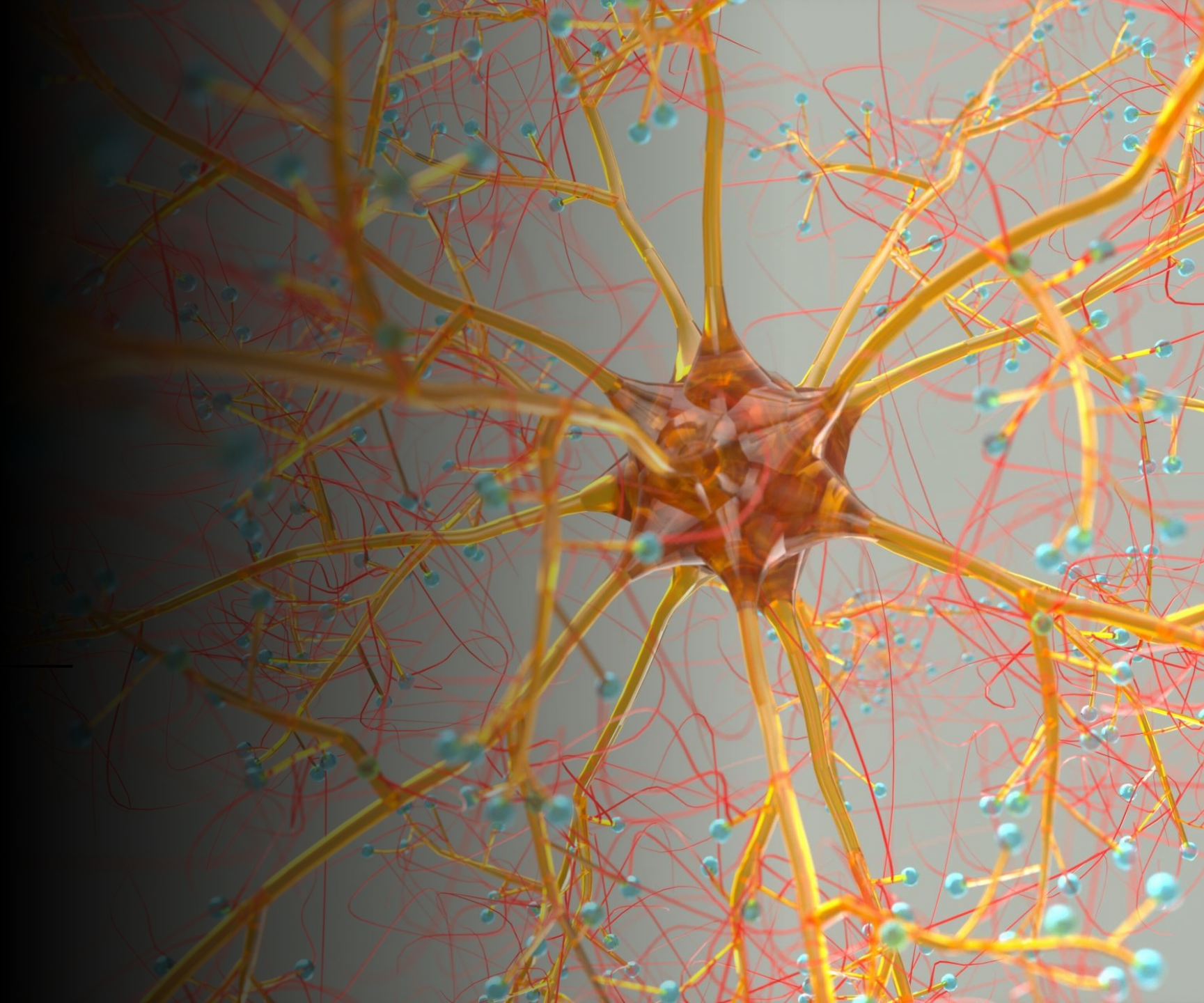




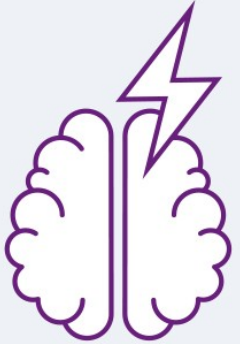
# Nerve Regeneration and Concussion recovery

By: Omar Mobasher





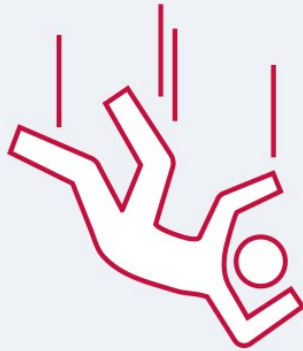
# Traumatic Brain Injuries



**Stroke (39%)**



**RTA's (14%)**



**Falls (14%)**



**Tumour (7%)**



**Assault (5%)**

# Effects of Traumatic Brain Injury

## HEALTHY



Frontal:  
Concentration, Problem Solving, Speech



Parietal:  
Sense of Touch, Pain, Temperature



Occipital:  
Healthy Vision



Temporal:  
Memory, Organization



Cerebellum:  
Balance & Coordination



Brainstem:  
Breathing, Steady Heart



## TBI



Frontal:  
Lack of Focus, Irritability, Language Difficulty



Parietal:  
Difficulty with Reading, Spatial Misperception



Occipital:  
Blind Spots, Blurred Vision



Temporal:  
Problems with Short- & Long-Term Memory

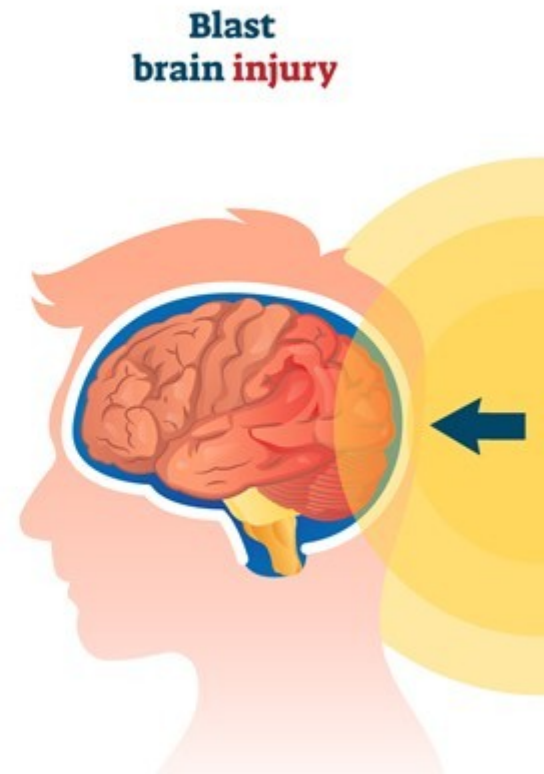
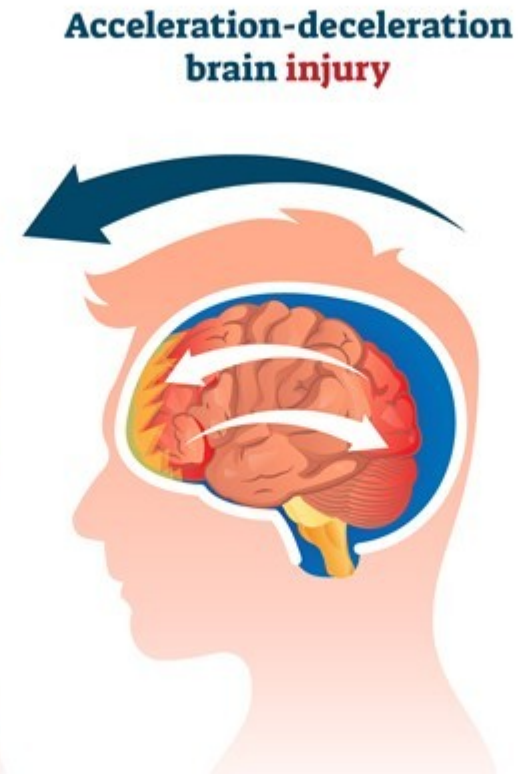
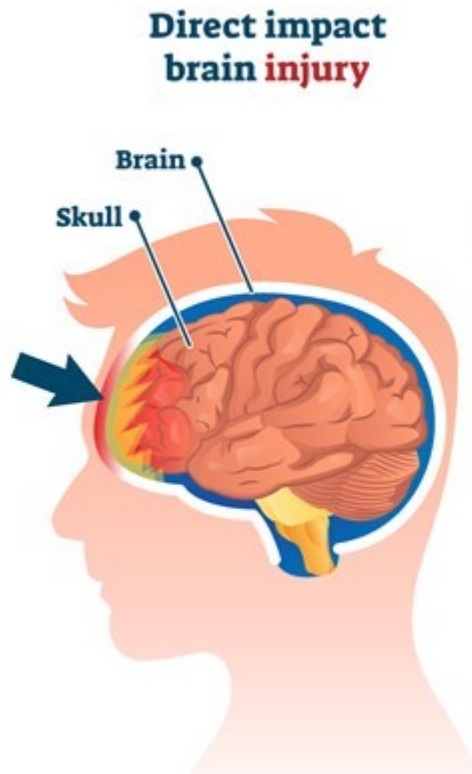
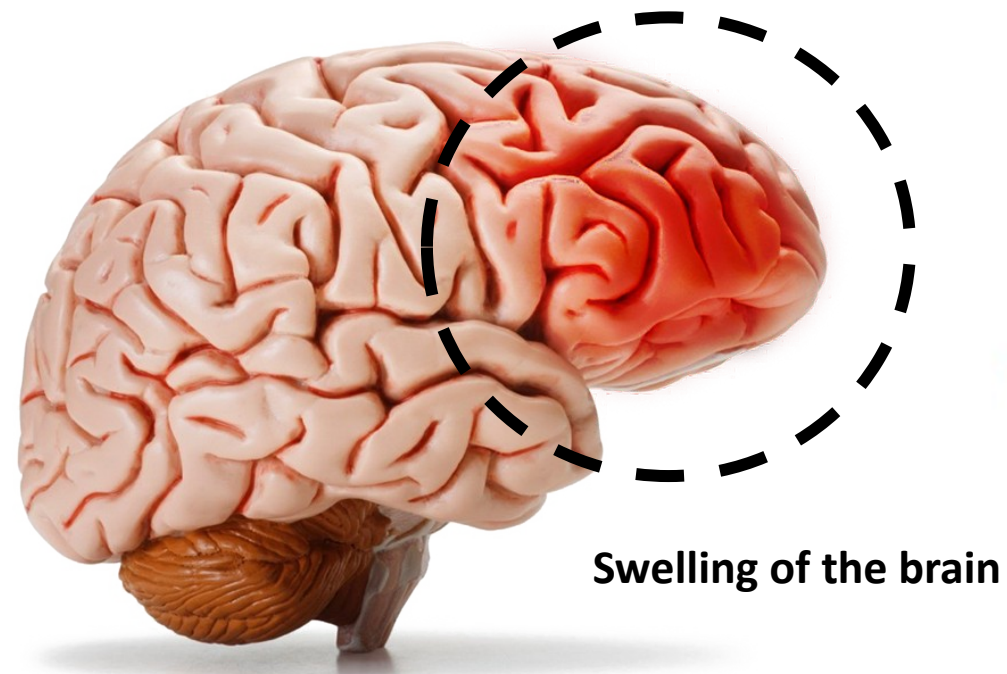


