# Nanomedicine and Nanoscale Delivery IV

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Icahn School of Medicine at Mount Sinai

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COLLEGE OF PHARMACY

# Nanomedicine-enabled Methylprednisolone Prodrug Promotes Neuroprotection and Functional Recovery and Mitigates Adverse Effects After Acute Spinal Cord Injury in Rats

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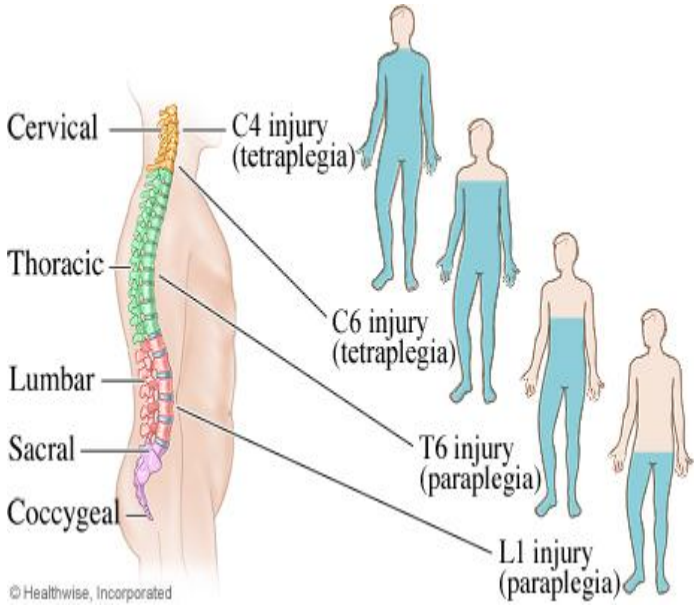
# Neuromusculoskeletal Disorders after Traumatic Spinal Cord Injury: Interventions & Mechanisms




**Challenges:**

- There are 300,000 persons with SCI in the United States with most chronically injured.
- Over 42,000 Veterans registered with the VA have SCI. VA provides care to more than 27,000 Veterans with SCI and related disorders each year, making the department the largest health care system in the world providing lifelong spinal cord care.
- To date, despite tremendous efforts made, there are no fully restorative therapies for functional recovery or dramatic musculoskeletal deteriorations in patients after SCI.


# Neuromusculoskeletal Disorders after Traumatic Spinal Cord Injury: Interventions & Mechanisms

I. **Neuroscience Program:** Developing a novel cutting-edge **nanomedicine** approach for drug-targeting delivery to improve neuroprotection and functional recovery in SCI.

II. **Bone Program:** Using animal models to study severe bone loss associated with SCI. The research focuses include developing **interventions** (translational) and exploring related **mechanisms** (basic). One particular interest is to study osteocyte functions.

III. **Bone and Muscle Interaction Program:** Studying the molecular basis of muscle and bone communication, with a focus on microRNA inside of extracelluar microvesicles -exosomes released from osteocytes.

The ultimate goal is to **improve bone and muscle quality and neurological functions,** in order to prepare SCI patients being able to benefit from emerging therapies:

-- stem cells-based neurorepair
-- activity-based rehabilitation
-- exoskeleton technologies for ambulation (e.g., the ReWalk or eLegs)
-- transcutaneous spinal cord stimulation for ambulation

↓

**Advance healthcare and the quality of life for Veterans with SCI**.

# Neuroprotection and Functional Recovery after Acute SCI

- SCI is a catastrophic medical problem that causes loss of sensory, motor, and autonomic function. To date, despite tremendous efforts made, there are no fully restorative therapies for SCI.
- The pathological changes resulting from SCI comprise both primary and secondary mechanisms. The primary mechanical injury serves as the sources of the injury, while the secondary injury evokes further damage and limits restorative processes.
- Main secondary mechanisms include hemorrhagic and ischemic, inflammatory reactions, oxidative stress, apoptosis, ionic disturbances and accumulation of various neurotransmitters.
- The glucocorticoid methylprednisolone (MP) is the only FDA approved agent used clinically, if systemically administered right (within 8 hours) after SCI, to improve sensory or motor function after SCI. The effects are mainly attributed to inhibit lipid peroxidation and local inflammation.
- The use of systemic high-dose MP in acute SCI remains controversial because its effect on functional recovery are modest, and largely offset by a number of adverse effects including infection, myopathy, bone loss, neuropathy, and disorders of carbohydrate metabolism.

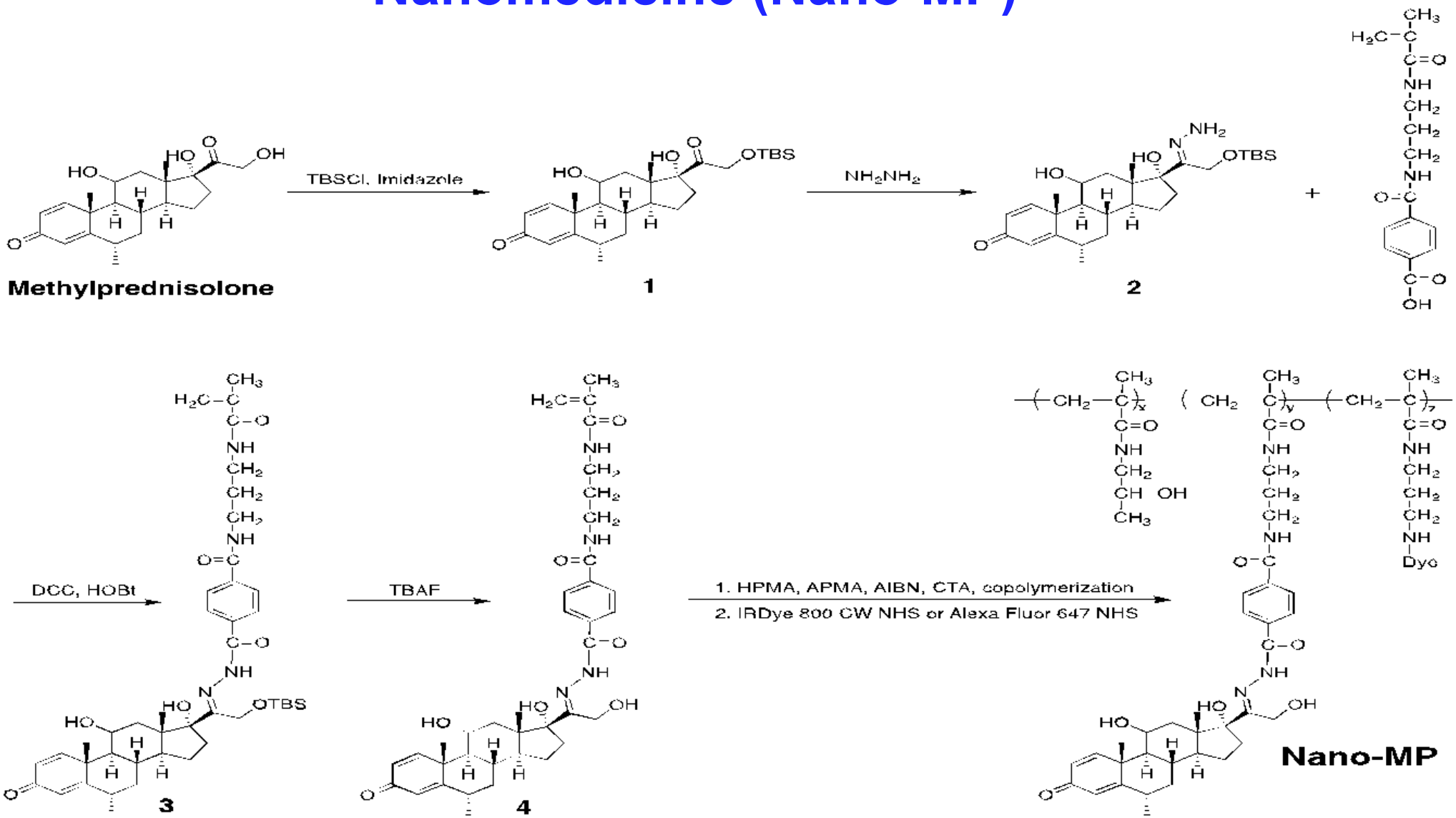
# Nanotechnology-enabled Methylprednisolone (MP) for Better Neuroprotection after Acute SCI

## The goal of this project

**is to develop a novel polymeric prodrug nanomedicine that**

- **Selectively delivers MP to sites of injured and/or inflamed spinal cord**
- **Minimizes unwanted distribution and exposure to other tissues**
- **Reduces untoward side effects (e.g., muscle, bone, immune cells and glucose metabolism).**
- **Improves neuroprotection and functional recovery.**

