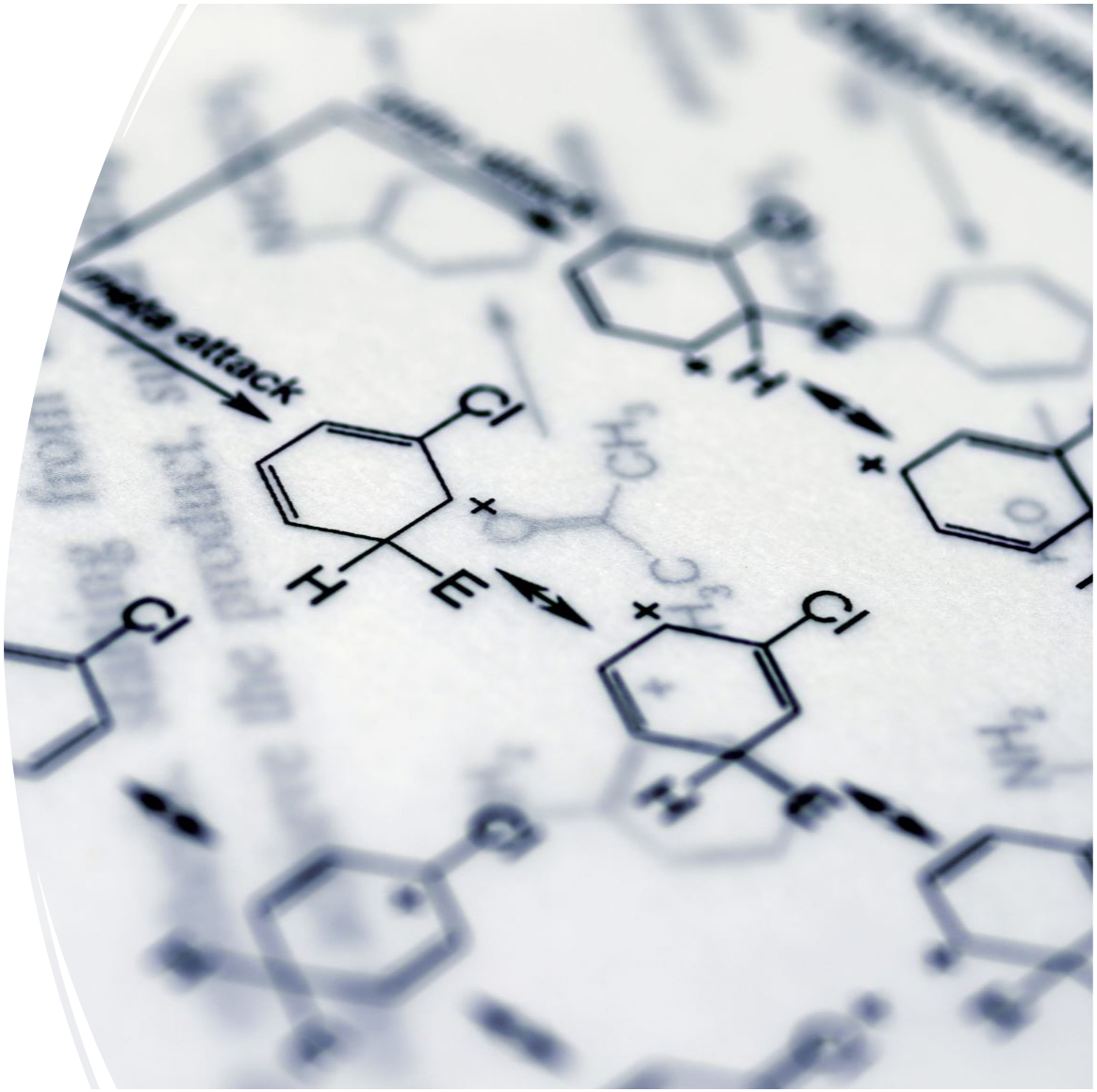
Regenerative Orthopedics

Dr. Stephen Matta, DO MBA

Meeting Point Health



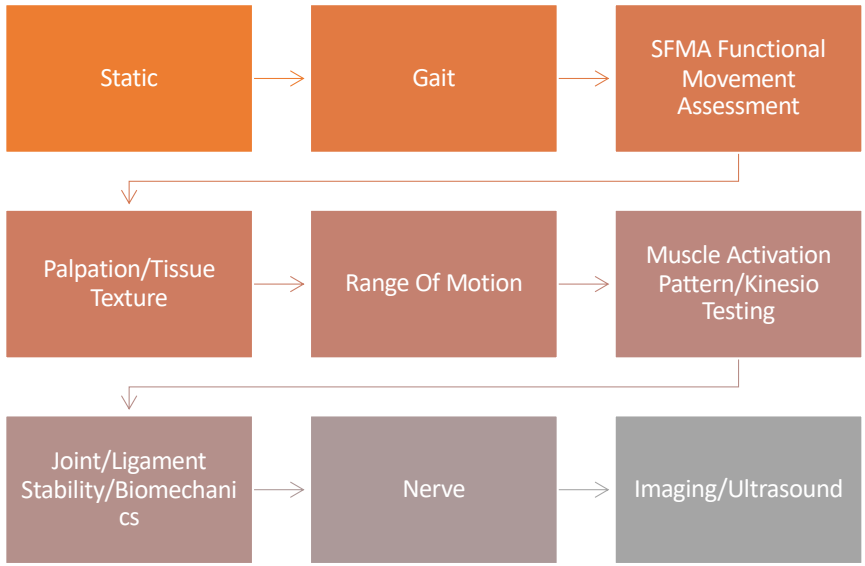
Objectives

- Determine Root Cause before Treatment
- Discuss peptide therapy use in orthopedics and regenerative medicine
- Discuss the use of regenerative injection therapies in the treatment of neuromusculoskeletal issues

Low Back Pain Case Study

- 33 yr old Male p/w right low back pain x 4 months. Radicular pain to right leg and foot. MRI showed L4/5 disc herniation. Currently pain worse with prolonged standing, better with sitting and rest. Main treatment is rest

Assessment


Static
Gait
SFMA Functional Movement Assessment
Palpation/Tissue Texture
Range Of Motion
Muscle Activation Pattern/Kinesio Testing
Joint/Ligament Stability/Biomechanics
Nerve
Imaging/Ultrasound

Low Back Pain Assessment

- Static: microedema in lumbar spine
- Gait: favors left limb
- SFMA: mobility restrictions globally in cervical, thoracic spine, scapulothoracic joint and pelvic motion; pain with forward flexion past 90 degrees and extension past 5 degrees, located in right lower lumbar area
- Palpation: Tissues restrictions with microedema in lumbar spine; TTP at L4/5 on the right; RSIJ; Right Piriformis
- ROM: Decreased R Hip ER/IR and Pelvic Rotation Right; Decreased Right Hip Extension>Flexion
- Muscle Testing: Neuro Exam 5/5 b/l; Inhibitions of Right Glut Max, Right Hip Flexion; Right Core
- Joint/Ligamentous: RSIJ hypomobile
- Nerve: Palpation of Pudendal nerve/sacral plexus/gluteal nerves tender
- Ultrasound: entrapment of sciatic nerve by Piriformis; Poor Piriformis mobility

How should I approach this patient?

