinase 2; MAPK, mitogen-activated protein kinase; PGE2, prostaglandin E2, TNF(R), tumour necrosis factor (receptor); NGF, nerve growth factor.

At the level of the peripheral dorsal root ganglion (DRG) neuron, TRPV1 can be upregulated at the mRNA, protein and functional level and many studies have implicated its role as an integrator of noxious stimuli and as a marker of hypersensitivity following injury and inflammation [24]. Indeed, many receptor mechanisms and regulatory pathways implicated in pain signalling demonstrate a level of convergence onto TRPV1 (Fig. 2). TRPV1 can therefore be considered to act as a sensor for acute and chronic effects of injury and inflammation which involve a range of sensitising or algogenic agents such as bradykinin, the release of proteases and increased acidification [25–27]. Following peripheral inflammation, TRPV1 upregulation appears to occur at central as well as peripheral terminals of DRG neurons, leading to pre-synaptic augmentation of glutamatergic signalling in the spinal cord [28]. Similarly, an apparent sensitisation and/or upregulation of spinal TRPV1 is thought to be involved in the development and/or maintenance of mechanical allodynia in the rat chronic constriction injury (CCI) model of neuropathic pain [29]. Consistent with this observation, centrally penetrant TRPV1 antagonists show superior efficacy compared to peripherally restricted agents exhibiting a similar pharmacological and pharmacokinetic profile; the activity at central TRPV1 receptors appears to be particularly important for the reversal of mechanical hyperalgesia [23]. A recent work by Kanai *et al.* also demonstrated that two chemically distinct TRPV1 antagonists, BCTC and SB-366791, behaved similarly in their ability to inhibit FCA-induced thermal hyperalgesia when dosed intraplantarly but only reversed mechanical hyperalgesia when dosed intrathecally [30]. In terms of supraspinal effects, TRPV1 expressed in the periaqueductal grey is also thought to contribute to the descending inhibitory modulation of pain via the regulation of 'on' and 'off' cells in the rostroventral medulla, implying, somewhat paradoxically, that TRPV1 activation here may produce beneficial analgesic effects [31]. Further studies are warranted to understand the role of endovanilloids in regulating such pathways and if, and how, these are modified as part of the plastic changes that are thought to accompany chronic pain. Likewise, the potential contribution of TRPV1 receptors expressed in higher brain centres such as the thalamus and anterior cingulate cortex deserves further attention [4].

Overall, these recent findings indicate that TRPV1 antagonists are likely to alleviate pain by acting at multiple sites rather than

**TABLE 1**

**Therapeutic strategies targeting TRPV1.**

| *TRPV1 targeted therapy* | Most advanced examples and route of administration | Advantages | Disadvantages |
|---|---|---|---|
| **TRPV1 chemical agonist** | Neurogesx NGX-4010 (dermal patch; Phase 3) | All are formulations of the natural product capsaicin (*trans* or *cis* isomers) | Agonists can cause pain and or erythema before desensitisation becomes effective |
| | Anesiva AlgrX-4975 (injectable/intraarticular; Phase 2) | Offer broad and long lasting mechanistic effects due to 'defunctionalisation' of sensory neurones | Requires application by physicians |
| | Winston Laboratories Civamide (inhaled/injectable; Phase 3) | | Systemic side effects prevent use as oral agents |
| **TRPV1 chemical antagonist** | See Figs 3,4 for a range of orally active compounds in development. Most advanced is currently Phase 2 | Avoid pain of agonist therapies | May offer reduced efficacy cf. agonist 'defunctionalisation' for some indications |
| | These agents could also be developed as intranasal, topical and injectable formulations | Rapid onset of action (no desensitisation required for effect) | TRPV1 implicated in some gastroprotective effects |
| | | Orally active/systemic drugs developable | Impact of hyperthermia not fully explored |
| | | | All are new chemical entities (NCEs) hence side effects not yet fully explored |
| **TRPV1 biological** | RNA inhibition (RNAi) or small interfering (si)RNA, for example Grunenthal (preclinical) | Rapid development | CNS penetration may be limited. |
| | Functional antibodies/domain antibodies | Selectivity of action | May require viral delivery and/or injection |
| | Former approach has gained initial proof of principle (see [67]). No examples of development reported | Avoid typical issues regarding small molecule mediated toxicology | Novel approach, hence not all issues known |

just reducing peripheral drive from injured or hypersensitive neurons. Hence, molecules that can target the central as well as peripheral sites of the pain pathway may offer the best potential as therapeutic agents. Of course, the compromise for hitting TRPV1 receptors in the CNS is the potential for increased levels or occurrence of centrally mediated side effects. Whether peripherally restricted or centrally penetrant compounds offer the best overall trade off between efficacy and side effects for the treatment of human pain therefore remains to be determined.