# Synthesis of HPMA Copolymer-based methylprednisolone Prodrug Nanomedicine (Nano-MP)



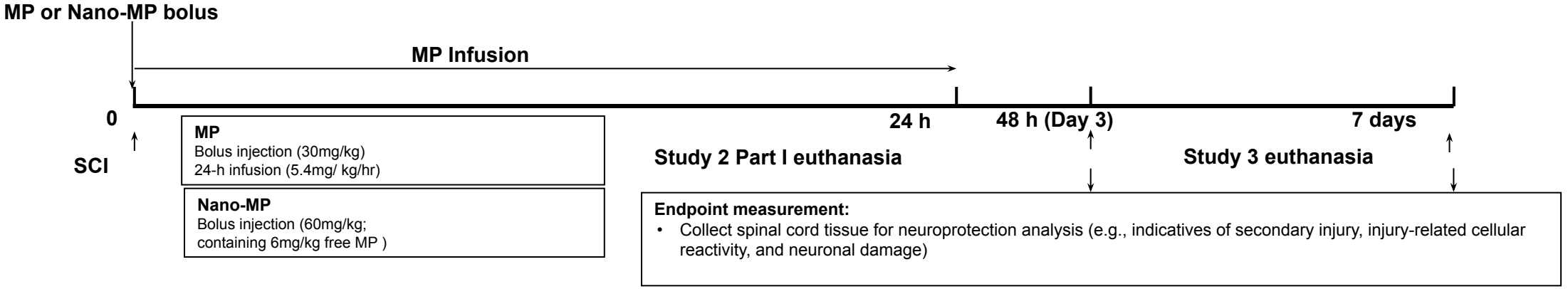

a *N*-(2-hydroxypropyl) methacrylamide (HPMA)

*Patent Application: PCT-US20-054559*

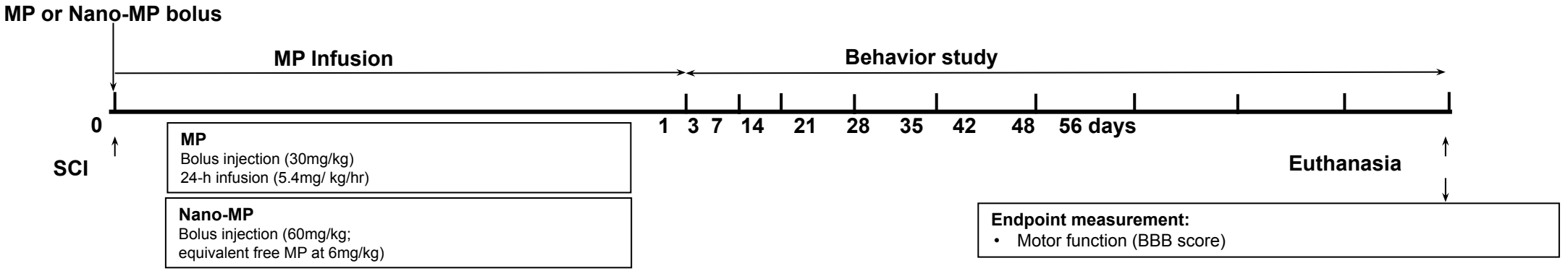
# Experiment Design (Efficacy Study)