Cerebellum:  
Difficulty Walking, Slurred Speech



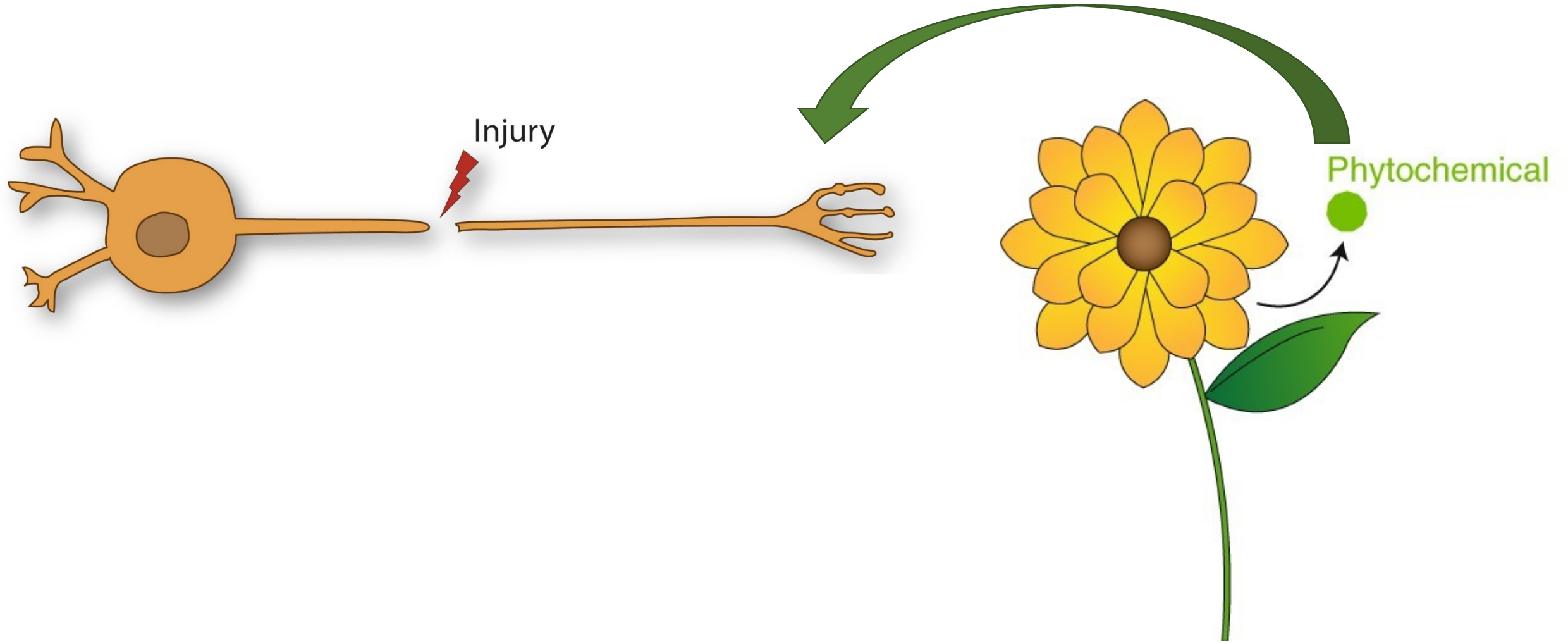
Brainstem:  
Changes in Breath, Difficulty Swallowing

# Concussion



**Prolonged Swelling Can Also Kill Off Neurons In The Brain.**

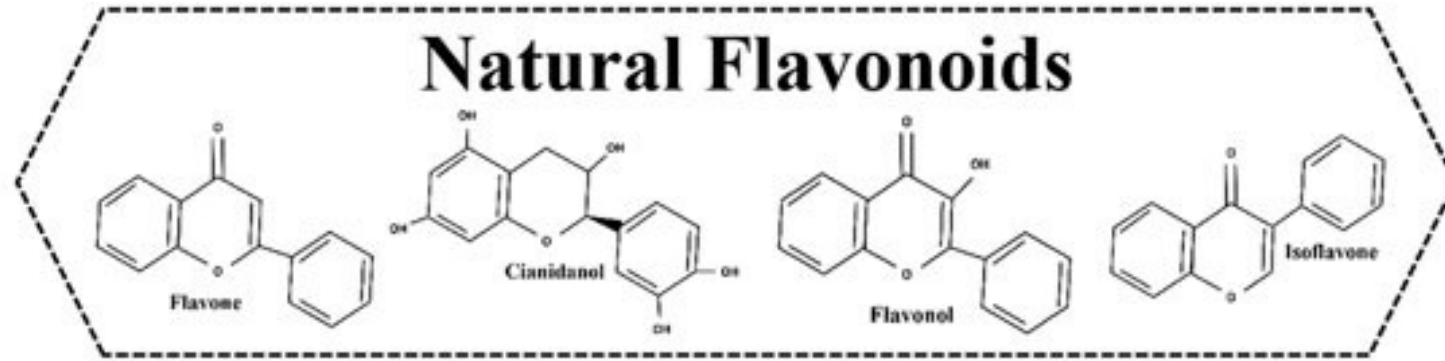
# Nerve Regeneration



**Healing Neurons Is Healing Concussions**



# Impact of Flavonoids



**Regulate autophagy**



The p53 pathway and LC3 deacetylated by SIRT1  
Increases fatty acid beta oxidation and mitochondrial bioenergetics

**Improve intestinal flora**



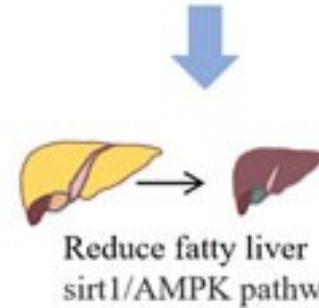
Firmicutes/Bacteroidetes ↓  
Regulate intestinal disorders  
Christensenellaceae ↑

**Antioxidant stress**



Clear damaged mitochondria  
FXR1/TGR5 pathway,  
Nrf2/HO-1 pathway  
SOD, CAT, GSH ↑ / ROS ↓

**Regulate lipid metabolism**

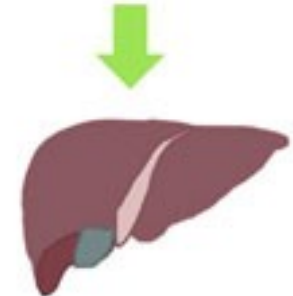


Reduce fatty liver  
sirt1/AMPK pathway



Inhibit fat accumulation

**Anti-inflammatory**



IL-1 $\beta$ , IL-6, TNF- $\alpha$  ↓  
in liver  
Inhibits the expression of  
nitric oxide synthase,  
NO ↓  
NF-kB pathway

# Comparison

## Flavonoids and antioxidants that help reduce inflammation in Somatic Cells

- Flavones (e.g., Apigenin, Chrysin, and Luteolin)
- Flavonols (e.g., Quercetin, Kaempferol, Myricetin, and Fisetin)
- Isoflavones (e.g., Genistin, Daidzin)
- Anthocyanidin (e.g., Apigenidin, Cyanidin)
- Flavanonol (e.g., Taxifolin, Silibinin)

(Ginwala et. al 2019)

## Flavonoids and antioxidants that help nerve cells regenerate.

- Flavonoid polyphenols ( e.g., epigallocatechin 3-gallate (EGCG) and quercetin)
- Non-flavonoid polyphenols (e.g., curcumin and resveratrol)
- Phenolic diterpenes (e.g., rosmarinic acid or carnosic acid)
- Organosulfur compounds, (e.g., isothiocyanate and L-sulforaphane)

(Ataie et. al 2016)

# Research Questions

**#1** What are the flavonoids and antioxidants that fight inflammation or help nerve regeneration, if so, do they help heal concussion symptoms?

**#2** Do sunflowers have flavonoids and antioxidants that fight inflammation or help nerve regeneration, if so, do they help heal concussion symptoms





# Approach and Methods

- Qualitative Systematic Review
- Boolean language
- 286 papers (since 1965)
- 5 papers
  - ✓ Concussions
  - ✓ Nerve-regeneration
  - ✓ Antioxidants
  - ✓ Flavionds
  - ✓ metablomics of Nerve cells/ Neurons



WEB OF SCIENCE

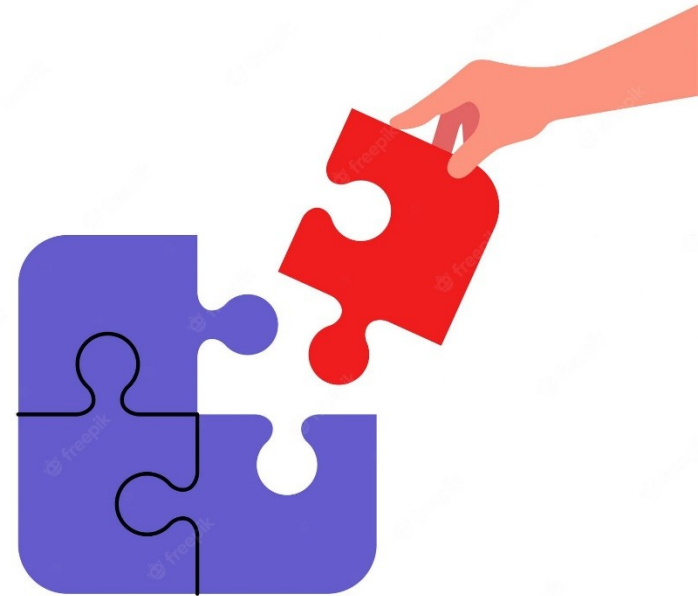
# Inclusion & Exclusion Criteria

- **Excluded**

- × cancer studies as fighting tumor inflammation
- × involve a mixture of pharmaceutical medicines

- **Included**

- ✓ manipulative experiment or in natural edible plants
- ✓ direct ingestion of plants, fruits or vegetables.
- ✓ empirical evidence of reduction in inflammation and nerve regeneration.
- ✓ peer-reviewed journal indexed



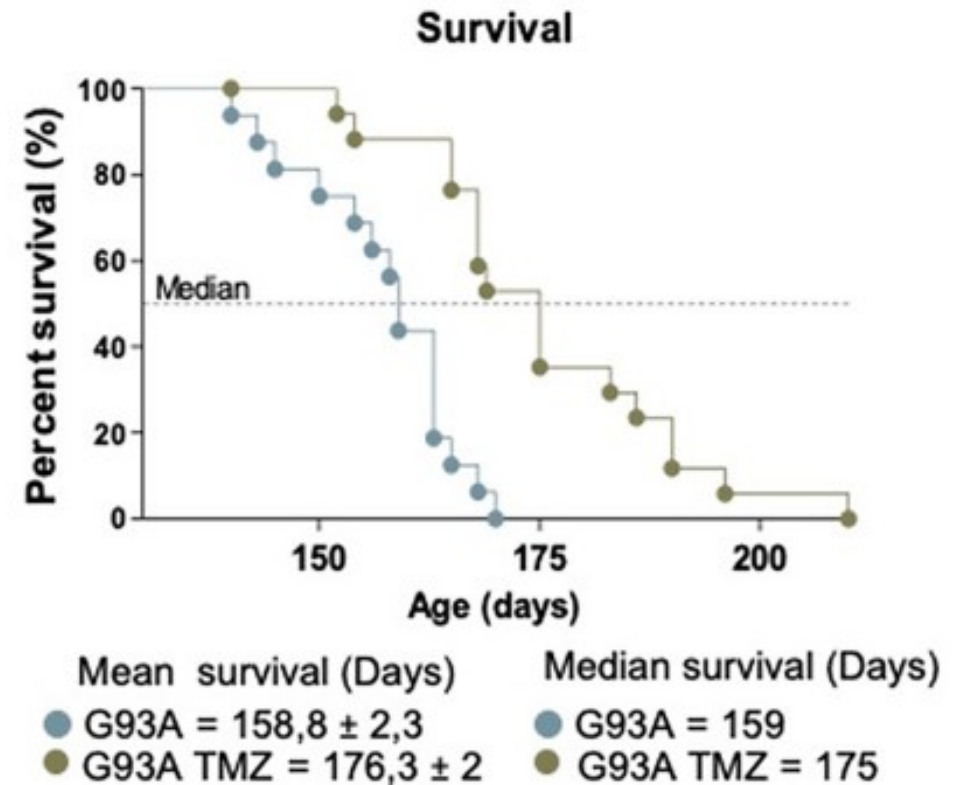
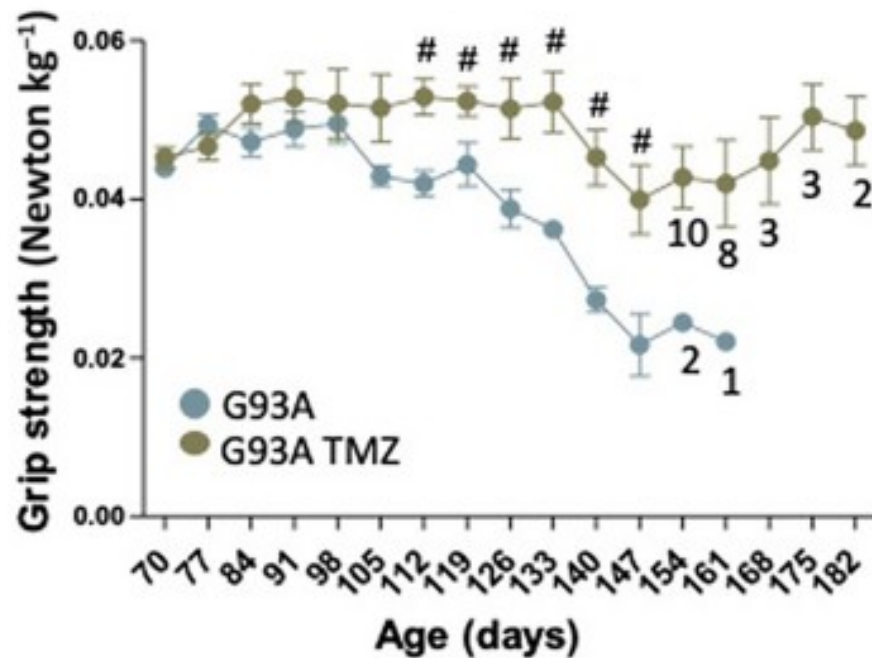
# Selected Studies