## TRPV1 antagonists in development

To date, the available public information suggests that at least seven orally active TRPV1 antagonist molecules have progressed into clinical development (Fig. 3 and Table 2). This may be expected to increase dramatically in the near future on the basis of the progression of compounds from preclinical development (Fig. 4) and early stage research that is underway at several pharmaceutical and biotechnology companies; indeed, the level of R&D investment in TRPV1 antagonists is somewhat staggering

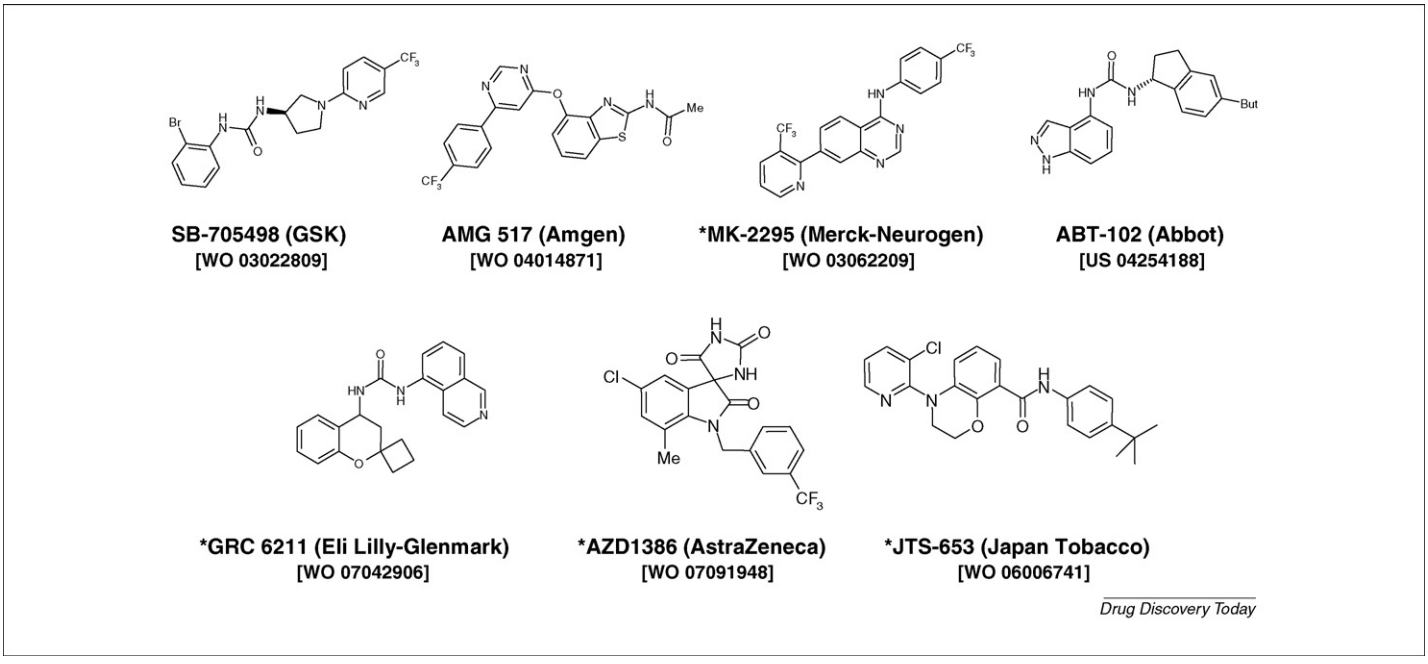


**FIGURE 3**

TRPV1 antagonists progressed into clinical development. TRPV1 antagonists that are known to have entered the clinic to date based on available collated public information derived from company press releases, analyst information, published patents and journal articles are illustrated with associated compound numbers and patent references (*indicates that the structure given represents a patent example illustrated since the identity of the lead molecule has not been disclosed).

