Targeting TRPV1: Challenges and Issues in Pain Management

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Abstract: Chronic neuropathic pain is notoriously difficult to treat. Standard pain drugs, even narcotic opioid analgesic agents, often provide unsatisfactory pain relief. The need for better drugs is universally recognized. However, despite a substantial investment of resources by the pharmaceutical industry to identify alternative treatments, the effective management of chronic pain remains an unmet medical need. Recently, preclinical research has uncovered new molecular mechanisms underlying the generation and transduction of pain, many of which represent new targets for pharmacological intervention. This review focuses on Transient Receptor Potential (TRP) channel Vanilloid 1 (TRPV1) as a target for treating chronic pain. TRPV1 is a multifunctional channel involved in thermosensation (heat) and taste perception (e.g. peppers and vinegar). Importantly, TRPV1 also functions as a molecular integrator for a broad variety of seemingly unrelated noxious stimuli. Indeed, TRPV1 is thought to be a major transducer of the thermal hyperalgesia that follows inflammation and/or tissue injury. Desensitization to topical TRPV1 agonists (e.g. capsaicin creams and patches) has been in clinical use for decades to treat chronic painful conditions like diabetic neuropathy. Currently, site-specific capsaicin and resiniferatoxin (an ultrapotent capsaicin analog) injections are being evaluated as "molecular scalpels" to achieve permanent analgesia. Most recently, a number of potent, small molecule TRPV1 antagonists have been advanced into clinical trials for pain relief. Perhaps not unexpectedly given the prominent role of TRPV1 in thermosensation, some of these antagonists showed worrisome adverse effects (hyperthermia and impaired noxious heat sensation) in men, leading to their withdrawal from the clinical trials. Clearly, the balance between the beneficial actions of drugs targeting TRPV1 and the adverse effects must be carefully and pragmatically evaluated to determine if these drugs could emerge as the next generation of pain killers.

Keywords: TRP channel, capsaicin, resiniferatoxin, TRPV1 antagonists, pain, neuropathic pain, heat, hyperthermia.

INTRODUCTION

Acute nociceptive pain is an unpleasant sensory experience, a fundamental physiological warning system that alerts us to injury and initiates a variety of protective responses. Chronic pain (defined as pain lasting longer than 3 months, outlasting the usual healing process) is, however, a debilitating pathological condition that affects a large sector of the population, an estimated 50 million Americans, and costs the country billions of dollars in health care costs and lost productivity (http://www.cnn.com/2008/health/conditions/04/28/pain). Indeed, the neuropathic pain market in the United States is expected to double from today's $2.6 billion to $5 billion by 2018. In recognition of this problem, the United States Congress declared 2001-2010 as the Decade of Pain Control and Research. Yet, the mainstay of chronic pain treatment remains morphine and its analogs. In the US, the dispensation of prescriptions for opioids (hydrocodone, oxycodone and morphine) exceeded 100 million in 2002 (http://www.dpt.samhsa.gov). Unfortunately, the long-term use of opioid analgesics can not only lead to unsatisfactory pain relief due to tolerance but the side-effects (e.g. respiratory depression and constipation) may also contribute to premature death. In Canada, the annual incidence of opioid-related death is estimated to be twice as high (27 per million) as the mortality from AIDS (12 per million) [1]. Sadly, prescription pain killers are often abused as highlighted by the tragic death of several prominent members of the music and entertainment industry last year.

Part of the difficulty in developing new successful treatments for chronic pain lies in our inability to resolve the complex interplay among mechanisms involved. The neuronal circuitry appears to be altered by the injury, leading to on-going pain perception even in the absence of nociceptive input from the periphery. If this occurs in the CNS, commonly used over-the-counter non-steroidal anti-inflammatory drugs (referred to as NSAIDs) may provide unsatisfactory pain relief. Unfortunately, brain nuclei that play a role in chronic neuropathic pain conditions are also involved in cognitive and affective functions; therefore, centrally acting analgesic agents often cause side-effects that severely interfere with the patient's ability to carry-out everyday chores. Consequently, patients suffering from disabling pain conditions often need complex and aggressive treatment plans that combine medical and surgical approaches [2-4]. Clearly, there is a great need for therapeutic agents acting *via* novel mechanisms in this field of medicine.

Over the past few years, significant scientific progress has been made in our understanding of the mechanisms that

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underlie pathologic pain. Generally speaking, pain is perceived when action potentials generated in nociceptive neurons are transmitted to the somatosensory cortex. The differences and overlaps among nociceptive, inflammatory and neuropathic pain are beginning to be understood. Preclinical research has identified a large number of potential targets for drug discovery and mechanisms that are involved in the development and maintenance of chronic pain. A key discovery was the molecular cloning of the vanilloid (capsaicin) receptor TRPV1 (**T**ransient **R**eceptor **P**otential, **V**anilloid subfamily member **1**). In the periphery, TRPV1 functions as a polymodal nociceptor expressed on primary sensory neurons [5]. In a much simplified manner, TRPV1 can be thought of as a heat-sensitive, non-selective cation channel with a preference for Ca^{2+} whose heat-activation threshold is lowered by agents in "inflammatory soup" [6-8]. TRPV1 can be both up-regulated and sensitized during inflammation and injury [6-10]. Indeed, TRPV1 was suggested to play a central role in peripheral sensitization. In keeping with this concept, mice whose TRPV1 gene has been deleted by genetic manipulation are devoid of the thermal hyperalgesia that develops following inflammation. Of note, some studies agree that TRPV1 is not involved in the development of mechanical hyperalgesia [11]. Importantly, there is emerging evidence that TRPV1 may also play an important role in the modulation of synaptic transmission in the spinal cord (first sensory synapse in the dorsal horn where TRPV1 is co-expressed with μ opioid receptors) well as supraspinal nuclei. In fact, a study comparing the analgesic effects of TRPV1 antagonists with and without access to the CNS provided compelling evidence that a dual (both peripheral and central) action is required for full analgesic action [12].

