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REVIEW

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A review of the patent literature surrounding TRPV1 modulators

Isabel Devesa, Gregorio Fernández-Ballester, Asia Fernandez-Carvajal and Antonio Ferrer-Montiel

Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche, Universidad Miguel Hernández, Elche, Spain

ABSTRACT

Introduction: TRPV1, a pivotal therapeutic target for chronic pain and pruritus, has been validated in the pathogenesis of several pathologies from diabetes to cancer. Despite the constellation of chemical structures and strategies, none of these molecules has yet been clinically developed as a new drug application due to safety concerns, particularly in thermoregulation. Thus, clinical development of TRPV1 modulators remains a challenge.

Areas covered: This review covers the patent literature on TRPV1 modulators (2019–2024, PubMed, Google Patents, and Espacenet), from orthosteric ligands to innovative compounds of biotechnological origin such as interfering RNAs or antibodies, and dual modulators that can act on TRPV1 and associated proteins in different tissues.

Expert opinion: Therapeutic strategies that preferentially act on dysfunctional TRPV1 channels appear essential, along with a superior understanding of the underlying mechanisms affecting changes in core body temperature (CBT). Recent findings describing differential receptor interactions of antagonists that do not affect CBT may pave the way to the next generation of orally active TRPV1 inhibitors. Although we have thus far experienced a bitter feeling in TRPV1 drug development, the recent progress in different disciplines, including human-based preclinical models, will set an interdisciplinary approach to design and develop clinically relevant TRPV1 modulators.

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1. Introduction

Although the first transient receptor potential (TRP) channel was described in 1969 [1], it was not until the end of the 1990s that the capsaicin receptor (renamed as TRPV1) was molecularly identified, cloned, and recombinantly characterized as a TRP channel that responded to chemical and physical stimuli [2]. Few years later, in 2021, David Julius was awarded the Nobel Prize in Physiology or Medicine for cloning TRPV1 and revealing the mechanisms underlying temperature and pain perception. TRPV1 is the prototypical nociceptive channel widely expressed in primary afferent neurons of the dorsal root, trigeminal and nodose ganglia. TRPV1 is a polymodal nonselective cation channel activated by temperature (>42°C), low pH (<6.5), osmolarity changes, vanilloids and endocannabinoids, and arachidonic acid metabolites [3,4]. TRPV1 is mainly known for its ability to sense a variety of pungent plant products, the most well-known being capsaicin, the bioactive compound in chili peppers. Other compounds from this category include resiniferatoxin, piperine, gingerol and zingerone, camphor and eugenol [5] (Figure 1). In the context of inflammation, it was found that activation of TRPV1 channels is notably potentiated by various pro-inflammatory agents such as prostaglandins, serotonin (5-HT), bradykinin, activators of the protease-activated receptors (PAR), ATP, nerve growth factor (NGF), histamine, calcitonin-gene-related peptide α (CGRP α), tumor necrosis factor α (TNFα) and interleukins [10–12].

In recent years, it became apparent that TRPV1 is also expressed in non-nociceptive neurons and other tissues [13,14]. This wide cellular and tissue expression enhances TRPV1 pathophysiology beyond pain, encompassing thermosensation [15], energy homeostasis [16], cancer [17], regulation of diet-induced obesity [18], insulin and leptin resistance [19], development of severe bronchial asthma [20], neurological disorders [21] and itch [22,23]. Consequently, academic researchers and pharmaceutical companies have shown massive interest in the discovery and development of TRPV1 channel modulators to intervene in a plethora of clinical conditions such as pain, stroke, cancer, dysphagia, diabetes, and obesity. Based on its involvement in various neurologic diseases, TRPV1 has also been signaled for the treatment of diseases including depression, anxiety, fear, emotional stress and drug abuse [24,25]. Additionally, a plethora of compounds have been or are being developed around TRPV1 modulation for skin and haircare, particularly to attenuate itch in sensitive skin and scalp [23,26].

This review covers the patent literature on TRPV1 modulators, from orthosteric ligands to the most innovative compounds of biotechnological origin such as interfering RNAs or antibodies, as well as dual modulators that can act on TRPV1 and other targets involved not only in pain but also in other diseases.

CONTACT Antonio Ferrer-Montiel aferrer@umh.es Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche, Universidad Miguel Hernández de Elche-IDiBE-UMH, Avenue De la Universidad Avda Universidad s/n, Elche 03202, Spain

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Article highlights

- TRPV1 is considered a therapeutic target to treat a variety of pathologies from chronic pain to cancer.
- Therapeutic targeting of TRPV1 has revealed challenging due to its role modulating thermoregulation.
- Progress in structural and computational biochemistry is unveiling the atomic intricacies and dynamics of polymodal gating and ligand interaction.
- Modulation of disease-induced TRPV1 expression opens new strategies for therapeutic receptor targeting.

2. Orthosteric antagonists

TRPV1 was described as a gateway of pain transduction in humans, and TRPV1 competitive antagonists were signaled after channel cloning as potential alternatives to opioids to control chronic pain. Among ion channels involved in pain signaling, TRPV1 was the first choice of most pharmaceutical companies to develop oral antagonists with the promise of exhibiting lower side effects than opioids, corticoids, and non-steroidal anti-inflammatory drugs (NSAIDs) [27,28]. However, since TRPV1 also plays an important role in thermoregulation, early TRPV1 antagonists failed in clinical studies because of hyperthermic effects or burns from alteration in noxious temperature sensing [29]. Thus, despite their enormous potential, the clinical development of TRPV1 antagonists has been notably impacted by their unwanted side effects, particularly on thermoregulation.

To reduce the side-effects, optimization of several small molecules based on different chemical pharmacophores, such as piperazines, pyrrolidines, isoflavones or benzimidazolone have been carried out to obtain modality-specific compounds directed to target one mode of TRPV1 activation. (Table 1, CN117736163A [30], CN111454233A [31], CN111423432A [32], WO2021215656A1 [33] CN116903571A [34], CN109761974A [35]).

Recently, Huang et al. 2024, by comparing the interaction of an oral competitive antagonist (AMG517) that produces hyperthermia with that of a non-hyperthermic inhibitor (SB-366791), provided experimental and computational evidence supporting a new and attractive hypothesis [6]. Subtle differences in the interaction within the vanilloid pocket appears linked to the differential impact of both antagonists on thermoregulation (Figure 1(b)). At variance with AMG517, SB-366791 binds to the upper domain of the vanilloid-binding site and does not interact with the S4-S5 linker and the TRP box. Interaction with these two TRPV1 domains appear to underlie the differential effect on thermoregulation. In support of this hypothesis, the authors performed a virtual screening