**TABLE 2**

**Properties of TRPV1 antagonists in the clinic.**

| TRPV1 antagonist | Activity (IC50) at human TRPV1 (unless stated)<br>Multimodal?<br>Competitive? | Activity in preclinical species *in vivo* | Brain penetrance? | Clinical data | Refs |
|---|---|---|---|---|---|
| SB-705498 | 3 nM capsaicin (1 μM)[a] 6 nM heat (50°C)[a] ~30 nM acid (pH 5.3)[b]<br>✓Multimodal<br>✓Competitive versus capsaicin, pA2 = 7.4 | $ED_{50}$ = 2 mg/kg p.o. versus mechanical hyperalgesia in guinea pig FCA. Also active in models of neuropathic and visceral pain<br>No overt hyperthermia over efficacious dose range (0.3–10 mg/kg) | Yes, brain:blood ratio = 0.5 (rat) | Phase 1 completed successfully (39 subjects; single dose up to 400 mg). Positive PD effects seen (heat pain threshold, capsaicin-evoked flare) at 400 mg.<br>No hyperthermia/hyperthermia associated AEs reported. Migraine and Dental Pain trials completed. No data reported. Rectal hypersensitivity trial terminated | http://www.gsk.com [38,68,69] |
| MK-2295 (NGD-8243) | Profile not known | Profile not known | Profile not known | Phase 1 completed successfully. PD effects reportedly seen confirming activity at target (Data not disclosed). Dental pain trial complete (Statement regarding preliminary positive finding released June2007 but no data yet disclosed). Compound now being progressed for Cough in further Phase 2 studies | http://www.merck.com<br>http://www.neurogen.com |
| AMG 517 | 0.8 nM capsaicin[c] 0.6 nM acid (pH 5.0)[c] 1.3 nM heat (45°C)[c]<br>✓Multimodal<br>✓Competitive versus capsaicin, pA2 = 8.2 | MED = 0.83 mg/kg versus thermal hyperalgesia in rat FCA (max effect of ~50% seen at ~10 mg/kg p.o.)<br>Hyperthermia (up to 1.5°C) seen at 0.3–3 mg/kg; tolerates out on repeat dosing (rat) | Yes, brain:blood ratio = 0.73 (rat) | Phase 1 completed successfully (39 subjects received single dose up to 25 mg; 17 subjects received multiple daily doses up to 10 mg over seven days). Dental pain trial seven-day repeat dose (at 2, 8 or 15 mg) terminated due to pronounced hyperthermia. Incidence of ~3°C increases seen at doses of 2 mg in one patient. No data on PD effects; no efficacy determined (only 9 subjects received active) | http://www.amgen.com/ [33,54,57] |
| GRC 6211 | Profile not known | Profile not known | Profile not known | Phase 1 completed successfully (72 subjects; single dose up to 200 mg and 12-day repeat dose at 25, 50 and 100 mg). Dental pain trial completed at end 2007 (data not disclosed). Phase 2b neuropathic pain and osteoarthritis trials underway | http://www.glenmarkpharma.com |
| AZD1386 | Profile not known | Profile not known | Profile not known | Phase 1 completed successfully. Dental pain trial initiated 2008. No further information available | http://www.astrazeneca.com |

**TABLE 2 (*Continued*)**

| TRPV1 antagonist | Activity (IC50) at human TRPV1 (unless stated)<br>**Multimodal? Competitive?** | Activity in preclinical species *in vivo* | Brain penetrance? | Clinical data | Refs |
|---|---|---|---|---|---|
| ABT-102 | 7 nM capsaicin (50 nM)[b]<br>6 nM acid (pH 5.5)[b]<br>Active against heat (50°C) at 100 nM (rat)[a]<br>✓Multimodal<br>✓Competitive versus capsaicin, pA2 = 8.3 (rat) | Active in a range of pain models including inflammatory, osteoarthritis, one cancer and postoperative pain in the rat<br>Hyperthermia seen ~1°C; tolerates out on repeat dosing | Yes, brain:plasma = 0.3:1 (rat) | Progressed into the clinic. No further information available | http://www.abbott.com [55,70] |
| JTS-653 | Profile not known | Profile not known | Profile not known | Recently progressed into a Phase 1 trial (2008) No further information available | http://www.jti.co.jp/JTI_E/ |

FCA, Freund's complete adjuvant; PD, pharmacodynamic; $ED_{50}$, effective dose exhibiting 50% reversal; MED, minimum effective dose (no $ED_{50}$ determination provided).
[a] Determination by electrophysiology (whole cell patch clamp).
[b] Determination by FLIPR-$Ca^{2+}$ assay.
[c] $^{45}Ca^{2+}$ uptake assay.

with estimates putting the total number of companies active in this area as >50 through organic growth or in-licensing activities (see [32]).

The first selective TRPV1 antagonists entered the clinic a few years ago [12]. SB-705498 has now successfully completed Phase 1 testing in healthy volunteers and progressed into further clinical studies evaluating the efficacy for postoperative dental pain, migraine and rectal hypersensitivity (http://clinicaltrials.gov/). Merck–Neurogen, and Eli Lilly–Glenmark who entered partnerships in 2005 and 2007, respectively, have also recently disclosed successful completion of Phase 1 studies with their lead molecules MK-2295 (NGD-8243) and GRC6211 and have gone on to evaluate these compounds in dental pain trials (Table 2). With little public information available regarding the actual results of these proof-of-concept (PoC) studies, or indeed the molecular profile of the drug candidates it is difficult to determine if the TRPV1 antagonist approach has achieved 'positive PoC' at this time. Some initial statements, such as the press release from Neurogen, stating that 'development activities for NGD-8243 (MK-2295) would continue, based on promising preliminary results from PoC [dental pain] studies in its collaboration with Merck & Co.' (http://www.neurogen.com/products/vr1index.html) are nevertheless encouraging, but an evaluation of the data will be the key in determining the level of confidence in progressing to large scale trials in disease populations. Subsequently to these updates, Merck–Neurogen have now aligned MK-2295 with further exploratory Phase 2 studies for the treatment of cough associated with upper airway disease and are focusing on a back-up compound, NGD-9611, currently in preclinical development for pain. Eli Lilly–Glenmark now appear to have initiated further Phase 2 clinical studies to investigate the efficacy of GRC6211 in patients with neuropathic pain and osteoarthritis.