WebMD says…

- NSAIDS?
- Corticosteroids
  - Oral
  - Local
- Refer for Surgery
- Pain Management

What's at the root of the problem

- Inflammation
- Tissue Senescence

We need the shift from bandaid solutions to regenerative solutions

- Our bodies are capable of repair and self-healing
- We now have tools and resources available to help our innate ability to repair

Why Is this Necessary

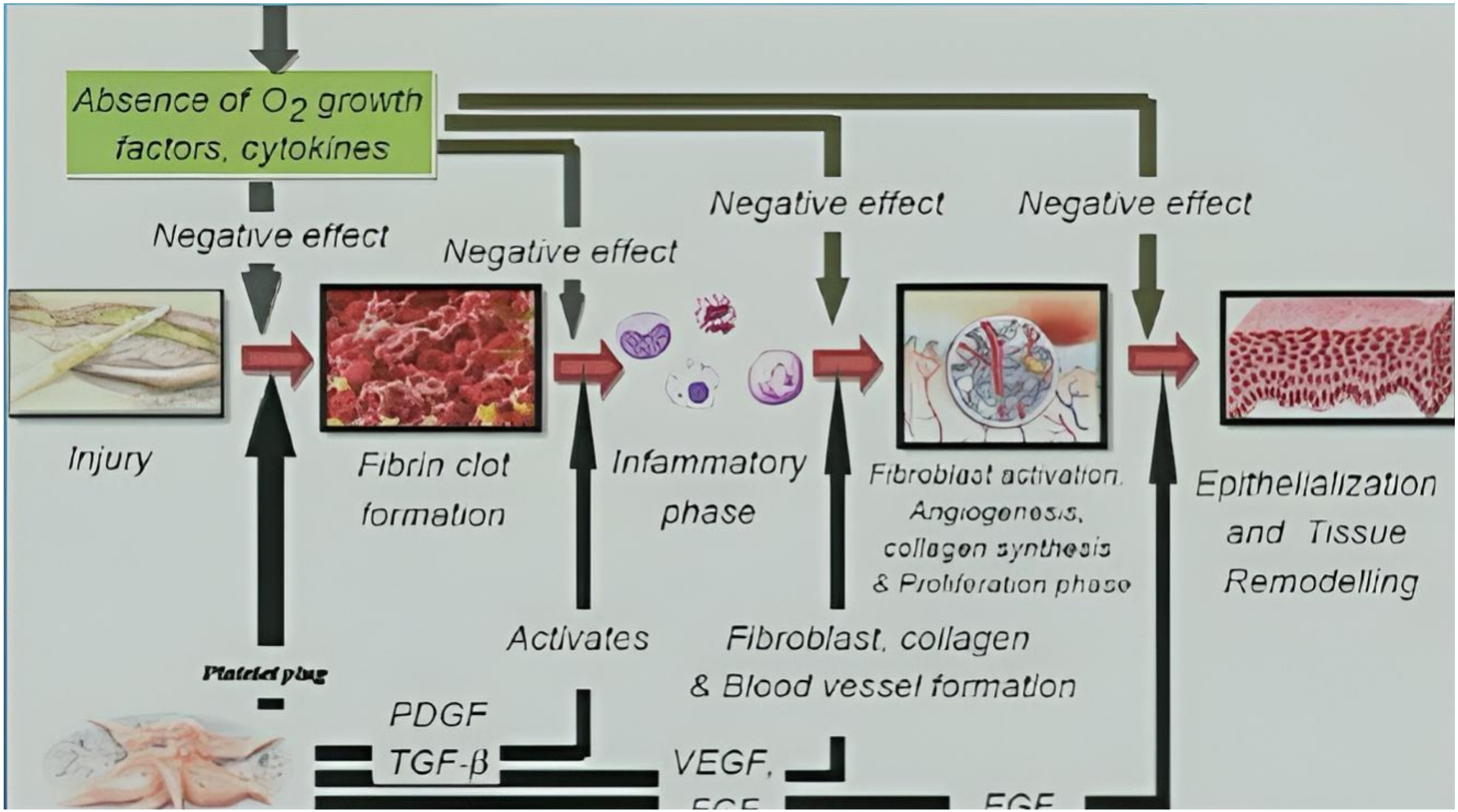
Imaging does not always correlate with pain

