

BPC-157

BPC-157

Rat **osteoarthritis was rescued** with BPC 157, (10 ng/kg either ip once daily or in drinking water 0.16 ng/ml/12ml/day) preserved cartilage and bone, confirmed by X ray exam, and walking, leg pressure force, knee mobility were improved, and rat's leg length maintained.

Sikiric, P. "Pentadecapeptide BPC 157 and Rat Osteoarthritis." *The FASEB Journal* 27, no. S1 (2013): 888.9-888.9.

BPC 157 induced faster **muscle healing in transected quadriceps muscle and muscle crush injury to full function restoration** and improved muscle healing **despite systemic corticosteroid treatment** when given intraperitoneally or locally and demonstrated functionally, macroscopically, and histologically at all investigated intervals

Pevec, D. "Impact of Pentadecapeptide BPC 157 on Muscle Healing Impaired by Systemic Corticosteroid Application." *Medical Science Monitor* 16, no. 3 (March 1, 2010): BR81-88.

BPC-157

Full recovery of the myotendinous junction

Staresinic, M. “Stable Gastric Pentadecapeptide BPC 157 and Striated, Smooth, and Heart Muscle.” *Biomedicines* 10, no. 12 (December 12, 2022): 3221.

Consistent, functional, biomechanical macroscopic and histological **healing of MCL** transection whether given oral/IP or topical x21 days

- More collagen type 1, less type 3 (organization)

- Absent postinjury contracture

- No valgus instability

- Reduced inflammation

Cerovecki, T. “Pentadecapeptide BPC 157 (PL 14736) Improves Ligament Healing in the Rat.” *Journal of Orthopaedic Research* 28, no. 9 (2010): 1155–61.

GW 501516

Cardarine

A selective PPAR delta agonist (peroxisome proliferator-activated receptors) - a group of steroid- and thyroid-sensing proteins that **control the expression of genes**, reducing hepatic glucose production, **increasing fatty acid catabolism in adipocytes and muscle** and lowering inflammation.

GW also regulates the various proteins that the body uses for energy, resulting in an increase in **energy and endurance**, and it may also mean an **increase in muscle mass**. It is also possible that GW might have a positive effect on **blood pressure and lipid** profile and osteoporosis.

Dosing is 10-15mg x 4 to 12 weeks. It does stack well with SARMS to further increase **fat loss** and **endurance**.

Smith RW, Coleman JD, Thompson JT, Vanden Heuvel JP. Therapeutic potential of GW501516 and the role of Peroxisome proliferator-activated receptor β/δ and B-cell lymphoma 6 in inflammatory signaling in human pancreatic cancer cells. *Biochem Biophys Res.* 2016;8:395–402. Published 2016 Nov 4.

GW501516

Suppresses macrophage-derived inflammation

Promotes fatty acid metabolism over glucose utilization

Reduces TNF α -mediated decrease adiponectin translation

Dosing: 10-20mg caps daily

SE: tumorigenic?

Chen, W. A metabolomic study of the PPAR δ agonist GW501516 for enhancing running endurance in Kunming mice. Scientific Reports. 2015;5:9884

Kim, W. PPARB/ δ agonist GW501516 inhibits TNF α -induced repression of adiponectin and insulin receptor in 3T3-L1 adipocytes. Biochemical and Biophysical Research Communications. 2019;510(4):621-8.

Phua, W. An aPPARent functional consequence in skeletal muscle physiology via peroxisome proliferator-activated receptors. Int J Mol Sci. 2018;19(5):1425.

Selank

Synthetic peptide derived by stabilizing the sequence of tuftsin, which is part of the IgG **antibody** and is naturally-occurring.

- improves **memory**;
- acceleration of reaction** that is important for many sports;
- reduces **emotional tension** providing a soothing effect;
- improves **concentration**;
- strengthens the **immune** system;

•Shabanov, P. "Psychopharmacological properties of peptides with nootropic type of action." *Medical academic journal* 9, no. 2 (June 15, 2009): 91–97.

•Sokolov, O.. "Effects of Selank on Behavioral Reactions and Activities of Plasma Enkephalin-Degrading Enzymes in Mice with Different Phenotypes of Emotional and Stress Reactions." *Bulletin of Experimental Biology and Medicine* 133, no. 2 (February 2002): 133–35.

SEMAX

ACTH fragment 4-10 with N-acetyl for stability

Works on BDNF>Tkrb receptor in hippocampus, DA, SA, Melanocortin receptor 3, 4

Contributes to mitochondrial stability under oxidative stress

Significantly **improves memory and attention** in healthy men under extreme conditions of activities

Due to effects on carboxypeptidase, may **increase physical performance and adaptation** to high intensity exercise

Antidepressant, antianxiety, mental fatigue

Check QA, KA prior to starting and replace appropriate B vitamins.

300-1000mcg SQ/IN qd for 6 weeks-3 months; twice a week alternating w Selank

SEMAX REFERENCES

Umnov, R. “[Neuroprotective effects of peptides bioregulators in people of various age].” *Advances in Gerontology = Uspekhi Gerontologii* 26, no. 4 (2013): 671–78.

Rusinova, E. V., and V. G. Skrebetskii. “[The influence of neuronal discharge on the effectiveness of its synaptic inputs].” *Zhurnal Vysshei Nervnoi Deiatelnosti Imeni I P Pavlova* 25, no. 6 (1975): 1312–15.

Vasileva, E. “Predominance of Nootropic or Anxiolytic Effects of Selank, Semax, and Noopept Peptides Depending on the Route of Administration to BALB/c and C57BL/6 Mice.” *Neurochemical Journal* 14, no. 3 (July 1, 2020): 268–78.

Manchenko, D. M., N. Iu Glazova, N. G. Levitskaia, L. A. Andreeva, A. A. Kamenskiĭ, and N. F. Miasoedov. “[Nootropic and analgesic effects of Semax following different routes of administration].” *Rossiiskii Fiziologicheskii Zhurnal Imeni I.M. Sechenova* 96, no. 10 (October 2010): 1014–23.

MOTS-C

Young and old mice given 5mg/kg (HE 25-40mg/day) or 15mg/kg/day (HE 70-120 mg/day) x10+d:

Improved **skeletal muscle insulin sensitivity**

Improved **physical capacity and motor coordination**

Retarded fat gain and increased lean mass regardless of diet.

The skeletal muscles of **non-exercised** mice **did not show** significant alterations in response to MOTS-c

Restoration of **metabolic flexibility**, respiratory exchange ratio, and **circadian rhythmicity** of metabolic flexibility

Reynolds, J. "MOTS-c Is an Exercise-Induced Mitochondrial-Encoded Regulator of Age-Dependent Physical Decline and Muscle Homeostasis." *Nature Communications* 12 (January 20, 2021): 470.

Lee, C. "MOTS-c: A Novel Mitochondrial-Derived Peptide Regulating Muscle and Fat Metabolism." *Free Radical Biology & Medicine* 100 (November 2016): 182.

RENIN ANGIOTENSIN SYSTEM (MORE PATHOPHYSIOLOGY)

Brain Renin Angiotensin System (RAS)

Renin cleaves Ang I, Ang I then converted to Ang II by ACE or Ang 1-7 by ACE2 or Ang IV

ANG II induces **insulin resistance** by **increasing cellular oxidative stress, impairing insulin signaling** and **insulin-stimulated glucose transport**

Angiotensin II receptors type 1(AT1R) causes release of **proinflammatory** cytokines, cell death, **oxidative stress and vasoconstriction**.

AT2R activation **decreases neuroinflammation and oxidative stress** and improves overall cell survival (Mirzahosseini 2021)

DIHEXA

An Angiotensin IV analog signals via AT4R/IRAP (insulin-regulated aminopeptidase)

Signaling **increases transport of GLUT4** to cell membrane of neurons, reduces inflammation, enhances cerebral blood flow, increases neuronal glucose uptake

Well-established **enhancement of cognitive function** in rodent models of CNS insult

Intracerebral or IP administration reverse **scopolamine-induced amnesia, ischemic stroke and knife cuts** to the brain

Janatpour, Z. "The Extended Renin-Angiotensin System: A Promising Target for Traumatic Brain Injury Therapeutics." *Neural Regeneration Research* 15, no. 6 (December 10, 2019): 1025–26.

DIHEXA

An AngIV analog metabolically stable, BBB permeant and orally active

Binds to HGF with high affinity, initiating increased cellular proliferation, motility and differentiation

Enhances hippocampal spinogenesis and synaptogenesis

The HGF/c-Met system is designed to **respond to injury** when markedly enhanced synaptic plasticity is beneficial, as seen in stroke and neurodegenerative diseases.

