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IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

NASAL INNOVATION FORUM

Intranasal Nose to Brain ST266 Amnion Cell Derived Secretome Delivery to Non-Human Primates and Clinical Translation

IPAC-RS Nasal Innovation Forum - September 18, 2025

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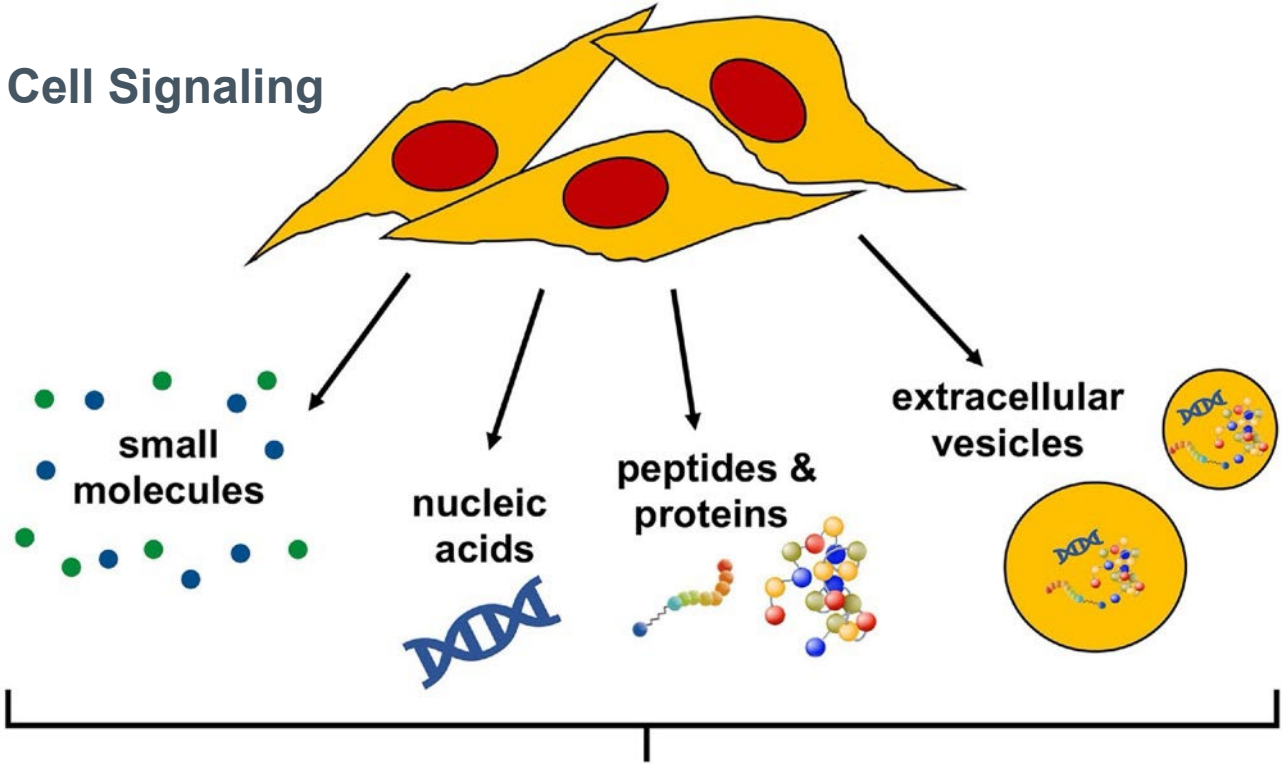
Presentation Overview

- ST266 cell secretome – “Cell therapy without the cell”
- Intranasal Nose-to-Brain Delivery
- In vivo preclinical studies:
  - Observed ST266 biological effects of intranasal delivery
- Clinical Translation
- Case study

ST266 “Cell Therapy without the Cell”: Secreted Cell Products that are Anti-inflammatory, Anti-apoptotic, Promote Cell Survival

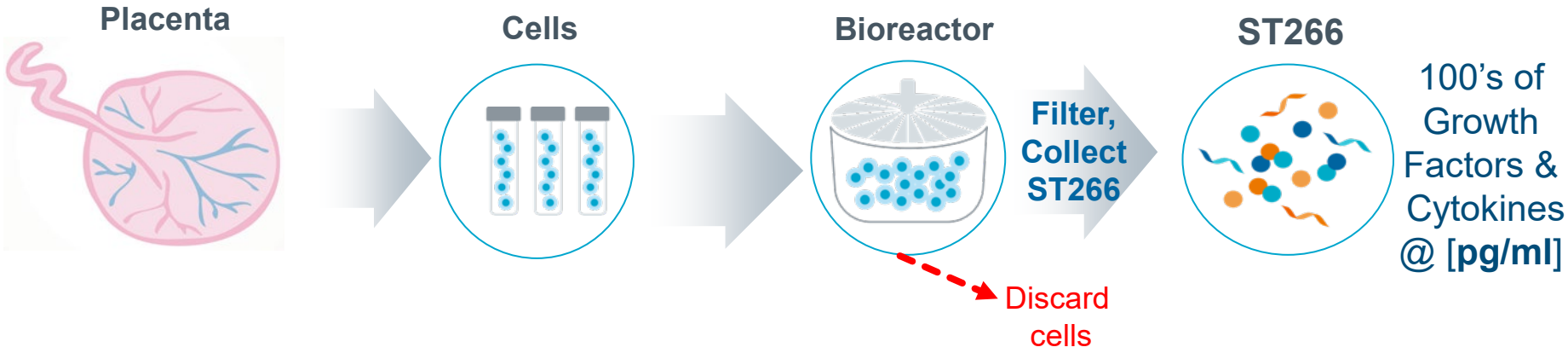


ST266 Amnion-derived Cell Secretome

anti-inflammatory, anti-apoptotic, promote cell survival

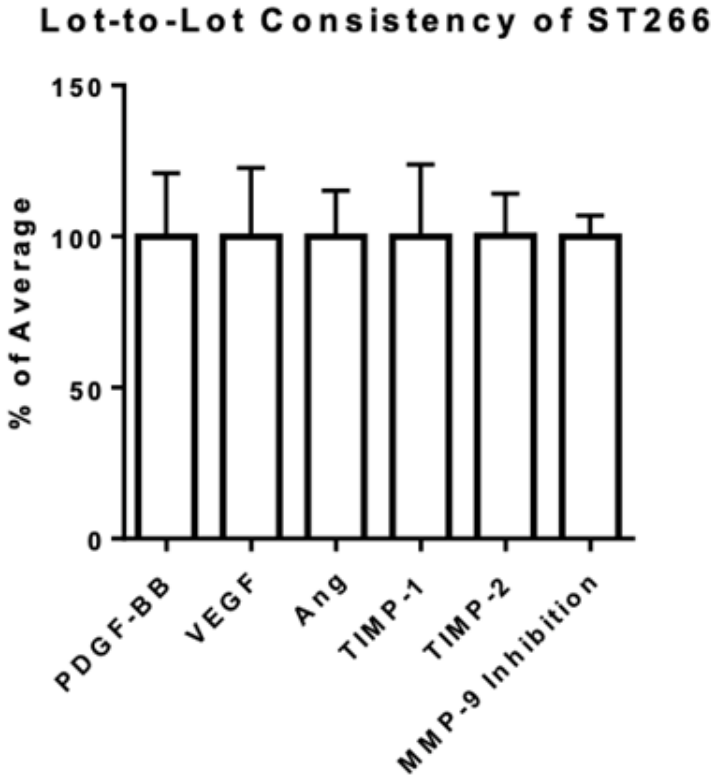
ST266 (formerly ACCS): Anti-Inflammatory, Neuroprotective, Anti-Apoptotic Growth Factors & Cytokines Derived from Proprietary Placenta Amnion Cells