**A. Study 1 (evaluate biodistribution)**


**B. Study 2 Part I & Study 3 (evaluate neuroprotection)**

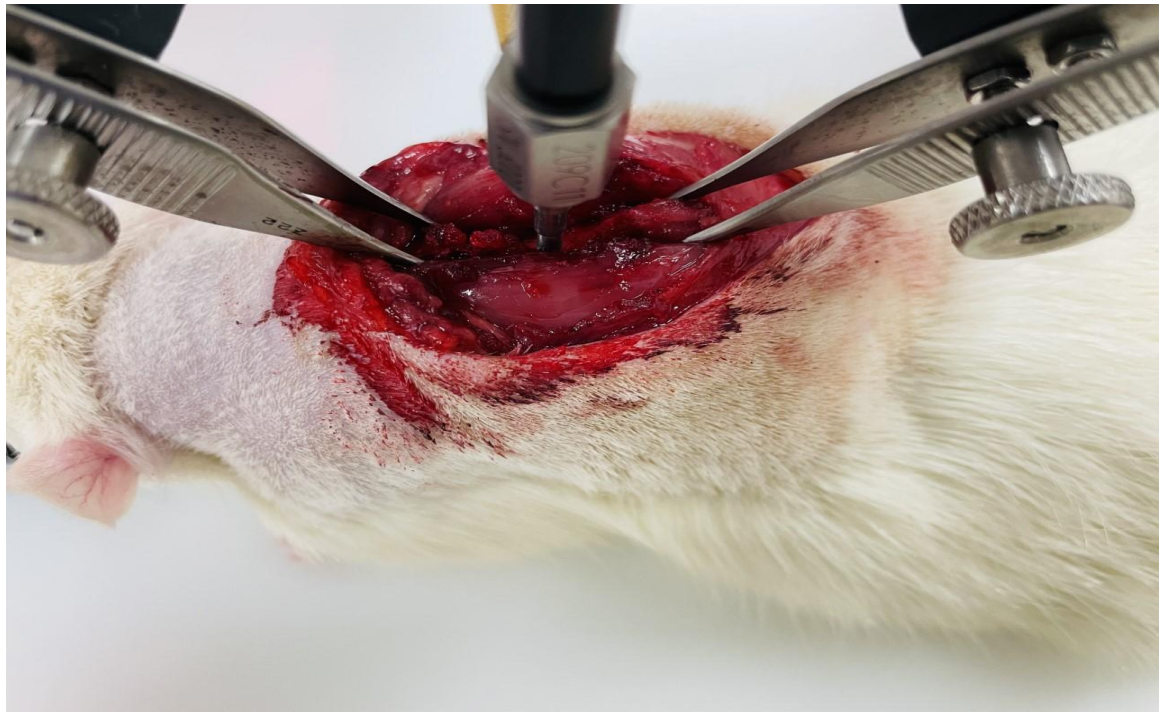



**C. Study 4 Part I (evaluate functional recovery)**



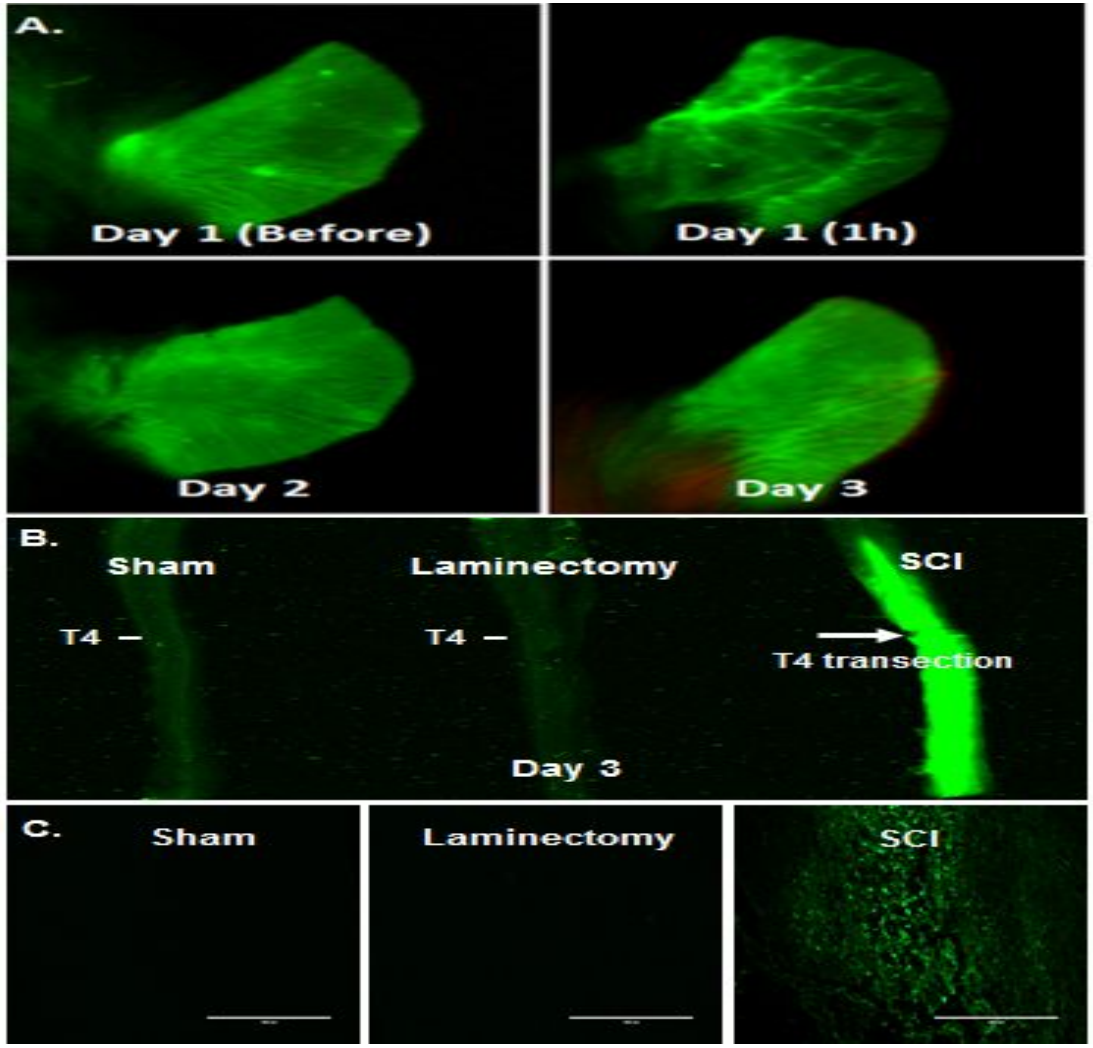

*Patent: Application PCT-US20-054559*

# Spinal Cord Injury Surgery



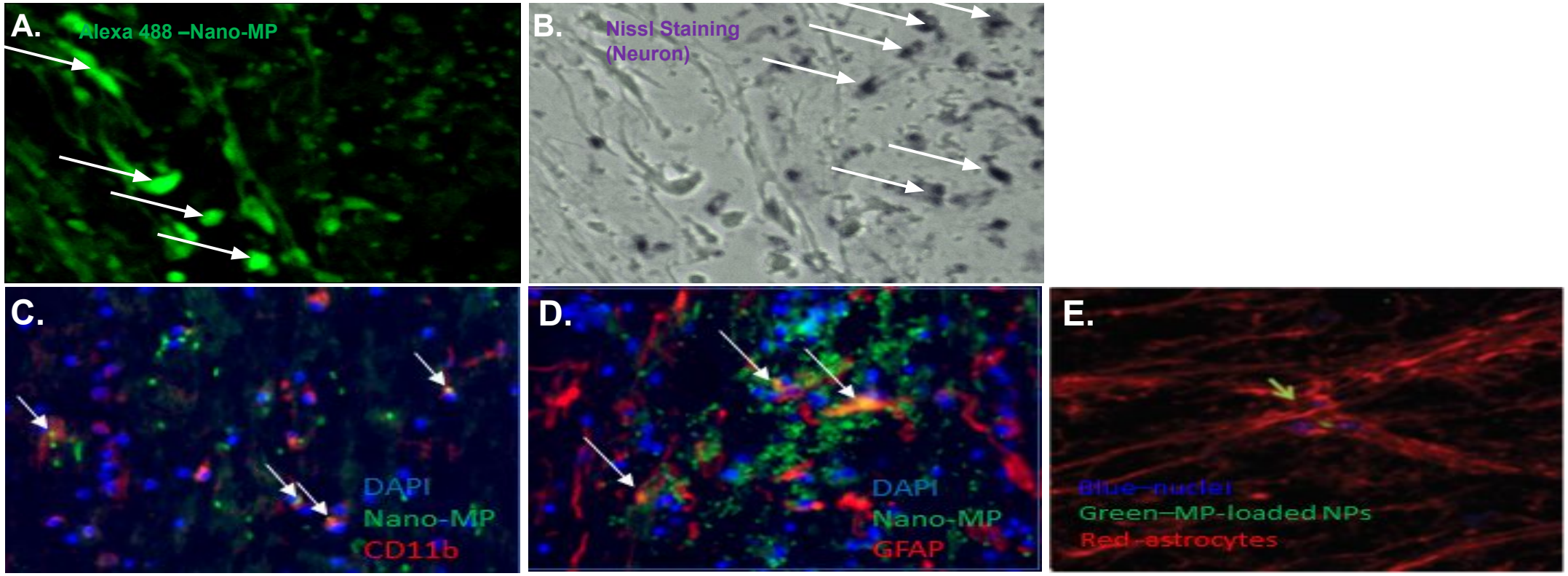
An Infinite Horizontal (IH) Impactor

# The Selective Uptake of Nano-MP in the Injured Spinal Cord




*Patent: Application PCT-US20-054559*

# Internalization of Nano-MP by microglia and astrocytes

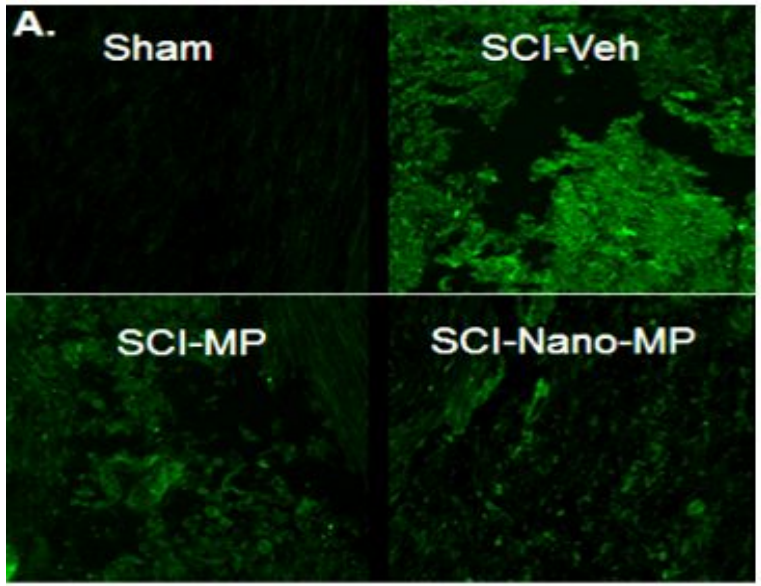



*(E). Cerqueira et al. (2013) reported that internalized nanoparticles (CMCht/ PAMAM-MP) at the lesion site of the spinal tissue 3 h after injury. By comparison, our Nano-MP-Alexa 488 (C and D) showed significantly higher fluorescent signal than CMCht/ PAMAM-MP could achieve (E), suggesting that a greater therapeutic efficacy can be achieved by our Nano-MP approach.*

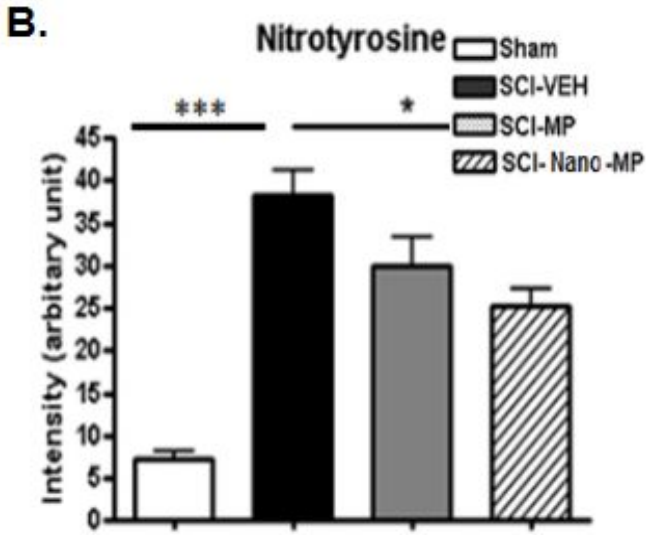
*Patent: Application PCT-US20-054559*

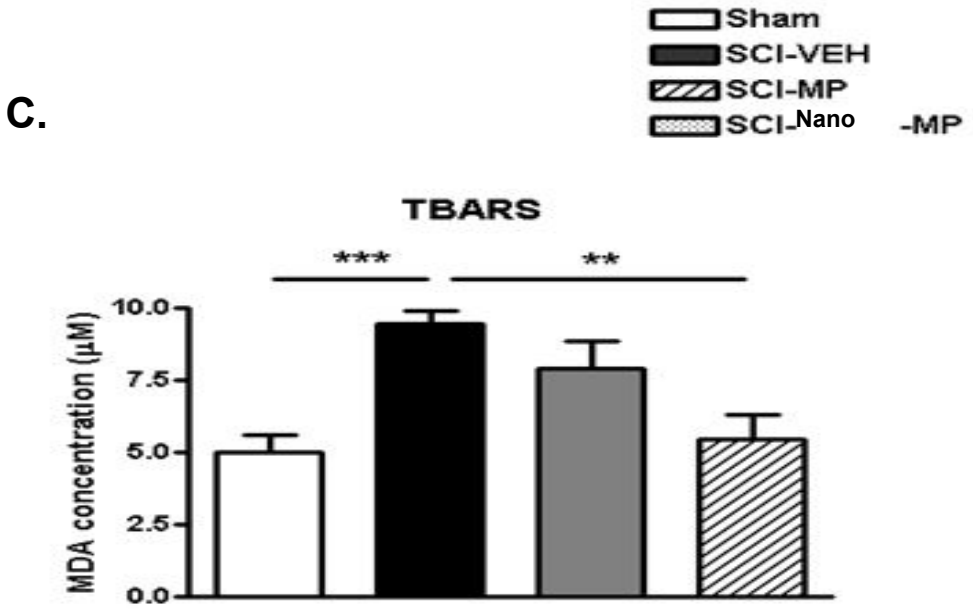
# Nano-MP Attenuated SCI-induced Oxidative Stress & Lipid Peroxidation in the Spinal Cord