For the sake of completeness it should be mentioned here that other heat-sensitive TRP channels, so-called "thermoTRPs," (e.g. TRPA1 and TRPV3) also represent promising targets for the development of novel analgesic drugs. These channels are discussed elsewhere in this supplement. This review exclusively focuses on evidence that validates TRPV1 as target for new-generation analgesic drugs, along with potential adverse effects that may limit their clinical value.

TRPV1 AND NOCICEPTION

Capsaicin, the compound in chili peppers (genus *Capsicum*) that makes them taste "hot," activates nociceptive nerve terminals in the skin, causing an initial excitation of the neurons and a period of enhanced sensitivity to heat (thermal hyperalgesia). This is usually perceived as itching, pricking, or burning and is accompanied by cutaneous vasodilatation (flare response) and edema formation ("neurogenic inflammation"). This capsaicin sensitivity is long considered as a functional signature of primary sensory neurons with thin-myelinated Aδ and unmyelinated C-fibers, hence the term capsaicin-sensitive afferent neurons. These neurons with somata in sensory (dorsal root and trigeminal) ganglia have slow conduction capacity and respond to noxious thermal, mechanical and chemical stimuli. The existence of a capsaicin receptor (now known as TRPV1) has long been anticipated from the specific action of capsaicin on nociceptive afferent neurons [13-16]. TRPV1-expressing primary sensory neurons release a variety of pro-inflammatory neuropeptides (e.g. substance P, SP, calcitonin gene-related peptide, CGRP and neurokinin A, NKA) that induce a series of local effects globally defined as neurogenic inflammation [17]. Neurogenic inflammation is thought to play a central role in the pathogenesis of various disease states that range from migraine through asthma to inflammatory bowel disease [17, 18].

TRPV1 is a polymodal receptor ("nocisensor") *par excellence*, sensitive to noxious heat (above 43ºC, Fig. **1**), acidosis (pH between 5 and 6), "endovanilloids" (anand-amide, arachidonic acid metabolites such as N-arachidonoyl-dopamine (NADA), 12-hydroperoxyeicosatetraenoic acid and others, Fig. **2**), ethanol, and to a variety of pungent compounds such as capsaicin, the ultra-potent capsaicin analog resiniferatoxin (RTX, Fig. **2**), piperine, gingerol, zingerone, camphor, eugenol, and venoms from jellyfish and spiders [7, 19-24]. Pro-inflammatory agents such as prostaglandins, bradykinin, adenosine triphosphate (ATP), 5-hydroxytryptamine and nerve growth factor (NGF) cause allosteric modification of TRPV1, either directly or indirectly, such that the probability of channel opening by heat, protons and capsaicin is enhanced [7, 19, 22-26] (Fig. **1**). Thus, TRPV1 functions as a molecular integrator in which each stimulus sensitizes the channel to other stimuli, with the result that TRPV1 acts as a molecular amplifier in the sensory neuron [27]. These findings have indicated TRPV1 as a promising target to relieve inflammatory pain (Fig. **1**). Indeed, both genetic deletion [28, 29] and pharmacological blockade of TRPV1 ameliorate heat hyperalgesia in rodent models of inflammatory pain [22, 30, 31].

The property of TRPV1 to become sensitized when exposed to painful stimuli has led to the hypothesis that TRPV1 is a prime contributor to the development of thermal hyperalgesia [32] which is believed to be secondary to "peripheral sensitization" (Fig. **1**). TRPV1 sensitization depends on several mechanisms among which phosphorylation of TRPV1 by protein kinase A (PKA), protein kinase C (PKC) and other kinases (Fig. **1**) is of pivotal importance [25, 33-40]. Indeed, several inflammatory mediators (e.g. prostaglandins) enhance activation of TRPV1 by capsaicin and/or heat *via* a PKA-dependent pathway. Bradykinin, NGF and anandamide increase TRPV1 activity through phospholipase C (PLC)-mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) [41]. Although, it has been demonstrated that PIP_2 could bind both C- and N-terminus of the channel [42, 43], there is controversy regarding the net effect of PIP_2 on TRPV1. The first reports suggested that the channel is inhibited by PIP_2 and the relief from inhibition could be obtained by activation of PLC and the resulting depletion of PIP_2 [42]. This idea was based on indirect experiments where the effects of phosphoinositides were not directly tested in excised patches. When tested in excised patches, PIP_2 was found to conversely activate TRPV1 [44]. Desensitization (the loss of activity of the channel) occurs after prolonged capsaicin application (see below). In this context, Rohacs and coworkers have found that Ca^{2+} influx activates PLC which, in turn, depletes PIP_2, leading to desensitization. In addition, PIP_2 exerts an inhibitory effect on the channel, but only at low capsaicin concentrations [45]. Qin and colleagues have shown that the recovery from desensitization occurs with high