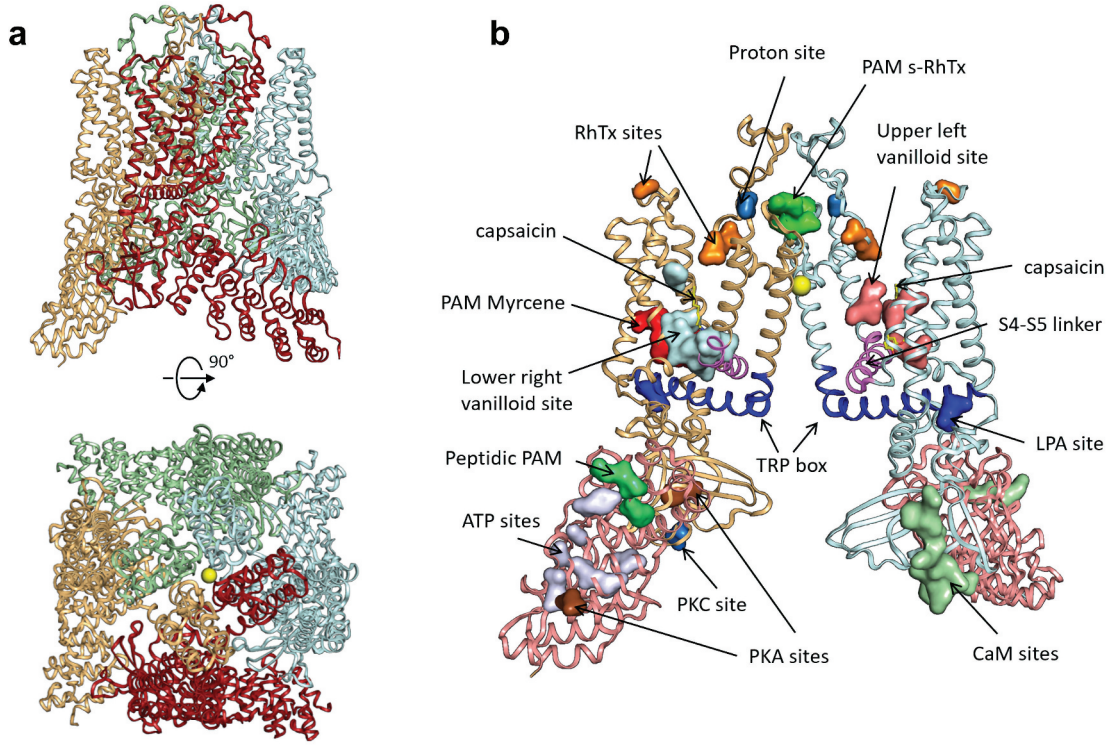

Figure 1. Structure of TRPV1 in complex with capsaicin (PDB code 7LR0). (a) Side and top view of TRPV1 represented in cartoon with different color for each subunit. The yellow sphere is a sodium ion trapped in the selectivity filter. (b) Representation of the main binding sites in the TRPV1. Two of the four subunits are removed for clarity. ARD domains are coloured salmon. Capsaicin is coloured yellow. TRP box is coloured blue (residues 681–713). Main residues involved in the 'lower right' vanilloid site [6] are represented in surface and colored pale cyan in the subunit on the left (residues 511, 512, 515, 543, 551, 557,570, 569, 573, and 670). The residues in the 'upper left' vanilloid site are colored deep salmon in the subunit on the right (residues 511, 512, 547, 550, 666, and 670). Loop S4-S5 is colored violet (residues 559–579). CaM sites are colored pale green (residues 200, 201, and 767–801). ATP sites are colored blue white (residues 115, 155, 160, 163, 199, 202, and 210). PKC sites are colored marine (residues 774, and 820), and PKA sites are colored brown (residues 116 and 370). Proton binding site is colored sky blue (residue 600). LPA site is colored blue (residue 710), and RhTx sites are colored orange (residues 460, 631, and 633). PAM Myrcene is colored red (residues 435, 438, 488, 512, 513, 516, 554, and 555T, as described in Jansen et al., 2019 [7]). PAM s-RhTx is colored green (residues 649 and 652, as described in [8]). Intracellular peptidic PAM is colored lime green (residues 243, 244, and 246, as described in [9]).

Table 1. Patent status of small-molecule TRPV1 modulators for pharmaceutical use.

Compound	McoA	Indication	Patent	Ref.
Phenylpiperazine based structure	TRPV1 antagonist	Pain	CN117736163A	[30]
4-(2-(pyrrolidine/piperidine-1-yl)benzyl)-piperazine urea	TRPV1 antagonist	Pain	CN111454233A	[31]
(S)-4/5-phenyl-2-(pyrrolidin-2-yl)thiazole	TRPV1 antagonist	Pain	CN111423432A	[32]
Benzimidazolone-based cinnamamide derivative	TRPV1 antagonist	Pain	CA3173067A1 WO2021215656A1	[33]
Isoflavone based structure	TRPV1 antagonist	Analgesic and hypoglycemic activities	CN116903571A	[34]
1,2,3,4-tetrahydro-9 h-pyridino[3,4-b]indole	TRPV1 antagonist	Pain	CN109761974A	[35]
Cyclobutanone derivative	TRPV1 antagonist	Antitumor activity	CN116217611A	NP
Quinazolinone derivative SAF312 (libvatrep)	TRPV1 antagonist	Ocular surface pain, postoperative dental pain	WO2024062389A1	[36]
1,3-substituted cyclobutyl derivatives	TRPV1 antagonist	Dry eye disease	WO2022201097A1	NP
Water-soluble prodrug derivative of a phenolic capsaicin	TRPV1 agonist	Pain. Related therapeutic fields of capsaicin and its analogues	CN116003285A	[37]
Water-soluble capsaicin pro-drug	TRPV1 agonist	Postsurgical pain	WO2022132650A1	[38]
Capsaicin derivatives with thiourea structure	TRPV1 agonist	Pain	CN117550996A	[39]
Capsaicin-derived photosensitizer	TRPV1 agonist	Antitumor activity	WO2023245857A1	[40]
Capsaicin-derived photosensitizer	TRPV1 agonist	Antitumor activity	US2023414758A1	[40]
SB366791	NAM-TRPV1 antagonist	Breast cancer	CN116966171A	NP
C. sativa extracts	PAM- TRPV1 agonist	Pain	CA3144983A1	NP

NP: not published.

on a chemical library, and readily identified a competitive TRPV1 antagonist that alleviated pain, without altering CBT. This finding may pave the way for future generations of safer receptor ligands for a plethora of TRPV1-mediated pathologies from chronic pain to cancer.

As an interesting case in point, compound SAF312 is a TRPV1 antagonist being clinically developed as a therapeutic for ocular pain (Table 1, WO2024062389A1 [36]) by Novartis. SAF312 is primarily directed to modulate the severe pain and discomfort resulting from nerve injury of the highly innervated cornea and conjunctiva [41], where TRPV1 is expressed and functionally altered by the surgical procedures underlying the patient discomfort [42]. Notably, this compound in humans decreased pain severity after ocular surgery [43], although one patient suffered pyrexia. Complementarily, TRPV1 has also been implicated in inflammatory responses occurring in dry eye syndrome [44], thus TRPV1 modulators are also being considered for the treatment of dry eye disease (Table 1, WO2022201097A1).

In recent years, cancer neuroscience is steaming up as tumor innervation is being recognized as central in cancer immunosurveillance and tumor growth and invasion [45]. Thus, neurotherapy of tumors has gradually received attention achieving certain curative effects in a variety of solid tumors. Accordingly, special attention has been given to TRPV1 antagonists as antitumor agents. Cyclobutanone derivatives have been discovered to promote local immune responses against tumors, destroy tumor blood vessels and ultimately kill cancer cells (Table 1, CN116217611A). Moreover, channel antagonists have been identified to disrupt tumor innervation and reduce tumor size (Table 1, CN116966171A). Although tumor denervation including surgical resection or drug blockade can inhibit tumor progression improving prognosis, there are still deficiencies that need to be improved, such as whether the tumor-neural axis can be specifically targeted to bring widespread clinical benefits [46]. The bridge in neuroimmune interactions and TRPV1 has also been investigated in neurological disorders, showing this ion channel as a promising drug target [21].

Another therapeutic application of TRPV1 competitive antagonists is chronic pruritus such as that present in dermatitis, psoriasis, cancer immune-oncology, uremia or cholestasis [47–49]. For this application, topical capsaicin has been the standard treatment since the 80ths; however, because of its pungent effect, patient adherence is poor [50]. Serafini et al. 2018, designed a family of capsaicinoid-based soft antagonists for modulation of epidermal nociceptive TRPV1 receptors [51]. This family incorporated an esterase-sensitive site to facilitate hydrolysis as a strategy to limit its dermal accumulation. This sort of soft drug is ideal to prevent the potential long-term effects of UV-induced generation of vanilloid-based radicals that may have oncogenic activity [52], and to preserve normal thermosensation. In animal models of pruritus, the topical application of an ointment containing compound AG1529 reduced both histaminergic and non-histaminergic pruritus [26]. Currently, we are developing a non-pharmacological topical formulation containing the analogue AG1549 (referred to as Calmapsin®), to alleviate chemotherapy-induced sensory symptoms in hands and feet produced by drugs, such as taxanes and platinum agents.