- Studies show asymptomatic imaging findings, etc

The structure is not the problem

Repair is multi-dimensional

Step 1: Control Inflammation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Fibrin clot formation
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Fibroblast activation, Angiogenesis, collagen synthesis & Proliferation phase
Epithelialization and Tissue Remodelling
Activates
Fibroblast, collagen & Blood vessel formation
Platelet plug
PDGF
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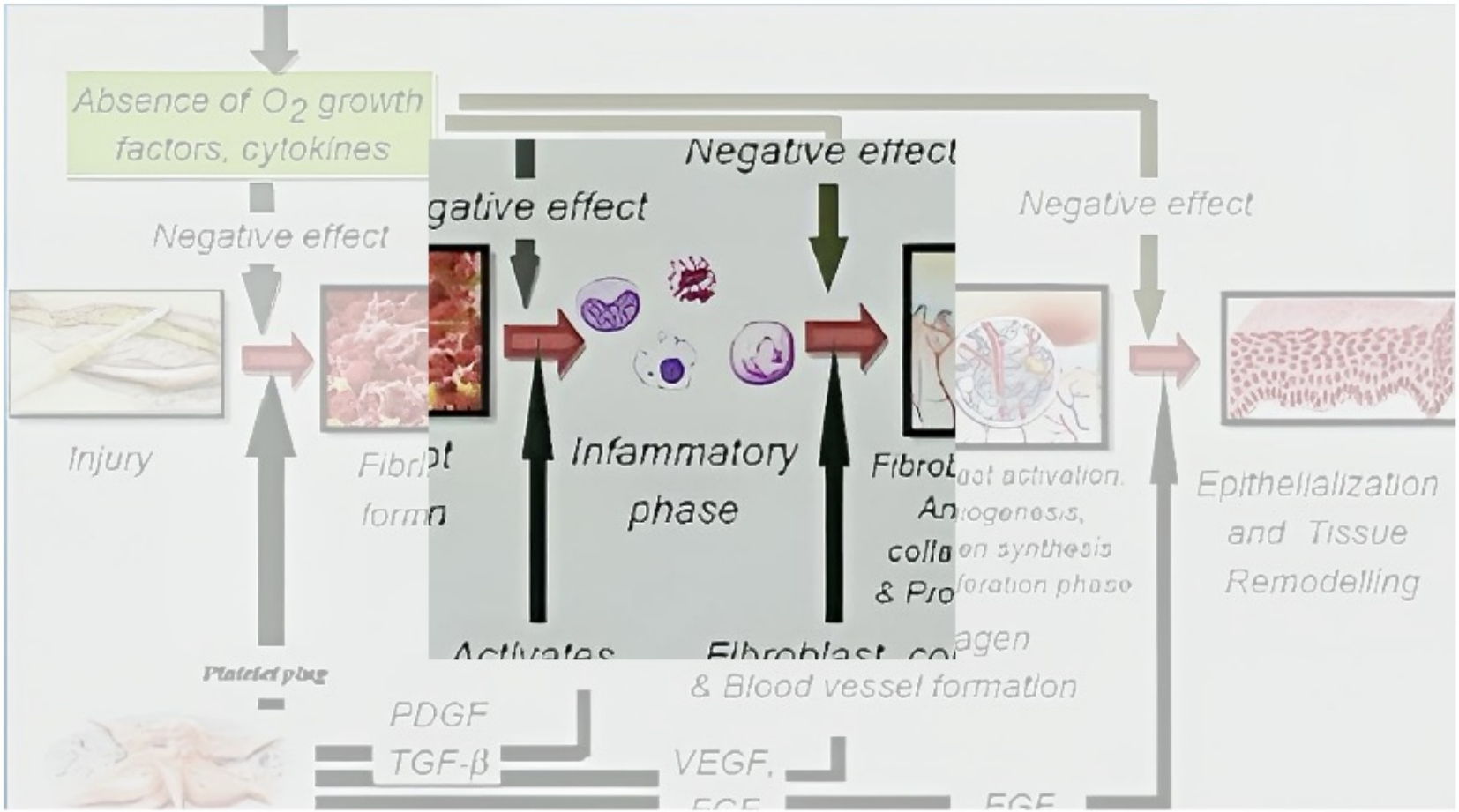
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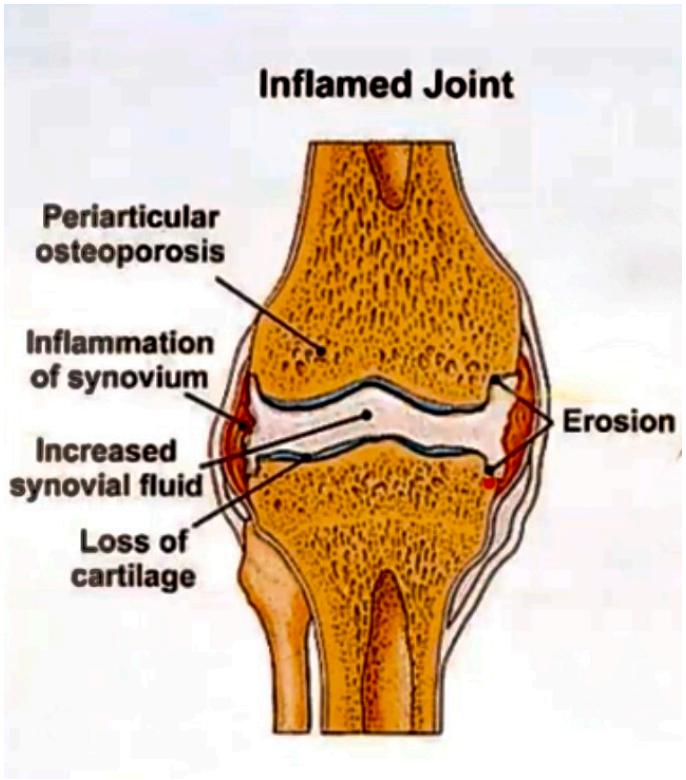
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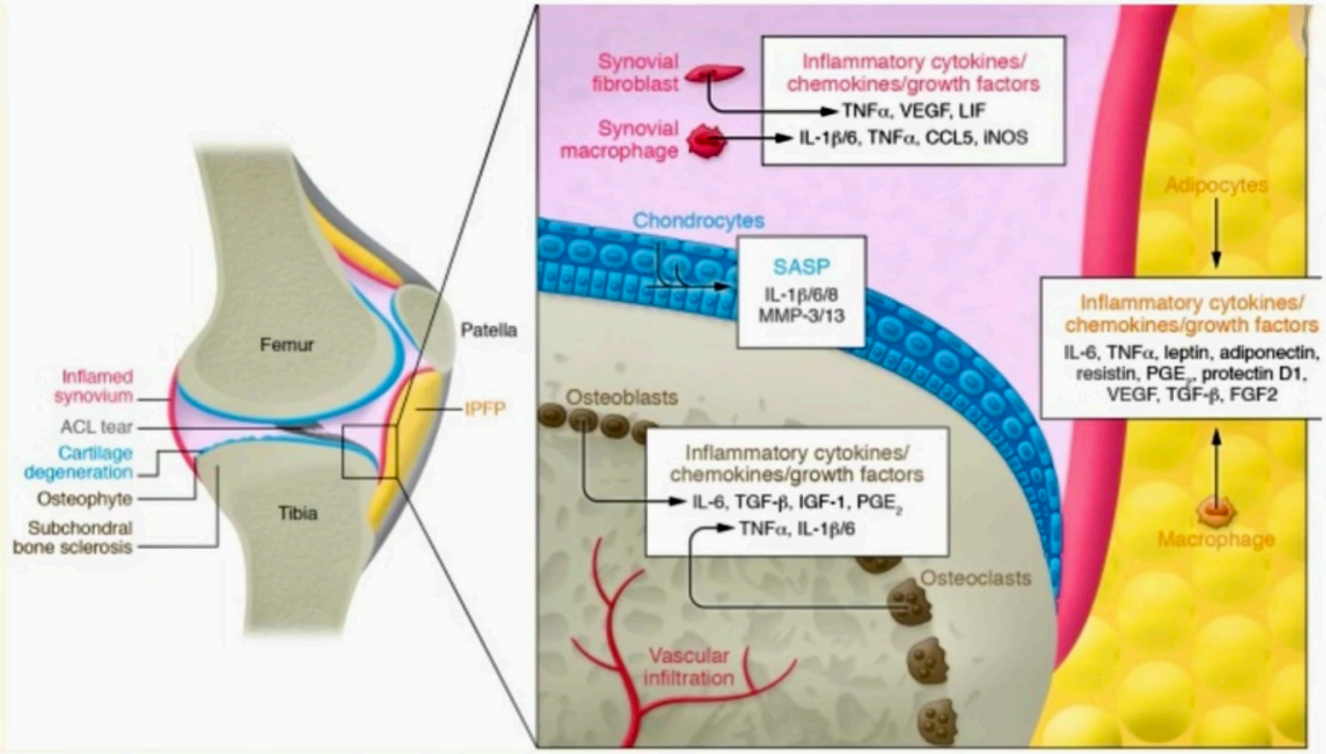
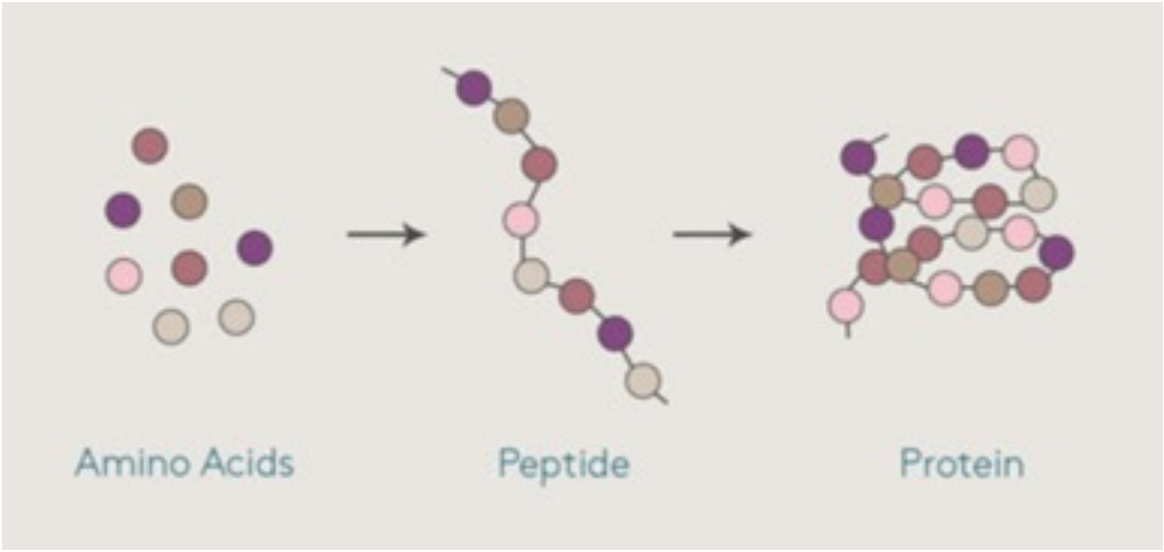
Periarticular osteoporosis
Inflammation of synovium
Increased synovial fluid
Loss of cartilage
Erosion



- Jeon OH, David N, Campisi J, Elisseeff JH. Senescent cells and osteoarthritis: a painful connection. J Clin Invest. 2018;128(4):1229-1237. doi:10.1172/JCI95147

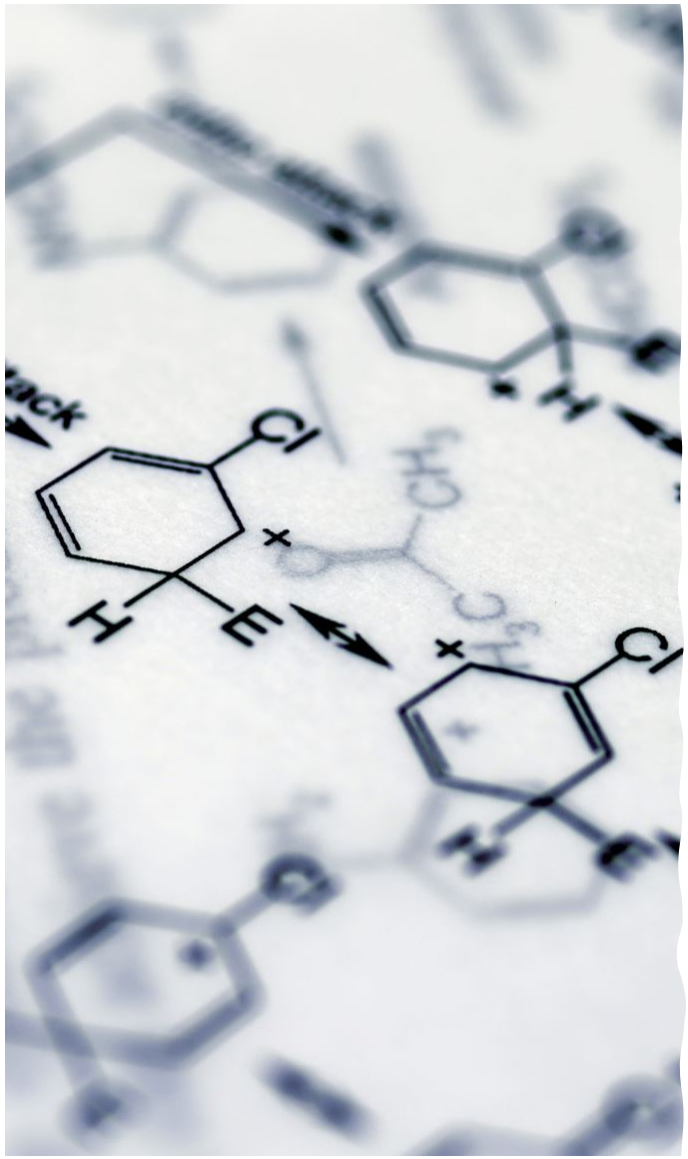
What can we use to fix inflammation?

