Dual Inhibition of Meningeal Mast Cells and Trigeminal Neurons via MRGPRX2 Antagonism in Migraine

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Disclosures

Last Two Years

Potential COI	Organization
Advisory Boards	• Delphian Therapeutics
Speaker / Speakers Boards	• n/a
Consultant	• **Evommune**
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Other	• Co-founder: PARMedics, Ted and Greg's • Stock ownership: Acadia Pharmaceuticals

Mast Cells are Hypothesized to Contribute to Migraine

Anatomical Relevance

- Abundant in meninges and perivascular spaces – regions innervated by trigeminal neurons

Neuroimmune Communication

- Trigeminal neuropeptides (CGRP, PACAP, VIP, Substance P) activate mast cells

Release Nociceptive Mediators

- Histamine, cytokines and proteases sensitize sensory neurons

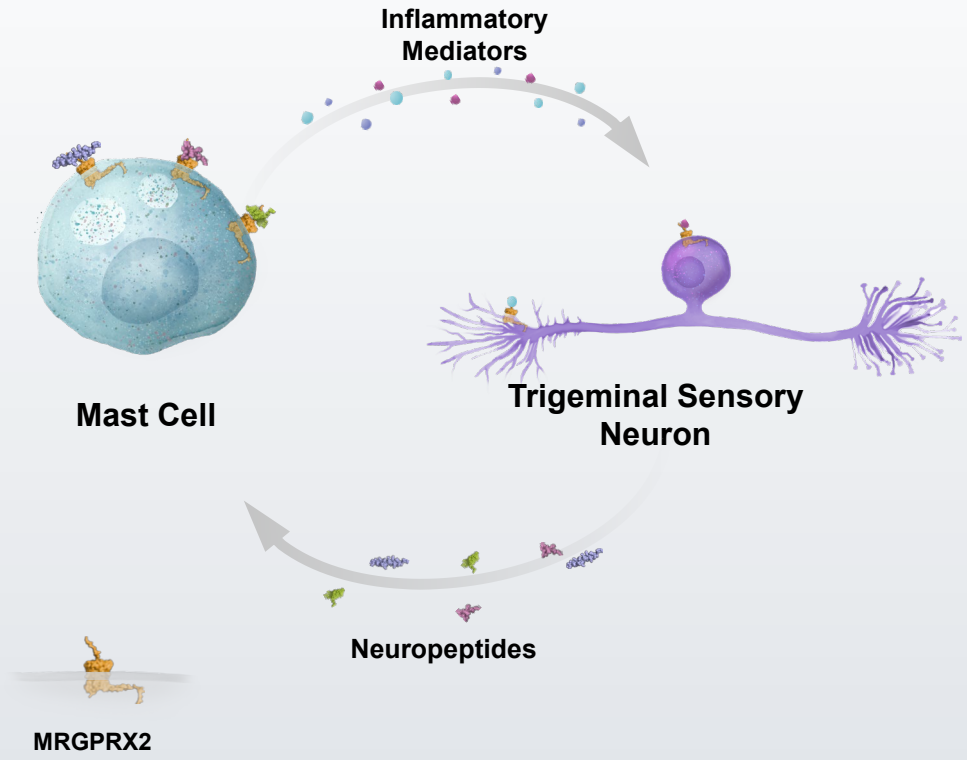
Positive Feedback Loop

- Increasing and sustaining migraine pain

Translational Support

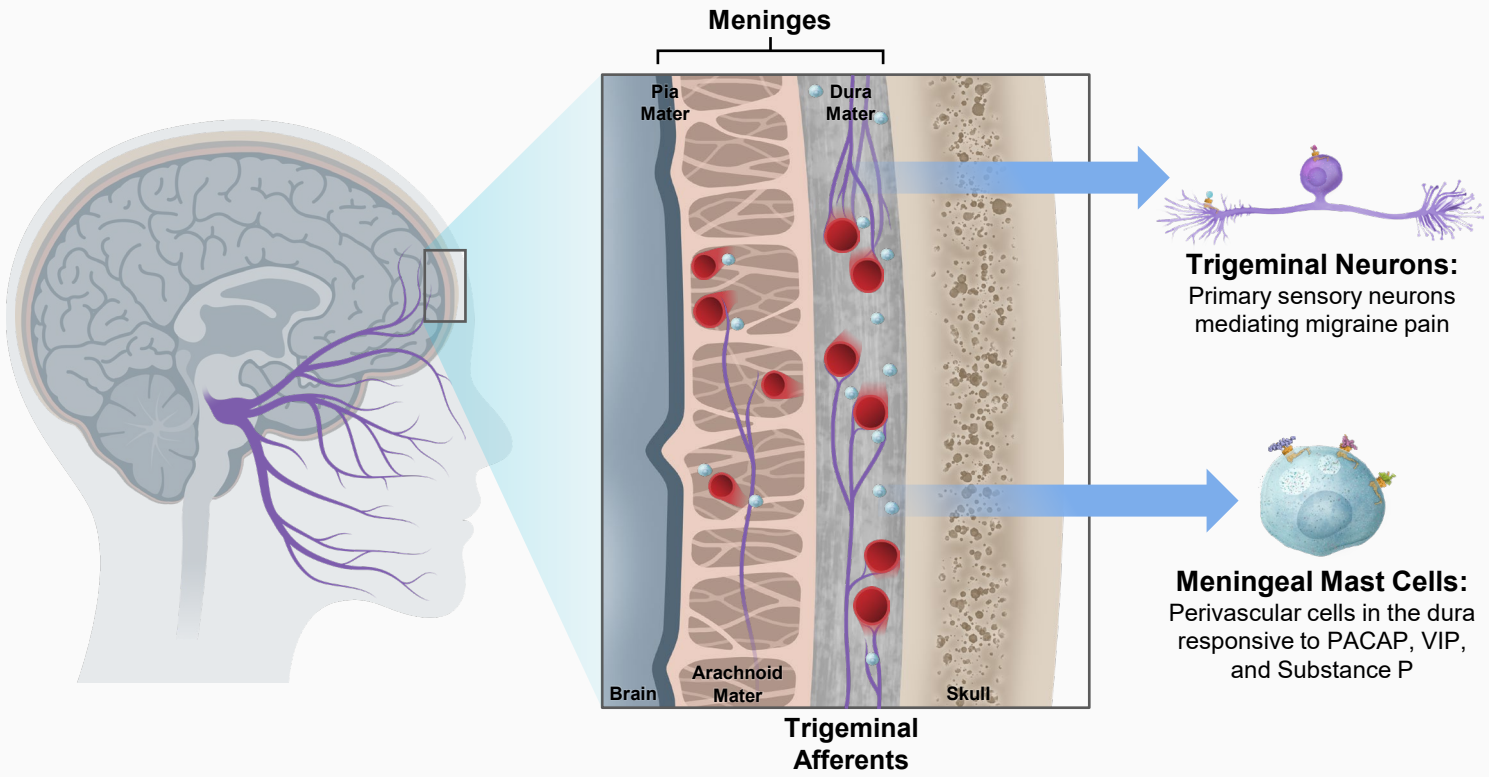
- Mast cell activation linked to migraine-like responses in animal models and higher prevalence of headache in mastocytosis

Dynamic Cross-Talk Between Meningeal Mast Cells and Trigeminal Sensory Neurons

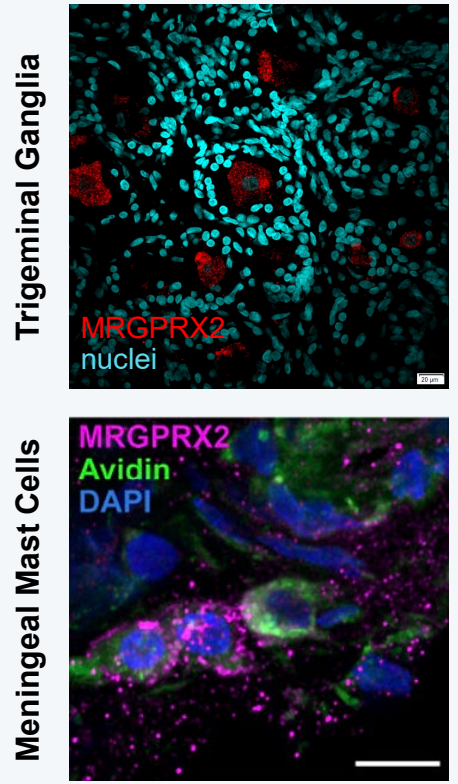


MRGPRX2: Positioned as a Key Mediator of the Interactions Between Mast Cells and Sensory Neurons in the Meninges

MRGPRX2 is Expressed on Both Meningeal Mast Cells and Trigeminal Sensory Neurons



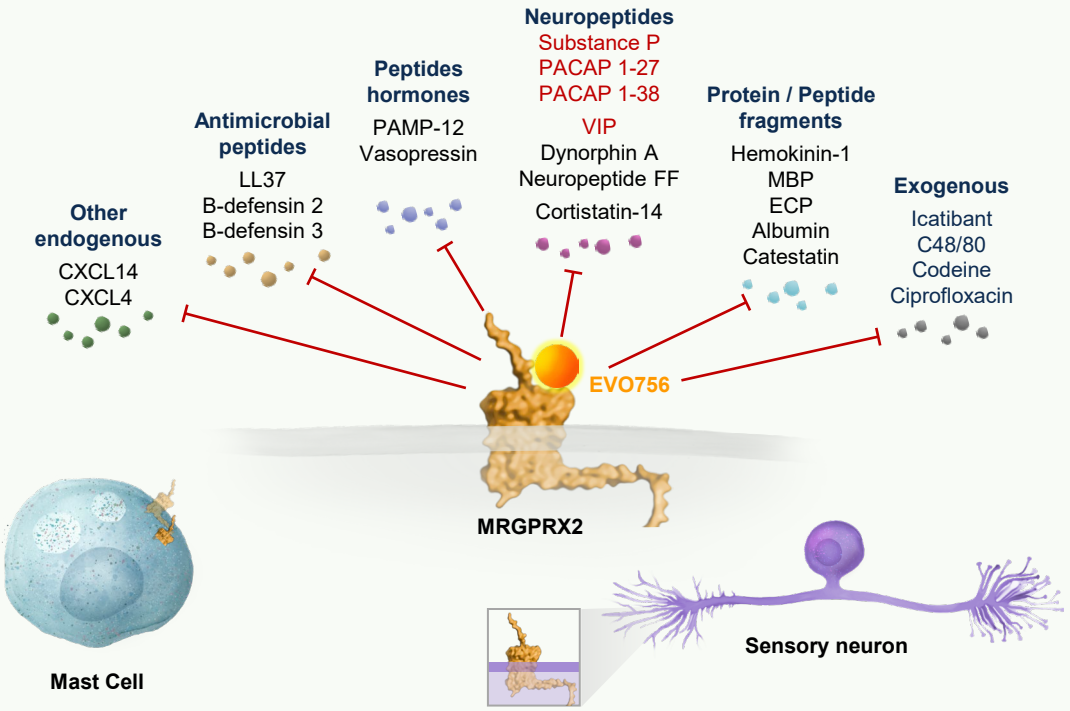
Expression Confirmed in Disease-Relevant Tissues



