# Autologous Plasma and Regenerative Techniques for Chronic Pain Due to Musculoskeletal Conditions, Neuropathy, and Scar Tissue

Dr. John Hughes, DO | OMED – VIRTUAL | October 2020

# Disclosure

The content of this presentation has been peer reviewed for fair balance and evidence-based medicine.

Dr. John Hughes, DO has no relevant financial relationships to disclose.

# Dr. John Hughes, DO

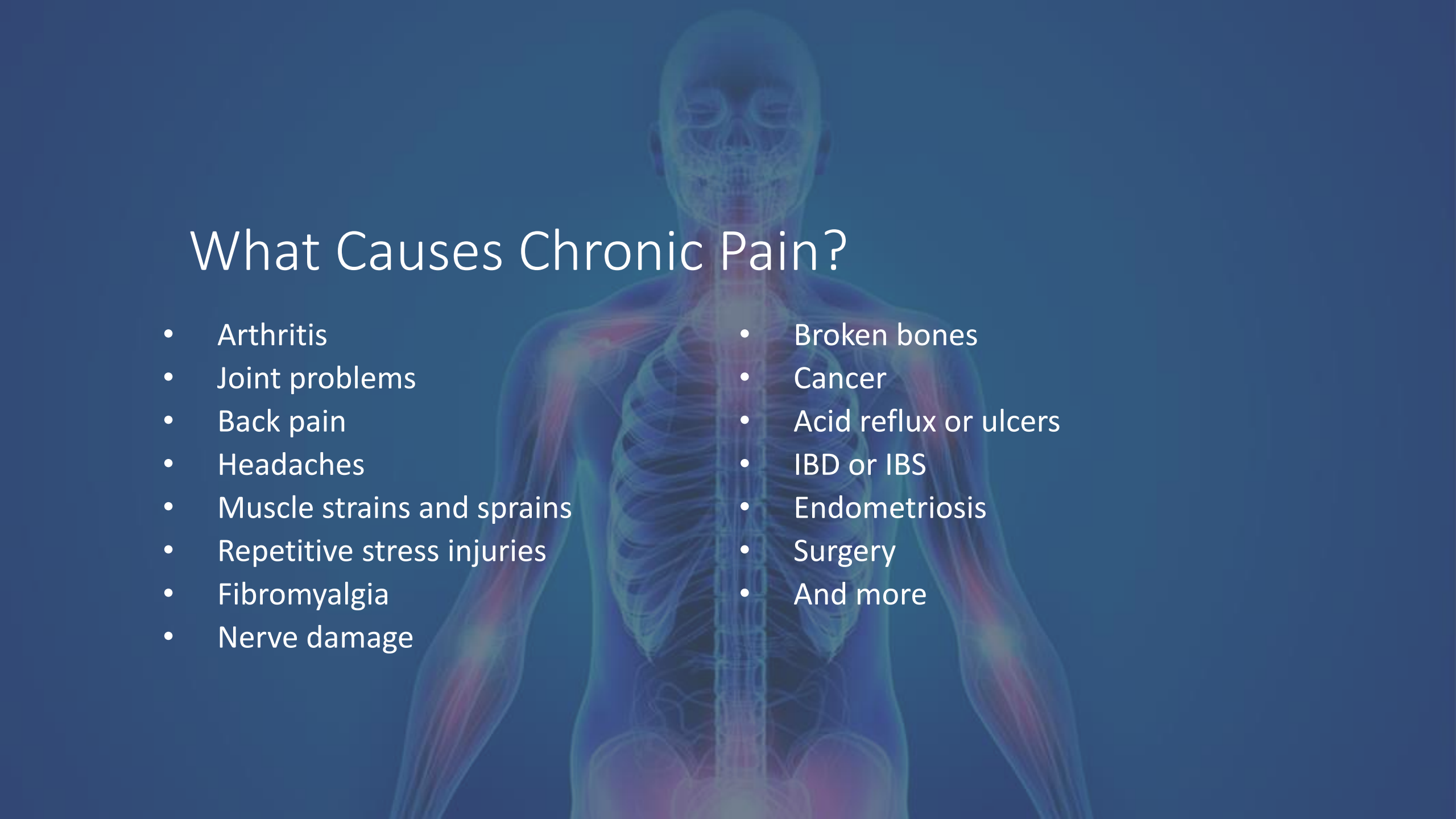
- Doctor of Osteopathy
- From Georgia
- Arizona College of Osteopathic Medicine - 2007
- Aspen Integrative Medicine - 2009
- TBI Therapy - 2014

# Learning Objectives

- Define and distinguish chronic pain
- Define and understand methods of obtaining autologous plasma
- Understand the benefits of regenerative medicine

# But first, what is pain?

- Pain results from tissue damage
- It is a part of the body's defense mechanism
- Acute: intense and short-lived
- Chronic: continuous and long-lived



# What Causes Chronic Pain?

- Arthritis
- Joint problems
- Back pain
- Headaches
- Muscle strains and sprains
- Repetitive stress injuries
- Fibromyalgia
- Nerve damage
- Broken bones
- Cancer
- Acid reflux or ulcers
- IBD or IBS
- Endometriosis
- Surgery
- And more

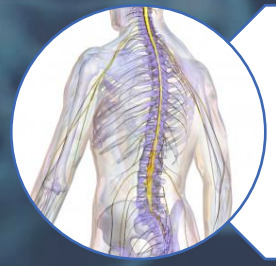
# Chronic Pain in the Body

- Bombardment of the central nervous system (CNS)
- Nociceptive impulses
- Inflammation

# 3 Types of Pain

**Nociceptive**

Normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones



**Neuropathic**

Pain initiated or caused by a primary lesion or disease in the somatosensory nervous system

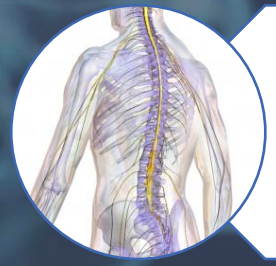
**Inflammatory**

Activation of an inflammatory cascade attempting to heal the injured area involving biochemical reactions

# Physiology of Pain from Injury

**Nociceptive**

Triggers the nervous system to react



**Neuropathic**

An overly sensitized nerve response due to nerve injury, impingement, or CNS dysfunction

**Inflammatory**

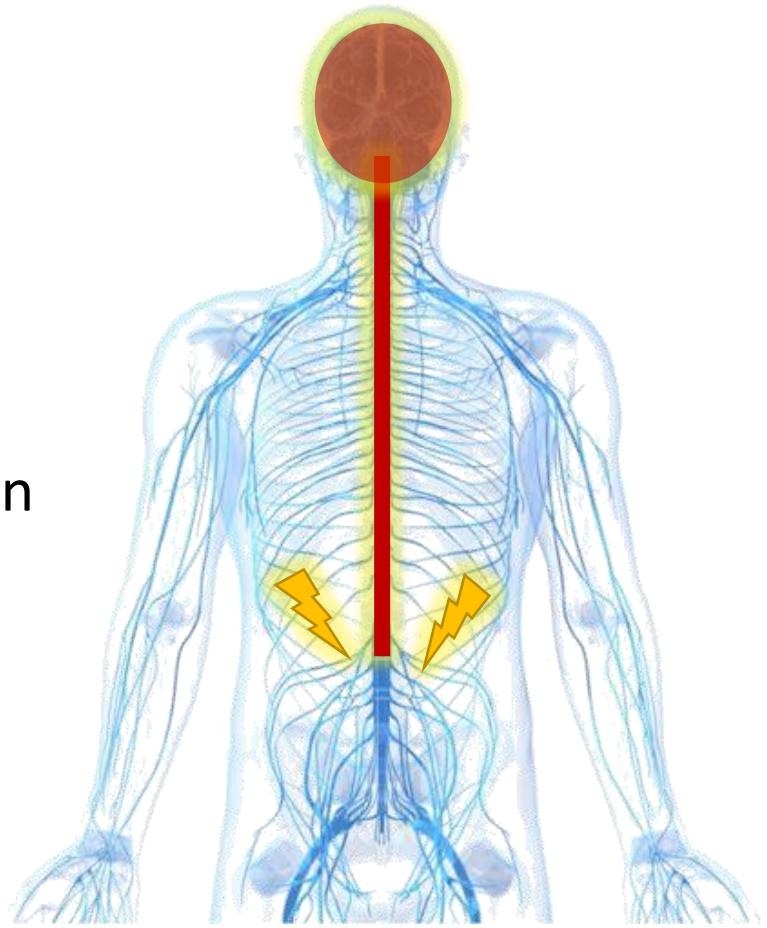
Triggers biochemical reactions to heal the area

May not reach full healing potential = chronic pain

# What happens when you strain your back?

## 1) Nociception

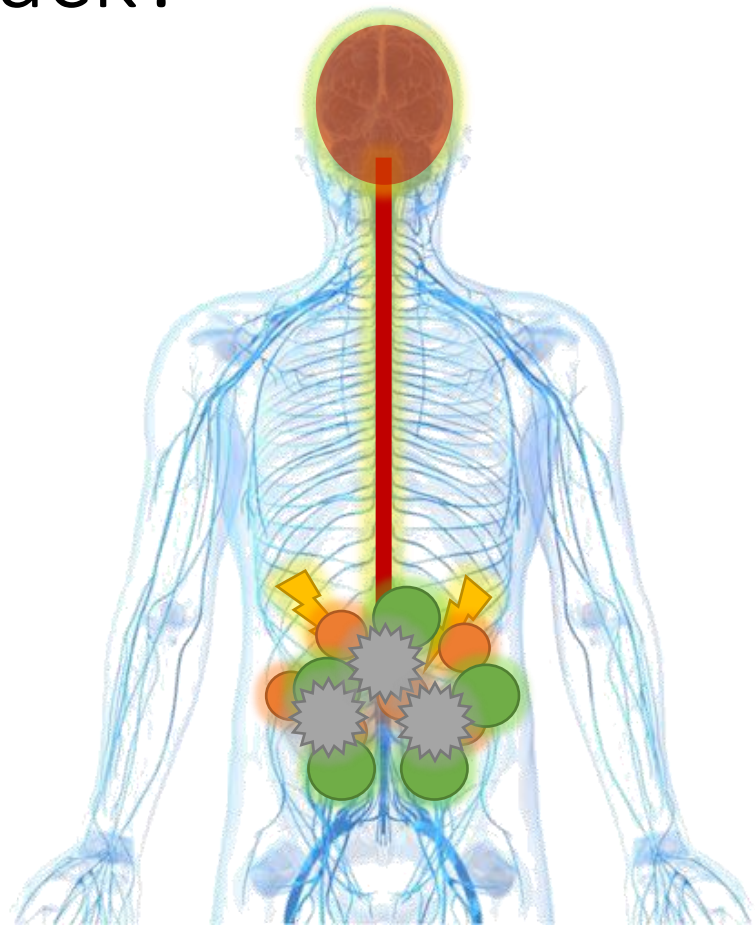
- Activation of nociceptive nerve fibers
- A signal is sent down the neuron via the spinal cord to the brain
- Signals upregulate the feeling of pain and initiates the inflammatory response



# What happens when you strain your back?

## 2) Inflammatory Response

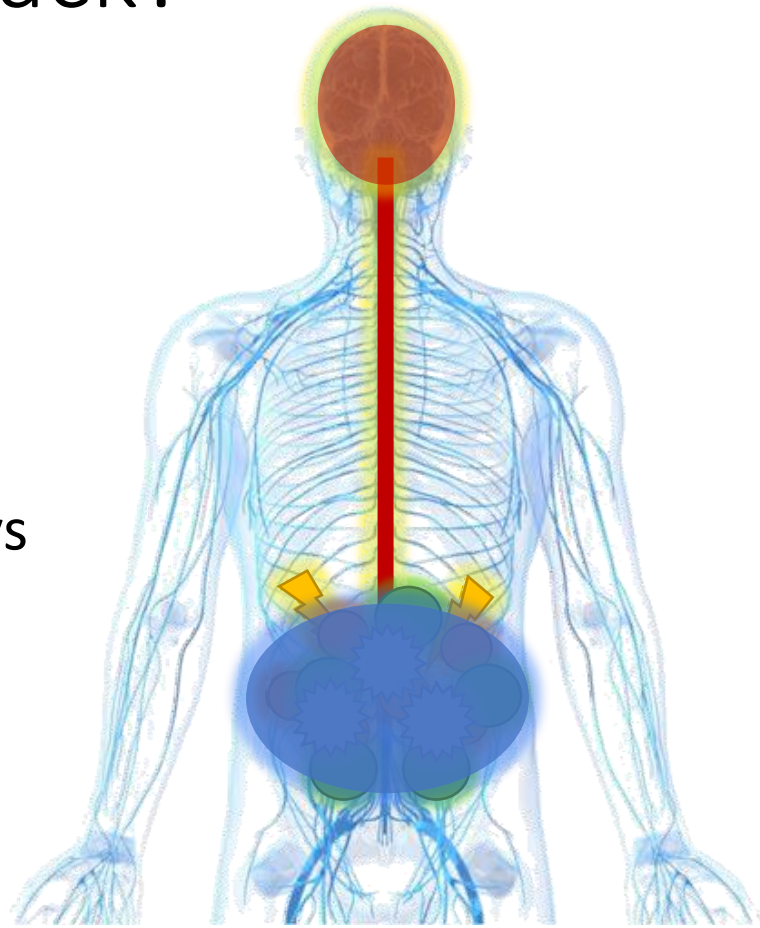
- Damaged cells release cytokines and other mediators
- Initiates vascular dilation and permeability
- PMLs, followed by macrophages enter the scene
- Stimulates the migration and proliferation of fibroblasts