3. Desensitizing agonists

Complementary, desensitizing TRPV1 agonists are also therapeutically interesting. Undoubtedly, the most explored TRPV1 desensitizing agonist is capsaicin. Its exposure to TRPV1-expressing nociceptor peripheral terminals results in initial excitation followed by a functional and potent desensitization due to channel inactivation and retrieval from the terminal [53]. Delivery systems are being developed to increase the safety and efficacy of capsaicin, although its pungency remains an issue for patient adherence. The use of skin patches such as Qutenza® can also cause skin irritation to medical staff due to its high content of capsaicin (8%) [54].

To circumvent the limitations of the vanilloid hydrophobicity, water-soluble capsaicin pro-drugs have been developed mainly for local infiltration (Table 1, CN116003285A, WO2022132650A1). Side-directed injections provide greater target engagement, which theoretically superior local analgesia, particularly after surgical trauma, osteoarthritis, or cancer pain. Based upon this, local delivery of a TRPV1 agonist throughout the tissues around the surgical site prior to wound closure maximized engagement and resulted in a reduction of post-surgical pain over several days to weeks [37]. This improved long-term pain relief can augment current multimodal analgesia or enhance recovery programs avoiding the need for supplemental opioid use [38]. Other strategies have involved modifications with thiourea groups. These derivatives are noteworthy owing to their higher analgesic potency *in vitro* and in rodent pain models (Table 1, CN117550996A [39]).

As mentioned above, recent studies have found that TRPV1 expression in cancer cells plays an important role in the pathogenesis of several tumors, such as breast cancer, endometrial cancer, prostate cancer, bladder cancer, melanoma and liver cancer, and is related to tumor cell proliferation [55]. Based on TRPV1 thermal sensitivity and agonist affinity, capsaicin has been conjugated with nano-photosensitizer, which allows specific activation of TRPV1 channels in tumors, causing a cumulative effect and inducing cell apoptosis in triple negative breast cancer (Table 1, WO2023245857A1, US2023414758A1 [40]).

Despite being a good therapeutic, the use of capsaicin or other potent and selective TRPV1 agonists causes high levels of discomfort during the initial applications prior to receptor desensitization. In addition, capsaicin-treatments are limited to topical application; while visceral pain, headache, and certain musculoskeletal pain disorders are not addressed by this therapy. Therefore, there is a need for therapeutic TRPV1 ligands that are more sophisticated than capsaicin. They should target the channel with higher efficacy and faster transition toward the desensitized state to lower the burning side effect, thereby causing less pain prior to desensitization. In this respect, resiniferatoxin, a potent desensitizing agonist, is being clinically tested as a complementary/alternative to capsaicin. For example, resiniferatoxin-induced cell death of TRPV1-expressing neurons appears to help treating intractable cancer pain, but it causes irreversible damage to neurons, which may limit its therapeutic application [56,57].

4. Allosteric ligands

Allosteric modulation of TRPV1 appears as a complementary strategy for therapeutic TRPV1 intervention. These compounds explore other receptor-binding sites and may be combined with orthosteric ligands for more potent and long-lasting modulation of dysfunctional channels. For example, uncompetitive antagonists, a sort of positive allosteric modulator, bind to receptor sites that are accessible in open channels. They promote inactivation of an active TRPV1 channel, thereby acting preferentially in regions of tissue damage or inflammation where the channels are dysfunctional.

Neuberger et al. 2023 reported the binding site of SB-366791 in hTRPV1 and proposed an allosteric mechanism of channel inhibition. This compound can bind both the channel closed state by displacing phosphoinositide binding and locking the channel in the closed state or by indirectly displacing capsaicin and promoting channel closure. The molecular and atomic details provided by this study on the binding site and the interacting mode opens new venues to design therapeutically valuable TRPV1 allosteric modulators [58].

A patent describes how to identify compounds containing chemical elements that are predicted to bind to a specific TRPV1 binding pocket and act as positive allosteric modulators (Table 1, CA3144983A1). This strategy was based on the discovery of TRPV1 binding sites specific for myrcene ('site 4') or cannabidiol (CBD) ('site 4A'), key amino acid residues involved in acute activation without inducing TRPV1 to enter the dilated state (Figure 1(b)). Using the newly discovered binding sites, numerous structurally diverse terpenes and cannabinoids were pre-screened to identify those with desired modulatory effects (Table 1, CA3144983A1). Notably, knowledge of the allosteric mechanisms underlying TRPV1 polymodal activation should contribute to refine the design of allosteric modulators targeting distinct conformational states, which may result in drugs with improved therapeutic index [59].

5. Multi-target-modulators

The development of multi-target directed ligands, which simultaneously interfere with multiple disease-related proteins, has attracted massive academic and pharmaceutical interest in the quest for therapeutics against diseases with complex pathology-like chronic pain. It can offer several advantages, such as synergism, delaying drug resistance, as well as the potential to avoid over-inhibiting a particular target and the associated side effects [60]. Thus, multi-target inhibitors combining TRPV1 antagonism and analgesic mechanisms are promising candidates for pain management (Figure 2).

In recent years, numerous targets have been involved in various pain-related pathologies. Some of them are enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which catalyze the production of pain mediators like prostaglandins (PGs) and leukotrienes (LTs), respectively, from arachidonic acid (AA). Inhibitors of these enzymes, known as NSAIDs, ameliorate inflammation and pain by blocking the conversion of AA [61] but, adverse gastrointestinal events have been reported [62]. Meanwhile, 5-LOX (LOX type 5) inhibitors have been withdrawn from the market owing to the hepatotoxicity [63]. It is believed that mono-inhibition of either the COX or LOX pathway would shift AA metabolism toward the other cascade, resulting in potential side effects. Knowing the important role of TRPV1 in the pain pathway, much effort has been put into the development of dual inhibitors that have synergistic effects and do not have unwanted side effects. This is the case with dual COX/TRPV1 inhibitors (Table 2, CN115105503A [64]). Furthermore, a rational approach to inhibit both COX and LOX simultaneously has also been proposed [65]. Indeed, in view of the importance of dual COX and LOX inhibition, as well as the medical potential of TRPV1 as an analgesic target, the discovery of COX-2/5-LOX/TRPV1 multi-target inhibitors may