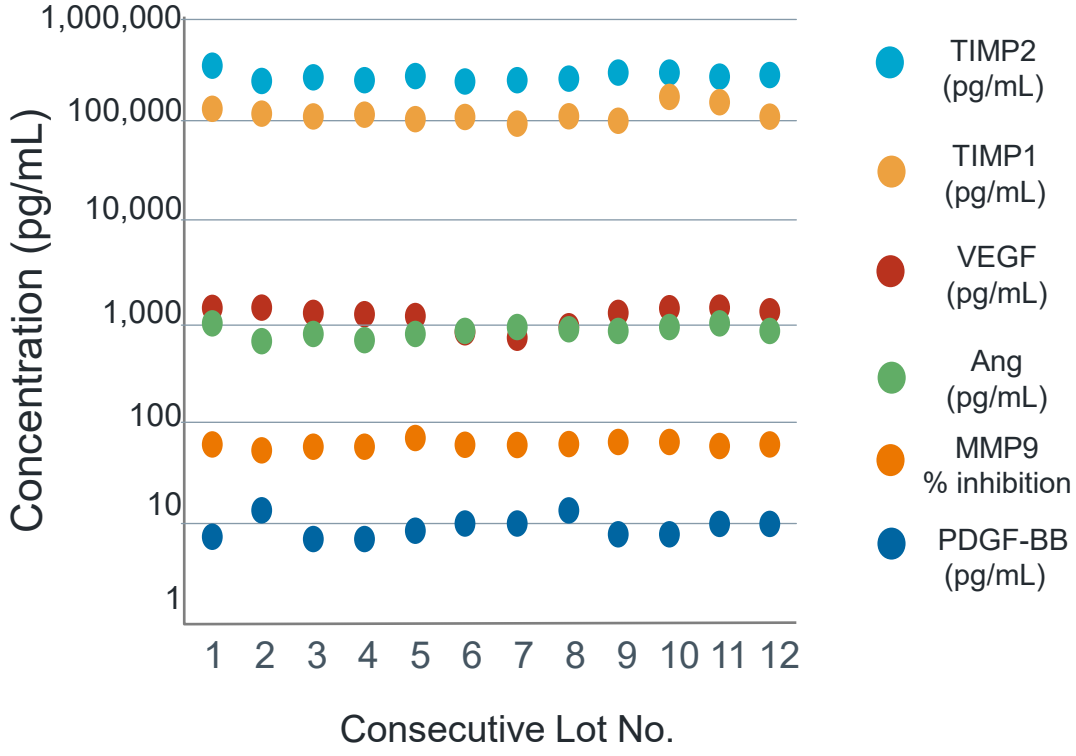
- Noveome collects and grows placenta-derived amnion cells to produce ST266 in a **GMP** manufacturing process.



Steed DL, et al. Amnion-derived cellular cytokine solution (ACCS) : a physiological combination of cytokines for wound healing. Eplasty. 2008 Apr 7;8:e18.

Reproducibility of Manufacture: 12 Consecutive Lots ± 2 Std Dev



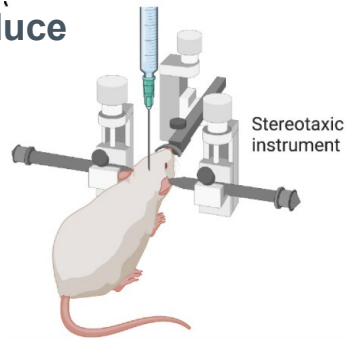


ST266 Properties: Cell Therapy Without Cells

- Neuroprotective
- Anti-inflammatory
- Anti-apoptotic
- Regenerative
- Decreases vascular permeability

ST266 Motor Function Neuroprotection and Anti-inflammatory Activity Following Penetrating Ballistic Brain Injury (PBBI)

1. Induce PBBI

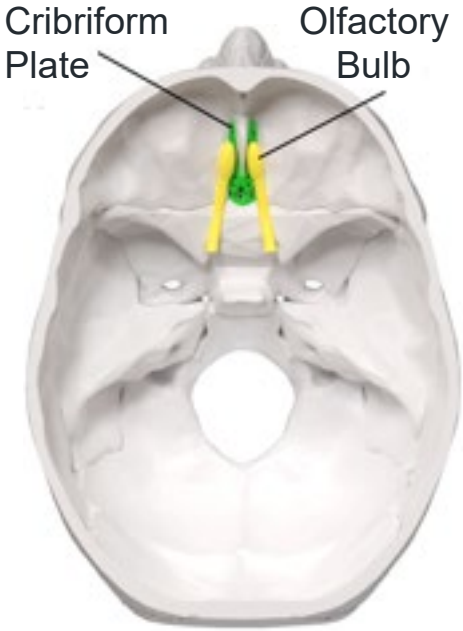


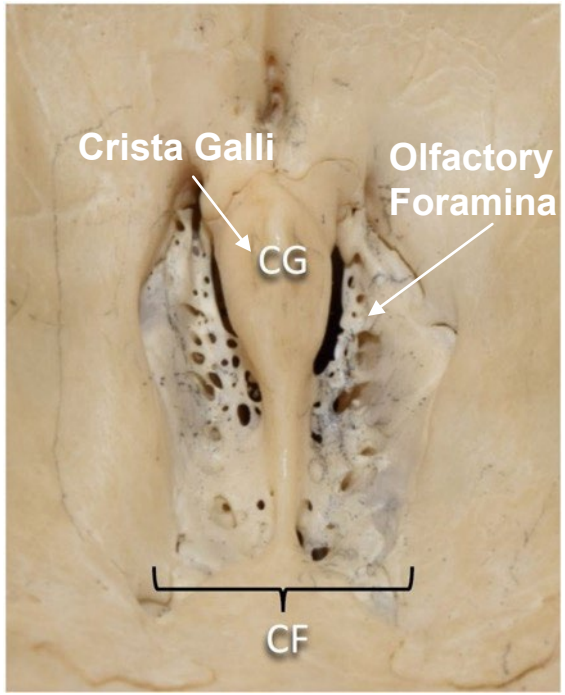
2. Intracerebroventricular ST266 delivery 1 µL/hr with SQ osmotic minipump for 1 to 4 weeks