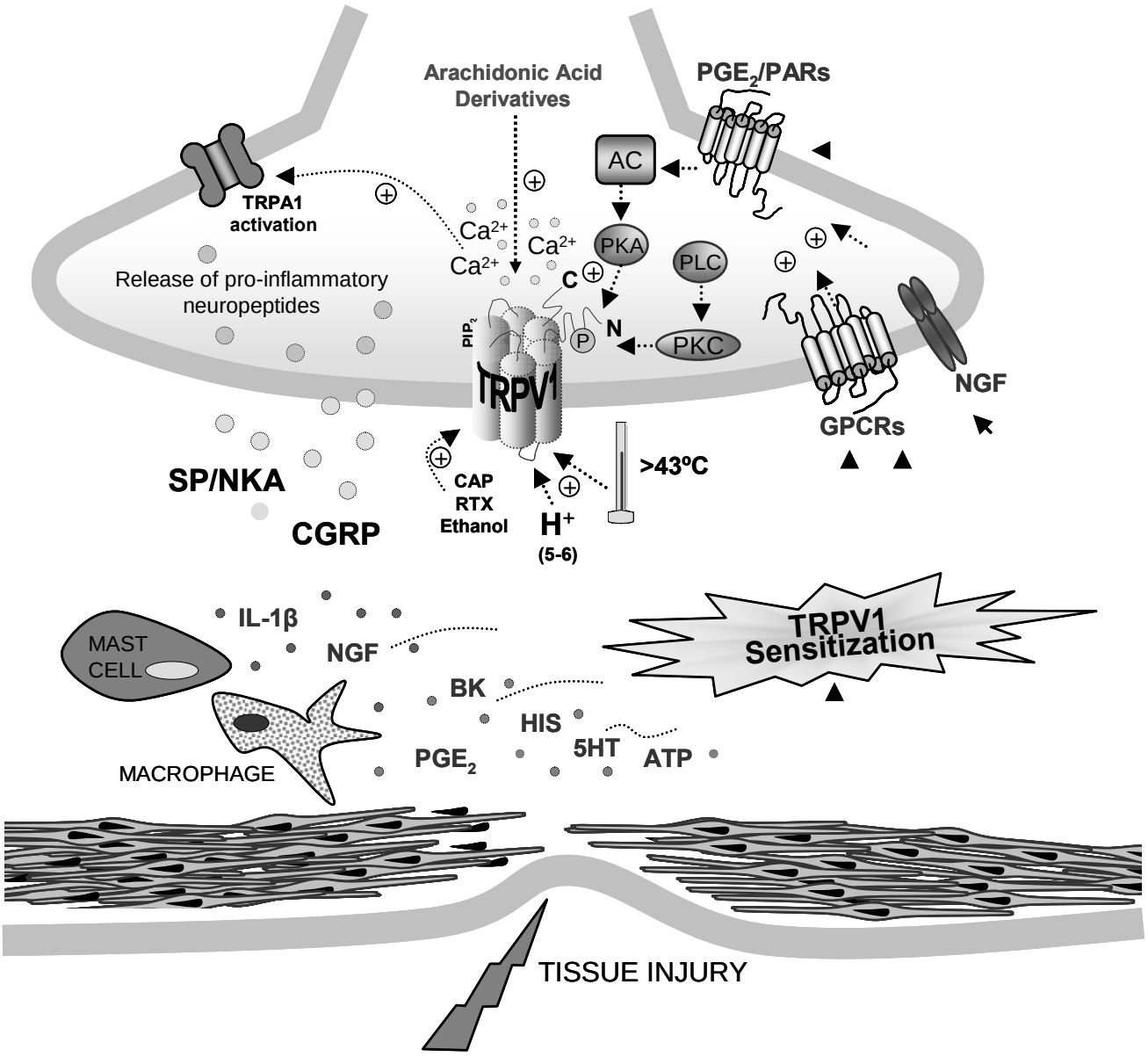

Fig. (1). Schematic diagram of some of the stimuli and intracellular pathways that contribute to the activation/sensitization of TRPV1 in sensory nerve terminals.

concentrations of ATP and re-synthesis of PIP_2 [45]. The overall evidence points to a role of ATP and PIP_2 in sensitization of the channel. However, the role of the interaction of PIP_2 with the N-terminus has not yet been fully demonstrated.

Dephosphorylation of TRPV1 by protein phosphatases promotes desensitization and represents a major mechanism of inhibitory regulation [46]. Desensitization of TRPV1 to capsaicin involves a number of intracellular components including PKA, ATP and calmodulin [43, 47-50]. There appears to be a dynamic balance between phosphorylation and dephosphorylation of TRPV1 that controls the activation/desensitization state of the channel [46, 51].

There is good evidence that TRPV1 is an important mediator of pathological pain (reviewed in [22, 30, 52]). TRPV1 agonists such as capsaicin and RTX have long been used to probe the function of sensory fibers in a variety of physiological processes such as the airway and urinary bladder (reviewed in [17, 30, 52, 53]). It has also been appreciated for some time that capsaicin and RTX treatment can either result in persistent, but fully reversible, desensitization of the sensory fibers, or, alternatively, may lead to permanent neuronal damage depending on the dose administered (reviewed in [15, 16, 30, 52]). Reversible desensitization has a clear therapeutical potential. Selective ablation of sensory neurons by site-specific capsaicin or RTX injections is an attractive approach for permanent pain relief in patients with disabling pain conditions like bone cancer pain and HIV-related polyneuropathy.

The mechanism of "capsaicin desensitization" is poorly understood but is likely to involve both TRPV1 channel tachyphylaxis/trafficking (short-term desensitization) and