Peptides



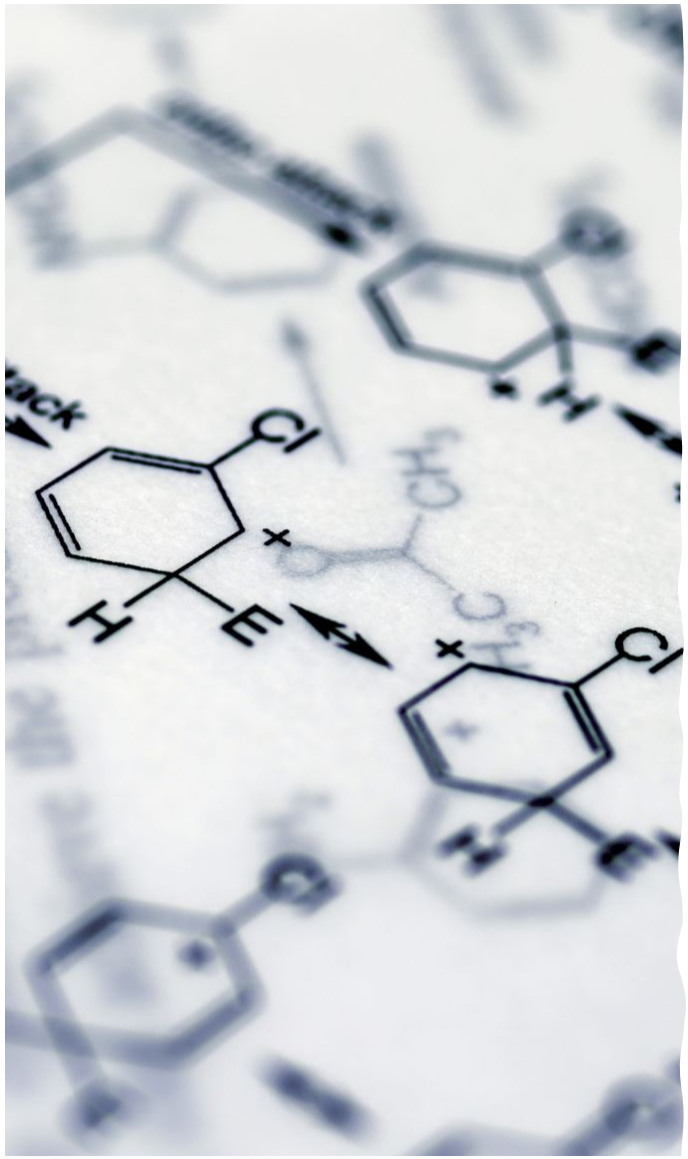
Peptides

- BPC157
- TB4
- GHK-CU
- Pentosan Polysulfate***
- KPV



BPC-157
(Body Protective Compound 157)

- Reported to improve cell survival under oxidative stress
- Increases fibroblast migration and dispersal
- Induces F-actin formation in fibroblasts
- Improves angiogenesis
- Enhances vascular expression of VEGFR2
- BPC-157 increases the extent of phosphorylation of paxillin and FAK proteins without affecting the amounts produced
- Can be used in deep skin burns, corneal injuries
- Heals injured skin, muscle, tendon, ligament or bone
- Very safe



BPC-157
(Body Protective Compound 157)

- Uses
  - Pain
  - Repair
  - Gut
- Dose
  - 500mcg – 1mg oral or Sub Q daily to twice a day

Thymosin Beta-4

- 43-amino acid water soluble acidic peptide originally isolated from bovine thymus tissue.
- TB4 is present in the majority of tissues and a variety of cell types but not in red blood cells and is found in particularly high concentrations in platelets, neutrophils, macrophages, and other lymphoid cells. The highest concentrations of TB4 are found in platelets.
- Much like BPC, stimulates multiple other pathways that promote wide ranging benefits
  - Pairs well with BPC

- **Reduces Inflammation - down regulates inflammatory cytokines - NFkB**
- Promotes cell migration of endothelial cells and keratinocytes - regulates F and G actin
- Protects cells from chemical cytotoxicity and oxygen deprivation - reduces intracellular
- ROS and increases anti-oxidant proteins
- Promotes angiogenesis - increases VEGF/AKT signaling
- Promotes **stem cell recruitment and differentiation** - skin, heart, and nerve cells
- Reduces apoptosis - increases expression of anti-apoptotic enzymes and decreases Bax/Bcl(2) ratio
- Accelerates collagen deposition and upregulates production of laminin-5
- Reduces scar formation: accelerates scar reduction, promotes better organization of collagen fibrils - prevents infiltration of myofibroblasts

Thymosin Beta-4

- Uses
  - Most things Orthopedic but particularly Nerve
  - Pain
  - Hair Loss
- Dose
  - 350 mcg sq 3 times a week

Pentosan Polysulfate***

Reduces Inflammation

- Works via reduction of NF-KB
- Downregulates IL-1 and TNF-alpha
- Inhibits MAP-kinases

Regenerates soft tissue

- Reduces and prevents cartilage degradation by inhibiting or binding cartilage degrading enzymes

KPV

- Tripeptide composed of lysine, proline, and valine
- α-MSH C-terminal peptide
- A small molecule with broad anti-inflammatory effect & antimicrobial action
- Modulates the expression of cytokines, chemokines, and growth factors.
- Taken orally 125 mcg twice a day

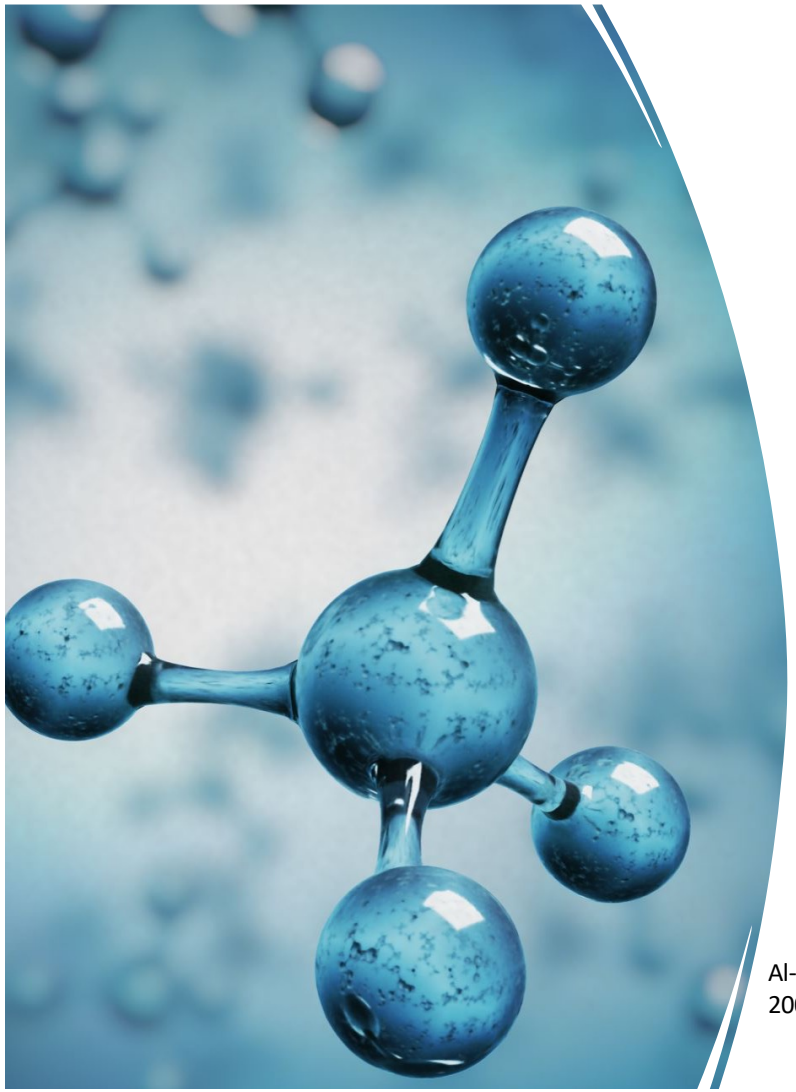
GHK-CU

- This peptide dramatically drops from age 20 to 60
- Promotes activation of wound healing
- Anti-inflammatory antioxidant
- Stimulates collagen
- Promotion of new blood vessels
- Modulates expression of large number of genes
- Appears to have antiaging properties
- May help with hair restoration
- Prevention of oxidative stress in degenerative conditions
- Uses
  - Anti-aging
  - Skin
  - Wound
  - Repair, Repair, Repair.
    - Fractures, Fibrocartilage
- Dose
  - 1-2mg sq daily x 3 weeks

Cerebrolysin

- Cerebrolysin is a neuropeptide derived from porcine brain tissue that has neuroregenerative properties.
- It has shown beneficial such as reducing excitotoxicity, oxidative stress, inflammation, and apoptosis, and enhancing neurotrophic factors, neural sprouting, and neural survival.
- It has been used in clinical trials for ischemic stroke and neurodegenerative disorders, with promising results.
- Uses
  - Concussion
  - Neuropathy
  - Degenerative Conditions
  - Trigger Point Therapy
    - 1-5ml into trigger point
  - Dose
    - 5-20ml IV

What else can be used for inflammation?