# What happens when you strain your back?

## 3) Proliferation Phase

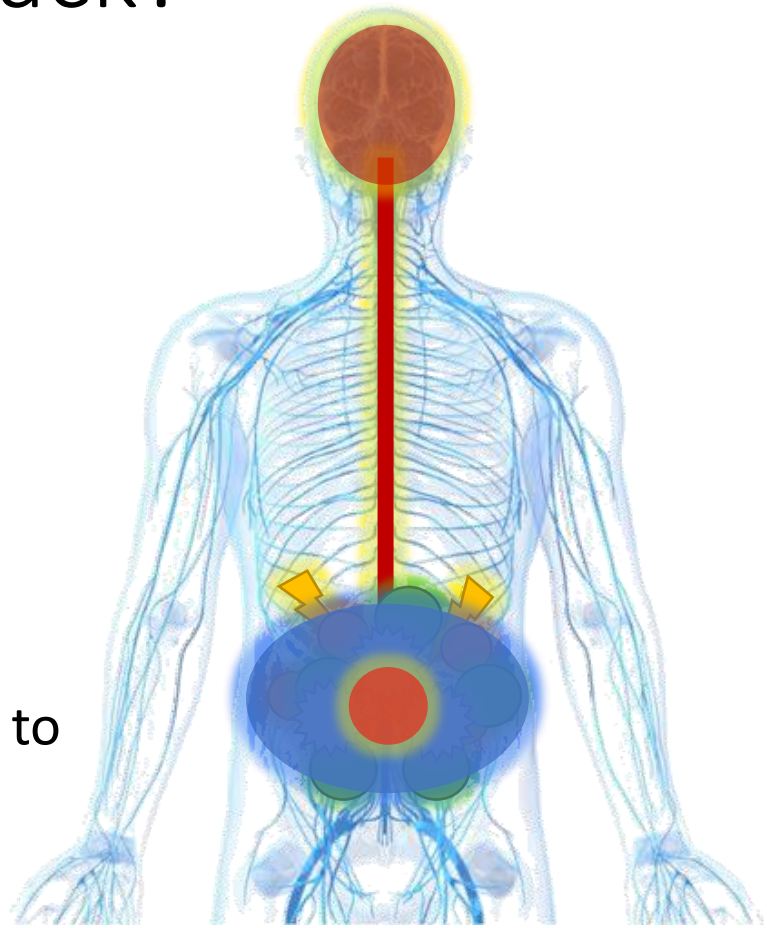
- Connective tissue begins to heal
- Fibroblasts encourage synthesis of procollagen matrix (2-3 days after injury)
- Vascular buds form increasing blood supply (3-4 days)



# What happens when you strain your back?

## 4) Remodeling Phase

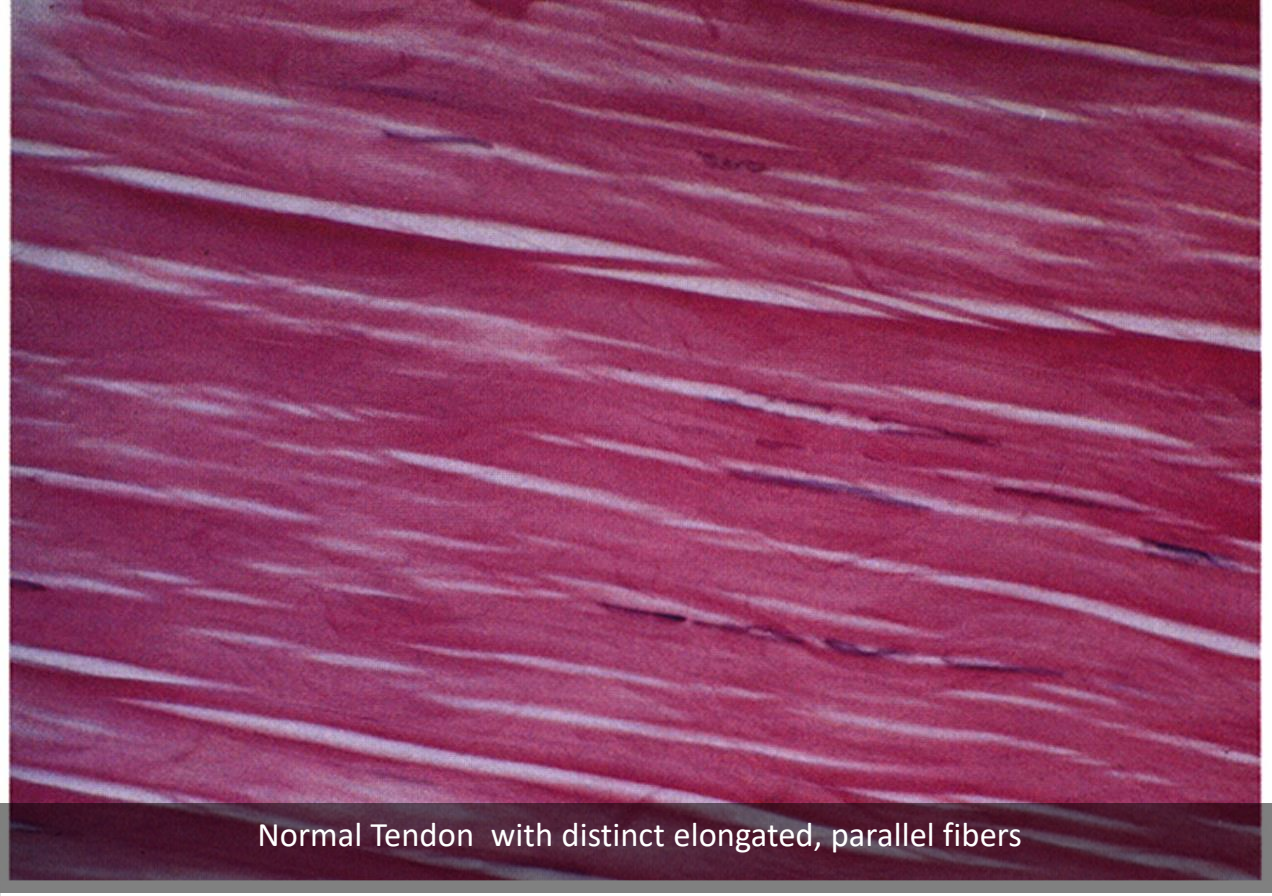
- Collagen type I changes to collagen type III
- Fibrils increase along lines of stress to become tightly packed (2-3 weeks)
- Collagen thickens and increases to preinjury length but with only 50 to 70 % tensile strength
- With severe injury, the healing process may stop before the tissue is sufficiently competent for everyday use



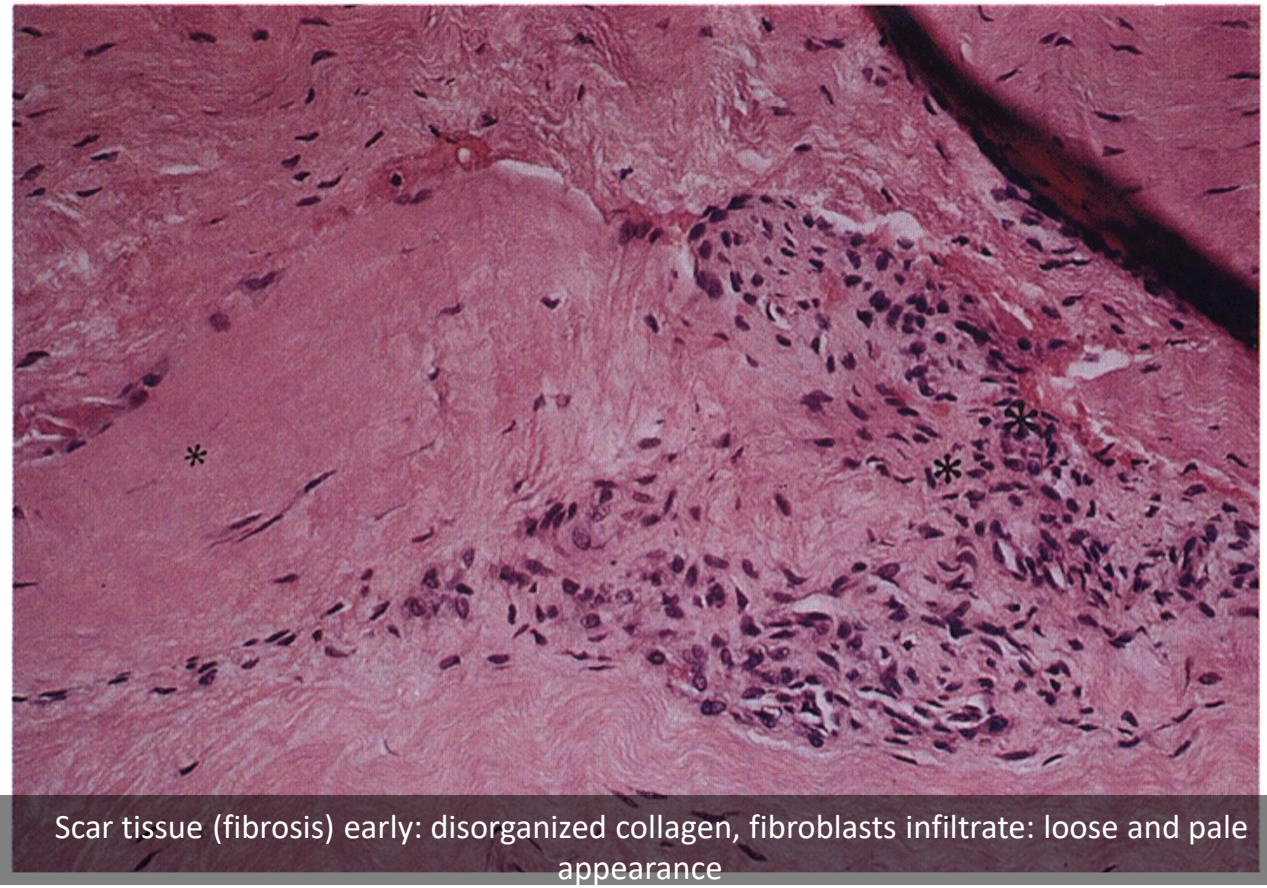
# Scar Tissue

- Aka Fibrosis and Tendinosis
- Due to injury or long-term inflammation
- Forms a web around the injured area in an attempt to support the muscle while it heals itself


http://www.parkwayphysiotherapy.ca/article.php?aid=245



Normal Tendon  with distinct elongated, parallel fibers



Scar tissue (fibrosis) early: disorganized collagen, fibroblasts infiltrate: loose and pale appearance

