

# Arguments to develop TRPV1 antagonist in neuropathic pain. Lessons for drug development

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## Abstract

AstraZeneca developed new leads based on TRPV1 antagonism for neuropathic pain in the past decade, and referred to this project for the first time in 2007. A leading pharmacologist from the company published a seminal paper in 2008 in favor of the rationale to focus on the TRPV1 target and to develop TRPV1 antagonists for neuropathic pain. We analyzed his expert arguments and a number of key papers in the field at that time, supporting the further development of TRPV1 antagonists in neuropathic and inflammatory pain. The papers reviewed however, presented a number of data, which would suggest to not further develop these antagonists in neuropathic pain indications. Furthermore, none of the publications, defined as milestone papers in the field leading to the TRPV1 antagonist development in neuropathic pain, used a gold standard, or tested the compounds in specific neuropathic pain models. Only inflammatory models were used. The conclusion at that time based on a key review titled 'Neuropathic pain: emerging treatments' that TRPV1 antagonists are suited for the treatment of neuropathic pain is not supported by the presented evidence at that time. Preclinical models play a key role in the decision of management in pharmaceutical industries to enter clinical development in certain indications. Based on the analyzed case, preclinical project target profiles should be installed to help in a timely manner not to engage in further development. Clear defined stopping rules will save the pharmaceutical industry much money and resources. Based on the data presented in a key paper in the beginning of TRPV1 antagonist development, one should have rather stopped the development at that time, than encourage i

## Introduction

Close reading of arguments supporting further drug development can reveal inconsistencies and help to avoid drug development mistakes later on during the phase of clinical trials. This article will use such 'close reading' approach to help understand the decisions made to continue developing TRPV1 antagonists at a critical time point in development. We will use a case around the TRPV1 antagonists, developed by AstraZeneca, in the last decade.

In a pipeline review of AstraZeneca, we find in 2007 for the first time mentioned the compound AZD1386 linked to the indication 'gastroesophageal reflux disease' (GERD) and an estimated filing date for the NDA was defined after 2009, which was not extremely precise [1]. At that time (2007), AstraZeneca documents available in the internet, defined the compound as a preclinical phase project [2]. One year later, in 2008, Dr. Dray from AstraZeneca Research and Development, included the compound in his review on new leads in neuropathic pain (NP), and indicated the compound was in phase I, while the indication mentioned was 'in progress'. AstraZeneca at that time also developed AZD 2066 within the field of NP, a mGluR5 inhibitor (phase I), and AZD 1940, a cannabinoid-receptor agonist (phase I) [3]. AZD 2066 was also related to other indications such as depression and GERD and was discontinued in phase I in 2011, while AZD 2066 for NP was discontinued in 2009, during phase I. Dray presented the preclinical and clinical data at that time and argued that the studies reviewed: 'herald the way for a number of Ph2 trials for competing antagonists'. We will review the arguments Dray, as a key opinion leader within the pharmaceutical field of new pain leads, brought forward to support the further development of TRPV1 antagonists in neuropathic pain.

## Rationale for TRPV1 antagonist in the treatment of neuropathic pain

Dr Andy Dray, a scientist working within the boundaries of the AstraZeneca laboratories, worked many years in the function of Director of Global Analgesia Strategy (1995-August 2011). In his seminal paper of 2008, he outlined the rationale behind selecting TRPV1 antagonists as targets for the treatment of NP. Due to this milestone publication we can analyze in detail the contemporary thinking around 2008 related to the topic and follow the string of argumentation leading to the development of TRPV1 antagonists in NP.

He first discussed both voltage-gated ion channels as targets for NP, as well as a series of ligand-gated ion channels. The first category he subsequently discussed was the mammalian transient receptor potential (TRP) channels, subdivided at that time into six subfamilies. He pointed out the focus for NP was mainly on TRPV1, TRPV3, and TRPM8. AZD1386 is an AstraZeneca compound and we will step by step walk through the argumentation of Dray why TRPV1 is such an important target for NP.