## 2 days




Nitrotyrosine → nitric oxide (NO)



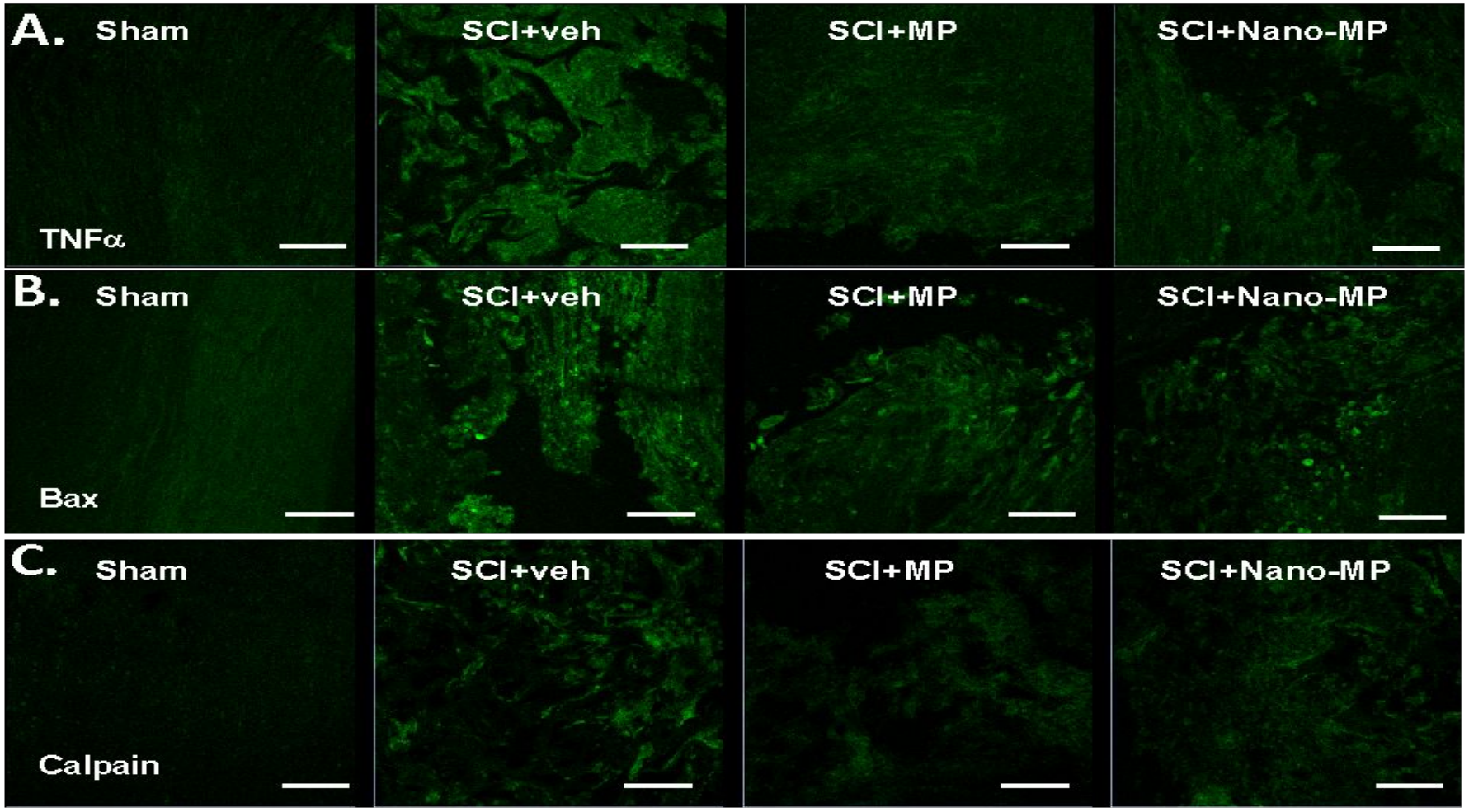



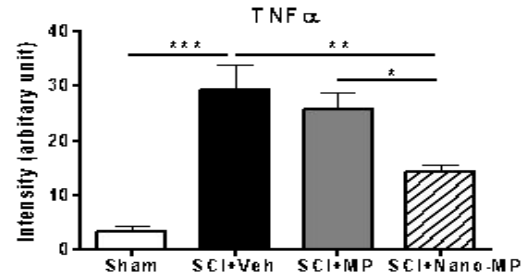

Malondialdehyde (MDA) as an indication of lipid peroxidation

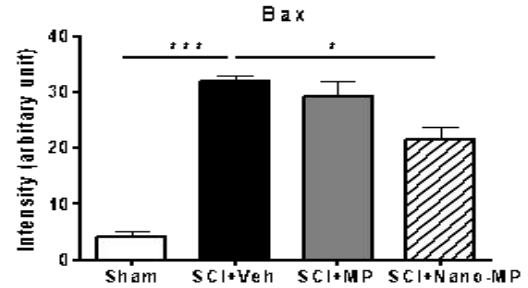
*Patent: Application PCT-US20-054559*

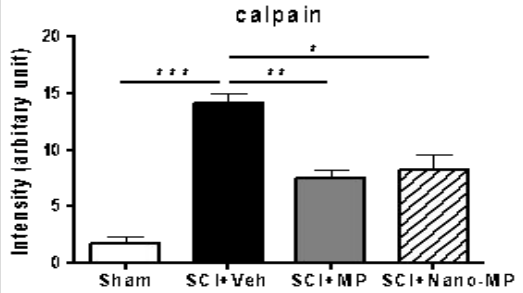
# Effects of Nano-MP on Inflammation and Pro-apoptotic Markers after Acute SCI