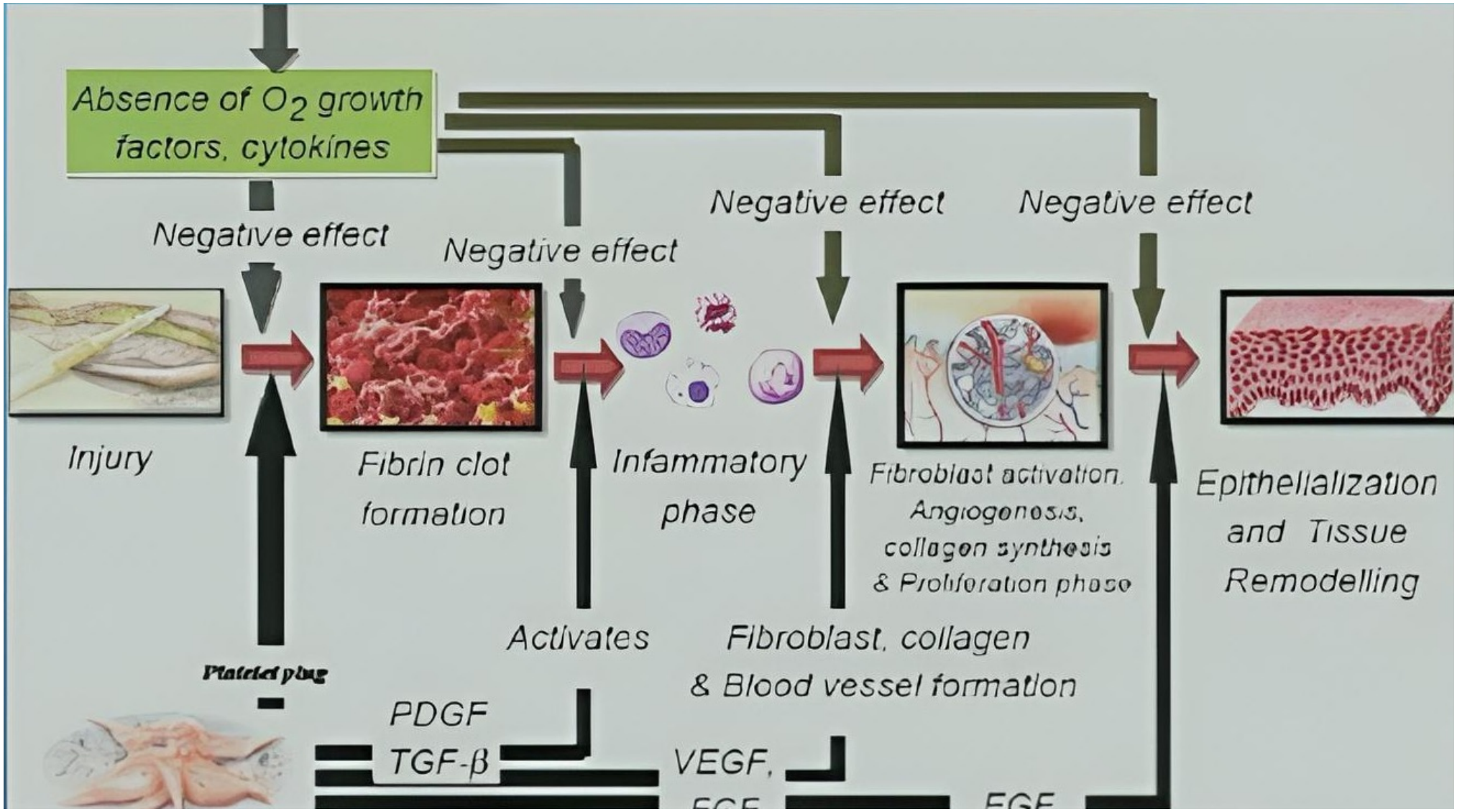
Ozone

- Oxygen-ozone solution (O2-O3) can improve tissue oxygenation and inhibit inflammatory mediators mediated by the down-regulation of TNFαand TNFR2.
- Can inhibit inflammatory responses
- According to a study, oxygen-ozone injection could induce some histological changes in the joint and consequently lead to pain killing effects
  Clinical trials have confirmed the efficacy and safety of ozone therapy in the management of lumbosacral disc herniation, failed back surgery syndrome, and shoulder disorders
- Ozone has a good effect in managing symptoms after traumatic meniscal injuries

Al-Jaziri AA, Mahmoodi SM. Pain killing effect of ozone-oxygen injec-tion on spine and joint osteoarthritis.Saudi Med J. 2008;29(4):553–557

Prolozone

- “Prolozone” - coined by Frank Shellenberger, MD
- Involves the combination of solution consisting of Dextrose, Procaine, and B Vitamins followed by Ozone
- Can modulate inflammation by reducing the production of pro-inflammatory cytokines, increasing the production of anti-inflammatory cytokines, and inducing apoptosis of senescent cells, which can break the cycle of inflammation and senescence
- can also reduce pain by inhibiting the transmission of pain signals, activating the endogenous opioid system, and restoring the balance of the autonomic nervous system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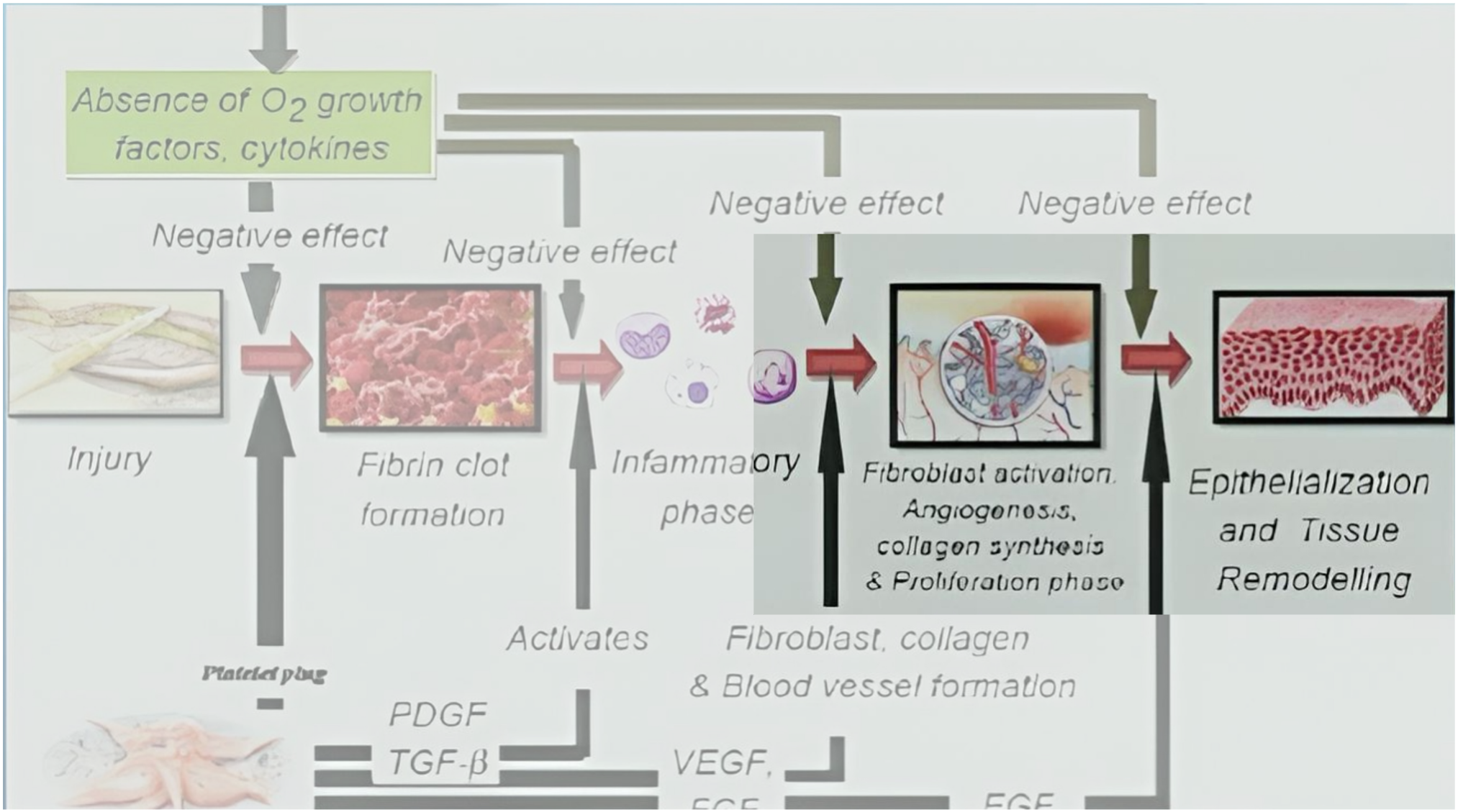
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Step 2: Repair