Dray described this non-selective cation channel as being regulated by a variety of inflammatory mediators and neuroregulators, such as anandamide and nerve growth factor (NGF). He defined this target as playing 'an important role in neural sensitization caused by mediators of inflammation and nerve injury' (p.51), based on two authoritative sources

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**Received:** December 13, 2016; **Accepted:** December 27, 2016; **Published:** January 04, 2017

[4,5]. He continued by pointed out that TRPV1 antagonists are aiming to selectively inhibit peripheral nerve fibre overactivity. He further memorized that competitive (AMG9810 and AMG628) as well as non-competitive TRPV1 antagonists (DD161515) have been evaluated in preclinical pain models and were found to block both chemical and thermal pain sensitivity, 'supporting the emergence of a novel therapy' [6-8]. In addition to the preclinical findings Dray referred to a human volunteer paradigm, demonstrating that oral SB705498 (GSK) attenuated capsaicin and UVC-induced pain and hyperalgesia, without side effects [9]. These preclinical and phase I studies, according to Dray, paved the way for a number of phase II clinical trials for compounds such as GRC 6211 Lilly/Glenmark, NDG6243 Merck/Neurogen and AZD1386 from AstraZeneca.

In the table, we summarized the status of the various TRPV1 antagonists mentioned by Dray in his paper, as well as the first PubMed indexed publications related to each of these compounds; all compounds seem to have been discontinued, based on information from Adis Insight or simply because nobody writes anymore about the compound [10] (Table 1).

First, TRPV1 was stipulated by Dray as an important target for NP due to its crucial role in neural sensitization. This statement was based on the paper 'An introduction to TRP channels' from 2006. However, the paper did not refer to such neural sensitization and on the contrary there was a reference made to TRPV1 and TRPV2 double-knockout mice, having normal in vivo thermal nociceptor responses. The second paper quoted by Dray was from 2001: 'Protein kinase C activation potentiates gating of the vanilloid receptor VR1 by capsaicin, protons, heat and anandamide'. This paper solely used an in vitro model of dorsal root ganglion neurone cultures and described the enhancement of capsaicin-gated membrane current by protein kinase C. We could not find any solid foundation for the role of TRPV1 in neural sensitization in these papers.

Secondly, the support for an 'emergence of a novel therapy' according to Dray was based on 3 papers.

The first paper, from 2001, on the 'attenuation of thermal nociception and hyperalgesia by VR1 blockers' covered a number of N-alkylglycines, compounds patented by a small pharmaceutical company, Diverdrugs, S.L. in 2001 [17]. This paper was written by a number of inventors from the Diverdrugs patent. Data were presented related to DD161515: i.p. administration of 0.2 mmol/kg BW of DD161515 did significantly attenuated thermal nociception in the hot plate test, but did not modify the withdrawal threshold in the von Frey hairs test. There was no gold standard used in the experiments, and only two doses were tested: 0,1 and 0,2 mm/kg BW ip. Intraplantar injection of capsaicin induced pain behavior and this could be reduced by the injection of 0.05 mmol/kg BW to 0.2 mmol/kg BW of DD161515, 30 min before the capsaicin intraplantar injection. Mustard oil was also applied, while the compound or a vehicle was administrated, but the paper did not

specify when the application took place, before or after the mustard oil provocation, and only once dose (0,2 mmol) was tested. The high doses needed, and the short duration of response, were commented in the discussion section, and were suggestive for a poor absorption, low bioavailability or extensive metabolism. The meagre results and the absence of a gold standard were not in line with the main conclusion in the abstract: 'These noncompetitive VR1 antagonists may likely be developed into analgesics to treat inflammatory pain'.

The second paper covered the in vitro and in vivo analgesic properties of the Amgen compound AMG9810 [18]. The models used were the capsaicin-induced eye wipe test, the complete Freund's adjuvant induced thermal and mechanical hyperalgesia and the thermal hyperalgesia test (all in the inflammation based model of intraplantar injection of the inflammation inducer Freund adjuvants. In vivo tests confirmed the TRPV1 blocking effect of AMG 9810, the compound was found to be a more potent antagonist than capsazepine in all models of TRPV1 activation. Application of 3, 10, and 30 mg AMG 9810/kg BW intraperitoneally, could dose dependently decrease capsaicin induced eye wipe behavior. However, in animals treated 60 min before capsaicin administration, significant reductions in eye wipes were only observed in animals treated with the highest dose. Furthermore, only treatment 100 mg/kg (intraperitoneal) of AMG 9810 could significantly increase the Freund adjuvants-induced paw withdrawal threshold at 30 and 60, and not at 90 min post-treatment. It was remarkable to notice that the paper discussed two parameters for analgesia, paw withdrawal latency and the paw withdrawal threshold. For the thermal hyperalgesia the first parameter was presented, and for the mechanical hyperalgesia, the second parameter.