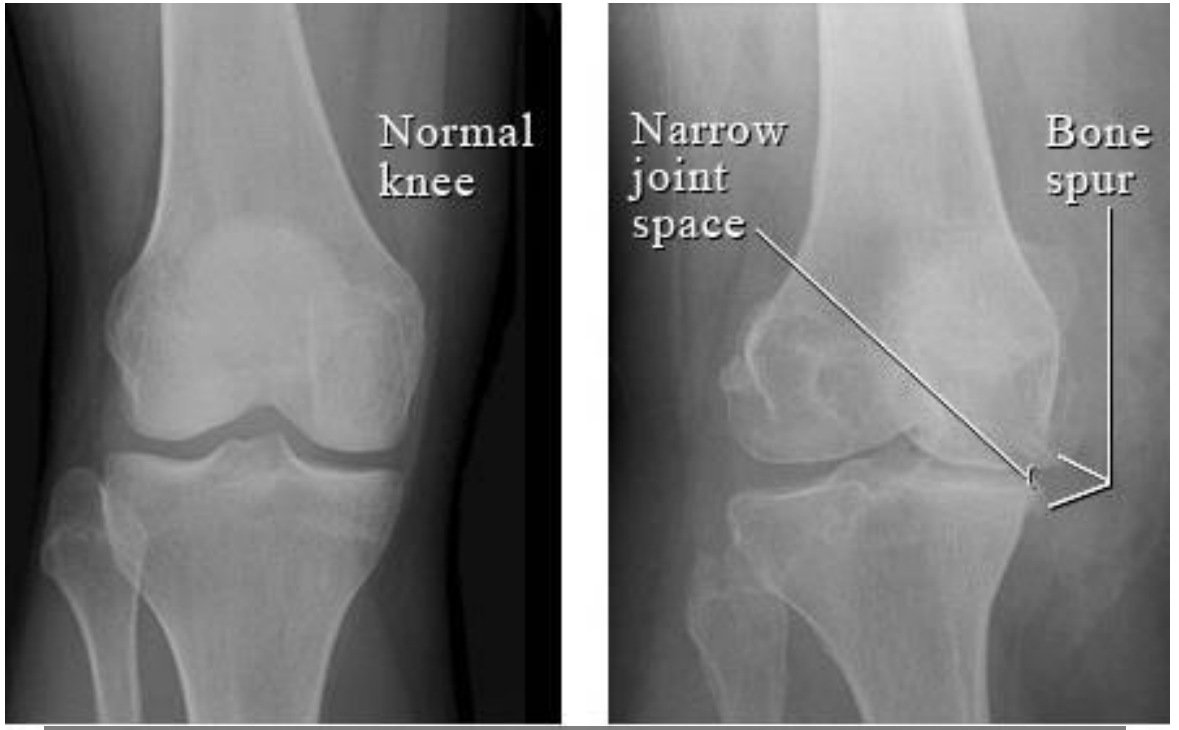
# Histology of Scar Tissue in Tendons

Adapted from *The Journal of Bone and Joint Surgery*

http://www.jbjs.org/article.aspx?Volume=81&page=259

# Bone Spurs

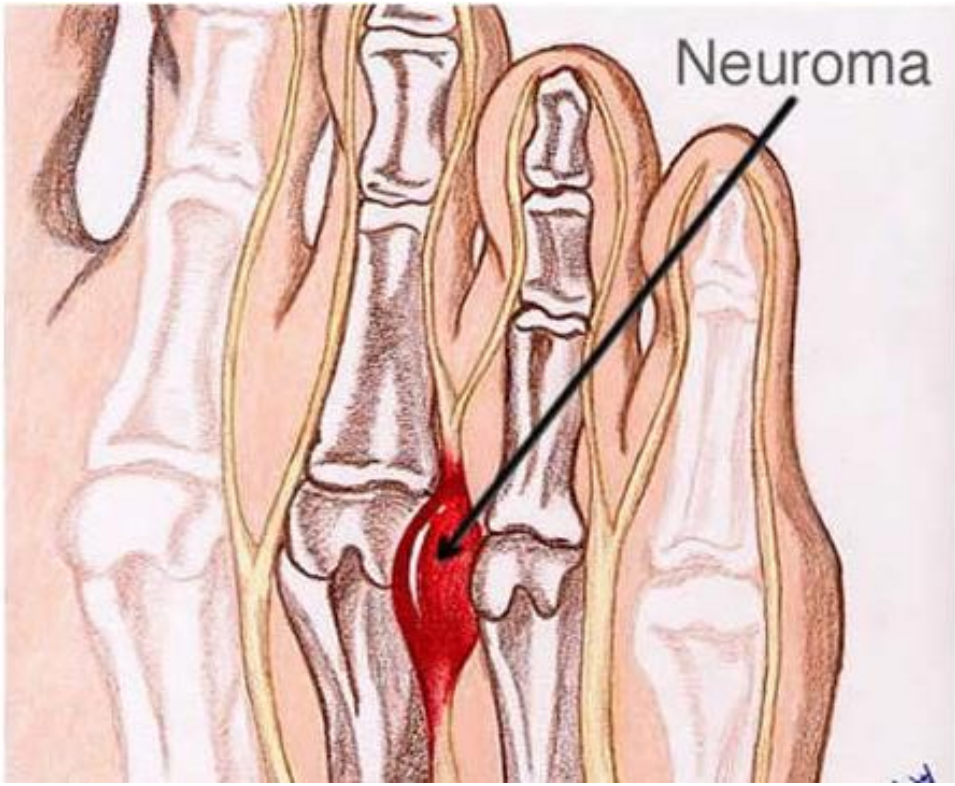
- Aka Osteophytes or Enthesophytes
- Bony projections that form along joints
  - Enthesophytes are bony projections which form at the attachment of a tendon or ligament
- Often seen in conditions such as arthritis
- Largely responsible for limitations in joint motion and can cause pain




http://physioindia.blogspot.com/2011/05/radiological-interpretation-of-joint.html

# Neuromas

- Morton's Neuroma
  - Thickening, or enlargement of a nerve leading to compression and irritation of the nerve
  - Usually located between the 3rd and 4th metatarsals
- Largely due to sodium channels, which are upregulated in neuromas
- *Accumulation of PN1 and PN3 sodium channels in painful human neuroma-evidence from immunocytochemistry*.




Treatment for Chronic Pain

# Are Cortisone Injections the Answer?

- Blocks inflammation
- Stops the healing / inflammation cascade
- Decreases immune function (risking microbial infection)
- Causes tendon weakening, atrophy, or ruptures

**= NOT A CURE**

# Are Anti-Inflammatory Drugs the Answer?

- Non-Steroidal Anti-Inflammatories (NSAIDS)
  - Inhibit COX enzymes and reduce the formation of prostaglandins
  - Damages the gastrointestinal track
- Opiates
  - Block spontaneous firing fibres and nociceptive activity
  - Damages the body and brain

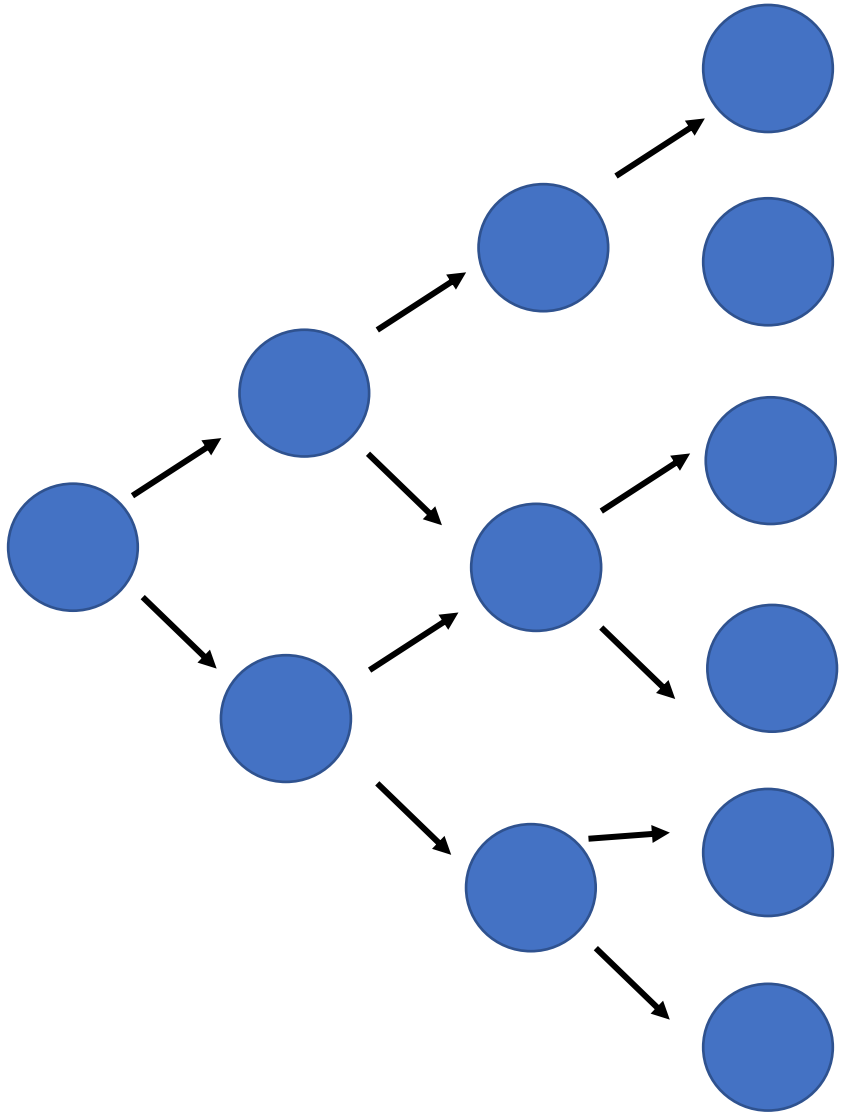
**= NOT A CURE**

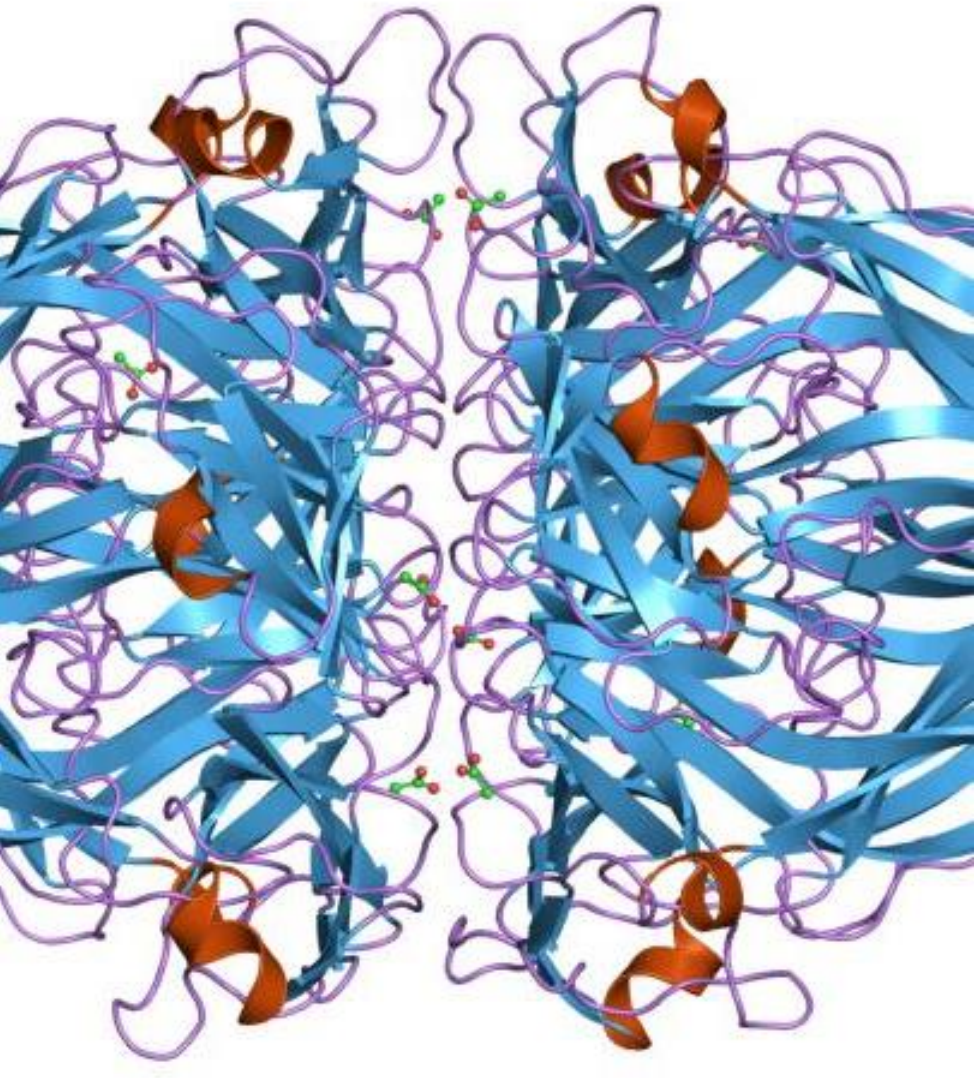
# Other Treatments for Pain

| |
|---|
| Surgery |
| TENS |
| Physical Therapy |
| Psychological Treatment |
| Acupuncture |
| Chiropractic Treatment |
| Therapeutic Touch / Reiki |
| Nutritional Supplements |
| Herbal Remedies |
| Cannabinoids |
| Proliferative Injections … |

# Proliferative Injections

- Proliferation: the growth or production of cells by multiplication of parts
- Proliferative therapy: injection of irritant or proliferant solutions into the affected ligaments, tendons, and/or joints
  - Leads to local inflammation in the injected area
  - Localized inflammation triggers a wound healing cascade





# Prolotherapy

- Causes a temporary, low grade inflammation at the injection site
- Activates fibroblasts to the area, which, in turn, synthesize precursors to mature collagen and thus reinforce connective tissue
- Direct exposure of fibroblasts to growth factors causes new cell growth and collagen deposition
- Inflammation creates secondary growth factor elevation
- Initiates a new connective tissue repair sequence which had prematurely aborted or never started

# Prolotherapy

- Dextrose is thought to “dehydrate” the injected tissues, causing an injury signal for the body, and initiating the healing process.
- Dextrose has been shown to be a growth stimulant
- Inflammation restarts the normal healing cascade that would occur with an acute injury

# Prolotherapy: Clinical Evidence

- 1800 patients followed for 2 years - 80% showed marked improvement in upper and lower body pain
  - Hackett GS: Prolotherapy in whiplash and low back pain. Postgrad Med 27:214-219, 1960
- Two RCTs (160 participants) found that prolotherapy injections, given with spinal manipulation, exercise, and other therapies, are more effective than control injections for chronic low-back pain and disability.
  - http://www.cochrane.org/reviews/en/ab004059.html

# Prolotherapy: Clinical Evidence

- 60% increase in collagen fibril diameter measured at 3 months after 6 weekly injections in patients with low back pain
  - Klein RG, Dorman TA, Johnson CE: Proliferant Injections for Low Back Pain: Histological Changes of Injected Ligagments and Objective Measurements of Lumbar Spine Mobility Before and After Treatment J Neurol Orthop Med Surg 10: 141-144, 1989
- Osmolarity studies: Elevation osmolarity by as little as 50 mOsm has been found to activate multiple growth factors including PDGF

# Prolotherapy: Clinical Evidence

- Response of Knee Ligaments to Prolotherapy in a Rat Injury Model
  - Am J Sports Med July 2008 vol. 36 no. 7 1347-1357
- Conclusion: Dextrose injections increased the cross-sectional area of MCLs compared with saline-injected and uninjured controls. Dextrose injections did not alter other measured properties in this model.

