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AACR Annual Meeting 2026 · Poster No. 5216

# NOVEL TRANSDERMAL CURCUMIN (VAS-101) ATTENUATES CISPLATIN-INDUCED NEUROPATHY

## *In a Mouse Model of Breast Cancer*

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**Topical curcumin (VAS 101)**
*Bioavailable transdermal formulation*

**Cancer + chemo pain model**
*C3TAg breast cancer · cisplatin chemotherapy*

**Preserved antitumor efficacy**
*While reducing hyperalgesia & neuro-inflammation*

# BACKGROUND · UNMET CLINICAL NEED IN CHEMOTHERAPY-INDUCED NEUROPATHY

## WHY THIS MATTERS

**Cisplatin-induced peripheral neuropathy** remains a major dose-limiting toxicity and an unmet clinical challenge in cancer treatment.[1]

Cisplatin disrupts mitochondrial homeostasis, raises reactive oxygen species, and drives neuronal injury that fuels pain hypersensitivity.[2]

**Curcumin** is anti-oxidant and neuroprotective — but oral/systemic delivery suffers from poor bioavailability after oral or systemic administration.[3]


**1. Goel Y et al.** Neuronal p38 MAPK signaling contributes to cisplatin-induced peripheral neuropathy. *Antioxidants* 2025;14(4):445.

**2. Podratz JL et al.** Cisplatin induced mitochondrial DNA damage in dorsal root ganglion neurons. *Neurobiol Dis* 2011;41:661–668.

**3. Bučević Popović V et al.** Bioavailability of Oral Curcumin in Systematic Reviews. *Pharmaceuticals* 2024;17:164.


## THE APPROACH · TRANSDERMAL CURCUMIN (VAS-101)

### Topical formulation

VAS-101 transdermal curcumin (TDC) crosses skin and reaches the blood and CNS.[4]

### Bypasses bioavailability cap

Avoids the absorption ceiling that limits oral curcumin.

### Translational model

C3TAg transgenic mice recapitulate the evolutionary spectrum of human breast cancer continuum, vs FVB/N control mice.[5]

### Constitutive hyperalgesia

C3TAg mice have palpable tumors and show pain — ideal to test cancer + chemo pain together while preserving antitumor efficacy.


**4. Goel Y et al.** Targeting sickle cell pathobiology and pain with novel transdermal curcumin. *PNAS Nexus* 2025;4(2):pgaf053.

**5. Maroulakou IG et al.** Prostate and mammary adenocarcinoma in transgenic mice carrying a rat C3(1) SV40 LT-Ag fusion gene. *PNAS* 1994;91:11236–11240.

# OBJECTIVE · THREE SPECIFIC AIMS

***Can transdermal curcumin (VAS-101) attenuate cancer- and cisplatin-induced pain while preserving cisplatin's antitumor activity?***

## 01 Reduce Pain

Test whether VAS-101 reduces cancer- and cisplatin-induced hyperalgesia in C3TAg and FVB/N mice — without blunting cisplatin's antitumor effect.

## 02 Block Stress Signaling

Determine VAS-101's effect on phospho-p38 MAPK activation in DRG neurons — a key driver of neuropathic pain.

## 03 Protect Neurons

Examine whether  prevents cisplatin-induced oxidative stress, mitochondrial depolarization, and calcium dysregulation in neuronal cells.

# METHODS · TREATMENT REGIMEN & READOUTS

## MODEL & GROUPS

**Animals** Female C3TAg (SV40 T-antigen, rat C3(1) promoter) + age-matched FVB/N controls.[5] ~4 mo at randomization. Blinded, IACUC-approved (#1618941).

