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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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

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

TRPV1 positive DRG neurons

Moiseenkova-Bell et al 2008 PNAS. 105:7451-5

Rat sensory neurons responding to capsaicin (calcium imaging)
TRPV1 – Target validation

TRPV1 knockout mice show reduced thermal hyperalgesia


Various distinct chemical scaffolds act as TRPV1 antagonists

AMG9810
Gavva et al 2005 JPET, 313:474-484

NVS Pyridopyrimidine

SB-705498

JYL1421 (SC0030)

AMG0347

AMG2674

AMG517
Doherty et al., 2007 JMC 50:3515-27
Gavva et al., 2005 JPET, 313:474-484
Gavva et al., 2007 JPET 323:128-137

AMG0347

ABT-102

AMG8562

SB-705498

BCTC

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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 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 blocks capsaicin-induced flinching in rats

Dose
AMG 517 p.o.

Inject Capsaicin
Into the Paw

60 min

Count # of Paw Flinches in 1 min

Gavva et al., 2007 JPET 323:128-137

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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

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
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

- 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

Gavva et al., 2008 Pain 136:202-210

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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

- Placebo (N=7)
- AMG 517 2mg (N=12)
- AMG 517 5mg (N=6)
- AMG 517 10mg (N=6)

(maximum tympanic temperature [mean ± SE, °C] presented)

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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<tr>
<td>AMG13731</td>
<td>145</td>
<td>3.9</td>
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<td>AMG21629</td>
<td>128</td>
<td>3.5</td>
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<td>AMG32915</td>
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<td>AMG41394</td>
<td>132</td>
<td>3.9</td>
<td>1.3</td>
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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
Evaluation of compounds exhibiting differential pharmacology - 2nd Approach

<table>
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<th>Capsaicin</th>
<th>pH 5</th>
<th>Heat</th>
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<tr>
<td>Block</td>
<td>Partial block</td>
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<td>Potentiate</td>
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<tr>
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<tr>
<td>Profile D</td>
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</table>

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

Lehto et al 2008 JPET 326:218-229
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>
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<tr>
<td>ABT-102</td>
<td>Abbott</td>
<td>Oral</td>
<td>Phase I</td>
<td>Initiated</td>
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<td>AstraZeneca</td>
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<td>Overactive bladder pain</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>
<thead>
<tr>
<th>Departments</th>
<th>Neuroscience</th>
<th>Chemistry</th>
<th>Process Chemistry</th>
<th>TRPV1 Core Team</th>
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<td>Neuroscience</td>
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## Collaborators

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<tr>
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<th>Andrey Romanovsky, Andras Garami</th>
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<tr>
<td></td>
<td>St. Joseph’s Hospital and Medical Center, Phoenix, AZ</td>
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