Source: Evommune internal data (trigeminal neurons; *in situ* hybridization on human tissue samples), PMID40712576 (meningeal mast cells)

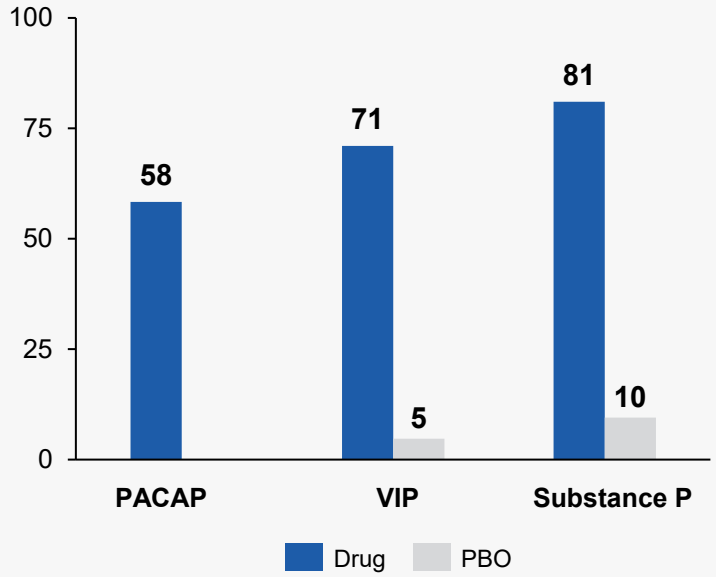
MRGPRX2 Ligands Induce Migraine Attacks in Humans

MRGPRX2 Ligands are Associated with Migraine



Red: Ligands associated with migraine

PACAP, VIP, Substance P Infusion All Induce Migraine-Like Headache in Migraineurs



- Similar to CGRP, which induces migraine in ~2/3 patients

Note: Data shown from PACAP-38; PACAP-27 also induces migraine. Sources: Adapted from PMID19052139, PMID34357396, PMID37009867, Al-Khazali et al., (2026). Note that there have been multiple studies inducing headache/migraine with ligands and experimental paradigms / results differed. Data shown represent cumulative observations pooled across multiple trials and cannot support definitive conclusions.

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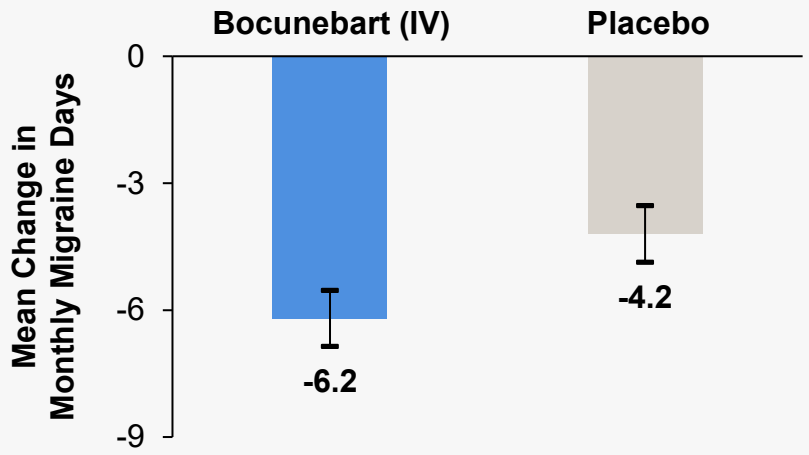
PACAP Inhibition Achieves CGRP-Like Efficacy in Migraine Prophylaxis

Lundbeck's Bocunebart Reduced Monthly Migraine Days by ~2



- Magnitude of benefit consistent with marketed CGRP inhibitors

Second Neuropeptide Axis Validated in Migraine Prevention

- PACAP is a key neuropeptide trigger of migraine attacks
- Antibody blockade reduced migraine frequency in controlled clinical study
- Effect size falls within range observed for approved CGRP therapies

Note: Lundbeck's bocunebart is a humanized mAb that neutralizes PACAP. Results above from Phase 2 a study in migraine prophylaxis (HOPE; N=237; single IV administration of bocunebart in patients that were a mix of episodic and chronic migraineurs). Source: Clinicaltrials.gov NCT05133323. Direct comparisons cannot be made in the absence of head-to-head trials because of differences in trial design, patient population and other factors.