The conclusion of the paper was: 'AMG 9810 was shown to be a potent and selective antagonist of TRPV1 that can significantly reverse thermal and mechanical hyperalgesia in an animal model of inflammatory pain'. Based on the data presented this conclusion seems much too robust, as only a dose of 100 mg/kg BW i.p. could inhibit the mechanical hyperalgesia. Furthermore, morphine (dose unspecified) was used as a gold standard, but the results of the standard were not presented.

The third paper from 2007 was written by experts from Amgen, and the topic was 'The Identification of a Second-Generation Clinical Candidate with Improved Physicochemical and Pharmacokinetic Properties' [8]. The conclusion of the paper was: 'Based on its improved overall profile, compound 16p (AMG 628) was selected as a second-generation candidate for further evaluation in human clinical trials as a potential new treatment for chronic pain'. The development of the lead compound AMG628 was discontinued, probably in that period, possibly due to preclinical side effects. The paper covered in great detail the organic synthesis and in vitro profiles, but only one small paragraph was focused on in vivo tests: in the capsaicin-induced flinching in rats. At a 10 mg/kg (p.o.), the lead compound blocked capsaicin-induced flinching up to 8 h. In the thermal hyperalgesia model (Freund's adjuvant) the minimum effect dose for compound was approximately 1 mg/kg, although no statistical tests were applied, and no details were provided. Effects plateaued at 45% inhibition, and no gold standard was used.

The last argument Dray presented was based on the results of a phase I provocation test in human volunteers by scientists from GSK and related to SB-705498 [16,17]. A cohort of 19 subjects received 400 mg SB-705498 and placebo on 2 dosing occasions in a randomized single-blind two-way cross-over fashion. The study did not use a gold

**Table 1.** TRPV1 antagonists discussed by Dray (2008) as examples to support the TRPV1 hypothesis for NP.

Compound	Company	Status
AMG9810 [11]	Amgen	Discontinued
AMG628 [8]	Amgen	Discontinued
DD161515 [12]	Diverdrugs SL	Discontinued
SB705498 [13]	GSK	Discontinued
GRC 6211 [14]	Lilly/Glenmark	Discontinued
NDG6243	Merck/Neurogen	Discontinued
AZD1386 [15]	AstraZeneca	Discontinued

standard for comparison. Two pain provocation models were followed: capsaicin test (0,075%) and UVB radiation. The compound did not increase pain thresholds during the capsaicin challenge, but did in the UVN challenge. The heat pain thresholds were increased significantly compared to placebo. Heat pain tolerance was not measured. The paradigm seems however quite sensitive to many variables, among which race, gender, time of day and whether the volunteers are morning or evening persons [18].

## Conclusion

The chapter TRPV1 antagonists for neuropathic pain is worthwhile studying in detail, using 'close reading'. In 2009 it was estimated that at least seven orally active TRPV1 antagonist substances were in clinical development and many more in preclinical development [19]. In 2016 no TRPV1 antagonists are available for the clinician. In PubMed we can find more than 1550 publications related to TRPV1 antagonists, but interestingly, the peak of publications was in 2011 (166 publications), and since 2011 the number of publications declined, up to less than 100 in 2016 (status mid-December 2016). We reviewed a number of arguments during the upsurge of interest in this target, presented by a leading TRPV1 scientist in the field, Dr Dray, from AstraZeneca. We also reviewed the milestone publications he used to argue that these ligands should make a difference in neuropathic pain. None of these preclinical publications presented however enough and consistent evidence for entering the clinic. Moreover, gold standards were missing and no neuropathic pain models were used at that time. Clearly there is a great need to optimize preclinical pharmacology, in such a way that we can stop without spending so much expenses in clinical phases. The definition of a preclinical target profile could help to avoid making overenthusiastic assumptions. The case presented clearly supports the necessity of developing such tool, which should be defined with painstakingly precision.

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