The Holy Grail?

Mesenchymal Stem Cells for Annular Repair

Emerging Strategies and Clinical Potential

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Disclosures

- Elliquence consultant and trainer for Spine Endoscopy

Romania

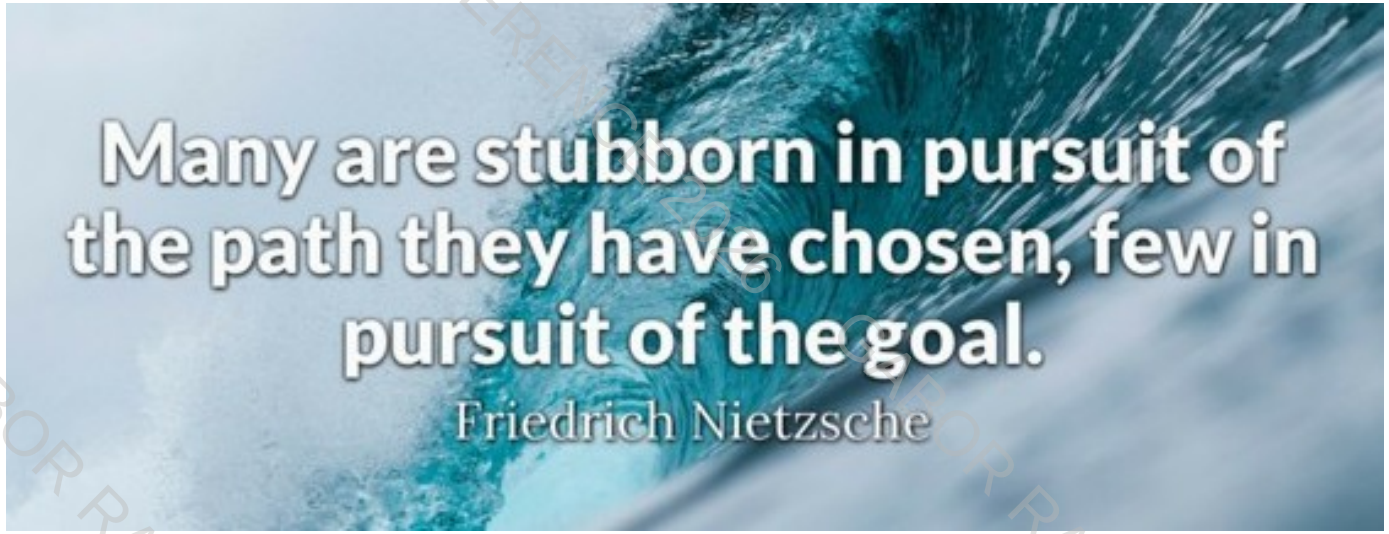
Who are we, who am I?

- Anesthesia and Critical Care
- 2010 Pain Management
- 2012 1st Multidisciplinary Pain Ctr
- 2016 ProVita Hospital Bucharest
- 2022 Nord Hospital

NORD Hospital, Bucharest Romania

The Goal Today

- **Regenerative Medicine Overview – SET EXPECTATIONS for DEFINITION of SUCCESS**
- Annular tears – mechanism, evolution, bla bla bla
- Strategies for the future
- **Evidence**
- **Ideal Patient**
- **Take home message**