Countering this excitement in the field, a recent publication from Amgen regarding their lead compound AMG 517, which also progressed into a dental pain trial, has clarified that safety concerns regarding the occurrence of pronounced hyperthermia in some patients led to an early termination of this study [33]. The occurrence of hyperthermia following TRPV1 antagonism in some respects typifies the risks associated with the targeting of a novel mechanism for which the biology and consequent risks associated with its modulation are not fully explored. In the case of TRPV1 it also suggests further unforeseen complexity in its role in core body temperature homeostasis and multimodal behaviour at the receptor level. Already a large amount of new data have led to an appreciation of this novel aspect of TRPV1 biology (see section below). A second clinical candidate, AMG 628, has also been progressed by Amgen [34]. It appears that it was selected to avoid the extremely long half-life associated with AMG 517 and improve aqueous solubility to increase its potential to progress into further development; its hyperthermia profile, however, has not been disclosed. Because there are no current public records of a clinical trial with this compound, it is presently unclear whether this molecule is in preclinical development or has been terminated for unknown reasons. Similarly, Abbot's initial lead molecule ABT-102 may have been terminated owing to the hyperthermia associated with this compound (Table 2) or for other, as yet unknown, reasons.

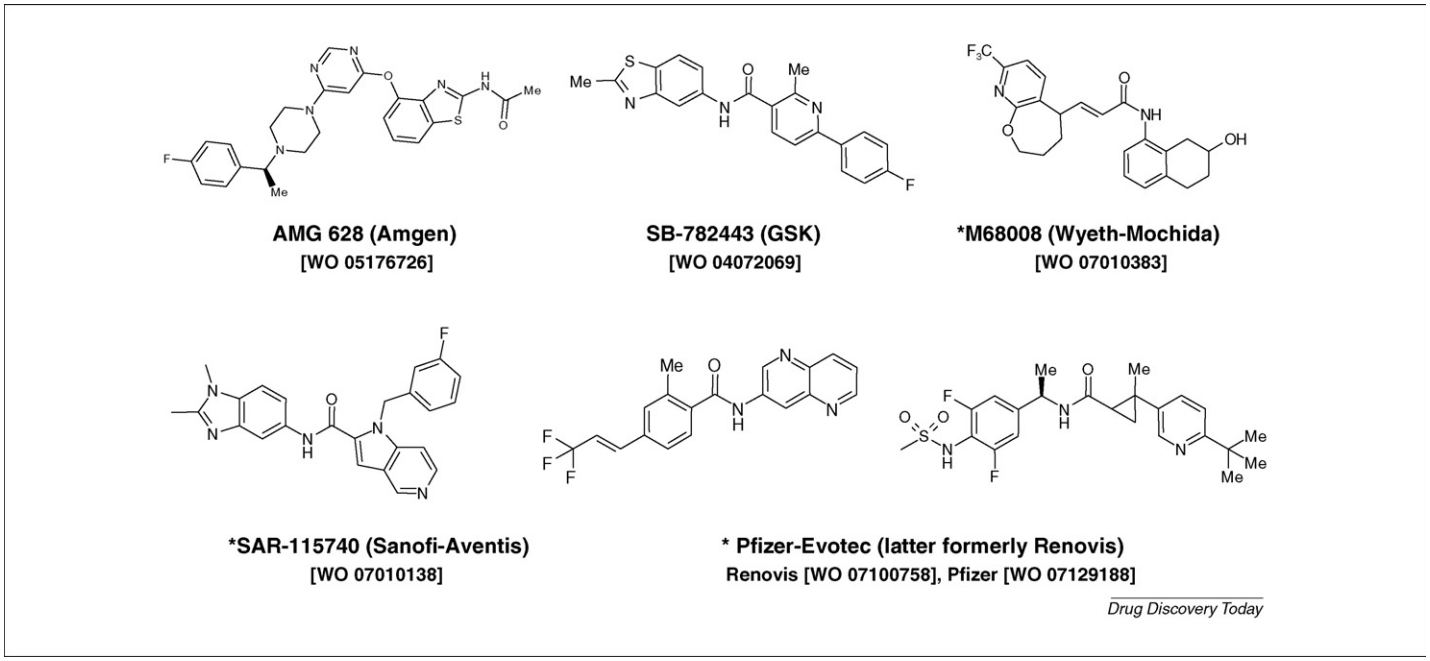


**FIGURE 4**

TRPV1 antagonists in preclinical development. In addition to the compounds that have entered clinical trials a large number of compounds selected as drug candidates have entered preclinical development. A representative set of compounds based on available collated public information derived from company press releases, analyst information, published patents and journal articles are illustrated with associated compound numbers and patent references (*indicates that the structure given represents a patent example since the identity of the candidate molecule has not been disclosed).