- Must tap into the body's natural repair mechanisms
- Growth factors for repair
- Paradox
  - These are often the same cytokines responsible for inflammation. Now ROS responsible for cell to cell communication
  - I believe inflammatory cytokines from senescence are different

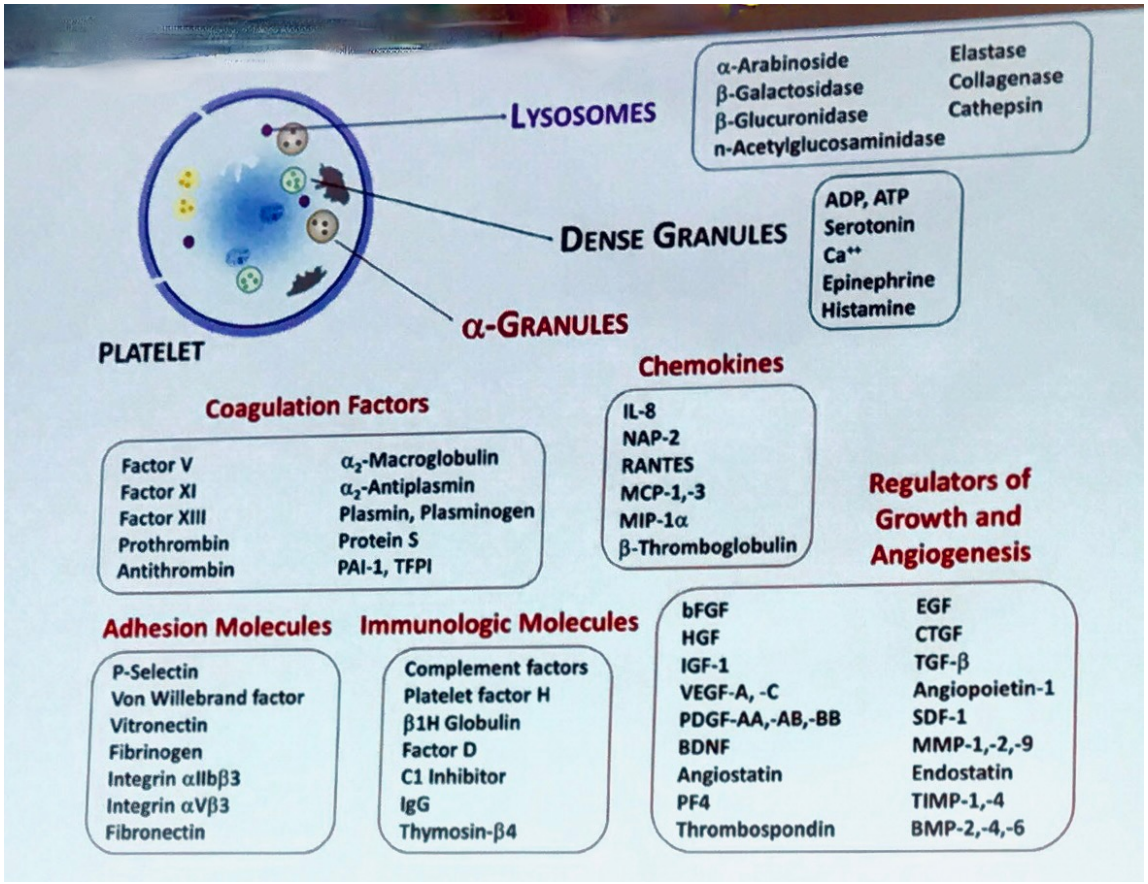
Prolotherapy

- Prolotherapy is a regenerative treatment that involves injecting a solution into damaged tissue to stimulate the body's natural healing process.
- The solution typically contains an irritant, such as dextrose, which triggers an inflammatory response and promotes the growth of new tissue.
- Prolotherapy is used to treat a variety of musculoskeletal conditions, including chronic pain, joint instability, and tendon and ligament injuries.

PRP

- PRP or platelet-rich plasma is a treatment that uses the patient's own blood to stimulate tissue regeneration.
- This treatment is done by first drawing blood from the patient, and then centrifuging a layer of rich plasma from that sample.
- Works by delivering a high dose of platelets and growth factors to the site of injury or degeneration
- Platelets and growth factors can activate the resident stem cells and recruit other cells to the area
- Stem cells and other cells can differentiate into various types of tissue cells, such as cartilage, bone, tendon, or muscle
- Platelets and growth factors can also modulate the inflammatory and immune responses, reduce pain, and enhance angiogenesis (the formation of new blood vessels)
- PRP can also provide a scaffold or matrix for the newly formed tissue to adhere and grow

Growth Factors



Cellular Therapies

PRP

- Platelet Volume
- Platelets per ml
- Leuko Rich vs Leuko Poor

MSCs

- Autologous
- Allogenic
  - Umbilical Cord Derived
  - Placental Tissue Matrix

MSCs

- **Source: fat, bone marrow, birth tissue products, peripheral blood**
- MSCs are defined by:
  - Plastic adherence
  - Fibroblast-like morphology
  - Phenotypic characteristics:
  - Negative: CD14, CD45, CD80, CD86, CD83
  - Positive: CD73 (SH2, SH3, SH4), CD105, CD166, CD90, CD29
  - Immunosuppressive properties
  - Differentiation:
  - Adipogenic Osteogenic Chondrogenic
- **Must differentiate to osteoblasts, adipocytes, and chondroblasts *in vitro***

MSCs

- MSCs are pericytes
  - Connective tissue cell that wrap around perivascular vessels
- Pericytes possess the following characteristics
  - Immunomodulatory
  - Anti-apoptotic
  - Angiogenic
  - Mitotic
  - Resist scar cascade
- **Accomplish regenerative capabilities via complex secretion and signaling of growth factors and cytokine**

PRP vs Stem Cells

Degree of degeneration

How long I expect the PRP to last

Efficacy of Oxygen-Ozone Therapy and Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis: A Meta-analysis and Systematic Review