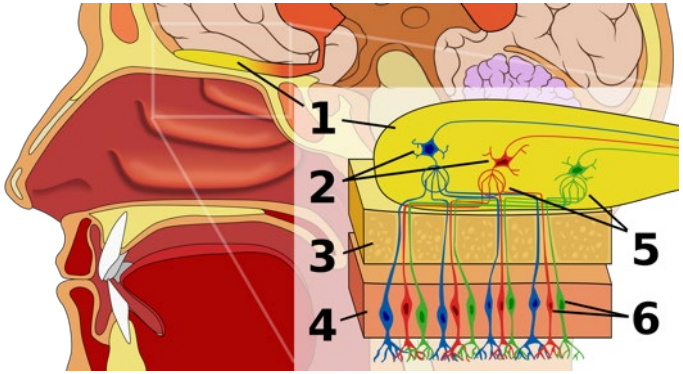
- **↑ Motor function**
- **↓ Neutrophil infiltration-1st inflammatory response**
- **↓ Axon degeneration**
- **↓ Microglial inflammatory reactivity**

Deng Bryant et al J Trauma Acute Care Surg Volume 73, Number 2, Supplement 1 (2012)

1989 – Professor William Frey II, University of Minnesota described intranasal macromolecule brain delivery via the olfactory neural pathway. (WO/1991/007947)[1]



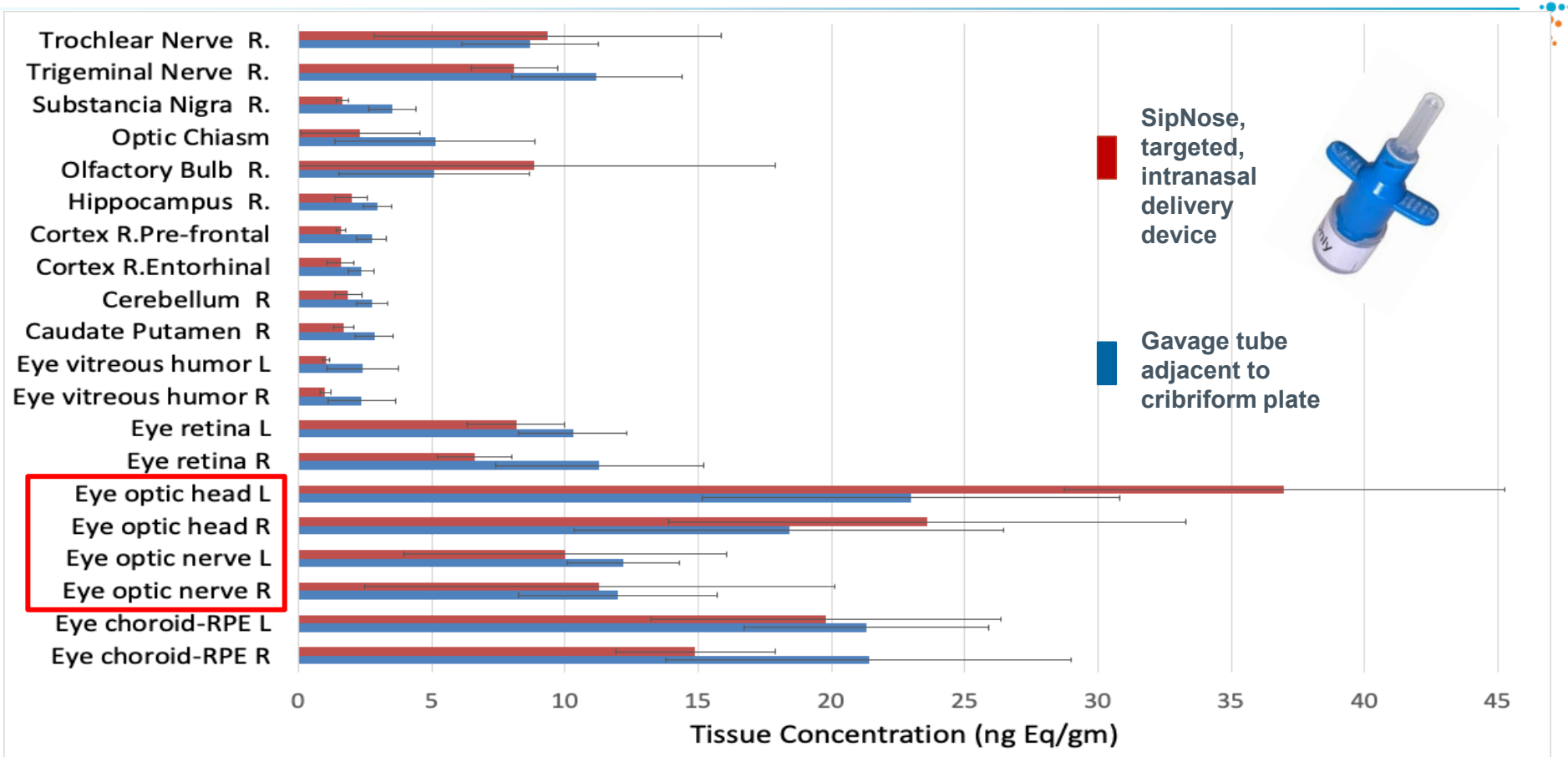




1. Olfactory Bulb
2. Mitral Cells
3. Cribriform Plate
4. Olfactory Epithelium
5. Glomerulus
6. Olfactory Receptor Neurons

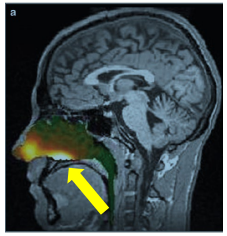
1. US Patent 5624898

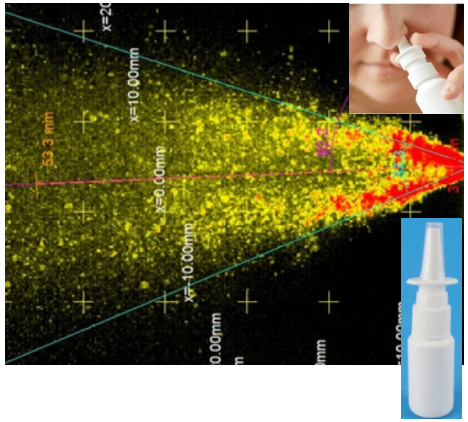
Intranasal [125-I] Labeled ST266 Brain Distribution in Non-Human Primates (N=3)/Group – Highest Concentration: Optic Nerve Head



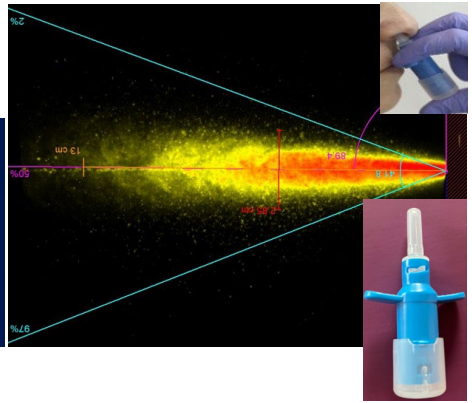
SipNose Device Targets the Cribriform Plate and Olfactory Nerves to Bypass the Blood Brain Barrier

Commercial Nasal Pump (wide angle)





SipNose Delivery (narrow angle)



