

#PeptideWC2022

The Most Influential Peptides (etc.) for Joint and Back Pain

@boulderlongevityinstitute

Elizabeth Yurth, MD

FAARM, FAARFM, ABAARM, FSSRP | Boulder Longevity Institute

What is Your Spirit Animal??

#PeptideWC2022





Myth:

Arthritis is just a wear and tear disease

We shouldn't just wear out!

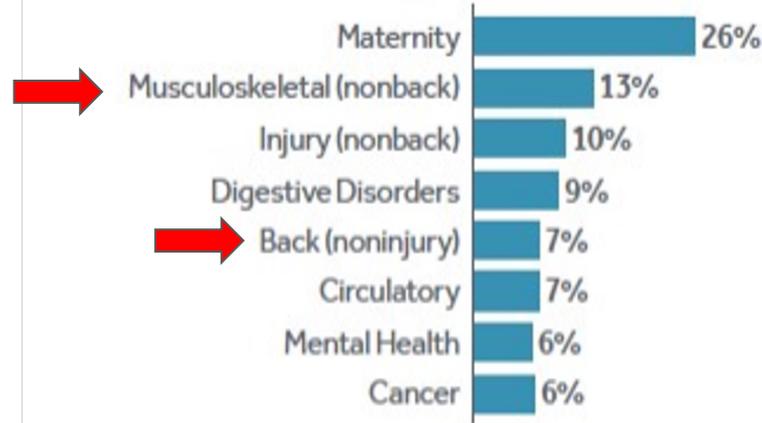


Myth:

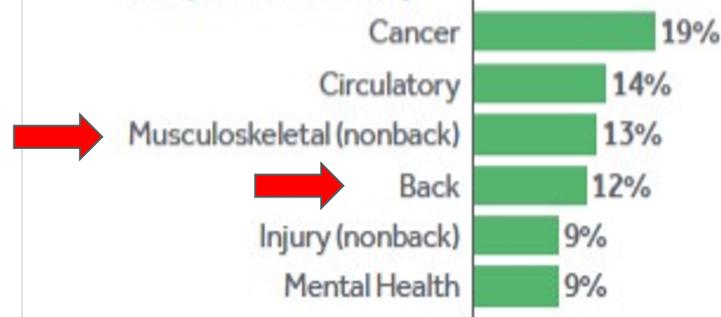
Osteoarthritis isn't
really that serious

Leading causes of disability claims*:

Short-Term Disability



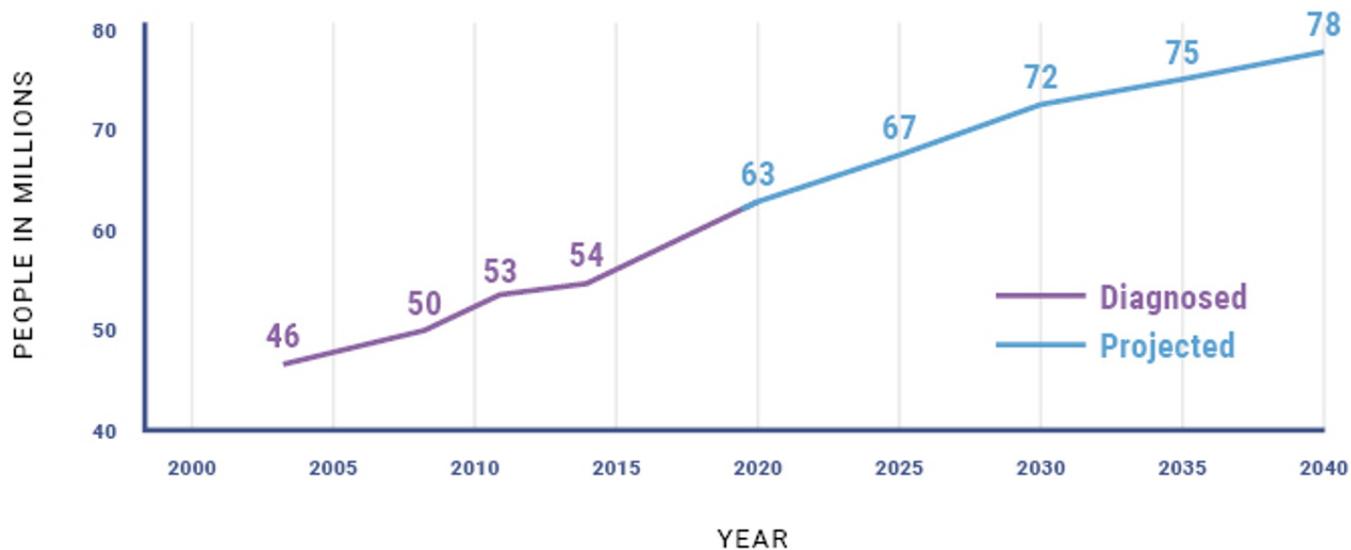
Long-Term Disability



Diagnosed and Future Projections* of Arthritis

ARTHRITIS WILL INCREASE AS THE POPULATION GROWS AND AGES

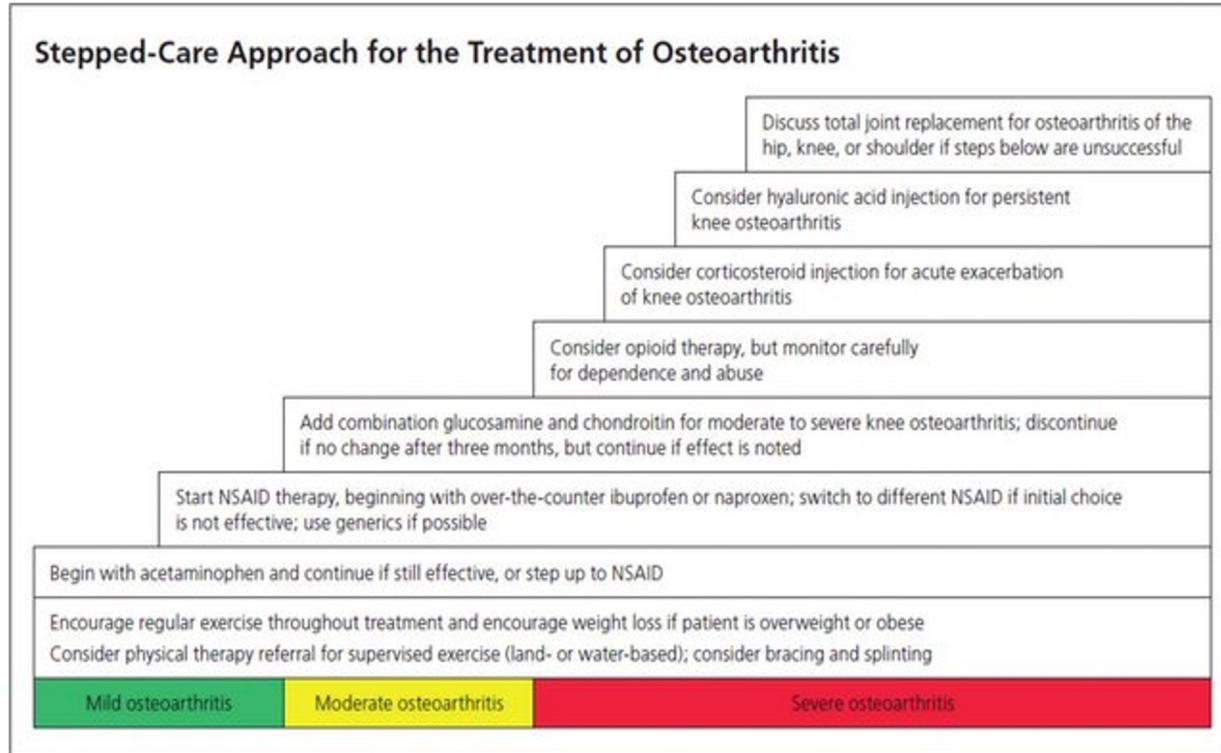
*Doctor Diagnosed



Data from: National Health Interview Survey 2013–2015

Treatments for Osteoarthritis

- **Currently no curative treatments are available**
- **Management strategies focus on symptom alleviation through pain relief**
- **Final Solution for restoration of function and pain relief is total joint arthroplasty**



Let's look at these recommendations....

American College of Rheumatology. Practice guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. <http://www.rheumatology.org/practice/clinical/guidelines/oa-mgmt.asp>. Accessed May 19, 2017

NSAID Therapy impedes recovery and contributes to chronic pain

Acute inflammatory response via neutrophil activation protects against the development of chronic pain

MARC PARISEIN , LUCAS V. LIMA , CONCETTA DAGOSTINO , NEHME EL-HACHEM, GILLIAN L. DRURY, AUDREY V. GRANT, JONATHAN HUISING, VIVEK VERMA 

CAROLINA B. MELOTO, [...] LUDA DIATCHENKO  +11 authors [Authors Info & Affiliations](#)

SCIENCE TRANSLATIONAL MEDICINE • 11 May 2022 • Vol 14, Issue 644 • DOI: 10.1126/scitranslmed.abj9954

Clinical data showed that the use of anti-inflammatory drugs was associated with increased risk of persistent pain, suggesting that anti-inflammatory treatments might have negative effects on pain duration.

Association between current medication use and progression of radiographic knee osteoarthritis: data from the osteoarthritis initiative

Thomas A Perry , Xia Wang, Michael Nevitt, Christina Abdelshaheed, Nigel Arden, David J Hunter

Rheumatology, Volume 60, Issue 10, October 2021, Pages 4624–4632,

Compared with current non-users, current use of NSAIDs was associated with a loss of joint space width on radiographic studies

Review [Am J Ther. 2020 Dec 10;29\(2\):e219-e228. doi: 10.1097/MJT.0000000000001309.](#)

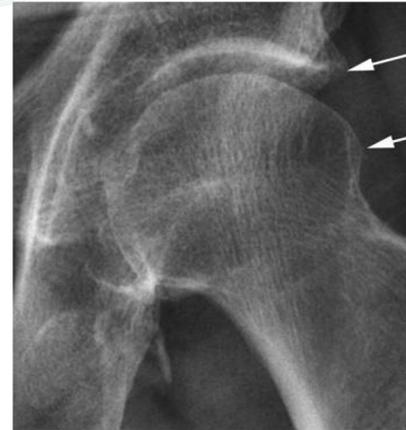
Local and Intra-articular Administration of Nonsteroidal Anti-inflammatory Drugs for Pain Management in Orthopedic Surgery

Nicholas M Bernthal ¹, Christopher M Hart ¹, Ketan R Sheth ², Sergio D Bergese ³, Hung S Ho ⁴, Christian C Apfel ⁵, Nicoleta Stoicea ⁶, Allen Rojhani ⁷, Jonathan S Jahr ⁸

NSAIDs reduce postoperative pain scores and opioid consumption in patients undergoing total joint arthroplasty but have potential chondrotoxicity and inhibition of bone and soft-tissue healing.

Corticosteroid Injections

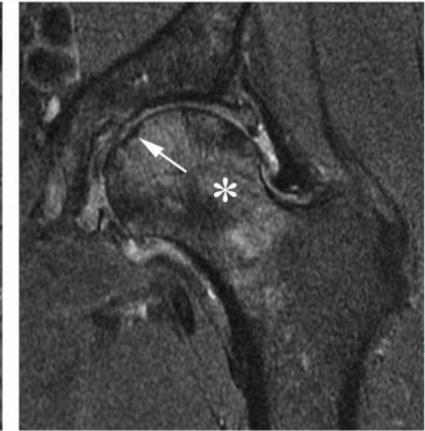
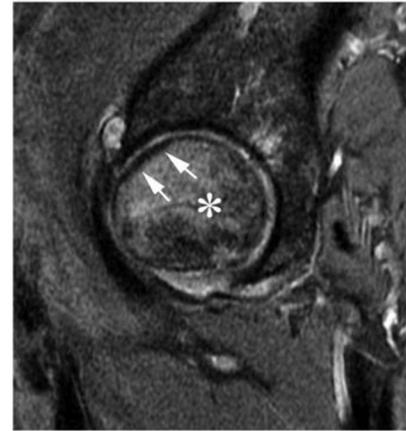
“Corticosteroid injections used to treat osteoarthritis pain in the hip and knee may be more dangerous than previously thought, according to a special report published in the journal *Radiology*. Researchers suggested that injection-associated risks like rapid progressive osteoarthritis, which eventually may lead to joint collapse, should be integrated into consent forms so that patients are aware of the potential risks associated with these treatments.”



a.



b.



15-OCT-2019 Steroid injections of hip and knee may damage joints

Peer-Reviewed Publication RADIOLOGICAL SOCIETY OF NORTH AMERICA

Hyaluronic Acid Injections

Researchers reviewed 169 trials involving 21,163 patients that compared viscosupplementation with placebo or no treatment for pain and function in patients with knee osteoarthritis

“Strong conclusive evidence indicates that, among patients with knee osteoarthritis, viscosupplementation is associated with a clinically irrelevant reduction in pain intensity and with an increased risk of serious adverse events compared with placebo,” the authors wrote. “Our findings do not support the broad use of viscosupplementation for the treatment of knee osteoarthritis.”

Pereira T V, JÃ¼ni P, Saadat P, Xing D, Yao L, Bobos P et al. Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis BMJ 2022; 378 :e069722 doi:10.1136/bmj-2022-069722

Arthroscopic Management

- Recent studies show that performing arthroscopic surgery on an arthritic joint may provide immediate relief, but will have substantially more detriment in the future.

MacFarlane, L. A., Yang, H., Collins, J. E., Guermazi, A., Jones, M. H., ... Spindler, K. P. (2019). Influence of Baseline Magnetic Resonance Imaging Features on Outcome of Arthroscopic Meniscectomy and Physical Therapy Treatment of Meniscal Tears in Osteoarthritis. *The American Journal of Sports Medicine*, 036354651881944. doi:10.1177/0363546518819444

Khan, Moin, et al. "Knee Osteoarthritis - When Arthroscopy Can Help." *Polish Archives of Internal Medicine*, 2018, doi:10.20452/pamw.4186.

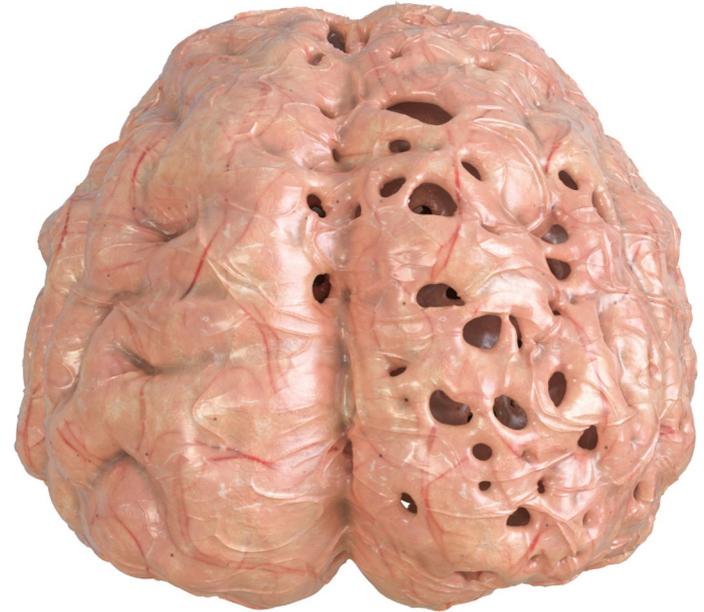
Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline

What you need to know

- We make a strong recommendation against the use of arthroscopy in nearly all patients with degenerative knee disease, based on linked systematic reviews; further research is unlikely to alter this recommendation
- This recommendation applies to patients with or without imaging evidence of osteoarthritis, mechanical symptoms, or sudden symptom onset
- Healthcare administrators and funders may use the number of arthroscopies performed in patients with degenerative knee disease as an indicator of quality care.
- Knee arthroscopy is the most common orthopaedic procedure in countries with available data
- This Rapid Recommendation package was triggered by a randomised controlled trial published in *The BMJ* in June 2016 which found that, among patients with a degenerative medial meniscus tear, knee arthroscopy was no better than exercise therapy

So...

