

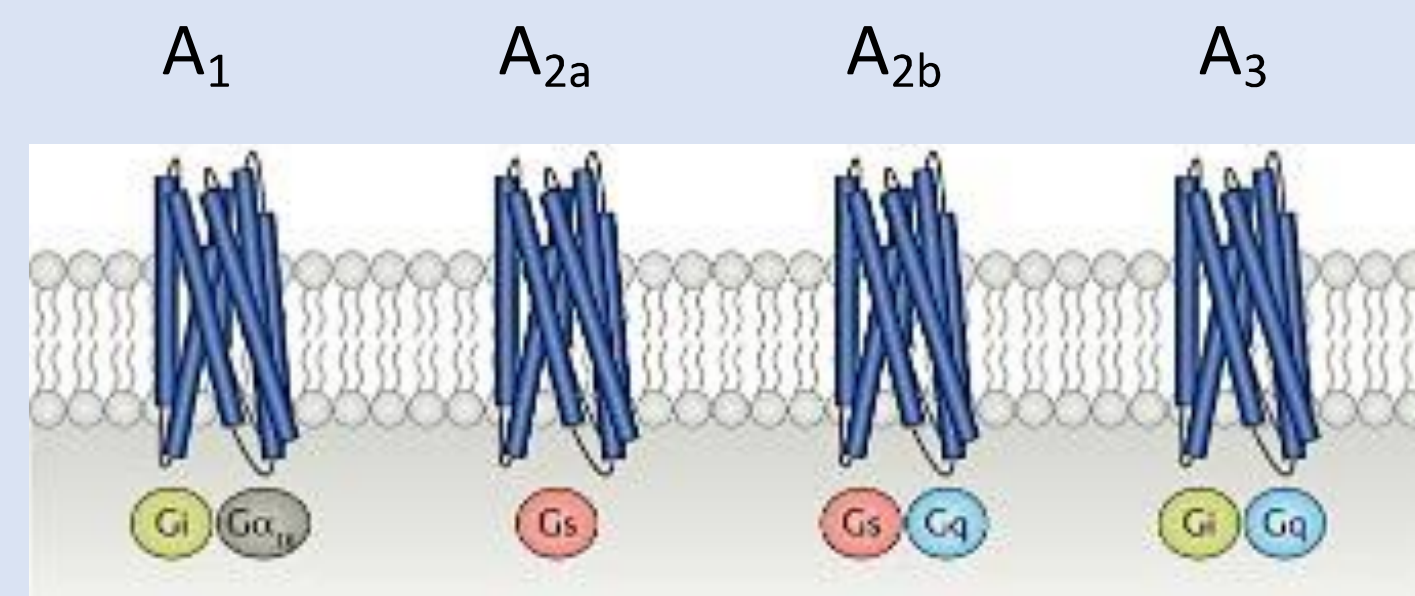
The Adenosine-3 Receptor as Analgesic Target: Computer Modeling of Allosteric Interaction

Robert B. Raffa, PhD; Joseph V. Pergolizzi Jr., MD; Michael Innaurato
Neumentum, Inc., Summit NJ

Overview

- ARs are the subject of extensive analgesic research
- Evidence identifies A3R subtype as the best target
- A novel A3R compound is described (NTM-006)

