RTX-1738 Exhibits Analgesic Activity Across a Broad Range of Preclinical Pain Models

Poster TU377

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Background

- There is an urgent need for pain medication with a novel mechanism of action that provides clinically meaningful analgesia along with improved tolerability
- AMPA receptors (AMPARs) are essential to pain sensitization processes involved in various disease states
- Nonselective AMPAR antagonists show analgesic properties in preclinical and clinical settings
  - Adverse effects of targeting AMPARs broadly throughout the brain limit the therapeutic index and clinical utility of these antagonists
- Transmembrane AMPAR regulatory proteins (TARPs) are AMPAR auxiliary subunits with region-specific expression that modulate AMPAR synaptic physiology and pharmacology
- TARPγ8 is selectively expressed in pain-processing regions: spinal cord dorsal horn, anterior cingulate cortex, hippocampus, and amygdala[1,2]
- The selective expression pattern of TARPγ8 offers opportunities to develop novel first-in-class analgesics with an improved therapeutic index
  - Rodents administered TARPγ8 inhibitors do not display motoric impairment on the rotarod test

Objective

- We evaluated RTX-1738, a highly potent, selective, brain-penetrant, orally bioavailable AMPAR/TARPγ8 inhibitor, in a variety of pain models

Methods

- All studies followed AAALAC guidance and were performed according to guidelines approved by the IACUC
- RTX-1738 was tested in preclinical models of acute thermal nociception and inflammatory, post-surgical, and neuropathic pain (**Table 1**)
- Statistical analyses
  - One-way ANOVA following multiple comparison testing was used, except for the PWT response in the SNL model
  - Two-way ANOVA followed by Dunnett's multiple comparison test was used for PWT in SNL

Table 1. Preclinical Models and Protocols

Model	Treatment groups	Induction procedure	Pain response measured	Indication/ nociceptive modality
Formalin SD rats, male, 6-8 weeks old n=8/group	· Vehicle *p.o.* · Gabapentin, 150 mg/kg *i.p.* · RTX-1738, 3 mg/kg *p.o.*	Formalin (5%, 50 µL) injection into dorsal surface of left hind paw, 1h post-treatment	**Nociceptive behaviors:** Duration of lifting, licking, biting, and trembling (s) · Phase 1 (0-10 min post-formalin injection) · Phase 2 (20-60 min post-formalin injection	Persistent pain
Spinal nerve ligation (SNL) SD rats, male, 6-8 weeks old n=10/group	· Vehicle Gabapentin, 75 mg/kg · RTX-1738, 3 mg/kg All groups *p.o., q.d.* Days 14-20	SNL surgery: Left L5 and L6 spinal nerves isolated and tightly ligated	**Von Frey** Paw withdrawal threshold (PWT; g)[a] 1.5h post-treatment on Days 14, 16, 18, and 20	Neuropathic pain
Complete Freud's adjuvant (CFA) SD rats, male, 6-8 weeks old n=10/ group	· Vehicle · Naproxen, 20 mg/kg · RTX-1738, 3 mg/kg All groups *p.o.*	Day 0: CFA injection (50 µL) sub-plantar to left hind paw	**Von Frey** PWT (g)[a] · Day 0: Pre-CFA baseline · Day 3: Pre-treatment baseline and 2h post-treatment	Inflammatory pain
Carrageenan SD rats, male, 6-8 weeks old n=10/group	· Vehicle Indomethacin, 10 mg/kg · RTX-1738, 3 mg/kg All groups *p.o.*	Carrageenan injection (3%, 100 µL) sub-plantar to left hind paw, 1h post-treatment	**Von Frey** PWT (g)[a] · Pre-treatment baseline · 3h and 5h post-treatment **Paw volume** (mL)[b] · 3h and 5h post-treatment	
Hot plate and tail flick SD rats, male, 6-8 weeks old n=10/group	· Vehicle *p.o.* · Gabapentin, 300 mg/kg *i.p.* · RTX-1738, 3 mg/kg *p.o.*	Hot plate: 51.5°C Tail flick: 36°C Average of 2 repeated tests	**Nocifensive responses:** Hot plate – licking (s); Tail flick – latency to tail withdrawal (s) · Pre-treatment · Post-treatment −2h, RTX-1738 −1h, gabapentin	Acute thermal nociception
Paw incision (PI) C57BL/6J mice, male, 6-8 weeks old n=10/group	No PI + vehicle; PI + · Vehicle · Naproxen, 90 mg/kg · RTX-1738, 3 mg/kg All groups *p.o.*	PI surgery: plantar muscles clamped and cut longitudinally[3]	**Hargreaves apparatus** Paw withdrawal latency (PWL; s)[c] · 2h post-incision[4] · 2h, 4h, and 6h post-treatment	Post-surgical pain

[a]Von Frey test: mechanical allodynia measured by PWT (g) over 30s maximum, repeated twice per subject per timepoint, averaged.