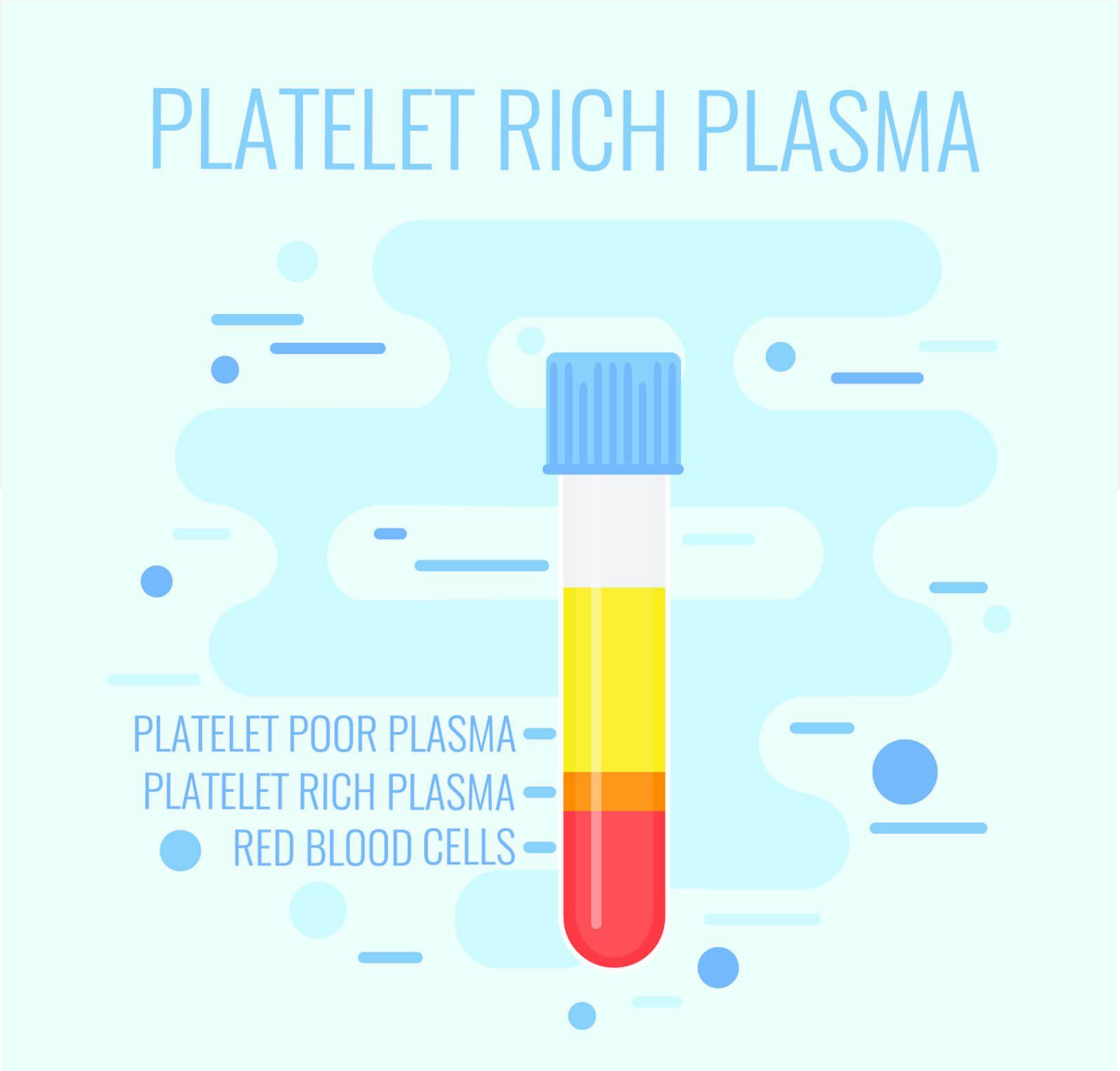
# Prolotherapy: Clinical Evidence

- A systematic review of four injection therapies for lateral epicondylitis: prolotherapy, polidocanol, whole blood and platelet-rich plasma
  - British Journal of Sports Medicine 2009;43:471-481
- Conclusions: There is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood and platelet-rich plasma injections in the treatment of LE.

# PRP = The Supercharged Proliferative Injection

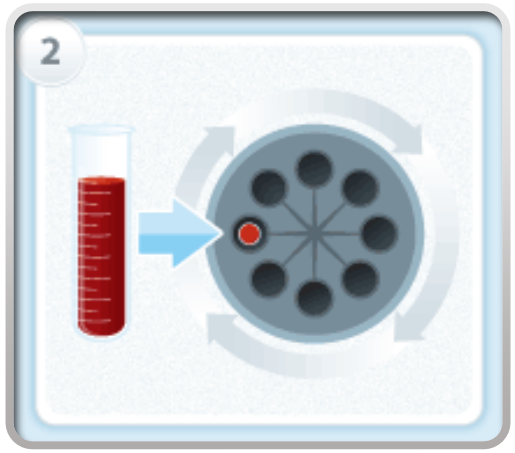
# What is Platelet Rich Plasma (PRP)?

- From autologous blood
- Contains levels of platelets above baseline levels
  - Cell ratios in normal blood contain only 6% platelets, in PRP contains 94% platelets
- Contains over 300 growth factors