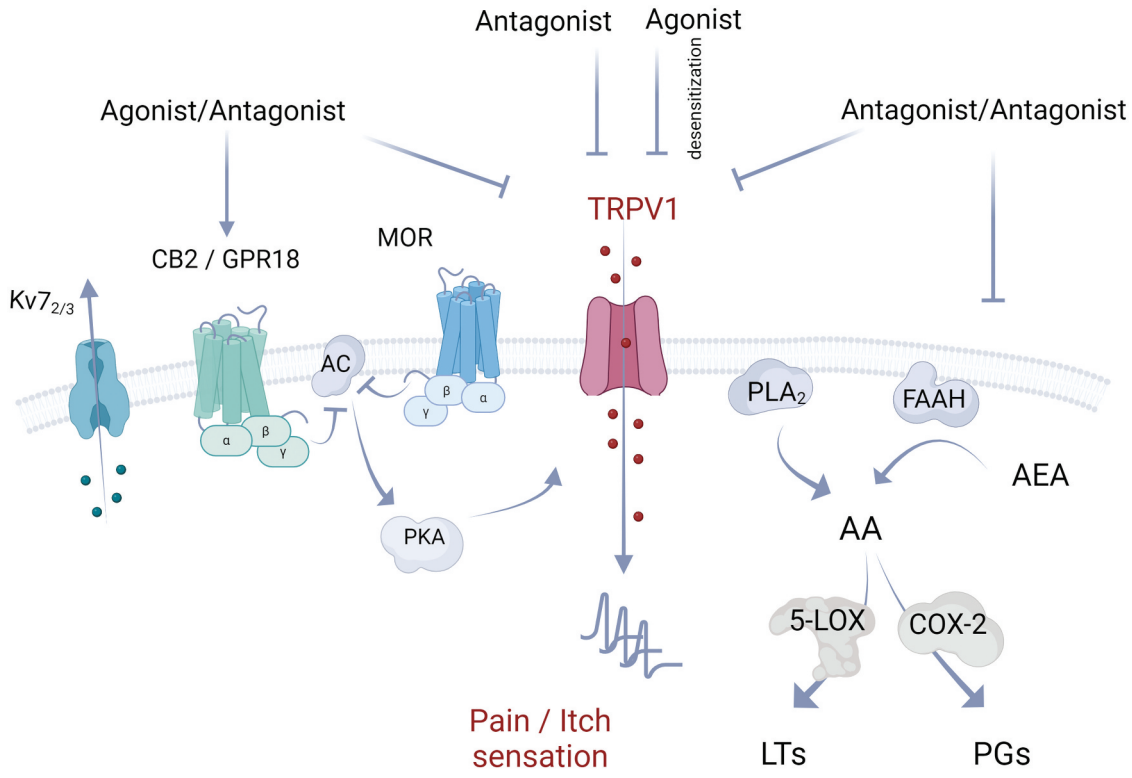

Figure 2. Multi-target modulators of TRPV1. Scheme of novel TRPV1 modulators acting on other molecular targets. TRPV1 channel gating generates neuronal excitability, which is involved in processes such as pain and itch. From left to right. Left. Novel compounds act simultaneously as activators of Kv7.2/3 heterodimers and inhibitors of TRPV1, reducing neuronal hyperexcitability and stabilizing responses to algesic stimuli. Dual modulators of cannabinoid receptor 2 (CB2) and TRPV1 antagonism are recognized as potent analgesics. CB2 agonism interferes with adenylate cyclase/pka phosphorylation and consequent potentiation of TRPV1. New dual-target drugs with TRPV1 antagonism and μ-opioid receptor (MOR) agonism are potent analgesic targets due to their direct crosstalk, enhancing analgesic effects. Centre. Classical antagonists directly inhibit TRPV1 gating, whereas TRPV1 agonists desensitize channel function upon activation, resulting in pain or pruritus relief in both cases. Right. A new compound has been discovered that targets either TRPV1/COX-2 or TRPV1/COX-2/5-lox to reduce inflammatory and pain mediators generated by the arachidonic acid (AA) cascade. Dual-target drugs have been developed that act directly as TRPV1 inhibitors but also block fatty acid amide hydrolase (FAAH), thereby reducing the generation of AA from anandamide (AEA). AA: Arachidonic acid, AC: Adenylate cyclase, AEA: Anandamide, CD2: cannabinoid receptor 2, FAAH: Fatty acid amide hydrolase, COX-2 cyclooxygenase-2, GPR18: G protein Receptor 18, Kv7 2/3: Potassium channel v 7 subtypes 2 and 3, 5-LOX: 5-lipoxygenase, LTs: Leukotrienes, MOR: μ-opioid receptor, PKA: Protein kinase A, PLA2: Phospholipase A2, PGs: Prostaglandins, TRPV1: Transient Receptor Potential Vanilloid Receptor 1.

Table 2. Patent status of multi-target-modulators.

Compound	McoA	Indication	Patent	Ref.
Flurbiprofen based structure	TRPV1 antagonism/ COX inhibition	Chronic pain	CN115105503A	[64]
N-(benzenesulfonyl) amide derivative	TRPV1/COX-2/5-LOX antagonist	Anti-inflammatory and analgesic activities	CN115784991A	[65]
Indoline piperidine-based structure	TRPV1 antagonism/ FAAH inhibition	Chronic pain and anxiety	CN114605385A	[66]
Carbamic acid ester-based structure	TRPV1 antagonism/ FAAH inhibition	Chronic pain, neurodegenerative diseases	CN114478359A	[66]
Carbamate and urea-based structure	TRPV1 antagonism/ FAAH inhibition	Pain	CN113233996A	[66]
Indoline piperidine urea-based structure	TRPV1 antagonistic and MOR agonistic	Pain, inflammation, immune dysfunction, neurological and psychiatric disorders, respiratory diseases, urinary and reproductive disorders	CN114591327A	[67]
Benzylpiperazine urea-based structure	TRPV1 antagonistic and MOR agonist	Pain, inflammation, immune dysfunction, neurological and psychiatric disorders, respiratory diseases	CN113292485A	[67]
Pyrazolylbenzene-1,3-diols based structure	TRPV1 antagonism/ GPCR18	Neurodegenerative diseases, pain, epilepsy, anxiety, depression	US2021323927A1	NP
Diphenylamine based structure	TRPV1 antagonism/ Kv7.2/3 agonist	Pain, tinnitus and pruritus	WO2023139581A1	NP

NP: not published.

provide a novel therapeutic weapon against pain by overcoming the drawbacks of approved anti-inflammatory and analgesic agents (Table 2, CN115784991A [68]).

Another classic pharmacological enzymatic target in the field of pain is fatty acid amide hydrolase (FAAH), a membrane enzyme that hydrolyses anandamide and related

amidated signaling lipids. Genetic or pharmacological inactivation of FAAH produces analgesic, anti-inflammatory, anxiolytic and antidepressant phenotypes, suggesting that FAAH is a promising therapeutic target [69]. Serotonin N-arachidonic acid (AA-5-HT) has been reported as having dual effects of FAAH inhibition and TRPV1 antagonism, with analgesic and anxiolytic effects in rodent models of acute and chronic pain, being more effective than FAAH inhibition or TRPV1 antagonism alone [70]. Therefore, different strategies based on modifications of the AA-5-HT structure have been developed to obtain a dual-target drug that acts on both TRPV1 and FAAH, which may be a new approach to treat chronic pain (Table 2, CN114605385A, CN114478359A, CN113233996A [66]).

Not only enzymes, but various ionotropic or metabotropic receptors have also attracted the attention of researchers searching for new pain therapies. As a member of the G protein-coupled receptor (GPCR) superfamily, the μ-opioid receptor (MOR) is currently recognized as the most potent analgesic target [71]. However, long-term use of such drugs results in the expression and release of chemokines, pro-inflammatory cytokines and nociceptive neurotransmitters in the spinal cord and dorsal root ganglia, which antagonize the analgesic effects of opioid receptors, leading to drug toxicity. The analgesic effect is reduced by increasing tolerance and dose [72]. According to the literature, there is a close relationship between the TRPV1 and MOR receptors [73]. The TRPV1 antagonist SB366791 inhibits morphine tolerance and tolerance-induced thermal hyperalgesia, enhancing the morphine analgesic effect and significantly reducing withdrawal symptoms. Therefore, the development of a new dual-target drug can use the interaction between the two targets enhancing analgesia, but it could also reduce the single-drug side effects, having the potential to become a new type of analgesic drug. Using the pharmacophore fusion strategy to design dual modulators, Gao et al. [67] developed a family of compounds having both strong MOR binding affinity and TRPV1 antagonist activity. Potent analgesic effects and no analgesic tolerance on repeated dosing were shown together with no apparent side effects of hyperthermia (Table 2, CN114591327A, CN113292485A [67]).

Several compounds have been developed acting synergistically on cannabinoid receptors and TRPV1 [74,75]. Recently, attention has focused on GPR18, a GPCR that responds to endocannabinoids, although it is still considered an orphan receptor. GPR18 has been suggested as an alternative target for pain relieve. For instance, nerve injury enhances the expression of GPR18 mRNA in spinal cord and/or the dorsal root ganglia, suggesting a potential role of GPR18 in the modulation of neuropathic pain [76]. Thus, these recent advances provide opportunities for the development of innovative strategies for diseases in which both systems, TRPV1 and GPR18, are involved (Table 2, US2021323927A1).