**Disease timeline (C3TAg)** Atypical ductal lesions ~8 wk → intraepithelial neoplasia ~12 wk → invasive carcinoma ~16 wk.[4]

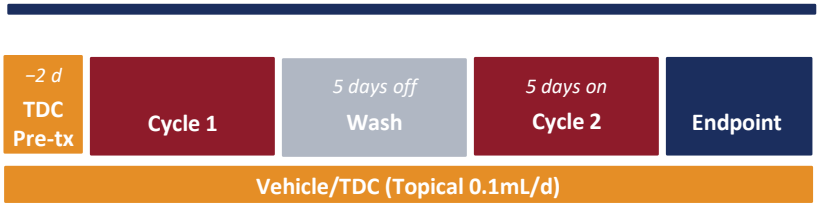
**I — Vehicle**
*Saline i.p. + VAS101 gel (0.1 mL/d)*

**II — Cisplatin**
*2.3 mg/kg/d i.p. (2 cycles, 5d on/ 5d off*

**III — TDC**
*VAS 101 gel 0.1 mL/d topical*

**IV — TDC + Cisplatin**
*VAS 101 gel 0.1 mL/d topical*
*Cisplatin 2.3 mg/kg/d i.p.*

## TIMELINE · 21-DAY STUDY

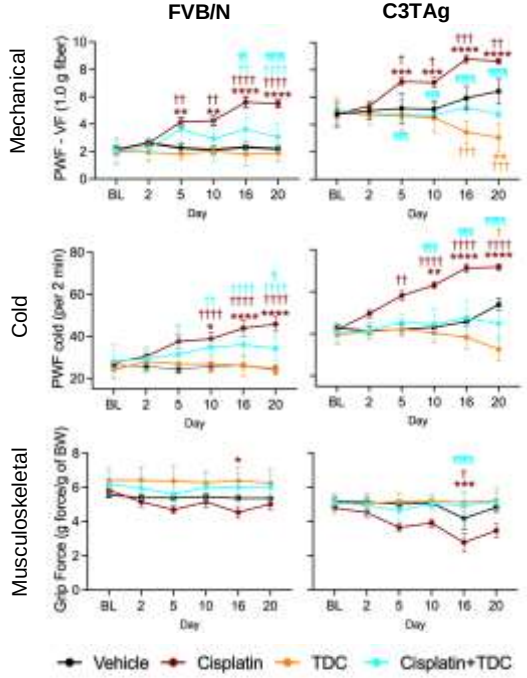



## READOUTS

- Hyperalgesia: von Frey (mechanical), cold plate, grip strength
- Tumor weight & number
- Spinal IL-17A (ELISA)
- P38 MAPK activation in neurons of DRG tissue
- Injury to DRG axon and hippocampal dendrites

# RESULT 1 · VAS-101 RELIEVES TUMOR & CISPLATIN-INDUCED HYPERALGESIA

*Figure 1 · Mechanical, cold plate, musculoskeletal indices of hyperalgesia across 21 days*




Mean ± SEM. Analysis: two-way ANOVA with Tukey's post-hoc test.

Significance: † vehicle vs cisplatin, †P < 0.05; ††P < 0.01; †††P < 0.001; ††††P < 0.0001. †vehicle vs. TDC, †P < 0.05; ††P < 0.01; †††P < 0.001. †vehicle vs. cisplatin + TDC, †P < 0.05; ††P < 0.01; †††P < 0.001, ††††P < 0.0001. ¶cisplatin vs. cisplatin + TDC, ¶P < 0.05; ¶¶P < 0.01; ¶¶¶P < 0.001; ¶¶¶¶P < 0.0001. *BL vs. cisplatin at different time points *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. °BL vs. TDC at different time points°P < 0.05; °° P < 0.01; °°° P < 0.001; °°°° P < 0.0001. **Abbreviations:** BL, baseline; BW, body weight; PWF, paw withdrawal frequency; TDC, transdermal curcumin; VF, von Frey.

## KEY FINDINGS

**VAS-101 ameliorates cisplatin-induced hyperalgesia in FVB/N control and C3TAg mice**

### Mechanical hyperalgesia ↓

VAS-101 reduced cisplatin-induced paw withdrawal frequency (von Frey) in C3TAg and FVB/N mice.