**Treating Arthritis Should NOT focus on simply
Cutting out or replacing damaged parts**



Impact Of Total Knee Replacement Practice: Cost Effectiveness Analysis Of Data From The Osteoarthritis Initiative

Conclusion of Study:

Current practice of total knee replacement as performed in a recent US cohort of patients with knee osteoarthritis had minimal effects on quality of life at the group level. If the procedure were restricted to more severely affected patients, its effectiveness would rise, with practice becoming economically more attractive than its current use.



**TIME
TO
RETHINK**



PEPTIDE **20**
WORLD
CONGRESS **22**

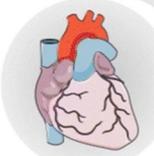
ARTHRITIS ISN'T JUST WEAR AND TEAR OR DAMAGE FROM INJURY...IT IS A DISEASE!





Neurological diseases

- Alzheimer's disease
- Parkinson's disease
- Depression



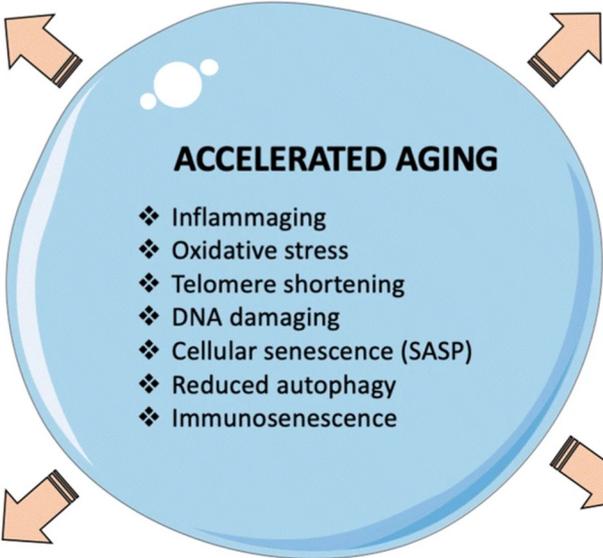
Cardiovascular diseases

- Atherosclerosis
- Hypertension
- Cardiac failure



Articular damage

- Osteoporosis
- Osteoarthritis
- Arthritis



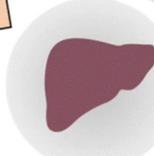
ACCELERATED AGING

- ❖ Inflammaging
- ❖ Oxidative stress
- ❖ Telomere shortening
- ❖ DNA damaging
- ❖ Cellular senescence (SASP)
- ❖ Reduced autophagy
- ❖ Immunosenescence



Cancers

- Carcinoma
- Melanoma
- Breast cancer



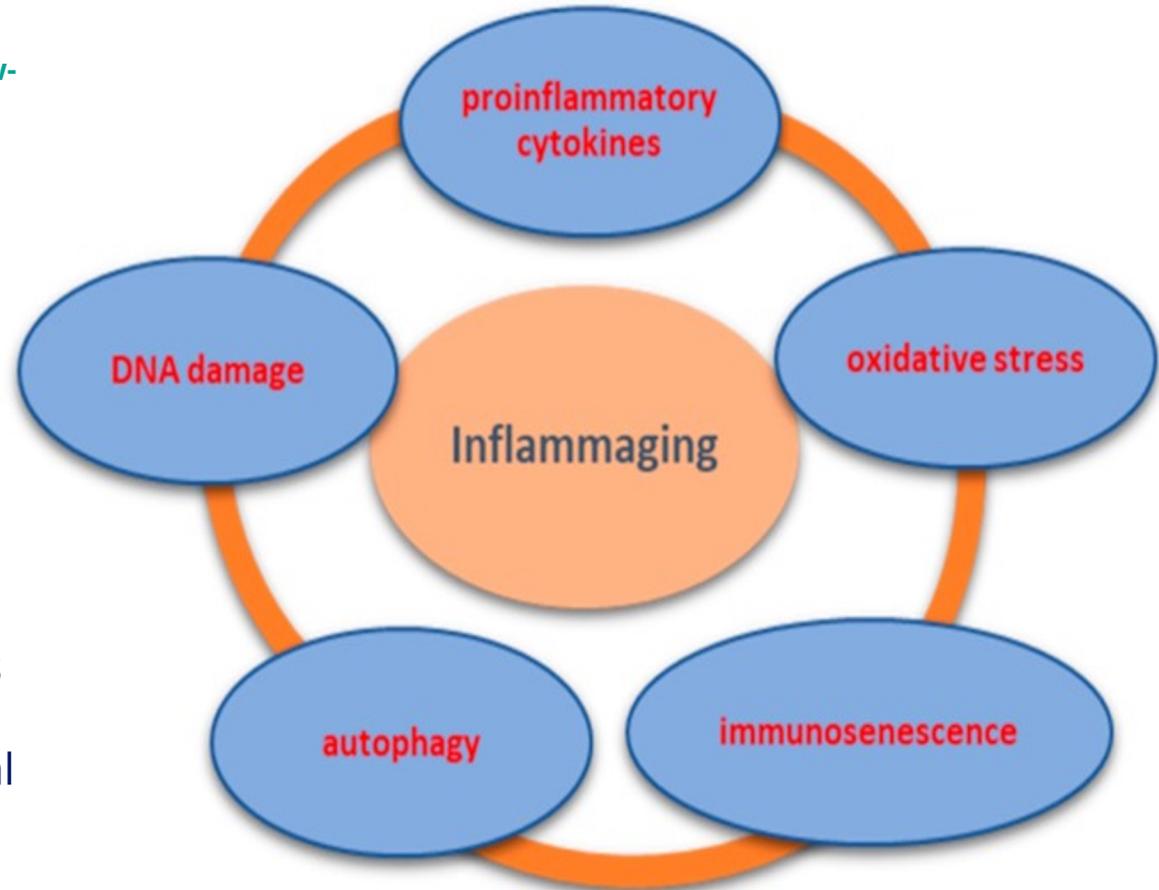
Metabolic diseases

- Type II diabetes
- Metabolic syndrome
- Obesity

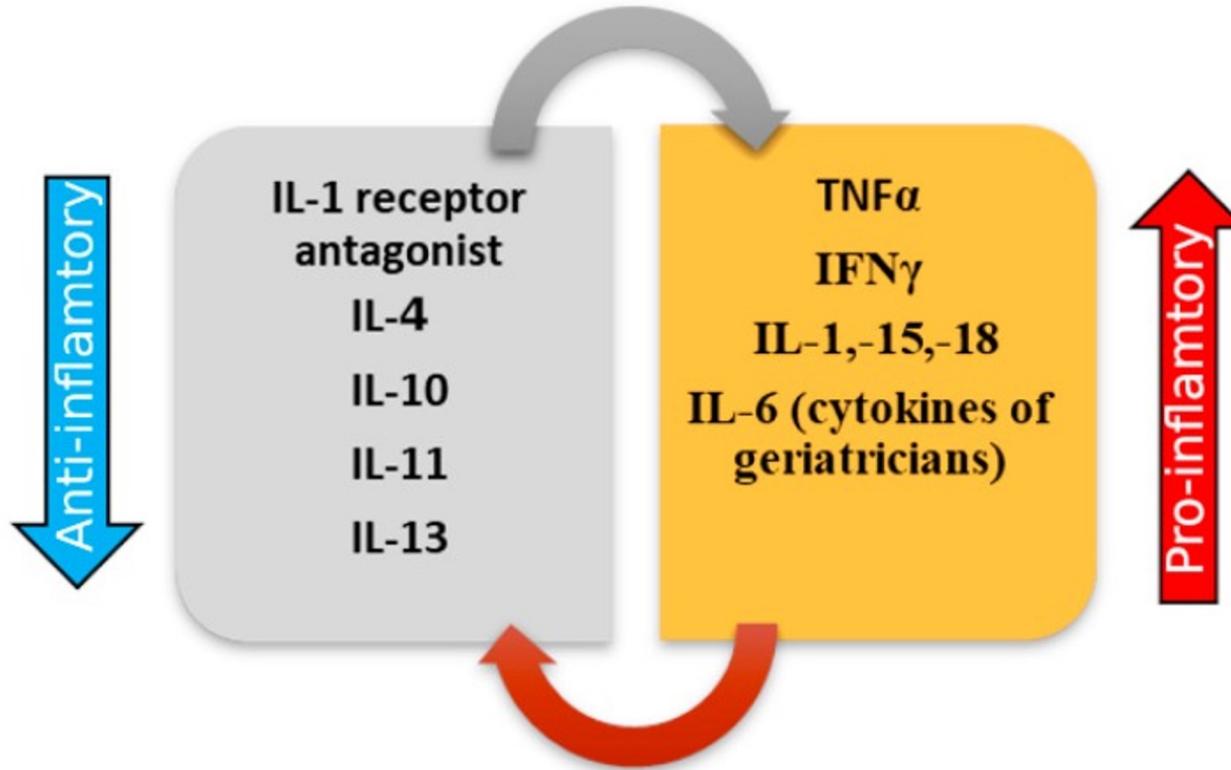
Inflammaging

Low-grade chronic systemic inflammation.

Altered levels of proinflammatory cytokines (proteins that are made by certain immune and non-immune cells and have an effect on the immune system like IL-6 and TNF- α), acute-phase reactants (C-reactive protein [CRP]), and decreases in anti-inflammatory cytokines (like IL-10) impair the maintenance of immunological homeostasis.

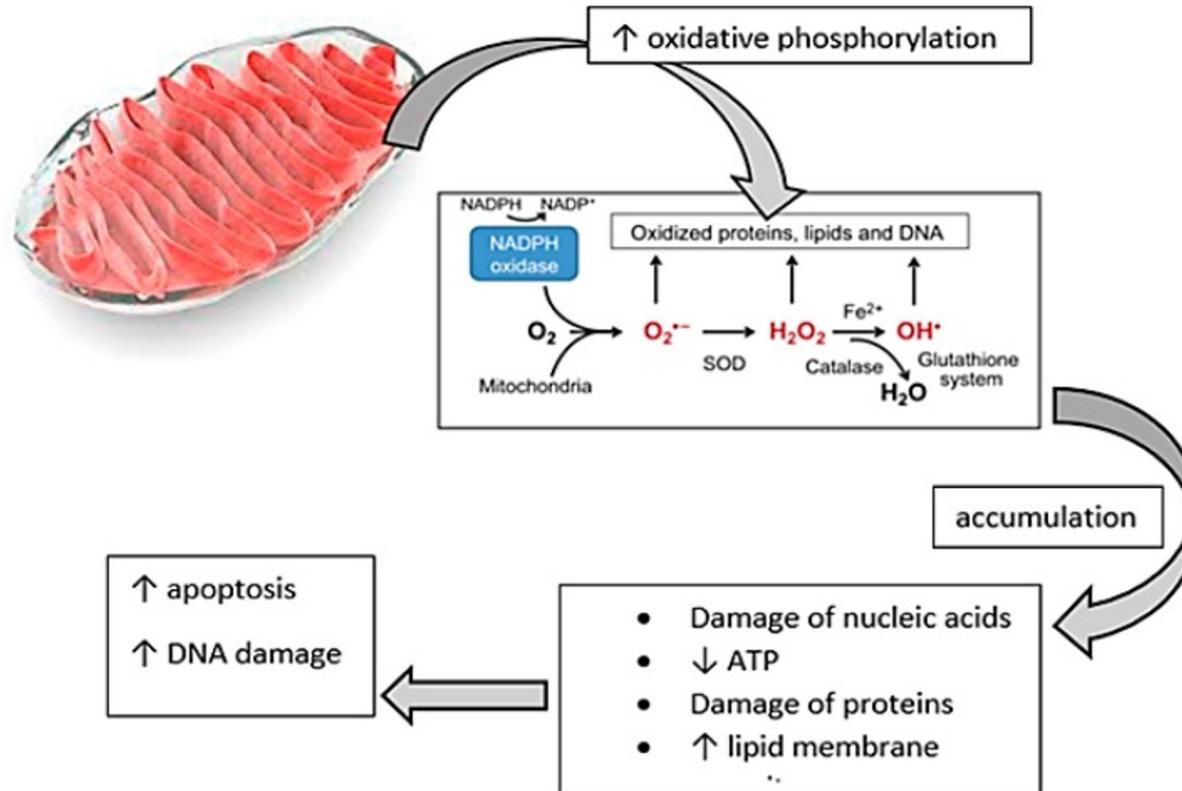


Imbalance between Anti-Inflammatory and Pro-Inflammatory Balance



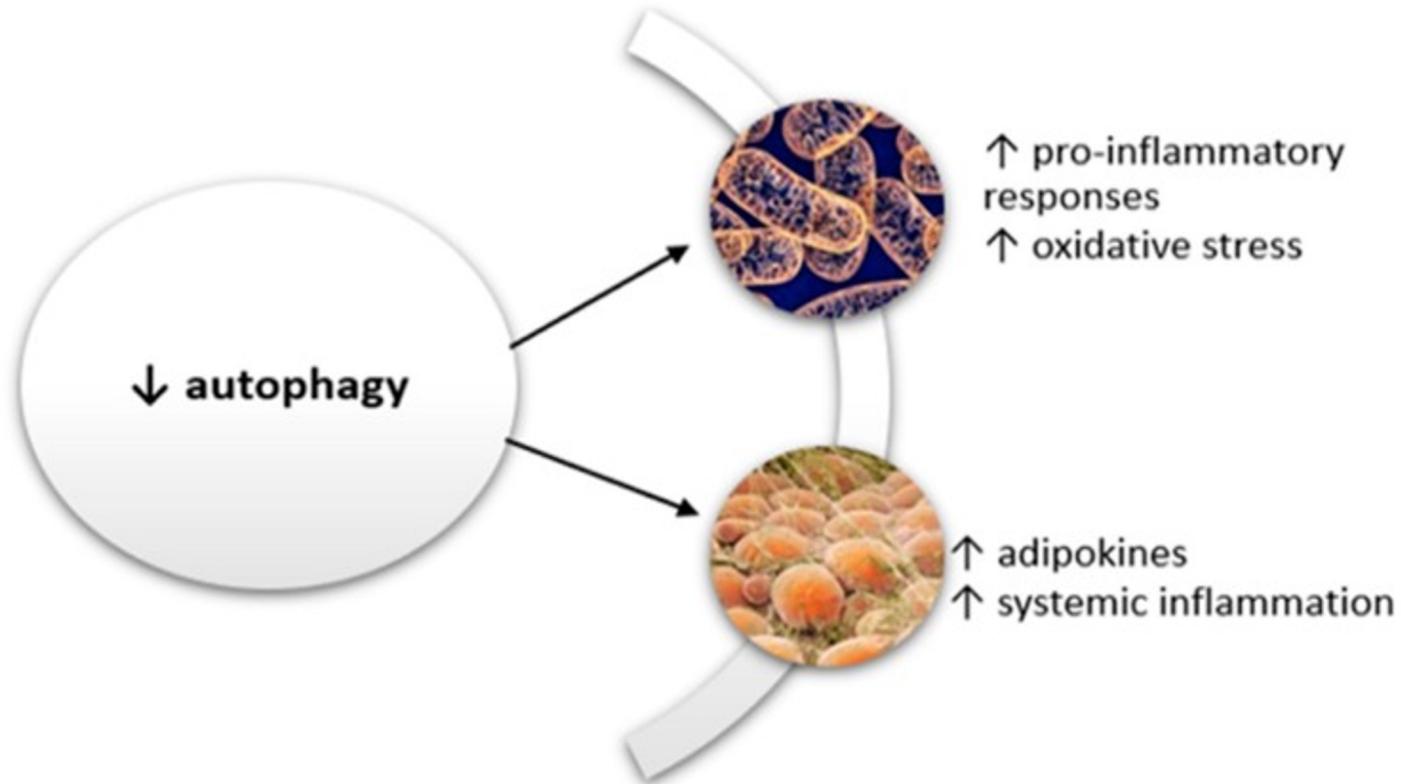
Rezuş E, Cardoneanu A, Burlui A, et al. *The Link Between Inflammaging and Degenerative Joint Diseases*. *Int J Mol Sci*. 2019;20(3):614. Published 2019 Jan 31. doi:10.3390/ijms20030614