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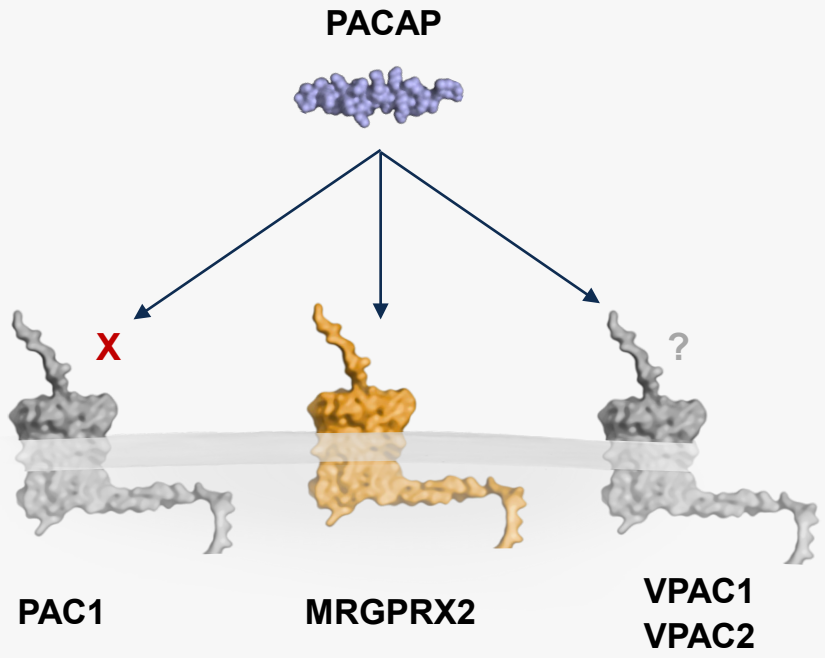
Receptor(s) PACAP Engages to Induce Migraine Not Yet Clear

PACAP May Be Triggering Migraine Through MRGPRX2



PACAP Receptor	Relevant Tissue Expression	Clinical Validation In Migraine?
PAC1	Neurons[1]	✗
VPAC1 VPAC2	Cranial Vessels Neurons (?)	*Not evaluated*
MRGPRX2	Mast Cells Sensory Neurons	TBD

1. Trigeminal sensory neurons, brainstem pain circuits, hypothalamus, cortex, thalamus. Note: In addition to MRGPRX2 PACAP binds PAC1, VPAC1, VPAC2, but PAC1 inhibition (Amgen's AMG301: PAC1 blocking mAb.) does not show therapeutic benefit in migraine. Sources: PMID33231489, PMID39085771, PMID37706270.

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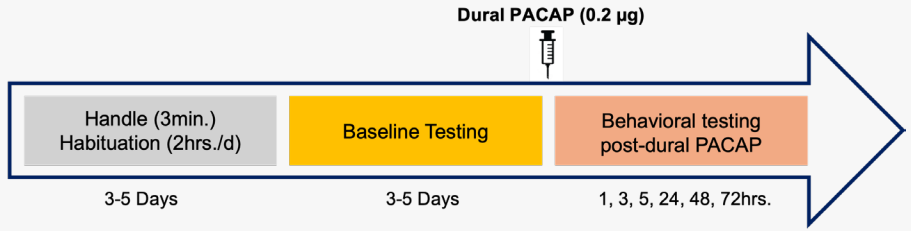
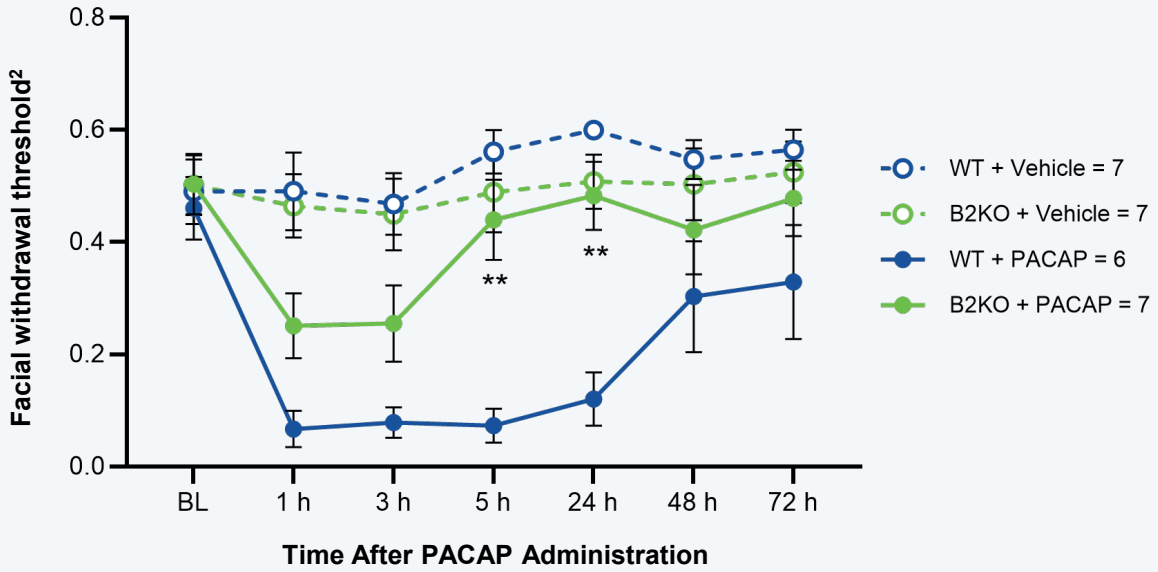
PACAP Causes Migraine-Like Behavior via MRGPRB2[1] as Primary Receptor *in vivo* in Mice