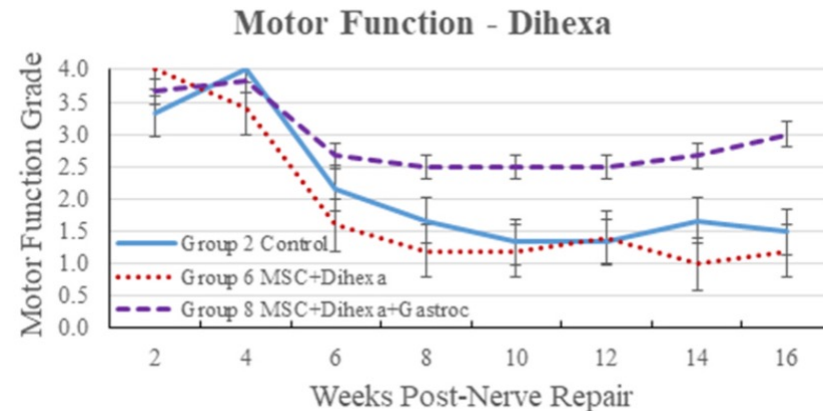
Benoist, C. "The Procognitive and Synaptogenic Effects of Angiotensin IV-Derived Peptides Are Dependent on Activation of the Hepatocyte Growth Factor/c-Met System." *The Journal of Pharmacology and Experimental Therapeutics* 351 (September 3, 2014).

DIHEXA

Rat sciatic nerve transection and repair

Dihexa 2-4mg/kg (HED 15) IM gastrocnemius +/- MSCs and G-CSF

Sensory and motor function in all nerve boundaries (peroneal, tibial, sural) returned to nearly normal by 8 weeks



Weiss, J. "Stem Cell, Granulocyte-Colony Stimulating Factor and/or Dihexa to Promote Limb Function Recovery in a Rat Sciatic Nerve Damage-Repair Model: Experimental Animal Studies." *Annals of Medicine and Surgery* 71 (November 1, 2021): 102917.

CEREBROLYSIN

A mixture of neurotrophic factors and peptides that acts in the brain to attenuate oxidative or cellular stress.

Early intervention (5 minutes to 1 hour) with Cerebrolysin (10-30 mcl) reduces BBB and BCSFB permeability changes, attenuates brain pathology and brain edema, and mitigates functional deficits in rat model of TBI.

Sharma, H. "Cerebrolysin Reduces Blood-Cerebrospinal Fluid Barrier Permeability Change, Brain Pathology, and Functional Deficits Following Traumatic Brain Injury in the Rat." *Annals of the New York Academy of Sciences* 1199 (June 2010): 125–37.

Intra-tail vein injection of 10mcl Cerebrolysin decreased astrocyte activation, oxidative stress and tau expression, suggesting neuroprotection after TBI.

Gang, H. 송희정, and 김동운. "Cerebrolysin Attenuates Astrocyte Activation Following Repetitive Mild Traumatic Brain Injury: Implications for Chronic Traumatic Encephalopathy." *Journal of Life Science* 23, no. 9 (September 30, 2013): 1096–1103.

PEPCK

In gluconeogenesis, converts oxaloacetate to phosphoenol pyruvate

Increased upon secretion of cortisol, glucagon

Inhibited by insulin

Decreases adipose tissue and muscle fatigue

Genetic PEPCK-Cmus mice use fatty acids as fuel more efficiently and produce less lactate than controls,

Little triglyceride in adipose despite eating 60% more than control

Hanson, R. Born to run; the story of PEPCK-Cmus mouse. Biochimie. 2008;90(6):838-42.

PEPCK

CAUTION: Overexpression may cause insulin resistance, cancer, aggression?

Dosing: 2.5mg weekly x6w WITH HIIT and CJC-Ipa, then every 2 weeks x6w

Lyophilized, must use within one week

AT1001/LARAZOTIDE


Larazotide is a novel, **locally acting**, non-systemic, synthetic **8-amino acid oral peptide**, discovered during functional screening of synthetic *Vibrio cholera* related peptides.

Larazotide acetate is a first-in-class **tight junction (TJ) regulator**

Larazotide prevents opening of intestinal TJs by **promoting TJ assembly and actin filament rearrangement**, which prevents gluten/gliadin and pathogens from reaching the intestinal submucosa and triggering an **inflammatory response**, macrophage recruitment and increases in **intestinal permeability** (Hoilat 2021)

Intestinal barrier dysfunction plays an integral role in arthritis pathology and can be targeted to ameliorate disease

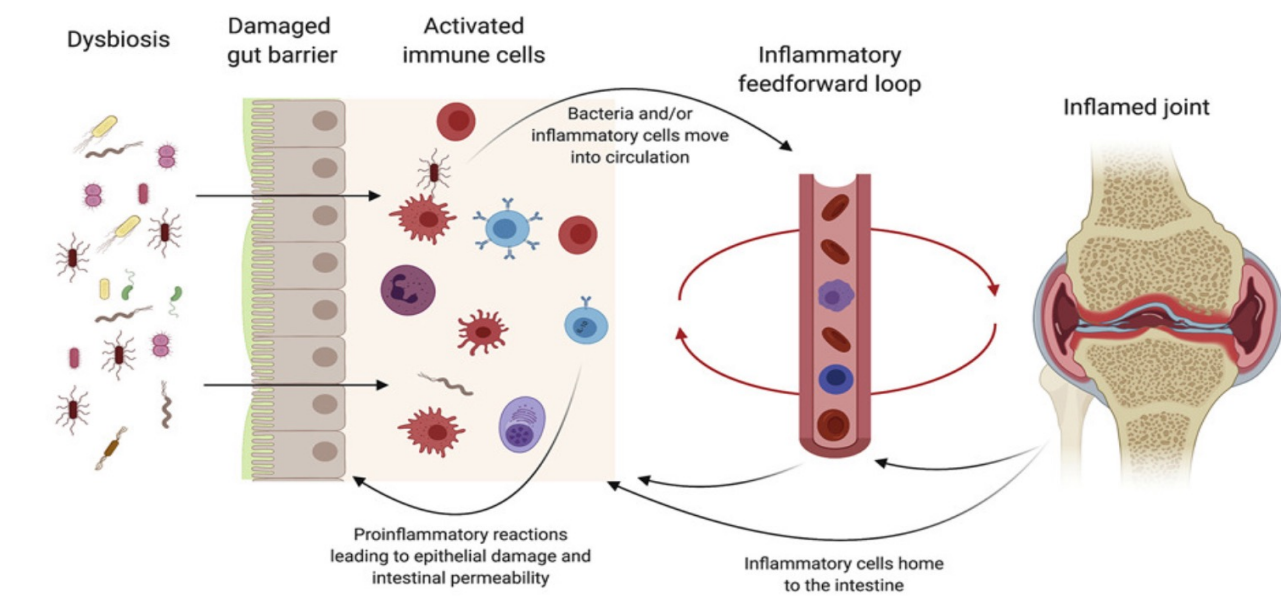
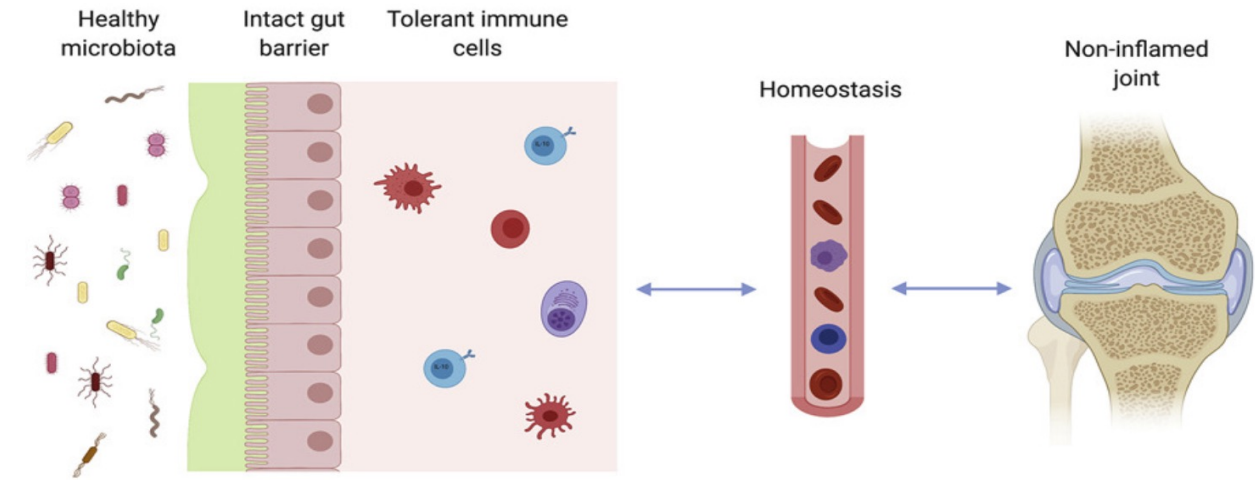
[Diana E. Matei](#) • [Madhvi Menon](#) • [Dagmar G. Alber](#) • ... [Nigel Klein](#) • [Paul A. Blair](#)  [15](#), [16](#) 

[Claudia Mauri](#)  [15](#)  • [Show all authors](#) • [Show footnotes](#)

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Arthritic mice display increased gut permeability from early stages of disease, as well as bacterial translocation, inflammatory gut damage, increases in interferon γ (IFN γ)⁺ and decreases in IL-10⁺ intestinal-infiltrating leukocyte frequency, and reduced intestinal epithelial IL-10R expression.