The neuronal Kv7 channels have been demonstrated to play key roles in controlling neuronal excitation. Kv7 channels, particularly Kv7.2/Kv7.3 heterodimers, underlie the M-current, a non-inactivating potassium current found in several neuronal cell types critical for neuronal repolarization. The current has a characteristic time and voltage dependence that results in stabilization of the membrane potential in response to multiple excitatory stimuli. In this way, the M-current is central to controlling neuronal excitability (for a review, see reference [77]). Kv7.2/3 channels and TRPV1 are uniquely co-expressed in afferent peripheral sensory neurons, which convey sensory signals and have opposite functions. TRPV1 channels trigger the pain signals, while Kv7.2/3 channels inhibit them [78]. Compounds that simultaneously function as activators (e.g. openers) of Kv7.2 and inhibitors (e.g. blockers) of TRPV1 can depress neuronal hyper-excitability associated with medical conditions such as pain, tinnitus, and pruritus (Table 2, WO2023139581A1).

6. Peptide-based agents targeting TRPV1 receptor

Sea anemone venoms contain a wide variety of peptides able to modulate targets such as ion channels. The first peptides characterized from *Heteractis crispa* as TRPV1 modulators were the serine protease inhibitors, APHC1, APHC2, and APHC3, with analgesic properties [79]. Lately, a new Kunitz-type bifunctional peptide, named HCRG21, was characterized as the first full TRPV1 antagonist [80]. This 56-amino acid peptide has high structural homology with APHC family, showing a three disulfide bonds that stabilize the structure. However, HCRG21 has a different mechanism of action, as it seems to block the pore, while APHC1 is predicted to interact with the outer P-loop area [81]. The potential of HCRG21 as an analgesic and anti-inflammatory agent was evidenced in several animal models, showing a long-lasting analgesic effect on pain-related syndromes (Table 3, WO2021235983A1 [81]). Recent data support novel pharmacological activities as a potential anxiolytic [85] or neuroprotector [86]. Whether these effects are related to a direct TRPV1 antagonism or not, remains to be further investigated, as HCRG21 is known to interfere with other ion channels function such as Kv [87].

Although sea anemone peptides have a demonstrated therapeutic potential, none of them has achieved full preclinical or clinical development yet. These peptides are too bulky to penetrate through the skin barrier. It is worth mentioning the successful development of a shortened derived synthetic peptide inspired by APHC1 toxin, which is currently commercialized in skin care products. Pentapeptide-59 is a synthetic biomimetic peptide that repeats the amino acid active sequence on TRPV1 modified to improve skin uptake. This short peptide is a TRPV1 antagonist commercially distributed by Mibelle AG as an ingredient for sensitive skin and hair care, offering skin comfort and calming sensation [88].

A novel family of short peptides has been recently described and patented also as TRPV1 antagonist (Table 3, CN115583988A). Molecular computer simulation predicted that peptides exert an inhibitory effect by blocking the R557 and E570 of the TRPV1 active site, resulting in the closure of the receptor. As TRPV1 channel blockers, they could be used for treating chronic pain, itch or inflammation among other applications. While in the cosmetic field they are claimed to be potentially used to improve or repair aged-skin or photoaging.

Table 3. Patent status peptides (PAMs, agonists, antagonists, PPI).

Compound	MoA	Indication	Patent	Ref.
Sea anemone peptide HCRG21	Antagonist/extracellular pore binding site	Pain, migraine, osteoarthritis, cough, overactive bladder, inflammatory airway diseases, asthma, bowel diseases diabetes, dermatitis, hyperthermia, neuroprotection, anxiety.	WO2021235983A1	[81]
Peptide family	Antagonist/binding to R557 and E570	Pain, itching, inflammation, allergy, repairing skin barrier, skin aging and photoaging.	CN115583988A	NP
Peptide family	PAM/Targeting intracellular ankyrin-repeated domain	Pain, pruritus, and cancer.	WO2022204524A2	[9]
Derived centipeptide s-RhTx	PAM/Targeting extracellular domain E649 site and/or the E652	Pain	WO2024099103A1	[8]
Centipeptide PvTx	Agonist/targeting extracellular site	Pain	CN116769007A	NP
Peptide family	PPI disruption SNARE-Snapin	Pain, itch, sensitive skin, aging, hyperhidrosis.	WO2019238683A1	[82]
Peptide and Calmapsin	TRPV1 antagonism/ SNARE PPI disruption	Sweating and hyperhidrosis	WO2023161264A1	NP
Peptide	PPI disruption TRPV1-CDK5	Ischemia-reperfusion-induced cerebral injury	CN113880923A CN113880923B	NP
Peptide	PPI disruption Nogo A-NgR1	Pain	CN113527462A	[83]
Peptide family	PPI disruption TRPV1-HR1	Itch	CN116693699A	[84]

NP: not published; PAMs: positive allosteric modulators; PPI: protein-protein interaction.

7. Peptides as allosteric modulators

Structure-guided peptide engineering of a positive allosteric modulator has been recently persuaded, targeting both intracellular as well as extracellular sites of TRPV1 (Figure 1(b)). For instance, peptides targeting the intracellular ankyrin-repeated domain (ARD) of TRPV1 were reported to allosterically enhance the vanilloid receptor activity. They showed analgesic effects in animal models without changing body temperature [9]. This strategy was lately patented as a potential novel method to treat conditions such as pain, pruritus, and cancer (Table 3, WO2022204524A2). The work perfectly described the computational design, the specific sequence and the main key structural features. Potential active peptides should contain at least two aromatic amino acids, preferably phenylalanine that interact with the ARD domain. In addition, peptides should comprise a three helix-loop folded in a three-helix bundle, and the hotspot phenylalanine should be located in helix 3. Similarly, their inability to pass cell membranes was a concern due to their sequence, length, and size. Therefore, intelligently, the authors followed a fusion strategy linking a TAT transmembrane peptide to the N terminus. The pharmacological effect of the cell penetrating candidate was demonstrated *in vivo*. However, potential and translational development seems more limited due to the modifications and synthesis required. Probably, further optimizations need to be implemented to become a successful preclinical candidate [9].

To overcome this limitation, allosteric peptides able to bind to the TRPV1 extracellular domain were persuaded. As example, a novel toxin able to potently activate TRPV1 channel was discovered in the venom of the Chinese red-headed centipede (Scolopendra subspinipes mutilans) [89]. The centipede toxin RhTx is a 27-amino-acid small, polarized peptide with high affinity that interacts to the outer pore of TRPV1 through the C-terminus (Figure 1). It has two pairs of disulfide bonds that hold the peptide folded and N-terminus flexible [89]. The retro-isomer RL-RhTx has comparable activity on TRPV1 with similar binding modes through residues L461, D602, Y632, and T634 [90]. Recently, a novel variant was identified containing four more residues at the N terminus, named RhTx2 [91], which rapidly desensitized TRPV1. Both RhTx and RhTx2 became promising starting molecules to develop novel analogues. Indeed, following an N-terminus modification strategy, a newly designed s-RhTx recently aroused being a three amino acid shortened form of RhTX [8]. This modification prevented direct activation of TRPV1. In contrast, the peptide selectively potentiated TRPV1 currents evoked by capsaicin and proton in a concentration-dependent manner. The desensitization process was slowed down without changing the heat activation threshold. The shortened peptide maintained the disulfide bound present in the original sequence. Docking studies revealed its interaction with E652 and/or E649 in the outer pore. The effects were also demonstrated *in vivo*, showing long-lasting effects in pain models. This innovative strategy was recently patented claiming and revealing the potential of this peptide for pain relief (Table 3, WO2024099103A1).