## 2 days



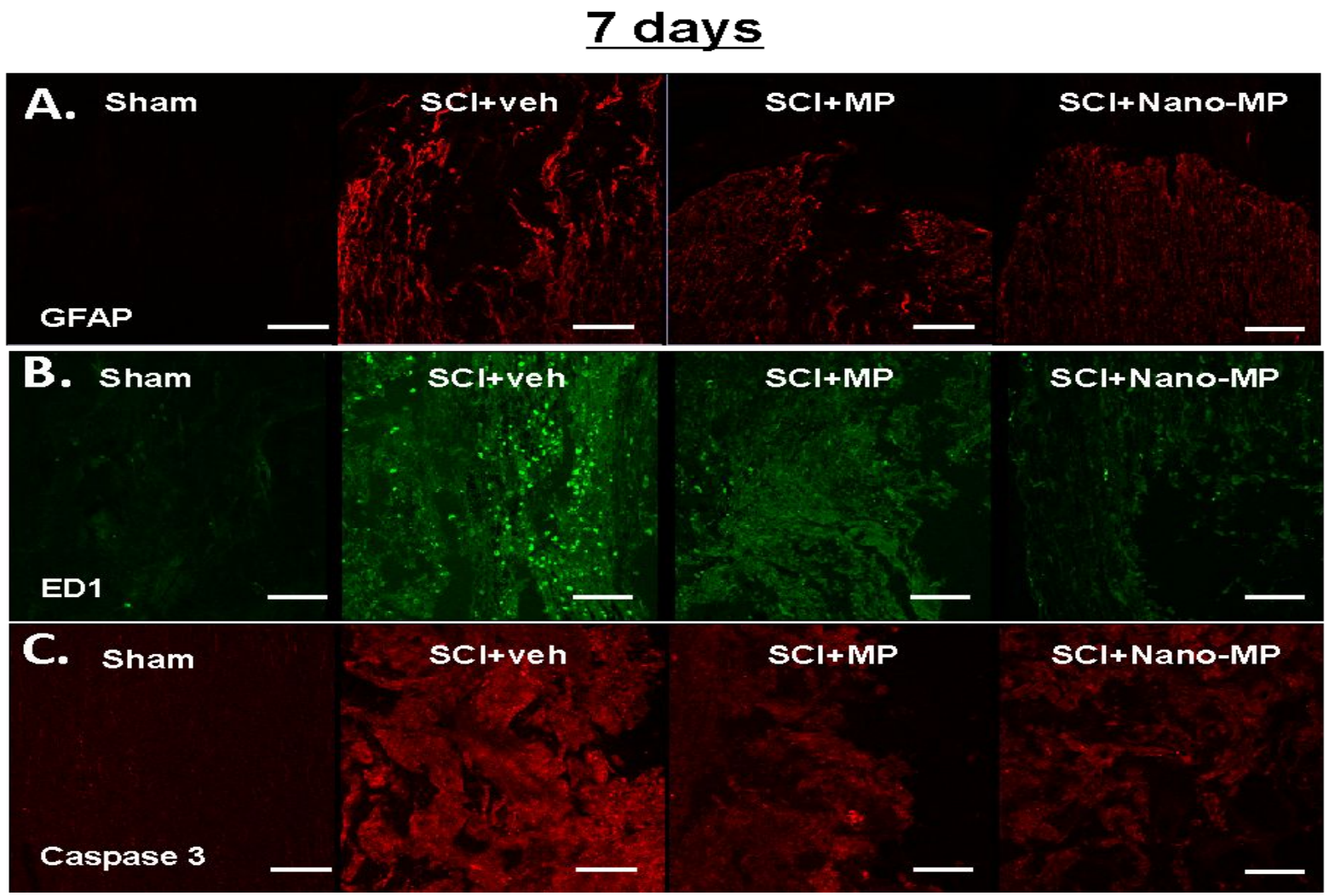



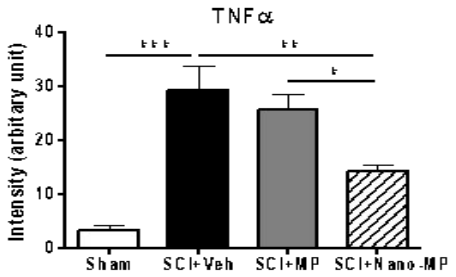



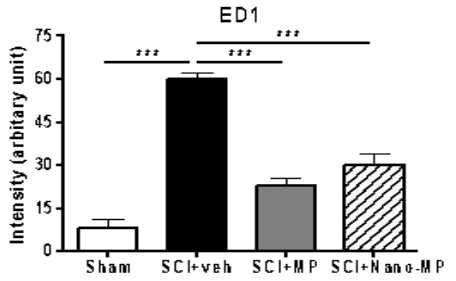



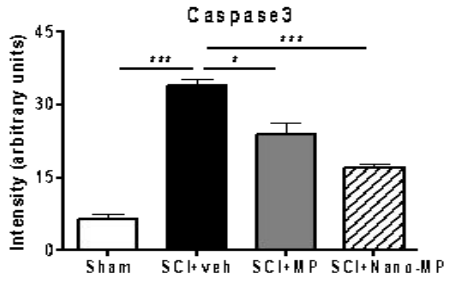

*Patent: Application PCT-US20-054559*

# Effect of Nano-MP on the Expressions of Injury-related Cellular Marker & Caspase-3 After Acute SCI



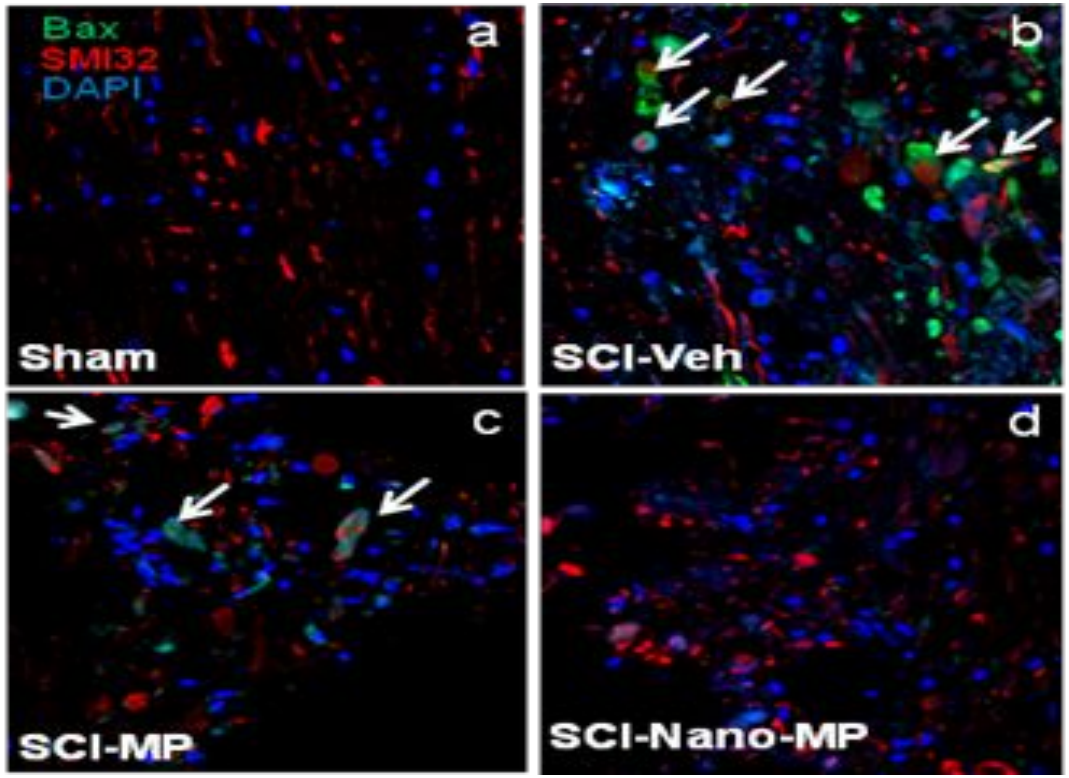



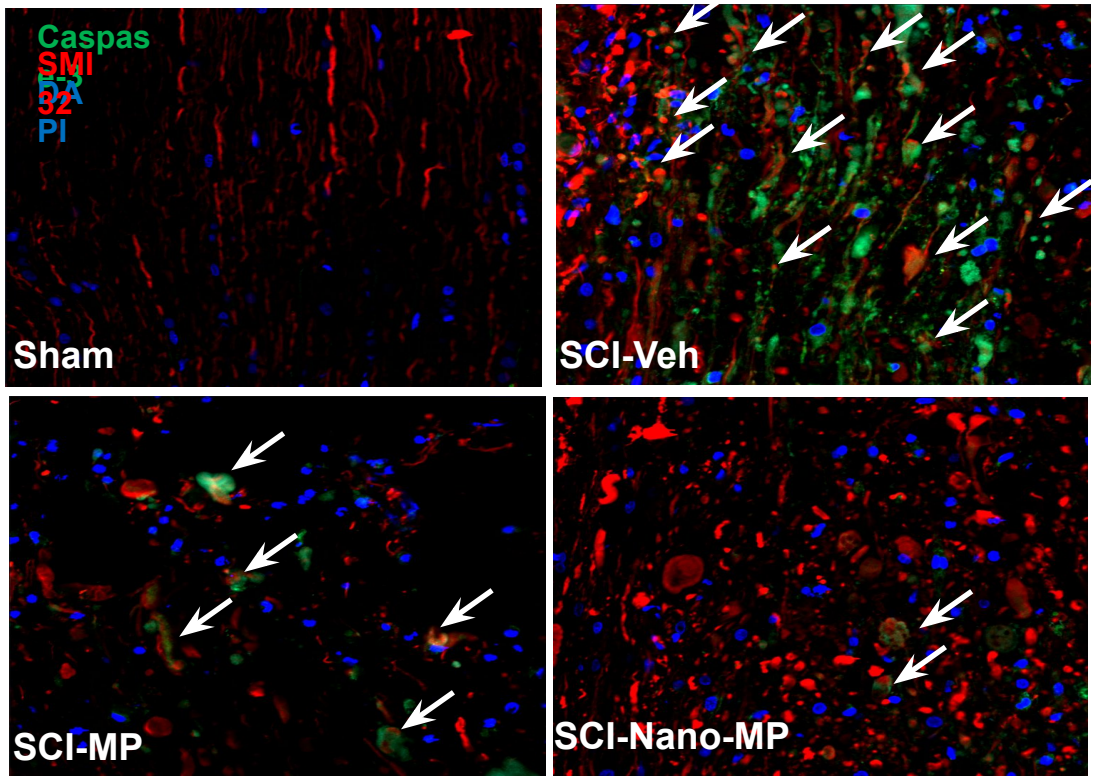

*Patent: Application PCT-US20-054559*

# Nano-MP Decreased SCI-induced Motor Neuron Apoptosis in the Spinal Cord

**Bax**



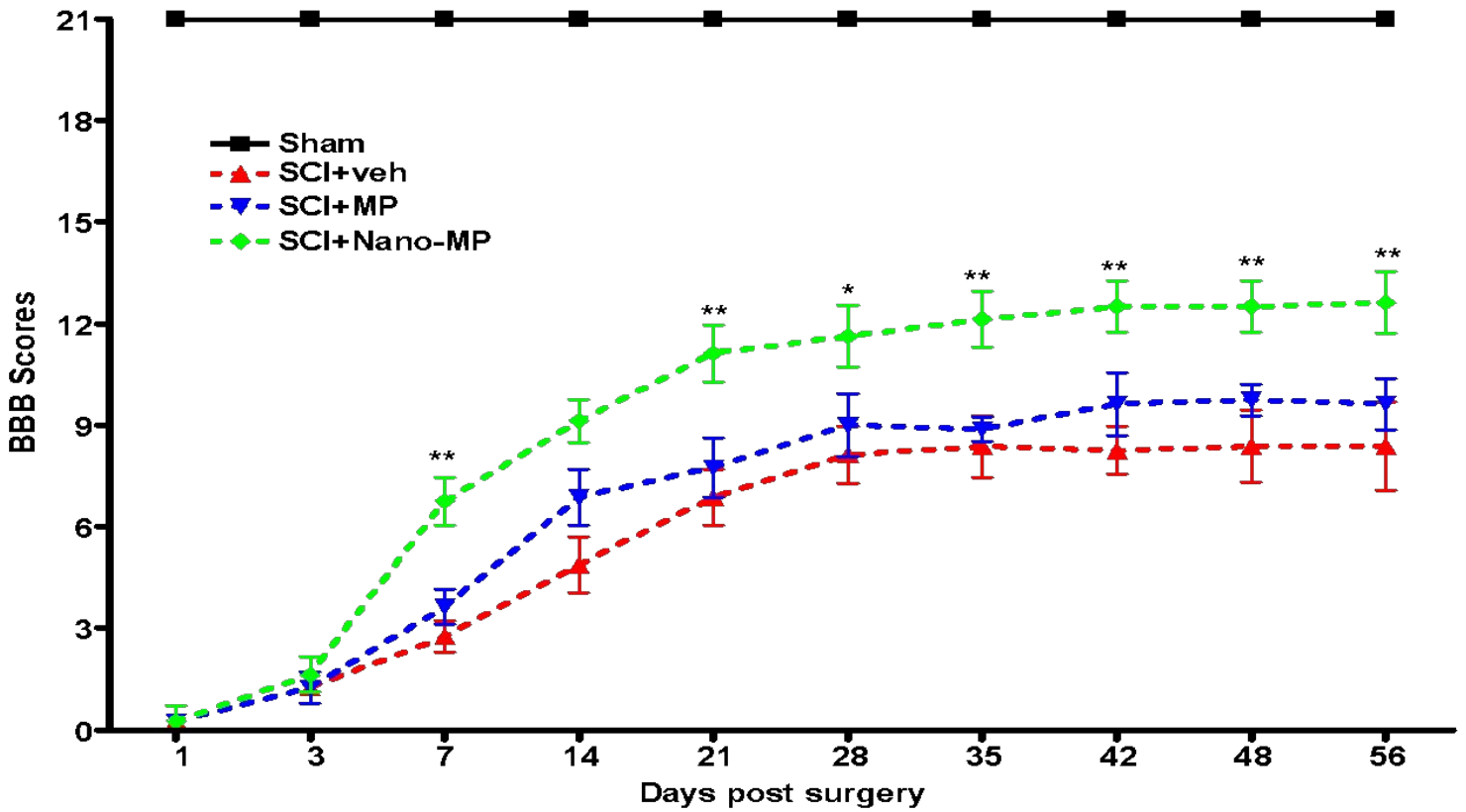