MRGPRX2 Ligand PACAP Induces Headache *in vivo*

1. PACAP injected directly onto meninges of wild type and knockout models
2. Facial withdrawal threshold used as functional pain readout



Knockout of MRGPRX2[1] Reduced PACAP-Induced Migraine Symptoms



- *in vivo* data support functional role of MRGPRX2[1] signaling in migraine

1. Mrgprb2 is rodent homologue of MrgprX2. 2. In grams, measured via Peri-orbital von Frey assessment.
Source: Internal Evommune data. Confirms data published in PMID37516794.

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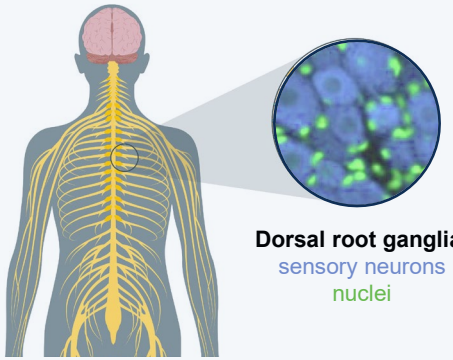
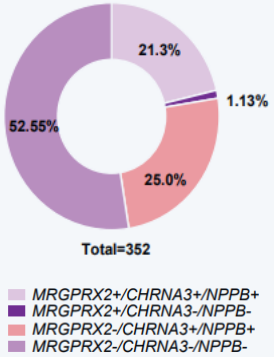
MRGPRX2 is Expressed in Human Sensory Neurons: Greater in TG

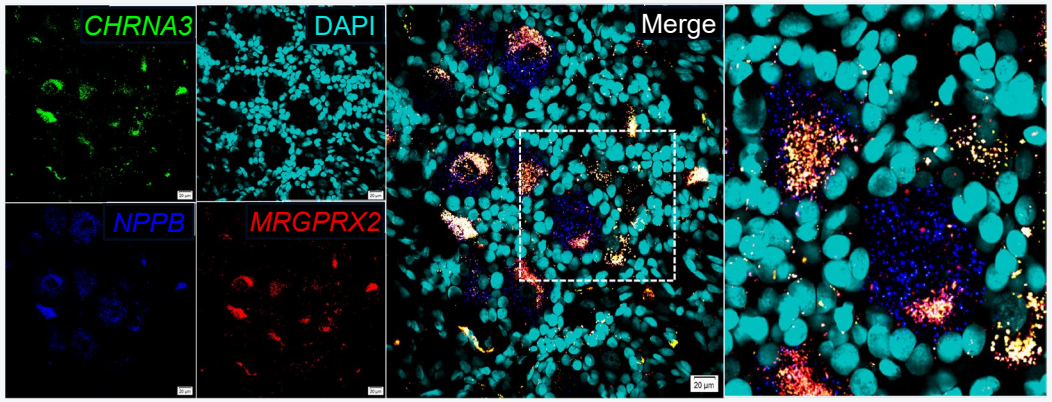
Targeting MRGPRX2 in Neurons Could Provide Greater Benefit Over Targeting Only in Mast Cells

MRGPRX2 is Expressed by 25% of DRG Neurons

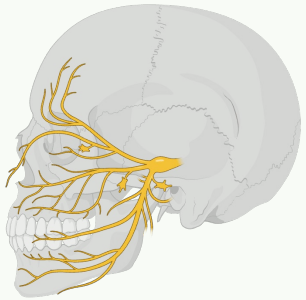


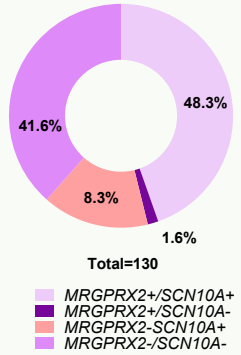
Dorsal root ganglia:
sensory neurons
nuclei