Medicine 1.0

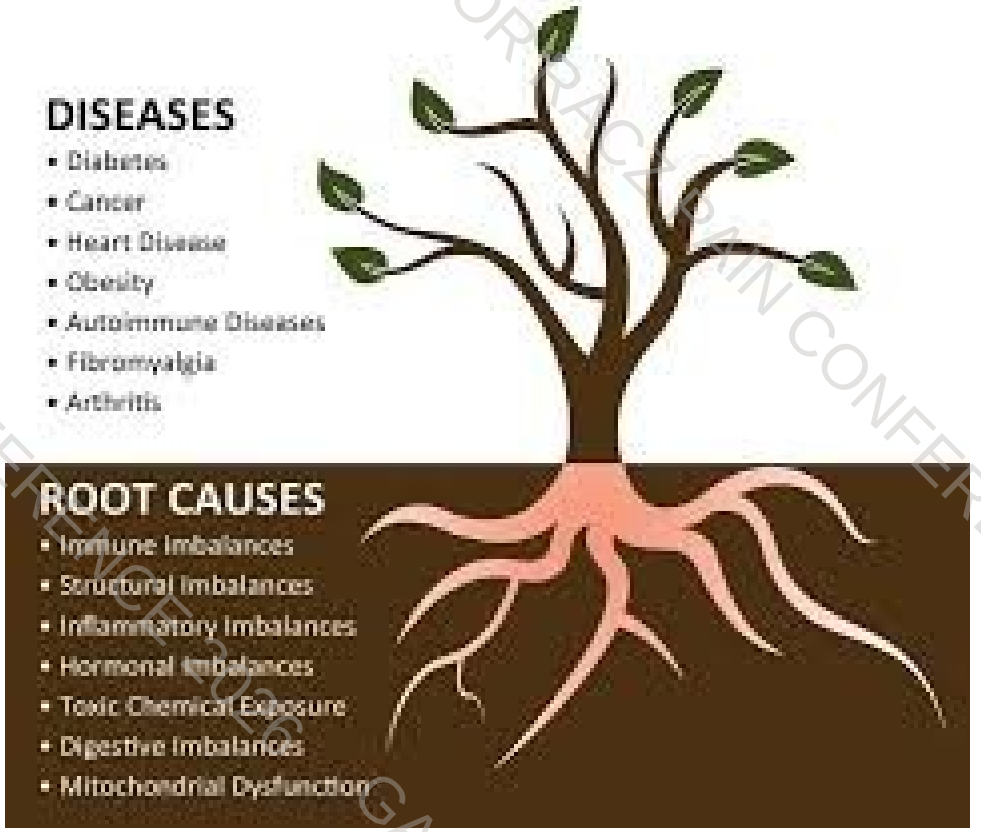
- **Medicine 1.0** – Treatments:
  - Healer like approaches,
  - Bizarre treatments like snake meat, spyders, venom, drinking weird tea, cutting under the tongue to heal jaundice, name it

Medicine 2.0

- **Medicine 2.0** – Evidence base medicine, guidelines – focused on disease treatment. Kind of a one size fits all ….

Medicine 3.0

- **Medicine 1.0** – Treatments: Wild-west approaches, bizarre treatments like consuming snake meat
- **Medicine 2.0** – Evidence base medicine, guidelines – focused on disease treatment. Kind of a one size fits all ….
- **Medicine 3.0** – Prevention, Personalized medicine, Technology integrated, patient centered care and empowerment, and most important addressing the cause!



Health Optimization

- For regenerative treatments to succeed, patient health must be optimized.
- Functional Medicine addresses lifestyle factors such as inflammation, hormonal imbalances, and metabolism to support the healing process.

Medicine 3.0 - Regenerative Approach

- Regenerative Medicine (**Medicine 3.0**) seeks to treat lumbar pain by addressing both the complexity of the spinal anatomy and optimizing the patient's health.
- Treatments utilize biologic agents like stem cells and platelet-rich plasma to regenerate not just the disc but also the surrounding structures.

What is Regenerative Medicine?

- Replaces or regenerates human cells, tissues, or organs to restore normal function.

- Applications include musculoskeletal treatments: joints, tendons, nerves, and spine.