Another centipede peptide with analgesic properties has been recently patented (Table 3, CN116769007A). Named PvTx, this invention provides an oligoacanthocentipede polypeptide with a completely different sequence from RhTx, but with similar pharmacological properties. This 34-amino acid peptide contains four pairs of disulfide. PvTx directly activates TRPV1, and it specifically mediates the inactivation of the heat-activated pathway, thereby producing a powerful analgesic effect without affecting body temperature. Its sequence points it out as a potential drug candidate targeting TRPV1, which could be rationally modified to become a novel allosteric modulator, avoiding the first burning sensation. However, its

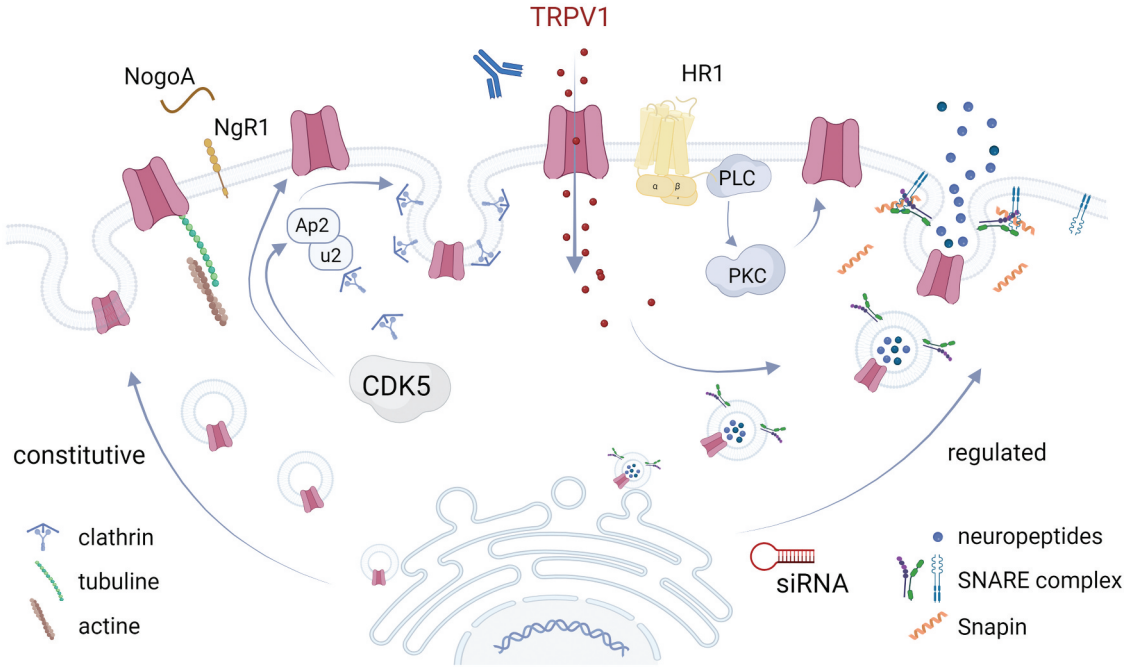

Figure 3. TRPV1 modulation by disruption of protein–protein interaction. Schematic representation of the complex regulation of TRPV1 function and membrane channel expression involved in pain or itch signaling. Only targeted interactions by novel patented molecules or strategies are represented. TRPV1 is regulated by post-transcriptional modifications such as phosphorylation, but its membrane expression is also highly controlled. Protein–protein interactions are key to the control of TRPV1 function and membrane expression. The development of novel peptides that interfere with protein–protein interactions shows promising therapeutic potential for treating conditions such as pain or itch. Left. TRPV1 trafficking to the membrane is mediated along the axon by the microtubule dynamics through its interaction with tubulin. Nogo-A binding to NgR1 modulates microtubule assembly, inducing polymerization and maintaining TRPV1 in the membrane. AP2μ2 binding to the N-terminus of TRPV1 stimulates its internalization. The neuronal kinase cyclin-dependent kinase 5 (CDK5) phosphorylates may directly interact with TRPV1 or through adaptor protein 2 (AP2μ2) regulating its expression and function. Right: Direct binding of H1R to the C-terminal region of TRPV1 transiently enhances its activity upon histamine binding. TRPV1 interacts with the SNARE protein SNAPIN contributing to its mobilization to the cell surface under inflammation through a regulated, snare-mediated exocytosis mechanism. Top: Novel antibodies have been developed to directly block TRPV1 channel activity. Bottom: A novel siRNA targeting TRPV1 expression is under clinical evaluation. AP2μ2: clathrin adaptor protein mu 2, CDK5: cyclin dependent kinase 5, H1R: Histamine receptor type 1 (H1R), NgR1: Nogo receptor 1, PLC: Phospholipase C, PKC: Protein Kinase C, SNARE complex: soluble N-ethylmaleimide-sensitive factor attachment proteins receptors, siRNA: small interference RNA.

exact binding process to TRPV1 is not fully described, but it seems different from RhTx.

8. Peptides involved in TRPV1 trafficking

TRPV1 channel has a complex modulation. Direct post-transductional modification regulates channel gating, while membrane expression is modulated through regulated and constitutive exocytosis (Figure 3, for review see [12]). Phosphorylation are the main known post-transductional mechanisms modulating channel gating. While, recruitment of novel TRPV1 channels to the cell surface is also a pivotal mechanism for algesic neuronal sensitization. Indeed, blockade of regulated calcium-dependent exocytosis by botulinum toxin variants or botulinomimetic peptides diminishes inflammatory-mediated TRPV1 membrane recruitment [12]. As a result, there is a minor presence of functional TRPV1 channels in the neuronal membrane which reduces pain signal [92].

Inspired by botulinum toxins molecular mode of action, *in silico* molecular modeling approach was recently used to design novel peptides targeting neuronal exocytosis and disrupting Snapin-SNARE complex formation [82]. These peptides reduced depolarized- as well as capsaicin-induced neurotransmitters release from sensory neurons. Moreover, inflammatory sensitization of TRPV1 was also impaired as the enhanced capsaicin-evoked electrical activity after exposure to an inflammatory cocktail was reduced, suggesting a clear effect on the gating potentiation. The selected candidate is reduced in a dose-dependent manner excessive sweating *in vivo*. Overall, these results opened the exploitation potential of the invention (Table 3, WO2019238683A1). The rational designed peptides could be used not only to treat excessive sweating but also conditions in which TRPV1 is involved such as pain or inflammation in the pharmaceutical field, as well as to ameliorate sensitive skin discomfort, itch, or photoaged-related signs among others.

Interestingly, and following this line, the combination of a direct TRPV1 blocking strategy and the disruption of neuronal exocytosis has been recently reported to show synergistic effects controlling sweating (Table 3, WO2023161264A1). The acetylated hexapeptide 6 (Argireline®) is a peptide derived from the N-terminal end of the SNAP-25 protein of the SNARE complex. This botulinomimetic peptide is a modest inhibitor of calcium-regulated neuronal exocytosis *in vitro*, and it has some effect in attenuating excessive sweating. The TRPV1 thermoreceptor modulator AG1549 (Calmapsin®) is used to calm sensitive skin in the cosmetic field, but it was unable to attenuate excessive sweating by itself. Surprisingly,

however, the combination of both active principles in a product resulted in a significant and synergic attenuation of excessive sweating, acting on both thermosensory and neuro-eccrine systems. The combination of the neurotransmitter release blockade involved in sweating plus the impact on the heat-sensitive TRPV1 membrane recruitment, together with the direct blockade of TRPV1 channel function resulted in a synergistic product able to better reduce excessive sweating.

Other protein–protein interactions can modulate TRPV1 function and expression. The neuronal kinase cyclin-dependent kinase 5 (CDK5) directly phosphorylates TRPV1 on T407 residue enhancing channel function, and promoting inflammatory thermal hyperalgesia and pain-related behavior [93–96]. Through a different mechanism, CDK5 has been reported to regulate the constitutive internalization of TRPV1 from the membrane by inhibition of clathrin-dependent mechanism [94,97]. Under basal conditions, the clathrin adaptor protein AP2μ2 binds to the N-terminus of TRPV1 stimulating its internalization. However, in an inflammatory context, CDK5 directly phosphorylates AP2μ2 thus negatively regulating the TRPV1 internalization. Based on the last mechanism, a cell-penetrating peptide was designed to interfere with CDK5 mediated phosphorylation of AP2μ2. This peptide reduced pain-related behavior diminishing TRPV1 levels on the neuronal membrane [94,97]. Detailed knowledge on TRPV1 internalization mechanism offers new potential targets for clinical application in pain but also to other applications.