Recent additions to the clinical pipeline include AZD1386 from AstraZeneca that has completed Phase 1 clinical trials and progressed to Phase 2 studies for the treatment of pain associated with gastro-oesophageal reflux disease (Co. Press release), and JTS-653 from Japan Tobacco that has progressed into a Phase 1 trial aligned with progression for pain and overactive bladder (Fig. 3 and Table 2). Further clinical candidates have also been progressed by Pfizer, who partnered with Renovis (now Evotec), and are poised to initiate Phase I Clinical trials in 2008 (Co. Press release). Sanofi-Aventis have identified SAR-115740 for the treatment of chronic inflammatory and neuropathic pain and Wyeth, who partnered with Mochida Pharmaceuticals, and have M68008 in preclinical development (Fig. 4). GSK have also recently disclosed the identification and characterisation of SB-782443, a further candidate molecule [35]. On the basis of the level of activity in this field, it is probable that additional companies have identified candidates that are progressing towards or even entered the clinic, however, at the time of writing, no other companies have publicly stated that they have initiated clinical trials with a TRPV1 antagonist.

On the basis of the available public information, it appears that all of the first generation TRPV1 antagonists are potent, multimodal and CNS penetrant (Table 2). Their competitive behaviour defined versus capsaicin, and insight gleaned from structure–function studies to date, also suggests that these compounds bind to the same site on the receptor. It will therefore be interesting to see if these compounds behave similarly in the clinic and whether or not a rationale for modality-selective or 'unimodal' antagonists develops or compounds with a more restricted distribution offer the best promise as therapeutic agents for pain. Clearly, the preclinical and clinical characterisation of compounds with modality-selective profiles will be key in this respect, and the growing availability of detailed structural information regarding TRPV1 receptor function will probably accelerate this next phase of drug development [36,37].

## Effects of TRPV1 antagonists in humans

### *Pharmacological effects of TRPV1 antagonists in humans and their implications*

The first data on the effects of TRPV1 antagonists in humans are beginning to appear. Results from a first time into human (FTIH) study with SB-705498 in healthy volunteers demonstrated the effects broadly consistent with its preclinical pharmacology [38]. The compound significantly elevated heat pain thresholds in normal skin compared with placebo, confirming the role of TRPV1 as a heat sensor in humans. Capsaicin-evoked flare, which is known to result from the activation of capsaicin-sensitive peptidergic afferents in the periphery [38,39], was also significantly reduced by SB-705498 versus placebo (Fig. 5). This finding implies the potential for TRPV1 antagonists to reduce neurogenic inflammation. Interestingly, the area, but not the intensity, of UVB-evoked skin inflammation in humans was also reduced by the compound. These data suggest a contribution of neurogenic mechanisms to the experimentally evoked inflammation and a lack of direct anti-inflammatory effects of TRPV1 antagonists. This may be important because neurogenic inflammation is considered an essential pathophysiological mechanism of migraine headache and painful arthritides [40–42]. Consistent with the proposed role of TRPV1 in inflammatory hyperalgesia, SB-705498 significantly attenuated UVB-evoked hyperalgesia compared with placebo. The pharmacokinetic/pharmacodynamic (PK/PD) analysis of the SB-705498 data suggests that the maximum effects were not achieved,

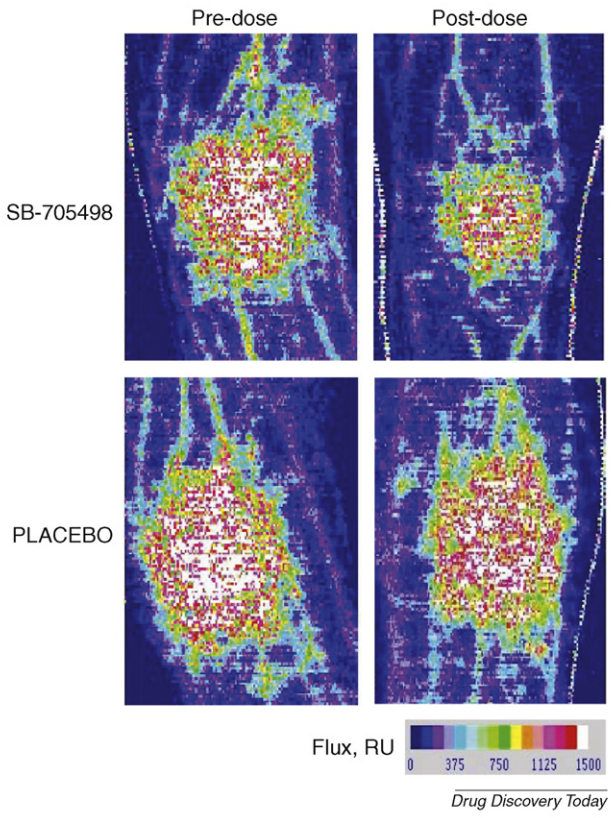


**FIGURE 5**

Pharmacodynamic effects of SB-705498 in humans. Attenuation of capsaicin-evoked axon reflex flare following single oral administration of the TRPV1 antagonist SB-705498 (400 mg) in humans. Laser Doppler images show the effects of capsaicin on skin blood flow (shown in arbitrary units as a heat map where warm colours indicate higher blood flow) at pre-dose and following SB-705498 or placebo. The data are from the same subject, with the SB-705498 and placebo sessions performed two weeks apart. At a group level ($n$ = 19), the effects of SB-705498 showed a significant difference from placebo (see [38] for further details).