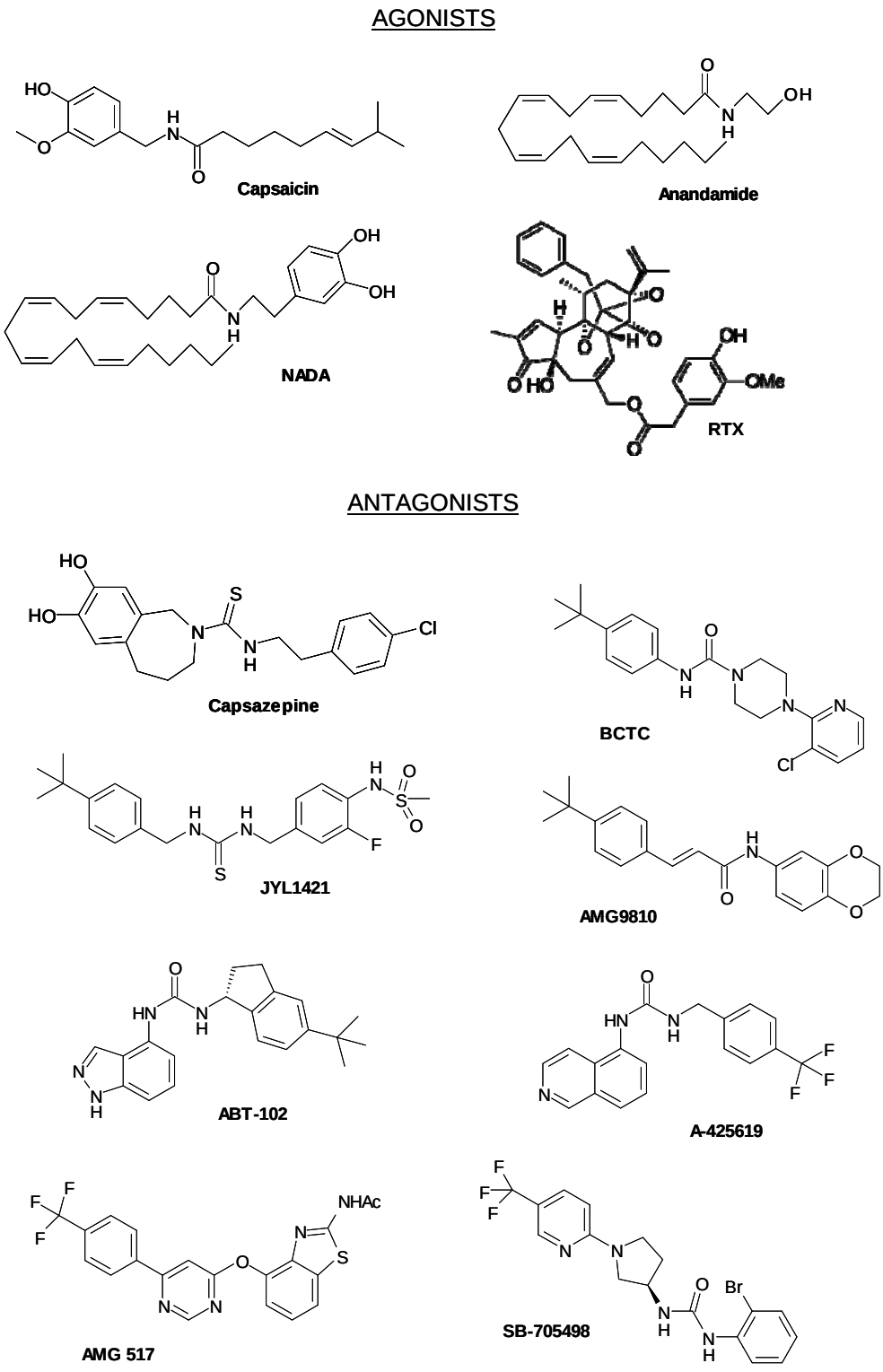

Fig. (2). Selected chemical structures of diverse TRPV1 ligands (agonists and antagonists). Chemical names of the compounds are: **Capsaicin**, 8-methyl-N-vanillyl-6-nonenamide; **Anandamide**, Arachidonic acid N-(hydroxyethyl)amide; **NADA**, N-[2,3-(4-Dihydroxy-phenyl)ethyl]-5Z, 8Z, 11Z, 14Z-eicosatetraenamide; **Resiniferatoxin**, 4-Hydroxy-3-methoxy-[(2S,3aR,3bS,6aR,9aR,9bR,10R,11aR)- 3a,3b,6, 6a,9a,10,11,11a-octahydro-6a-hydroxy-8,10-dimet hyl-11a-(1-methylethenyl)-7-oxo-2-(phenylmethyl)-7H-2,9 b-epoxyazuleno[5,4-e]-1,3-benzodioxol-5-yl]benzeneacetate; **Capsazepine**, N-[2-(4-Chlorophenyl)ethyl]-1,3,4,5-tetrahydro-7, 8-dihydroxy-2H-2-benzazepine-2-carbothioamide; **BCTC**, N-(4-Tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide; **JYL1421**, N-(4-[(([(4-tert-butylbenzyl)amino]carbonothioyl)amino)methyl/-2-fluorophenyl)methanesulfonamide; **AMG9810**, (E)-3-(4-t-butylphenyl)-N-(2,3-dihydro-benzo[b] [1, 4] dioxin-6-yl)acrylamide; **ABT-102**, (R)-(5-tert-butyl-2,3-dihydro-1H-inden-1-yl)-3-(1H-indazol-4-yl)-urea; **A-425619**, N-isoquinolin-5-yl-N′-[4-(trifluoromethyl)benzyl]urea; **AMG 517**, N-(4-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl)-acetamide and **SB-708495**, N-(2-bromophenyl)-N′-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea.

Table 1. Diverse Therapeutic Strategies to Target TRPV1

Therapeutic Strategy	Advantages	Disadvantages/Undesiderable effects
Agonists (capsaicin)	- Defunctionalisation of sensory neurons - Long lasting (weeks) effects - No/minor systemic side effect	- Pain, neurogenic inflammation, cytotoxicity at the site of application - Require physicians - Topical/local application only - Need pre-application of local anaesthetics (lydocaine) - Unspecific effect
Antagonists (small molecules)	- No induction of pain - Systemic administration - Selective effect on target	- No neuronal 'defunctionalisation' (weaker effect ?) - Hyperthermia - Impaired heat pain perception (to be further confirmed)
Biological RNAi (si)RNA Antibodies	- High selectivity - Rapid development - Novel approach	- Novel approach (not well known) - May require viral delivery and/or injection

Table 2. Current Clinical Trial Status of Several TRPV1 Ligands

Compound	Company	Therapeutic Indication	Development Stage (Status)	Ref.
AGONISTS				
Aldea (ALGRX-4975)	Anesiva	Total knee replacement, bunionectomy	Phase III (ongoing)	[72]
Civamide (WN-1001)	Winston Laboratories	Cluster headache, osteoarthritis	Phase III (completed)	[73]
Qutenza (NGX-4010)	NeurogesX	Postherpetic neuralgia	Phase III (ongoing)	[74, 148]
ANTAGONISTS				
ABT-102	Abbott	Pain associated with inflammation, tissue injury and ischemia	Phase I	[61]
AMG-517	Amgen	Pain	Phase Ib (terminated)	[140]
AZD-1386	Astra Zeneca	Chronic nociceptive pain	Phase II (ongoing)	[62]
DWP-05195	Daewoong Pharm.	Neuropathic pain	Phase I (ongoing)	[64, 66]
GRC-6211	Glenmark/Lilly	Pain, migraine and urinary incontinence-associated pain and osteoarthritis	Phase II osteoarthritis trial (suspended)	[67, 68]
JTS-653	Japan Tobaco	Pain	Phase I (ongoing)	[69]
MK-2295	Merck/Neurogen	Pain	Phase II (completed)	[70]
PHE377	PharmEste	Neuropathic pain	Phase I (ongoing)	[71]
SB-705498	GSK	Pain, migraine, rectal pain	Phase II migraine and rectal pain (terminated)	[59, 63]