### Cold hyperalgesia ↓

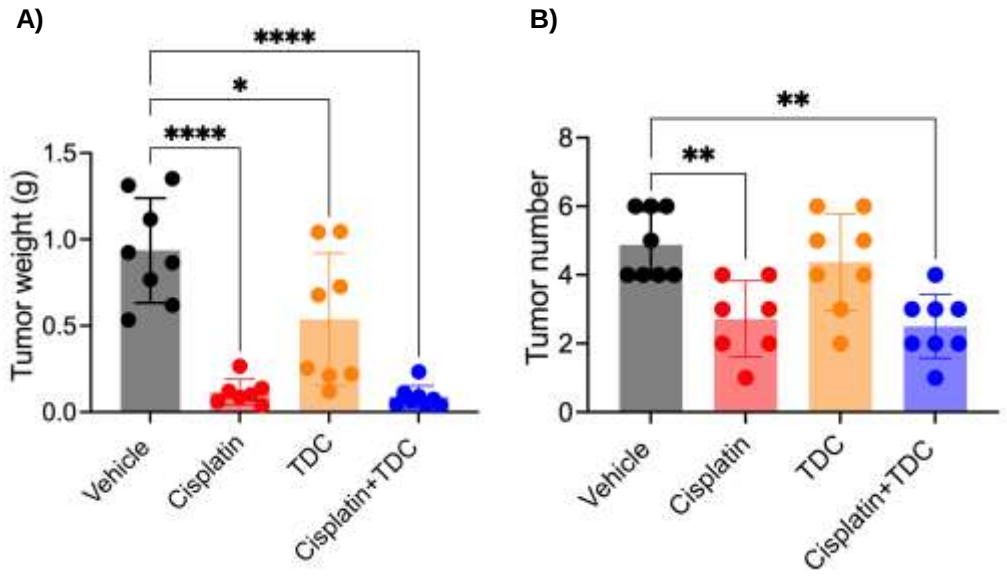
VAS-101 blunted cold-evoked withdrawal responses through Day 21.

### Musculoskeletal hyperalgesia ↓

Grip force was preserved with VAS-101 vs. cisplatin alone.

# RESULT 2 · VAS-101 PRESERVES ANTITUMOR EFFICACY

*Figure 2 · Tumor weight (A) and tumor number (B), Day 21*




Mean ± SEM. Analysis: one-way ANOVA with Tukey's post-hoc test. Significance: *P < 0.05, **P < 0.01, ****P < 0.0001. **Abbreviations:** BW, body weight; TDC, transdermal curcumin.

## KEY FINDINGS

**Antitumor efficacy PRESERVED**

**A) VAS-101 AND CISPLATIN SEPARATELY, AND AS COTHERAPY, REDUCED TUMOR WEIGHT**

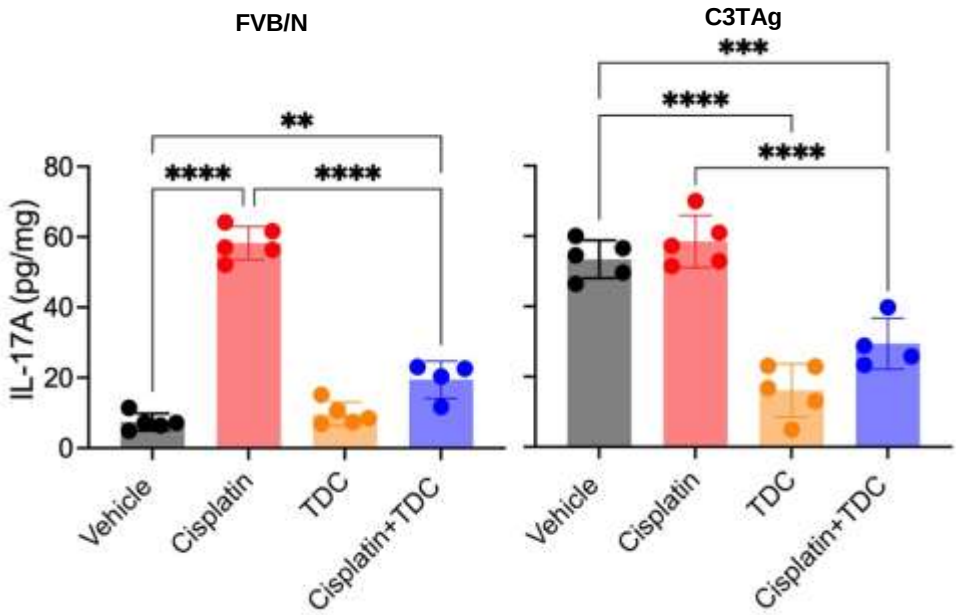
__ vs. vehicle in C3TAg mice.