and that higher exposures could have caused greater pharmacodynamic efficacy. Thus, the report on the effects of SB-705498 in humans broadly confirms the spectrum of TRPV1 pharmacology expected on the basis of preclinical data. It also highlights the utility of heat pain measures, capsaicin-evoked flare and inflammatory hyperalgesia as markers of TRPV1 antagonism in humans. What remains to be established is the level of pharmacodynamic activity required for clinical efficacy in pain states. Merck–Neurogen have also reportedly seen pharmacodynamic effects defining activity of their compound at the TRPV1 target, but no details of the tests or magnitude of effect seen have yet been disclosed.

It is also interesting to reflect on the markers that did not turn out to be useful for detecting TRPV1 antagonism in humans. Thus, capsaicin-evoked heat hyperalgesia did not change following the administration of SB-705498 [38]. This is puzzling, as the effects of either capsaicin (i.e. flare) or heat (i.e. heat pain threshold) given separately were reduced by the antagonist, as was the inflammatory heat hyperalgesia. One possible explanation for this is that, in line with the receptor properties of TRPV1 (Fig. 1), the combined effect of the two activators, heat and capsaicin, may result in a greater level of TRPV1 receptor activation that would require a much higher concentration of the antagonist to produce a detectable effect.

In the same Phase I study of SB-705498, an exploratory capsaicin taste challenge was also employed, which involved detection by volunteers of the threshold for the typical taste in a series of diluted capsaicin solutions. This did not demonstrate any threshold change following the treatment with SB-705498 compared with placebo (Chizh *et al.*, unpublished data). Although it is possible that the lack of effect was due to methodological issues or differences in tissue distribution of the antagonist, it suggests that TRPV1 antagonism may not have a profound effect on taste at dose levels that reduce pain.

### *Clinical efficacy of TRPV1 antagonists*

Following Phase I, SB-705498 was investigated in clinical studies of acute migraine, dental pain and rectal pain; the results of these studies are not yet available for publication. Merck–Neurogen have also completed a study of the effect of MK-2295 and an active control on dental pain following third molar extraction (http://clinicaltrials.gov). Although the results of this study have not been disclosed, the press release from Neurogen regarding promising preliminary results from their PoC studies does provide basis for cautious optimism. Dental pain is a well-established model that meets FDA requirements for proof of efficacy in acute pain; it has been used extensively to demonstrate efficacy of NSAIDs, COX2 inhibitors, opioids and paracetamol products [43]. Efficacy in this model would suggest that TRPV1 antagonists may have utility in acute postoperative pain. Clearly the availability of the full dataset will be important for determining the level of confidence in the mechanism and the relationship between pharmacodynamically active and efficacious doses. Such results may provide confidence for exploring TRPV1 antagonists in other pain states.

It should be borne in mind that chronic pain conditions, such as painful osteoarthritis and neuropathic pain, are likely to involve mechanisms rather different from those engaged in acute postoperative pain. Thus, the pain following surgical tissue injury such as third molar extraction is associated with acidosis, release of prostaglandins and other pro-nociceptive agents [44,45]. Prostaglandins and other products of arachidonic acid metabolism are known to sensitise the TRPV1 to protons and heat (Figs 1,2), thus creating a peripheral milieu in which the contribution of these receptors to pain is likely to be high. The preclinical models in which the efficacy of TRPV1 antagonists has been demonstrated typically involve a marked inflammatory component. The intensity of peripheral inflammation in osteoarthritis is, however, limited [46], and it remains questionable whether it would be sufficient to involve TRPV1 receptors to any significant degree (although the efficacy of COX inhibitors implicates the prostaglandin mechanisms in OA pain; [47]). Likewise, central sensitisation mechanisms are believed to be of importance in OA [48,49] and neuropathic pain [50]; hence, preclinical data suggesting that TRPV1 antagonists may have a central site of action in models of neuropathic pain [23] are encouraging. Given these insights, it would be valuable to investigate the effects of TRPV1 antagonists on central sensitisation in human pain models, for example secondary hyperalgesia following the capsaicin challenge or

UVB inflammation; however, no such data have been reported to date.

## Safety profile of TRPV1 antagonists

Even though preclinical safety and toxicology packages have been assimilated for the five compounds that have successfully completed Phase 1 clinical trials (Table 2), relatively little data are yet to be found in the public domain. The obvious success in the progression of multiple chemical entities with potent TRPV1 antagonist activity into preclinical development and into the clinic points towards an overall encouraging profile for this class; however, some new biological findings of note have triggered further study and re-consideration regarding current strategies for progression.