changes in the expression profile of neuropeptides (e.g. SP and CGRP) and receptors (e.g. CCK receptor) involved in pain perception and processing (long-term desensitization). The latter phenomenon was referred to as "vanilloid-induced messenger plasticity" (reviewed in [16]). Regardless of the underlying mechanism, the net result is *in vivo* analgesia, a therapeutic effect that justifies continued efforts to develop site-specific capsaicin formulations for use as analgesics (reviewed in [54, 55]) (Tables **1** and **2**) or for the treatment of urinary incontinence (reviewed in [53, 56]) (see below).

TRPV1 as a target for novel analgesic drugs has already been validated preclinically by genetic deletion [28, 29] and pharmacological blockade experiments (reviewed in [31, 57, 58]). A number of small molecule TRPV1 antagonists are currently undergoing clinical trials for indications related to pain [59-74].

TRPV1 Deficient Animals

Two independent gene-targeting studies deleting TRPV1 alleles conclusively showed that TRPV1 is a critical channel that mediates thermal hyperalgesia under inflammatory pain conditions in mice [11, 28, 29]. In addition, one study showed that TRPV1 null mice are significantly less sensitive to acute noxious heat stimulation; $TRPV1^{(-/-)}$ mice exhibit significantly larger withdrawal latencies in response to noxious heat in the hotplate assay than their wild-type littermates [28]. The phenotype of the TRPV1 knockout

mice generated tremendous interest in developing small molecules antagonists with an anti-hyperalgesic profile.

In wild-type mice, the endogenous fatty acid oleoylethanolamide (OEA), which is synthesized and released from the intestine upon feeding, evokes visceral pain-related behaviour. This effect was prevented by TRPV1 antagonism and was absent in TRPV1$^{(-/-)}$ mice [75].

Other loss-of-function studies such as transgenic mice expressing TRPV1 shRNA (short hairpin RNA) have shown that silencing the gene encoding for TRPV1 by RNA interference significantly attenuates capsaicin-induced pain behavior and sensitivity towards noxious heat, a similar phenotype that was observed in the TRPV1 "knockout" mice [76]. Interestingly, and unlike the TRPV1$^{(-/-)}$ mice, the TRPV1 shRNA mice did not develop mechanical hypersensitivity in the spinal nerve injury model of neuropathic pain. In addition, antisense oligonucleotides and siRNAs have been reported to characterize the role of TRPV1 in pain [77-79]. Surprisingly, injection of short interference RNA targeting TRPV1 significantly reduced the sensitivity of the rats to noxious heat but had no effect on the development of thermal hyperalgesia, which is highly impaired in the knockout mice. This finding may be interpreted to suggest marked species-related differences in the contribution of TRPV1 to pain states that may hinder the extrapolation of animal studies to man. An antibody directed at the extracellular loop that precedes the pore domain is an antagonist *in vitro*, but no *in vivo* characterization was reported [80].

Mice lacking a functional TRPV1 gene did not display pain behavior following intraplantar injection of phorbol 12-myristate 13-acetate (PMA), a PKC activator, suggesting that PMA-induced pain behavior was dependent on TRPV1 [11].

Combined, the above mentioned evidence strongly implicates TRPV1 as a pivotal polymodal receptor whose function is to combine multiple noxious physical and chemical stimuli in a nociceptive response predominantly during inflammatory conditions and tissue damage.

Brain TRPV1 Receptors and Pain

In mice, TRPV1 receptors have been identified in various brain nuclei known for their role in pain transmission or modulation [81-84]. These regions include the rostroventral medial medulla (RVM), periaqueductal gray matter (PAG), amygdala, solitary tract nucleus, somatosensory cortex, anterior cingulated cortex and insula [85]. Importantly, the presence of TRPV1 was also demonstrated in the human cortex and basal ganglia [81]. The TRPV1 receptor is localized in cell bodies and dendrites of sensory neurons, in astrocytes and in perivascular structures within the brain [81, 82, 86, 87]. Intracerebroventricular (ICV) capsaicin injection decreased nociceptive threshold and reduced morphine- and stress-induced analgesia [88, 89]. Moreover, the ICV administration of TRPV1 receptor antagonists attenuated pain behavior induced by an intradermal injection of capsaicin or formalin in mice [90].

TRPV1 AGONISTS IN PAIN MANAGEMENT

As mentioned above, capsaicin-sensitive sensory neurons are bi-functional. When stimulated by capsaicin, a burning pain sensation is perceived (afferent function) and the resulting neuropeptide release triggers local vascular (vasodilatation, plasma protein extravasation) and extravascular (bronchoconstriction, mucus secretion) effects as efferent function. This initial neuronal excitation by capsaicin is followed by a refractory state with reduced sensitivity and, after repeated applications, persistent desensitisation, in large part due to depletion of neuropeptides [91] (Table **1**). Per definition, this desensitization is reversible. Indeed, biopsies taken from human urinary bladder mucosa show no evidence of neuronal degeneration following capsaicin desensitization. High-dose capsaicin or RTX treatment can, however, result in degeneration of epidermal nerve fibres [91]. This phenomenon (first considered to be a worrisome adverse effect of capsaicin therapy) can be taken advantage of to induce permanent pain relief *via* site-specific degeneration of nerves involved in transmitting intractable bone cancer or HIV-neuropathy pain (concept of "molecular scalpel"). In fact, the National Cancer Institute is now recruiting patients with localized but debilitating cancer pain for clinical trials with site-specific RTX injections (http//: www.clinicaltrials.gov/ct2/show/NCT00804154).