**B) Cisplatin reduced tumor number**

— and VAS-101 co-treatment did not impair this antitumor effect.

# RESULT 3 · VAS-101 LOWERS SPINAL IL-17A

*Figure 3 · Spinal cord IL-17A (ELISA), FVB/N (A) and C3TAg (B)*




Mean ± SEM. Analysis: one-way ANOVA with Tukey's post-hoc test. Significance: **P<0.01; ***P<0.001; ****P < 0.0001. **Abbreviations:** BW, body weight; ELISA, enzyme linked immunosorbent assay; IL-17A, interleukin-17A; TDC, transdermal curcumin.

## INTERPRETATION

### FVB/N (control mice)

Cisplatin significantly raised spinal IL-17A; VAS-101 normalized it.

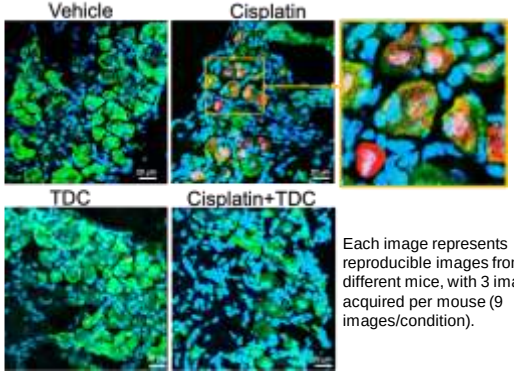
### C3TAg (tumor-bearing)

Cisplatin did not further increase IL-17A, but VAS-101 reduced spinal IL-17A with and without cisplatin.

***VAS-101 suppresses an inflammatory cytokine pathway centrally implicated in chemotherapy-induced pain.***

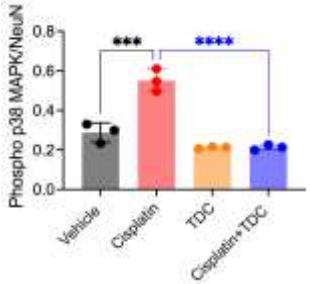
# RESULT 4 · VAS-101 BLOCKS p38 MAPK ACTIVATION IN DRG NEURONS

*Figure 4A · Phospho-p38 MAPK / NeuN colocalization*




Each image represents reproducible images from three different mice, with 3 images acquired per mouse (9 images/condition).

*Figure 4B · Cisplatin-induced phospho-p38MAPK nuclear translocation (Pearson's)*




Mean ± SEM. Analysis: one-way ANOVA with Tukey's post-hoc. Significance: *vehicle vs. cisplatin, ***P<0.001. *cisplatin vs. cisplatin + TDC, ****P<0.0001. **Abbreviations:** DAPI, 4',6-diamidino-2-phenylindole; LSCM, laser scanning confocal microscope; MAPK, mitogen activated protein kinase; TDC, transdermal curcumin

## MECHANISTIC TAKEAWAY

Cisplatin drives nuclear translocation of phospho-p38 MAPK in DRG neurons — a stress signal linked to peripheral neuropathy.