### *Phase 1 safety and tolerability data*

In the Phase 1 study of SB-705498, the compound was safe and well tolerated with only mild to moderate intensity adverse events [38]. Their overall incidence was similar in subjects treated with the TRPV1 antagonist and placebo (47% versus 42%, respectively), with the most frequent events in both groups being headache (32% versus 16%), nasopharyngitis (16% versus 5%) and contact dermatitis (11% versus 21%). The incidence of adverse events did not appear dose-related, and most of the effects were considered not related to the study medication. None of the clinical laboratory parameters, vital signs data or ECG values of potential clinical concern were symptomatic or reported as adverse events. No reports or ECG changes consistent with pyrexia were reported.

Other brief reports on TRPV1 antagonists in humans also suggest their generally good tolerability, with the exception of hyperthermia reported with some compounds (see below). Merck and Neurogen's press release on the Phase I study of MK-2295 includes a statement about good tolerability and lack of serious adverse events in healthy volunteers at single doses that were active at the TRPV1 target. Similarly, recent updates from Glenmark clarified that GRC-6211 was also well tolerated in single and repeat dose Phase 1 studies (Table 2).

### *TRPV1 antagonists and hyperthermia*

Recent research by Gavva *et al.* [51] has defined a key role of tonic TRPV1 receptor activity in thermoregulation with many chemically distinct TRPV1 antagonists causing hyperthermia, typically in the range of 0.5–1.5°C, in preclinical species such as rat, mouse, dog and monkey. This biological role of TRPV1 was not apparent from TRPV1 KO studies which exhibit normal core body temperature and regulation in response to thermal challenge. However, the clear 'loss' of hyperthermic effects of TRPV1 antagonists in the KO confirms an 'on target' and potential 'class effect' for these agents [52]. TRPV1 may therefore have a constitutive role in thermoregulation for which compensatory mechanisms act in KO animals. The recent report of hyperthermic effects of AMG 517 in humans [33] confirms the translation of this pharmacological effect from preclinical species in this case and clearly questions the developability of TRPV1 antagonists and/or their utility in clinical practice [33,53]. Consequently, research has already begun to understand the underlying mechanism with a view to controlling, minimising or perhaps even avoiding this issue.

Because the hyperthermic effects seen preclinically upon acute dosing were noted to be transient in nature, and tolerate on repeat dosing [54,55], dose escalation/titration, often employed to reduce side effects/improve tolerance of a range of therapeutic agents, has been contemplated as a simple management strategy. Recently reported clinical work with AMG 517 appears to counter early enthusiasm for this option; however, although repeat dosing yielded a reduction in hyperthermic effects on days 2–7 at the highest dose tested (10 mg; c.f. peak on day 1), hyperthermia was not completely eliminated [33]. Should a simple dose-titration strategy be inadequate to manage the hyperthermic effects of TRPV1 antagonists then acetaminophen and other antipyretic drugs may be of use. This approach appears to have been validated preclinically, but its utility in the clinical setting is unclear [33]. This recently published work also raises the possibility that certain individuals may exhibit higher susceptibility to the hyperthermic effects of TRPV1 antagonists because outliers in this respect were not readily correlated with exposure to AMG 517. Furthermore, the possibility of higher perturbations in core body temperatures in patients undergoing third molar extraction surgery compared to the initial healthy volunteer group also raises the issue that effects may be more pronounced in such patients. Further clinical monitoring and research is clearly required to understand if this is reflective of the impact of the surgical procedure itself or the resultant inflammatory response (or both) and whether this will be predictive of the patient populations for which such compounds are ultimately intended. It should also be noted that because no information regarding the pharmacodynamic or efficacious effects of AMG 517 is available in humans the dose–response or concentration–response relationship between the hyperthermic effects and efficacy is currently unclear.

Insight into the location of the TRPV1 receptors mediating thermoregulatory control has also suggested potential ways forward. Although mechanistically it was hypothesized that central TRPV1 receptors may be key to the thermoregulatory role of TRPV1 on the basis of their known expression in preoptic and anterior regions of the hypothalamus associated with the control of thermoregulation, recent studies in which visceral TRPV1 receptors were 'selectively' desensitized by intraperitoneal injection of resiniferatoxin suggested a predominantly peripheral site of action [52]. Furthermore, a comparison of peripherally restricted and centrally penetrant molecules infers that the hyperthermic effects of TRPV1 antagonists are associated with both. However, there are complications associated with the interpretation of the compound-based studies in that additional effects at a central site that may be poorly shielded by the blood–brain barrier such as the hypothalamus may have contributed to the effects noted; indeed, a recent publication adds further credence to this possibility providing evidence of the direct involvement of TRPV1 receptors in thermoregulation through the thermosensitive control of vasopressin release from the hypothalamus [56]. The issue of hyperthermia is therefore relevant to the use of systemically administered compounds and the selection of non-brain penetrant compounds does not necessarily offer an advantage nor an explanation for differences between compounds [57]. Furthermore, as discussed earlier, the peripheral approach may also be expected to have downsides with respect to efficacy [23]. Such considerations apply to the development of topical or injectable

formulations of TRPV1 antagonists with a view to replicating the utility of TRPV1 agonists such as ALGRX and NGX-4010 whilst avoiding the systemic side effects (Table 1).