Treatment of mice with AT-1001, a molecule that prevents development of gut permeability, ameliorates arthritis.



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Leffler, D. “Larazotide Acetate for Persistent Symptoms of Celiac Disease Despite a Gluten-Free Diet: A Randomized Controlled Trial.” *Gastroenterology* 148, no. 7 (June 2015): 1311-1319.e6.

9 Meters Biopharma, Inc. “A Phase Ib, Randomized, Double-Blind, Placebo Controlled Study to Determine the Safety, Tolerance, Pharmacokinetic and Pharmacodynamic Effects of Single Doses of Larazotide Acetate (AT-1001) in Celiac Disease Subjects.” Clinical trial registration. clinicaltrials.gov, September 8, 2017. <https://clinicaltrials.gov/ct2/show/NCT00386165>.

Hoilat, G. “Larazotide Acetate for Treatment of Celiac Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.” *Clinics and Research in Hepatology and Gastroenterology*, July 31, 2021, 101782. <https://doi.org/10.1016/j.clinre.2021.101782>.

MELANOTAN II

α MSH is a 13aa peptide posttranslationally processed from proopiomelanocortin (POMC) released during stress, leptin exposure. It inhibits food intake, stimulates energy expenditure, regulates hair and skin pigmentation, reproductive and immune function

Melanotan II is a 7aa cyclic, truncated α MSH analog which has superpotent melatotrophic activity.

MELANOTAN II

16 elite wrestlers and 21 elite water polo players (mixed athletes)

Significant correlation in VO₂, HR **recovery** and αMSH blood levels

SE: stretching, yawning, nausea, spontaneous penile erections, increased skin pigmentation, caution? PMHx/FMHx melanoma (Wu 2020)

Dose: 50-200mcg SC twice a week

Popovic, D. "The Alpha-Melanocyte Stimulating Hormone Is Related to Heart Rate during Exercise Recovery." *Heliyon* 6, no. 11 (November 1, 2020): e05380.

Wu, J. "Topical MTII Therapy Suppresses Melanoma Through PTEN Upregulation and Cyclooxygenase II Inhibition." *International Journal of Molecular Sciences* 21, no. 2 (January 20, 2020): 681.

GLP-1

Found in skeletal muscle and muscle microvasculature

Restores GLUT4 mRNA, promoter activity and protein to **enhance glucose uptake**

Stimulates PGC1a, stimulates SIRT1 for **mitochondrial biogenesis**

Enhances physical endurance via skeletal muscle remodeling via AMPK signaling

Jeon, J. "GLP-1 Improves Palmitate-induced Insulin Resistance in Human Skeletal Muscle via SIRT1 Activity." *International Journal of Molecular Medicine* 44, no. 3 (September 1, 2019): 1161–71.

Haitham, A. "Physiological Mechanisms of Action of Incretin and Insulin in Regulating Skeletal Muscle Metabolism." *Current Diabetes Reviews* 10, no. 5 (August 31, 2014): 327–35.

GLP-1

Liraglutide 20mcg IA (rat) alleviated pain-related behavior, lowered inflammatory cytokines and catabolic enzymes in chondrocytes and shifted macrophages to anti-inflammatory M2 phenotype superior to dexamethasone at 10 days.

Meurot, C.. “Liraglutide, a Glucagon-like Peptide 1 Receptor Agonist, Exerts Analgesic, Anti-Inflammatory and Anti-Degradative Actions in Osteoarthritis.” *Scientific Reports* 12, no. 1 (January 28, 2022): 1567.

Que, Q. “The GLP-1 Agonist, Liraglutide, Ameliorates Inflammation through the Activation of the PKA/CREB Pathway in a Rat Model of Knee Osteoarthritis.” *Journal of Inflammation (London, England)* 16 (2019): 13.

“Safety, Tolerability and Pharmacokinetics of Intra-Articular (IA) Single Ascending Dose of 4P-004 in Patient With Kellgren and Lawrence Grade 2 to 4 Osteoarthritic (OA) Knee - Tabular View - ClinicalTrials.Gov.” Accessed February 1, 2023.

OXYTOCIN

Hypothalamic nonapeptide controls reproductive behavior, energy balance and lipolysis acting at oxytocin and vasopressin receptors in brain and gut.

Combined w beta 3 agonist (CL 316243) (what about AOD?) in rats produced synergistic weight loss 15% vs 7% alone

Edwards, M. "Effects of Combined Oxytocin and Beta-3 Receptor Agonist (CL 316243) Treatment on Body Weight and Adiposity in Male Diet-Induced Obese Rats." *Frontiers in Physiology* 12 (September 8, 2021): 725912.

1mg=600IU, recommended dosing 24-80IU intranasal or IV will cross BBB

Reduces caloric (primarily carbohydrate) consumption in obese>lean rodents

Affects autonomic nervous system and CCK, GLP1

Lawson, E. "The Effects of Oxytocin on Eating Behaviour and Metabolism in Humans." *Nature Reviews. Endocrinology* 13, no. 12 (December 2017): 700–709.

OXYTOCIN

Attenuates activation of food motivation and increases self-control in human brains on fMRI

Kerem, L. "The Effects of Oxytocin on Appetite Regulation, Food Intake and Metabolism in Humans." *International Journal of Molecular Sciences* 22, no. 14 (July 20, 2021): 7737.

Prevents cartilage destruction by regulating MMPs

Wu, Y. "Oxytocin Prevents Cartilage Matrix Destruction via Regulating Matrix Metalloproteinases." *Biochemical and Biophysical Research Communications* 486, no. 3 (May 6, 2017): 601–6.

Oxytocin is anabolic to muscle and bone

"Metabolic Effects of Oxytocin | Endocrine Reviews | Oxford Academic." Accessed September 29, 2021.
<https://academic.oup.com/edrv/article/41/2/121/5658523>.

NNMT (A LITTLE MORE PHYSIOLOGY)

NNMT is a phase II metabolizing enzyme in the SAM-dependent methyltransferases

Through interactions with sirtuins, it **modulates energy expenditure** in adipose tissue and controls glucose, cholesterol, and triglyceride metabolism in hepatocytes

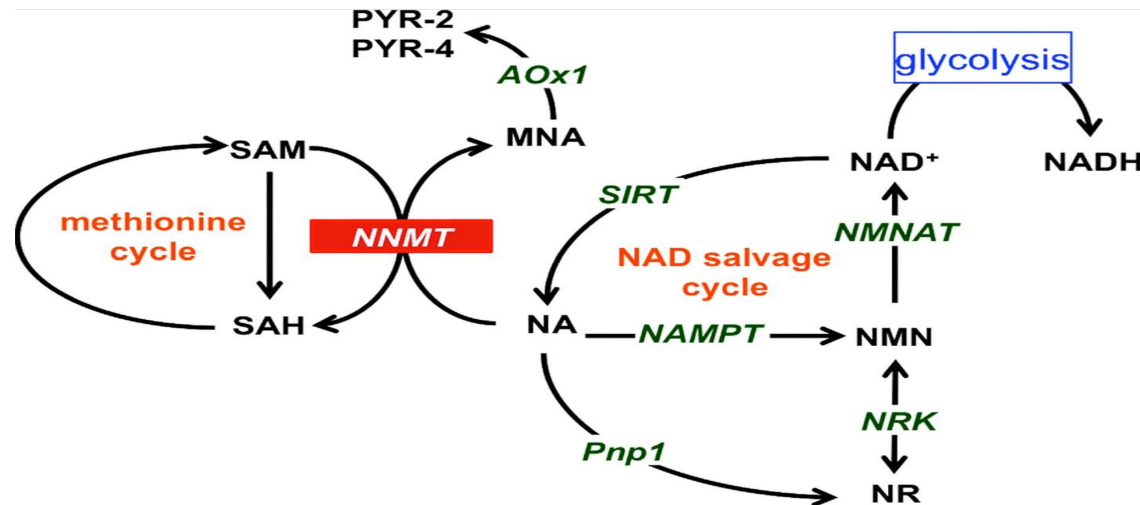
In C. elegans **extends lifespan** by producing a starvation signal and inducing autophagy.