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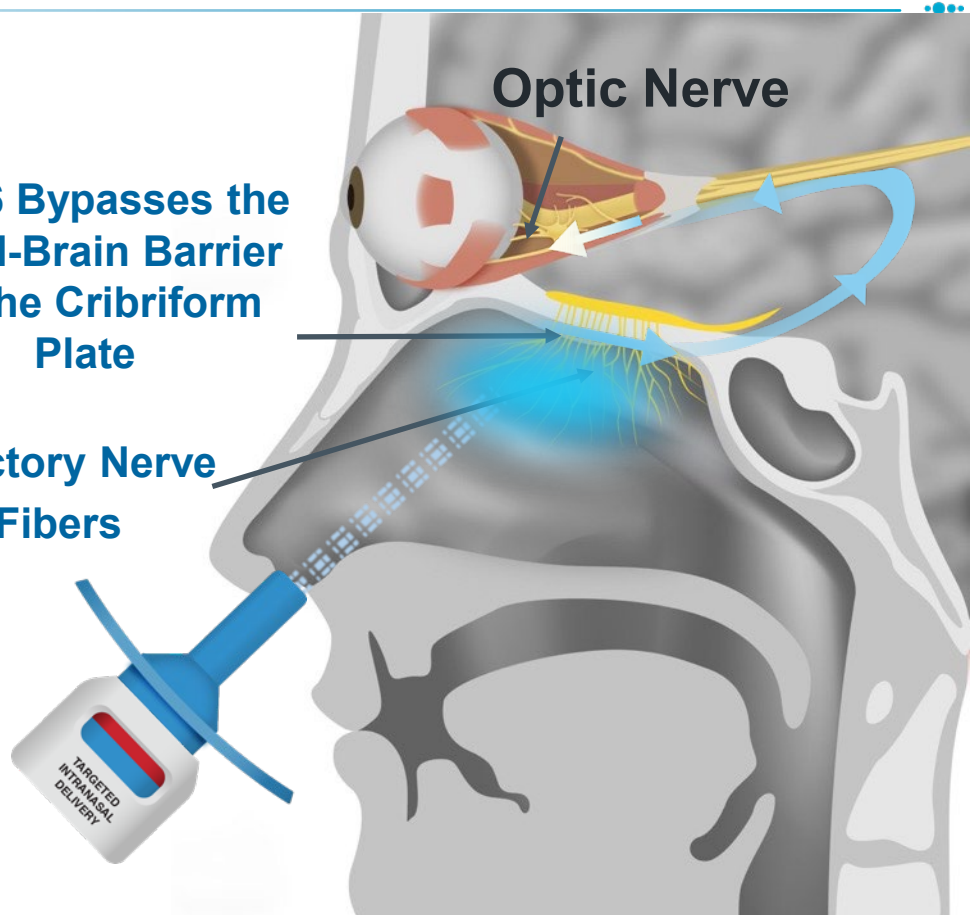
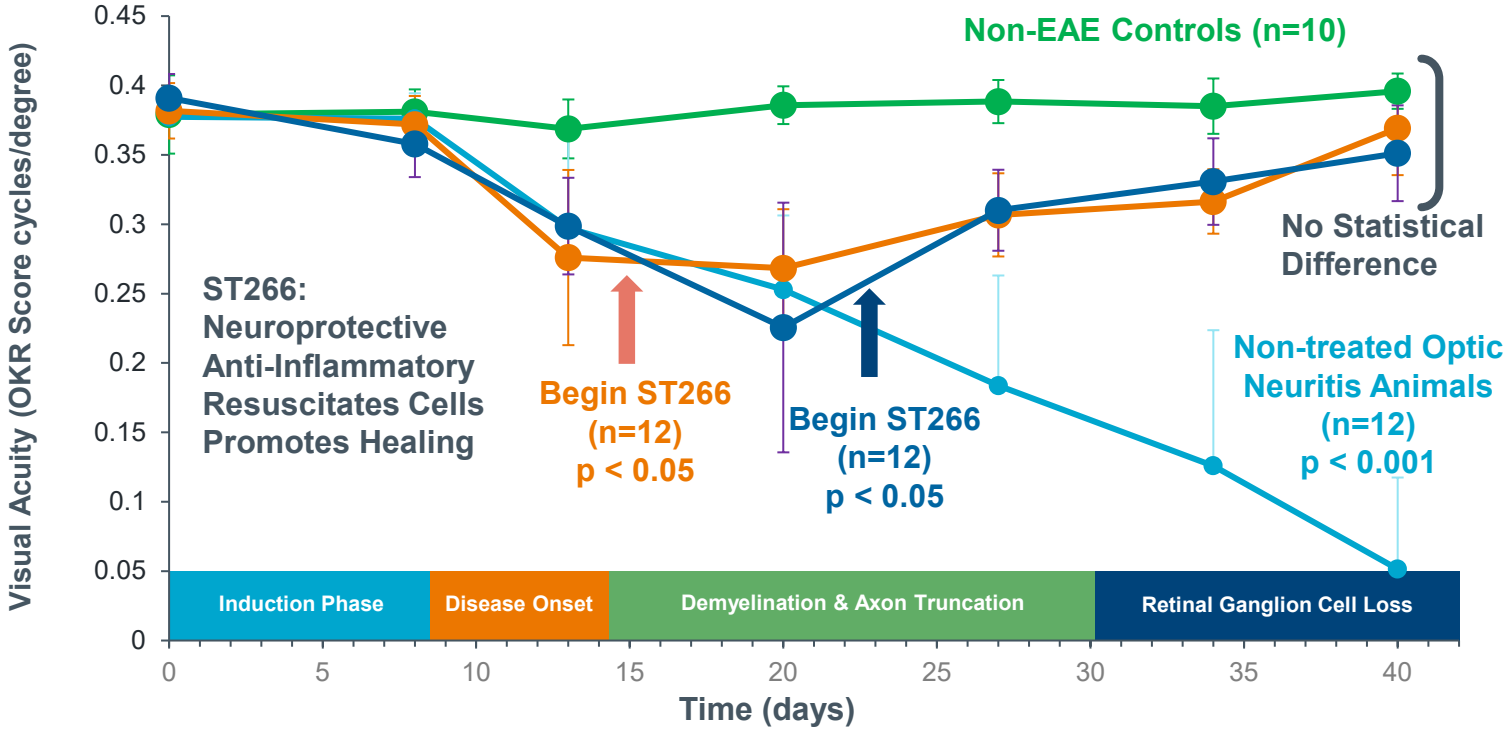
ST266 Bypasses the Blood-Brain Barrier via the Cribriform Plate