Conditions for Success

- **Early in the degenerative process or after injury**
- Correct diagnosis
- Appropriate biologic agent
- Precise delivery
- Combine with health optimization – need to zoom out and remember we are doctors, not technicians

Platelet-Rich Plasma (PRP)

- Derived from blood, platelets assist in healing and regeneration
- Used for conditions like osteoarthritis and nerve, tendon, muscle injuries
- Preparation involves concentrating platelets using a centrifuge

Bone Marrow-Derived Stem Cells

- Harvested from bone marrow (usually from the hip)
- Used to treat spinal discs, nerves, and joints
- Performed under imaging guidance for precise delivery

Adipose-Derived Stem Cells

- Stem cells from adipose (fat) tissue used for regenerative therapies

- FDA restrictions despite success in thousands of procedures

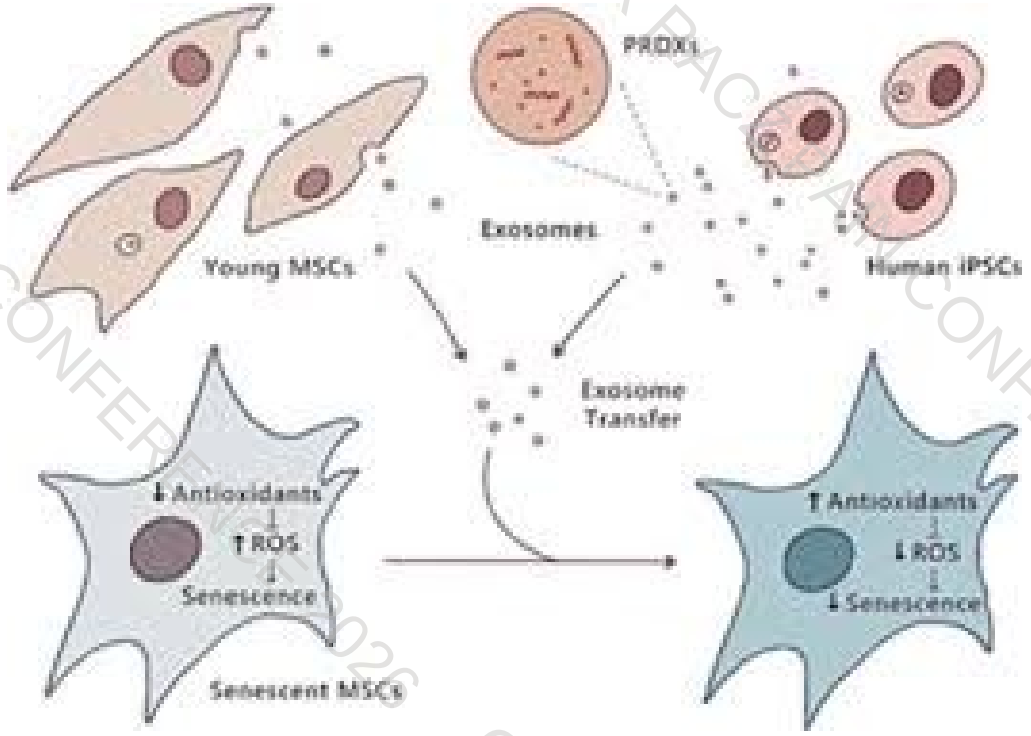
Perinatal Tissue Stem Cells

- Derived from discarded birth tissues (placenta, umbilical cord)
- Benefits: Minimal side effects but debate over freezing processes
- Stem cells from perinatal tissues show potential for treating various conditions

Exosomes

- Tiny healing vesicles released by stem cells

- Penetrate tissues to promote healing, especially in osteoarthritis and tendon injuries



N=1 Medicine (Precision Medicine)

- Is the patient a candidate?
- Optimal state of health? ABCs of Precision Medicine
- Personalized treatment approach

Regenerative and Functional Medicine

- Patient selection
- Precision Medicine diagnosis
- Precise, guided delivery
- Optimization of general health
- Optimization of physical function

Applications of Regenerative Medicine

- Treats conditions like osteoarthritis, spinal injuries, tendon tears, and nerve damage

- Tailored approaches based on severity and health of individual patients

Tensegrity and Lumbar Spine Health

Tensegrity refers to the balance of tension and structural integrity.