Overproduced in cancers, PD, AD, HTN, pulm HTN, atherosclerosis and other diseases of endothelium

Aged skeletal muscle

fatty liver disease/fibrosis

(Gao 2021)



IRW

Tripeptide from ovotransferrin

Increases both NAMPT and NAD⁺ 2x in muscle cells

SIRT1-dependent

Protects osteoblasts against Ang II induced decline in cell proliferation and restores protein levels of collagen type I alpha 2 chain

Lowers COX2, NFKb and RANKL

Bhullar, K. "Tripeptide IRW Upregulates NAMPT Protein Levels in Cells and Obese C57BL/6J Mice." *Journal of Agricultural and Food Chemistry* 69, no. 5 (February 10, 2021): 1555–66.

Liu, N. "Effects of IQW and IRW on Inflammation and Gut Microbiota in ETEC-Induced Diarrhea." *Mediators of Inflammation* 2021 (September 24, 2021): e2752265.

Shang, N. "Tripeptide IRW Protects MC3T3-E1 Cells against Ang II Stress in an AT2R Dependent Manner." *Molecules* 27, no. 12 (January 2022): 3684.

NOT PEPTIDES

BUT USEFUL IN TREATING ATHLETIC INJURIES ALL THE SAME

5-AMINO 1-MQ

A small molecule NNMT inhibitor

In aged (24m) mouse muscle injury study, 5 amino 1-MQ at 12-123mg/kg HED for 1-3 weeks post injury

Elevated muscle stem cell proliferation

Nearly 2x muscle cross sectional area and shifts in fiber size

Greater contractile function post injury

70% increased peak torque

Neelakantan, H. "Small Molecule Nicotinamide N-Methyltransferase Inhibitor Activates Senescent Muscle Stem Cells and Improves Regenerative Capacity of Aged Skeletal Muscle." *Biochemical Pharmacology* 163 (May 1, 2019): 481–92.

5-AMINO 1-MQ

SE: weight loss, fatigue in endurance athletes, hearing loss (Miwa 2021)

Dosing: 50-150mg oral caps

PROCAINE

60 patients w lateral epicondylitis treated steroid or neural therapy w procaine

Pain relief and functional improvement greater for neural therapy at 3 and 6 months post-treatment w no complications.

Yilmaz, E. "Comparision of the Efficacy of Neural Therapy versus Steroid Injection in the Treatment of Lateral Epicondylitis (Tennis Elbow)." *European Journal of Integrative Medicine* 23 (October 1, 2018): 77–83.

102 patients w piriformis syndrome treated stretching or neural therapy and stretching demonstrated improvement in pain and functioning vs control

Nazlıkul, H. "Evaluation of Neural Therapy Effect in Patients with Piriformis Syndrome." *Journal of Back and Musculoskeletal Rehabilitation* 31, no. 6 (January 1, 2018): 1105–10.

PROCAINE

280 chronic pain patients (mostly back pain).

After one year, 60 patients' pain was unchanged, 52 patients reported slight improvement, 126 were considerably better and 41 were pain-free. 74% of patients who took analgesics before needed less or no more analgesics at all. No adverse effects or complications

Egli, S. "Long-Term Results of Therapeutic Local Anesthesia (Neural Therapy) in 280 Referred Refractory Chronic Pain Patients." *BMC Complementary and Alternative Medicine* 15, no. 1 (June 27, 2015): 200.

60 patients PT vs neural therapy for chronic back pain

NT demonstrated improved physical activity and social isolation vs PT-treated. Both were effective on pain, quality of life, anxiety and depression.

A. "Comparison of Efficacy of Neural Therapy and Physical Therapy in Chronic Low Back Pain." *African Journal of Traditional, Complementary and Alternative Medicines* 10, no. 3 (May 1, 2013): 431–35.

OZONE

A bioregulator in chronic inflammation improving redox balance

Improves pain, stiffness, recovery of function in knee OA

Raeissadat, S. "Intra-Articular Ozone or Hyaluronic Acid Injection: Which One Is Superior in Patients with Knee Osteoarthritis? A 6-Month Randomized Clinical Trial." *Journal of Pain Research* 11 (January 4, 2018): 111–17.

Manoto, S. "Medical Ozone Therapy as a Potential Treatment Modality for Regeneration of Damaged Articular Cartilage in Osteoarthritis." *Saudi Journal of Biological Sciences* 25, no. 4 (May 1, 2018): 672–79.

Sconza, C. "Oxygen–Ozone Therapy for the Treatment of Knee Osteoarthritis: A Systematic Review of Randomized Controlled Trials." *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 36, no. 1 (January 1, 2020): 277–86.

Sire, A. "Oxygen–Ozone Therapy in the Rehabilitation Field: State of the Art on Mechanisms of Action, Safety And Effectiveness in Patients with Musculoskeletal Disorders." *Biomolecules* 11, no. 3 (March 2021): 356.

RAPAMYCIN

Macrolide from *S hygrosopicus* first isolated in 1972 on Easter Island aka Rapa Nui

An **mTORc1 inhibitor** that protects organs and mice against age-related decline

Chronic activation of mTORc1 stimulates progressive **muscle damage** and loss

Rapamycin **rejuvenates muscle (satellite) stem cells** and prevents senescence, contributing to hyperplasia (number) and hypertrophy (size) of fibers.

Rapamycin promotes autophagy

Blagoskonny, M. "How Rapamycin Prevents Muscle Loss and Sarcopenia (First Draft)." Dr. Blagosklonny, M.D., Ph.D., January 7, 2020. <http://www.mikhailblagosklonny.com/blog/how-rapamycin-prevents-muscle-loss-and-sarcopenia-first-draft/>.

RAPAMYCIN

Rapamycin completely prevents androgen-induced growth of heart muscle without affecting skeletal muscle growth

Rossetti, M. "Androgens Induce Growth of the Limb Skeletal Muscles in a Rapamycin-Insensitive Manner." *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 315, no. 4 (October 1, 2018): R721–29.

Ye, L. "Rapamycin Doses Sufficient to Extend Lifespan Do Not Compromise Muscle Mitochondrial Content or Endurance." *Aging* 5, no. 7 (July 16, 2013): 539–50.

PENTOSAN POLYSULFATE

Semi-synthetic heparin-like nonselective anti-inflammatory

Supports chondrocyte and fibroblast anabolic activities while attenuating catabolic events associated with destruction of cartilage

Directly inhibits catabolic enzymes

Downregulates gene expression of metalloproteinases

Dosing 1-2mg/kg IBW weekly –twice a week

Caution: maculopathy?

PENTOSAN POLYSULFATE

114 patients with OA knee 4 weekly injections associated w significantly improved duration of joint stiffness and pain at rest compared to control for 20 weeks after cessation of treatment and significantly improved pain on walking and overall function for 8 weeks after cessation of treatment.

SE: mild bruising at the injection site

Ghosh, P. "Effects of Pentosan Polysulfate in Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Pilot Study." *Current Therapeutic Research, Clinical and Experimental* 66, no. 6 (November 2005): 552–71.

PENTOSAN POLYSULFATE

Suppresses expression of NGF mRNA to alleviate pain associated with knee OA

Stapledon, C. "Human Osteocyte Expression of Nerve Growth Factor: The Effect of Pentosan Polysulphate Sodium (PPS) and Implications for Pain Associated with Knee Osteoarthritis." *PLOS ONE* 14, no. 9 (September 26, 2019): e0222602.

Reduces virus-induced arthritis from Ross River virus, chikungunya and alphavirus

(Herrero 2015, Krishnan 2021, Rudd 2021)

20 knee OA patients underwent two test at 25mg and 50mg followed by 6 weekly 2mg/kg PPS SC. Significantly improved hydrarthrosis, flexion, pain with walking, pain after climbing stairs, pain after ROM exercise for almost one year after cessation.