Olfactory Nerve Fibers

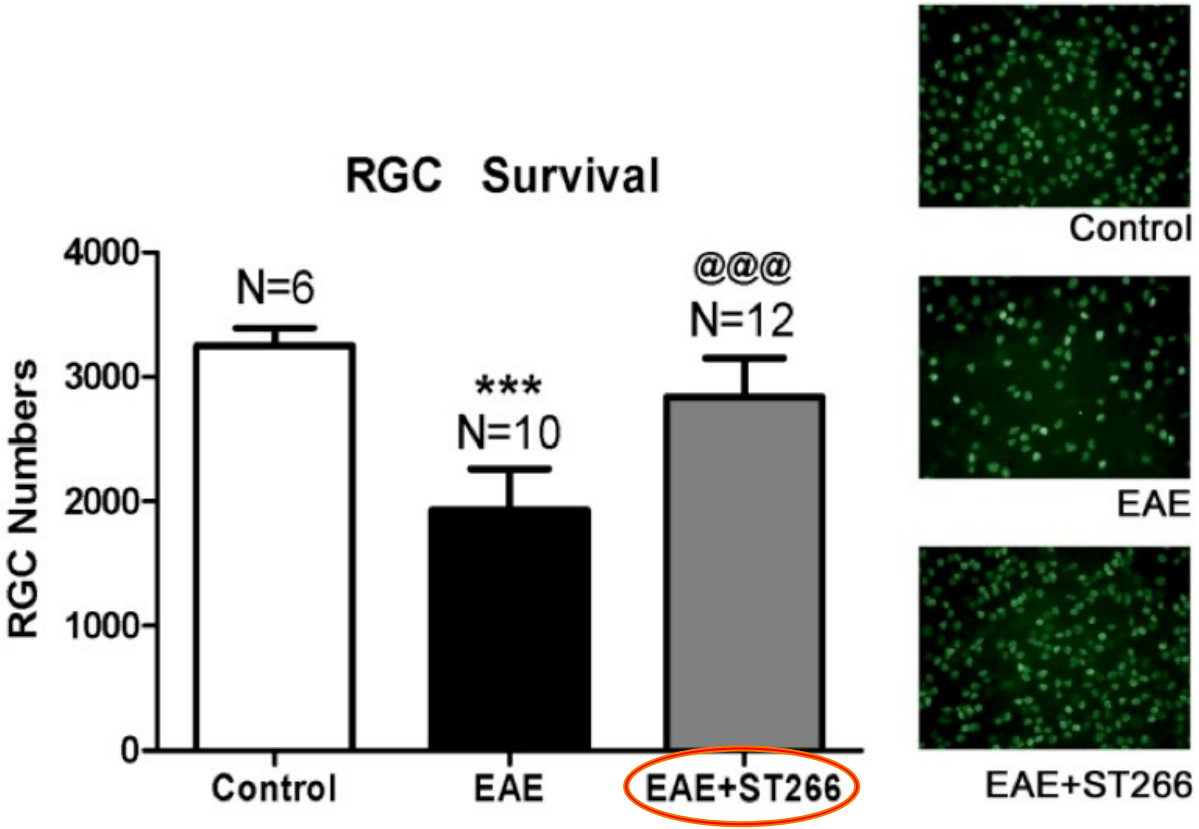


Intranasal ST266 Restores Vision in Experimental Autoimmune Encephalomyelitis (EAE) Mouse Model of Optic Nerve Disease



Khan, R. S. *et al. Nature Scientific Reports* **7,** 41768 (2017).

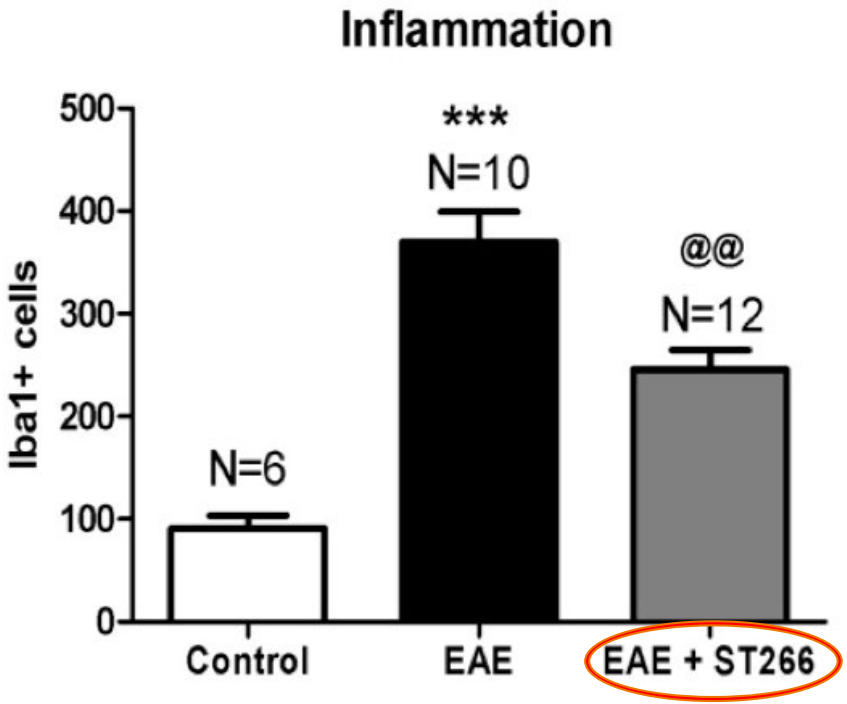
Intranasal ST266 Enhances of Brn3a labeled Retinal Ganglion Cell (RGC) Survival