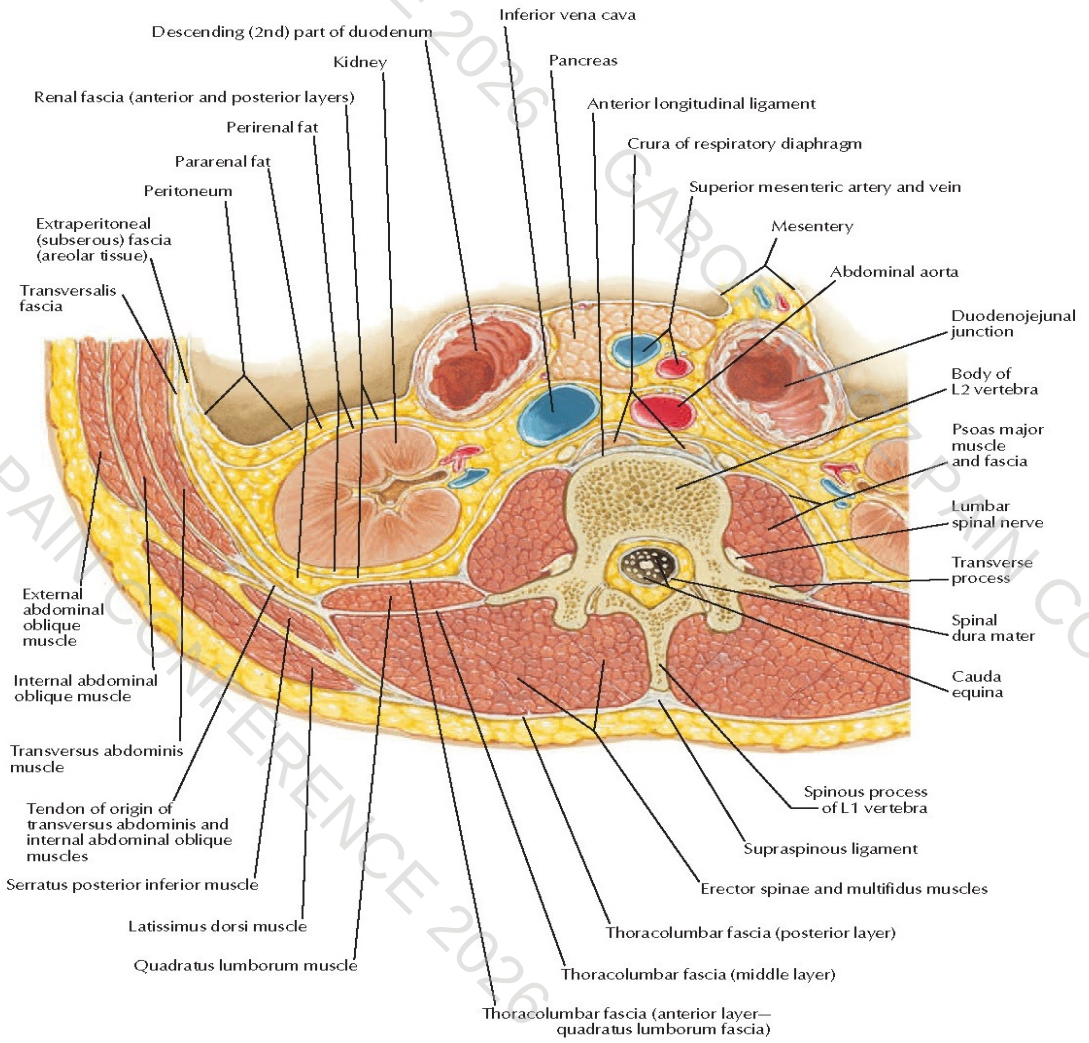
The spine's mechanical health depends on the proper tension of the surrounding soft tissues.

When this tension is lost, the spine's mechanics degrade, leading to degeneration.

