Setbacks in the Clinical Development of TRPV1 Antagonists: What Next?

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Abstract: TRPV1 antagonists have been considered as potential treatments for pain associated with inflammatory diseases and cancer. During Phase I clinical trials with AMG 517, a highly selective TRPV1 antagonist, we found that TRPV1 blockade elicits marked, but reversible, and generally plasma concentration-dependent hyperthermia. Furthermore, in a Phase Ib study, AMG 517 administered after molar extraction (a surgical cause of acute pain) elicited long-lasting hyperthermia with maximal body temperature surpassing 40 °C, suggesting that TRPV1 blockade elicits undesirable hyperthermia in susceptible individuals.

Since TRPV1 blockade elicited hyperthermia is a major hurdle, we investigated the possibility of eliminating hyperthermia while maintaining antihyperalgesia by two approaches: i) peripheral restriction of TRPV1 antagonists, ii) characterization of TRPV1 modulators that exhibit differential pharmacology. Results from the preclinical studies of both approaches will be discussed.

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Setbacks in the Clinical Development of TRPV1 Antagonists: What Next?

Narender R. Gavva Ph.D.
Department of Neuroscience
Outline

- Introduction
- Functional assays
- AMG 517 preclinical studies
- TRPV1 antagonism - hyperthermia
- Mechanisms of hyperthermia
- AMG 517 clinical trial results
- Peripherally restricted antagonists – hyperthermia
- Differential pharmacology of antagonists – no hyperthermia
- Conclusions
TRP channels are integrators of multiple noxious stimuli


- Agonists of TRPA1 and TRPV1 cause pain in humans and pain behavior in rodents

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TRPV1: A polymodal detector of painful stimuli

TRPV1 Expression in E19 Rat

White Areas Show Expression In DRG Neurons in Rats

TRPV1 is activated by:
- Chemical ligands (capsaicin, RTX etc)
- Heat
- GPCR signaling
- Phosphorylation
- Low pH

Rat sensory neurons responding to capsaicin (calcium imaging)

TRPV1 positive DRG neurons

Moiseenkova-Bell et al 2008
PNAS. 105:7451-5
TRPV1 – Target validation

TRPV1 knockout mice show reduced thermal hyperalgesia


Various distinct chemical scaffolds act as TRPV1 antagonists

- AMG9810
- NVS Pyridopyrimidine
- AMG0347
- JYL1421 (SC0030)
- AMG2674
- AMG 517
- SB-705498
- BCTC
- ABT-102
- AMG8562

Gavva et al., 2005 JPET, 313:474-484
Doherty et al., 2007 JMC 50:3515-27
Gavva et al., 2007 JPET 323:128-137

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Strategy for SAR development

- High-throughput screening of our corporate database identified several \( N \)-aryl cinnamides as TRPV1 antagonists

- Constrained analogs of s-cis cinnamides provided an entry into a novel chemical series of TRPV1 antagonists

- Further optimization lead to the clinical candidate AMG 517
AMG 517 blocks all modes of TRPV1 activation

- AMG 517 is a potent antagonist of rodent, dog, monkey and human TRPV1
- AMG 517 does not block TRPA1, TRPV2, TRPV3, TRPV4, and TRPM8
AMG 517: Pharmacokinetic profile

<table>
<thead>
<tr>
<th>Species</th>
<th>Intravenous dosing</th>
<th>Oral dosing</th>
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<tbody>
<tr>
<td></td>
<td>AUC_{0-inf} (ng.hr/mL)</td>
<td>CL (mL/hr/kg)</td>
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<tr>
<td>Rat</td>
<td>8800</td>
<td>120</td>
</tr>
<tr>
<td>Dog</td>
<td>7400</td>
<td>140</td>
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<tr>
<td>Monkey</td>
<td>37000</td>
<td>30</td>
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<tr>
<td>Human (projected)</td>
<td>50</td>
<td>4500</td>
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- Good Oral Bioavailability
- Low Clearance
- Long Half-life
- Linear PK (1-10 mg/kg)
AMG 517 blocks capsaicin-induced flinching in rats

<table>
<thead>
<tr>
<th>Dose</th>
<th>AMG 517 p.o.</th>
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<tr>
<td></td>
<td>60 min</td>
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<tr>
<td></td>
<td>Inject Capsaicin Into the Paw</td>
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<tr>
<td></td>
<td>Count # of Paw Flinches in 1 min</td>
</tr>
</tbody>
</table>

Gavva et al., 2007 JPET 323:128-137
AMG 517 blocks inflammation-induced thermal hyperalgesia

Inject CFA into the paw

22 h

Dose AMG 517, p.o.