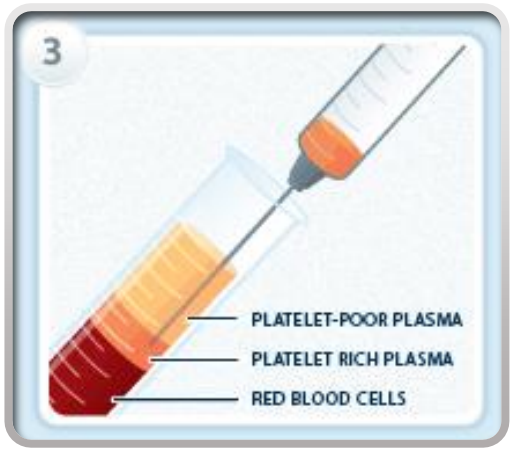


# Process of PRP

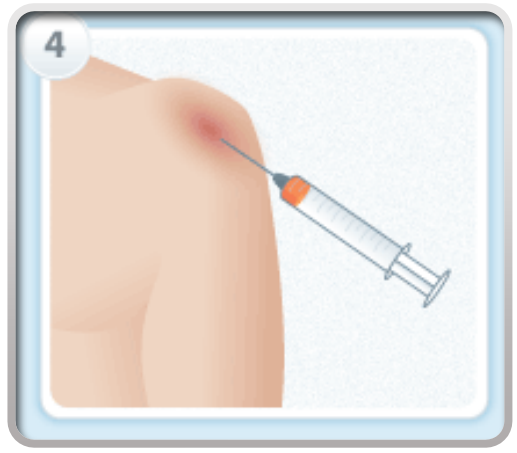

1) Collect blood




2) Separate the platelets



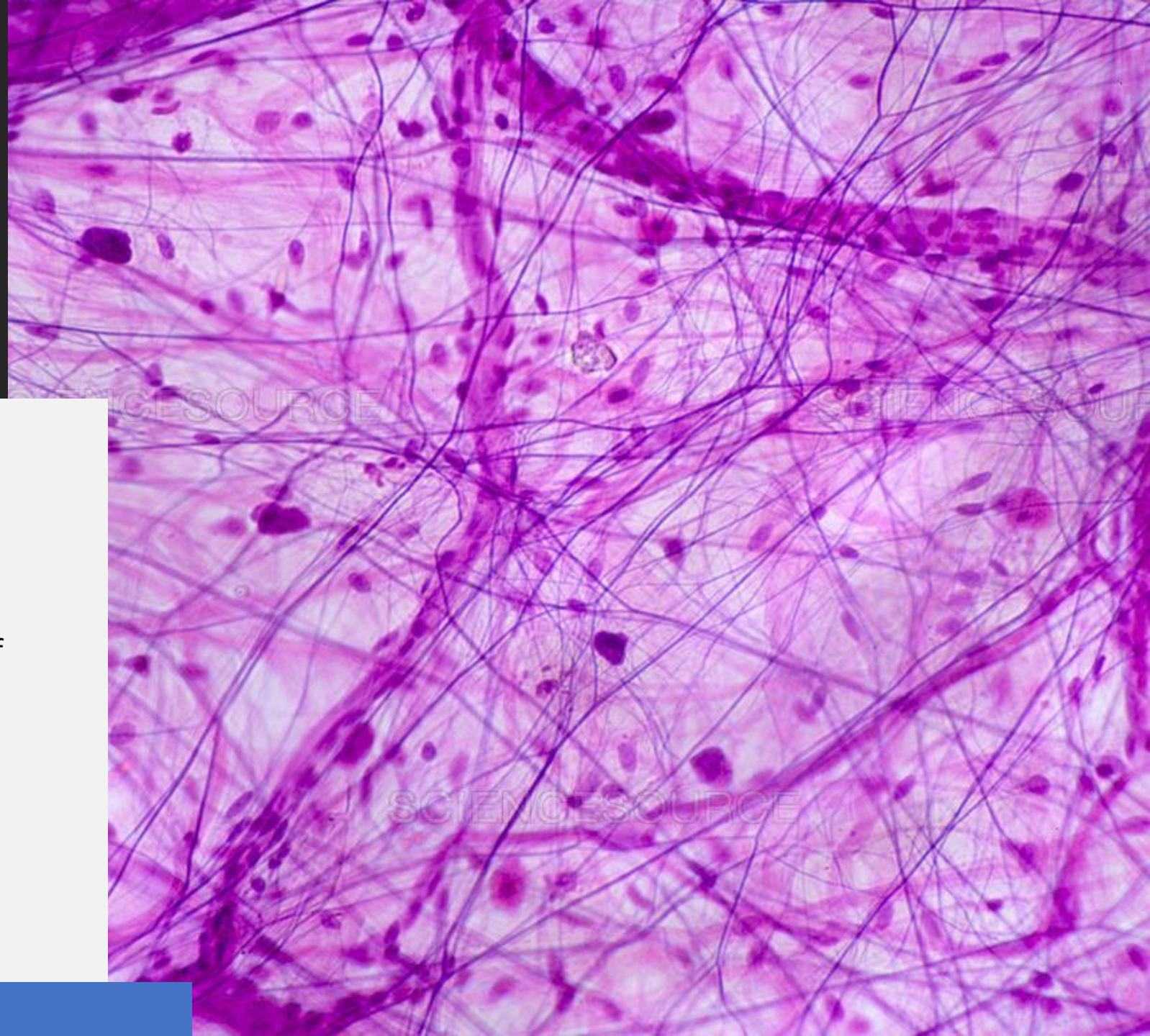

3) Extract platelet-rich plasma




4) Inject injured area with PRP

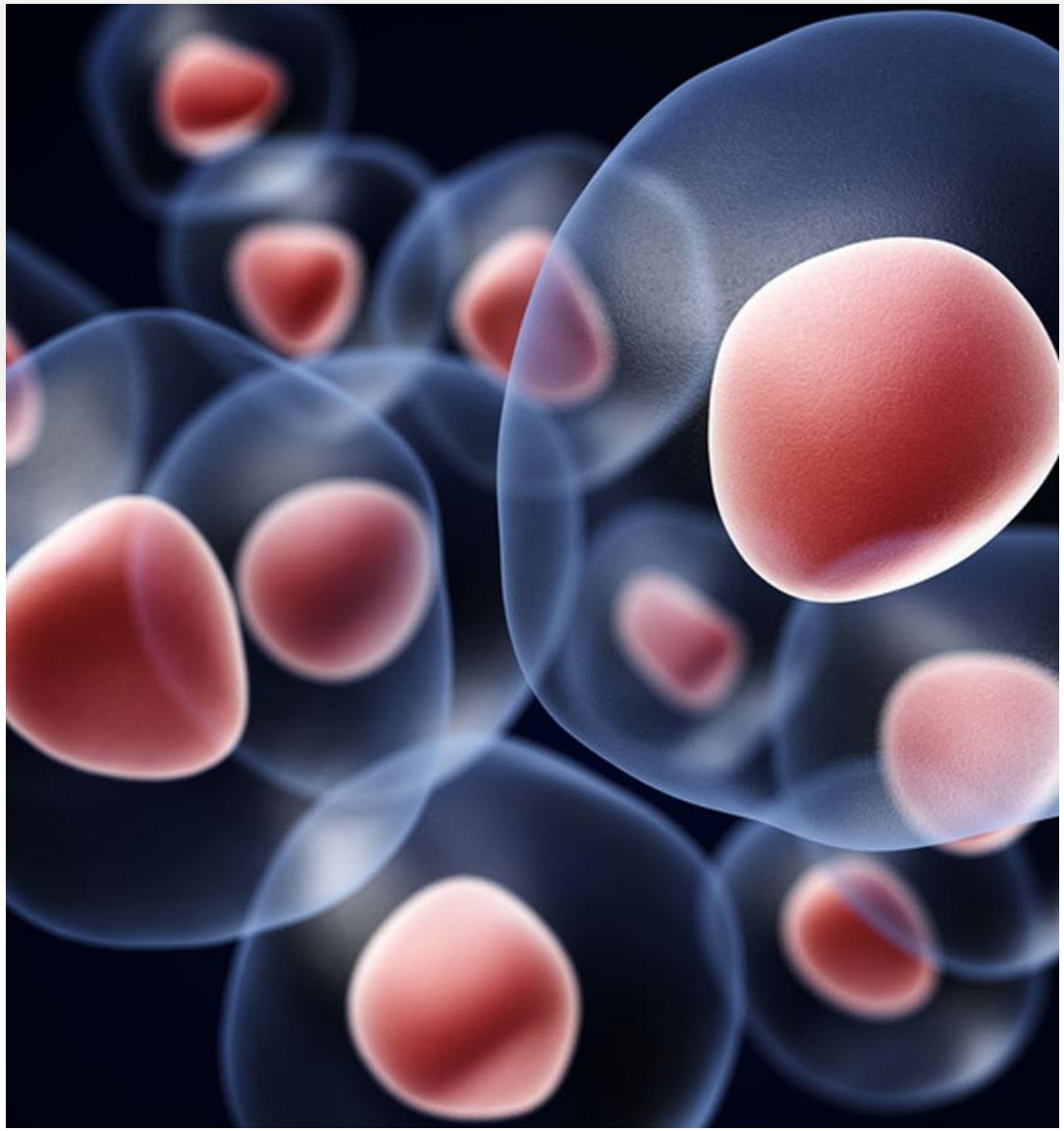
# How Does PRP Work?
# 1) Formulates Collagen

- The main component of connective tissue
- Found in ligaments, tendons, skin, blood vessels, cartilage, and many other parts of the body
- New collagen shrinks as it matures – tightening damaged tissue – making it stronger



# How Does PRP Work?
# 2) Releases Growth Factors

- Regulates cell division and cell survival
- Activates cellular proliferation and differentiation
- Promotes cell growth
- Functions as hormones-like regulator signals
- Improves metabolism of nutrients
- Guide stem cells to area of injury
- Nurture stem cells to maturity



# Growth Factors

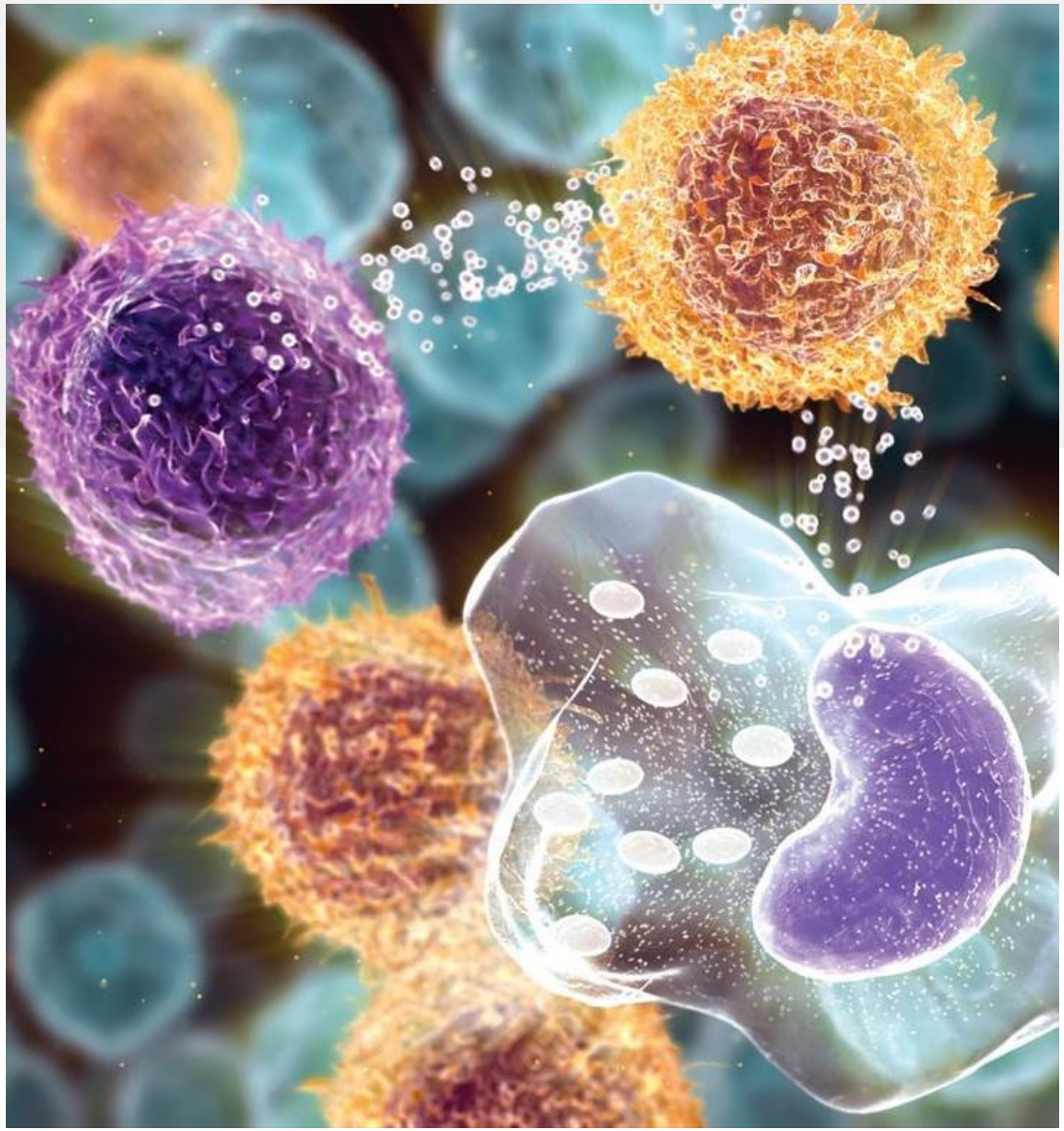
| Growth Factor | Cellular Factor |
|---|---|
| PDGF<br>Platelet Derived Growth Factor | Macrophage activation and angiogenesis<br>Fibroblast chemotaxis and proliferative activity<br>Enhances collagen synthesis<br>Enhances the proliferation of bone cells |
| IGF-1<br>Insulin-like Growth Factor-I | Chemotactic for myoblast and fibroblasts and stimulates protein synthesis<br>Mediator in growth ad repair of skeletal muscle<br>Enhances bone formation by proliferation and differentiation of osteoblasts |
| TGF-p<br>Transforming Growth Factor-β | Enhances the proliferative activity of fibroblasts<br>Stimulates biosynthesis of type I collagen and fibronectin<br>Induces deposition of bone matrix<br>Inhibits osteoclast formation and bone resorption<br>Regulation in balance between fibrosis and myocyte regeneration. |
| PDEGF<br>Platelet Derived Endothelial Growth Factor | Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts |
| PDAF<br>Platelet Derived Angiogenic Factor | Induces vascularization by stimulating vascular endothelial cells |
| EGF<br>Endothelial Growth Factor | Cellular proliferation<br>Differentiation of epithelial cells |
| VEGF<br>Vascular Endothelial Growth Factor | Angiogenesis<br>Migration and mitosis of endothelial cells<br>Creation of blood vessel lumen<br>Creation of fenestrations<br>Chemotactic for macrophages and granulocytes<br>Vasodilation (indirectly by release of nitrous oxide) |
| HGF<br>Hepatocyte Growth Factor | Stimulates of hepatocyte proliferation and liver tissue regeneration<br>Angiogenesis<br>Mitogen for endothelial cells<br>Antifibrotic |

# Growth Factor Animal Studies

- Autologous PRP was injected into normal patellar tendons of New Zealand White rabbits
  - Histological analysis at 6- and 12-weeks post-injection revealed a robust angiogenic response
- Locally injected PRP into a wounded rat patellar tendon
  - Resulted in an increased number of circulation-derived cells involved in the tendon healing
- Combined PRP/Losartan injections resulted in improved muscle strength, as measured in peak twitch and tetanic forces
  - Suggesting that combination treatment with PRP/Losartan can improve muscle healing by exerting anti-fibrosis, pro-angiogenesis, and pro-myogenesis effects through inhibition of TGFβ1
- PRP-mediated effects on tendon healing could be secondary to improved vascularity (with careful consideration of the potential degradative properties of angiogenesis)
- Anti-inflammatory effects of growth factors known to increase with exogenous administration of platelets
- PRP has been shown to suppress cyclooxygenase (COX)-1, COX-2, and membrane prostaglandin E synthase (mPGES) expression in vitro – all involved in the inflammatory pathway

# How Does PRP Work?
# 3) Secretes Cytokines

- Proteins released by cells
- Lymphokine, monokine, chemokine, and interleukin
- There are anti- and pro-inflammatory cytokines



# PRP Helps Treat Unresponsive Chronic Pain & Injuries

Over time, the body stops recognizing the area as something to repair

PRP creates a purposeful, mild inflammation response to the damaged tissue

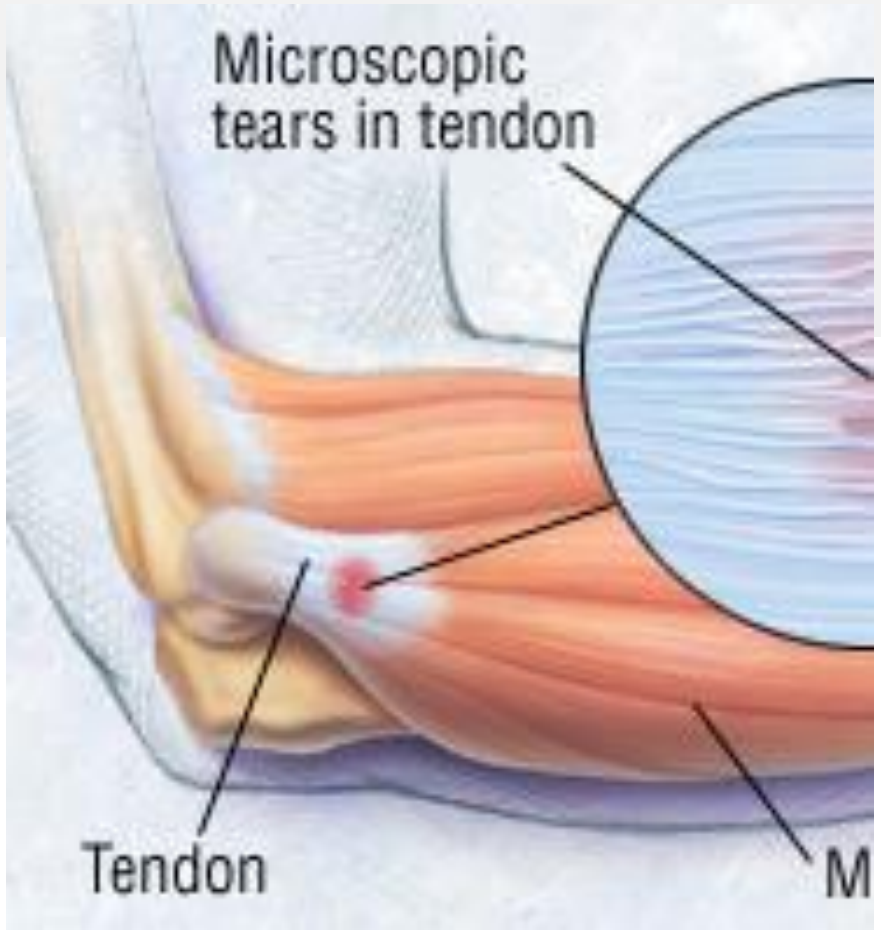
This restarts the healing process and allows new fibers to grow back