For instance, in ischemia-reperfusion-induced cerebral injury, TRPV1 channels have a dual role, both agonists and antagonists may produce neuroprotection. While TRPV1 channel blockers or the lack of TRPV1 channels may prevent harmful inflammatory responses, agonists may confer neuroprotection [98]. Therefore, regulation of TRPV1 could have some future potential in this area. For example, a new small peptide relieved cerebral ischemia injury, reducing mouse brain damage and providing the experimental basis for its potential as a drug (Table 3, CN113880923 A/B). This cell-penetrating peptide is claimed to interfere with CDK5 and TRPV1 interaction preventing TRPV1 membrane transfer; however, no direct data on TRPV1 membrane expression were shown. Whether the disruption of TRPV1 and CDK5 binding by the peptide promotes changes on TRPV1 membrane expression or function remains to be still elucidated.

TRPV1 also interacts with cytoskeleton components, being microtubule a major constituent. Apart from constitutive transport, the dynamics of microtubules regulate TRPV1 channel expression and function toward activation stimuli [99]. Indeed, there is a physical and functional interaction of the C-terminus of TRPV1 near the TRP box with tubulin dimers. The importance of the TRPV1-tubulin complex was postulated to have relevance in chemotherapy-induced peripheral neuropathy as well as lately on inflammatory pain. In this context, Nogo-A is a modulator of microtubule assembly inducing polymerization, and it has been shown to maintain TRPV1 functionality in inflammatory pain [100]. Nogo-A binds to the receptor NgR1 triggering the expression and function of TRPV1 in inflammatory pain, mainly through the new functional domain of Nogo-A (846–861 aa) [83]. Based on this, a novel small peptide antagonist as well as a specific antibody tethering this protein–protein interaction have successfully diminished inflammatory heat hyperalgesia and reduced TRPV1 content and function in dorsal root ganglia. This strategy offers new tools and molecular mechanisms to treat chronic pain through an indirect modulation of the TRPV1 channel (Table 3, CN113527462A).

In addition to pain, TRPV1 is also involved in the transduction of pruritus, being determinant in histaminergic itch [101], but less in non-histaminergic itch [102]. When histamine binds to its receptors, TRPV1 is activated by coupling to the Gq/11-phospholipase C pathway eliciting itch. Indeed, TRPV1 inhibition reduced histamine 1 receptor (H1R)- but also H4R-mediated itch. Therefore, the TRPV1 antagonists are also considered as potential candidates to treat pruritus [23]. Clinical assessments of topical TRPV1 antagonists are showing successful results on dermatological conditions characterized by itch [103].

Interestingly, H1R also directly binds to the C-terminal region of TRPV1, through residues 715–725 and 736–749. Upon histamine stimulation, TRPV1 is transiently enhanced in sensory neurons through deSUMOylation [104], a mechanism additional to the PLC/PKC phosphorylation pathway. Two TAT cell-penetrating peptides were designed from the TRPV1 C-terminal to disrupt the H1R-TRPV1 binding, and they attenuated histamine-induced itch, but not chloroquine-induced non-histaminergic itch *in vivo*. These peptides reduced the coupling efficiency of TRPV1 and HR1, suppressed histamine-induced currents, but not the capsaicin-induced TRPV1 channel gating [104]. Therefore, therapeutic potential to treat pruritus was evidenced. Consequently, a peptide TAT-TRPV1-C together with their structural analogues and longer variants were recently patented to treat itch-related diseases (Table 3, CN116693699A [84]).

9. Biotechnological modulators

The side effects associated with classical agonists and antagonists have encouraged the exploration of other ways to modulate TRPV1 activity such as RNAi, a technique used to suppress the expression of specific target genes. RNAi has gained popularity as the most widely employed method for gene suppression due to its high affinity, precision and efficacy. In recent years, an increasing number of studies have used siRNAs as new molecules targeting TRPV1 to treat pain [105,106].

AAV-mediated siRNA targeting of TRPV1 resulted in a significant reduction in both the mRNA and protein levels of TRPV1 in the spinal cord, successfully alleviating mechanical allodynia and thermal hyperalgesia [106]. Intrathecal administration of TRPV1 siRNA effectively ameliorated mechanical allodynia and thermal hyperalgesia induced by bone cancer [106]. In addition, it reduced peripheral neuropathy and pain sensitivity by suppressing TRPV1 expression in the spinal cord [107]. Another study found that TRPV1 siRNA was also effective in reducing paclitaxel-induced peripheral mechanical sensitivity [108].

Unfortunately, the efficacy of systemic siRNA administration is hampered by the presence of nuclease enzymes in serum

Table 4. Patent status of TRPV1 biotech modulators.

Compound	McoA	Indication	Patent	Ref.
siRNA	TRPV1 antagonist	Dry eye disease	EP3853317A2	[111]
TRPV1 antibodies	TRPV1 antagonist	Pain	WO2022123040A1	[112]
TRPV1 antibodies	TRPV1 antagonist	Pain	WO2021116341A1	[112]
TRPV1 antibodies-nanoparticles	TRPV1 antagonist	Asthma, dyspnea, chest tightness,	CN113975405A	[113]

that degrade siRNA, as well as immune cell responses and elimination of siRNA by the kidneys [109]. Consequently, exposed siRNAs are often degraded before reaching their intended cellular destinations. It is therefore necessary to develop a delivery mechanism that protects siRNA molecules during systemic distribution and optimizes their access to the target cells. Ongoing research is focusing on it. For example, the lifespan and efficacy of siRNAs have been improved through the application of nanoengineering and bioconjugation processes [46]. One of the most challenging aspects of *in vivo* RNAi research is its systemic delivery. Various techniques are emerging for the delivery of siRNA into a body system. The use of the nano-drug delivery system could provide a medium that improves *in vivo* accessibility, ensures significantly lower toxicity, encapsulates large amounts of siRNA, biodegradable delivery system, stable storage, easy synthesis, and feasible scale-up development [110].

Despite the boom in research, very few of these innovations are translated successfully to the clinics. This is the case with Tivanisiran, a 19-siRNA targeting the hTPRV1, developed as an ophthalmic treatment for dry eye disease (Table 4, EP3853317A2 [111]). Tivanisiran has been investigated both *in vitro* and *in vivo*, showing promising results. In clinical trials, Tivanisiran, administered as preservative-free eye drops, was well tolerated and able to reduce ocular pain/discomfort in patients [114]. Additional results on Tivanisiran efficacy will be obtained from a double-masked Phase 3 study (NCT03108664) in patients with moderate-to-severe dry eye disease, which has been recently completed, but not data are available yet [115].

Another biotechnological approach to target TRPV1 has been the development of antibodies. They have previously been generated [116], but some of them are not able to inhibit capsaicin-induced TRPV1 activity or, when they do, they also generate the undesirable side effect of hyperthermia. To circumvent it, regions in the extracellular region of TRPV1 have been identified that are particularly useful to target with antibodies to preferentially inhibit capsaicin-induced TRPV1 activation without altering heat-induced TRPV1 activation (Table 4, WO2021116341A1, WO2022123040A1 [112]).

A step further was the development of PLGA-PEG @ICG@TRPV1 pAb (PIT) photothermal nanoparticles targeting bronchial TRPV1 for photothermal therapy against ovalbumin- and lipopolysaccharide-induced severe murine asthma. PIT was formulated with a poly(lactic-co-glycolic acid) (PLGA) coating grafted with polyethylene glycol (PEG) as a skeleton to encapsulate indocyanine green (ICG) and conjugated with a polyclonal antibody against transient receptor potential vanilloid 1 (TRPV1 pAb). The nanoparticles exhibited potent photothermal effects both *in vivo* and *in vitro*, and showed good TRPV1 targeting ability due to their selective cellular uptake and specific cellular toxicity toward TRPV1-overexpressing cells. PIT treatment effectively reduced asthma symptoms in mice through a combination of photothermal and TRPV1 targeting effects (Table 4, CN113975405A [113]).