Although the risks apparent at the current time are not necessarily insurmountable, it would clearly be preferable to progress an agent devoid of this issue. Although defined as an 'on target' effect, there are indications from preclinical and clinical work that not all TRPV1 antagonists are equal: for example several potent TRPV1 antagonists do not cause prominent hyperthermia *in vivo* [51] and no adverse events related to hyperthermia have been reported for SB-705498 [38], consistent with a clear separation between doses that are active in the guinea pig FCA model of inflammatory pain and those that are hyperthermic in the same species [58]. Furthermore, compounds such as A-425619, which have recently been evaluated in detail, are associated with hypothermic effects and are influenced by diurnal variations in core body temperature [59]. This, together with recent insight into the complexities arising from the multimodal nature of TRPV1 (Fig. 1) and the potential for different modes of action to be associated with particular physiological and pathophysiological roles offers additional options for addressing hyperthermia risks. Initial evidence suggesting that, somewhat unexpectedly, non-thermal regulation of TRPV1 appears key for its contribution to thermoregulation [52], and the fact that antagonists that do not block all modes of TRPV1 activation still demonstrate efficacy [60], opens up the possibility for progressing 'next-generation' TRPV1 antagonists with modality-specific profiles of activity. The possibility that the current molecules under study also have additional pharmacological activities that contribute to their *in vivo* profile also needs to be considered.

### *TRPV1 and CNS side effects*

Although often thought of as a marker of nociceptive sensory neurones, the expression of TRPV1 in rodent and human brain was highlighted in many initial studies [3,61,62]. Its functional role has, however, remained more elusive. As discussed above, TRPV1 appears to contribute to the maintenance of pain at spinal and supraspinal levels, but recent studies also suggest a broader role of TRPV1 in synaptic plasticity in the central nervous system. For example, the contribution of TRPV1 to mechanisms of long-term depression in the hippocampus may suggest a physiological role in certain aspects of learning and memory and a possible pathological contribution to epilepsy [63] and other diverse neurological and psychiatric disorders such as anxiety and depression [21]. With regard to CNS side effects, we note that no issues have been reported from the preclinical safety studies or clinical studies conducted to date with TRPV1 antagonists, however, work on other molecules such as Rimonabant (SR141716), which may have additional activity at TRPV1 (and many other receptors) in addition to its primary pharmacology, in this case at cannabinoid CB1 receptors, has recently kindled debate [21,64]. Further studies are therefore now warranted to investigate these initial findings in more detail (especially following long-term antagonist exposure) and understand if some of the strategies outlined above for tackling the issue of hyperthermia, for example reduced CNS penetrance, may also prove useful here.

## Perspectives for TRPV1 antagonists as novel therapeutic agents for the treatment of pain

TRPV1 antagonists offer a new mechanism of action for the potential treatment of a wide range of acute and chronic pain disorders. Should the initial promise from preclinical and Phase 1 work discussed above be borne out by emerging data from PoC studies conducted in patients then the TRPV1 antagonist class of compounds may offer one of the first novel mechanistic treatments for pain for many years. In targeting a novel receptor, these agents offer the potential for an improved side effect profile compared to existing medications such as the COX2/NSAID class for inflammatory pain that are associated with gastrointestinal and cardiovascular risks. Likewise, the need for titration and poor tolerability often encountered with current treatments for neuropathic pain, such as gabapentinoids and duloxetine, provide clear opportunities for a novel agent to succeed. Furthermore, the key role for TRPV1 as a key downstream target of mechanisms implicated in pain signalling and the broad spectrum of activity defined for TRPV1 antagonists in preclinical studies also offers promise for patients with chronic pain that are refractory to currently available treatments. As with any novel mechanism, further preclinical and clinical work can introduce new risks and challenges such as the role of TRPV1 in core body temperature regulation and the propensity for some TRPV1 antagonist to cause hyperthermia. Here, the complexity of TRPV1 receptor activation means that not all compounds are equal and diligence, good science and some fortuity are doubtlessly required to find the right clinical compound to meet patients' needs. Recent emerging data also suggests that TRPV1 may be an important contributor to the efficacy of paracetamol [65] and the development of tolerance and thermal hyperalgesia in response to chronic morphine use [66]. Clearly, we still have much to learn about the contribution of TRPV1 to pain biology.

## Disclosure statement

The authors are employees of GlaxoSmithKline PLC and hold shares in this company.

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