Nerve Regeneration through Antioxidants	Concussions and neuron metabolomics
Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice	The role of mitochondrial bioenergetics and oxidative stress in depressive behavior in recurrent concussion model in mice
Mitochondrial-targeting antioxidant MitoQ modulates angiogenesis and promotes functional recovery after spinal cord injury	BRAIN HYDROXYL RADICAL GENERATION IN ACUTE EXPERIMENTAL HEAD-INJURY
Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress	



# Nerve Research Findings

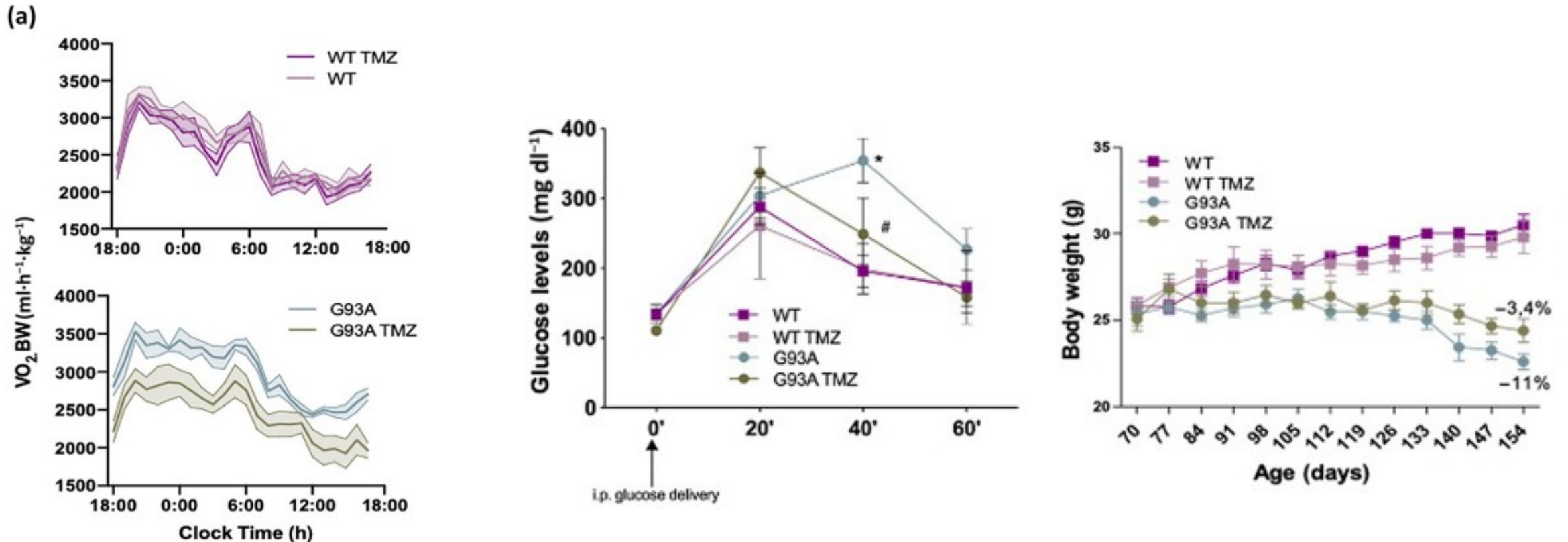
Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice



**Trimetazidine (TMZ) Improves Muscle Strength And Extends Lifespan Of SOD1G93A Mice**

# Nerve Research Findings

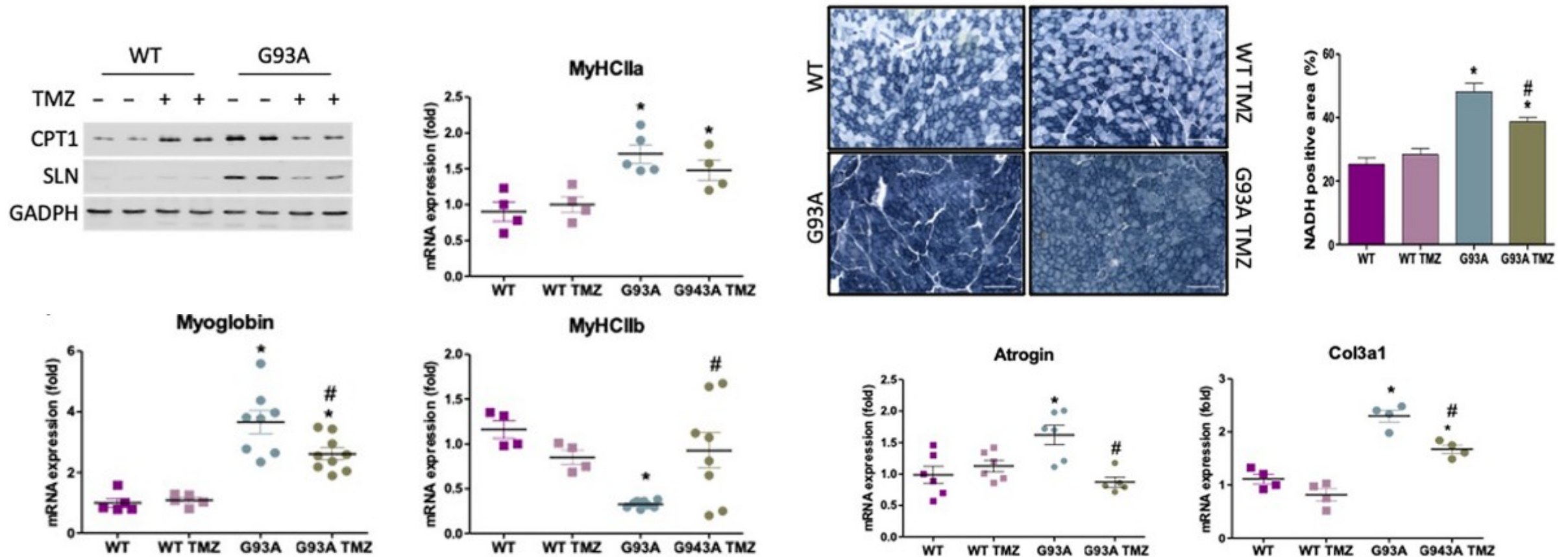
Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice



**Trimetazidine (TMZ) Prevents Metabolic Alterations In SOD1G93A Mice**

# Nerve Research Findings

Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice

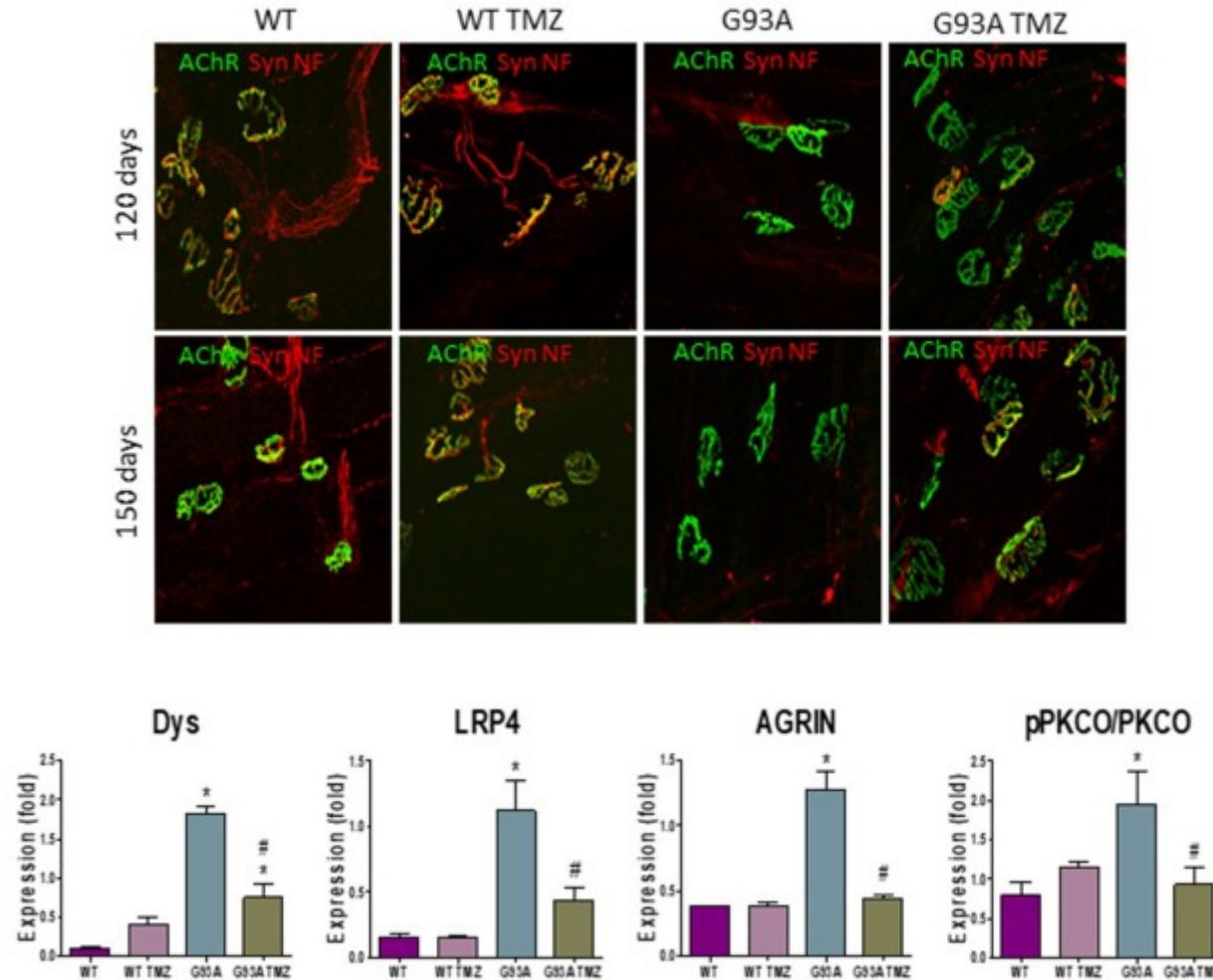


**Trimetazidine (TMZ) Restores The Glycolytic Phenotype And Reduces Atrophic/Fibrotic Markers In The Tibialis Anterior (TA) Muscle**



# Nerve Research Findings

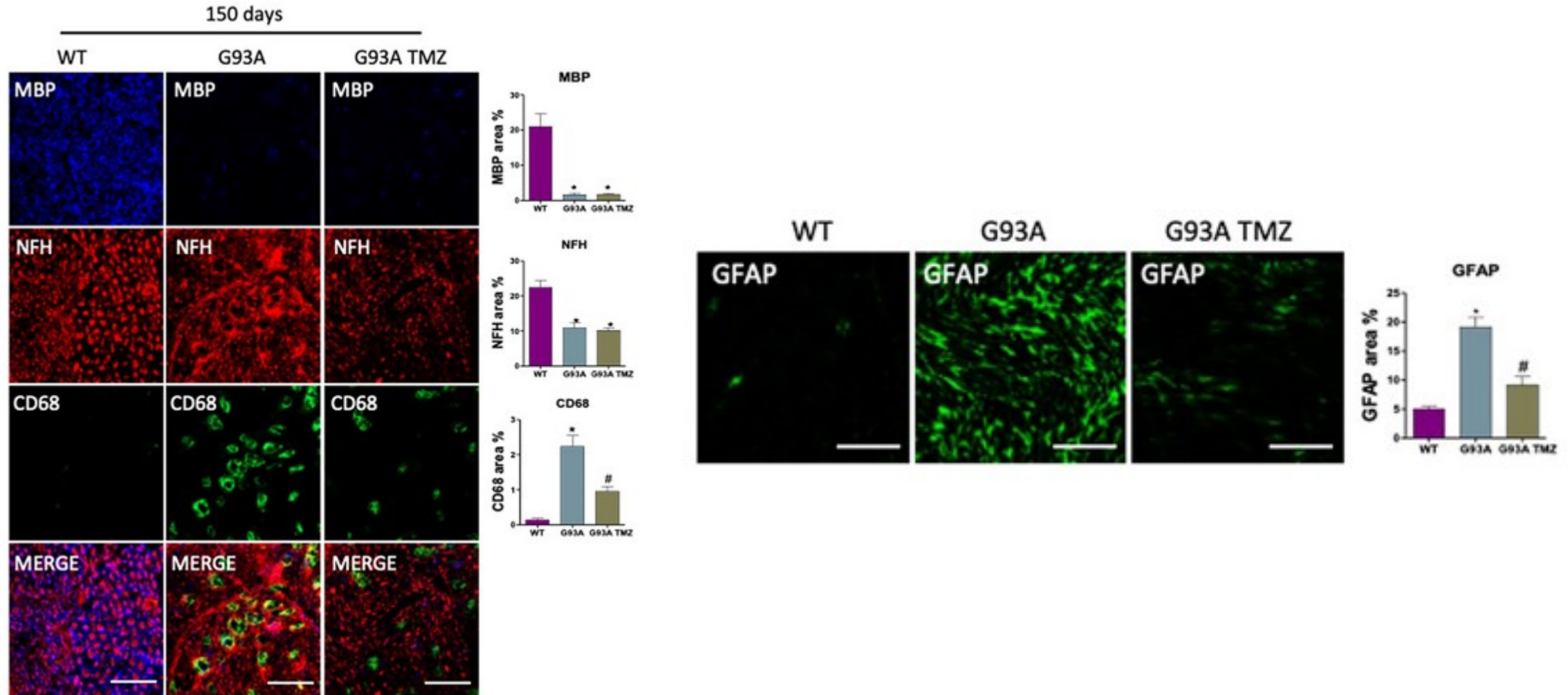
Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice



**Trimetazidine (TMZ) Preserves The Integrity Of Neuromuscular Junctions (NMJs)**

# Nerve Research Findings

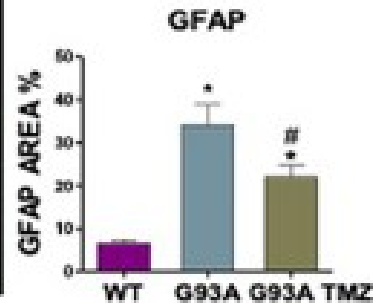
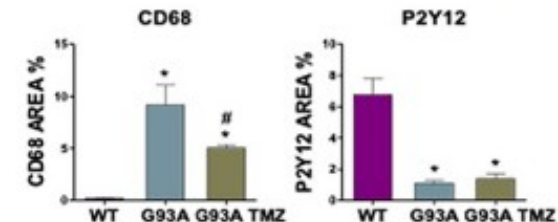
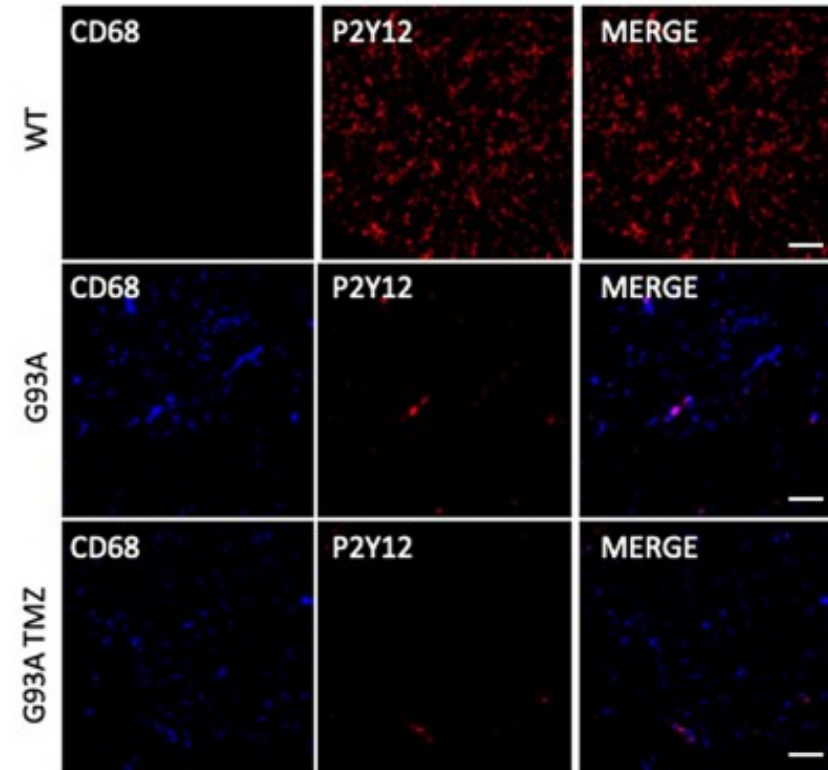
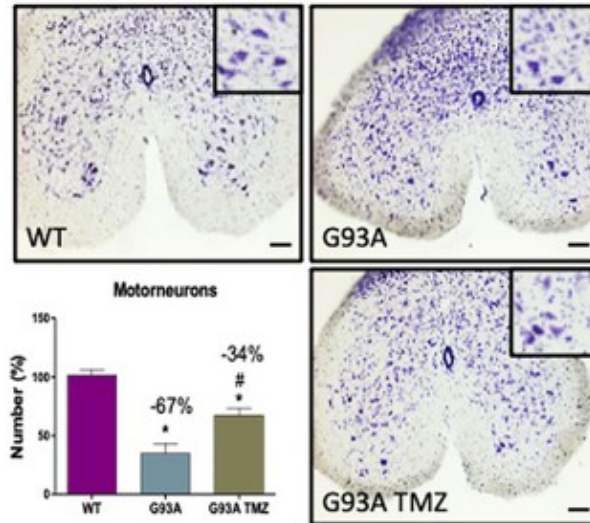
Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice



**Trimetazidine (TMZ) Preserves Sciatic Nerve Integrity**

# Nerve Research Findings

Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice



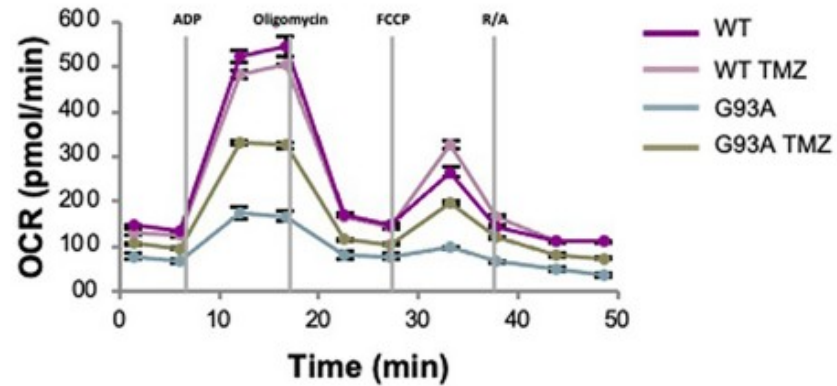
Trimetazidine (TMZ) Protects From Motor Neuron Loss And Neuroinflammation



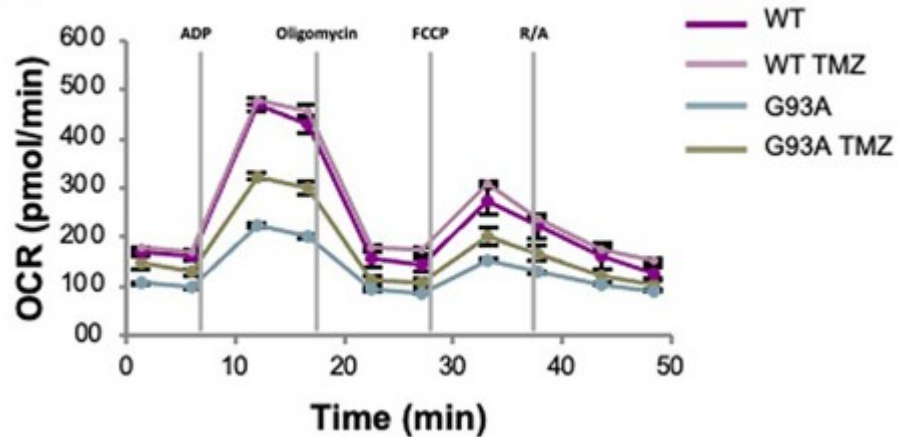
# Nerve Research Findings

Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice

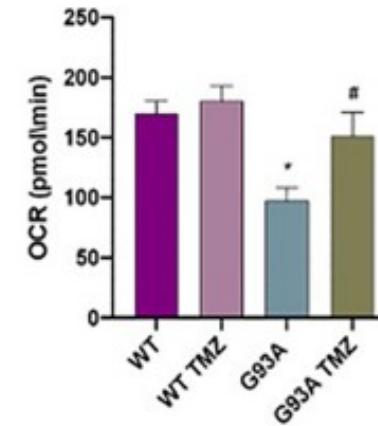
(a) Coupling assay\_Tibialis Anterior



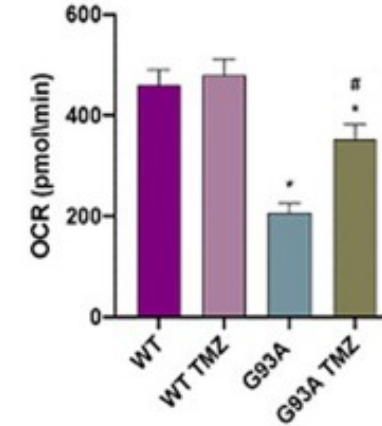
(b) Coupling assay\_Spinal Cord



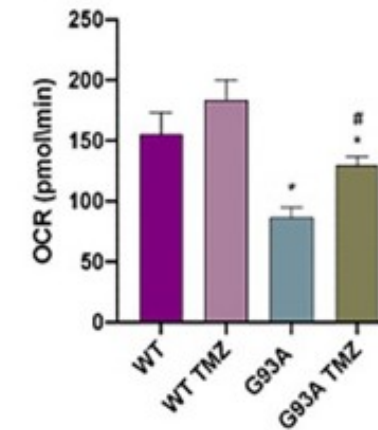
BASAL



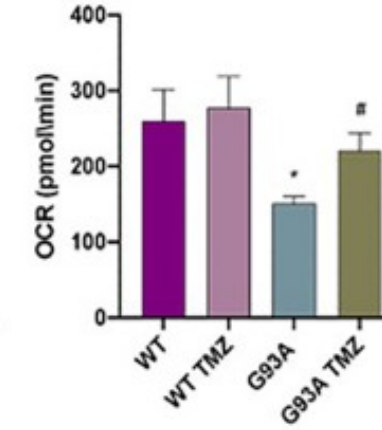
STATE 3



STATE 4o



STATE 3u

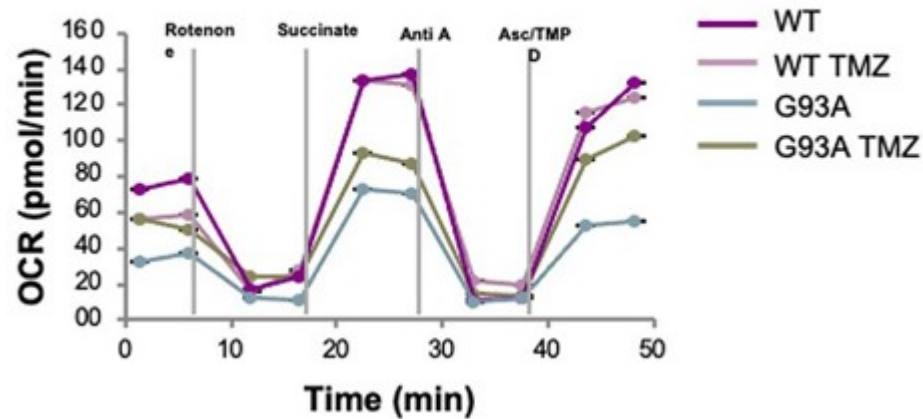


Trimetazidine (TMZ) Improves Mitochondrial Coupling State

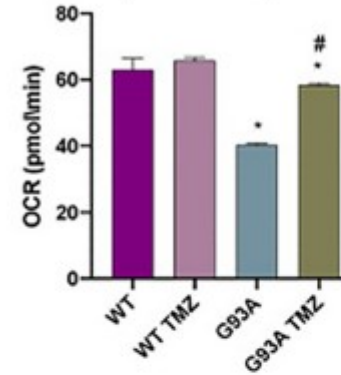
# Nerve Research Findings

Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice

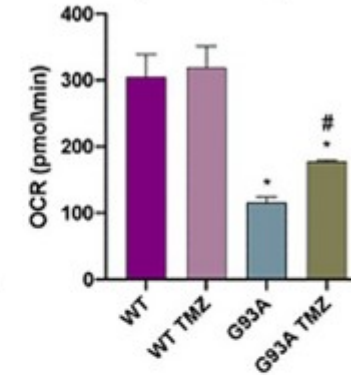
(a) Electron flow assay\_Tibialis Anterior