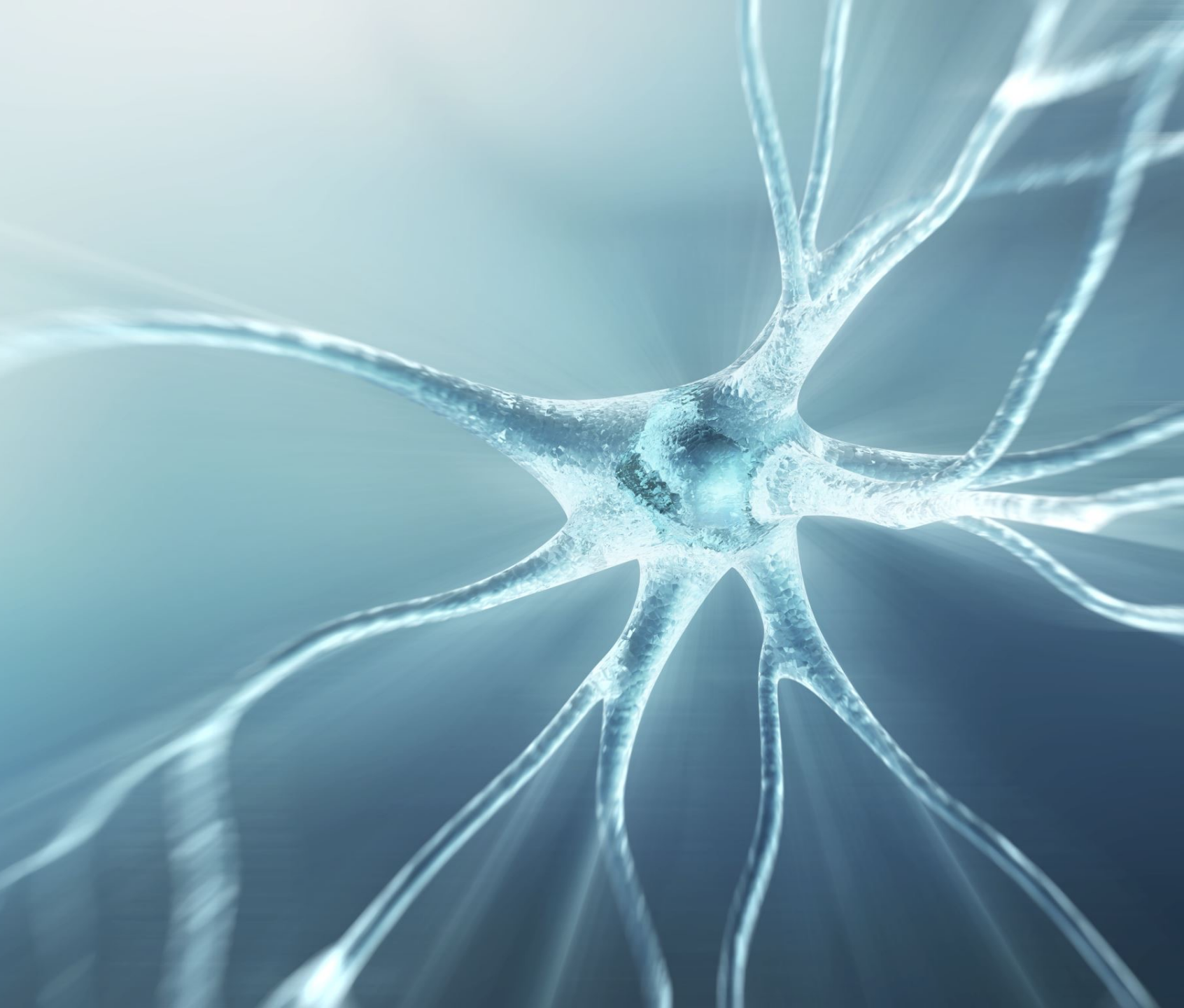
Kumagai, K. "Sodium Pentosan Polysulfate Resulted in Cartilage Improvement in Knee Osteoarthritis - An Open Clinical Trial-." *BMC Clinical Pharmacology* 10 (March 28, 2010): 7.

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Herrero, L. “Pentosan Polysulfate: A Novel Glycosaminoglycan-Like Molecule for Effective Treatment of Alphavirus-Induced Cartilage Destruction and Inflammatory Disease.” *Journal of Virology* 89, no. 15 (May 27, 2015): 8063–76.

Krishnan, R. “Pentosan Polysulfate Sodium for Ross River Virus-Induced Arthralgia: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study.” *BMC Musculoskeletal Disorders* 22, no. 1 (March 12, 2021): 271.

Rudd, P. “Pentosan Polysulfate Sodium Prevents Functional Decline in Chikungunya Infected Mice by Modulating Growth Factor Signalling and Lymphocyte Activation.” *PLOS ONE* 16, no. 9 (September 7, 2021): e0255125.



SOME STACKS

ENDURANCE

Optimize hormones and diet

L-theanine 200mg oral daily

CJC-Ipamorelin at least 6 weeks prior to event 1.1mcg/kg qhs fasting

BPC-157 100mcg SC daily

TA-1 1.5mg SC q week

IRW 2.5mg/kg SC qd

Semax IN

Consider cardarine, stenabolic <2 weeks prior to event

Larazotide 0.5mg caps qd-tid

STRENGTH

Dietary and hormone optimization

Creatine 2-5g per day

-(-)Epicatechin 600mg or Urolithin A 500mg

IGF-1 100mcg/day after workouts, max 2g per week

CJC-Ipamorelin 1.1mcg/kg 5/7 days (fasting)

cycle with tesamorelin 10mg/kg 5/7 days x3 months

Oxytocin 40IU SC after workouts

Rapamycin 5mg oral once per week on “off days”

Melanotan II twice per week on “off days”

STRENGTH

Approaching competition:

Maintain protein intake, hydration, sleep

Dihexa 20mg 3 caps on training days for neural input

5 amino 1-MQ 150mg caps+/-MOTs-C 4mg twice weekly to “make weight”

Day of competition:

AOD 9604 300mg SC

PEP-CK 2.5mg SC or GW501516 20mg SC

MOTS-C 4mg SC

IRW 2.5mg/kg SC

BODY-BUILDING

Optimal dietary and hormonal balance

Melanotan II 200mcg SC twice per week on “off days” 6w out from competition

Creatine 2-5g per day

-(-)Epicatechin 600mg or Urolithin A 500mg

BPC-157 100mcg SC daily

During bulk:

IGF-1 100mcg/day after workouts into exercised muscles, max 2g per week; monitor IGF-1 and IGFBP3

CJC-1pamorelin 1.1mcg/kg 5/7 days (fasting)

Cycle with tesamorelin 10mg/kg 5/7 days

Stenabol 20mg/Oxandrolone 10mg daily

Oxytocin 40IU SC/IN daily after workouts

Cycle with Mk677 10-25mg daily

Oxandrolone 10mg daily/stenabol 20mg daily

BODYBUILDING

Approaching competition/ cut:

Maintain or increase protein intake, hydration

AOD 9604 300mcg daily

MOTS-c 4mg SC twice a week

5 amino 1-MQ 50-150mg daily in the morning

Semaglutide 0.1-3.0mg SC per week, increase to nausea

Tanning: melanotan II 200mcg SC **daily**

Larazotide 0.5mg caps qd-tid

MIXED ATHLETE

Dietary and hormone optimization

Creatine 2-5g per day

-(-)Epicatechin 600mg or Urolithin A 500mg

BPC-157 100mcg SC daily

CJC-1pamorelin 1.1mcg/kg 5/7 days (fasting)

cycle with tesamorelin 10mg/kg 5/7 days x3 months

Oxytocin 40IU SC after workouts

Rapamycin 5mg oral once per week on “off days”

Melanotan II twice per week on “off days”

MIXED ATHLETE

Approaching competition:

Maintain protein intake, hydration, sleep

Dihexa 20mg 3 caps on training days for neural input

Day of competition:

AOD 9604 300mg SC

PEP-CK 2.5mg SC or GW501516 20mg SC

MOTS-C 4mg SC

IRW 2.5mg/kg SC

TREATMENT OF TBI

Estrogen 8mcg/kg HED IP in mouse inhibits microglia and astrocyte activation (Chakrabarti 2016, Wang 2021)

Progesterone IM <8mg/kg/day decreases cerebral edema, restores BBB integrity, reduces inflammatory response, prevents cellular necrosis and apoptosis vs oral/IV administration (Pan 2019)

Rapamycin 5mg (HED) 1 and 4h after TBI improved inflammatory response (Campolo 2020)

Methylene blue 10-20mg in D5W IV, then orally daily diminished BBB disruption, decreases inflammatory microglial activation, reduces functional impairment (Genrikhs 2020)

D-betahydroxybutyrate (BHB) ester drink at 5 ml (HED)/day reduced lesion volume, improved neurobehavior severity (Almeida-Suhett 2022)

PEPTIDES IN TBI

TB4 4mg/kg (HED)SC q24h reduced lesion volume by 30% and reduced hippocampal cell loss within 6h in rat (Xiong 2012), reduced activation of microglia (Osei 2017)

BPC-157 1mcg/kg (HED) SC marked attenuation of damage and improved functional recovery and mortality (Vukojevic 2022, Tudor 2010)

Oxytocin IN/IV attenuates pain (Meidahl 2017), suppresses NFkB and MMP9 (Momenabadi 2021)

SS-31 0.4mg/kg HED reversed mitochondrial dysfunction in mouse TBI (Zhu 2018)

TBI REFERENCES

Almeida-Suhett, C. "The Ketone Ester, 3-Hydroxybutyl-3-Hydroxybutyrate, Attenuates Neurobehavioral Deficits and Improves Neuropathology Following Controlled Cortical Impact in Male Rats." *Nutritional Neuroscience* 25, no. 6 (June 2022): 1287–99.