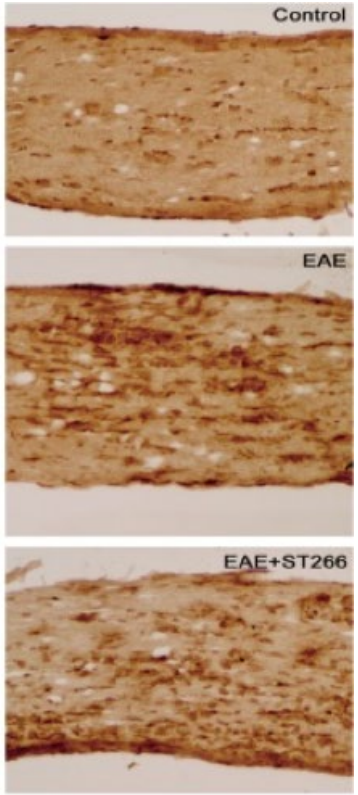


Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

Intranasal ST266 Reduces Inflammation

Reduced Iba1 microglia expression

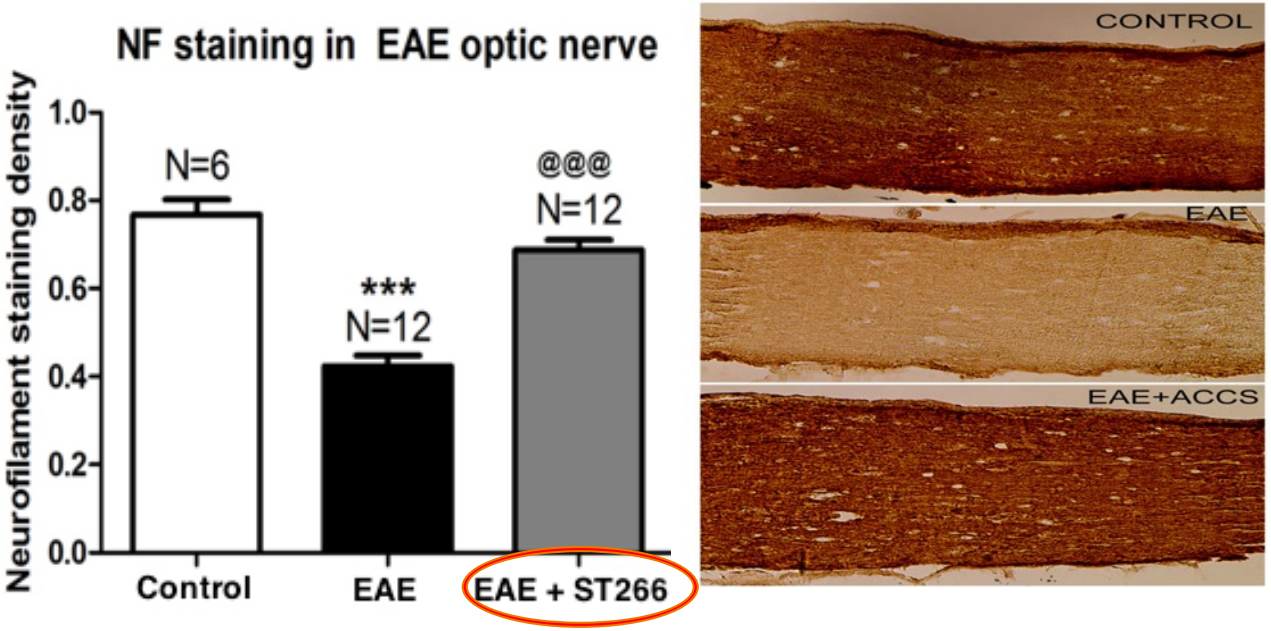




*** p < 0.001 vs control
@@ p < 0.01 vs EAE

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

Early ST266 Treatment Attenuates Axonal Loss

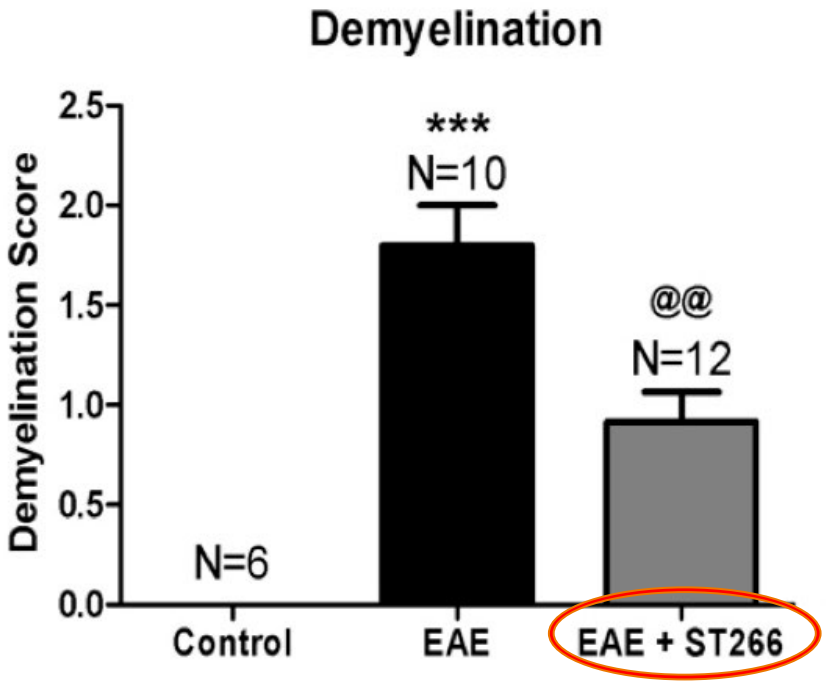


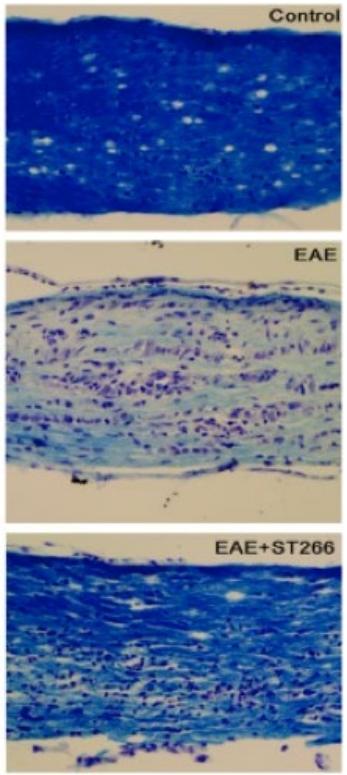
*** p < 0.001 vs control
@@@ p < 0.001 vs EAE

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

Intranasal ST266 Reduces Nerve Demyelination in a Mouse Model of Optic Nerve Disease