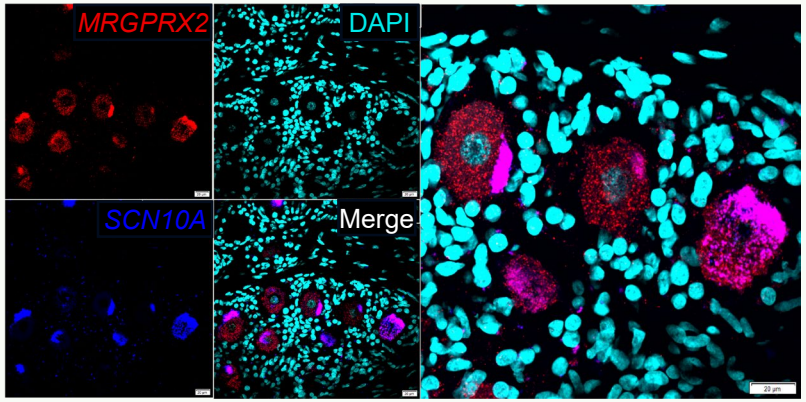




MRGPRX2 is Expressed by >50% of TG Neurons







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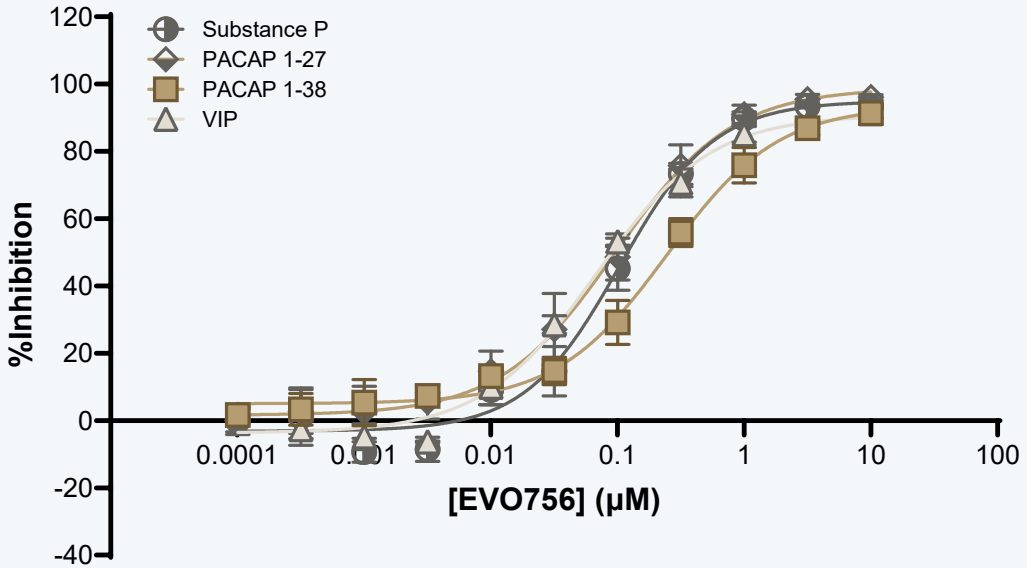
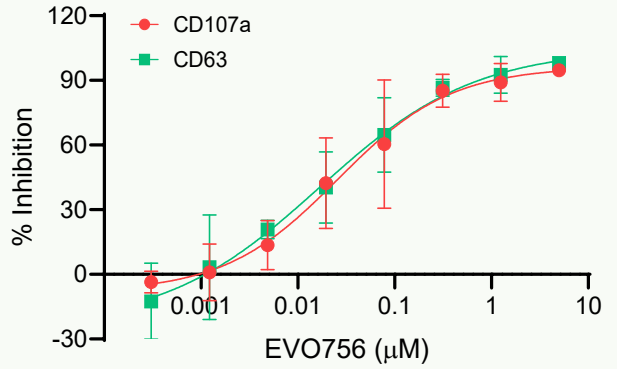
EVO756: Small Molecule Potently (low nM) Inhibits PACAP, Substance P, and VIP-Induced MRGPRX2 Activation *in vitro*

EVO756 Inhibits Migraine Relevant Endogenous Ligands in X2-CHO Cells



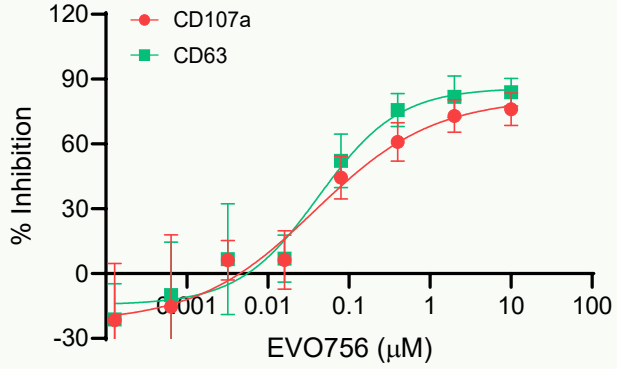
EVO756 Inhibits PACAP and SP-Induced Primary Human Mast Cell Activation *in vitro*



PACAP 1-27 Concentration: 5 µM (~EC80)

CD107a IC50: 25.8 nM

CD63 IC50: 16.7 nM



SP Concentration: 30 µM (>EC80)

CD107a IC50: 38.3 nM

CD63 IC50: 42.2 nM

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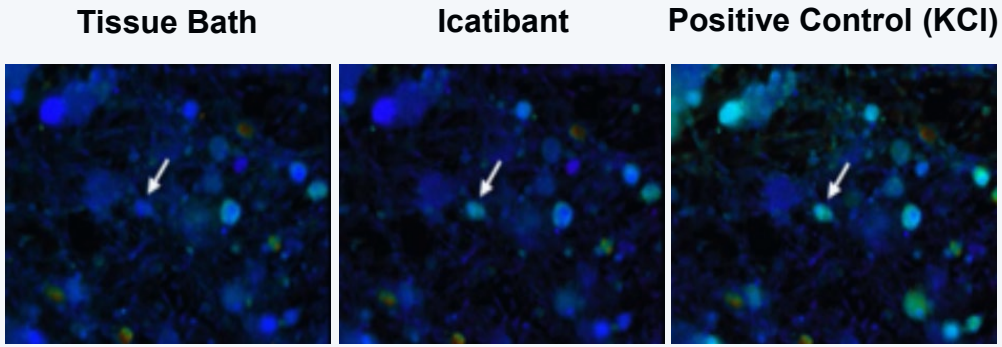
EVO756 Prevents Human DRG Sensory Neurons Activation