Mitochondrial Dysfunction Plays as Integral Role in Development of Arthritis



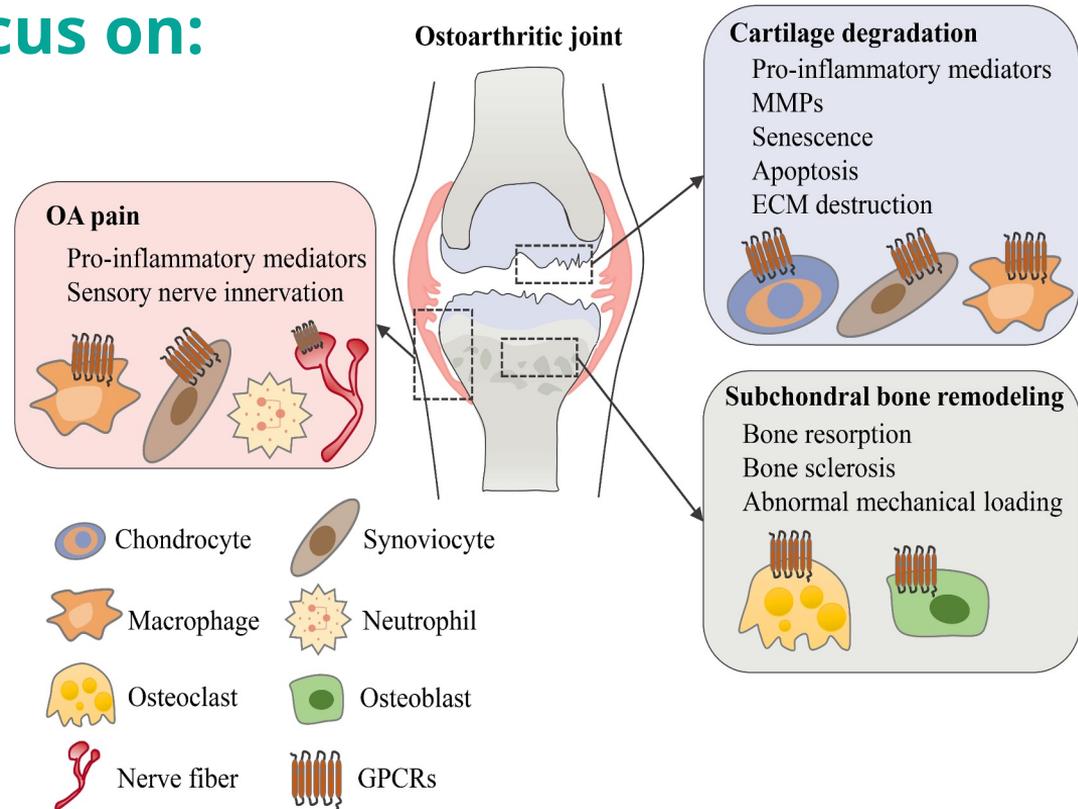
Rezuş E, Cardoneanu A, Burlui A, et al. *The Link Between Inflammaging and Degenerative Joint Diseases. Int J Mol Sci.* 2019;20(3):614. Published 2019 Jan 31. doi:10.3390/ijms20030614

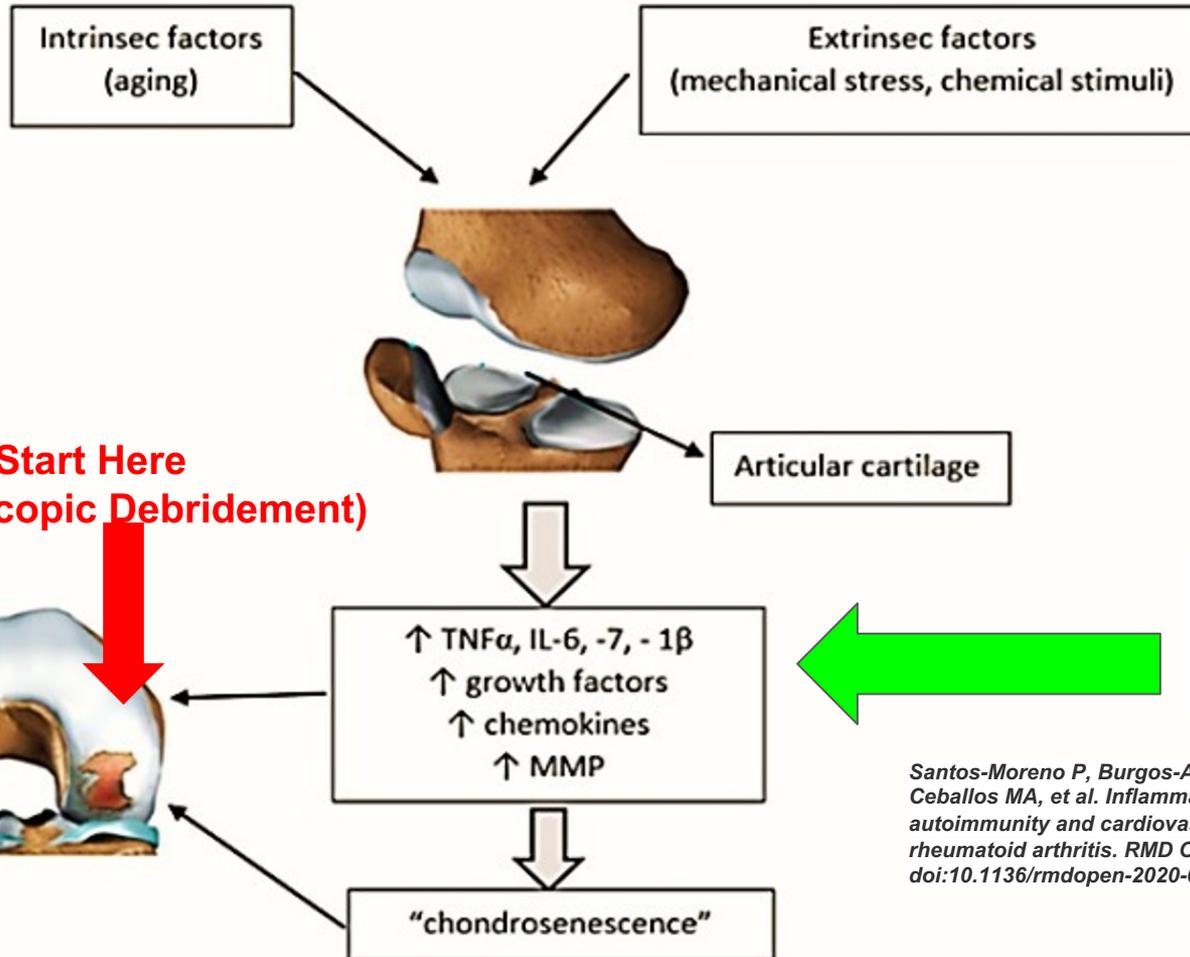
Altered Autophagy Further Damages Cartilage



Treatment needs to focus on:

- Reducing inflammatory cytokines
- Blocking degradative enzymes
- Enhancing Autophagy of senescent cells
- Address Mitochondrial dysfunction
- Repair of Extracellular matrix



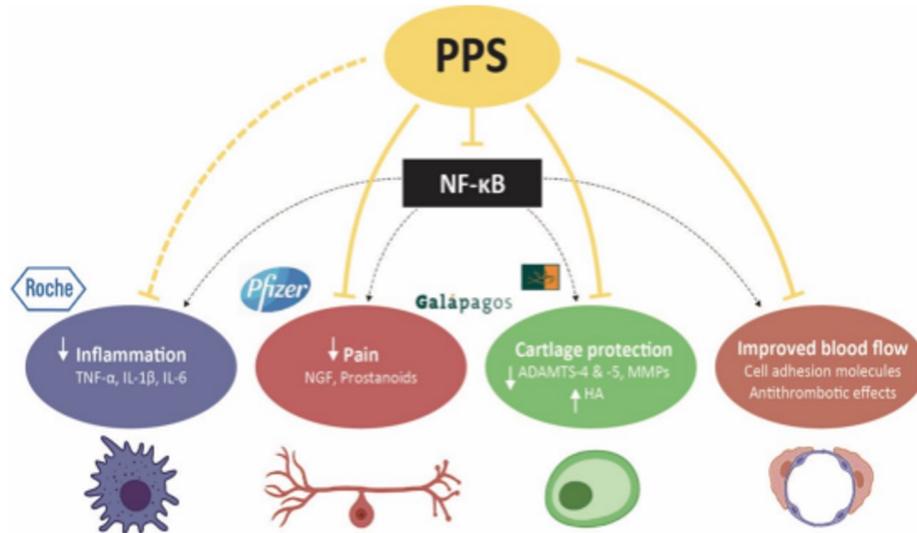


**Do NOT Start Here
(Arthroscopic Debridement)**

**Start here!
(PPS,A2M)**

Santos-Moreno P, Burgos-Angulo G, Martinez-Ceballos MA, et al. Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumatoid arthritis. *RMD Open*. 2021;7(1):e001470. doi:10.1136/rmdopen-2020-001470

Pentosan Polysulfate (PPS)



- Semi-synthetic drug manufactured from European beech xylans that are sulfated to produce a negatively charged product that mimics glycosaminoglycans (GAGs).
- These complex carbohydrates have a regulatory role in the body through interacting with proteins involved with inflammation.
- PPS also has a mild antithrombotic activity.
- .5cc twice weekly. Can continue weekly as needed maintenance

Pentosan Polysulfate may be the BEST treatment for arthritis treatment and prevention!

Paradigm's IPPS (Zilosul®) treatment vs OA drug candidates currently in development

	Paradigm (ZILOSUL®)	NSAID (ibuprofen etc)	Opioid (oxycodone etc)	Corticosteroid/ Cortisone	Joint Replacement
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology	✓				✓
Well-tolerated	✓				
Non-addictive	✓	✓		✓	✓
Anti-inflammatory	✓	✓		✓	
Non-surgical	✓	✓	✓	✓	

Source: EBSCO

Zilosul® - the only OA drug/treatment in its class that treats pain, is safe, and preserves joint integrity.

	Paradigm (ZILOSUL®)	Anti-NGFs (Tanezumab®)	Stem Cell & PRP treatments	Invozza® TissueGene's Cell/ Gene Therapy	CNTX-4975 Centrexion's trans-capsaicin
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology (potentially disease modifying)	✓	X	✓	✓	✓
No undesirable side-effects (safe for repeat use)	✓	X	?	?	
Non-addictive	✓	✓	✓	✓	✓
Anti-inflammatory	✓	X	?	✓	
Non-surgical	✓	✓	X	✓	
Affordable		X	X	X	

Reduces Inflammatory Cytokines

Biological Process	Chronic Disease	Key Pathological Mechanisms	PPS Therapeutic Action	Reference
Inflammation	Osteoarthritis Heart Failure	<p>*Overexpression of the inflammatory cytokines IL-1 beta and TNF-alpha instigate tissue damaging cellular immune responses within heart tissue and cartilage.</p> <p>*These cytokines are common to inflammation in OA and Heart Failure.</p>	<p>*PPS Blocks translocation of transcription factor NF-kB from the cytoplasm to the nucleus mediated by IL-1 or TNF-alpha.</p> <p>*Reduced NF-kB transcription results in down-regulation of IL-1 and TNF synthesis, leading to reduction in inflammation in cartilage and heart tissues.</p>	<p>Inhibitory effects of pentosan polysulfate sodium on MAP-kinase pathway and NF-κB nuclear translocation in canine chondrocytes in vitro.</p> <p>Sunaga T, Oh N, Hosoya K, Takagi S, Okumura M. J Vet Med Sci. 2012 Jun;74(6):707-11. Epub 2011 Dec 28.</p>

Binds Degradative Enzymes

#PeptideWC2022

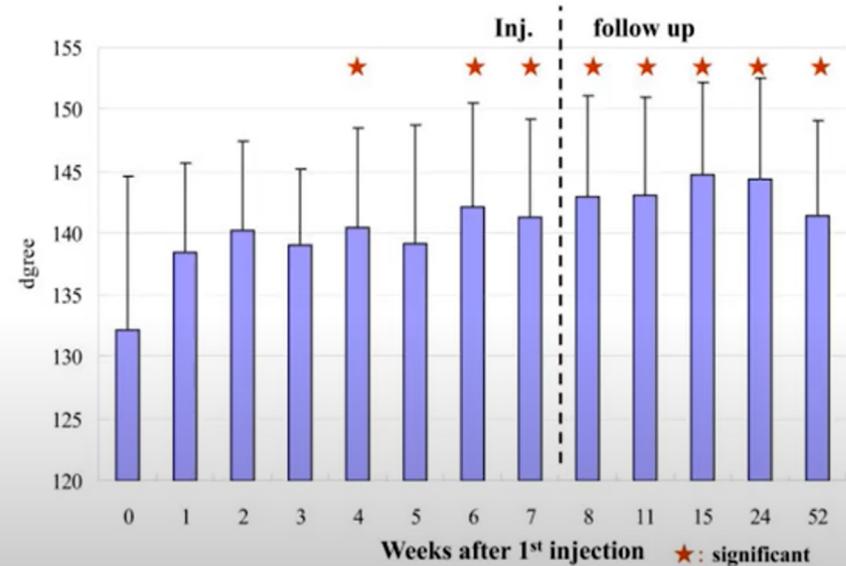
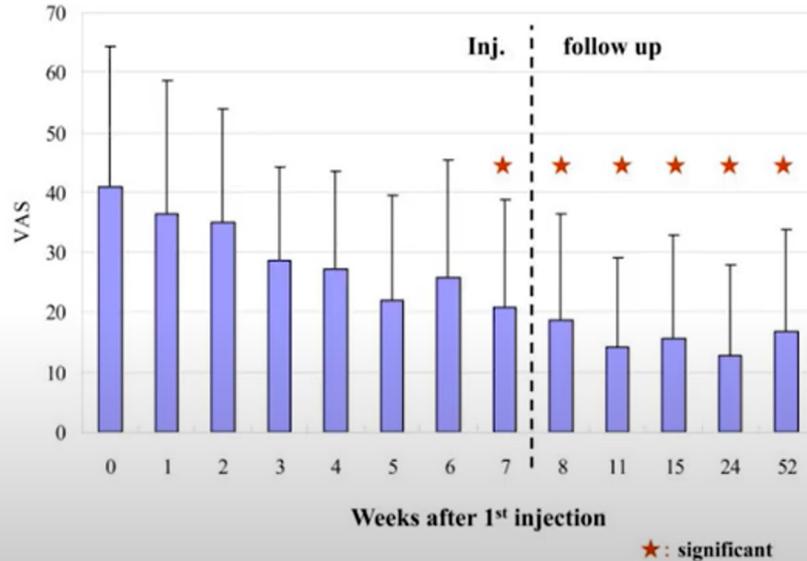
Biological Process	Chronic Disease	Key Pathological Mechanisms	PPS Therapeutic Action	Reference
Tissue Damage & Adverse Remodelling	Osteoarthritis	<p>*Increased levels of cartilage degrading enzymes ADAMTS-4, ADAMTS-5, MMP3.</p> <p>*Involved in impairment of joint function and potentially cause bone marrow edema and bone pain.</p>	<p>*PPS forms a stable complex with the enzyme inhibitor (TIMP-3) for ADAMTS-4 and ADAMTS-5 (Ref: Troeberg).</p> <p>*PPS also inhibits the synthesis of the metalloproteinase MMP-3 (Ref: Troeberg) involved in degrading cartilage.</p> <p>*PPS thus reduces or prevents cartilage degradation in OA by inhibiting and/or binding cartilage degrading enzymes.</p>	<p>Pentosan polysulfate increases affinity between ADAMTS-5 and TIMP-3 through formation of an electrostatically driven trimolecular complex.</p> <p>Troeberg L, Mulloy B, Ghosh P, Lee MH, Murphy G, Nagase H. Biochem J. 2012 Apr 1;443(1):307-15. doi: 10.1042/BJ20112159.</p> <p>https://paradigmbiopharma.com</p>