Anatomy of the Lumbar Spine

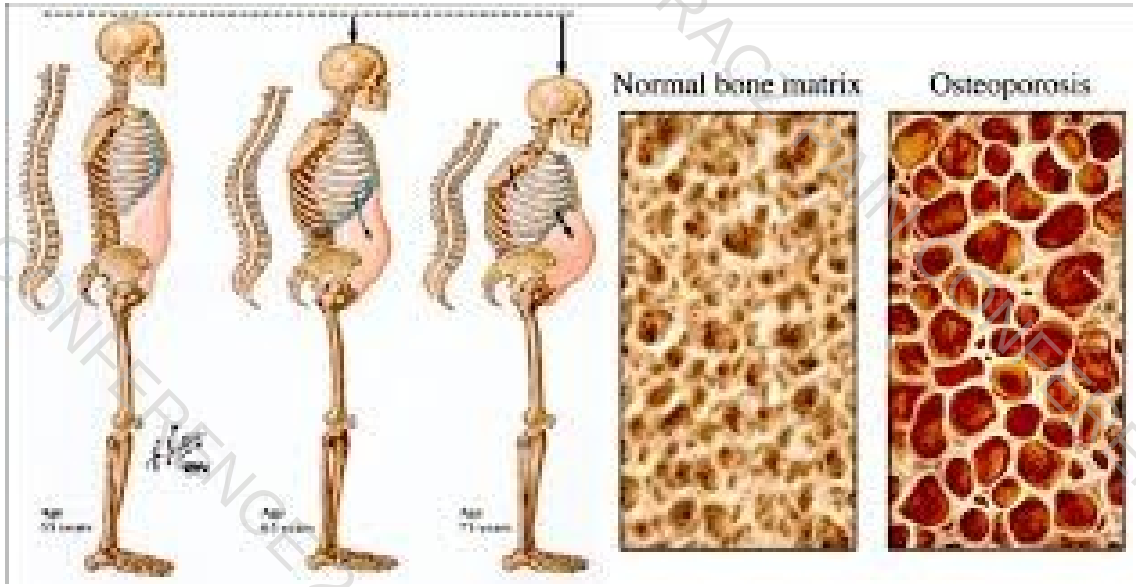
Structures that can cause lumbar pain:

- Skin
- Lumbar fascia
- Spinal muscles
- Tendons and ligaments
- Bones (vertebrae)
- Lumbar nerves
- Facet joints
- Discs
- Thecal sac coverings



Mechanisms of Discogenic Pain

- Gravitation Instability ☺
- Lack of posture adaptation to daily gravitational stress
- Rarely congenital
- Mostly due to:
  - Sedentarism/sarcopenia
  - Overweight
  - Bad nutrition