# Injuries Treated by PRP

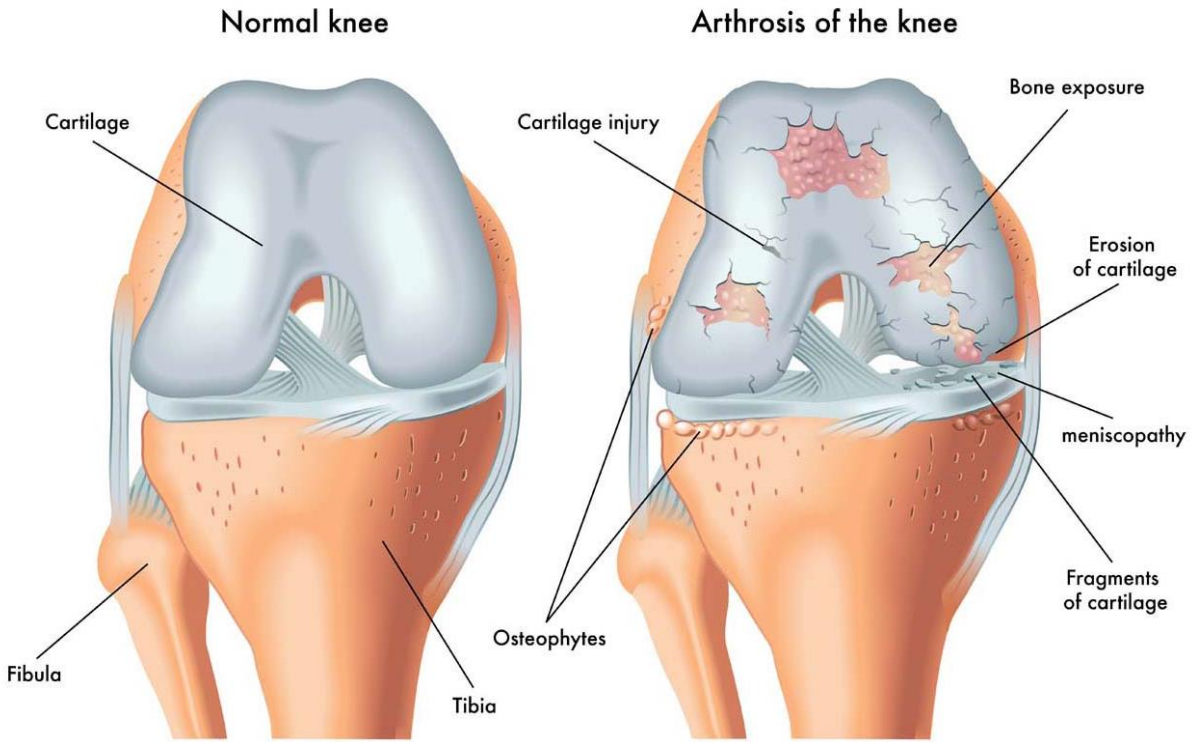
- Chronic Sports Injuries (ex. Tennis Elbow, Achilles Tendonitis, and Runner's Knee)
- Degenerative Joint & Disc Disease
- Chronic Sprains and Strains
- Cervical, Thoracic, and Lumbar Spine Strains
- Traumatic Brain injuries
- Arthritic Joints
- Shoulder Pain, Hip Pain, and Knee Pain
- Ligament Laxity or Tears
- Tendon and Ligament Injuries
- Carpal Tunnel Syndrome

# PRP Reduces Tendonitis Symptoms

- 30 – 50% of all sports-related injuries are tendon disorders
- 93% reduction of pain at the 2 year follow up
- Achilles tendon or elbow, extensor or flexor tendonitis/tendinosis or tears
- Collateral ligament tears



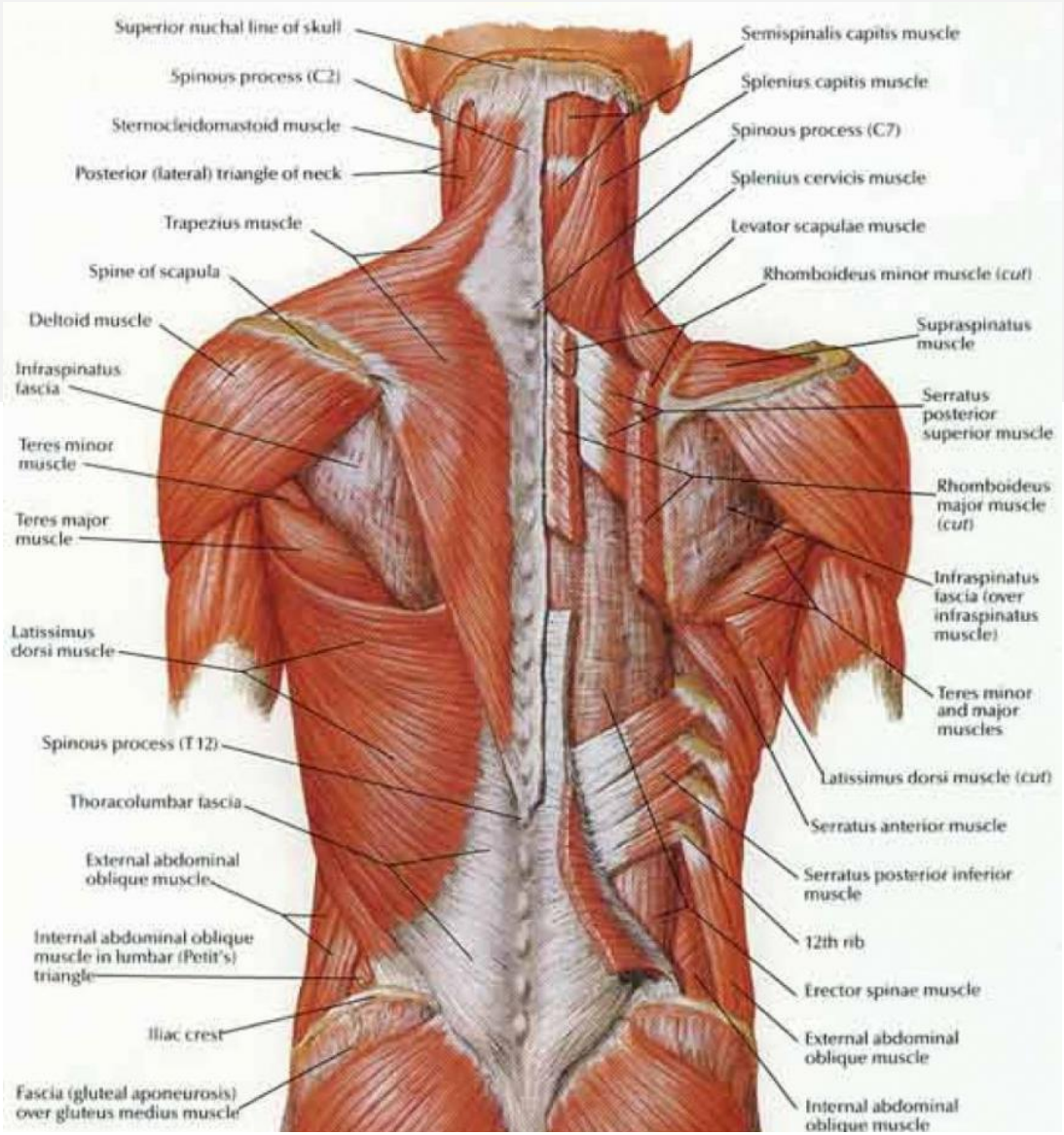
# PRP Helps Decrease Osteoarthritis Symptoms




- Restores hyaluronic acid concentrations
- Improves angiogenesis
- Reverses joint damage and stops disease progression

# PRP Reduces Lower Back Pain

- Treats structural ligaments (such as iliolumbar, sacroiliac, lumbosacral and supraspinous ligaments), muscle strains, and muscle fibrosis
- Improve stability and dispersion of weight



# Other Uses of PRP

- Reversing hair loss
- Facial rejuvenation

# Celebrities for PRP

**Angelina Jolie:** It has been reported that Angelina Jolie took the PRP skin rejuvenation treatment to boost her collagen.

**Tiger Woods:** In 2008, Tiger Woods had a serious ACL injury. After reconstruction Woods received PRP injections to recover faster. And due to his speedy healing, 2009 was one the best years of his golfing career.


**Alex Rodriguez:** The Yankees player A-Rod had 5 PRP sessions after his hip surgery back in 2009. He was able to get back into shape for playing again way sooner than anticipated by his physician.


**Kobe Bryant:** Kobe Bryant would fly to Germany to heal his knee faster with PRP and avoid the threat of having to retire early.

http://www.chicagostemcelltherapy.com/five-celebrities-who-chose-prp-treatments/

# Other Regenerative Treatment Options for Chronic Pain

# Prolozone

- Injection of ozone into the tissue
- Increases blood supply and flow of healing nutrients
- Stimulates the deposition and activity of fibroblasts and chondroblasts
- Synthesize collagen and cartilage to repair damaged ligaments and joints
- Natural, highly reactive, and safe = highly therapeutic
- Antimicrobial and sterilizing

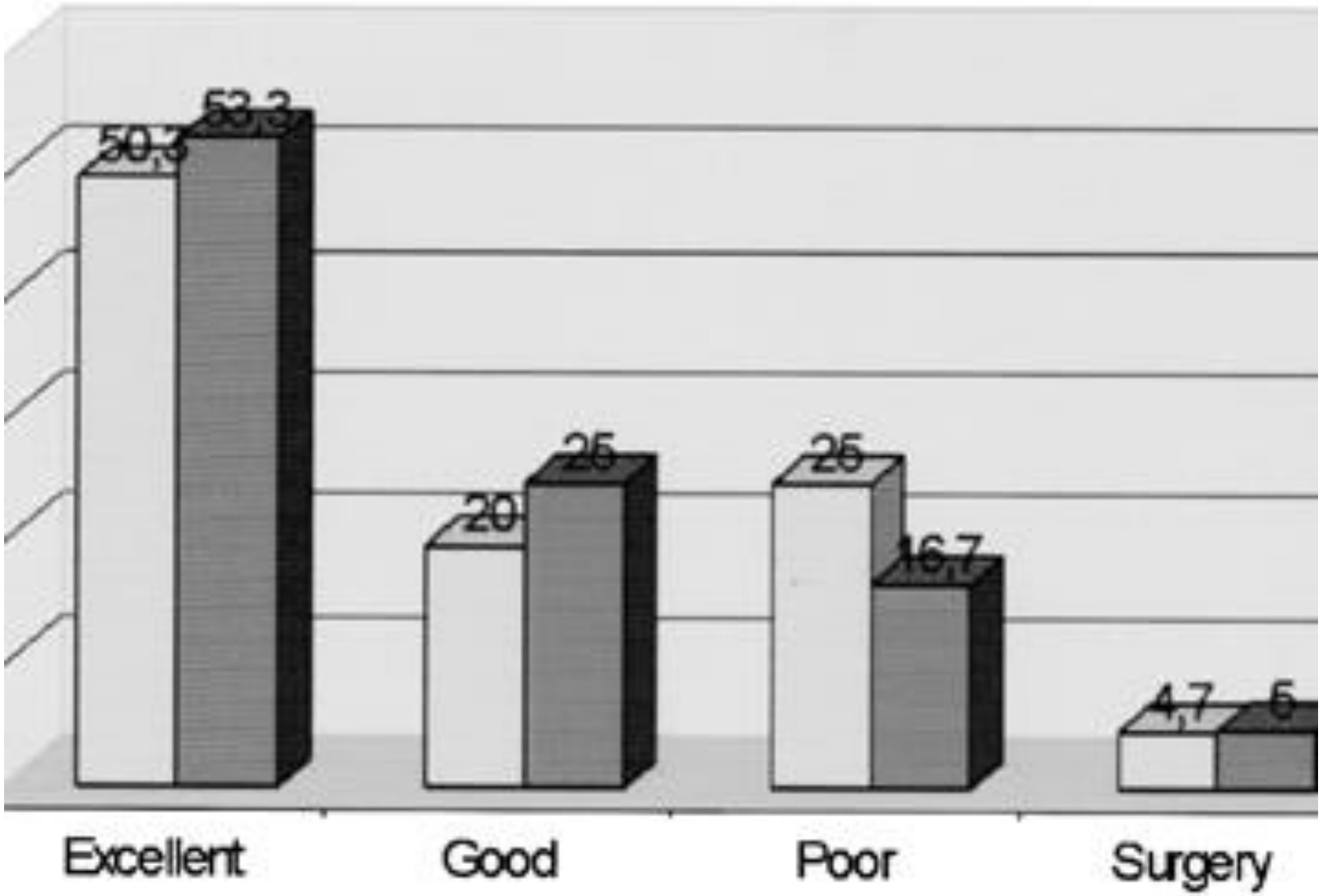
# Intervertebral O3 injections--Italian Study

http://www.ajnr.org/cgi/content/full/24/5/996/F2

- 1999 to 2001
- 600 patients aged 20–80 years
- Treated with a single dose of oxygen-ozone therapy
- 300 patients (Group A) received an intradiscal (4 mL) and periganglionic (8 mL) injection of an oxygen-ozone mixture with an ozone concentration of 27 µg/mL
- The other 300 patients (Group B) received identical oxygen-ozone injections, followed by a periganglionic injection of corticosteroid (1 mL of Depo-Medrone 40 mg and anesthetic (2 mL of Marcain 0.5%

Puncture at L4-L5 performed under CT guidance.