Stabilizes Abnormal Growth Factors Causing Pain

Biological Process	Chronic Disease	Key Pathological Mechanisms	PPS Therapeutic Action	Reference
Pain	Osteoarthritis	Increased expression of NGF mRNA and protein in osteocytes in the subchondral bone of osteoarthritic joints	*PPS	Human osteocyte expression of Nerve Growth Factor: The effect of Pentosan Polysulfate Sodium (PPS) and implications for pain associated with knee osteoarthritis. Stapledon CJM, Tsangari H, Solomon LB, Campbell DG, Hurtado P, Krishnan R, Atkins GJ. PLoS One. 2019 Sep 26;14(9):e0222602. doi: 10.1371/journal.pone.0222602. eCollection 2019.

Visit PGIC scores	WOMAC subjects (N = 34)
Post-Baseline	
No change (or condition has got worse)	0
Almost the same, hardly any change at all	2 (5.7%)
A little better, but no noticeable change	2 (5.7%)
Somewhat better, but the change has not made any real difference	0
Moderately better, and a slight but noticeable change	8 (22.9%)
Better and a definite improvement that has made a real and worthwhile difference	13 (37.1%)
A great deal better and a considerable improvement that has made all the difference	9 (25.7%)

Pentosan Polysulfate



BMC Clin Pharmacol. 2010 Mar 28;10:7. doi: 10.1186/1472-6904-10-7.

Sodium pentosan polysulfate resulted in cartilage improvement in knee osteoarthritis--an open clinical trial.

Kumagai K^{#1}, Shirabe S^{#2}, Miyata N^{#1}, Murata M^{#1}, Yamauchi A^{#3}, Kataoka Y^{#3}, Niwa M^{#4}.

TGA Special Access Scheme – Real World Evidence – 45 patients treated

All patients (median age of 57.6 years - range 31 to 84 years) had pain and failed current standard of care - analgesics, NSAIDs or corticosteroids.

At six weeks after the initiation of PPS treatment:

Pain

- 38 out of 45 patients (84.4%) showed a reduction in pain;

Function

- 38 out 45 patients (84.4%) showed an improvement in knee function;

Patient A MRI – Pre PPS Treatment

Pre treatment Scores

- High NRS Pain Score = 8
- Lysholm Score: 37 (Poor knee function)

BME Lesions

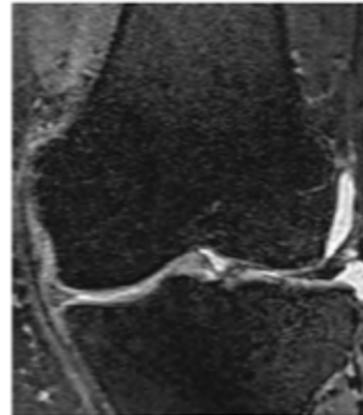
Joint Space Effusions



Patient A MRI – Post PPS Treatment

Post Treatment Results

- Complete resolution of BME lesions and effusions
- Pain NRS = 0 (pain resolved)
- Lysholm Score: 65 (Fair knee function)



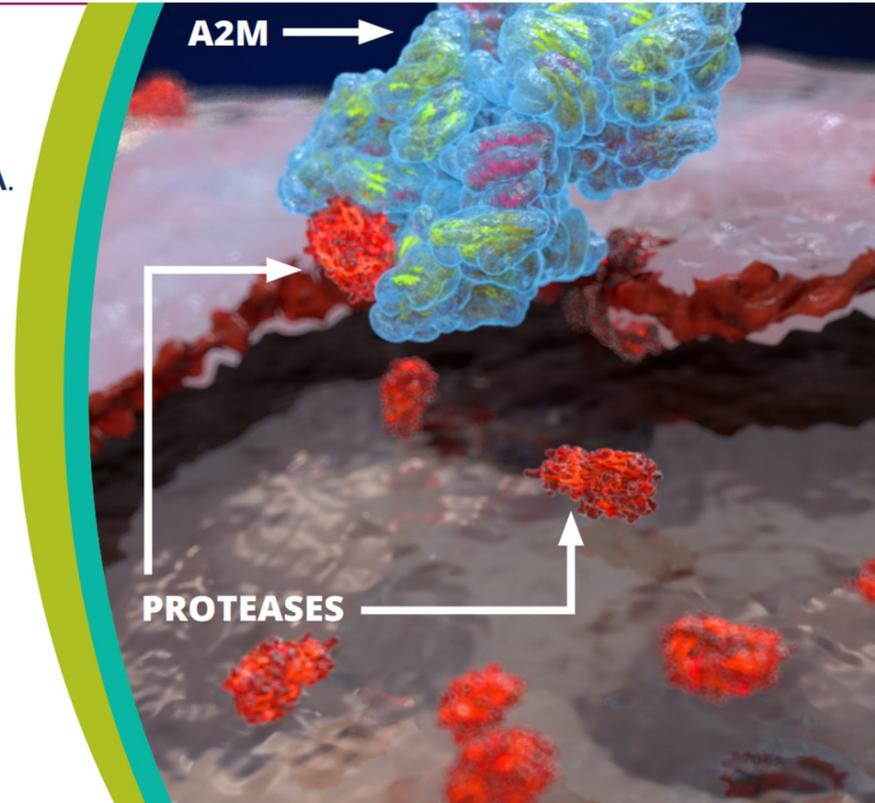
Alpha 2 Macroglobulin (A2M)

Alpha-2-Macroglobulin (A2M) is a blood serum protein that plays a small role in the clotting cascade. A2M is a well characterized, broad-spectrum **protease inhibitor** that has demonstrated potent inhibitory activity against the **proteases that are upregulated in OA**.

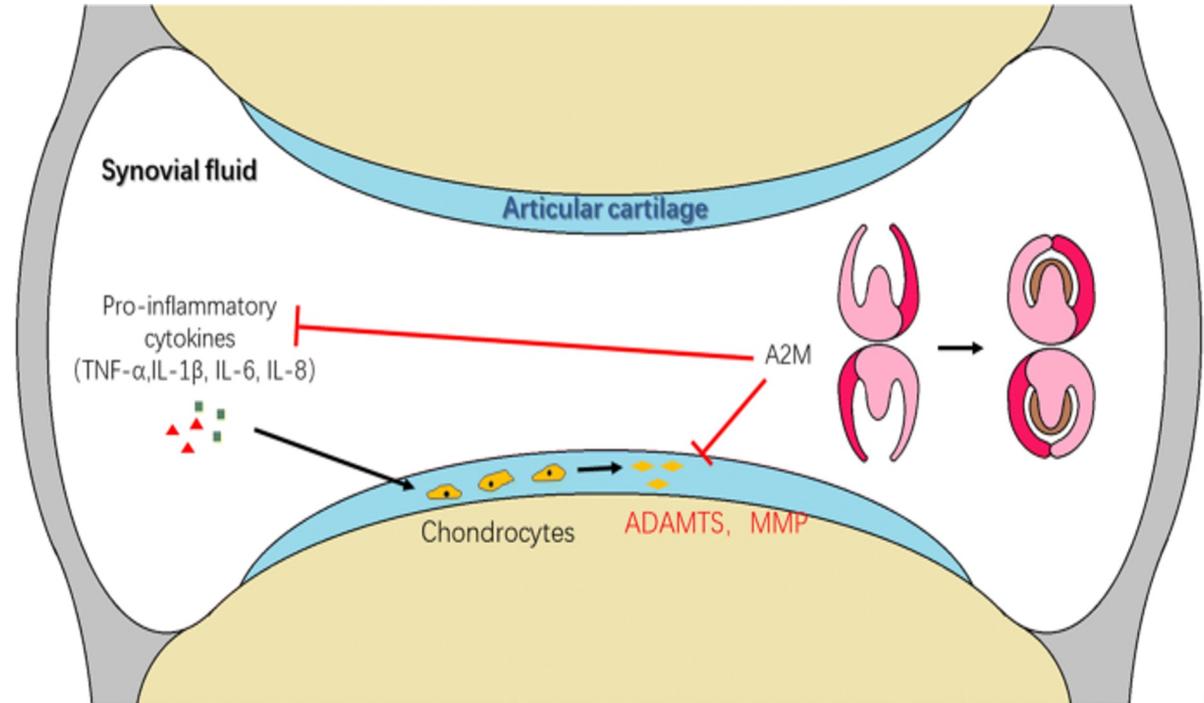
Unfortunately, the levels of naturally occurring A2M are too low to lend any therapeutic benefit to damaged joints. However, we theorized that:



Delivering high concentrations of A2M directly into the joint space could bind to and inhibit the proteases, slowing and eventually halting the progression of OA.

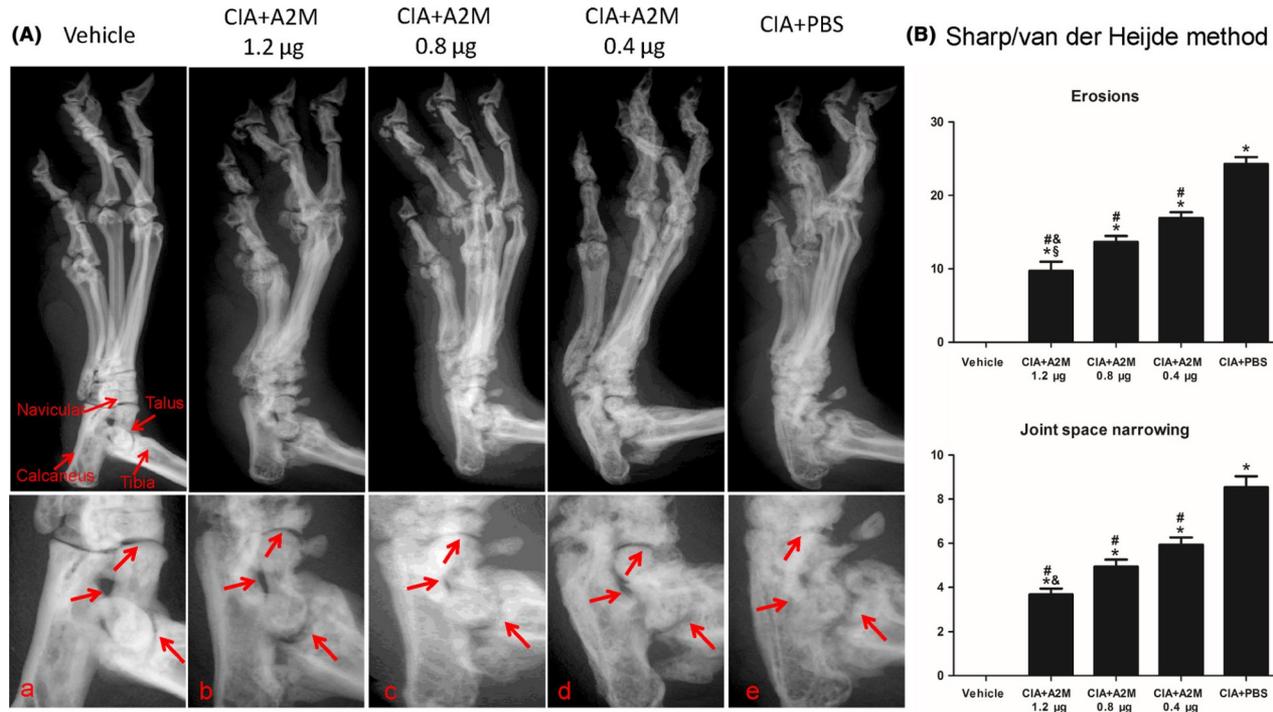


A2M captures inflammatory cytokines through changing its conformation, then protects cartilage from those destructive cytokines



Zhu, M., Zhao, B., Wei, L. et al. alpha-2-Macroglobulin, a Native and Powerful Proteinase Inhibitor, Prevents Cartilage Degeneration Disease by Inhibiting Majority of Catabolic Enzymes and Cytokines. *Curr Mol Bio Rep* 7, 1–7 (2021).