**Caspase-3**




**7 days**

*Patent: Application PCT-US20-054559*

# Nano-MP Promoted functional Recovery After Acute SCI

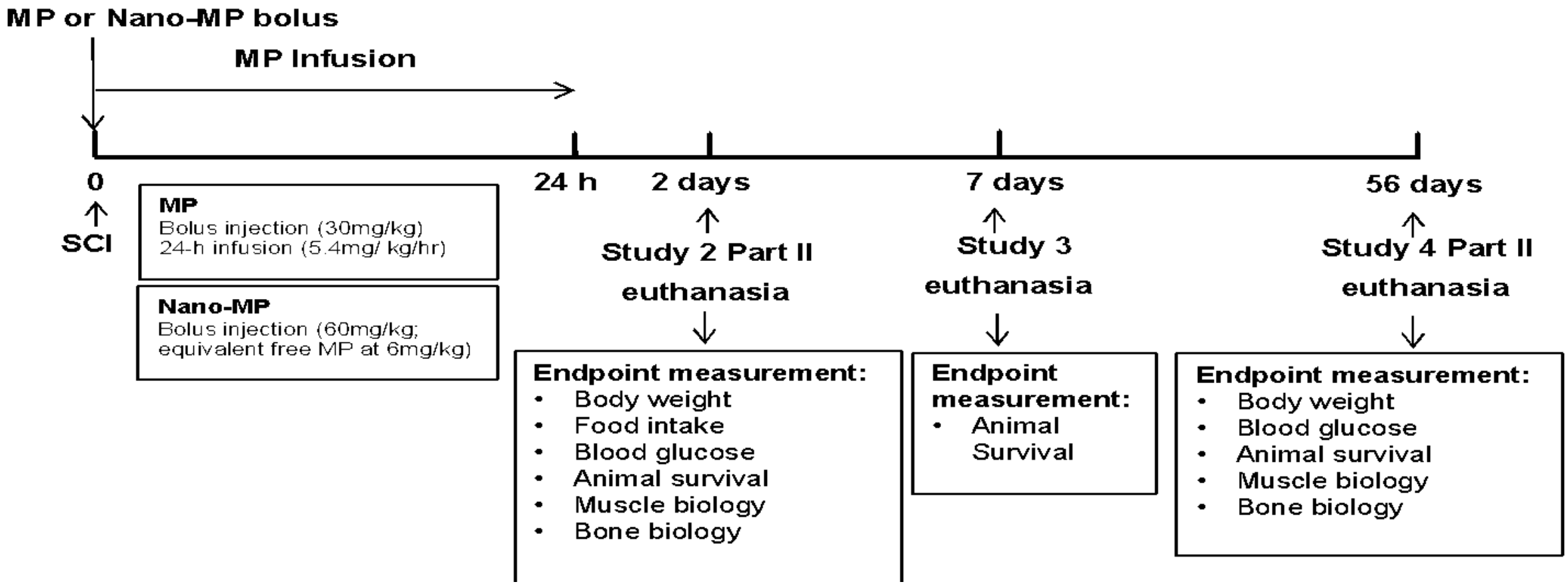



**Locomotor function testing ty the Basso, Beattie and Bresnahan (BBB) locomotor scale analysis**

*Patent: Application PCT-US20-054559*

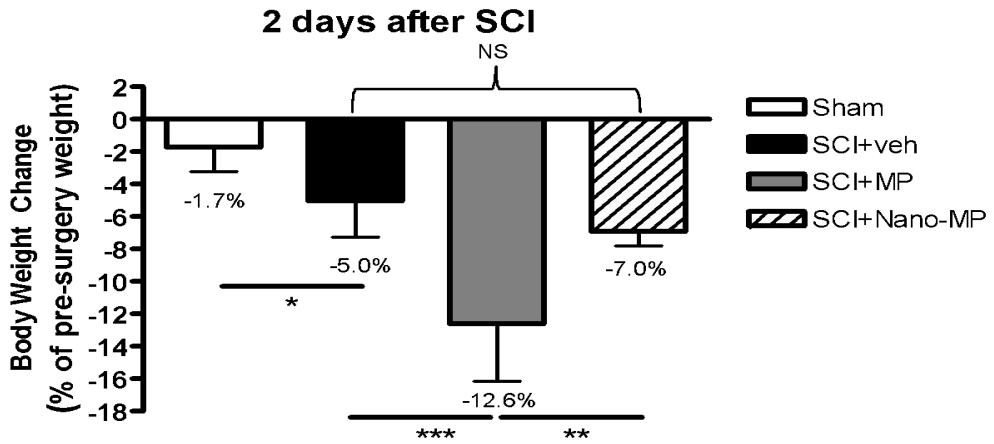
# Experiment Design (Side Effect Study)

## Study 2 Part II, Study 3 & Study 4 Part II (evaluate side effects)

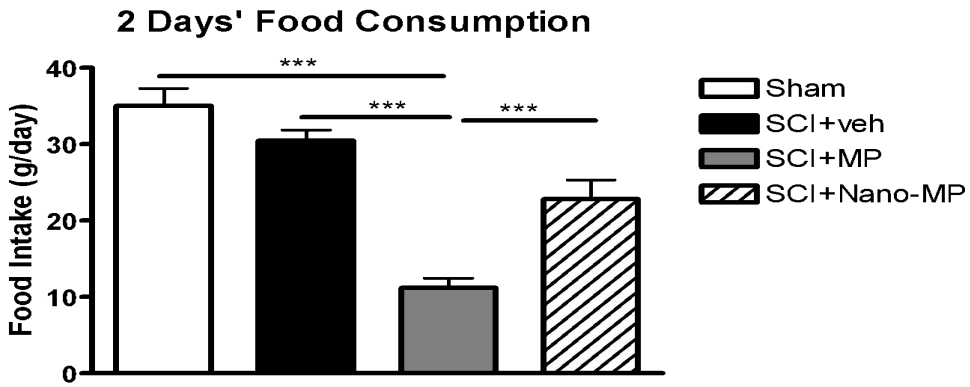


# General Heath Parameters

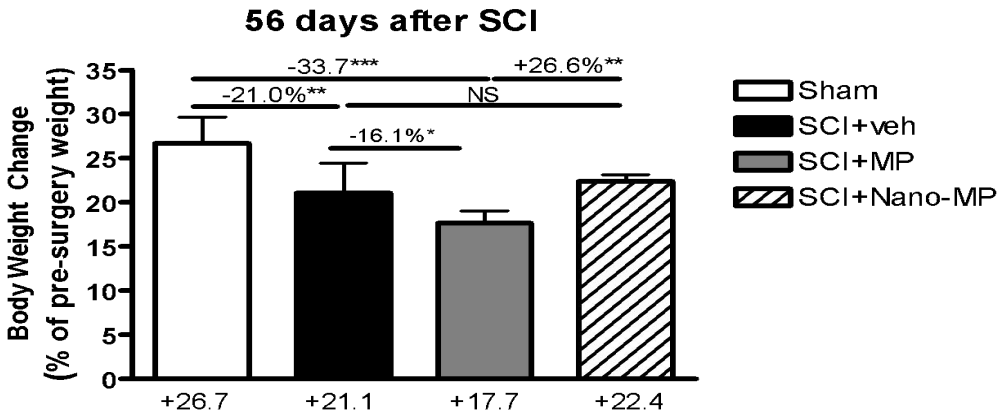
A.