The L4–5 level was the most frequently treated (61.8%); L1–2, 0.7%; L2–3, 1.2%; L3–4, 8.7%; L5-S1, 27.6%.




Therapeutic outcome 6 months after oxygen-ozone therapy.

Light gray bars indicate group A (n=300); dark gray bars, group B (n=300). Numbers at top of bars are percentages.

# Combining Prolotherapy, PRP, Prolozone

- If prolotherapy, PRP, and prolozone all are effective in their own ways, would it not be synergistically better to combine all of these therapies in one procedure?
- Unfortunately, many practitioners do not have the skills or knowledge yet on how to do this alchemy.  The secret mix, however, is pretty simple.
- Here's the Steps in the next slides

# Combining Prolotherapy, PRP, and Prolozone

1. **Make up the local anesthetic/light prolotherapy solution**

   -- Start with preservative free 1% ropivacaine*. Dilute with normal saline to 0.3%. Note: Do not use lidocaine, procaine, nor any other local anesthetic. Create a 8 cc solution in a 10 or 12 cc syringe.

   --Add 2 cc of D50 to the 0.3% ropivacaine make a D10 solution. Then add ¼ cc of magnesium chloride to the solution.

2. **Make up the PRP/plasma solution using peripheral autologous blood**

   -- Add 10cc of ozone at 20ug/cc to a 30 or 60 cc syringe. Pull up the desired amount of blood from an IV catheter from the patient. Keep in mind that plasma is roughly 55% of total blood volume

   --Add the whole plasma to yellow top 8.5 ml sodium citrate tubes (You do not need a special kit for PRP—most of them are waste of money)

   --Spin the plasma at 3400 rpm for 8-10 min. A standard lab/blood draw centrifuge will work.

   --Pull off all the plasma, not just the bottom layer using a 20g 3.5 inch spinal needle; be careful not to pull up any red cells. If you get a small amount of red cells, it's okay but too many red cells can damage joints.

   --Add the PRP to a 20cc syringe containing 10cc of ozone at 20ug/cc and 2 cc D50, ½ of 3% HCL, ¼ cc Ascorbate (nutrients)

   --Activate the PRP cocktail by adding ¼ cc Magnesium chloride to the solution and let sit for 5-10 min (or use a green laser light for 10 min)

*Ropivacaine is used because it does not harm the growth factors or stem cells in the PRP

# Combining Prolotherapy, PRP, and Prolozone

1. **Make up the ozone solution**

   -- Use a 10-60 cc syringe and pull up ozone at 20 ug/cc

2. **Identify the areas for injection by palpation or ultrasound**

3. **Injection of Local/Prolotherapy and Gentle Curettage**

   -- Inject the ropivacaine/D10 cocktail first; most small tendon/ligament areas require 3-5 cc and larger ligament areas 7-10 cc. Large joints such as the hip joint can require 12 or more cc depending on the patient's injury and pain tolerance

   --Scrape away any fibrosis, enthesopathy, or bone cysts present

# Combining Prolotherapy, PRP, and Prolozone

**4. Injection of PRP cocktail**

-- Most areas will require an equivalent amount of PRP

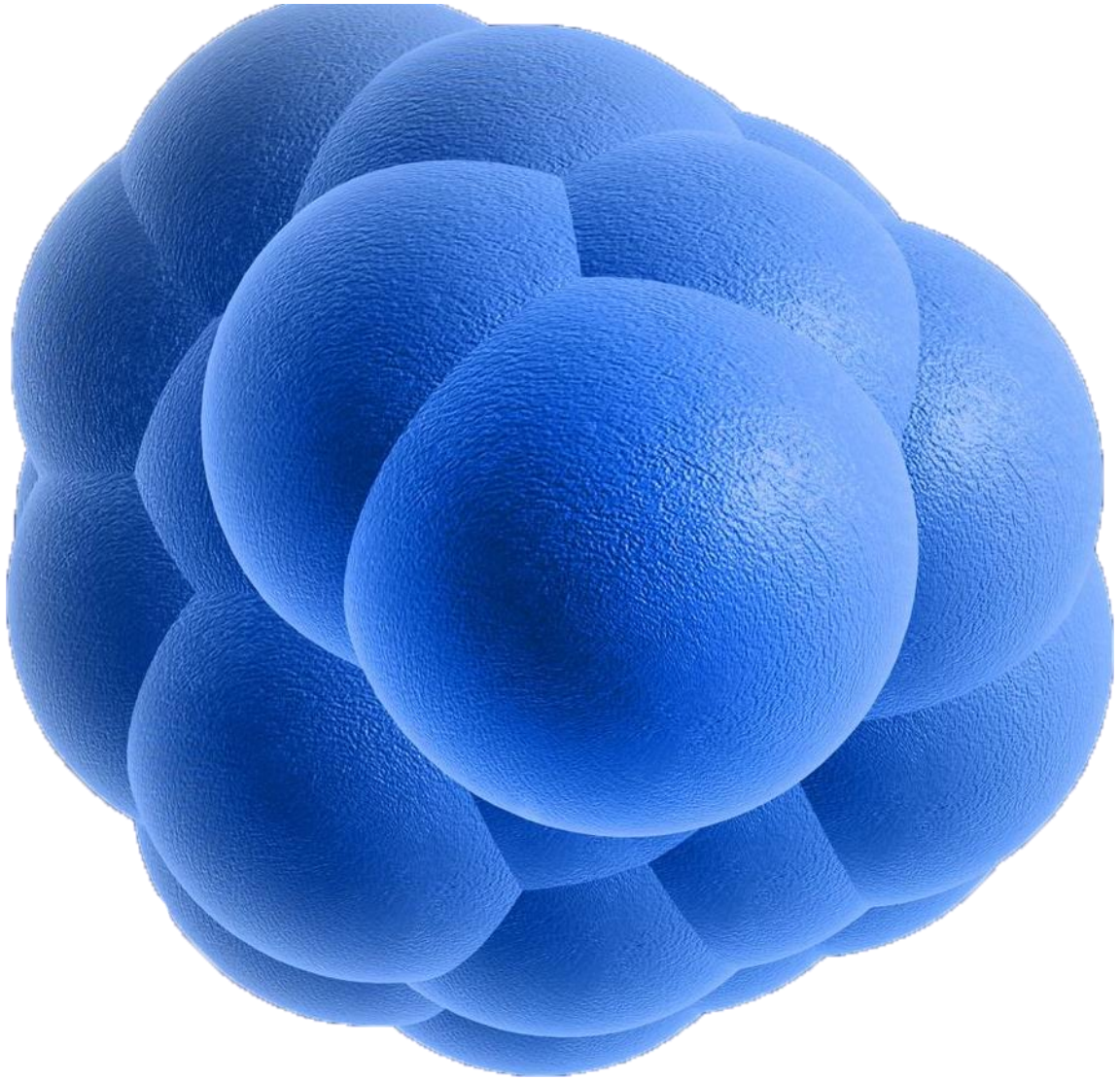
**5. Injection of Ozone**

-- Inject 5-10 cc of ozone gas into the affected tendon, ligament, or joint

In sum, the local/prolotherapy solution and PRP act like guided missiles to break down fibrosis/bone spurs while also regenerating damaged tissues. Acting like a bomb, the ozone accelerates this regenerative process and naturally steriles the area

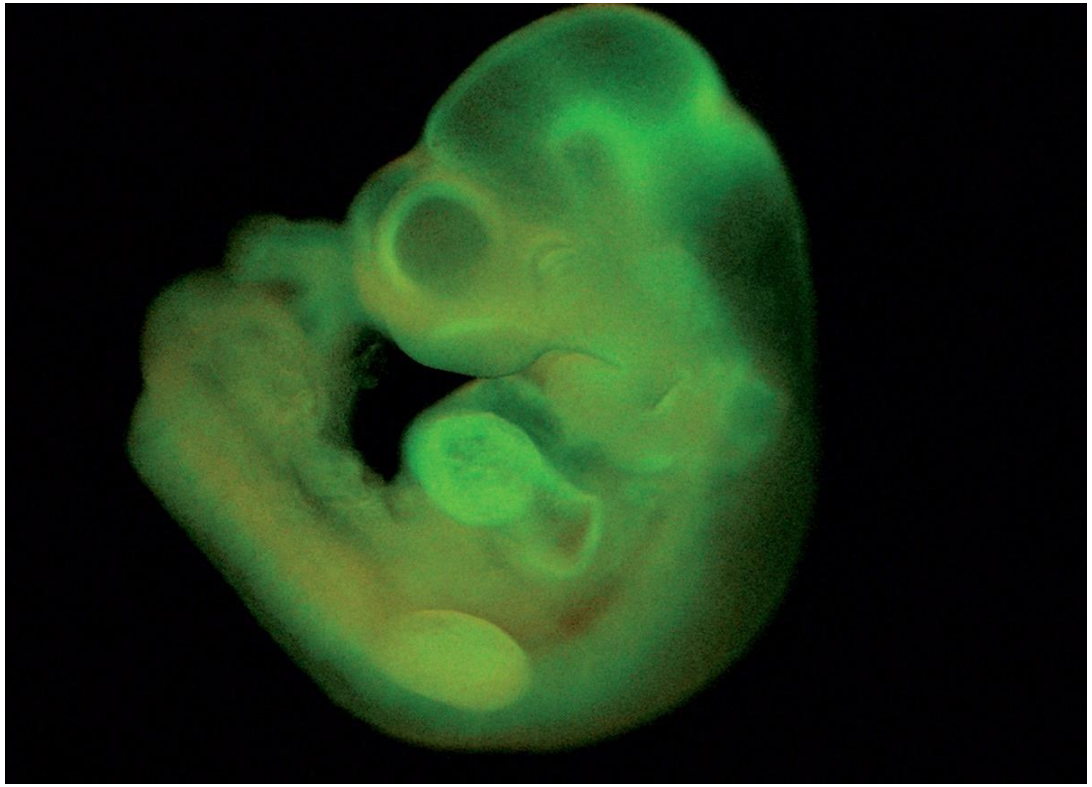
# Stem Cells

- Undifferentiated biological cells
- Divide and generate all cell types of the organ from which they originate
- Stimulate tissue re-growth and greater blood flow to the affected areas