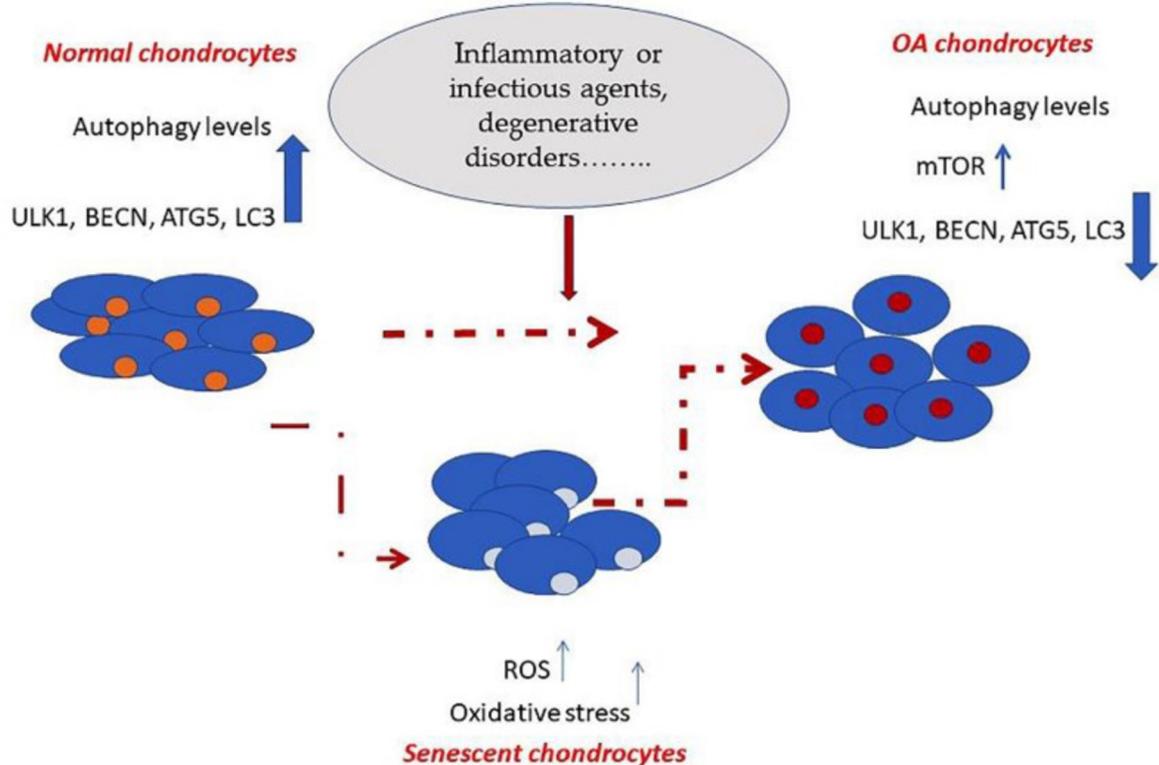
Intra-articular A2M exerts an anti-inflammatory effect and attenuates cartilage and bone damage



Li, S, Xiang, C, Wei, X, et al. Early supplemental α 2-macroglobulin attenuates cartilage and bone damage by inhibiting inflammation in collagen II-induced arthritis model. *Int J Rheum Dis*. 2019; 22: 654–665. <https://doi.org/10.1111/1756-185X.13457>

Next: Address Impaired Autophagy/ Mitochondrial Dysfunction

Autophagy
dysregulation is closely
related to the
pathogenesis of
osteoarthritis (OA)



Review

Mitophagy in degenerative joint diseases

Kai Sun, Xingzhi Jing, Jiachao Guo, Xudong Yao & Fengjing Guo 

Received 22 May 2020, Accepted 04 Sep 2020, Published online: 24 Sep 2020

“Conclusion and future prospects

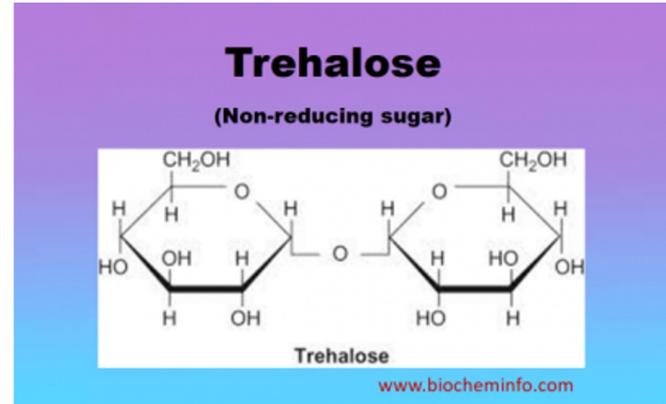
Both OA and IVDD are degenerative diseases that strongly correlate with age and the breakdown of cartilaginous tissue. There is a similar pathological process between IVDD and OA in term of mitochondria dysfunction, senescence, cell apoptosis and ECM degradation

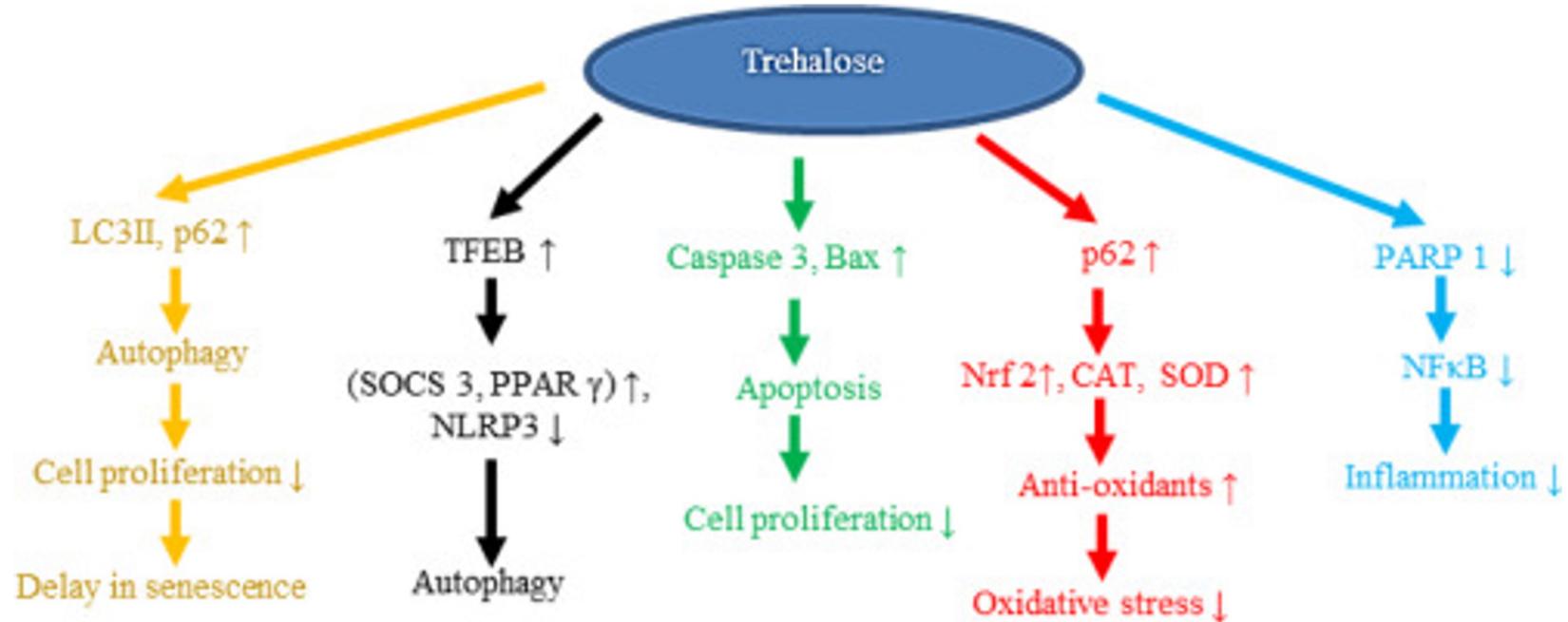
The maintenance of mitochondria homeostasis governs fate and characteristics of functional cells including NP cells, chondrocytes and other cells with rich mitochondria.

Therefore, selective autophagy toward impaired mitochondria, mitophagy, is tightly associated with IVDD and OA and could be a critical regulatory mechanism to develop therapeutic approaches for these degenerative diseases.”

Trehalose

- A natural sugar compound in plants, made up of two glucose molecules.
- Studies have suggested that trehalose may be one of the most effective sugars in protecting cellular membranes.
- Trehalose is also a main source of energy for some bacteria, fungi, plants and invertebrates.





Review article

Molecular mechanisms of action of Trehalose in cancer: A comprehensive review

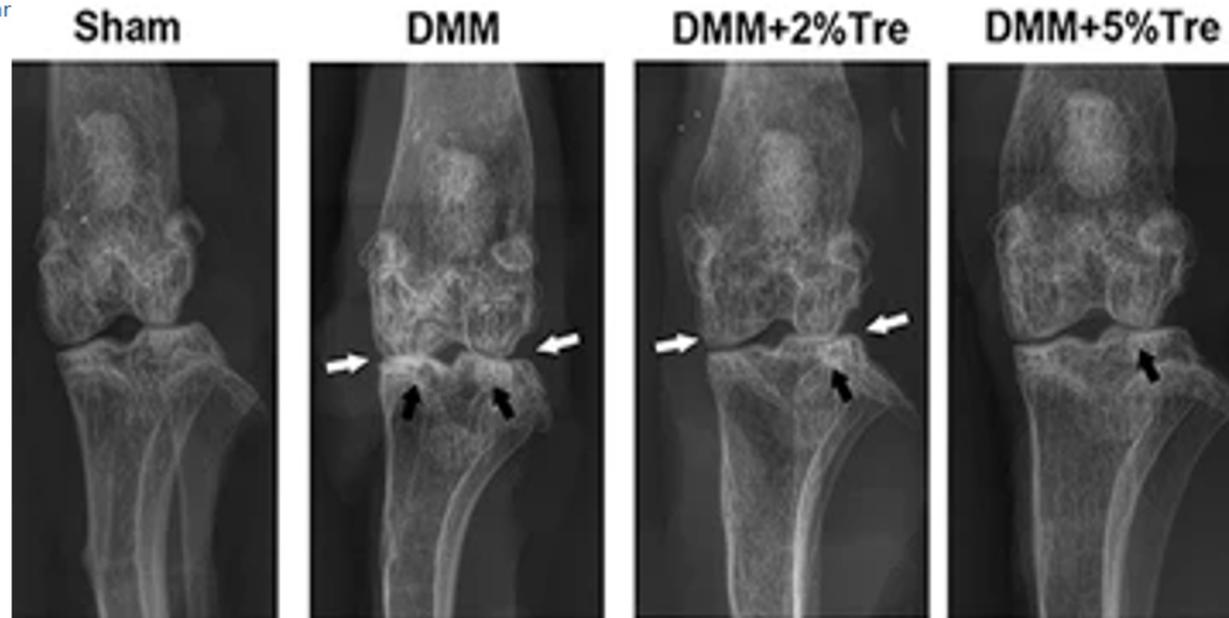
Nyshadham S N Chaitanyaa Arpita Devib Sibani Sahuc Phaniendra Alugojud

Trehalose ameliorates oxidative stress-mediated mitochondrial dysfunction and ER stress via selective autophagy stimulation and autophagic flux restoration in osteoarthritis development

Qian Tang, Gang Zheng, Zhenhua Feng, Yu Chen, Yiting Lou, Chenggui Wang, Xiaolei Zhang, Yu Zhang, Huazi Xu ✉, Ping Shang ✉ & Haixiao Liu ✉

Cell Death & Disease 8, e3081 (2017) | Cite this article as
4758 Accesses | 1 Altmetric | Metrics

“In summary, we demonstrated that autophagic flux marker p62 and apoptosis marker cleaved caspase 3 were upregulated in human OA and TBHP-treated mouse chondrocytes. Trehalose administration targeted activated mitophagy and restored oxidative stress-induced autophagic flux disruption in mouse chondrocytes, which was associated with the activation of AMPK but not mTOR-dependent pathway. Autophagic changes stimulated by trehalose protected chondrocytes against apoptosis by attenuating mitochondrial dysfunction and ER stress”



**Or could
primordial soup,
semen, and
rotting flesh hold
clues to healthy
aging?**

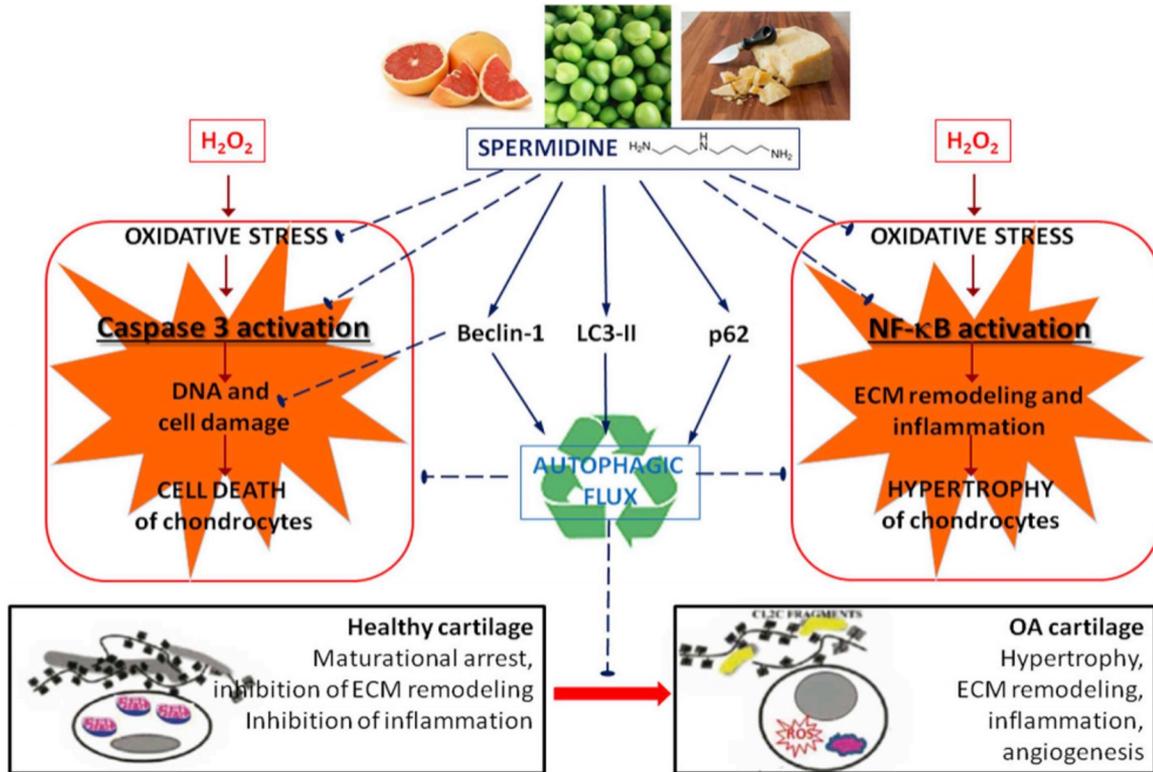


Spermidine

- A naturally occurring Polyamine found in high levels in semen, breast milk and foods like aged cheese, soybeans, broccoli and wheat germ
- Also naturally found in the body
- Higher levels of polyamines like spermidine are associated with longevity and health
- Boosts Mitophagy (getting rid of damaged mitochondria) and dampens oxidative stress

Spermidine rescues the deregulated autophagic response to oxidative stress of osteoarthritic chondrocytes

Stefania D'Adamo^{a,b}, Silvia Cetrullo^a, Serena Guidotti^b, Ylenia Silvestri^a, Manuela Minguzzi^b, Spartaco Santi^{c,d}, Luca Cattini^e, Giuseppe Filardo^f, Flavio Flamigni^a, Rosa Maria Borzi^{e,*}



6mg daily for 4-6 weeks to induce autophagy. Repeat quarterly

Then maintenance 2mg daily

Rapamycin



International Journal of
Molecular Sciences



Article

Rapamycin Maintains the Chondrocytic Phenotype and Interferes with Inflammatory Cytokine Induced Processes

Andrea De Luna-Preitschopf ^{1,*}, Hannes Zwickl ², Stefan Nehrer ¹, Markus Hengstschläger ³ and Mario Mikula ³

- Rapamycin was able to protect chondrocytes from cell death in an OA-model shown by reduced Caspase 3/7 activity and diminished LDH release.
- Inhibition of mTORC1 preserved the chondrogenic phenotype of OA chondrocytes, but also reduced inflammatory processes within the OA-model.
- This study highlights that blocking mTORC1 is a new and promising approach for treating OA.
- Low side effects make rapamycin an attractive implementation to existing therapeutic strategies.
- Rapamycin's chondroprotective property might be due to an interference with IL-1 β triggered inflammatory processes"

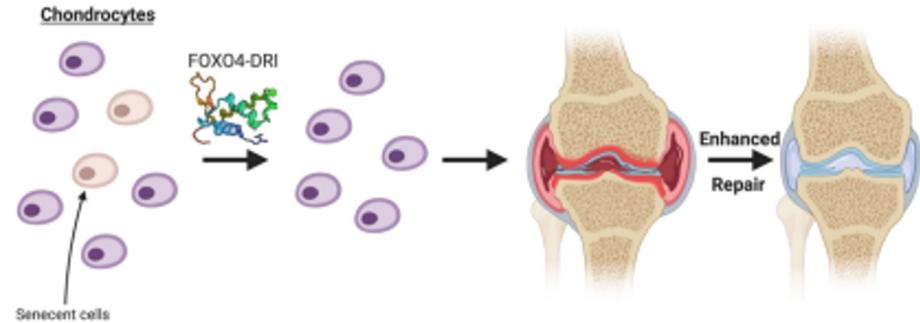
Dosing:

**5-6 mg once weekly
or 2-3 mg every
other week**

FOXO4-dri

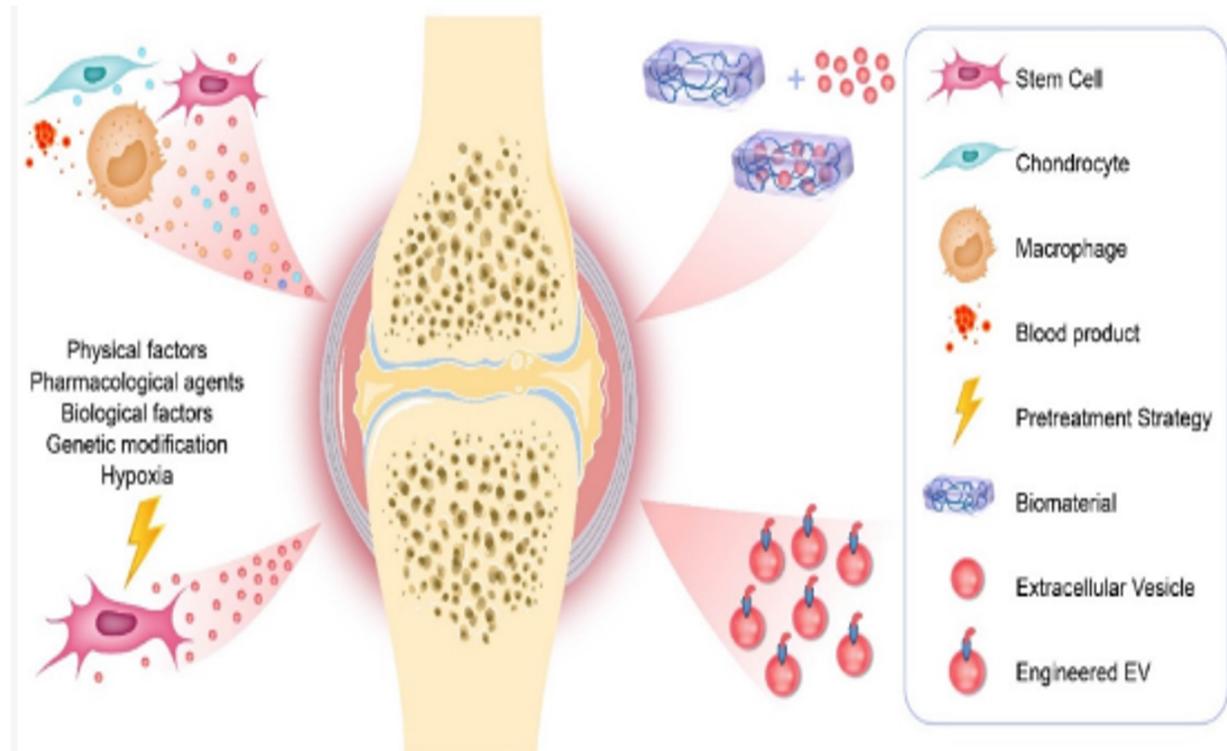
Enhancing the reparative outcome of autologous chondrocyte implantation (ACI) by selectively removing senescent cells with peptide FOXO4-DRI

Presenter: Yuchen He
Mentor: Hang Lin, PhD



Repair:

- AOD/HA
- BPC-157
- Thymosin beta 4
- Platelets/stem cells/extracellular vesicles



Peptide -AOD 9064

- C-terminal growth hormone fragment
- Increases chondrocyte, proteoglycan, and collagen production and quality, enhancing repair and regeneration and accordingly may improve cartilage production or quality
- Enhances the differentiation of adipose mesenchymal stem cells
- Rabbit study - combined injections of AOD9604 and HA showed better outcomes than the groups that received AOD9604 or HA alone
- High molecular weight of HA significantly protects chondrocytes against oxygen-derived free radical action

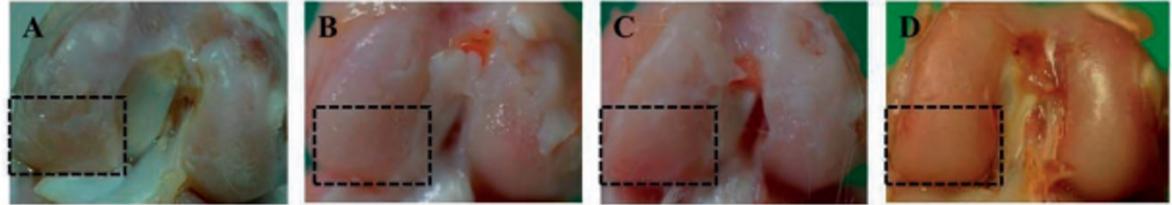
Kwon DR, Park GY. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model. Ann Clin Lab Sci. 2015; 45: 426-432.

Group 1: 0.6 ml saline

Group 2: 0.6 ml HA

Group 3: 0.6 ml AOD

Group 4: 0.6 ml HA with 0.6 ml AOD



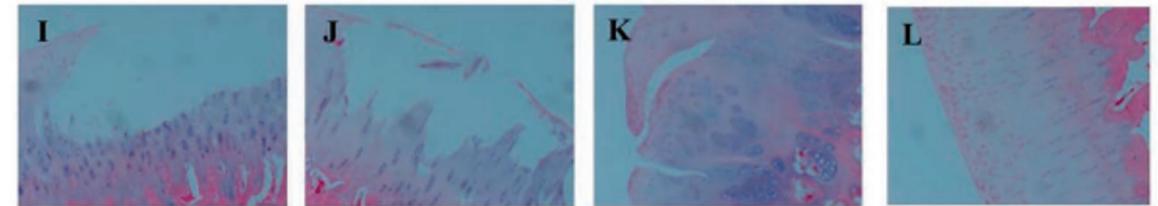
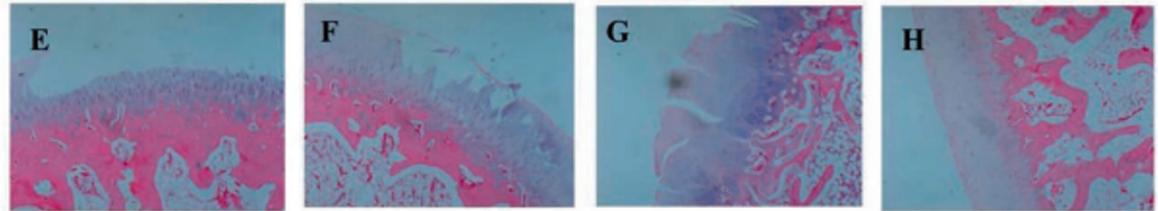
Ulceration

Fibrillation

Erosion

Softening

AOD/HA induces cartilage repair



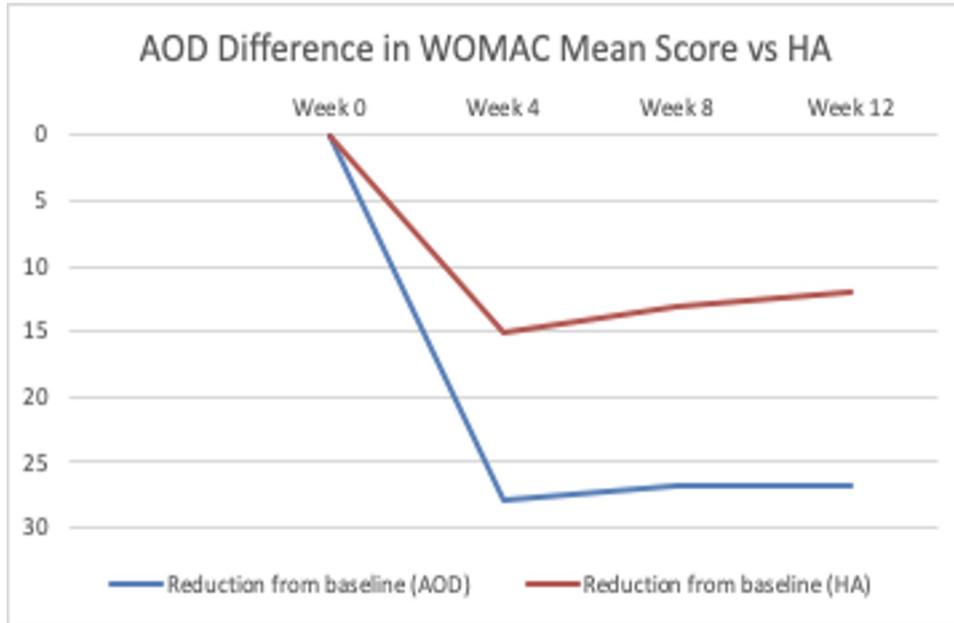
Disorganized

Cleft to transitional zone

Cleft to radial zone

Surface irregularity

HA/AOD Peptide

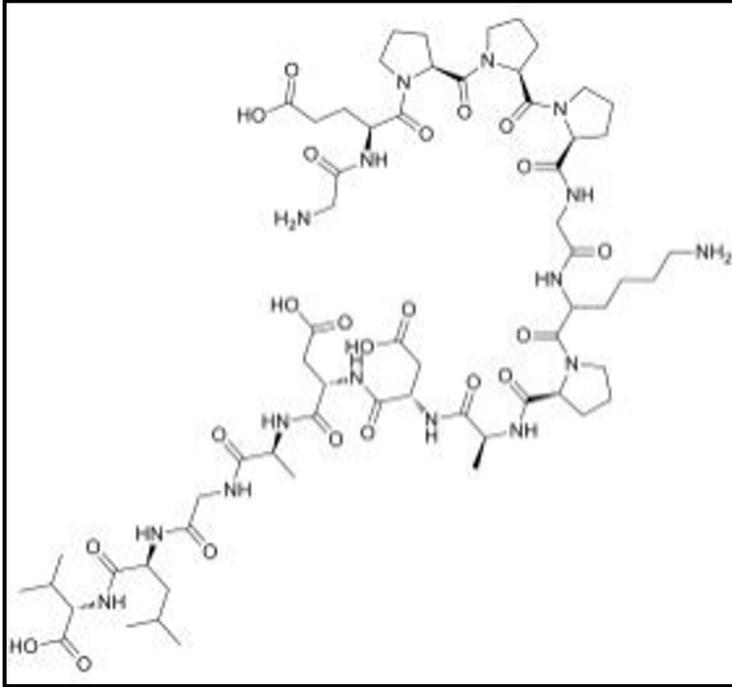


34 patients
KELGREN LAWRENCE Stage 3,4
Intra anticircular injections 1cc,
1200 mcg
5 injections once a week

3 month follow up
significant improvement
pain, stiffness, function

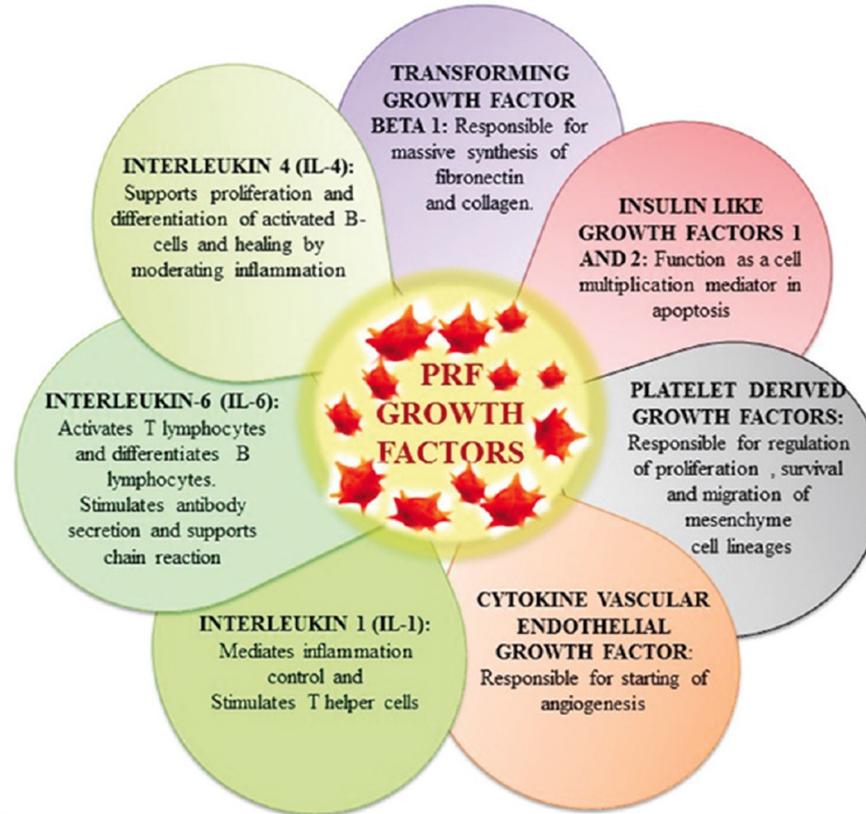
International Peptide society HA/AOD IRB Single Center

BPC-157



- BPC-157 works by encouraging production of crucial growth factors and it enhances the nitric oxide pathway
- It promotes complex physiological processes that take place in the event of wound healing and tissue regeneration and repair throughout the body
- 500 mcg sq injection daily

Growth Factors are ESSENTIAL for Healing



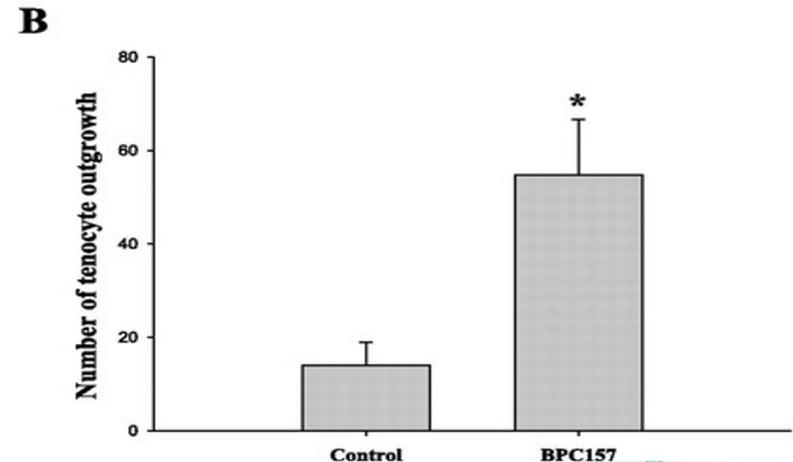
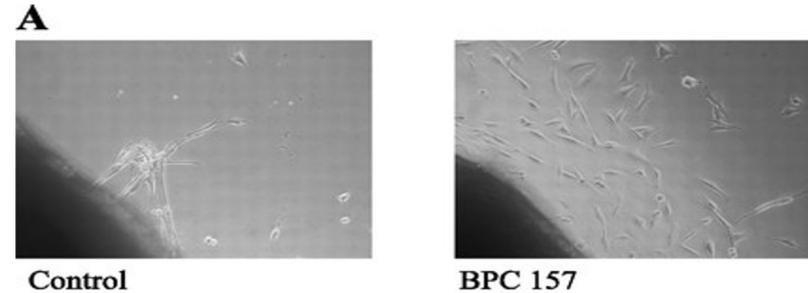
BUT..