In man, capsaicin-containing topical patches (e.g. NGX-4010 by NeurogesX, marketed as Qutenza by Astellas Pharma) and injectable capsaicin preparations (e.g. Adlea by Anesiva) were reported to provide relief from pain associated with diabetic neuropathy (0.075% cream 3-4 times daily for eight weeks), AIDS-related neuropathy, osteoarthritis (0.025% cream four times daily), rheumatoid arthritis and post-herpetic neuralgia [54, 92, 93] (Table **2**). Although capsaicin-containing creams have been in clinical use for decades, a systematic clinical evaluation of capsaicin as a therapeutic agent only began recently and is still in progress. Of note, capsaicin has also been used to treat pain associated with pruritus, psoriasis, buniectomy, Morton's neuroma, mastectomy, bladder disorders, and cluster headaches [92]. Unfortunately, many of the reports involve only a small number of patients or are not blinded, thus the clinical benefit of capsaicin is difficult to evaluate. To avoid the initial pain caused by capsaicin, a prior application of lidocaine was used in some studies. Generally speaking, capsaicin was safe. Adverse events occurred mainly at the application site (burning, stinging, erythema, cytotoxicity, Table **1**), and systemic events were rare [92]. Respiratory irritation was reported from inhalation of dried cream [94]. This can be prevented by covering the application site with plastic or using patches.

In experimental animals, the analgesic effects of capsaicin and RTX were confirmed in diverse *in vivo* pain models: hot-plate test, tail-flick latency, spinal cord injury-induced cold allodynia, and acetic acid-induced writhing [16, 54, 95]. Furthermore, both molecules possess analgesic properties in a mouse model of bone cancer pain [96].

Since the initial burning pain caused by capsaicin was considered as a potential problem for development, early studies focused on generating non-pungent capsaicin analogs as analgesics. Olvanil (NE 19950, oleyl vanillylamide) was identified as a non-pungent, putative analgesic [97-103]. Olvanil showed good efficacy in rodent pain models (acetic acid-induced writhing and tail-flick latency tests). Olvanil,

however, did not progress into clinical trials because of its non-favorable pharmacokinetic properties.

In animal experiments, systemic (intravenous) administration of capsaicin was shown to trigger various reflex responses leading to a drop in blood pressure, slow heart rate and shallow breathing (collectively referred to as the Bezold-Jarisch reflex). Even worse, high-dose systemic capsaicin treatment was reported to cause potentially fatal respiratory arrest. To circumvent this problem, clinical trials with capsaicin was restricted to topical (creams or patches applied to the skin or solutions administered to nasal or bladder mucosa) or site-specific, injectable local delivery methods. Several articles provide an in depth review of preclinical and clinical agonist approaches [16, 54, 55] (Tables **1** and **2**).

Clinical Development

Adlea™ (ALGRX-4975) was developed by Anesiva (http://www.anesiva.com) as an injectable preparation of capsaicin for the potential management of pain associated with osteoarthritis (OA), tendonitis and postsurgical conditions, as well as for neuropathic pain occurring secondary to nerve injury. Clinical results with ALGRX-4975 are promising. ALGRX-4975 (4 ml of 0.25 mg/ml) was reported to significantly reduce mean VAS pain scores at 8 h and 24 h post unilateral bunionectomy [104] after a single intra-operative instillation. ALGRX-4975 (0.5 ml of 0.2 mg/ml) produced a significant reduction in pain of intermetatarsal neuroma at week 1 and 4 compared to placebo [105]. Furthermore, ALGRX-4975 significantly reduced pain scores and improved grip strength in patients with lateral epicondylitis [106] and lowered pain scores [104] in patients with end-stage OA of the knee waiting for knee replacement. During inguinal hernia repair, intraoperative instillation of ALGRX-4975 (15 ml of 0.067 mg/ml) improved analgesia relative to placebo during the first 3–4 days following surgery [107].

Intranasal Civamide (50 μg), a synthetic isomer (*cis*) of capsaicin developed by Winston Laboratories (http://www.winstonlabs.com), was reported to significantly reduce episodic cluster headache [108, 109]. Moreover, a single dose of either 20 μg or 150 μg of Civamide demonstrated clinical efficacy against migraine headache, with or without aura [109]. As per the clinicaltrials.gov website, three Phase III studies of Civamide have been completed, two in cluster headache and one in osteoarthritis of the knee [110]. The results of these trials are yet to be made public.

Recently, the U.S. Food and Drug Administration (FDA) has approved NGX-4010 (Qutenza^{TM}) developed by Neuroges-X (www.neurogesx.com) and marketed by Astellas Pharma for the management of neuropathic pain due to postherpetic neuralgia (PHN). NGX-4010 is a dermal high-concentration (8%) capsaicin patch. Results from two studies that investigated NGX-4010 patch for treatment of painful HIV neuropathy have been recently published [111, 112]. A single NGX-4010 application was safe and provided at least 12 weeks of pain reduction in patients with HIV-associated distal sensory polyneuropathy [112]. In an open-label, 12-week pilot study performed in patients with painful HIV-associated distal sensory polyneuropathy (DSP), a single application of NGX-4010 (capsaicin 640 μg/cm^2, 8% w/w) was well-tolerated and associated with significant reduction in pain over the 12 weeks studied [111].

TRPV1 ANTAGONISTS

The rationale for using potent and selective small molecule TRPV1 antagonists to relieve inflammatory pain is the recognition that TRPV1 is directly activated by agents that are present in the inflammatory soup, the so-called "endovanilloids" (reviewed in [9, 22]) (Fig. **1**). In other words, TRPV1 antagonists prevent activation of TRPV1 by endovanilloids.

The first competitive TRPV1 antagonist, capsazepine, was developed by systemic modification of capsaicin [113]. Though extremely useful in the research laboratory, capsazepine was a poor clinical candidate. Most important, capsazepine is not selective for TRPV1; in fact, it inhibits nicotinic and voltage-gated calcium channels (reviewed in [16, 22]), as well as TRPM8 [114, 115].