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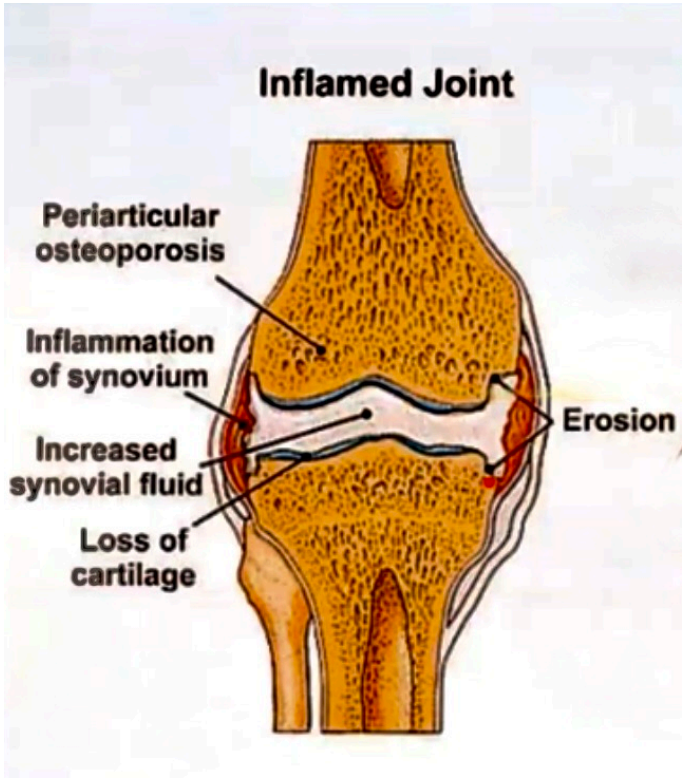
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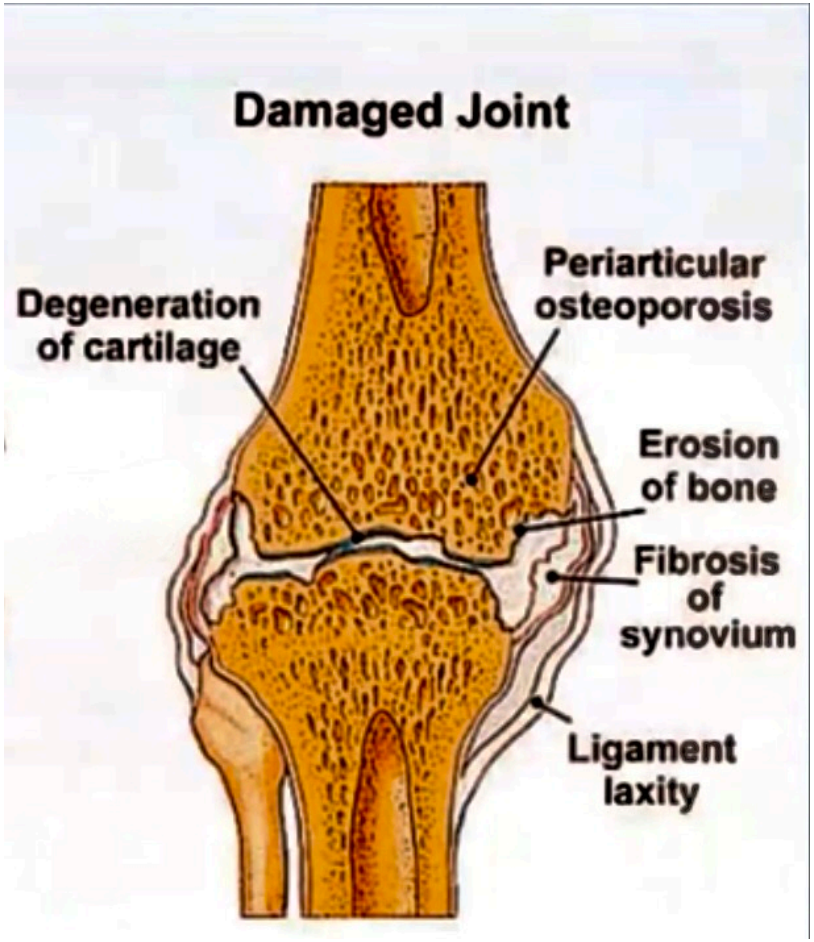
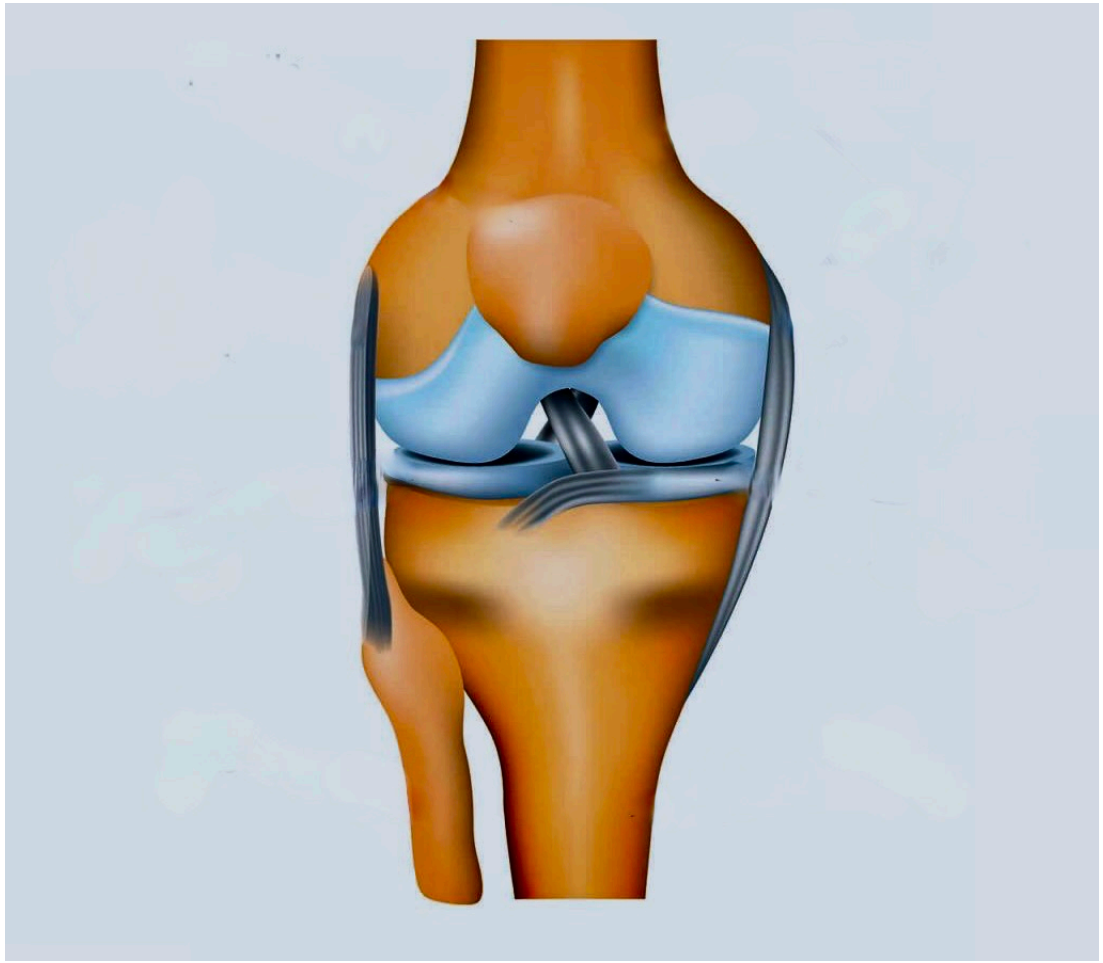
Periarticular osteoporosis
Inflammation of synovium
Increased synovial fluid
Loss of cartilage
Erosion


Damaged Joint
Degeneration of cartilage
Periarticular osteoporosis
Erosion of bone
Fibrosis of synovium
Ligament laxity



Low Back Pain Plan

Tissue Restrictions: Gua Sha, Cupping, Myofascial Release

Mobility Restrictions: Manipulation including Muscle Energy and Soft Tissue Techniques

Muscle inhibitions: Electro acupuncture at Lumbar/Sacral Spine, Gluts

Low Back Pain
Plan: Injection Therapies

Week 1	Week 2, Week 6 (1 month apart)	Follow Up:

• Peptide injections:
  • L5 Dorsal Root Ganglion
  • Sacral Plexus
  • Cluneal Nerves
  • Caudal
• Prolozone:
  • L4, L5 facet joints
  • RSIJ
	• Repeat Peptide Injections
	• Used umbilical cord tissue growth factors in place of Prolozone (still used Ozone, though)
		• Patient is now able to go on jogs, work, and perform daily activities with minimal to no pain

“Knee Pain” Case Study

- 40 year old female presents with knee pain. Started with the knee pain 3 years ago. Previously ran several marathons but had to stop because she was unable to run without knee pain. Pain would start around mile 3 and worsen as she continued to run. Pain in the back of her knee. Pain was bilateral. Imaging unremarkable. Unimproved with physical therapy.