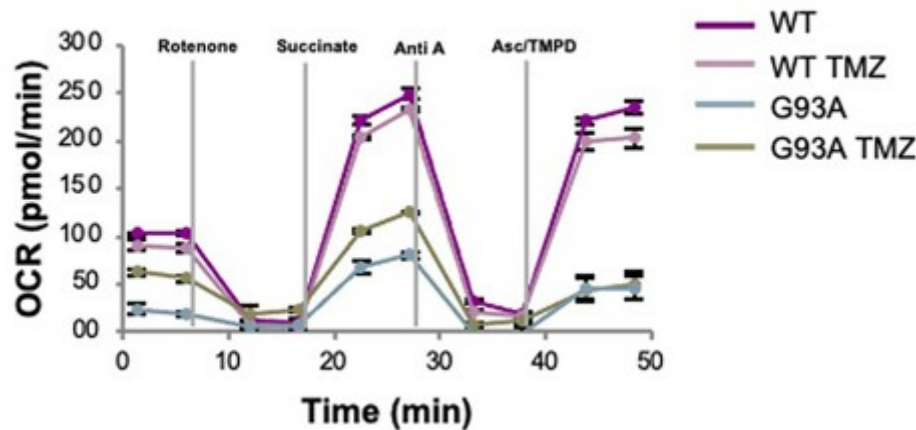
Complex I dependent respiration



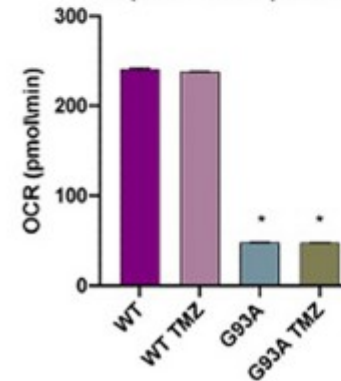
Complex II/III dependent respiration



(b) Electron flow assay\_Spinal Cord



Complex IV dependent respiration



**Trimetazidine (TMZ) Improves Electron Transport Chain Complex Activity**

# Nerve Research Findings

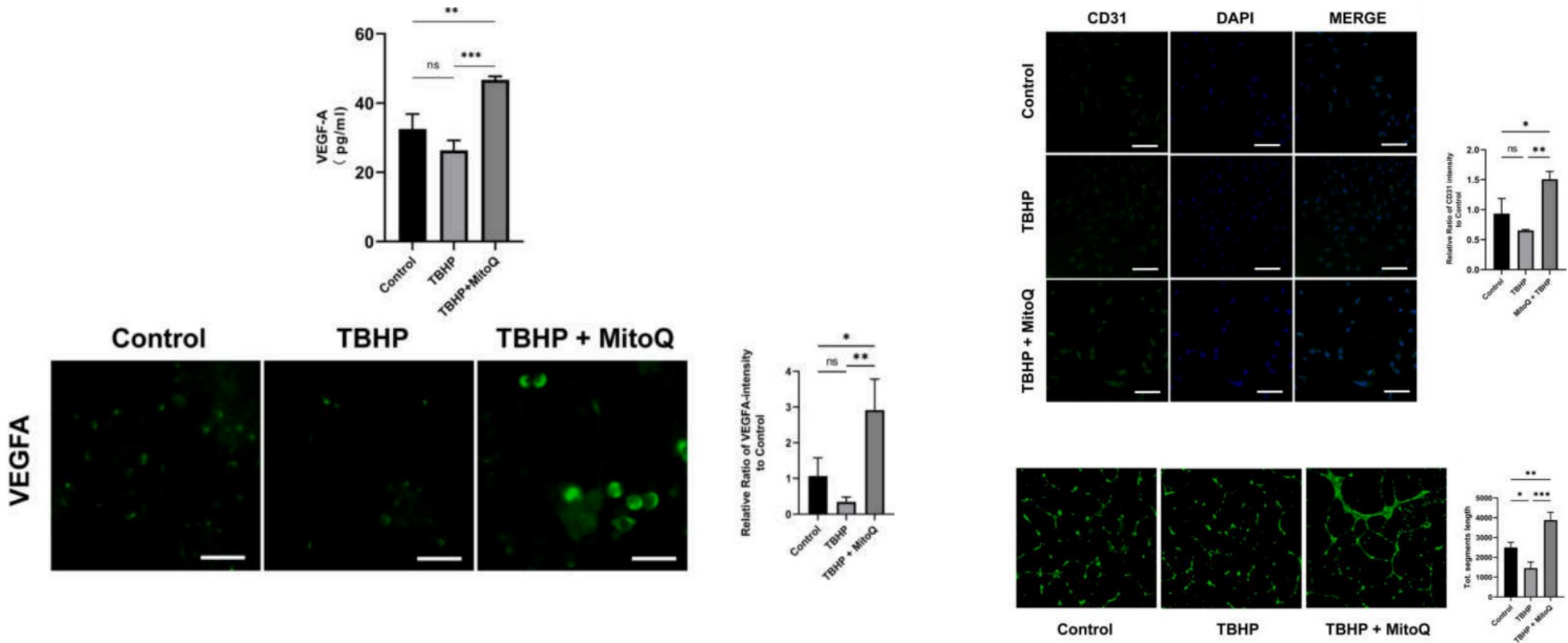
## Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1(G93A) mice

*Take away:*

- Trimetazidine enhances mitochondrial metabolism and promotes nerve regeneration.
- Trimetazidine administration delays motor function decline, improves muscle performance and metabolism, and significantly extends overall survival of SOD1
- Therapeutic effect of Trimetazidine is underpinned by its action on mitochondrial function in skeletal muscle and spinal cord.

# Nerve Research Findings

Mitochondrial-targeting antioxidant MitoQ modulates angiogenesis and promotes functional recovery after spinal cord injury

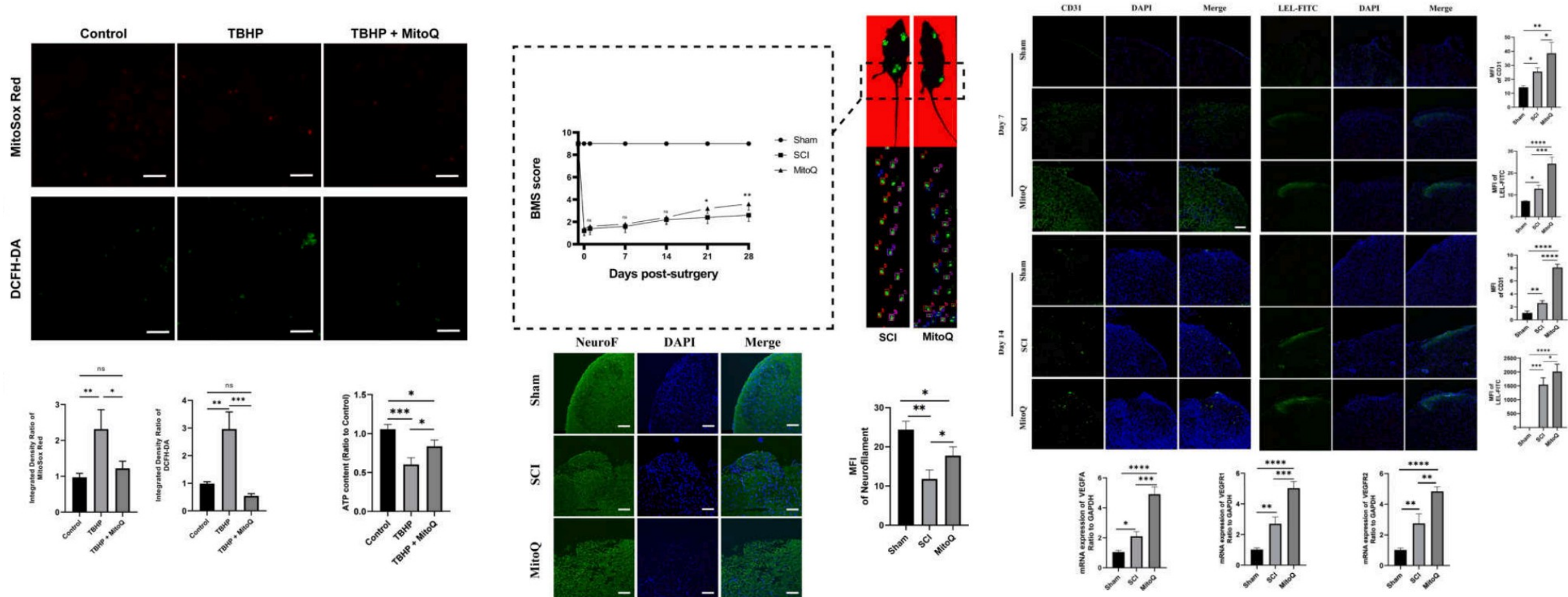


**MitoQ Promotes The Secretion Of VEGFA And Angiogenesis In BV2 Cells After TBHP Treatment**



# Nerve Research Findings

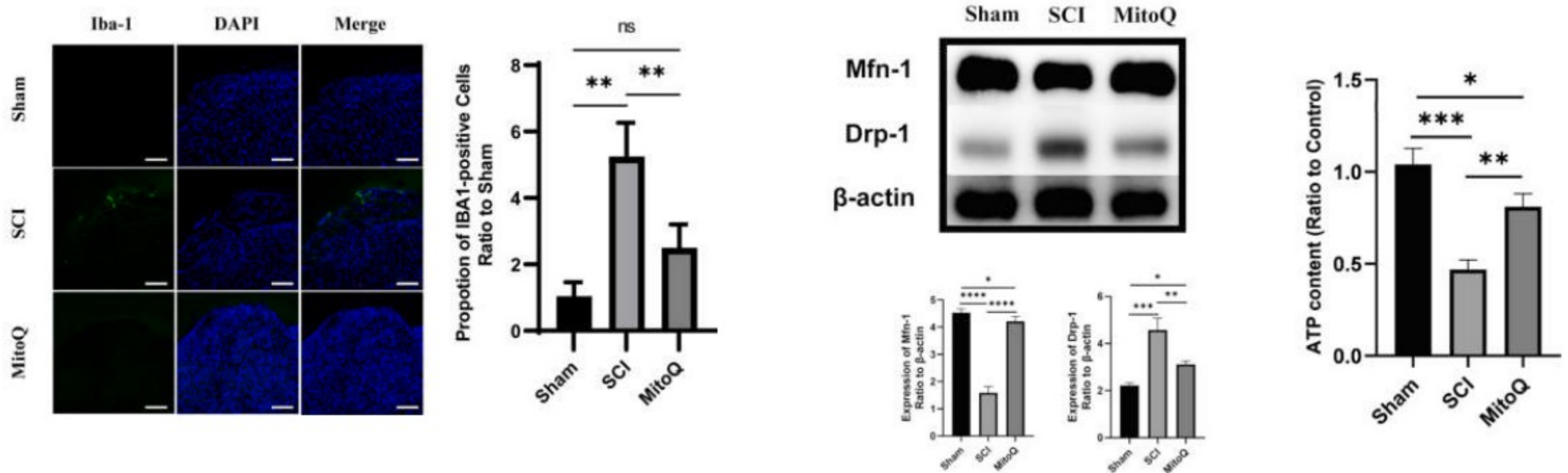
Mitochondrial-targeting antioxidant MitoQ modulates angiogenesis and promotes functional recovery after spinal cord injury



MitoQ promotes mitochondrial function, functional recovery and neural repair, and angiogenesis after SCI

# Nerve Research Findings

Mitochondrial-targeting antioxidant MitoQ modulates angiogenesis and promotes functional recovery after spinal cord injury