Following the molecular cloning of TRPV1, numerous pharmaceutical companies have initiated programs to identify potent small-molecule TRPV1 antagonists for the treatment of different pain states. This has resulted in the identification of a large (and still growing) number of potent and efficacious TRPV1 antagonists (see Table **2** and Fig. **2**; reviewed in [31, 57, 58, 116]). As discussed above, TRPV1 is activated by multiple stimuli that interact with different domains of the channel protein. Some TRPV1 blockers are stimulus-specific whereas others appear to block several means of activation [117, 118]. For instance, AMG0610 and SB-366791 inhibit the activation of rat TRPV1 by capsaicin but not by acid, whereas I-RTX, BCTC, AMG6880, AMG7472, AMG9810 and A-425619 are TRPV1 antagonists that do not differentiate between capsaicin and protons [117, 119-121] (see Fig. **2**). On the other hand, AMG8562 does not block heat-evoked activation of rat TRPV1 [118]. Importantly, there are also species-related differences in the stimulus selectivity of TRPV1 blockers. For instance, capsazepine and SB-366791 are more effective in blocking proton-induced gating of human TRPV1 than of rat TRPV1 [117, 122], and AMG8562 antagonizes heat activation of human but not rat TRPV1 [118]. Of these inhibitors, I-RTX, the urea analog BCTC and the cinnamide analog SB-366791 are the best studied. Within this group I-RTX and SB-366791 are quite selective *vs*. other receptors and channels, whereas BCTC is also a good inhibitor of TRPM8 [123].

Several structurally different TRPV1 antagonists such as capsazepine, BCTC, A-425619, A-784168, GRC-6211, PHE377 and the quinazolinone "Compound 26" are reported to decrease hypersensitivity in rat neuropathic pain models [12, 67, 68, 124-130].

A recent study showed that a new TRPV1 receptor antagonist, ABT-102 (Table **2**, Fig. **2**), which has just entered in clinical trials, exhibits analgesic properties in several rodent pain models, including chronic inflammatory, bone cancer, and postoperative pain [61, 131, 132].

It should be mentioned here that preclinical models of pain may result in an underestimation of the clinical utility of TRPV1 antagonist because they do not adequately address

the extent of spontaneous or ongoing pain in rodents [133]. It is also worth noting that while pain due to cancer may only partly arise from neuropathy, TRPV1 antagonists have exhibited utility in models of cancer pain [96, 134].

TRPV1 and Body Temperature Regulation

Capsaicin is known to decrease body temperature (transient hypothermic response) in various species including man. This effect was attributed to a combination of increased heat loss (skin vasodilation in animals and gustatory sweating in man) and reduced heat production [16, 135]. It was postulated that capsaicin alters the thermosensitivity of preoptic heat sensors, thereby tricking the animals to believe that they feel hot. Indeed, capsaicin microinjected into the preoptic area mimicked the hypothermic action of systemic capsaicin administration and morphological alteration similar to those seen in sensory ganglia was detected in preoptic area neurons. Interestingly, animals desensitized to capsaicin lose their ability to regulate their core temperature: when placed in hot environment, such animals suffer heat stroke. Nonetheless, capsaicin-desensitized animals display normal body temperature when kept in ambient temperature environment. Therefore, it was somewhat unexpected that some TRPV1 antagonists paradoxically cause hyperthermia in several species including man [128, 136, 137].

The question which still remains to be answered unequivocally is whether the hyperthermic action of TRPV1 antagonists is site-specific, that is unseparable from the analgesic action. Not all TRPV1 antagonists appear to induce hyperthermia. Nonetheless, a new provocative concept (most recently refuted by Romanovsky and colleagues [138]) suggests that the predominant function of TRPV1 is body temperature regulation [139]. This concept is based on the profound (>1ºC) hyperthermic action of some TRPV1 antagonists, implying an endogenous tone for TRPV1 [137, 140]. The initial observation was that the urea analog TRPV1 antagonist "Compound 41" increased core body temperature when administered to rats [128]. As mentioned above, the hypothermic action of capsaicin was linked to a central site, namely the preoptic area. Therefore, it was a reasonable assumption that TRPV1 antagonists cause the opposite effect (hyperthermia) by interacting at the same site. However, it appears to be not the case: the low CNS penetrant TRPV1 antagonist AMG0347 is no more effective in causing hyperthermia when administered into the brain (intracerebroventricularly) or spinal cord (intrathecally) than when given systemically (intravenously) [141]. This evidence was interpreted to imply that TRPV1 expressed on a peripheral site mediated the effect of TRPV1 antagonist on core body temperature [141]. This site is now believed to be in the abdomen, probably the GI tract.

Several strategies were tried to mitigate the hyperthermic action of TRPV1 antagonists. Similar to agonist-induced hypothermia that disappears after repeated administration, antagonist-induced hyperthermia also shows attenuation after repeated dosing [142]. It was suggested that the initial hyperthermia can be adequately managed by common antipyretic agents like acetaminophen.

A more attractive approach is to eliminate the undesirable side-effect of TRPV1 antagonists on thermoregulation by chemical modification of the pharmacophore. Studies by Lehto and coworkers concluded that in the rat it was feasible to eliminate hyperthermia while preserving antihyperalgesia by differential modulation of distinct modes of TRPV1 activation [118]. Unfortunately, the observations made in rats did not hold true in dogs, indicating that it would be very problematic to extrapolate results to humans.

The magnitude of the febrile response is clearly chemotype-dependent. During a Phase I clinical trial of AMG517, plasma-concentration-dependent hyperthermia was observed in healthy subjects with the maximum body temperature reaching 38.8°C [140]. Consequently, for safety concerns AMG517 was withdrawn from clinical trials [140]. Other antagonists were reported to evoke only mild hyperthermia or no detectable change in body temperature.

Hyperthermia is believed to occur due to blockade of TRPV1 channels. Since antagonists mentioned above are highly selective, it was predicted that TRPV1 is tonically active and plays a key part in body temperature regulation [137]. A tonic activation of TRPV1 under physiological conditions may be maintained by a concomitant activity of endogenous chemical agonists (anandamide, oleoyldopamine, N-arachidonyl dopamine, 12-hydroperoxyeicosatetraenoic acid and low pH) and TRPV1 phosphorylation, modulators that are known to sensitize each other (Fig. **1**) [139]. Obviously, more research is needed to resolve these conflicting findings, and to appreciate the impact of TRPV1 antagonism on body temperature.