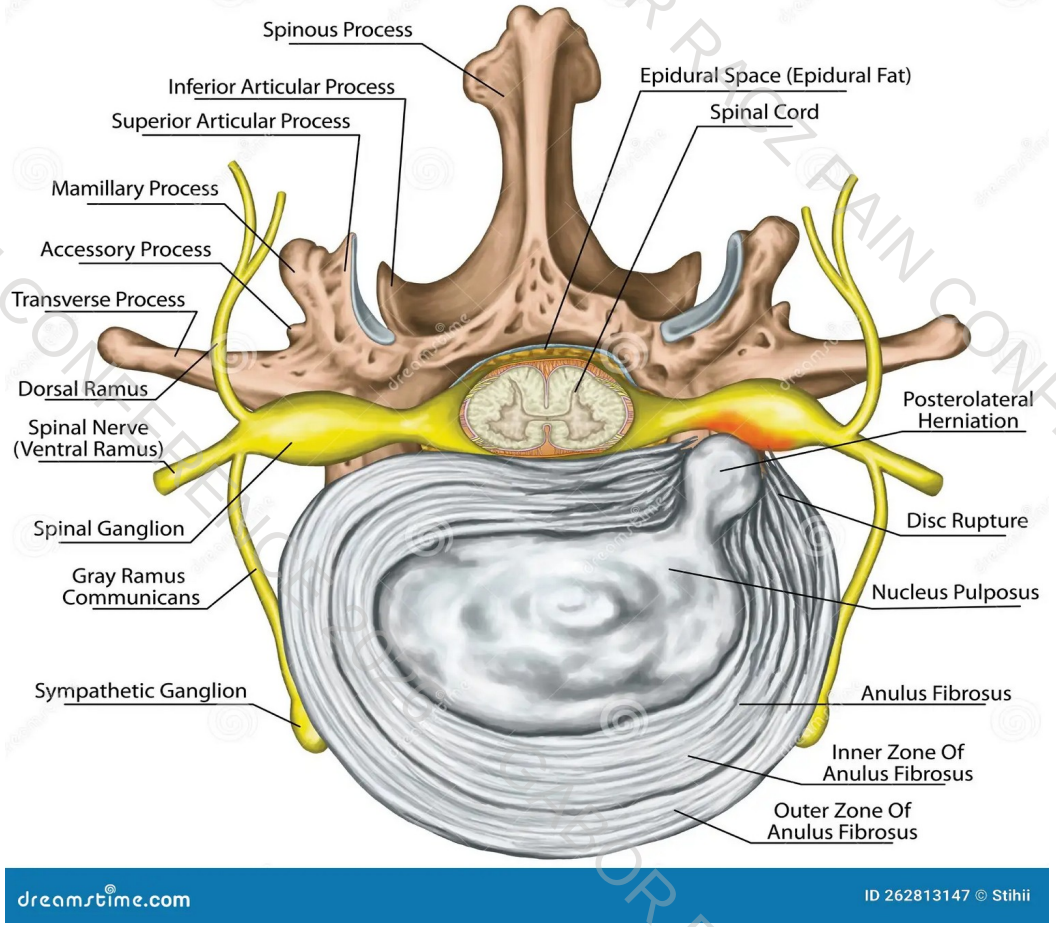


Lumbar Disc Anatomy

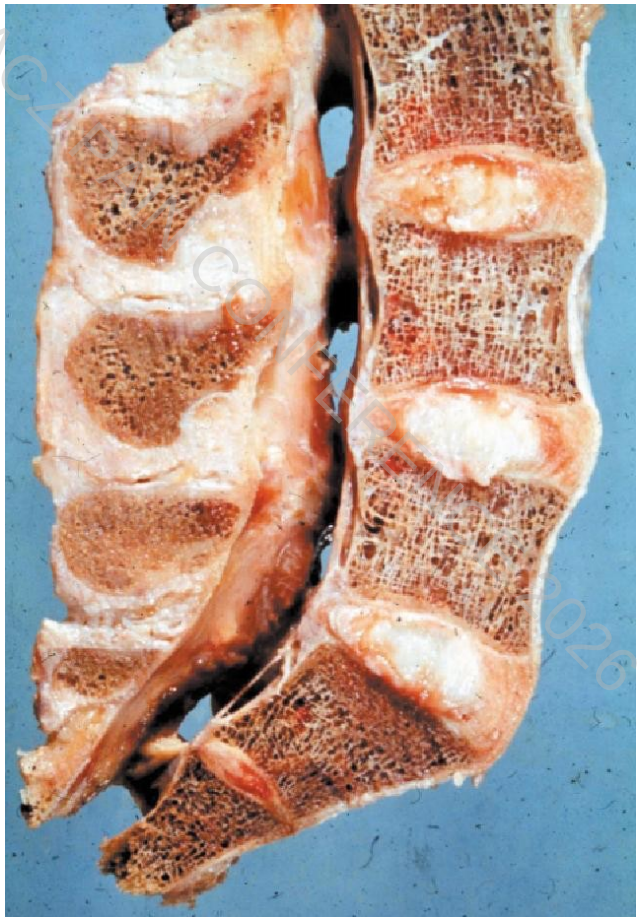
The disc consists of a hydrated nucleus, typically avascular and non-innervated, surrounded by the fibrous annulus fibrosus, formed by collagen.