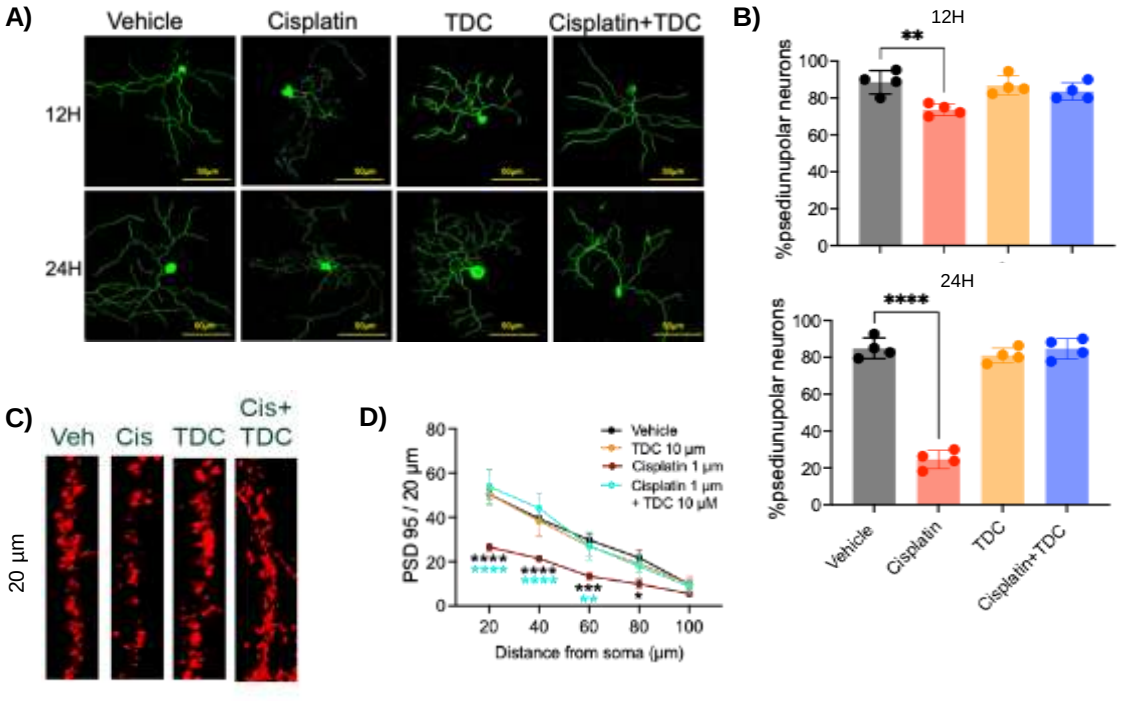
**VAS-101 inhibits this activation, returning phospho-p38/NeuN colocalization to vehicle levels.**

**↑ ~2×**
**Cisplatin vs. vehicle**
****P < 0.001*

**↓ to baseline**
**Cisplatin + VAS-101 vs. cisplatin**
*****P < 0.0001*

*p38 MAPK signaling is a known driver of neuronal injury (Goel et al., Antioxidants 2025).*

# RESULT 5 • VAS-101 PRESERVES NEURONAL STRUCTURE




Each image represents reproducible images from three different mice, with 3 images acquired per mouse (9 images/condition). Data: Mean ± SEM. Analysis: one-way (B) or two-way (D) ANOVA and Tukey's post-hoc test. Significance at matching timepoints: *vehicle vs cisplatin *P<0.05; **P<0.05; ***P<0.001; ****P<0.0001; *cisplatin vs cisplatin + TDC, *P<0.05, **P<0.05, ****P<0.0001. **Abbreviations**: Cis, cisplatin; DRG, dorsal root ganglia; PSD 95, pos-synaptic density protein 95; TDC, transdermal curcumin.

## STRUCTURAL PROTECTION

### DRG neuron-axons preserved

Cisplatin reduced pseudounipolar DRG neurons and produced fragmented & dying-back neurites at 12 H and 24 H. VAS-101 restored neuron morphology and number toward vehicle levels (Fig. 5A–B).

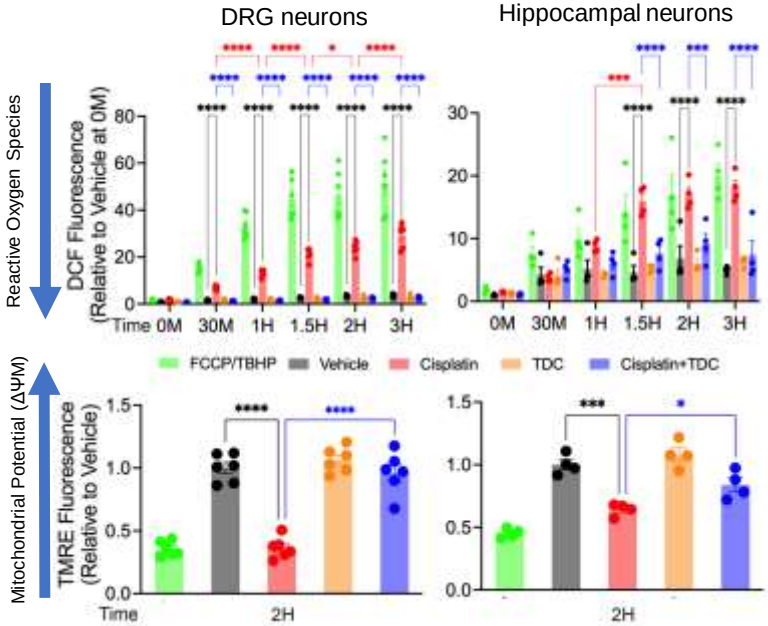
### Hippocampal dendritic spines protected