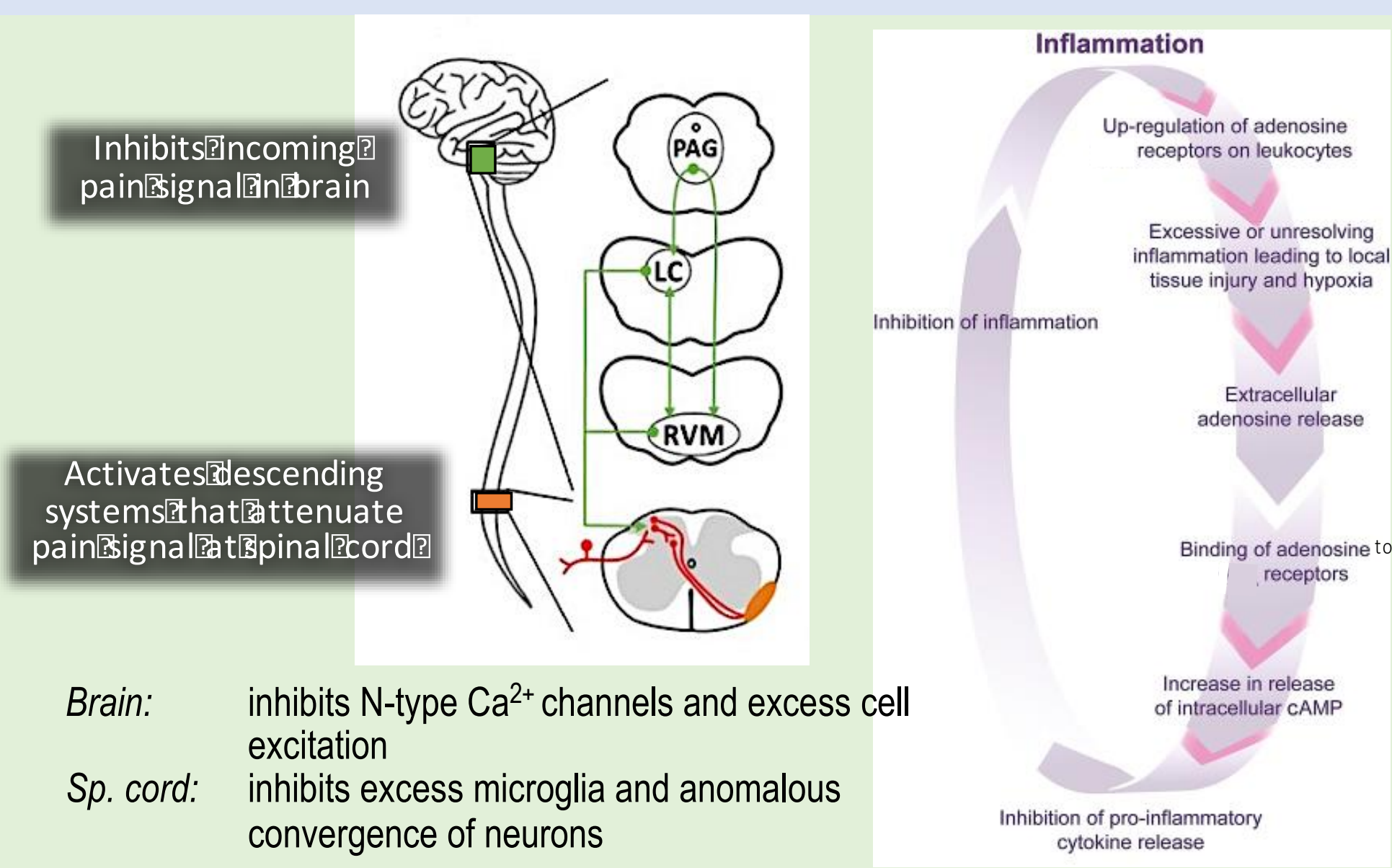
Adenosine: receptors & analgesia



Different G protein subtypes
2nd messenger signal transduction

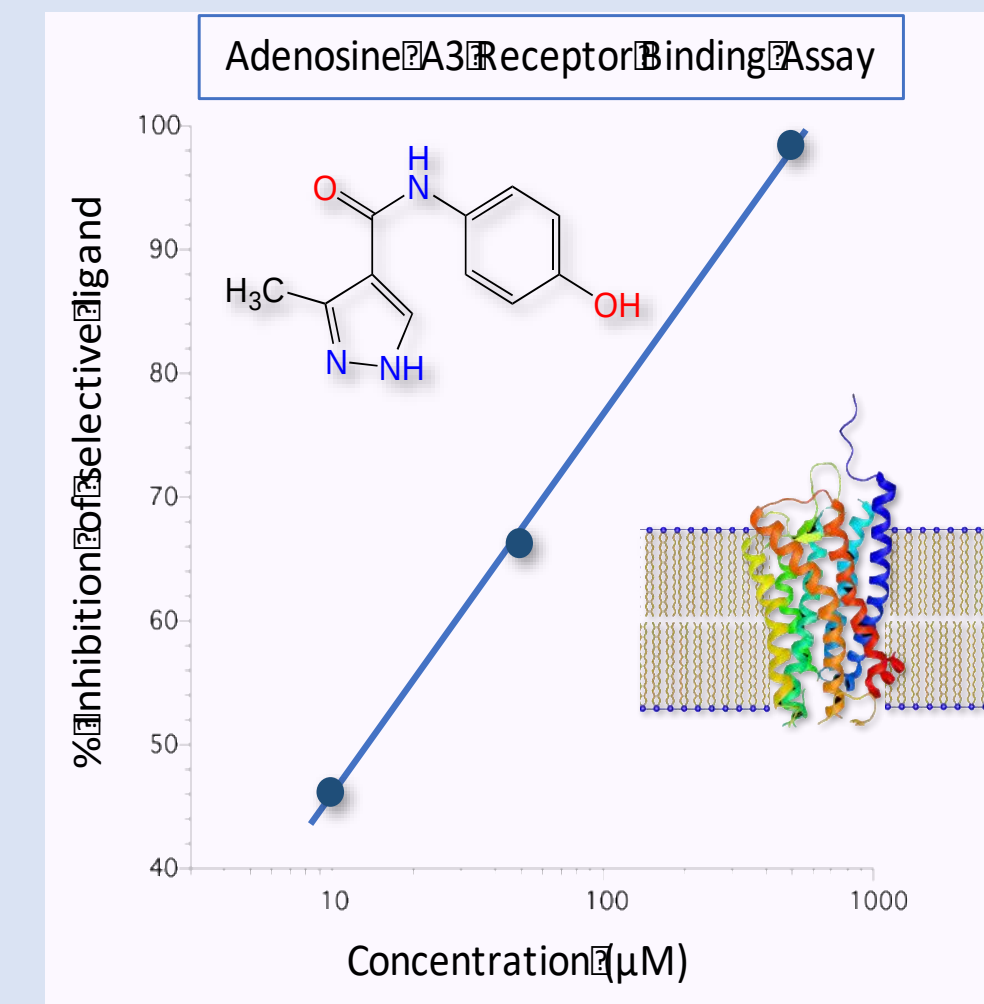
Subtype	Analgesic Efficacy	CV AEs
A ₁ -AR	Yes	Yes
A _{2a} -AR	Yes	Yes
A _{2b} -AR	No	—
A ₃ -AR	Yes	No