MitoQ promotes mitochondrial functions after SCI

# Nerve Research Findings

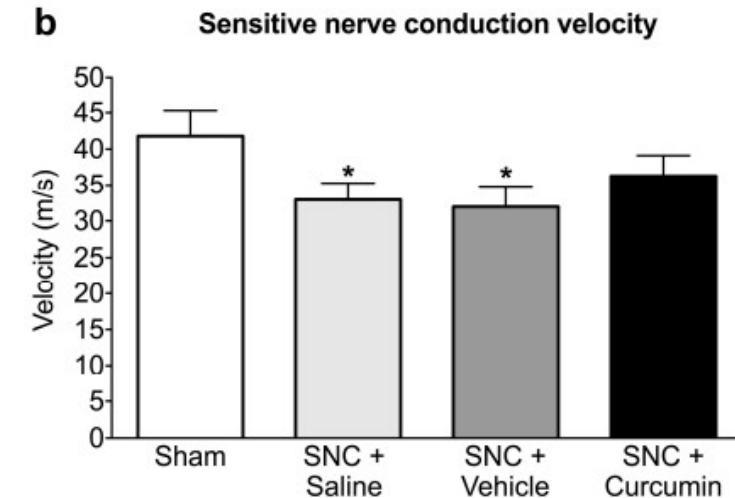
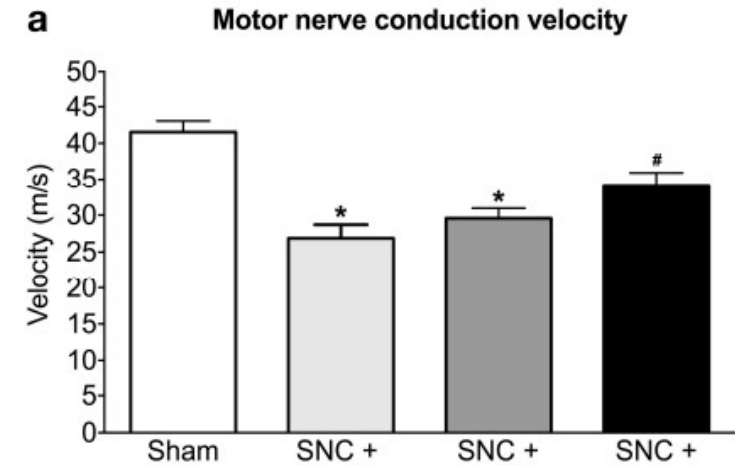
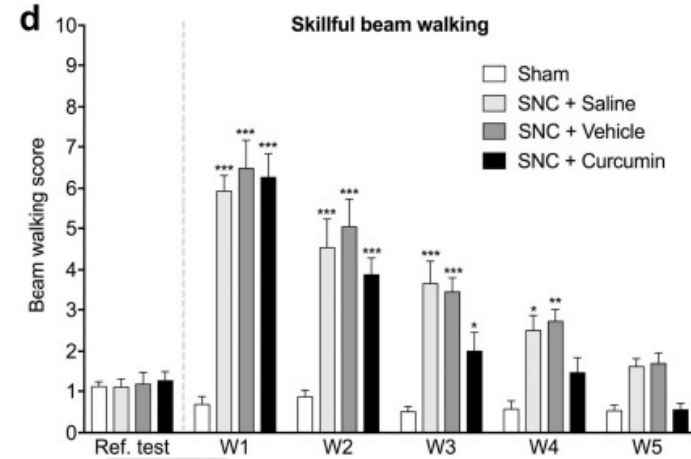
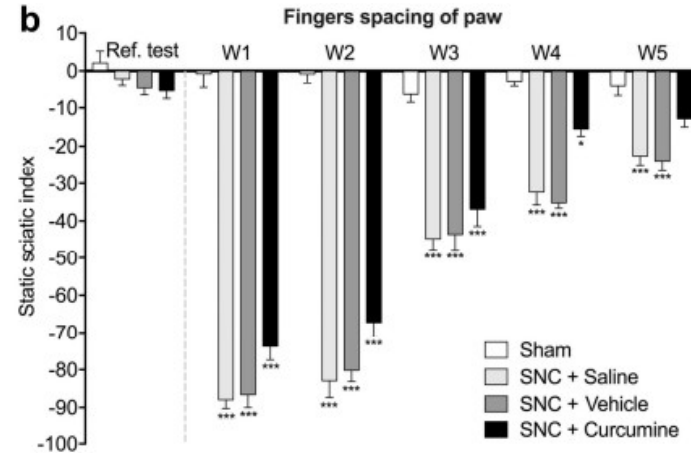
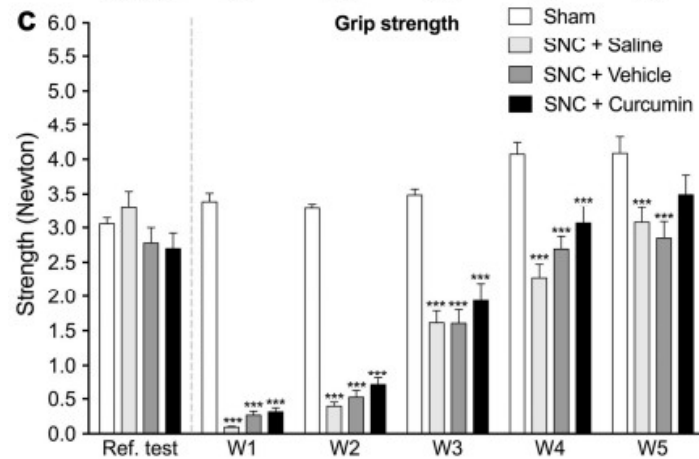
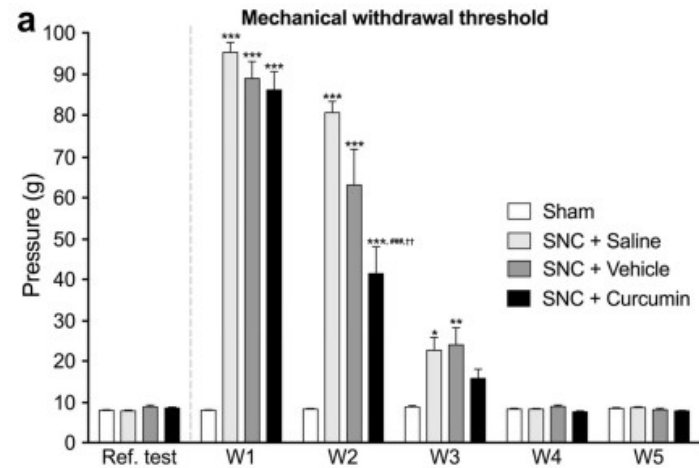
## Mitochondrial-targeting antioxidant MitoQ modulates angiogenesis and promotes functional recovery after spinal cord injury

*Take away:*

- The angiogenic promotion of MitoQ-treated BV2 cells was evaluated by tube formation and immunofluorescence assays (CD31) in a coculture system of BV2 cells and HUVECs.
- Immunofluorescence and fluorescence assays indicated that MitoQ could promote angiogenesis and inhibit macrophage/microglia activation in lesion-site after SCI.
- The mitochondrial-specific antioxidant MitoQ promotes functional recovery and tissue preservation through the enhancement of angiogenesis with the modification of mitochondrial function after SCI.

# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress



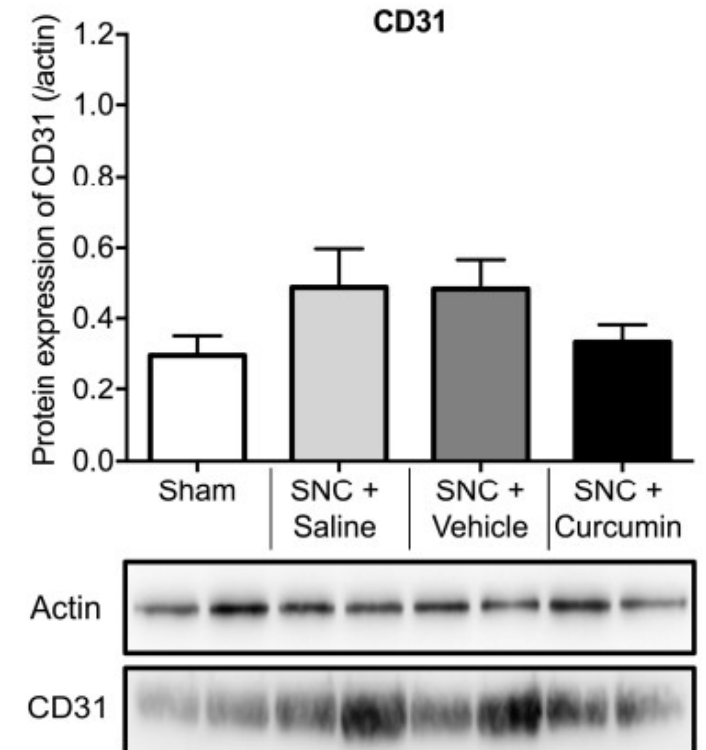
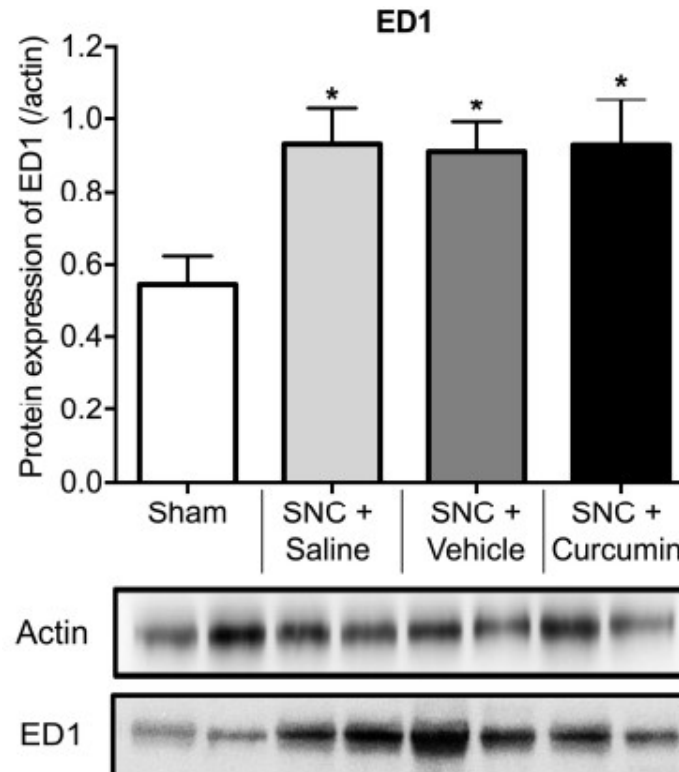
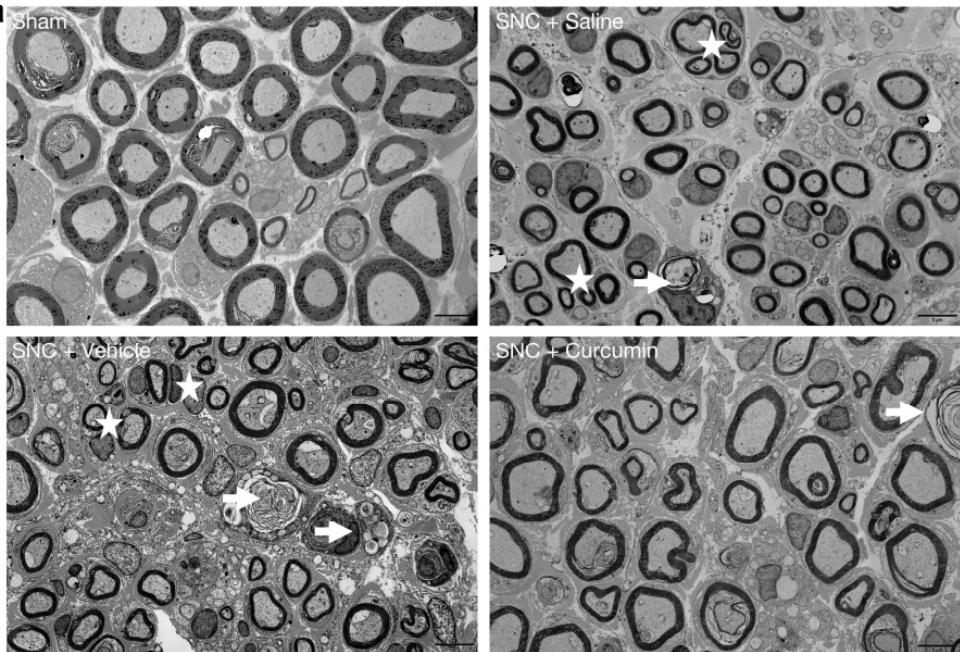
**Curcumin Has Beneficial Effects On Behavioral Recovery & Nerve Sensitive Function**



# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress

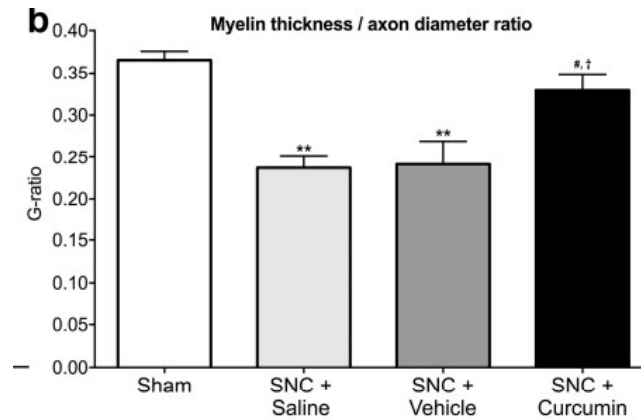
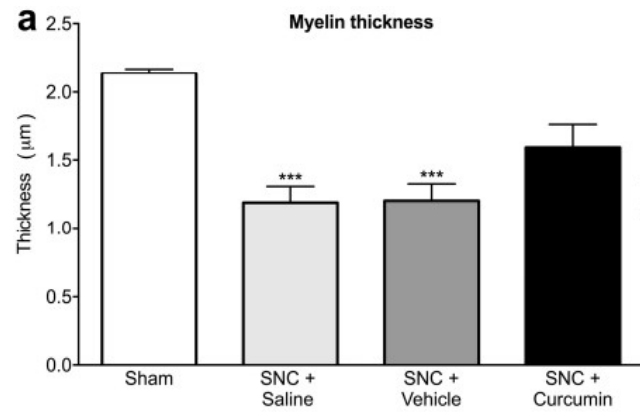
Total number of	Sham	SNC + Saline	SNC + Vehicle	SNC + Curcumin
Axonal clusters of regeneration	0.0 (± 0.0)	18.3 (± 3.1)***	19.5 (± 2.9)***	10.1 (± 2.3) #,†
Macrophages	5.7 (± 0.8)	47.5 (± 6.8)***	45.4 (± 5.5)***	44.3 (± 4.8)***
Blood vessels	14.7 (± 0.9)	16.2 (± 0.9)	17.2 (± 1.4)	14.0 (± 1.4)