2 h

Record thermal sensitivity

Gavva et al., 2007 JPET 323:128-137
TRPV1 antagonists block capsaicin-induced hypothermia and cause hyperthermia by themselves

- On-target challenge model
  - Capsaicin, a TRPV1 agonist produces an “on-target” decrease in body temperature
  - Pretreatment with a TRPV1 antagonist should block capsaicin-induced hypothermia


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AMG 517 causes hyperthermia in multiple species

- TRPV1 antagonists caused hyperthermia in rodents, dogs, monkeys

Gavva et al., JPET 2007 323:128-137
Agonists and antagonists do not cause body temperature changes in TRPV1 knockout mice

- Agonist-induced hypothermia & antagonist-induced hyperthermia are entirely TRPV1 mediated

Steiner et al., J Neurosci. 2007 Jul 11;27(28):7459-68

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AMG 517 causes hyperthermia by vasoconstriction and increased thermogenesis

Individual effectors

- **Skin vasomotor tone**
  - Skin blood vessel

- **Nonshivering thermogenesis**
  - Brown adipose tissue

- **Shivering**
  - Skeletal muscle

Gavva et al., 2008 Pain 136:202-210
Antipyretic acetaminophen suppresses TRPV1 antagonist-induced hyperthermia

Rat radiotelemetry

- AMG8163 is a ‘boc’ analogue of AMG 517
- Similar to AMG 517, AMG8163 blocks all modes of TRPV1 activation

Gavva et al., JPET 2007 323:128-137
Repeated administration of AMG 517 attenuates hyperthermia

TRPV1 is tonically activated and plays a role in body temperature regulation
Role of TRPV1 in thermoregulation can be compensated
Clinical trial design

- **Vehicle of all studies**: A suspension in a 100 ml of 2% Pluronic 108 in OraPlus® followed by two 75 ml water washes

- **1st Phase I – single dose safety & pharmacokinetic study**
  - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
  - Healthy subjects received 1, 2, 5, 10, 20, or 25 mg AMG 517
  - End points: number and incidence of treatment emergent-events, oral and tympanic body temperature measurements

- **2nd Phase I – Repeated dose study**
  - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
  - Placebo, 2, 5, or 10 mg of AMG 517
  - Treatment emergent-events, difference in max body temperature on day 1 versus subsequent days, through day 7

- **Phase Ib – Dental pain study**
  - Double-blind, placebo-controlled, randomized, Parallel group, multi-center study
  - Inclusion criteria: moderate to severe post-operative pain
  - Single doses of placebo, 2, 8, or 15 mg of AMG 517

More details can be found in: Gavva et al., 2008 Pain 136:202-210
AMG 517 has a long half-life in healthy subjects

- Plasma half life: ~ 300 hrs

Gavva et al., 2008 Pain 136:202-210
AMG 517 elicits transient hyperthermia in humans

Body temperature & $C_{\text{max}}$ versus time

(mean ± SD of the max body temperature [tympanic] presented)

Gavva et al., 2008 Pain 136:202-210
AMG 517 caused plasma concentration-dependent hyperthermia in healthy subjects

- Single dose, oral suspension in a 100 mL of 2% Pluronic 108 in OraPlus®
- Plasma half life of AMG 517 in humans: ~ 300 hrs
Trend of hyperthermia attenuation after repeated administration of AMG 517

Body temperature versus time

![Graph showing body temperature versus time with different doses of AMG 517 and placebo.](image)

(mean ± SD of the max body temperature [tympanic] presented)

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Gavva et al., 2008 Pain 136:202-210
AMG 517 caused marked hyperthermia in subjects who underwent molar extraction

- TRPV1 antagonists causing hyperthermia in rodents, dogs, monkeys, and humans indicates an evolutionarily conserved role of TRPV1 in thermoregulation

Gavva et al., 2008 Pain **136**:202-210
First approach to address hyperthermia: Peripheral restriction of antagonists

**Hypothesis**

- Thermoregulation is CNS mediated
- Can we minimize hyperthermia by restricting antagonists to the periphery?

**Strategy**

- Reduce brain exposure: peripherally restricted TRPV1 antagonists
  - Increase polar surface area (PSA)
  - Decrease logP
  - Increase number of hydrogen-bond donors
Profiles of peripherally restricted TRPV1 antagonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>PSA</th>
<th>clogP</th>
<th>Cap IC$_{50}$</th>
<th>B/P ratio</th>
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<tbody>
<tr>
<td>AMG13731</td>
<td>145</td>
<td>3.9</td>
<td>2.9</td>
<td>0.02</td>
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<tr>
<td>AMG21629</td>
<td>128</td>
<td>3.5</td>
<td>0.5</td>
<td>0.05</td>
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<tr>
<td>AMG32915</td>
<td>141</td>
<td>1.9</td>
<td>0.2</td>
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<tr>
<td>AMG41394</td>
<td>132</td>
<td>3.9</td>
<td>1.3</td>
<td>0.04</td>
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</tbody>
</table>
Effect of AMG13731 and AMG21629 on rat body core temperature

Site of action for TRPV1 antagonist-induced hyperthermia is outside the BBB

Tamayo et al 2008 J Med Chem. 51:2744-57

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Evaluation of compounds exhibiting differential pharmacology - 2nd Approach