[b]Paw volume measured via liquid displacement once per timepoint.

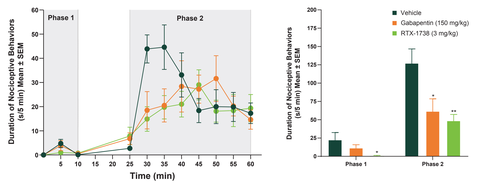
[c]Hargreaves apparatus: thermal hyperalgesia measured by PWL (s) over 20s maximum, repeated twice per subject per timepoint, averaged.

CFA, complete Freud's adjuvant; PI, paw incision; PWL, paw withdrawal latency; PWT, paw withdrawal threshold; SD, Sprague-Dawley; SNL, spinal nerve ligation.

Results

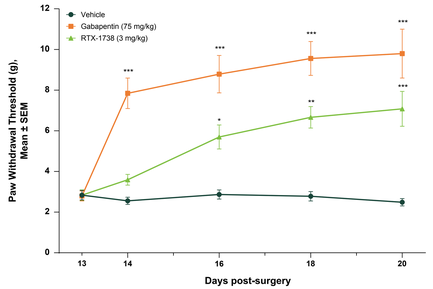
- RTX-1738 (3 mg/kg, *p.o.*) attenuated inflammatory and neuropathic pain-related behaviors in a comparable manner to gabapentin (150 or 300 mg/kg, *i.p.*), indomethacin (10 mg/kg, *p.o.*), and naproxen (20 mg/kg, *p.o.*; **Figures 1-5**)

Figure 1. RTX-1738 Attenuated Acute Persistent Inflammatory Nocifensive Behavior in the Formalin Model



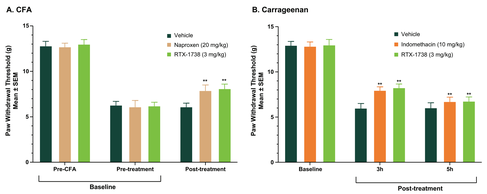
*p<0.05, **p<0.01; vs vehicle.

Figure 2. RTX-1738 Attenuated Tactile Allodynia in the SNL Model of Neuropathic Pain



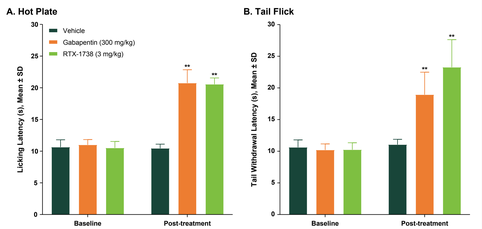
*p<0.05, **p<0.01, ***p<0.001; vs vehicle.

Figure 3. RTX-1738 Attenuated Mechanical Allodynia in the CFA and Carrageenan Models of Inflammatory Pain



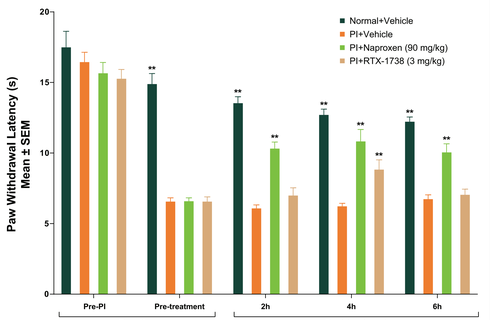
**p<0.01, vs vehicle.

Figure 4. RTX-1738 Increased Latency to Thermal Response in the Hot Plate and Tail Flick Assays



**p<0.01, vs vehicle.

Figure 5. RTX-1738 Provided Moderate Attenuation of Paw Incision (PI)-Induced Thermal Allodynia



**p<0.01, vs vehicle.

Safety

- There were no observations of neurological or muscular dysfunction
- Cage-side observations yielded some hyperactivity in animals treated with RTX-1738, but there were no abnormal clinical signs

Conclusions

- RTX-1738, a highly potent, selective, brain-penetrant, orally bioavailable AMPAR/TARPγ8 inhibitor, showed statistically significant efficacy across broad modalities of pain processing
  - These results support the role of AMPARs in pain processing and the potential of selectively targeting TARPγ8 AMPARs in the development of novel broad-spectrum analgesics
- The regiospecificity of TARPγ8 expression is aligned with key areas of pain processing
  - RTX-1738 was well tolerated in rodents at efficacious doses
- Use of AMPAR/TARPγ8 inhibitors for clinical testing across a broad range of pain indications is warranted

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DISCLOSURES

JAM, WD, LPV, BTS, DB: employees of Rapport Therapeutics, Inc; stock ownership in Rapport Therapeutics, Inc.

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