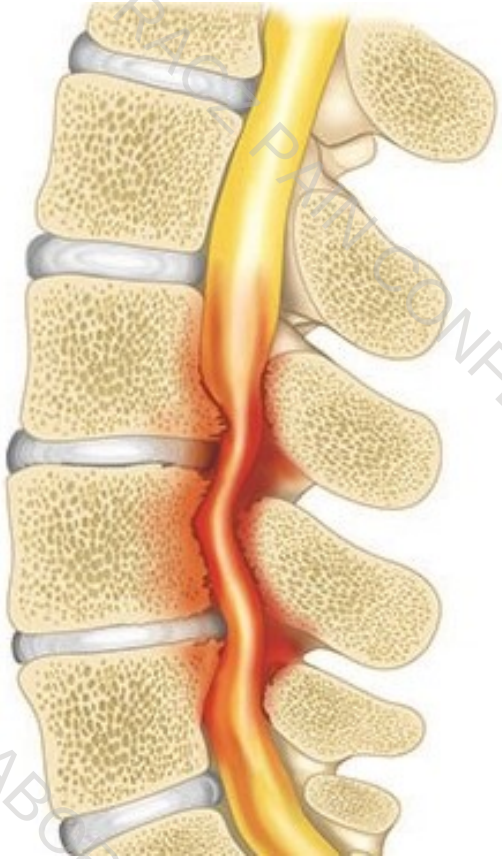
As the disc degenerates, it loses water and height, which decreases tensile strength.

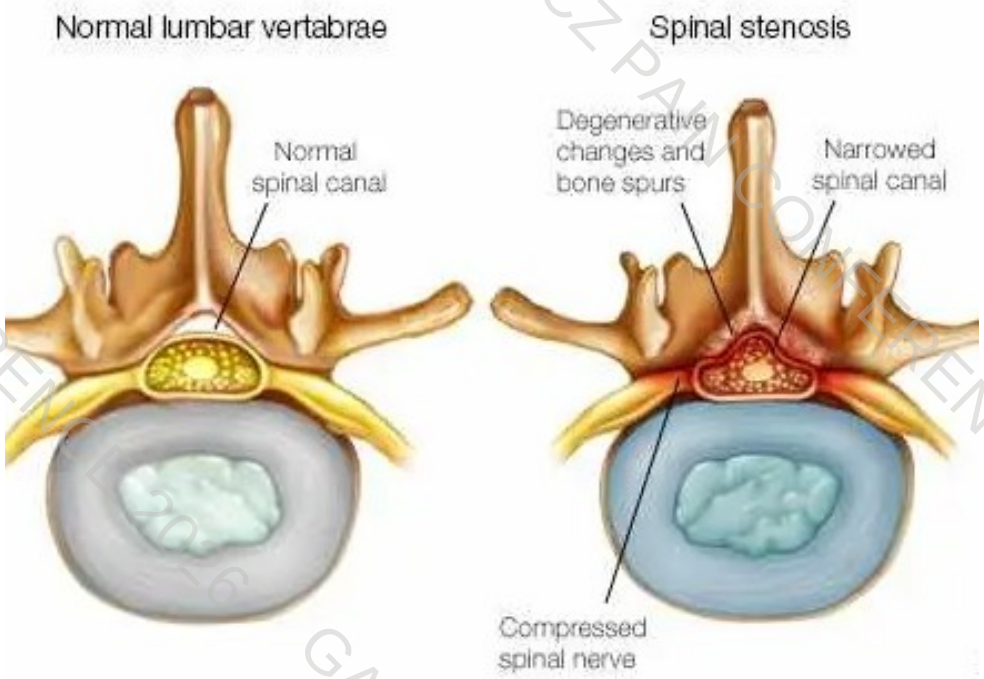
Radial fissures form and allow blood vessels and nerves to invade the disc, causing pain.