Cisplatin significantly reduced PSD-95 puncta in primary hippocampal neurons. TDC co-treatment restored spine density (Fig. 5C–D), consistent with preservation of synaptic architecture.

Peripheral + central neuronal architecture
**PROTECTED BY VAS-101**

# RESULT 6 · VAS-101 PROTECTS AGAINST OXIDATIVE & MITOCHONDRIAL INJURY

*Figure 6 · ROS (DCF) and ΔΨM (TMRE) in DRG and hippocampal neurons*




Mean ± SEM. Analysis: A) one-way or B) two-way ANOVA with Tukey's post-hoc test. Significance: *vehicle vs cisplatin, ***P<0.001; ****P<0.0001. *cisplatin vs cisplatin + TDC, *P<0.05; ***P<0.001; ****P<0.0001. *cisplatin vs consecutive cisplatin timepoints, *P<0.05; ***P<0.001; ****P<0.0001. **Abbreviations:** DCF, dichlorofluorescein; DRG, dorsal root ganglia; FCCP, Carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone; ROS, reactive oxygen species; TDC, transdermal curcumin; THBP, tert-butyl hydroperoxide; TMRE, tetramethyl rhodamine ethyl ester.

## MECHANISM

**ROS suppressed**
Cisplatin's burst in reactive oxygen species (DCF) was reduced by VAS-101 across the 3 h time-course.

**ΔΨM restored**
Cisplatin reduced mitochondrial membrane potential; VAS-101 brought TMRE signal back towards baseline.

**Both DRG & hippocampal**
Effects observed in primary DRG neurons and hippocampal neurons — consistent with peripheral and central protection.

# CONCLUSIONS · VAS-101 IS A VIABLE THERAPY WITH ADDED NEUROPROTECTIVE PROPHYLAXIS IN BREAST CANCER TREATED WITH CISPLATIN

## Pain relief without compromise

VAS-101 alleviates cancer- and chemotherapy-induced hyperalgesia while preserving cisplatin's antitumor efficacy.

## Inflammatory + stress signaling blocked

VAS-101 reduces spinal IL-17A and neuronal phospho-p38 MAPK activation, supporting inhibition of inflammatory and stress signaling pathways.

## Neuronal structure & function protected

VAS-101 protects neuronal structure and function by reducing oxidative stress and improving mitochondrial homeostasis.

## Translational potential

VAS-101 shows the potential to ameliorate cisplatin-induced neuronal injury and attenuate peripheral neuropathy.

## REFERENCES

**1. Goel Y et al.** Neuronal p38 MAPK signaling contributes to cisplatin-induced peripheral neuropathy. *Antioxidants* 2025;14(4):445.

**2. Podratz JL et al.** Cisplatin induced mitochondrial DNA damage in dorsal root ganglion neurons. *Neurobiol Dis* 2011;41:661–668.

**3. Bučević Popović V et al.** Bioavailability of Oral Curcumin in Systematic Reviews. *Pharmaceuticals* 2024;17:164.

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**5. Maroulakou IG et al.** Prostate and mammary adenocarcinoma in transgenic mice carrying a rat C3(1) SV40 LT-Ag fusion gene. *PNAS* 1994;91:11236–11240.

## ACKNOWLEDGEMENTS

Supported by NIH grants R01 HL147562 and R01 CA263806, the Susan Samueli Scholar Award (KG), the A.P. Giannini Foundation Fellowship and K99 AT012494 (DAA), and NCATS/NIH TL1 TR 1415-8 (NL).

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