A3R: Pain & Inflammation

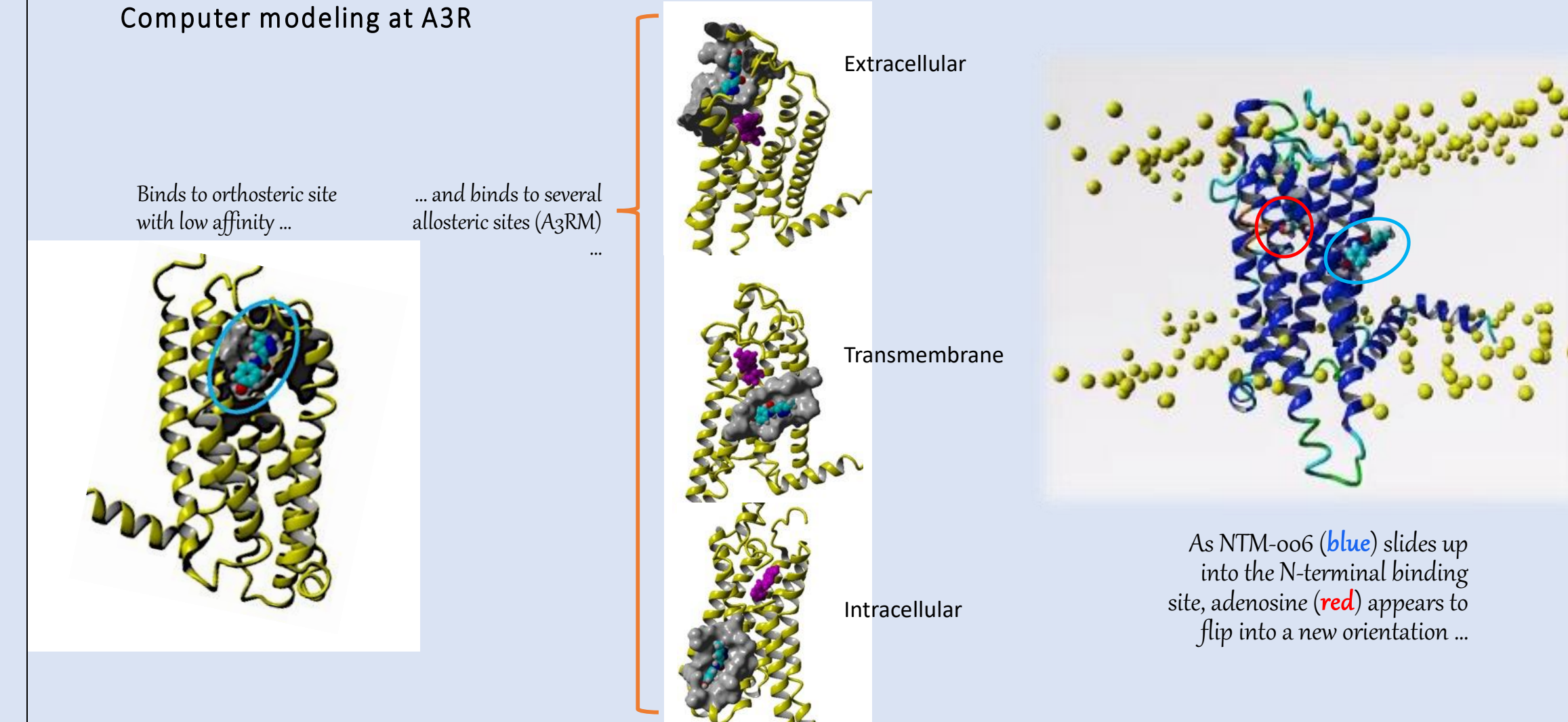


NTM-006

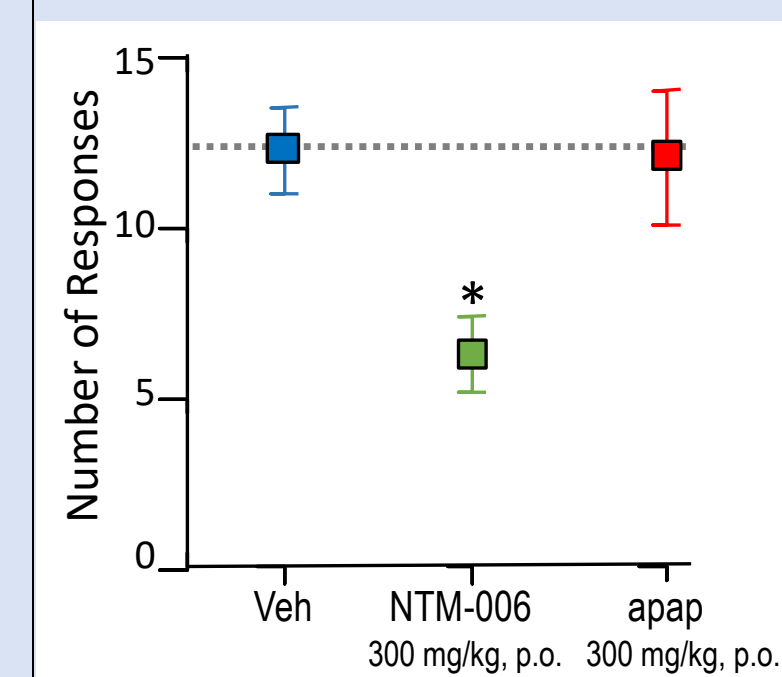
- Non-opioid (MOR, DOR or KOR)
- Non-NSAID
- Inactive at other receptors
- Inactive at uptake transporters
- Inactive at ion channels
- Orally active
- No ECG effects
- Phase-2 metabolism (fewer DDIs)
- APAP precursor? (no liver tox)
- Additional MoA?