B.




C.

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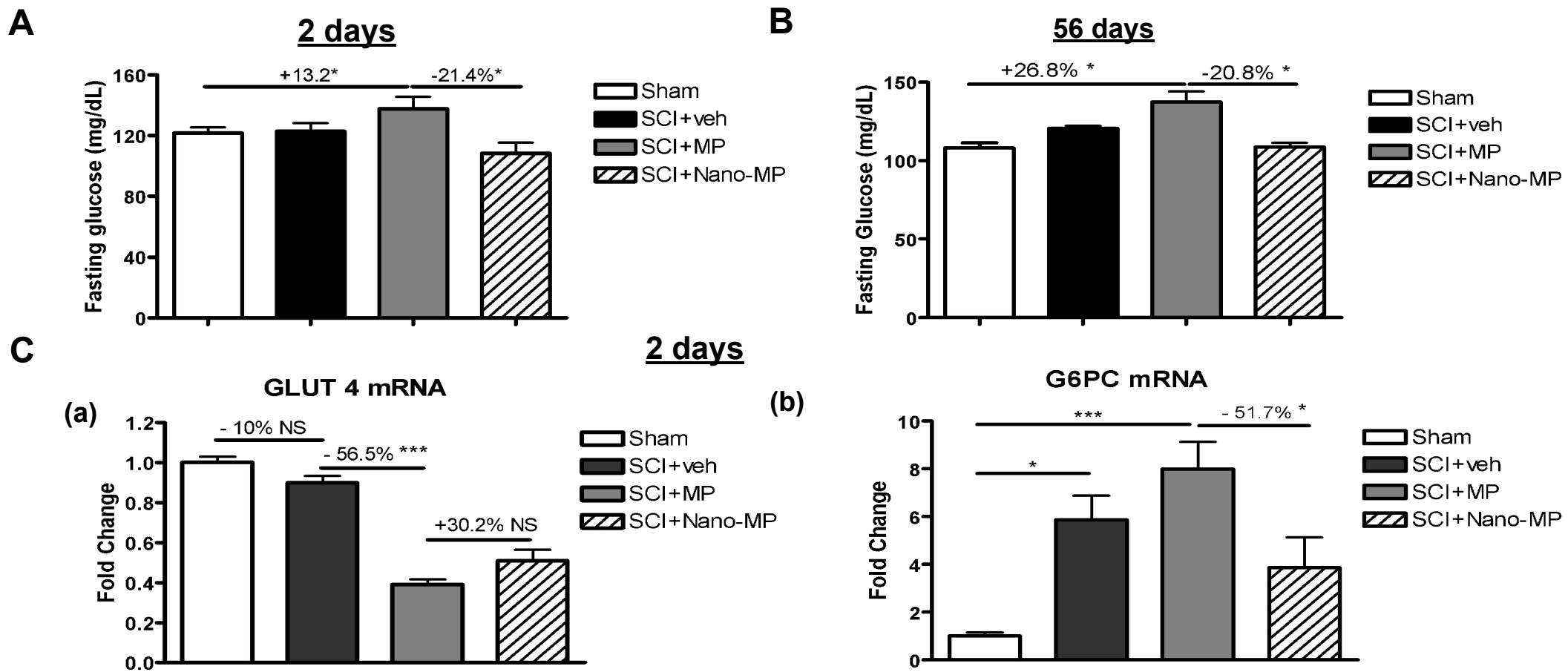
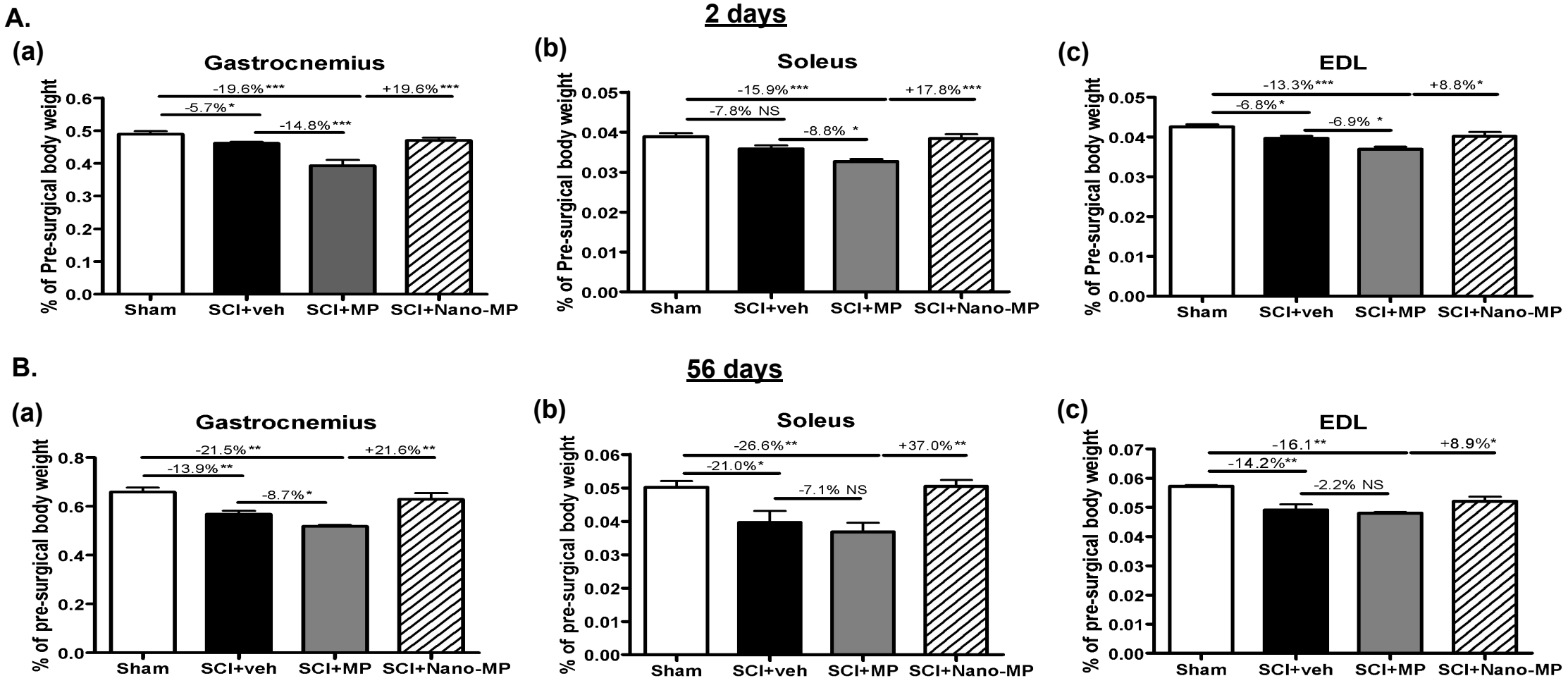
# Glucose Metabolism