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CASE STUDIES

AVASCULAR NECROSIS

51 year old WF crossfit

history Raynaud, Hashimoto thyroiditis

presented with 8/10 L hip and buttock pain and antalgic gait, radiated to L ankle.

Treated with exercise modification, PT without relief.

Normal XR. MRI showed avascular necrosis without collapse.

Began ketone esters 5g daily, hydrolyzed collagen with vitamin C, BPC-157 100mcg SC bid, Pentosan 250mcg IM weekly and AOD-HA 1200mcg IA weekly x4 weeks

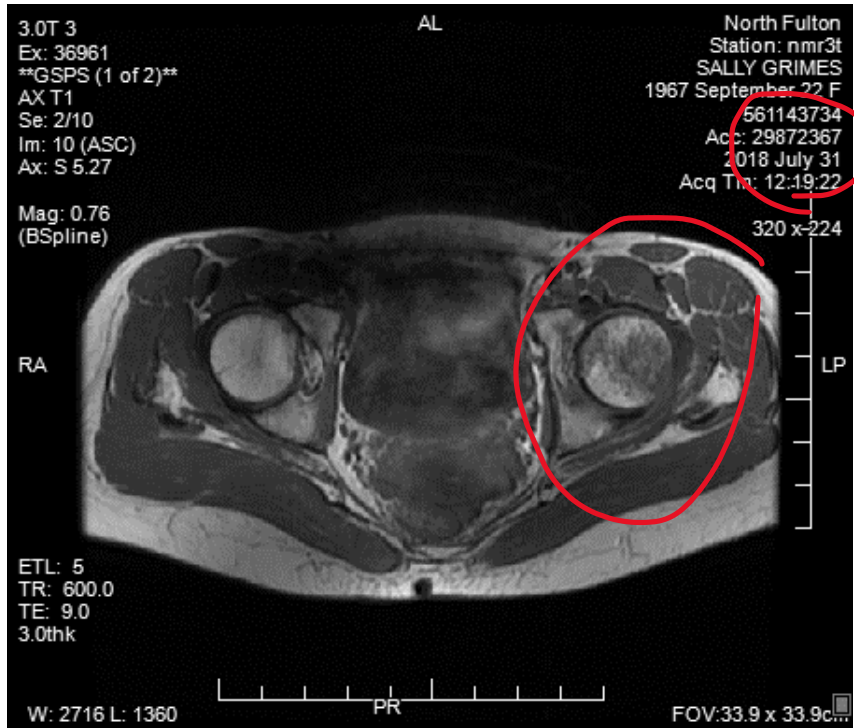
She reported a 60% improvement in the first two weeks, but experienced a hematoma related to the pentosan use. Switched to oral pentosan 100mg tid.

Pain worsened temporarily with increased activity and ran out of BPC-157, so restarted BPC-157 with return to 4/10 pain improvement.

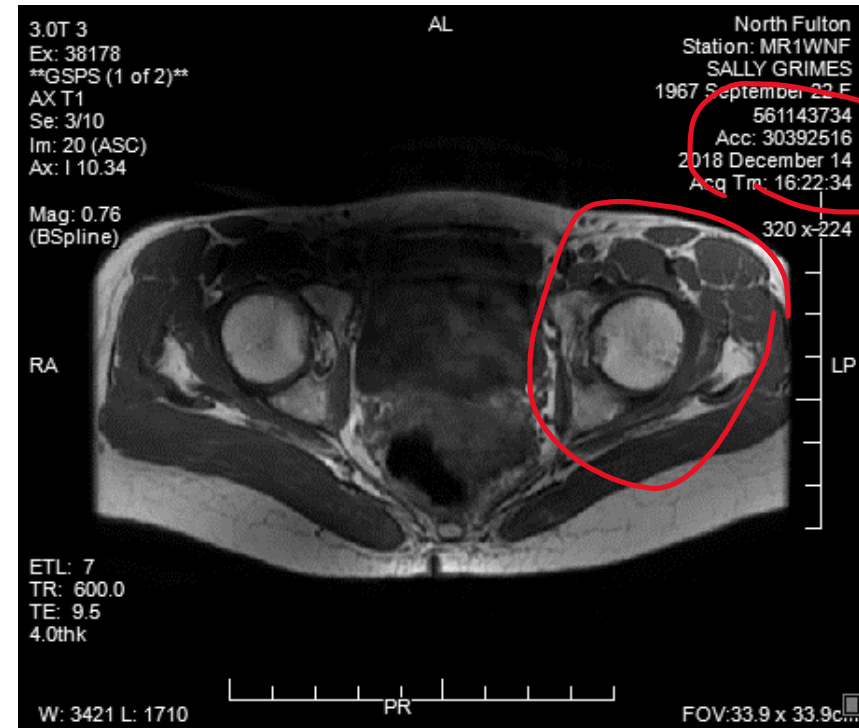
In week 4, we added GHK-Cu 400mcg daily and changed AOD-HA to monthly injections. After adding the GHK-Cu, she reported improvement in pain to 2/10.

Repeat MRI showed “marked interval improvement” with “near resolution” of marrow edema and subchondral femoral head fracture.

JULY



DECEMBER



AJ

Competitive high school basketball player

High hamstring strain w painful 10/10 squatting, running. For tournament this weekend that she will skip, but would like to make tournament next weekend

Increased dietary protein to 1.5g/kg/day

Ke4 25mg tid

Injected AOD 1mg, HA 10mg x1 w some persistent pain

AOD-HA, Cerebrolysin 250mg IT weekly x2 more

Played 4 games in tournament day before with pain 4/10 yesterday after 3rd game, 2/10 today

Due to distance from her home and significant improvement, did not continue full series of injections

JK 40 YO MALE

Training 6 days per week for Boston marathon, has running coach, qualified for Boston Marathon 2020, but shut down d/t Covid pandemic. No libido, insomnia, daytime fatigue.

PMHx: recurrent sinusitis postop x2 s relief, GERD, compartment syndrome shins, facial eczema

L high hamstring pain radiates to distal ankle and heel, worse with running>sitting

Albumin 4.6, Testosterone 303, SHBG 28, Free T 50, E2 17.8, E1 92, IGF-1 188

Hb 16.2, monos 5.5, lymphs 25, ESR 2, hsCRP <0.2

Vitamin b12 382, B9 7.8, D 42, iron 103, Mg 2.2, total protein 6

Cortisol 12, DHEA 118

JK MARATHON RUNNER

Optimize nutrition, hormones

Sleep study+ did not tolerate CPAP, considering oral appliance and progesterone 200mg (Andersen 2006)

BPC-157 500mcg caps bid

Larazotide 500mcg cap twice daily before meals one month, then Semax IN 4 days per week

CJC-Ipamorelin 1.1mcg/kg SC tid 30 minutes prior to food

Procaine 1% into sacral foramen L every 3 days x5

AOD-BPC to high hamstring tendon

Placed 228/2000 in his age group and PR'd his time

“AGING ATHLETE”

43 yo trying to lose weight w cardio

Fatigue, low energy to do cardio, cold hands and feet, at 60% 1RM

Nausea after going to the gym, constipation “my whole life”

Weight gain 6-8m despite strict diet/exercise, nausea began about the same time

Insomnia

Normal, light menses

FMHx CAD and wants to stay “ahead of the curve.” Previous CCS zero.