Computer modeling at A3R

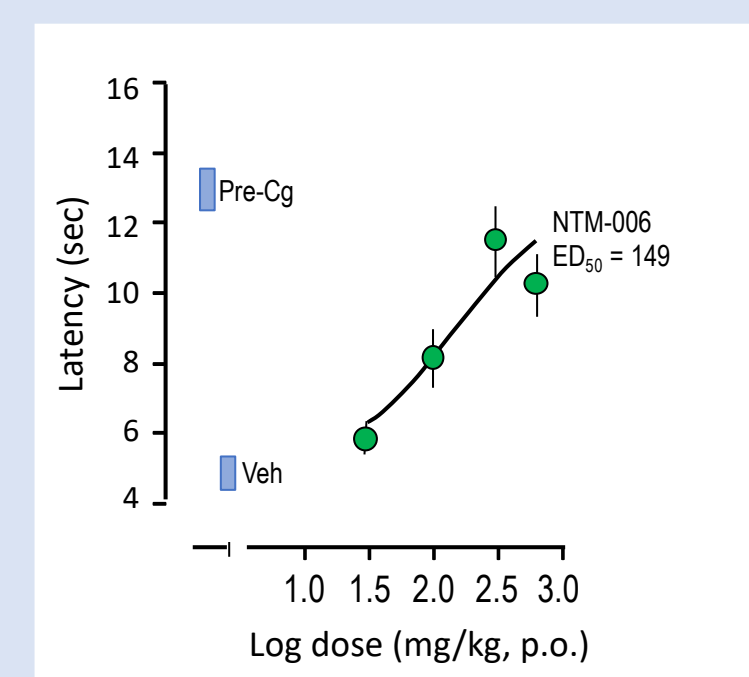


Antinociceptive



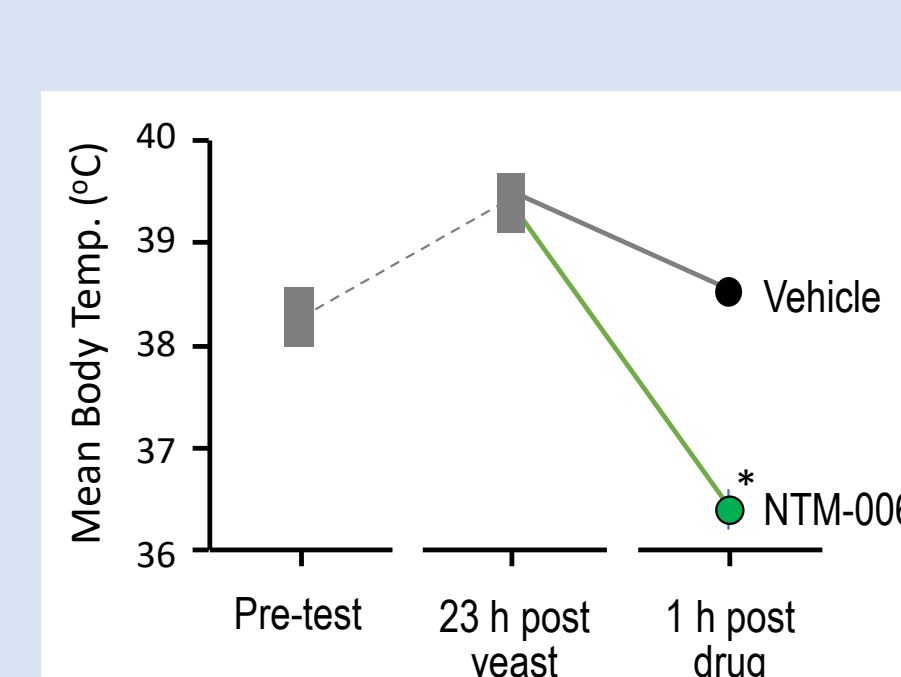
Antinociceptive effect in phenylquinone-induced abdominal irritant model. * P < 0.05. Mice