TRPV1 Antagonists and Noxious Heat Perception in Humans

In keeping with its function as a noxious heat sensor, an impaired detection of painful heat was described in TRPV1 knockout mice [28]. Moreover, TRPV1 antagonists were reported to elevate the withdrawal reflex threshold in response to noxious heat [143-145] in preclinical species.

Most recently, clinical studies have confirmed the role of TRPV1 as a noxious heat sensor in humans demonstrating the involvement of the channel in heat perception in healthy volunteers. Indeed, heat pain threshold was significantly elevated in non-sensitized skin of healthy volunteers following 400 mg SB-705498 (GlaxoSmithKline) oral administration [59, 146]. Subsequently, investigators at Merck-Neurogen have reported that compound MK-2295 markedly blunted heat perception in healthy human subjects (quantitative thermal sensory tests, pain evoked by hand immersion into or sipping hot water) with no sign of tachyphylaxis [145, 147]. Similar results were observed by AstraZeneca with the TRPV1 antagonist, AZD1386. AZD1386 was investigated in two phase I trials in healthy volunteers and found to increase mean thresholds for heat-induced pain [146]. Interestingly, the enhancement in heat pain threshold persisted after repeated dosing of compound AZD1386.

The enhanced heat pain threshold and tolerance induced by TRPV1 antagonists in healthy volunteers (which is apparently greater than those observed in pre-clinical species) is worrisome for its potential to cause scalding injury. Indeed, some subjects taking MK-2295 perceived potentially harmful temperatures as innocuous. These individuals could have suffered scalding injuries when taking hot shower or drinking hot coffee. Importantly, the

effect of TRPV1 antagonists on heat pain sensation does not attenuate after multiple dosages.

TRPV1 Antagonist Undergoing Clinical Trials for Indications Related to Pain

Several small molecule TRPV1 antagonists are currently undergoing phase I and II clinical trials for indications related to pain (Table **2**).

Phase I data obtained with SB-705498 (GSK) have been reported [59]. In the first part of the study, single doses of SB-705498 ranging from 2 to 200 mg did not display efficacy in the capsaicin-evoked flare test. However, in the second part of the study, a single oral dose of 400 mg SB-705498 substantially reduced pain from cutaneous capsaicin challenge (0.075% capsaicin cream applied to the forearm) compared to placebo. In December 2005, an active-controlled, placebo-controlled, randomized, single-blind, phase II trial (NCT00281684, VRA105345) was initiated in subjects with dental pain following third molar tooth extraction. The subjects were to receive a single oral dose of SB-705498, placebo or co-codamol. The study was completed by February 2008 and no results have been revealed, yet [63].

AstraZeneca is developing AZD-1386 for the potential oral treatment of chronic nociceptive pain and gastroesophageal reflux disease (GERD). In April 2008, an active-controlled, placebo-controlled, randomized, double-blind phase II trial (NCT00672646, D5090C00010) was initiated in subjects with pain. The study was expected to complete in June 2008 [62]. No result was made public.

A phase II trial with GRC-6211 (Glenmark-Eli Lilly) for ostheoarthritic pain was suspended due to undisclosed reasons. Additional indications include incontinence and neuropathic pain [67, 68].

Merck-Neurogen is developing MK-2295 (NGD-8243; MRK-2295) for the potential treatment of pain and cough [70].

Japan Tobacco is developing an oral TRPV1 antagonist, namely JTS-653, for the potential treatment of pain and overactive bladder. In February 2008, a Japanese phase I study was ongoing [69].

Compound PHE377 [71], a potent TRPV1 antagonist developed by PharmEste to treat diabetic neuropathic pain and post herpetic neuralgia is currently undergoing a Phase I clinical trial.

Daewoong Pharmaceutical has received approval from the KFDA (Korean Food and Drug Administration) to enter into clinical trials with compound DWP05195. These clinical trials are set to take place at Seoul National University Hospital and the first phase will be performed on healthy patients to test for safety and tolerance [64, 66].

CONCLUSIONS

TRPV1, a polymodal receptor on primary sensory neurons, represents an attractive target for the development of a new generation of analgesic drugs. TRPV1 blockers aim to relieve pain by interacting at a peripheral site where pain is generated. TRPV1 may be "silenced" by either agonists (desensitization) or antagonists (pharmacological blockade). However, agonists and antagonists represent very different therapeutic approaches. Agonists have the advantage of not only preventing all means of TRPV1 activation but also impairing other receptors that are co-expressed with TRPV1 on primary sensory nerves. Their use is, however, limited to topical application (creams, patches and site-specific injections) by the potential adverse effects of systemic capsaicin administration (bradycardia, hypotension, and respiratory depression). Moreover, capsaicin is initially painful, especially if administered without lidocaine pretreatment. In contrast, antagonists block some, but not all, means of TRPV1 activation. Since all means of TRPV1 activation appears to be relevant for pathological pain, TRPV1 antagonists may not be as effective as agonists in achieving analgesia.

A presumed advantage of TRPV1 antagonists was that they, unlike agonists, can be safely administered systemically *per os*. If so, TRPV1 agonist treatment is best suited to ameliorate localized pain amenable to patches or site-specific injections whereas TRPV1 antagonists may be used to treat deep or visceral pain or pain whose anatomic origin cannot be delineated.

Based on preclinical studies, TRPV1 antagonists were presumed to be safe and devoid of significant side-effects. This may not be completely true. Some TRPV1 antagonists were reported to evoke a dangerously high febrile reaction, prompting their withdrawal from clinical trials. Others appear to interfere with noxious heat perception, raising concerns for scalding injury. The beneficial therapeutic effects of TRPV1 antagonists should be carefully, but pragmatically, weighed against their adverse effects to decide whether these drugs can join the armory of pain specialists.

CONFLICT OF INTEREST

MT is an employee of PharmEste (www.pharmeste.com).

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