Works 16-20h days

Covid vaccines x3 w hives

TESTING

Food allergy to casein, gluten, egg, peanut, S cerevisiae

Nutrient test showed high need for B vitamins, ketotic, high malabsorption and dysbiotic markers, high toxin load including mercury

Dried urine hormone test showed flattened cortisol curve, low melatonin

Low iron, ferritin

TSH 0.10 on thyroid combo she got while in Mexico, fT4 1.1, fT3 6.2, RT3 13

IGF-1 170, E1 34, FSH 2.9, P 20, E2 63, T80, SHBG 70

Cortisol 15, DHEA 145

AGING ATHLETE C

Elimination diet, gut repair started, hormones balanced

Iron infusion for IDA

Changed job to similar w non-profit, daily gratitude practice

Modified workout to 15 minute HIIT and 45 minute weights- 3 sets to failure each group

BPC-157 500mg caps- open one and take 2nd one whole 1-2x per day

Semaglutide 0.25mg SC q week in increasing doses

Tesamorelin 500mcg SC 5/7 days per week

FOLLOW UP

Resolution cold hands and feet, muscle weakness after iron infusion, feels “better than I ever have” w strength 80-90% previous 1RM, sleep improved on Mg, progesterone

Lost 8#/2mos, all fat per BIA w no loss muscle mass

Ferritin 173

TSH 0.85, fT4 1, fT3 4, T3R 12

FINDINGS:

A small knee joint effusion is present with synovitis. No significant popliteal cyst. Peripatellar fat pad edema and swelling is evident.

There is a complex flap tear involving the posterior horn/body of the medial meniscus with flipped fragment in the tibiofemoral recess, peripheral extrusion, and inflammation along the medial joint line (coronal image 11 and sagittal image 6). The lateral meniscus is preserved.

The ACL, PCL, MCL, and lateral collateral ligament complex are intact.

The quadriceps and patellar tendons are intact. The patellar alignment is normal. The tibial tubercle-trochlear groove distance measures 14 mm.

No fracture or worrisome marrow replacing lesion. No focal cartilage defect.

IMPRESSION:

1. Complex flap tear involving the posterior horn/body of the medial meniscus with flipped fragment in the tibiofemoral recess, peripheral extrusion, and inflammation along the medial joint line.
2. No ligamentous injury.
3. Small knee joint effusion with synovitis and peripatellar fat pad edema/swelling.

COMPETITIVE CYCLIST

Injured knee while running, lack of stability and popping 2 months

Tenderness medial joint line and pes anserine bursa

Pos McMurray

COMPETITIVE CYCLIST C

Referred for PT

Started AOD-HA injection, pain down from 7-8/10 to 1-2/10 after first injection

Continued weekly x4 interrupted w having Covid, given pentosan 125mg IM, TA-1 6mg IVP

Pain 0/10 after 6th AOD-HA injection, back to cycling normally

Two years later still pain free and cycling competitively

OLD GOLFER

Would like to play golf but L ankle pain prevents

PE: obese (BMI 32.9), overpronation L>R ankle

Sent to PT for glut strengthening

Stacks as follows: AOD-BPC IA injections weekly x5, then monthly x5

Return to sport 3-4 days per week

Checks back in every 6 months for a “tune up” injection

GOTTA MAKE IT TO 75

70 yo WF, active but sweet tooth

All family members died by age 75, goal: make it to 75

Balanced hormones, fixed her gut

Got trainer in her home three times per week

High protein, vegetable diet

Her antiaging stack: tesamorelin 500mcg, ipamorelin 6U 5/7days per week, rapamycin 5mg orally weekly, BPC-157 100mcg twice daily.

ANATOMY REVIEW
OF THE SHOULDER, HIP, AND KNEE

ANATOMY SHOULDER

Complete Anatomy

Region: Upper Limb (Right)

MUSCULAR SYSTEM UPPER LIMB (RIGHT) PECTORAL REGION (RIGHT) **PECTORALIS MINOR MUSCLE (RIGHT)**

Home Undo

Pectoralis Minor Muscle (Right)

Musculus pectoralis minor

ISOLATE
HIDE
FADE
HIDE OTHERS
FADE OTHERS
MULTI SELECTION

Info Motion Cross-Sections O/I

QUICK FACTS
Origin: Anterior ends of third to fifth ribs.
Insertion: Coracoid process of scapula.
Action: Protracts and downwardly rotates pectoral (shoulder) girdle at acromioclavicular and sternoclavicular joints.
Innervation: Medial and lateral pectoral nerves (C5-T1)
Arterial Supply: Pectoral and deltoid

Anterior Lateral Posterior

Models Skeletal Off Connective T. **Layer 7 Muscular** Off Arterial Off Venous Off Lymphatic Off Nervous Off Respiratory Off Digestive Off Endocrine Off Urogenital Off Integumentary

Tools

ANNOTATE TOOLS
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Cut Fracture

GROWTH TOOLS
Growth Spurs

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PHYSICAL EXAM SHOULDER

Begins by watching them take off their shirt

Wash your hands

General inspection and comparison to unaffected side

Examine elbow and cervical spine first for tenderness, deformity

Test for ROM by having the patient raise their arms overhead (forward flexion)

Abduction and adduction (across the body)

External rotation (elbows at sides)

Extension (palms down)

Internal rotation (touch as high as you can)

Watch all from front and back, watching for asymmetry or weakness

SUPRASPINATUS

Arms flexed at 90 deg abduction, 30 deg forward flexion, palms up and down against resistance



INFRASPINATUS/TERES MINOR

Elbows at sides, forearms at 90 deg, palms up. Resist internal and external rotation



SUBSCAPULARIS “LIFT OFF”

Affected hand to back at lumbar region

Resist pushing the hand away from the body



PHYSICAL EXAM KNEE

Complete Anatomy

Region: Lower Limb (Right)

MUSCULAR SYSTEM LOWER LIMB (RIGHT) LEG (RIGHT) ANTERIOR COMPARTMENT (RIGHT) EXTENSOR DIGITORUM LONGUS MUSCLE (RIGHT)

Home Undo

Extensor Digitorum Longus Muscle (Right)

Musculus extensor digitorum longus

ISOLATE
HIDE
FADE
HIDE OTHERS
FADE OTHERS
MULTI SELECTION

Info Motion Cross-Sections O/I

QUICK FACTS

Origin: Lateral condyle of tibia, proximal three quarters of fibula, and adjacent interosseous membrane of leg.

Insertion: Dorsal aspects of bases of both the middle and distal phalanges of the second, third, fourth, and little toes.

Action: Extends second, third, fourth, and little toes; dorsiflexes foot at ankle joint.

Innervation: Deep fibular nerve (L5-S1).

Anterior Lateral

Models Skeletal Connective T. Muscular Layer 7 Off Arterial Off Venous Off Lymphatic Off Nervous Off Respiratory Off Digestive Off Endocrine Off Urogenital Off Integumentary

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PHYSICAL EXAM KNEE

Watch the patient walk, stand from sit

Wash your hands

Evaluate hip and ankle for tenderness, ROM

Standing squat, single leg squat

Seated: assess temperature, swelling

Firmly palpate tendons and joint line

Passive and active ROM (flexion-ext, varus-valgus, int-ext rotation)

LACHMAN TEST



For ACL damage, more sensitive than anterior drawer

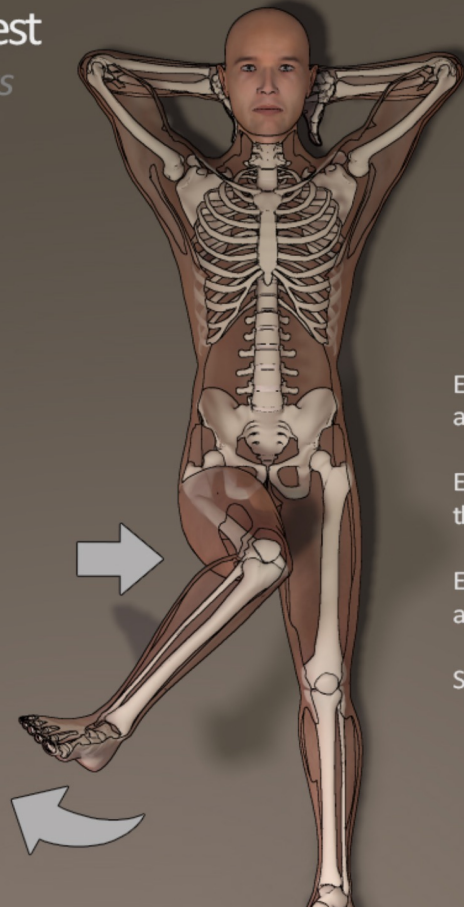
Supine, foot on table with knee in 20-30 deg flexion