Antihyperalgesic



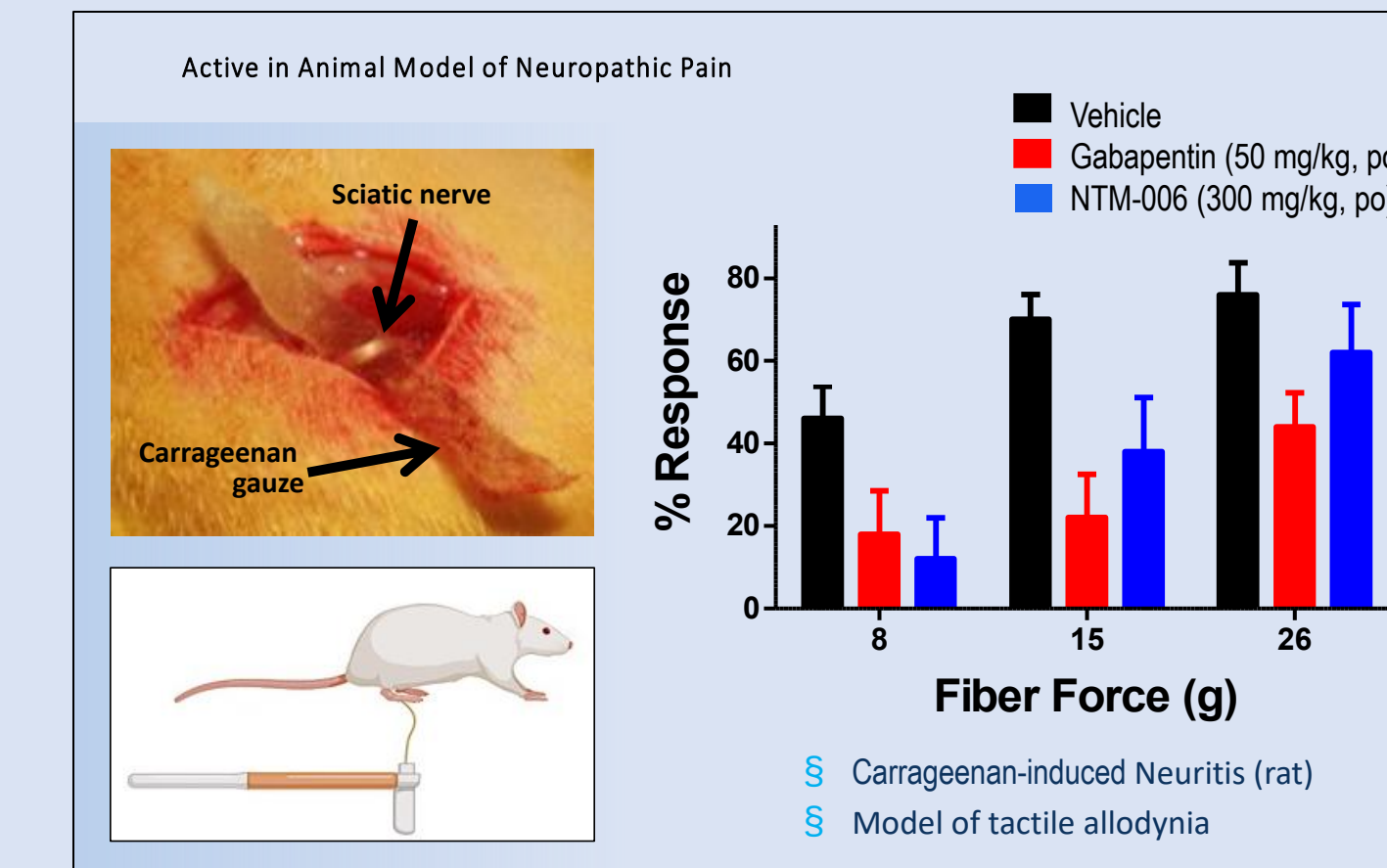
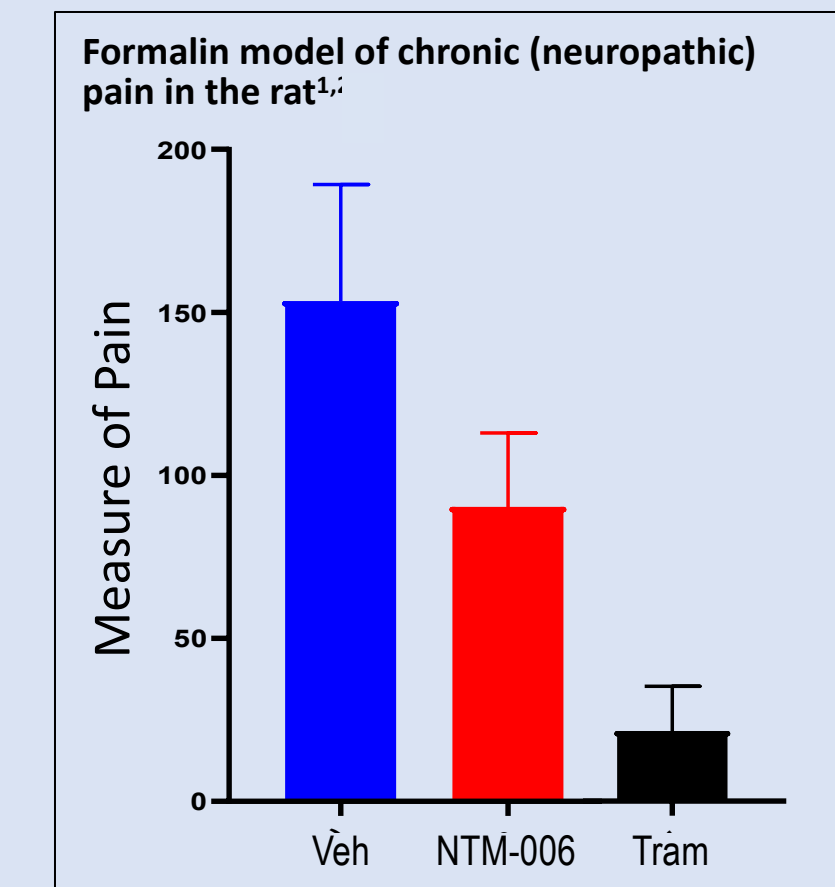