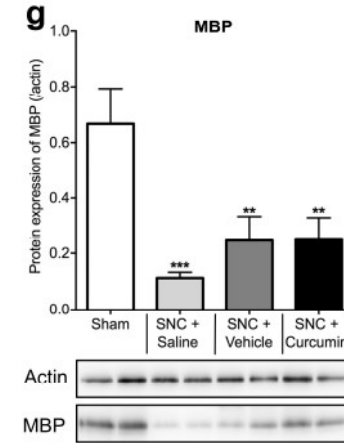
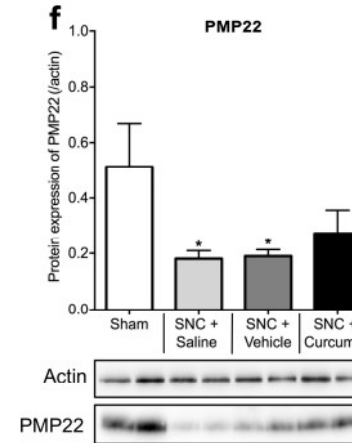
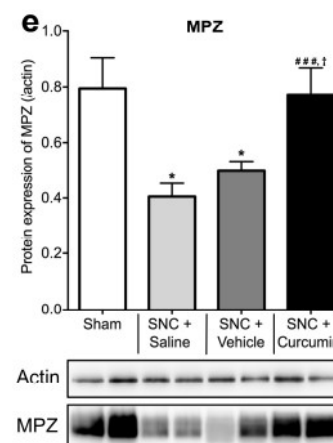
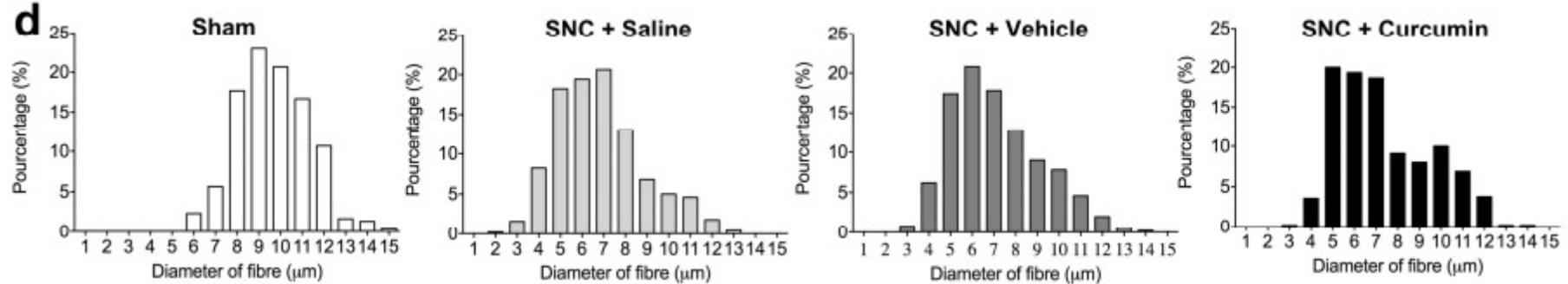
**Curcumin Decreased Clusters of Regeneration in Crushed Sciatic Nerves**

# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress



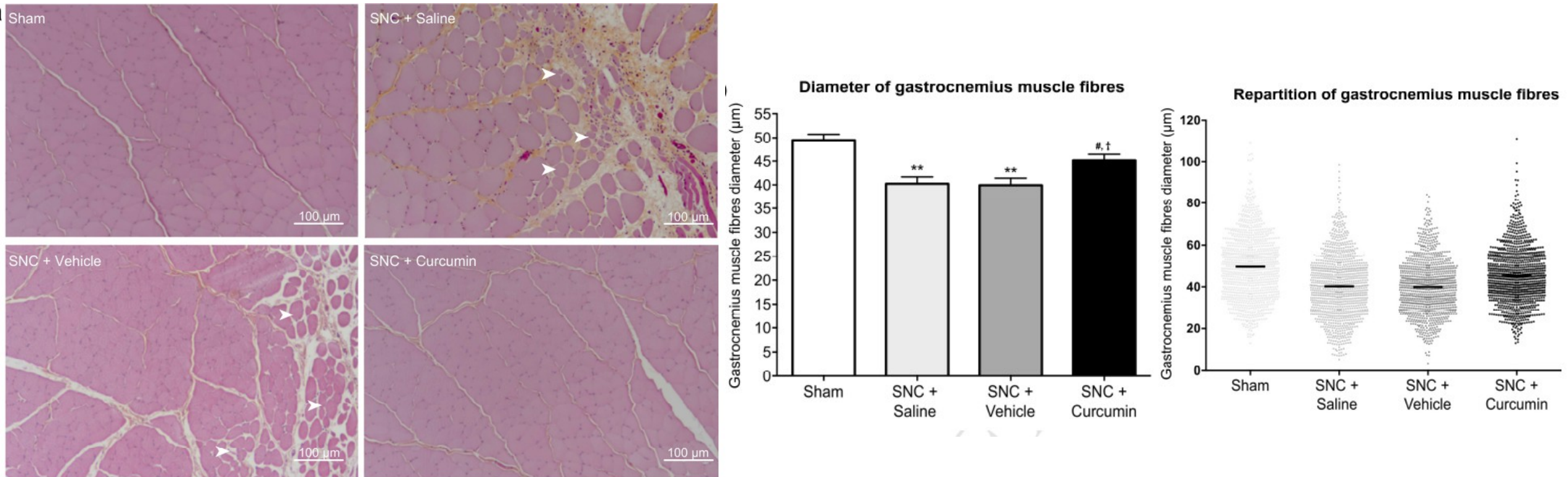
Myelinated axons	Sham	SNC + Saline	SNC + Vehicle	SNC + Curcumin
Total number	23 631 (± 679.5)	20 067 (± 941.5)**	20 371 (± 775.6)*	20 051 (± 655.5)**
Diameter of axons	5.87 (± 0.29)	4.94 (± 0.28)	5.06 (± 0.29)	4.79 (± 0.31)
Diameter of axons + myelin	10.18 (± 0.33)	7.32 (± 0.50)*	7.47 (± 0.42)*	8.01 (± 0.66)



Curcumin had Beneficial Effects on Myelin Regeneration

# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress

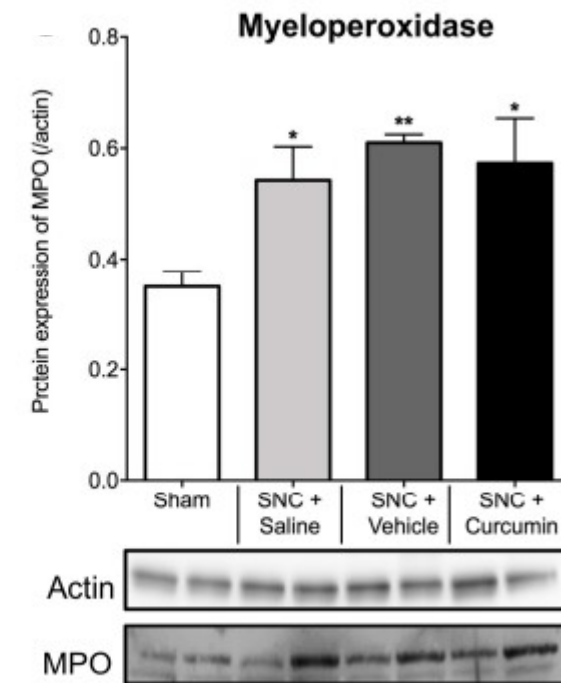
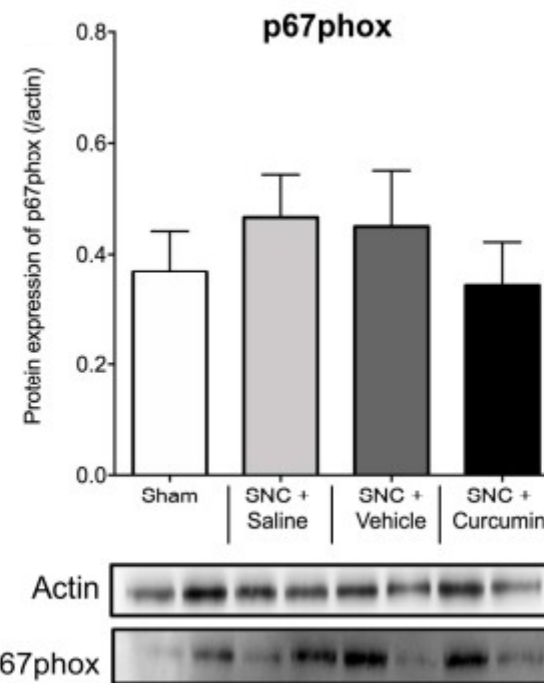
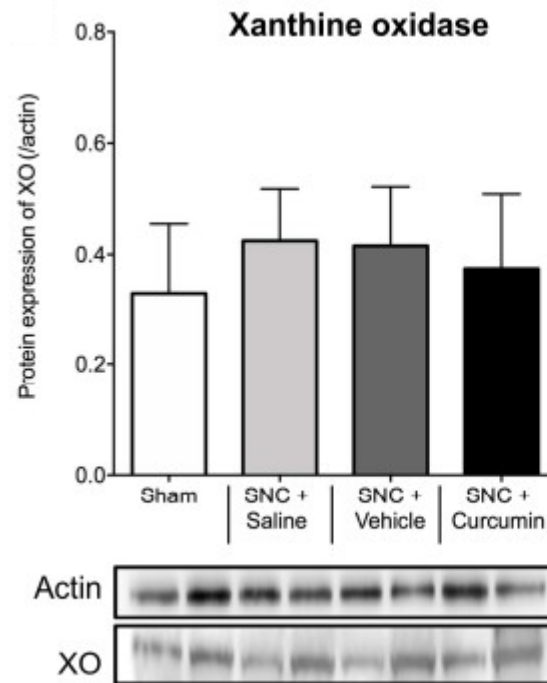
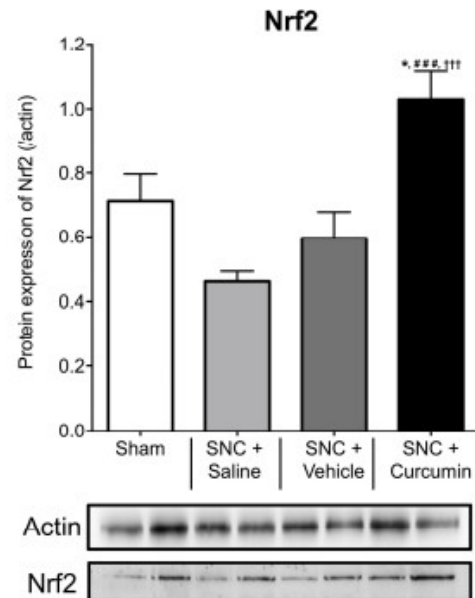
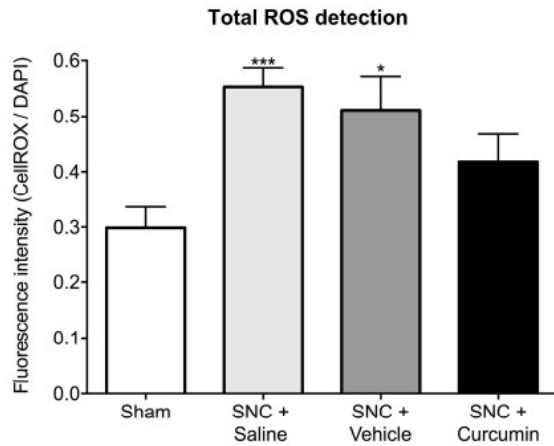