10. Conclusion

Thus far, despite the clinical relevance of TRPV1, therapeutics have been focused on topical desensitizing vanilloid agonists to prevent the hyperthermic effect produced by antagonists. Notably, the development of novel structure-based TRPV1 modulators is currently entering a new phase, which emphasizes the importance of structural information. To facilitate a more logical and systematic approach, it is necessary to obtain TRPV1 structures in both antagonist- and agonist-bound states from the Protein Data Bank. Following the publication of rat TRPV1 structures at near atomic resolution, several studies have documented the discovery of new TRPV1 agonists and antagonists using docking calculations [35,117]. Follow-up studies have established the orientations of specific candidates, but there is currently no up-to-date evidence comparing the docking postures of similar molecules. Recent studies investigating therapeutic applications as well as mechanistic investigations have demonstrated the potential to discriminate between analgesic and hyperthermia-induced side effects [118]. The particular structure of TRPV1, such as the presence of upper and lower gates in the pore domain that can be opened or closed in response to various stimuli, including capsaicin, protons and heat, provides a potential for the development of TRPV1 antagonists [119]. Partial inhibition of proton-activated TRPV1 antagonists and targeting multiple receptors with a single compound may further prevent increases in body temperature. It is anticipated and expected that these novel strategies will be thoroughly validated in the clinic in these coming years, substantiating the pivotal role of TRPV1 in the pathophysiology of neuropathies and cancer.

The primary methods used to design and produce novel TRPV1 antagonists are structural optimization, fragment-based drug design and molecular hybridization. Recently, detailed structural insights into TRPV1, a key protein involved in pain perception, have been facilitated by advances in cryogenic electron microscopy (cryo-EM) [120,121]. Interestingly, to speed up the design of drugs targeting TRPV1, artificial intelligence has also recently been applied [122]. Machine learning techniques to estimate the physicochemical properties, bioactivity and toxicity of small molecule bioactive chemicals are also being used in drug development. Compared to traditional methods, these techniques are more affordable and expedient [118].

11. Expert opinion

Since its discovery, TRPV1 (initially known as the capsaicin receptor) has been considered a pivotal therapeutic target for chronic pain and pruritus and it has been validated in the pathogenesis of several pathologies from diabetes to cancer. Unexpectedly, however, the clinical development of drugs targeting this thermosensory polymodal channel has been disheartening despite massive efforts carried out by academic and pharmaceutical laboratories. This has resulted in a plethora of patented molecules covering a vast chemical space from small molecules to biologics. Despite the constellation of chemical structures and strategies, none of these molecules has yet been clinically developed as a new drug application due to safety concerns, particularly due to their effect on thermoregulation. Modulation of pathological TRPV1 is still primarily accomplished based on the use of the desensitizing properties of capsaicin applied locally either as ointments or patches, since oral capsaicin produces hypothermia. A significant progress in capsaicin therapy is exemplified by Qutenza® patches (8% capsaicin) that are clinically effective treating resistant neuropathies such as chemotherapy-induced peripheral neuropathy (CIPN) GIII and GIV, although their application is challenging.

Numerous attempts to develop therapeutic TRPV1 potent oral antagonists have failed because most of them produce hyperthermia. Indiscriminate modulation of pathological and healthy TRPV1 receptors with highly potent antagonists disrupts the thermosensory activity of the channel leading to dysregulation of CBT and the capacity of noxious thermal sensing, raising safety concerns. Thus, alternative therapeutic strategies that preferentially act on dysfunctional TRPV1 channels appear essential, along with a superior understanding of the underlying mechanisms affecting CBT. In this regard, the recent discovery of a differential binding details of receptor antagonists that affect CBT and those not altering it may pave the way to the next generation of orally active TRPV1 antagonists, although the off-target effect on healthy TRPV1 channels remains to be investigated, particularly its role in noxious thermal sensing.

An attractive alternative that may provide therapeutics is the proteolysis-targeting chimaeras (PROTACs) directed to induce the degradation of TRPV1 channels [123]. Akin to exocytosis modulators, PROTACs are aimed at reducing the surface expression of TRPV1 promoted by pro-inflammatory, algogenic agents and tumors, thus preferentially targeting dysfunctional cells and tissues that show an abnormally high expression of the receptor. Recently, a novel and potent approach referred to as regulated-induced proximity targeting chimeras (RIPTACs) has been proven efficaciously eliminating tumors without harming healthy tissues [124]. RIPTACs represent an innovative class of heterobifunctional molecules whereby one is the target cell which is specifically expressed in pathological cells/tissues and the other is an essential protein for cell survival (effector protein). This approach could be used to target tumors showing an increased expression and pathological contribution of TRPV1. In principle, it could be tailored to target and eliminate dysfunctional channels taking advantage of the altered TRPV1 channelosome present in inflamed or neuropathic tissues. Its potential application in other pathologies remains to be tested, but the potential appears worth investigating.

Other strategies to be considered are recent developments in delivery systems that are getting more precise targeting pathological tissues. By exploiting the presence of disease-validated biomarkers, they may act as pathological GPS-like cues guiding loaded nanoparticles to the target tissue. Likewise, delivery approaches that enhance dermal access will be highly valuable for local delivery of TRPV1 modulators. Not least, new advances in RNA-based therapies may provide additional therapeutic means that may be suitable for some neuropathies or TRPV1-mediated diseases.

Additionally, topical formulations of TRPV1 antagonists remain a useful mode for treating peripheral neuropathies whereby epidermal nociceptive terminals expressing TRPV1 are functionally sensitized. Pathologies such as CIPN, diabetic neuropathy, trigeminal neuralgia, atopic dermatitis and other may benefit from non-pungent vanilloids that desensitize these terminals, relieving patients from the burdensome sensory symptoms and contributing to a faster resolution of the pathology. These conditions have traditionally been treated with topical capsaicin, although with limited adherence of patients due to its pungency. Furthermore, dermal accumulation of capsaicin in the skin has raised safety concerns as UV exposure may generate vanilloid radicals that have oncogenic activity. Notably, the development of TRPV1 soft antagonists that act in the epidermis and are enzymatically hydrolyzed in the dermis provide a safer alternative to classical capsaicinoid molecules.

Recent advances in TRPV1 structural biology and molecular dynamics are providing detailed information on the architecture and dynamics of the channel and its drug-binding sites. Atomic information of ligand-binding sites, along with the conformational changes they experience when transiting from the closed to the open state or to the desensitized conformation, will aid in designing better modulators. This is essential considering the gating complexity of this polymodal receptor able to differentially respond to physical and chemical stimuli and to be modulated by post-translational chemical modifications such as phosphorylation. State-dependent ligand sites, particularly those exposed in the channel open states, are a prime target as these sites may have a longer exposure in pathologically sensitized channels, thus directing drugs toward the disease relevant cells and minimizing the action in healthy tissues. Another aspect that should be taken into consideration is the kinetics of channel inhibition, being therapeutically relevant those molecules exhibiting fast off kinetic constants that will minimize any use-dependent channel blockage. Initial attempts targeting the channel ionic pore were unsuccessful due to the pore dilation experienced by this channel that prevented a stable binding of small molecules acting as open channel blockers. This limitation may now be circumvented using the open structures for docking and exploring new sites for non-competitive antagonism.

Taken together, although we have thus far experienced a bitter feeling in TRPV1 drug development, the recent progress in different disciplines will allow for an interdisciplinary approach to finally design and develop clinically relevant TRPV1 modulators. The current development of human-based preclinical *in vitro* models (organoids, organs-on-chip) will also contribute to this quest enhancing the clinical translation of lead

compounds targeting dysfunctional TRPV1 channels. The future looks brighter than ever for TRPV1 drug discovery.

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Declaration of interest

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ORCID

Antonio Ferrer-Montiel http://orcid.org/0000-0002-2973-6607

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