“Knee Pain” Assessment

- Static: microedema popliteal space
- Gait: decreased dorsiflexion; decreased hip extension; forefoot strike with gait
- SFMA: mobility restrictions with pelvic motion; restrictions with spine extension
- Palpation: joint lines nontender in knees bilaterally; microedema palpated in popliteal space, otherwise no knee swelling
- ROM: Decreased hip extension B/L; decreased ankle dorsiflexion B/L;
- Muscle Testing: Neuro Exam 5/5 b/l; Inhibitions of Glut Max bilaterally
- Joint/Ligamentous: unremarkable
- Nerve: Palpation of Tibial Nerve in Popliteal space reproduced symptoms of posterior knee pain
- Ultrasound: entrapment of Tibial nerve see in Popliteal space bilaterally; No joint effusion; no joint space narrowing, DJD, or osteophytosis

“Knee Pain” Plan

- Tissue Restrictions: Gua Sha, Cupping of posterior knees and thighs
- Mobility Restrictions: Manipulation including Muscle Energy and Soft Tissue Techniques to improve pelvis restrictions and decreased hip extension; Manipulation to improve ankle mobility
- Muscle inhibitions: Electro acupuncture at Lumbar/Sacral Nerves, Gluts, and posterior thigh, tibial nerve

Knee Pain Plan

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“Knee Pain” Plan

- Injection therapies:
    - Peptide Hydrodissection x 4
        - TB4
        - BPC157
    - Home Peptide therapy with TB4 and BPC157

- Result:
    - Immediate Relief after first hydrodissection
    - Just completed London Marathon 2 weeks with and PR’d

Low Back Pain
Plan: Injection Therapies

Peptide injections:

- Peptide Hydrodissection of Tibial Nerve x 4
  - TB4
  - BPC157

Home Plan

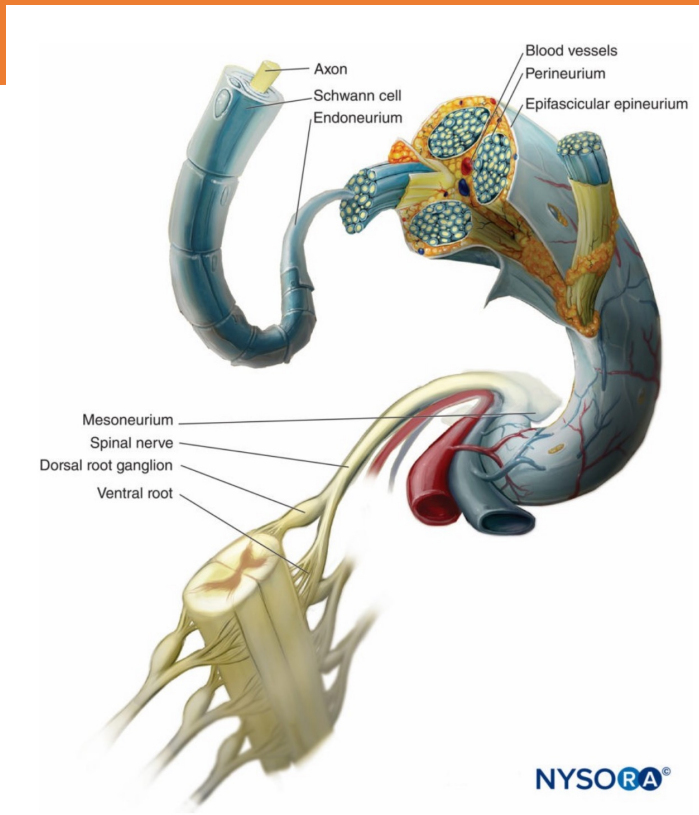
- Home Therapy with TB4 and BPC157

Follow Up:

- Result:
  - Immediate Relief after first hydrodissection
  - Just completed London Marathon 2 weeks with and PR'd

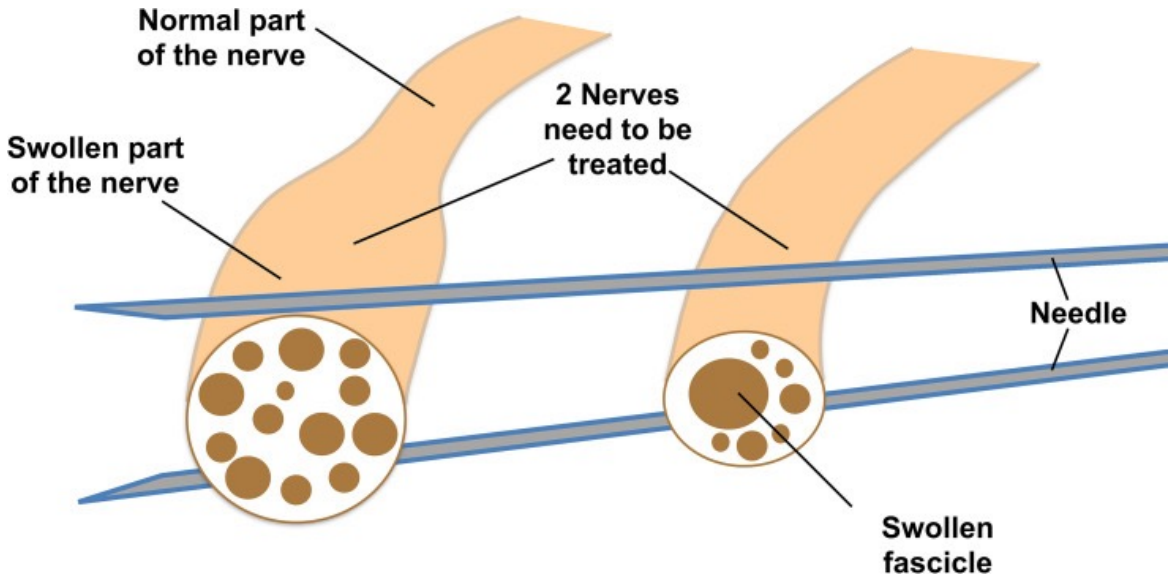
Nerve Entrapment

- Normal Nerve Histology and Anatomy
- Vasonervorum
- Nerve Entrapment
  - Swelling of nerve
  - Fibrosis
  - Poor Nerve Conduction
  - Pain
  - Decreased Nerve Function
    - Decreased Muscle Contraction
    - Decreased Sensation
    - Atrophy



Nerve Hydrodissection

- Ultrasound Guided
- Hydro=Fluid
- Dissection=Separation of Entrapment
- Essentially identical to nerve block except without anesthetic



Nerve Hydrodissection

- Dextrose 5%
- Peptides
  - Thymosin Beta 4
  - BPC157
  - Epitalon; TA1
- Prolozone
  - Use lower gamma (5-15)
  - Use Last: Image distortion
- PRP
  - RBC Poor/Leukocyte Poor/ 0-1x or just 1 spin
  - PPP
- VittiPure
- Exosomes; Pure MSCs (No ECM)

What do I use for...

Ligament

- Needs more stability
  - Prolotherapy – Dextrose 15%
  - Ozone – Higher Gamma
  - PRP
    - High concentration of Platelets per ml
    - Maybe some monocytes

Tendonopathies

- Also needs more proliferation
- Usually using PRP (plus O3 at the end)
- I like to add GHK-Cu for more repair
- Always use BPC157
- Maybe TB4. Tendonpathies has fibrosis, neovascularization, and degeneration which much be resolved.

What do I use for...

Joint

- Peptide Therapy to clean up the joint a few weeks before IA injection
- Pentosan Polysulfate to regenerate soft tissue
- IA Injections
  - Mild-Moderate - Maybe 2 Prolozone + 2 PRP
  - Moderate-Severe
    - Prolozone
      - PRP
      - Additional PRP or MSCs

Nerve

- Opposite of above for Proliferative
- Don't want to inflame nerves
- Injectate
  - Mostly use Dextrose 5%, with or without TB4 & BPC157
  - Low gamma ozone – 5-15 gamma
  - Vitti-pure great around nerves
  - Rarely use MSCs except maybe spine

Stress Facture Case

18 yr old female AAU volleyball athlete, D1 prospect, present with left shin pain. Worked up by orthopedics including Xray and MRI which confirmed a stress fracture of her tibia.

Beginning of AAU winter season and was told her season is over

What should I do?

Stress Facture Case

Plan

Ultrasound-guided injection of BPC157, TB4, and GHK-Cu around the fracture weekly x 2 weeks.

Home therapy

- BPC157 1mg sq daily
- GHK-Cu 2mg sq daily

Result

4 weeks later presents to Orthopedics who couldn't understand how the fracture could possible have healed so quickly and "disgruntled" released to full sports

She played the final 2 tournaments of the season, received a scholarship to D1 University and the past year completed her first season at the school

Resources

- MedMasters
- Functional Movement
  - SFMA
  - Immaculate Dissection
- Peptides
  - SSRP
  - A4M
- Regenerative Medicine
  - AASCP
  - Vitti
  - AAOM
- Ultrasound
  - MSKUS