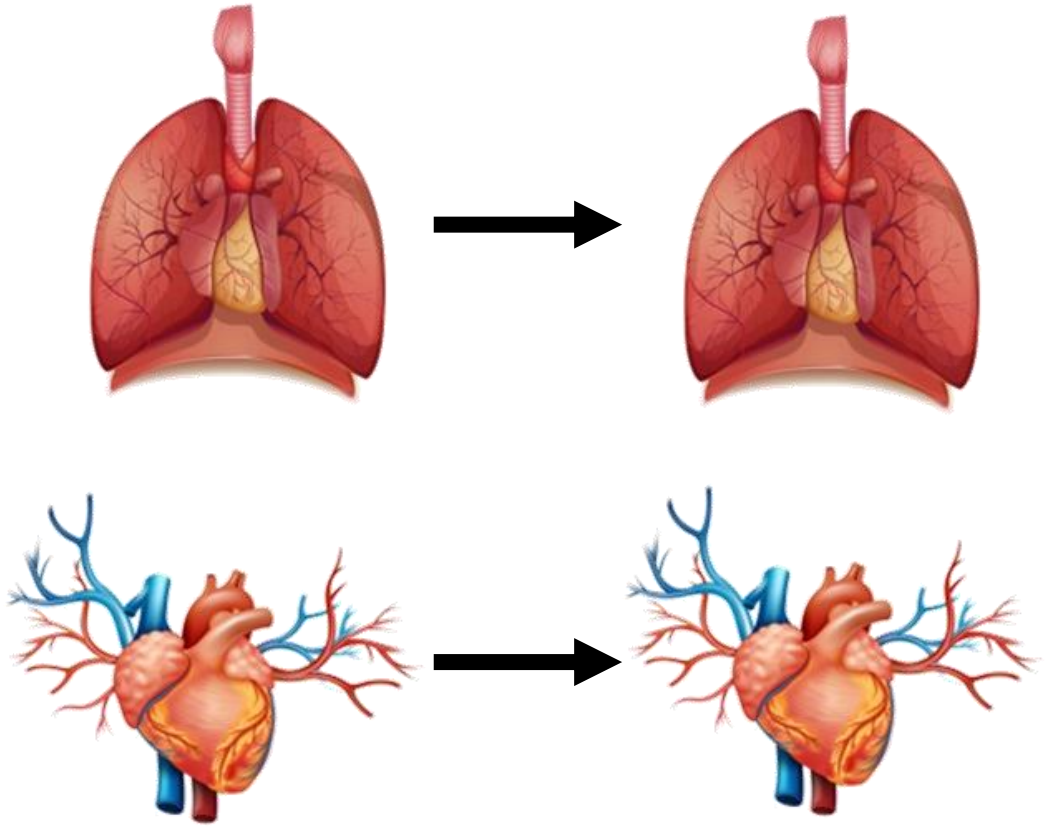
# What Are Stem Cells?
# **Embryonic**

- Mostly derived from embryos that develop from eggs *in vitro*
- Expensive
- Not autologous
- Ethically controversial
- Not readily available – research only



# What Are Stem Cells?
## Tissue-Specific

- For the specific tissue or organ in which they live
  - Lung – Lung
  - Heart – Heart
- Do not self-renew as easily
- Difficult to find

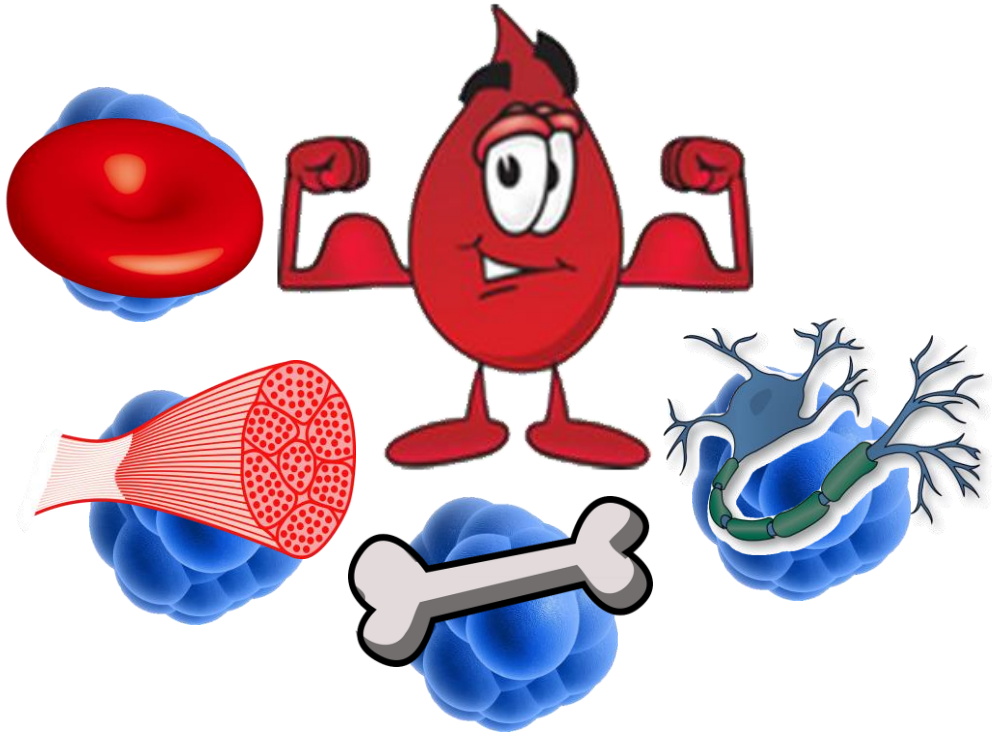


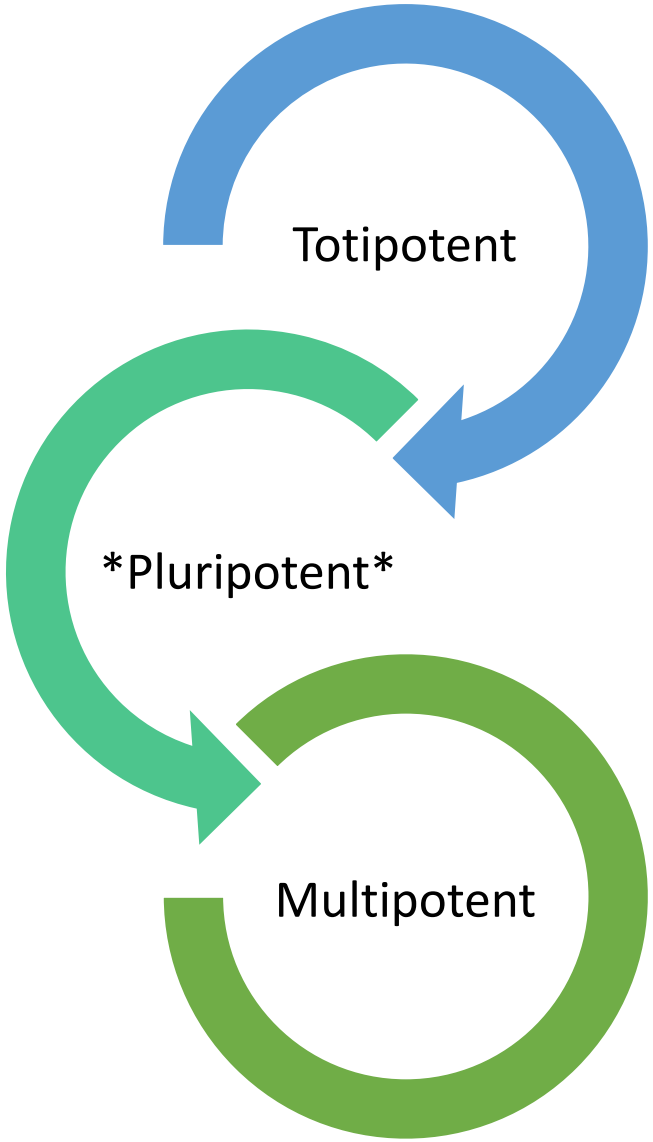
# What Are Stem Cells?
# **Mesenchymal**

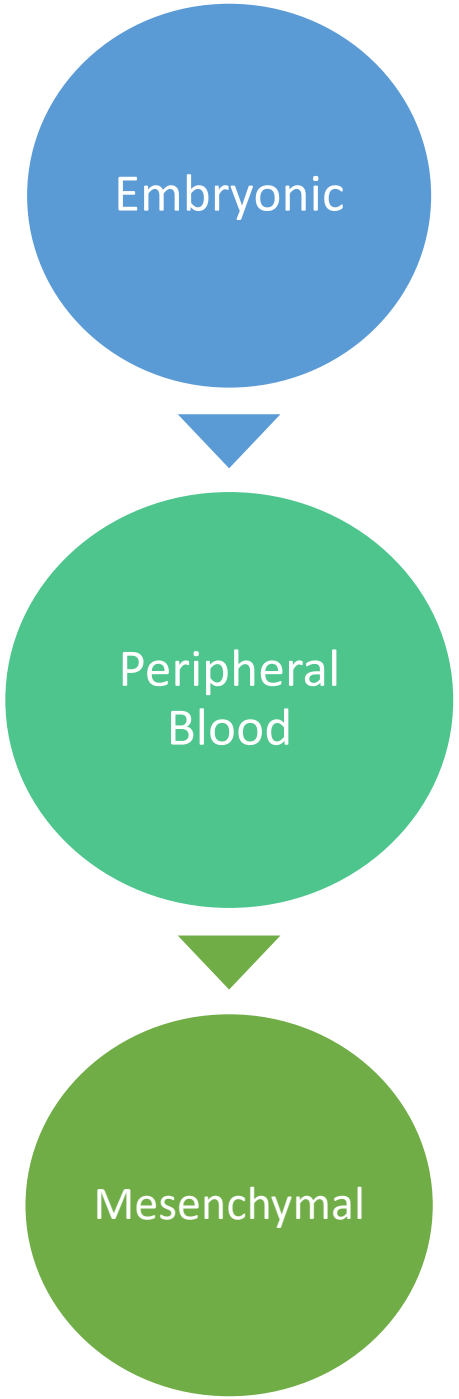
- From bone marrow, fat, and cord blood
- Immunomodulatory properties
- On a development trajectory towards specific target tissues (aka lineage committed)
- Therapeutic effects are short-lived

# What Are Stem Cells?
## **Pluripotent**

- Recently discovered in peripheral blood
- Behave like embryonic stem cells
- Give rise to all the cell types
- Long lifespan

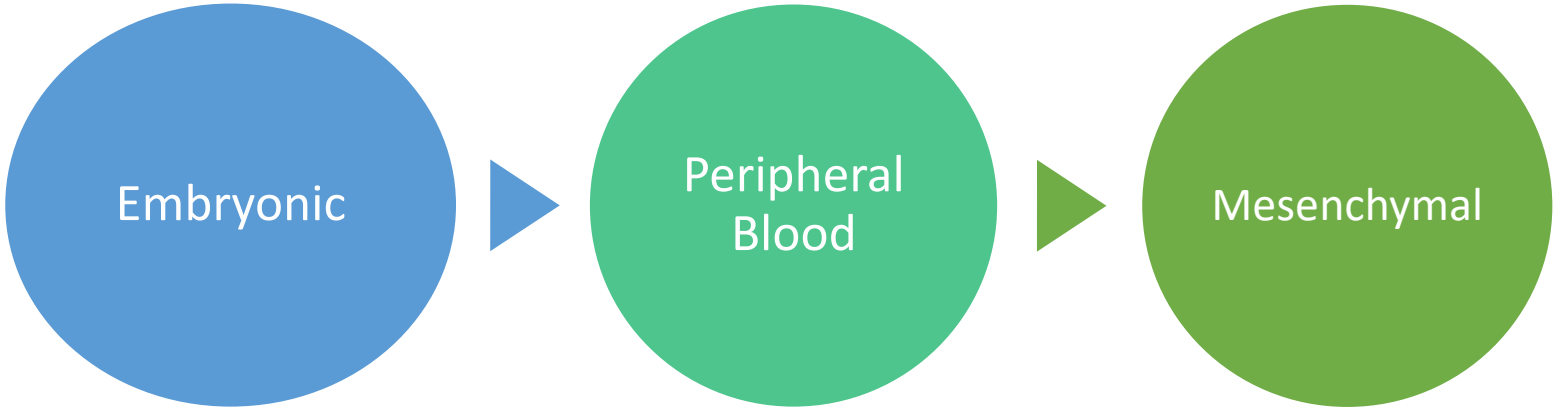





# Stem Cell Potency

# Stem Cell Uses




- Research
- Degenerative Diseases

- Degenerative Diseases:
  - Diabetes
  - Osteoarthritis
  - Osteoporosis
  - Alzheimer's Disease
- Regeneration:
  - Brain Injuries
  - Joint/Ligament Repair
  - Anti-aging
  - Post Cancer Treatment
  - Fertility

- Same tissue Replacement
- Systemic Inflammatory Conditions

# Regenerative Stem Cell Uses

- Chronic Sports Injuries (ex. Tennis Elbow, Achilles Tendonitis, and Runner's Knee)
- Degenerative Joint & Disc Disease
- Chronic Sprains and Strains
- Cervical, Thoracic, and Lumbar Spine Strains
- Traumatic Brain injuries
- Arthritic Joints
- Shoulder Pain, Hip Pain, and Knee Pain
- Ligament Laxity or Tears
- Tendon and Ligament Injuries
- Carpal Tunnel Syndrome

# How to Treat Chronic Pain

- Surgery – expensive, risky, potential side effects
- Physical Therapy – only manages pain, therapeutic but not long term
- Cortisone Injections – temporary fix, manages inflammation, rarely solves source of pain, potentially damaging
- Regenerative Injection Therapy – natural, autologous, treats cause of pain rather than symptom, long term

# Chronic Pain Treatment Costs

- Surgery = $40,000 - $100,000
- Physical Therapy = $50 - $350 per session
- Embryonic Stem Cells = only research purposes
- Mesenchymal Stem Cells = $7,000 - $300,000
- Pluripotent Stem Cells = $8,000 - $10,000
- Platelet Rich Plasma (PRP) = $1,200 - $2,500

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