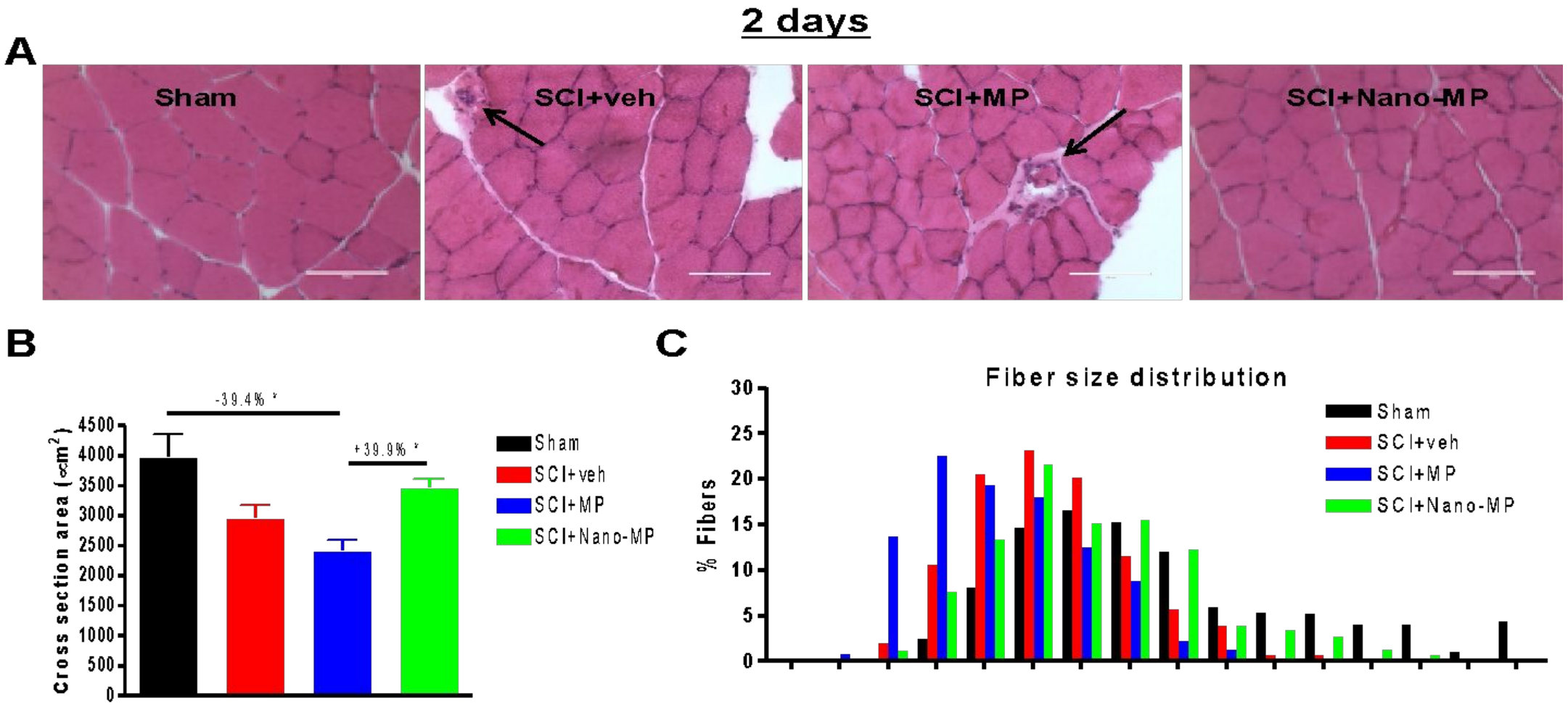

*Patent: Application PCT-US20-054559*

# Nano-MP Administration Reduces MP-associated Muscle Atrophy after Acute SCI



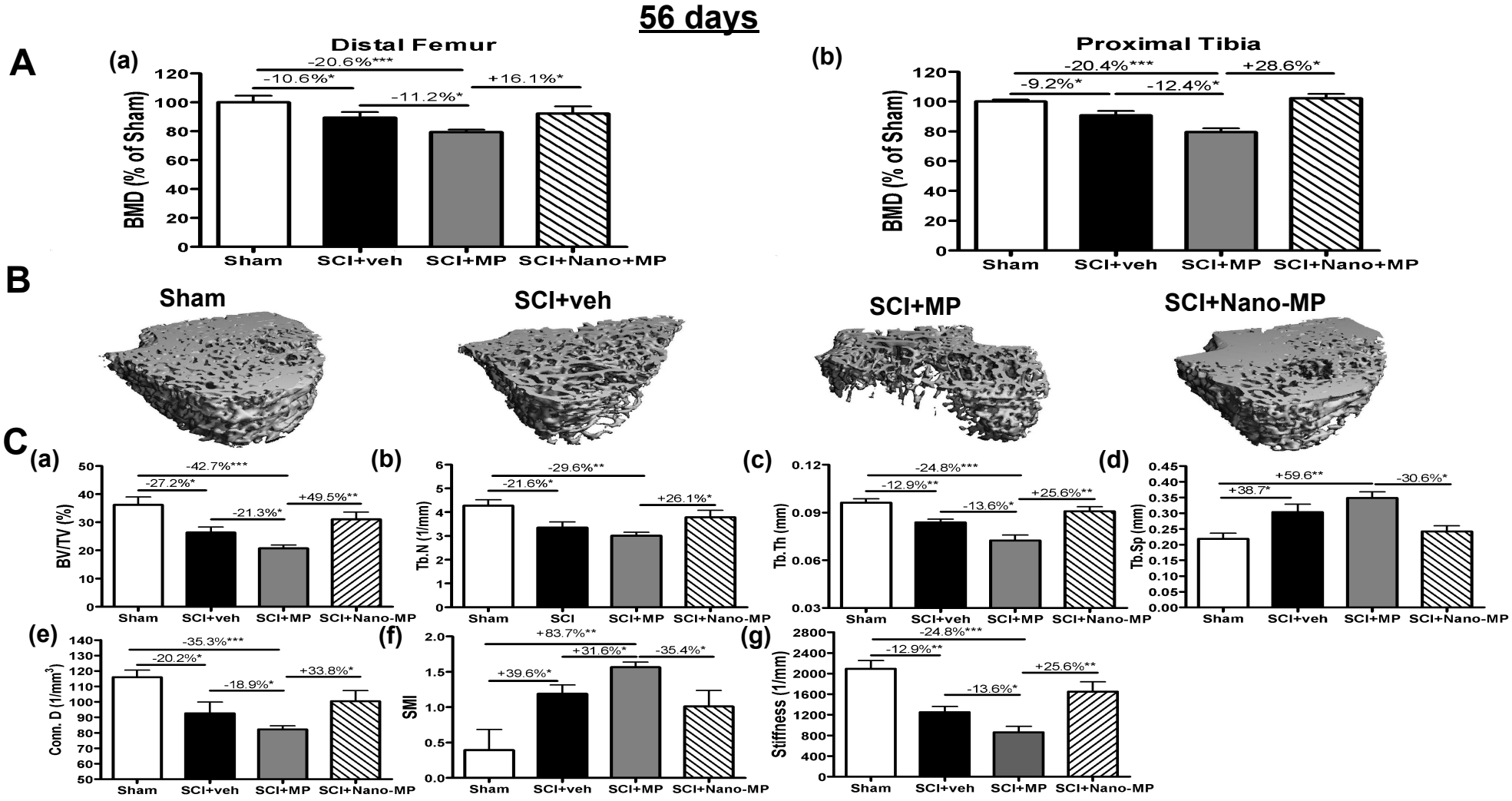

*Patent: Application PCT-US20-054559*

# Nano-MP Administration Reduces MP-associated Muscle Structure Defects after Acute SCI




*Patent: Application PCT-US20-054559*

# Nano-MP Administration Reduces MP-associated Impairment on Bone Integrity at 56 Days after Acute SCI




*Patent: Application PCT-US20-054559*

# Key Findings

- **Targeted delivery:** We developed a novel polymeric MP prodrug nanomedicine (Nano-MP) that delivers MP to the sites of injured and/or inflamed spinal cord, minimizing unwanted distribution and exposure to other tissues.

- **Improved neuroprotection:** Targeted delivery of low dose of Nano-MP is significantly more effective than MP in attenuating the reactivity of early markers of injury/secondary injury, such as oxidation, lipid peroxidation, inflammation, neural apoptosis, thereby improving neuroprotection and functional recovery.

- **Reduced side effects:** Our data clearly demonstrate that systemic administration of a Nano-MP prodrug in a rat model of SCI protects animals from high dose MP-induced glucose dysregulation, muscle atrophy and osteoporosis.

- **Clinical implication:** This systemically administered, yet SCI site targeted **low-dose** of Nano-MP may serve as an innovative therapeutic strategy for neuroprotection with potential to reduce unwanted side effects in patients with acute SCI.

# Future Directions

- Perform a temporal and/or dose-response curve of Nano-MP and/or other adjunctive therapies on biologic, pathologic and functional outcome measures in the future to facilitate clinical translation of Nano-MP therapy.

- Perform additional experiments to develop in-depth understanding of Nano-MP's mechanism of action (*e.g.*, inflammatory cascades, glia scar formation, axon regeneration, *etc.*). Bioinformatics to discover novel key drivers, pathways and gene networks

- Extrapolate the same design principle in this study to several other drug candidates in order to improve their efficacy and safety, including CSP inhibitors which reduce glia scar, PTEN, Nogo-A and Rho inhibitors, or other neurotrophic factors which promote axon regeneration.

# Acknowledgement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