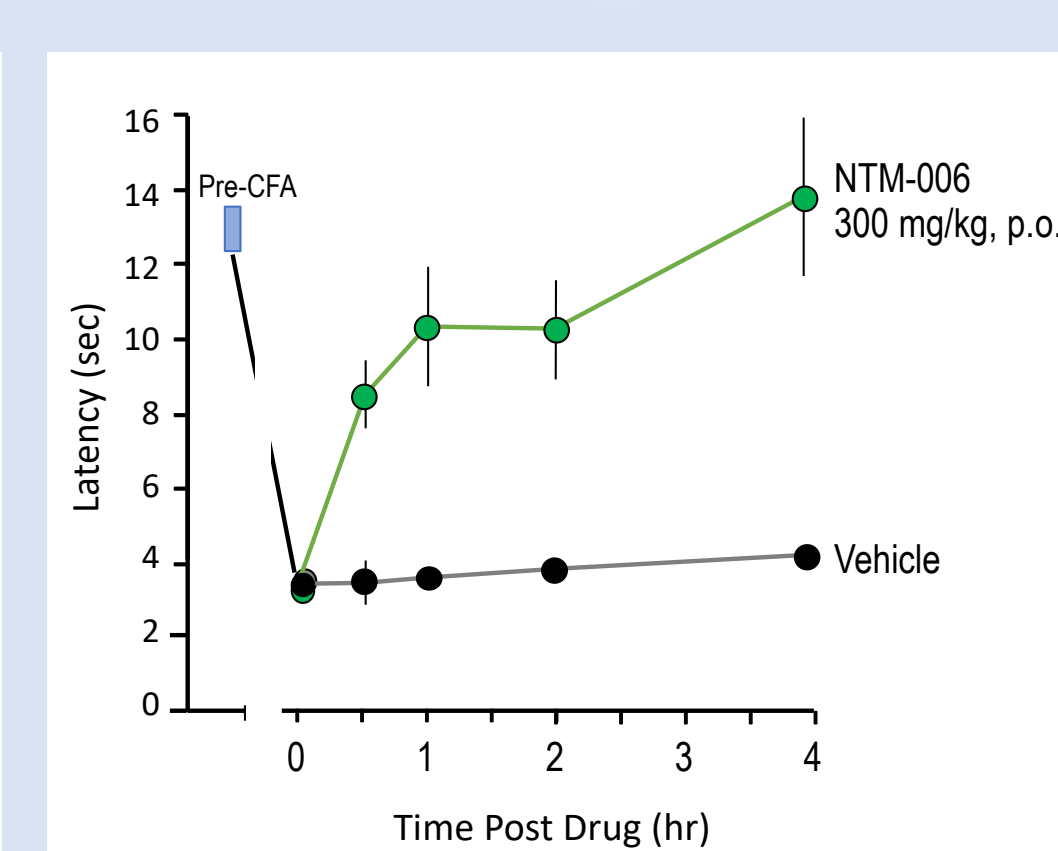
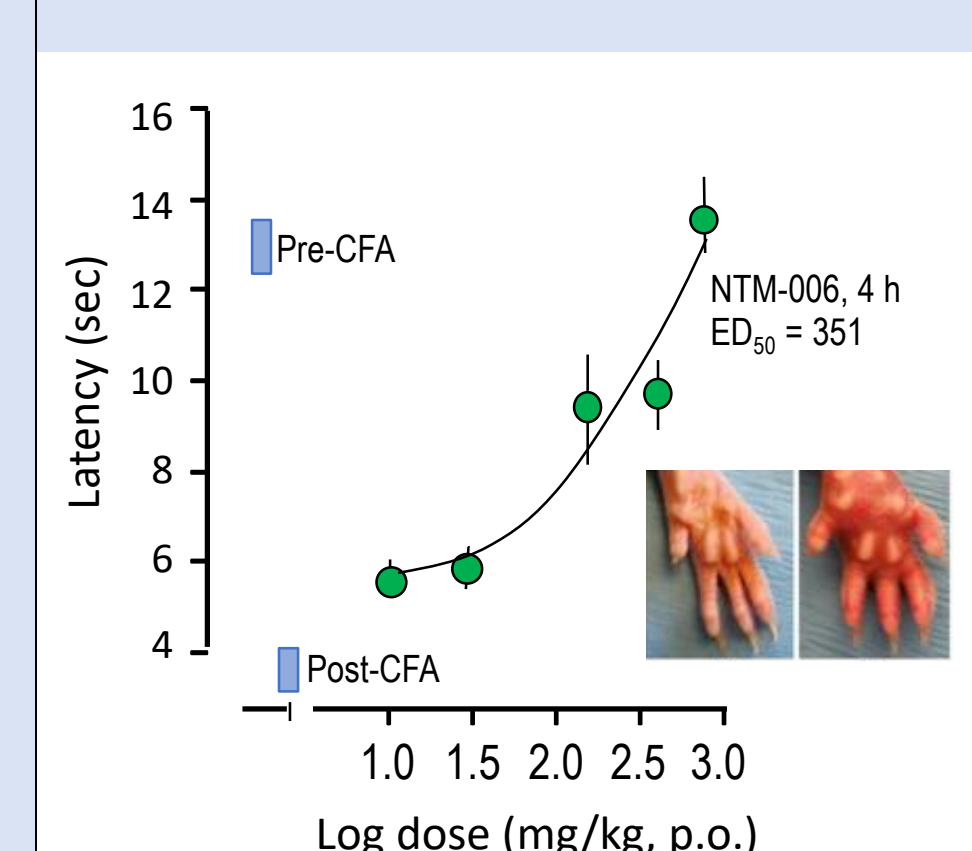
Antihyperalgesic effect in carrageenan (Cg)-induced thermal hyperalgesia. Rats.