- Indiscriminately injecting growth factors like VEGF (vascular endothelial growth factor) or IGF to promote healing can stimulate growth where you don't want it! Scar, tumorigenesis..
- Using BPC-157 to promote natural, modulatory production of growth factors, on the other hand, is a safe option – an option with a plethora of potential health benefits.

BPC-157 Rapidly Heals Tendons

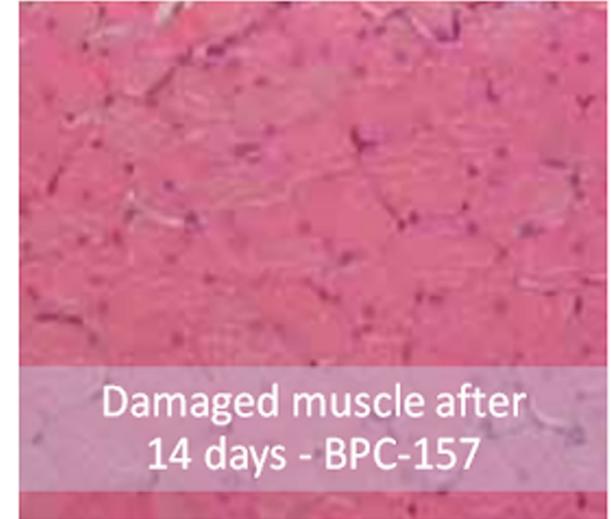
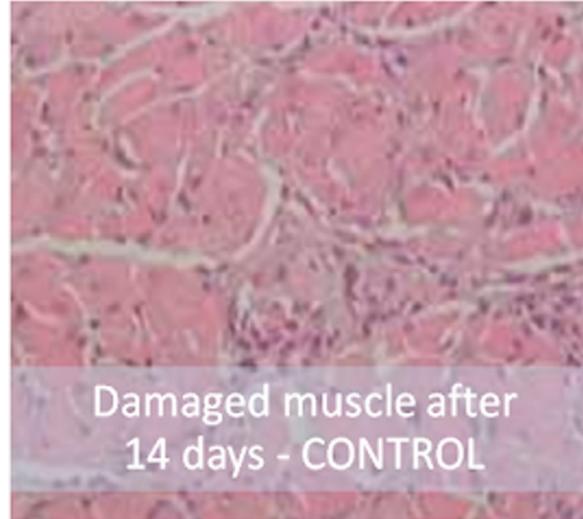
2011 study published in the Journal of Applied Physiology showed significant tendon regeneration and wound healing in animals.

J Appl Physiol (1985). 2011 Mar;110(3):774-80. doi: 10.1152/jappphysiol.00945.2010. Epub 2010 Oct 28. The promoting effect of pentadecapeptide BPC 157 on tendon healing involves tendon outgrowth, cell survival, and cell migration. Chang CH¹, Tsai WC, Lin MS, Hsu YH, Pang JH.



BPC Heals Damaged Muscle

BPC-157 blocked the negative effects of corticosteroids on muscle healing AND it super-charged the healing process!



Novinscak T, Brcic L, Sipos K, Jukic I, Staresinic M, Mise S, Brcic I, Kolenc D, Klicek R, Banic T, Sever M, Kocijan A, Berkopic L, Radic B, Buljat G, Anic T, Zoricic I, Bojanic I, Seiwerth S, Sikiric P. Med Sci Monit. 2010 Mar;16(3):BR81-88. Impact of pentadecapeptide BPC 157 on muscle healing impaired by systemic corticosteroid application.

Intra Articular BPC-157 4mg injection

*ALTERNATIVE THERAPIES, JUL/AUG 2021 VOL. 27 NO. 4 Lee—
Injection of BPC 157 for Multiple Types of Knee Pain*

Figure 1. Overall pain in all 16 patients; 14 out of 16 (87.5%) had improvement in knee pain.

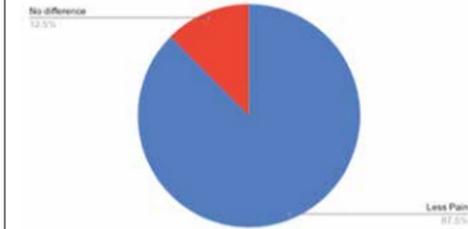


Figure 2. Overall mobility in all 16 patients; 75% had improvement in mobility.

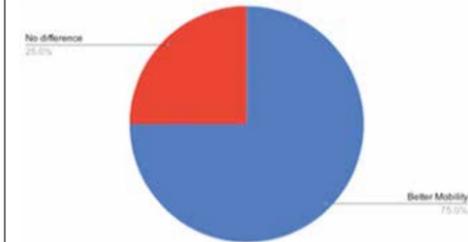
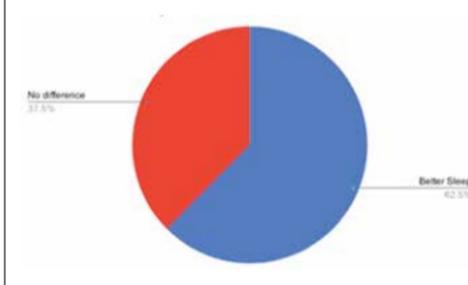


Figure 3. Overall sleep in all 16 patients; 62.5% had better sleep.



Thymosin Beta 4

TB4 is a potent modulator of actin. Actin is a vital structural component within human tissues that serves as both a cellular “highway” for communication and a building block for structural integrity.

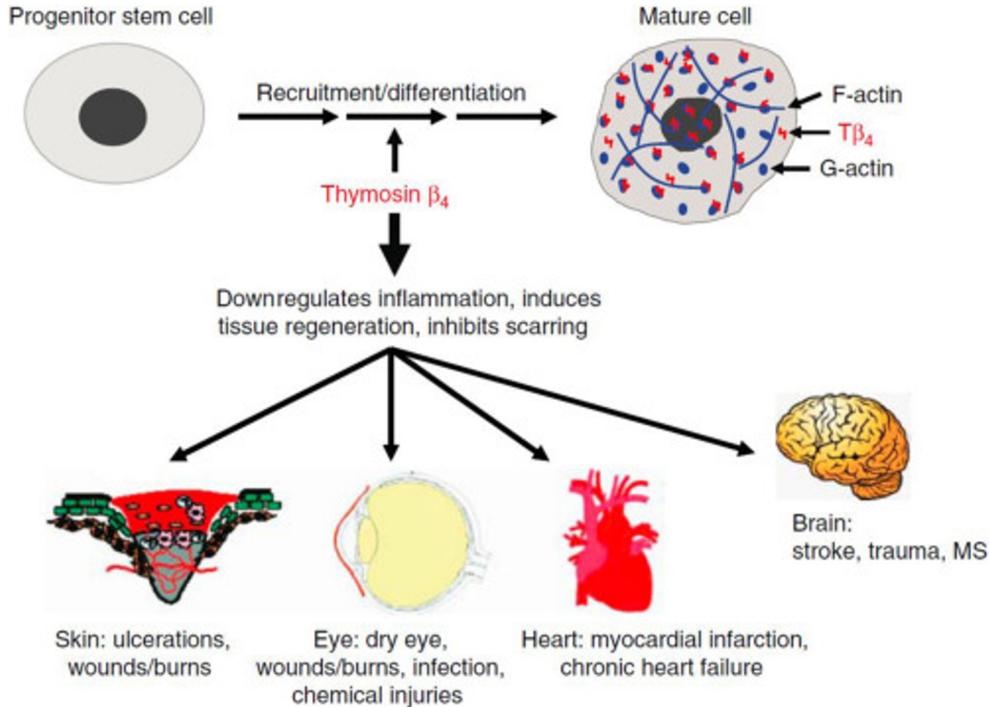
TB4 has been shown to promote tissue healing via improving:

- Migration and dispersal of cells to injury
- Angiogenesis (blood flow)
- Collagen deposition
- Inflammation

W. Freeman,^{*}1 Brian R. Bowman,[†] and Bruce R. Zetter^{*},2 ^{*}(MAR2011). Regenerative protein thymosin -4 is a novel regulator of purinergic signaling. *The FASEB Journal. Research Communication. Vascular Biology Program and Department of Surgery, Children’s Hospital, Boston, and Harvard Medical School, Boston Massachusetts, USA; and* [†]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, USA

Crockford, D., Turhman, N., Allan, C., & Angel, J. (2010). *Thymosin beta 4: structure, function, and biological properties supporting current and future clinical applications. Annals of the New York Academy of Sciences*, 1194(1), 179-189. DOI: 10.1111/j.1749-6632.20109.05492.x

Thymosin Beta 4



- Improves muscle generation
- Increases rate of cell healing
- Supports cell migration to the site of injury
- Repairs soft tissue, tendons, and ligaments
- Reduces scar tissue
- Improves hair regrowth
- Extends life expectancy
- Enhances anti-aging appearance
- Accelerates muscle growth, tone, and stamina

GHK-Cu

- Tripeptide glycyl-histidyl-lysine
- Found in biological fluids in either a free form or as a complex formed with the ion Cu^{2+} (GHK-Cu).
- Blood concentration of this molecule is believed to be around $200\mu\text{g l}^{-1}$ in people aged 20-25 but after the age of 60, it can fall to $80\mu\text{g l}^{-1}$
- Offers multiple biological effects particularly for anti-ageing. Its mechanism of action is based on the reconfiguration of normal gene expression to resemble that of young, healthy individuals.
- Restricts the expression of genes linked to fibrinogen synthesis, and reduces production of pro-inflammatory cytokines such as IL-6
- Activates DNA repair genes.
- Stimulates 14 genes associated with the antioxidant system and restricts the expression of two genes linked to oxidation.
- Benefits tissue regeneration through its influence on growth factors from the TGF- β superfamily. This effect appears to be especially significant during remodelling, the final stage of healing.

Collagen Peptides

- Type 1 and 3 collagens are generally used to support bones and skin health.
- Type 2 is used to support joints.
- Studies have shown positive benefits with 10 to 15 g doses — sometimes even just 5g.
- Vitamin C increases efficacy

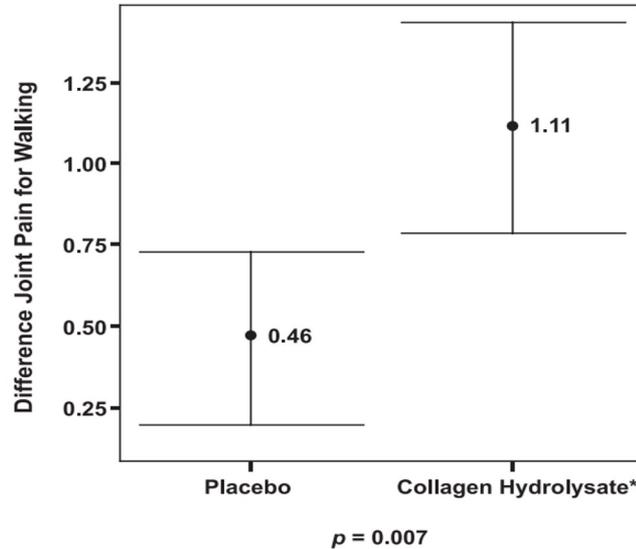


Collagen Peptide Study

50 male and female athletes with CAI completed a randomized, double-blinded and placebo-controlled study with a daily oral administration of either 5 g SCP or 5 g placebo (Maltodextrin) over a period of six months.

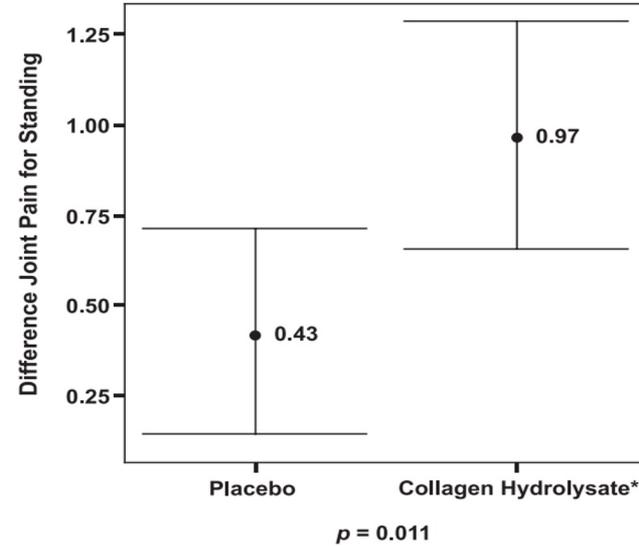
- ***Collagen peptides significantly improved subjective perceived function of the ankle in activities of daily living and sports exercise.***
- ***Decreases in ankle sprains and the risk of ankle injuries were shown in a three-month follow-up period.***

Dressler P, Gehring D, Zdzieblik D, Oesser S, Gollhofer A, König D. Improvement of Functional Ankle Properties Following Supplementation with Specific Collagen Peptides in Athletes with Chronic Ankle Instability. *J Sports Sci Med.* 2018;17(2):298–304. Published 2018 May 14.



*CH-Alpha

Figure 2. Change of pain perception for the parameter walking in the analysis population ($n = 97$) according to the visual analogue scale throughout the study phase (difference: score visit 5 – score visit 1) at 24 weeks. The numbers illustrated are the mean \pm the 95% confidence interval. The larger the number, the greater the decrease in pain



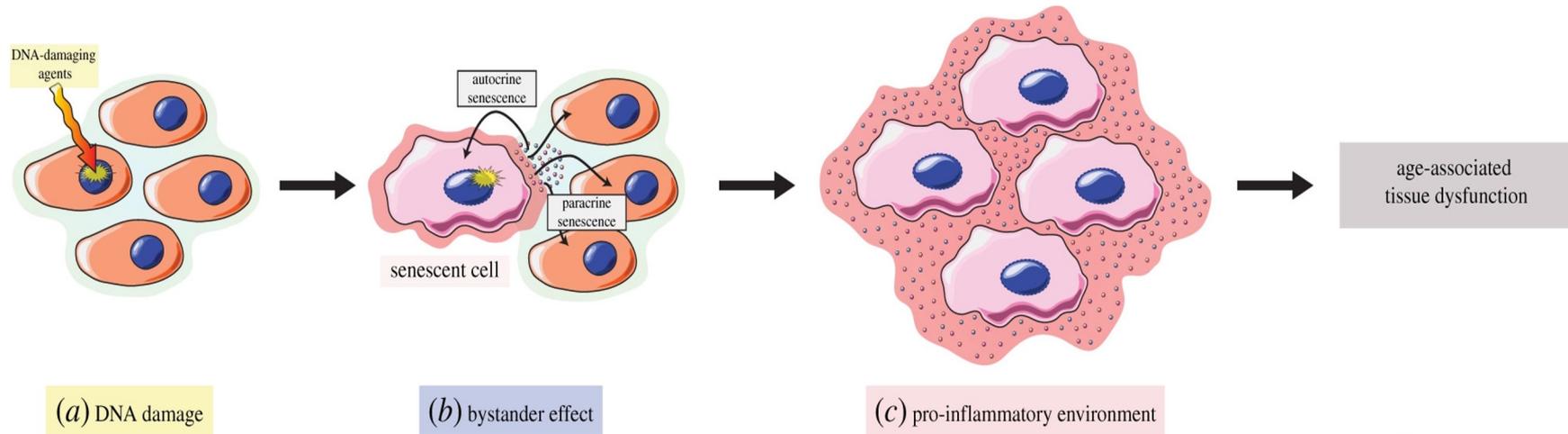
*CH-Alpha

Figure 3. Change of pain perception for the parameter standing in the analysis population ($n = 97$) as recorded with the use of the visual analogue scale during the study (difference: score visit 5 – score visit 1) at 24 weeks. The numbers illustrated are the mean \pm the 95% confidence interval. The larger the number, the greater the decrease in pain

Clark, K. L., Sebastianelli, W., Flechsenhar, K. R., Aukermann, D. F., Meza, F., Millard, R. L., ... Albert, A. (2008). 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. *Current Medical Research and Opinion*, 24(5), 1485–1496. doi:10.1185/030079908x291967

Regenerative Therapies: Concerns

In this new study, Japanese scientists discovered that MSCs derived from osteoarthritis patients contain a large fraction of senescent cells, which might be an important cause of the decline in their regenerative potential. Not only are senescent stem cells unable to differentiate into chondrocytes, but they also damage neighboring stem cells by secreting the senescence-associated secretory phenotype (SASP), a cocktail of mostly pro-inflammatory molecules.