*** p < 0.001 vs control
@@ p < 0.01 vs EAE





Luxol Fast Blue Stain

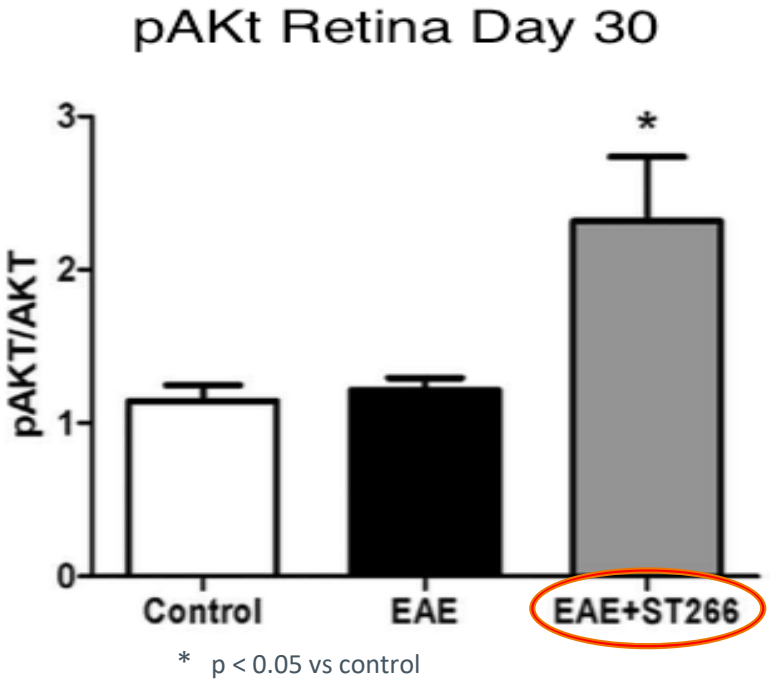
Control

EAE Disease

EAE Disease + ST266

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

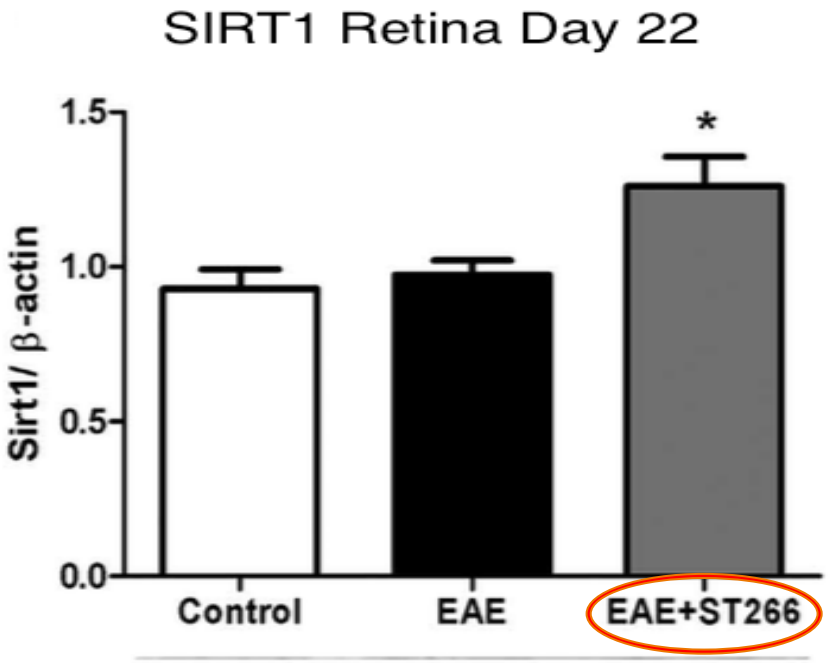
Mechanism: ST266 Upregulates pAKt Cell Survival Pathway



- **Reduces oxidative stress**
- **Inhibits cell death genes**
- **Inhibits apoptosis**
- **Neuronal survival enhanced via PI3 kinase**

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

Mechanism: Intranasal ST266 Upregulated Retinal SIRT1

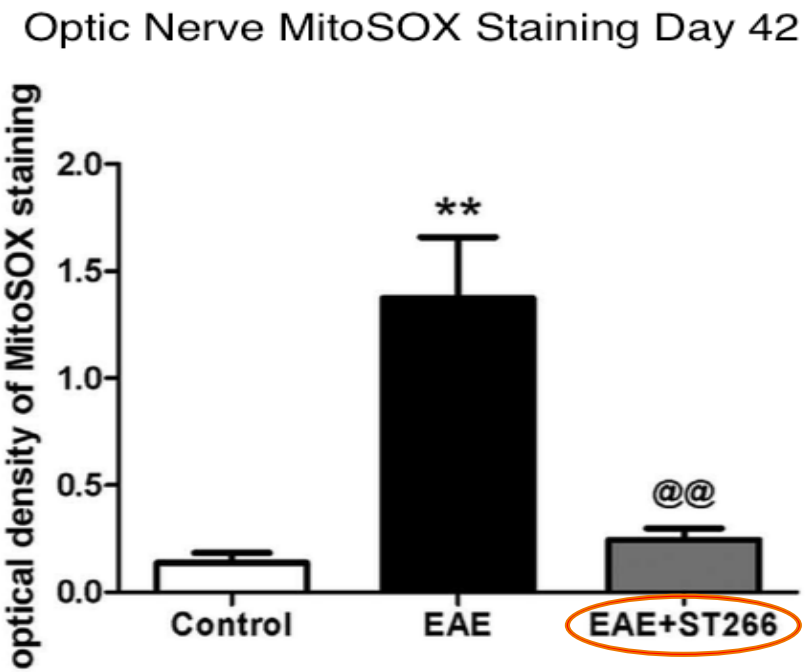


* $p < 0.05$ vs control

- **SIRT1 promotes cell stress responses and cell survival**
- **Anti-inflammatory properties**
- **Activation of SIRT1 prevents RGC loss**

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

Mechanism: Intranasal ST266 Suppresses Reactive Oxygen Species Accumulation in EAE: Present in normal cells at low and stationary levels in



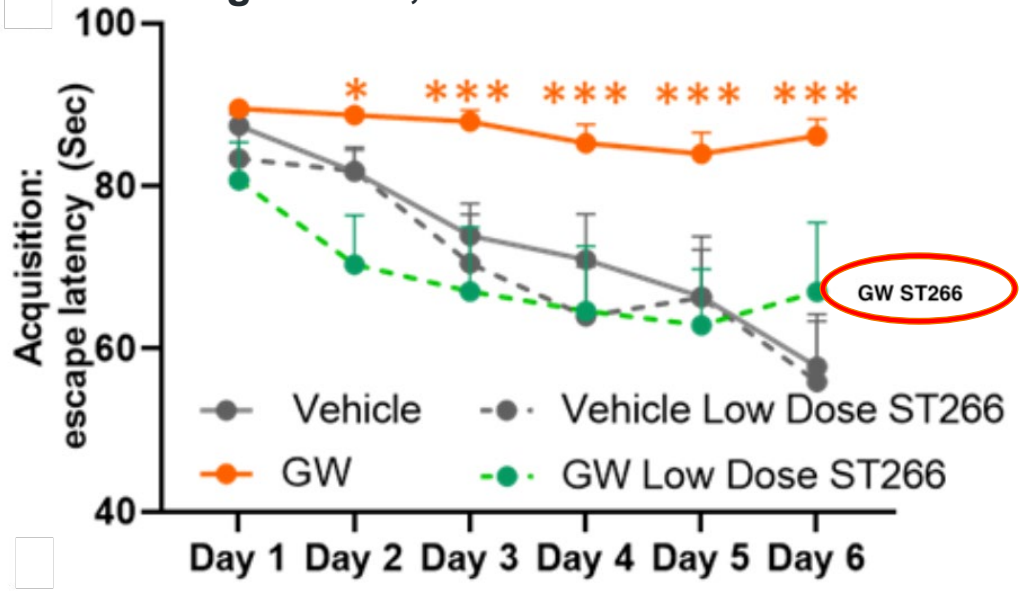
** p < 0.01 vs control
@@ p < 0.01 vs EAE

- **Decreases mitochondrial oxidization by superoxide**
- **Can cause irreversible damage to DNA**

Khan, R. S. *et al. Scientific Reports* **7,** 41768 (2017).

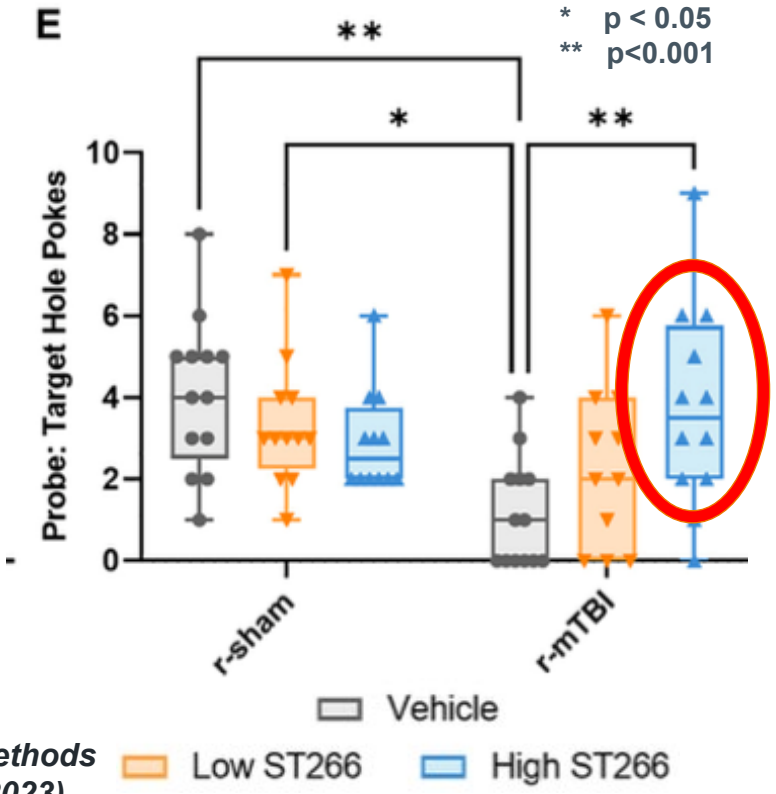
Intranasal ST266 Improved Cognitive Deficits in Barnes Learning Maze: Gulf War Neurochemical and Repeat Mild TBI Mouse Models