Attempt to pull the tibia anterior relative to the femur

MCMURRAY

Test for meniscus stress

McMurray Test
Medial Meniscus



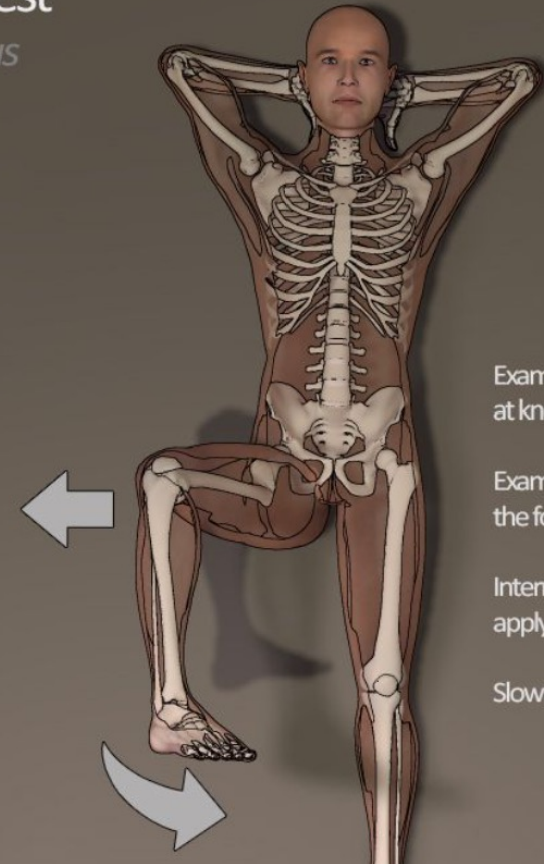
Examiner applies one hand at knee along medial meniscus.

Examiner's other hand holds the foot and ankle.

Externally rotate the foot, and apply valgus stress at the knee.

Slowly extend the knee.

McMurray Test
Lateral Meniscus



Examiner applies one hand at knee along lateral meniscus.

Examiner's other hand holds the foot and ankle.

Internally rotate the foot, and apply varus stress at the knee.

Slowly extend the knee.

EASIER AND MORE SENSITIVE?

Thessaly test



PHYSICAL EXAM HIP

Observe the patient walk, sit and rise from sit

Wash your hands

Examine the lumbar spine and knee for general tenderness or weakness

Supine: ROM flexion-extension, internal and external rotation, abduction and adduction passive and against resistance

LOG ROLL



With the patient supine, examiner rotates the leg internally and externally looking for hip pain indicating fracture/osteoarthritis

“Log Roll Test.” Accessed February 2, 2023.
<https://medschool.co/exam/hip/log-roll-test>.

COMPRESSION TEST AT FOOT OR KNEE

Patient supine, examiner raises leg at foot to 45 deg and firmly taps on the heel

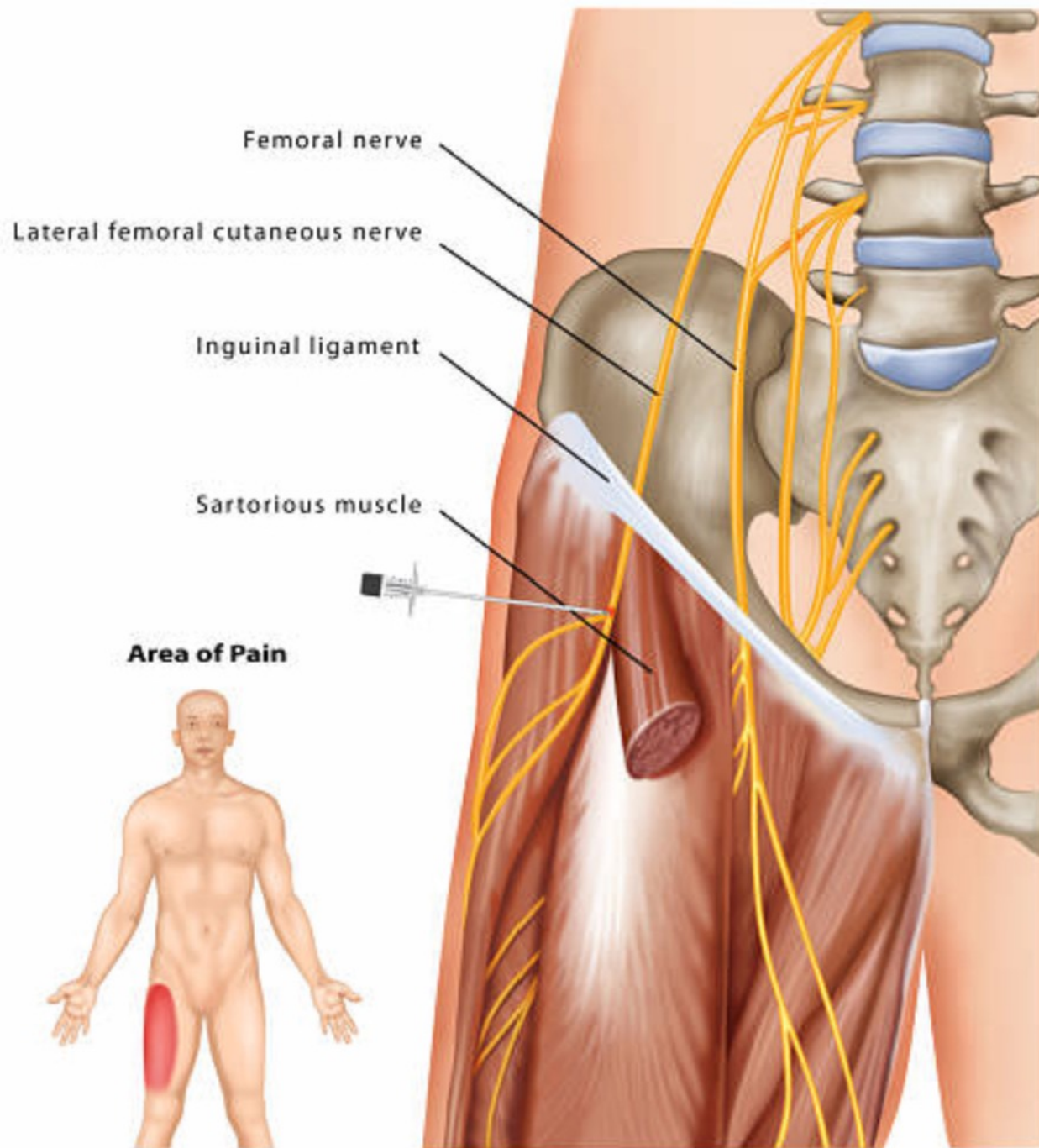
Or: examiner bends the knee with the hip in 45 deg flexion and firmly taps on the knee toward the hip

Stanford Medicine 25. "Hip Region Exam, Approach to." Accessed February 2, 2023.
<https://stanfordmedicine25.stanford.edu/the25/HipRegionExam.html>.



GREATER TROCHANTERIC BURSITIS





MERALGIA PARESTHETICA

Burning pain common in diabetics

Pain Spa. "Lateral Femoral Cutaneous Nerve Block | Pain Treatment | Pain Spa, Bristol, UK." Accessed February 2, 2023. <https://www.painspa.co.uk/procedure/lateral-femoral-cutaneous-nerve-block/>.

INJECTABLE DOSES

AOD 9604 6mg reconstituted to 1mg/ml inject 0.3-1.0ml (50U) IA/IT (depending on size of joint) weekly x3-5, then monthly x3+

BPC-157 2000mcg/ml inject 0.3-1.0ml (50U) IA/IT weekly with AOD or 0.1-0.5ml (10-50U) SC daily-bid depending on severity of injury/disease

Thymosin beta 4 3000mcg/ml inject 0.3-1.0ml (50U) IA/IT weekly or 0.1-0.5ml (10-50U) SC daily-twice daily depending on severity of injury/disease; use commonly with chronic injury that may have developed fibrosis or infection

Pentosan polysulfate 125mg/ml 1ml SC/IM (NOT IA) weekly to twice weekly

Procaine 2% diluted to 1% for injection subdermal and/or IA

Ozone 2-10ml of 20-30g in ozone-safe syringe

TREATMENT OF TBI/SRC

In mice, sodium butyrate restores BBB, improves neurological deficits, decreases brain edema, attenuates neuronal degeneration (Li 2016)

Phosphatidylcholine ameliorates the damage of neurons and modulates neuronal plasticity (Magaquian 2021)

Oral Resveratrol recovers NRF2 signaling and attenuates cognitive deficits in TBI rats (Shi 2018, Mishra 2022)

Omega 3 fatty acids

Urolithin A activates autophagy, alleviates BBB disruption and attenuates neuronal apoptosis (Gong 2022)

TUDCA (Sun 2017)

Trehalose protects against oxidative stress, increases chaperone molecules and enhances autophagy in mouse TBI (Portbury 2017)

FOXO6

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