<table>
<thead>
<tr>
<th></th>
<th>Capsaicin</th>
<th>pH 5</th>
<th>Heat</th>
<th>Body temp</th>
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<tbody>
<tr>
<td>Profile A</td>
<td>Block</td>
<td>Block</td>
<td>Block</td>
<td></td>
</tr>
<tr>
<td>Profile B</td>
<td>Block</td>
<td>Partial block</td>
<td>Block</td>
<td></td>
</tr>
<tr>
<td>Profile C</td>
<td>Block</td>
<td>Potentiate</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Profile D</td>
<td>Block</td>
<td>Potentiate</td>
<td>Potentiate</td>
<td></td>
</tr>
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</table>

Profiles defined by agonist-induced $^{45}\text{Ca}^{2+}$ uptake assays
AMG8562, a profile C compound that does not cause hyperthermia in rats

**In vitro data**

- Capsaicin
- pH 5
- Heat

**Rat radiotelemetry**

- Vehicle (n=6)
- 10 mg/kg (n=6)
- 1 mg/kg (n=6)
- 30 mg/kg (n=6)
- 3 mg/kg (n=6)

Lehto et al 2008 JPET 326:218-229

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AMG8562 is modestly effective in capsaicin-challenge and pain models

Capsaicin-induced flinch
- Number of flinches
- Plasma concentration (ng/ml)

CFA-induced thermal hyperalgesia
- Latency (sec)
- Plasma concentration (ng/ml)

Acetic acid-induced writhing
- Number of writhes
- Plasma concentration (ng/ml)

Lehto et al 2008 JPET 326:218-229
AMG8562, exhibits profile B modulation of human TRPV1

- Profile B modulators cause hyperthermia in rats

Lehto et al 2008 JPET 326:218-229
## Current status of TRPV1 antagonists in the clinic

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Company</th>
<th>Route of administration</th>
<th>Indication</th>
<th>Stage</th>
<th>Current status</th>
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<tbody>
<tr>
<td>ABT-102</td>
<td>Abbott</td>
<td>Oral</td>
<td></td>
<td>Phase I</td>
<td>Initiated ?</td>
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<tr>
<td>AMG 517</td>
<td>Amgen</td>
<td>Oral</td>
<td>Dental pain</td>
<td>Phase Ib</td>
<td>Terminated</td>
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<tr>
<td>AZD1386</td>
<td>AstraZeneca</td>
<td>Oral</td>
<td>Dental pain</td>
<td>Phase II</td>
<td>Completed</td>
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<tr>
<td>GRC 6211</td>
<td>Lilly/Glenmark</td>
<td>Oral</td>
<td>Dental pain</td>
<td>Phase II</td>
<td>Suspended</td>
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<tr>
<td>JTS-653</td>
<td>Japan Tobacco</td>
<td>Oral</td>
<td>Overactive bladder pain</td>
<td>Phase I</td>
<td>On going</td>
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<td>MK 2295</td>
<td>Merck/Neurogen</td>
<td>Oral</td>
<td>Dental pain</td>
<td>Phase II</td>
<td>Completed</td>
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<td>SB-705498</td>
<td>GSK</td>
<td>Oral</td>
<td>Migraine</td>
<td>Phase II</td>
<td>Terminated</td>
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<td></td>
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<td>Rectal pain</td>
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<td></td>
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<td>Dental pain</td>
<td>Phase II</td>
<td>Completed</td>
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<td>PF-4065463</td>
<td>Evotec/Pfizer</td>
<td>unknown</td>
<td>unknown</td>
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Conclusions

• Genetic and pharmacological evidence suggests that TRPV1 contributes to hyperalgesia
  ▪ TRPV1 antagonists block capsaicin-induced flinch (on-target challenge) and act as anti-hyperalgesics
• AMG 517, a selective TRPV1 antagonist caused plasma concentration dependent hyperthermia in humans
• Antagonist-induced hyperthermia showed a complete and clear attenuation after repeated dosing in preclinical species but not in humans
• Mechanisms of hyperthermia include antagonist-induced vasoconstriction and increased thermogenesis
• Peripherally restricted TRPV1 antagonists caused hyperthermia
• Profile C modulators of TRPV1 did not cause hyperthermia and demonstrated modest efficacy in pain models
• Clinical trial results of other TRPV1 antagonists are eagerly awaited
## Outstanding questions and next steps

### Preclinical
- ‘Profile C’ modulators of both rodent and human TRPV1
- Efficacy after repeated dosing of TRPV1 antagonists
- TRPV1 function in non-pathophysiological states (e.g., thermosensation)

### Clinical
- Development by different routes of administration (e.g., topical application)
- Development of short half-life antagonists
- Development of antipyretic + TRPV1 antagonist combination
- Development of TRPV1 antagonists in primary indications (e.g., Osteoarthritis)
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The Team

<table>
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<tr>
<th>Departments</th>
<th>Neuroscience</th>
<th>Chemistry</th>
<th>Process Chemistry</th>
<th>TRPV1 Core Team</th>
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<tr>
<td>Neuroscience</td>
<td>Leyla Arik</td>
<td>Yunxin Bo</td>
<td>Charles Bernard</td>
<td>Narender Gavva</td>
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<td>Ning Chen</td>
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