Antipyretic

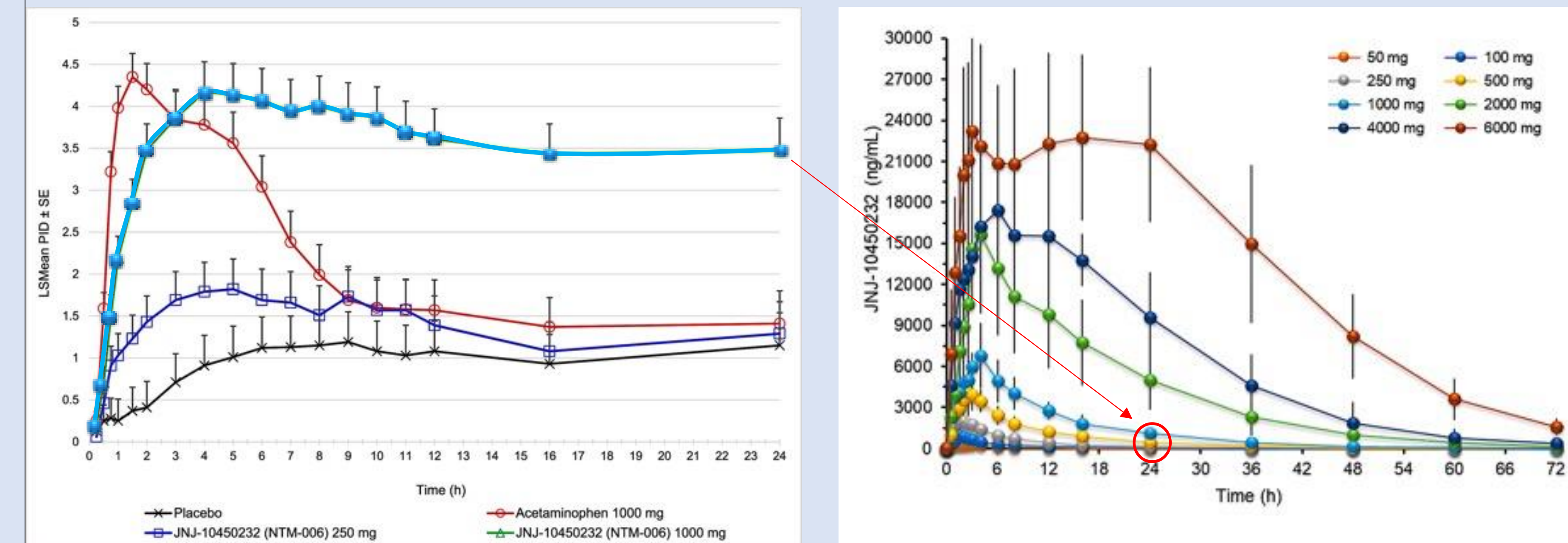


Antipyretic evaluation at 600 mg/kg, p.o. in a yeast-induced pyrexia model. Rats.

Chronic inflammatory arthritis and chronic-pain model in the rat



CLINICAL RESULTS^{1,2}



Summary

- NTM-006 (previously JNJ-10450232) displays orally-active and long-acting activity in preclinical models of acute and chronic/neuropathic pain, inflammation, and fever
- This profile is consistent with combined mechanisms of action, putatively acetaminophen-related and adenosine-3 receptor related
- Clinical results from a 3rd-molar extraction model reveals efficacy, long duration of action, and good safety profile

References

- Gelotte et al. (2022). First-in-human study to evaluate the safety, tolerability and pharmacokinetics of a novel analgesic and antipyretic drug with structural similarity to acetaminophen. Regul Toxicol Pharmacol 134:105236.
- Gelotte et al. (2023) JNJ-10450232 (NTM-006), A novel non-opioid with structural similarities to acetaminophen, produces relatively long-lasting analgesia after a single dose in patients undergoing 3rd molar extraction. Regul Toxicol Pharmacol 105480