Gulf War Model: DEET, Nerve Agent DFP, Cortisone



Browning et al MHSRS 2024 Conference, Orlando FL

Repeat Mild Traumatic Brain Injury



McCartan, Molecular Therapy: Methods &Clinical Development 29:303, (2023)

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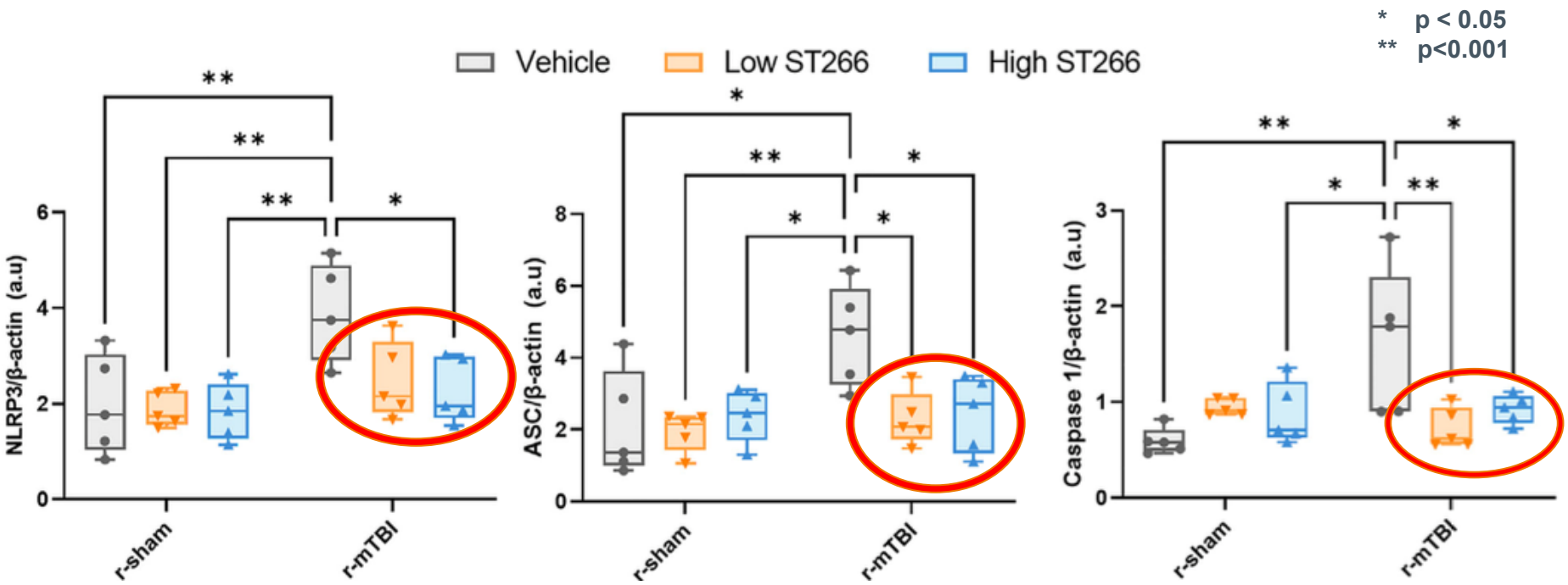
Intranasal ST266 significantly attenuated inflammatory biomarkers NLRP3, ASC, and Caspase-1 following Repeated Mild TBI.



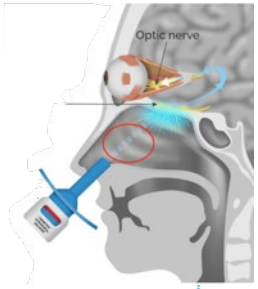
McCartan, Molecular Therapy: Methods &Clinical Development 29:303, (2023)

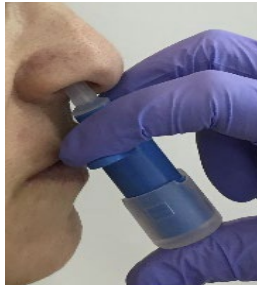
Dose Escalating Clinical Study in Glaucoma Suspects (ClinicalTrials.gov : NCT0390178)

Cohort	Nostril	Administered Dose	Days	Total Daily Dose	N
1	alternating	200 µL	14	200 µL	3
2	bilateral	200 µL	14	400 µL	3
3	bilateral	200 µL	28	400 µL	3

Inclusion criteria (any of):

- ocular hypertension
- optic nerve cupping
- family history of glaucoma





SipNose Ltd
Cribriform Targeted Device

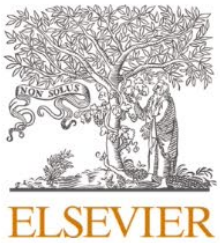
9 Subjects

Exclusion criteria included:

- IOP > 29mmHg either eye
- High risk factors of ocular hypertension
- Evidence of angle closure
- Recent laser or incisional glaucoma surgery
- Subjects requiring glaucoma medication
- History or evidence of sinus or nasal pathology
- Current use of intranasal medication
- Stroke or TIA within past 5 years
- Neurocognitively impaired assessed by RBANS

Phase 1 Intranasal ST266 in Glaucoma Suspects Safety Trial ClinicalTrials.gov : NCT0390178

- Intranasal ST266 Safety established, supports use for optic neuropathies
- Published unexpected neuroprotective efficacy observation:



Contents lists available at ScienceDirect

Otolaryngology Case Reports

journal homepage: www.elsevier.com/locate/xocr

- Resolution of COVID-19 induced anosmia following treatment with ST266

  Devica L. Bhutania, Ahmara G. Rossa,b, Amanda Y. Lehmana, Kenneth S. Shindler

  Otolaryngol Case Rep. 2022 Nov;25:100475. doi: 10.1016/j.xocr.2022.100475.

- 28-days of intranasal ST266 resolved 13-months complete anosmia

Summary: Intranasal ST266 Neuroprotective Therapy

- Demonstrated noninvasive, cribriform plate targeted delivery of large molecular weight ST266 proteins to the brain and optic nerve
- ST266 secretome neuroprotective efficacy via multiple signaling pathways
  - Optic neuritis model → Preserved retinal ganglion cells
  - Brain injury models → Decreases microglial inflammation, optic nerve demyelination, NLRP3 inflammasome
  - Improved Barnes Maze learning and cognitive performance in GW and TBI models
- Phase 1 dose escalation safety study of ST266 in glaucoma suspect
- Unexpected resolution of Covid-19 induced anosmia

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