**Curcumin has Beneficial Effects on Tissue Integrity**



# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress

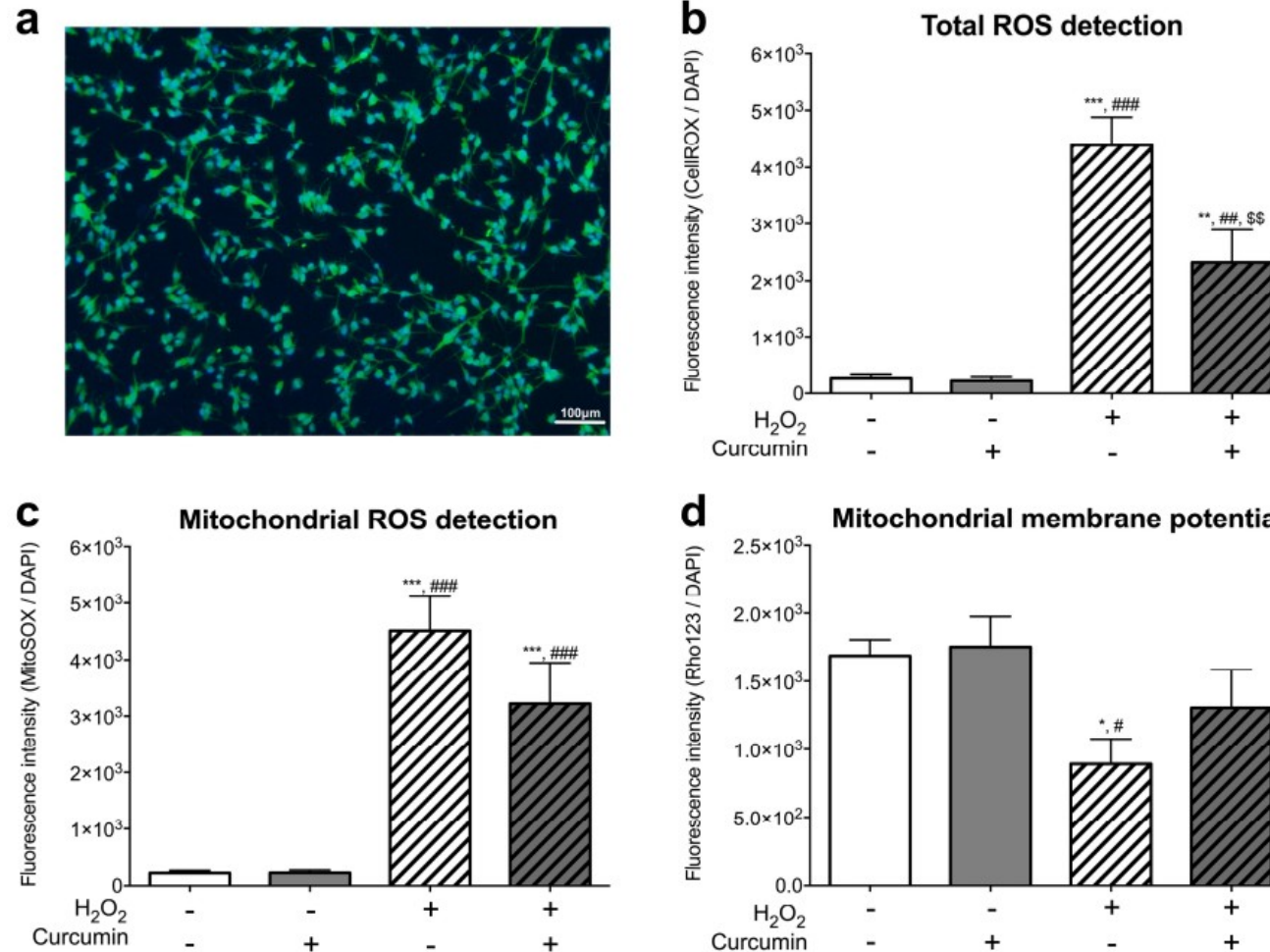


**Curcumin Reduced Oxidative Stress in Sciatic Nerves**



# Nerve Research Findings

Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress



Curcumin decreased mitochondrial superoxide production

# Nerve Research Findings

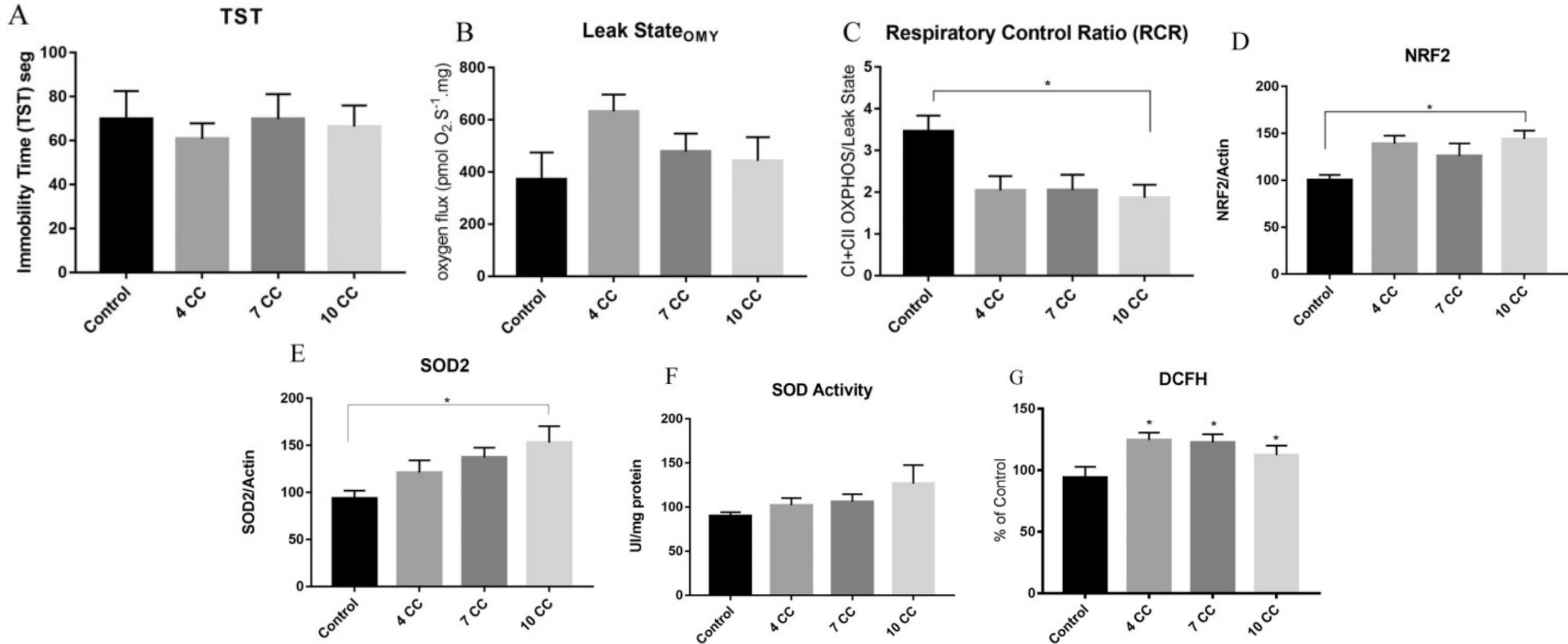
**Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress**

*Take away:*

- The curcumin treatment increased expression of compact myelin proteins, myelin sheath thickness and, correspondingly, increased motor and sensitive nerve conduction velocity.
- Curcumin treatment reduced the production of reactive oxygen species lipid peroxidation and increased expression of transcription factor Nrf2.
- Low doses of curcumin represent a promising therapy for peripheral nerve regeneration

# Concussion Research findings

The role of mitochondrial bioenergetics and oxidative stress in depressive behavior in recurrent concussion model in mice



**Concussions Reduced Mit. Oxygen Flux & Increased Expression Of Antioxidant Enzymes**

# Concussion Research findings

## The role of mitochondrial bioenergetics and oxidative stress in depressive behavior in recurrent concussion model in mice

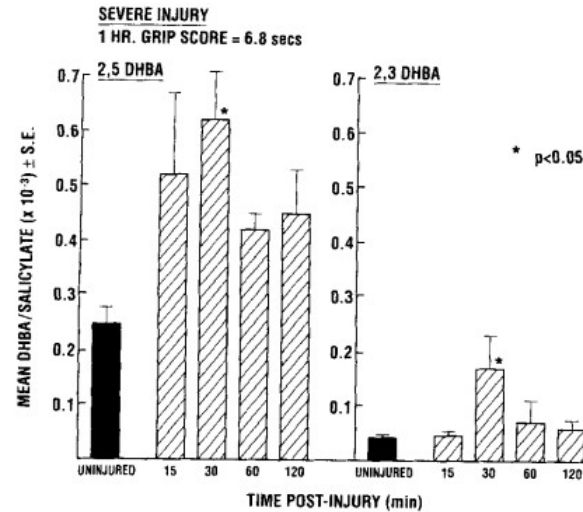
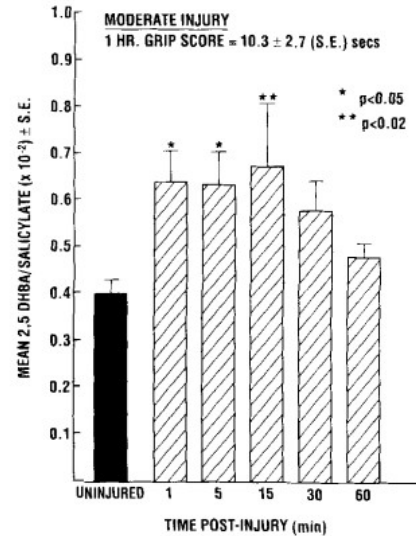
*Take away:*

- Most of the research of this injury has been focused on oxidative stress and functional deficits
- recurrent concussion protocols alter depressive-like phenotype behavior, and whether mitochondria play an indispensable role in this behavior.
- protocol of recurrent concussions decreased hippocampal mitochondrial respiration and increased expression of proteins such as nuclear factor erythroid 2-related factor 2 (Nrf2) and superoxide (SOD2).



# Concussion Research findings

## BRAIN HYDROXYL RADICAL GENERATION IN ACUTE EXPERIMENTAL HEAD-INJURY

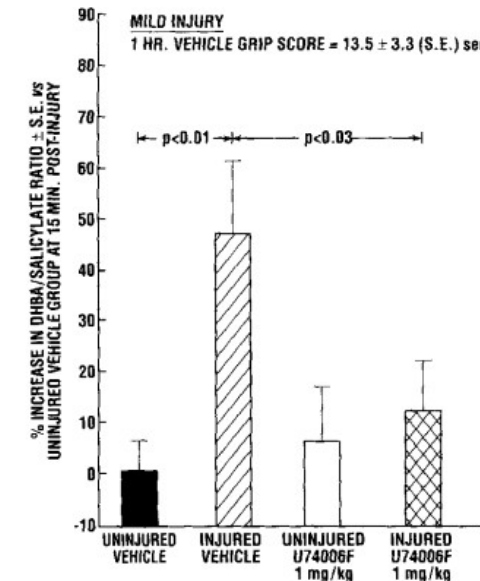
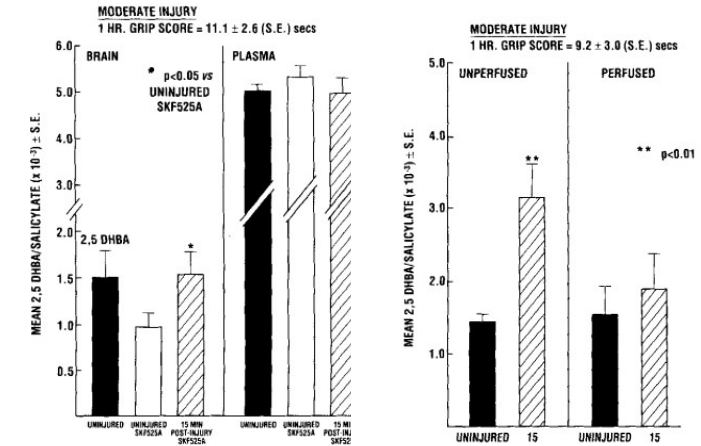


**TABLE 1.** Mouse brain salicylate levels as a function of time after a severe concussive head injury

Time after injury (min)	Salicylate ( $\mu\text{g/g}$ wet wt)
0 (Uninjured)	$4.0 \pm 0.6$
15	$2.9 \pm 0.6$
30	$2.8 \pm 0.5$
60	$2.5 \pm 0.3$
120	$2.2 \pm 0.3^a$

In each group, a 300 mg/kg i.p. dose of salicylate was administered 15 min before killing. Values are the mean  $\pm$  SEM for five mice.

<sup>a</sup>  $p < 0.05$  vs. uninjured group via one-way analysis of variance.



**Concussions were Associated with OH-Radical in Brain Injury**

# Concussion Research findings

## BRAIN HYDROXYL RADICAL GENERATION IN ACUTE EXPERIMENTAL HEAD-INJURY

*Take away:*

- In mice injured with a concussion of moderate severity as defined by the 1-h posttraumatic neurologic recovery (grip score), a 60% increase in 2,5-DHBA formation was observed by 1 min after injury compared with that observed in uninjured mice.
- The administration of the 21-aminosteroid lipid antioxidant, tirilazad mesylate, which possesses .OH scavenging properties
- further supporting that it reflects an increase in .OH radical formation. These results are the first direct demonstration of the occurrence and time course of increased .OH production in injured brain.

# Conclusion

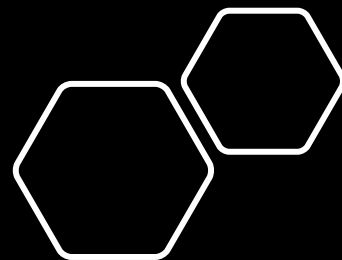
**Antioxidants help reduce oxidative stress on the mitochondria which can help regenerate and heal Nerve cells.**

**Flavonoids in Sunflower have not yet been identified to be directly involved in Nerve Regeneration or Concussion Healing**

# References

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Any Questions