Miura, Y., Endo, K., Komori, K., & Sekiya, I. (2022). Clearance of senescent cells with ABT-263 improves biological functions of synovial mesenchymal stem cells from osteoarthritis patients. *Stem Cell Research & Therapy*, 13(1), 1-15

So, optimally approach is best stepwise

1) Reduce inflammatory cytokines

- Pentosan polysulfate .5cc 2x weekly
- A2M injection
- Start BPC 500mcg sq daily and TB4 750mcg sq daily. Can do BPC IA injection 4mg

2) Address Autophagy and mitochondrial dysfunction

- Spermidine 6mg daily for 4-6 weeks
- Trehalose 5gms 3x daily
- Rapamycin 3mg once every other week
- Continue PPS, BPC and TB4

3) Regenerative Therapies:

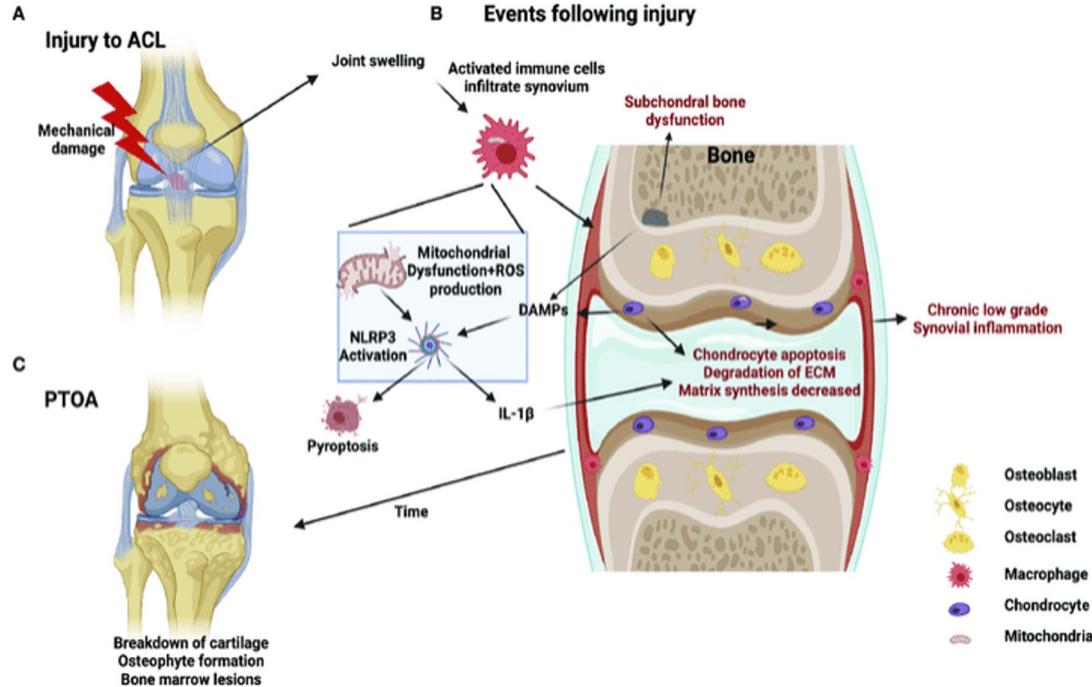
- AOD/HA IA .5-1ml weekly for 4-5 weeks
- Platelet Fibrin Matrix/stem cells/extracellular vesicles

DO NOT NEGLECT TREATING ACUTE INJURIES!!

- Acute trauma progresses to arthritis!
- On average, 50% of people with joint trauma may develop post-traumatic arthritis
- We need to focus much more on prevention!



ACL tears: Even with good repair as many as 80% will develop arthritis



Use the same things you just learned!

A2M after trauma prevents cartilage damage

[Arthritis Rheumatol. 2014 Jul; 66\(7\): 1843–1853.](#)

doi: [10.1002/art.38576](#)



Identification of Alpha 2 Macroglobulin (A2M) as a master inhibitor of cartilage degrading factors that attenuates post-traumatic osteoarthritis progression

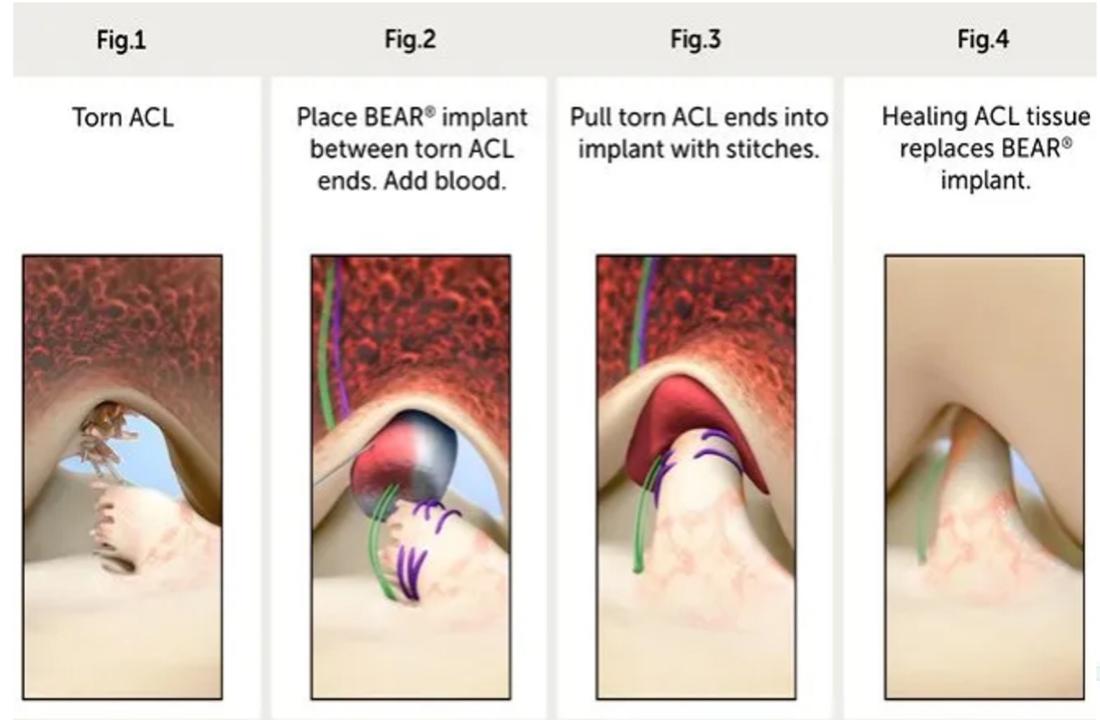
[Shaowei Wang](#),^{1,2,6} [Xiaochun Wei](#),^{2,†} [Jingming Zhou](#),¹ [Jing Zhang](#),^{1,3} [Kai Li](#),^{1,2} [Qian Chen](#),¹ [Richard Terek](#),¹ [Braden C. Fleming](#),¹ [Mary B. Goldring](#),⁴ [Michael G. Ehrlich](#),¹ [Ge Zhang](#),⁵ and [Lei Wei](#)^{1,2,*}

Results: In both normal and OA patients, the levels of A2M were lower in SF compared to serum, and MMP-13 was higher in SF than serum of OA patients. In vitro, A2M inhibited the induction of MMP-13 by IL-1 in a dose-dependent manner in human chondrocytes. In the rat ACLT OA model, supplemental intra-articular injection of A2M reduced the concentration of MMP-13 in SF, had a favorable effect on OA-related gene expression, and attenuated OA progression.

Conclusions: A2M is a plasma protease inhibitor that is not present in sufficient concentrations to inactivate the high concentrations of catabolic factors found in OA SF. Our findings suggest that supplemental intra-articular A2M provides chondral protection for post traumatic OA.

Improving ACL long-term outcomes

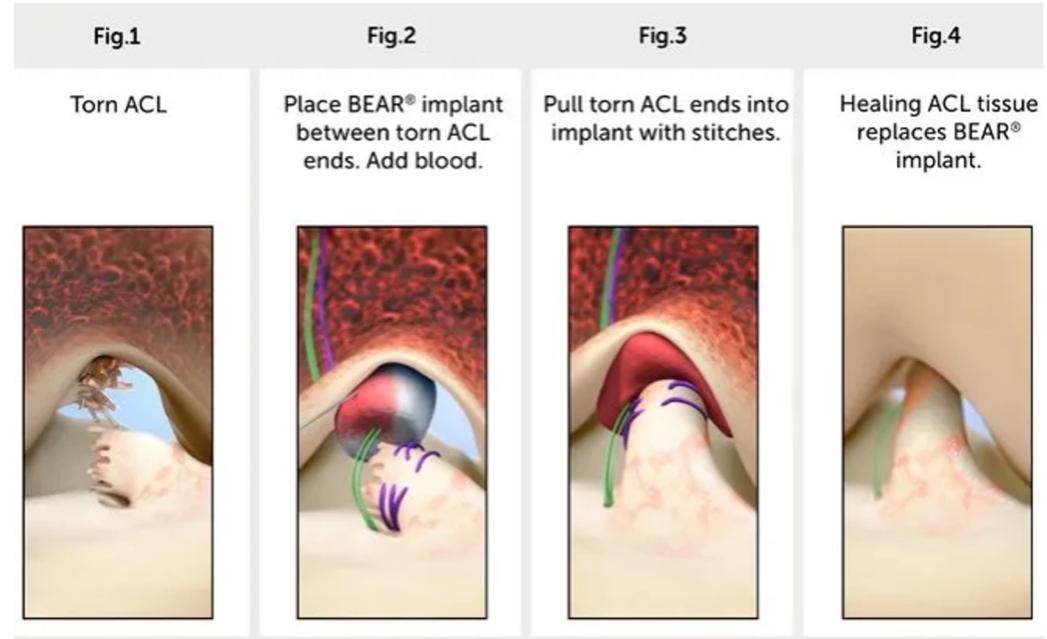
- Repair as naturally as possible to restore mechanics (BEAR ACL)
- Inject A2M either at time of surgery or shortly after
- Start PPS 1 week after repair . (Don't start before since is a weak blood thinner.)
- Spermidine 6mg for 4 weeks after surgery
- BPC with TB4
- Collagen peptides
- GHK -Cu to encourage wound healing



Bridge Enhanced ACL Repair (BEAR)

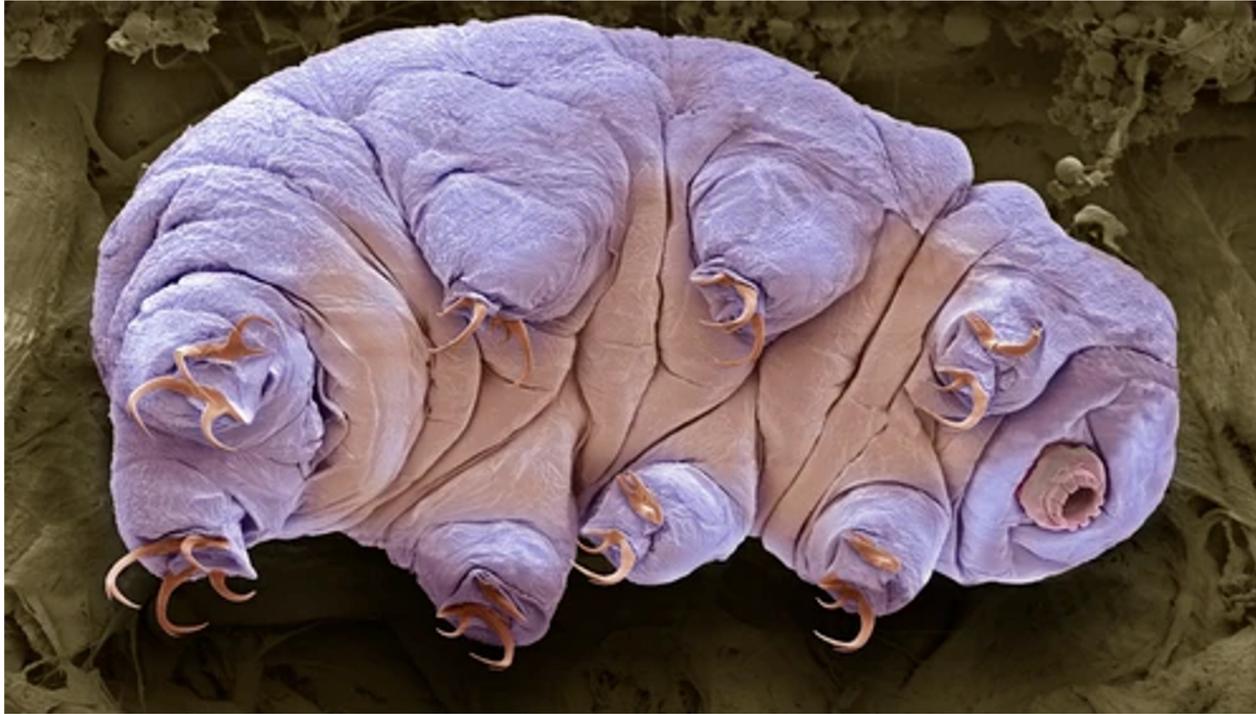
Improving ACL long-term outcomes

- Repair as naturally as possible to restore mechanics (BEAR ACL)
- Inject A2M either at time of surgery or shortly after
- Start PPS 1 week after repair . (Don't start before since is a weak blood thinner.)
- Spermidine 6mg for 4 weeks after surgery
- BPC with TB4
- Collagen peptides
- GHK -Cu to encourage wound healing



Bridge Enhanced ACL Repair (BEAR)

Scientists Shot Tardigrades from a Gun to See If Interplanetary Travel Is Survivable



Scientists used a special type of scientific equipment called a two-stage light gas gun to fire out their tardigrade-laced projectiles.

The researchers then fired a total of six shots, each containing a few tardigrades, at speeds ranging from about 1,240 to 2,230 miles per hour, which is faster than a bullet exiting a traditional firearm. The animals impacted the sand target at shock pressures ranging from 0.61 to 1.31 GPa.

Amazingly, tardigrades in the four out of the six shots survived the high-speed and shock pressure of the impact.

Alas, the tardigrades shot at the two highest speeds—around 2,000 and 2,230 miles per hour—did not survive.

In fact, their bodies were fragmented when they were recovered, revealing that even the sturdy tun state could not protect them from the shock of impact.



The results indicate that the upper limit of impact speeds that tardigrades can survive hovers somewhere around 1,845 miles per hour.

The Moral: Sadly... Humans can destroy even those who are invincible



#PeptideWC2022

THANK YOU!

Elizabeth Yurth, MD

FAARM, FAARFM, ABAARM, FSSRP, SSRP FACULTY

bli@boulderlongevity.com

Boulder Longevity Institute | Boulder, CO