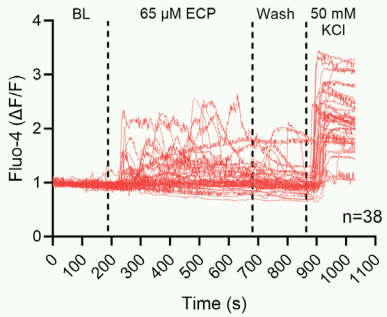
Targeting MRGPRX2 in Neurons Could Lead to Reduction in Neurogenic Inflammation and Itch/Pain Relief

Functional Calcium Mobilization System for Neuronal Activation

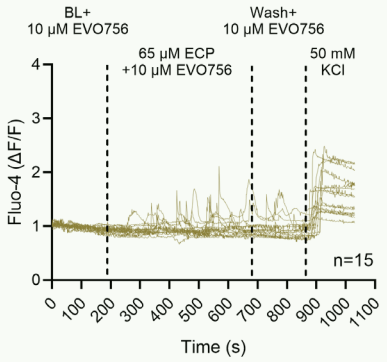


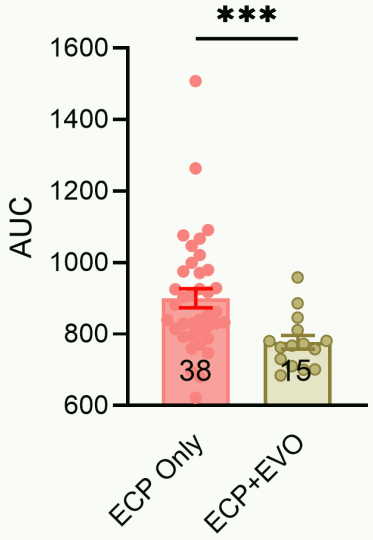
Calcium Imaging Reveals that MRGPRX2 in Neurons is Active, and Its Activity Can be Blocked by EVO756

Neuronal Activation in Response to ECP



Neuronal Inhibition by EVO756





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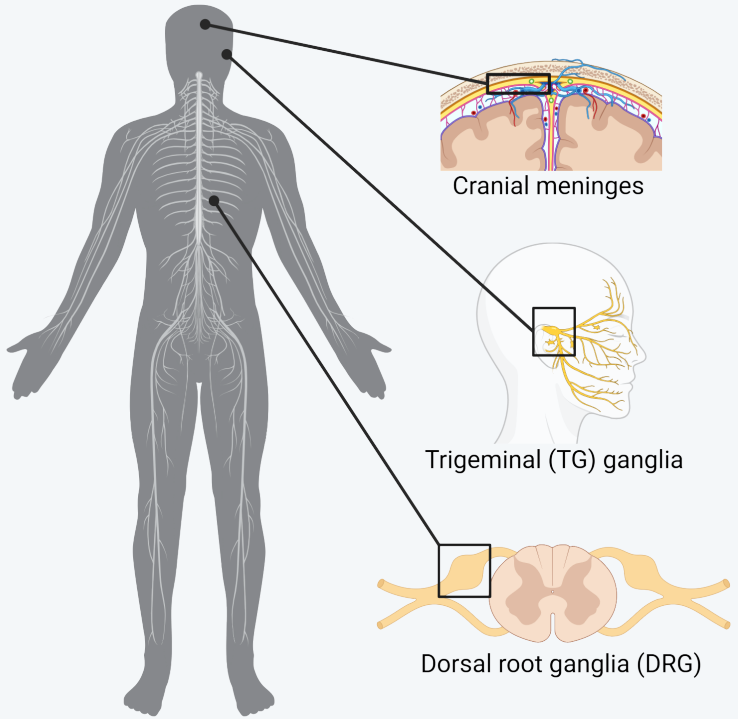
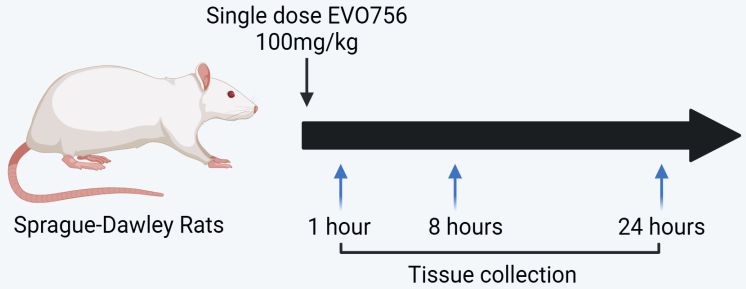
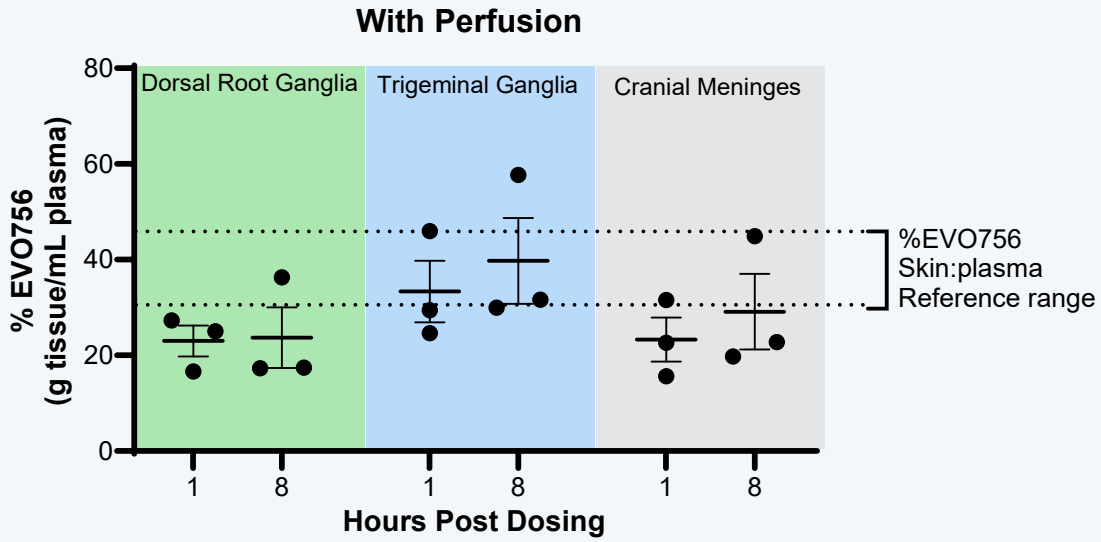
EVO756 is Distributed in Migraine-Relevant Tissues

Sensory Neurons and Mast Cells are Present in Tissues Critical for Migraine Pathophysiology





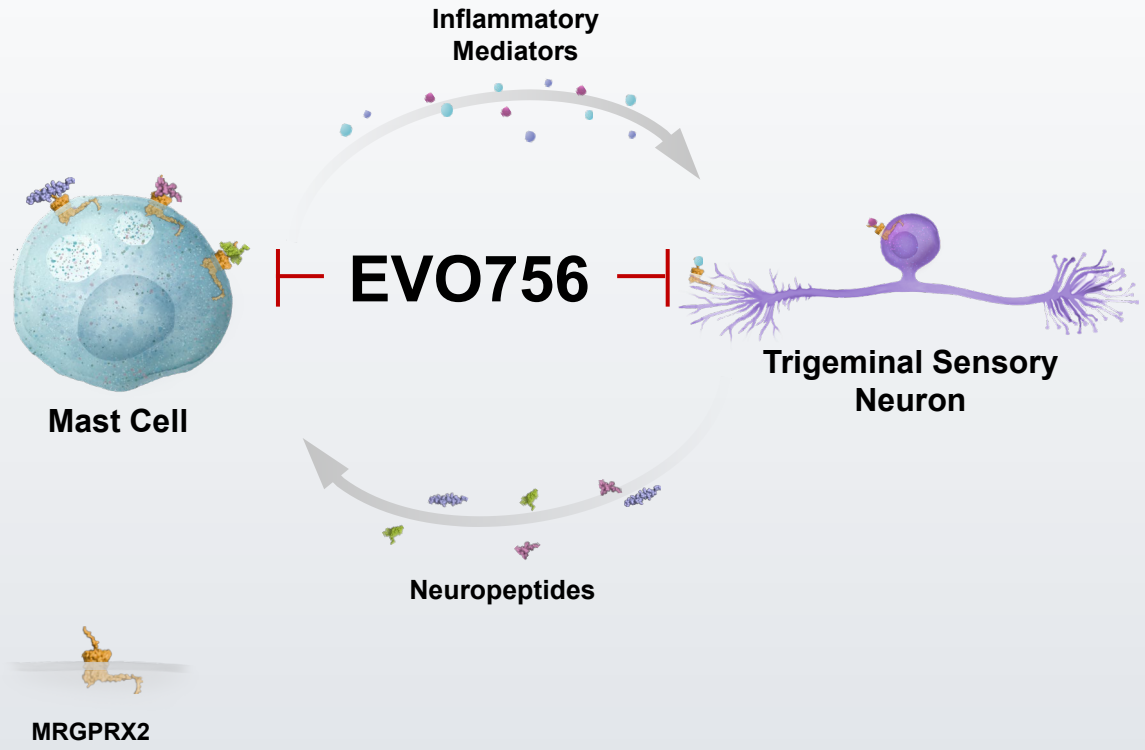


Skin: Plasma reference range used is from tissue distribution imaging study of radiolabeled 10mg/kg EVO756 in rats

MRGPRX2 Inhibition: a Promising New Direction in Migraine Therapy

- **Multiple migraine triggers converge on MRGPRX2** — PACAP, VIP, and Substance P are all MRGPRX2 agonists
- **MRGPRX2 positioned at the neuroimmune interface** — expressed on meningeal mast cells and >50% of trigeminal neurons
- **Preclinical support for a causal role in migraine** — PACAP-induced headache behavior attenuated in MrgprB2 knockout mice
- **EVO756 delivers differentiated dual inhibition** — blocks both mast cell degranulation and trigeminal neuron activation, with delivery into migraine-relevant tissues
- **EVO756 is advancing toward Phase 2b** as a differentiated non-CGRP migraine therapeutic

EVO756 Interrupts the Migraine Neuroimmune Circuit



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