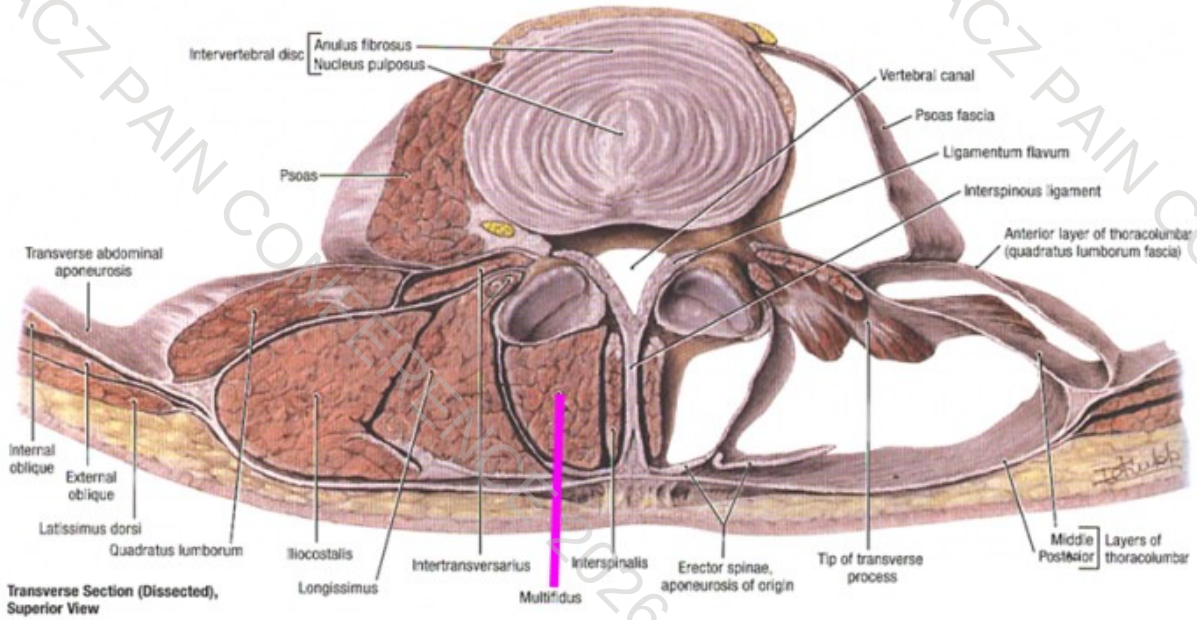
Lumbar spine structures
Hard Tissues

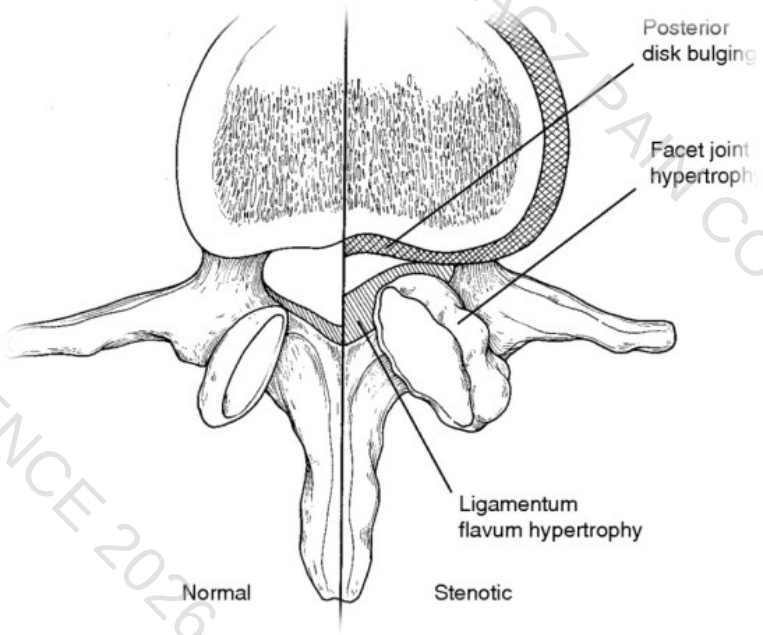






Lumbar spine structures
Soft Tissues

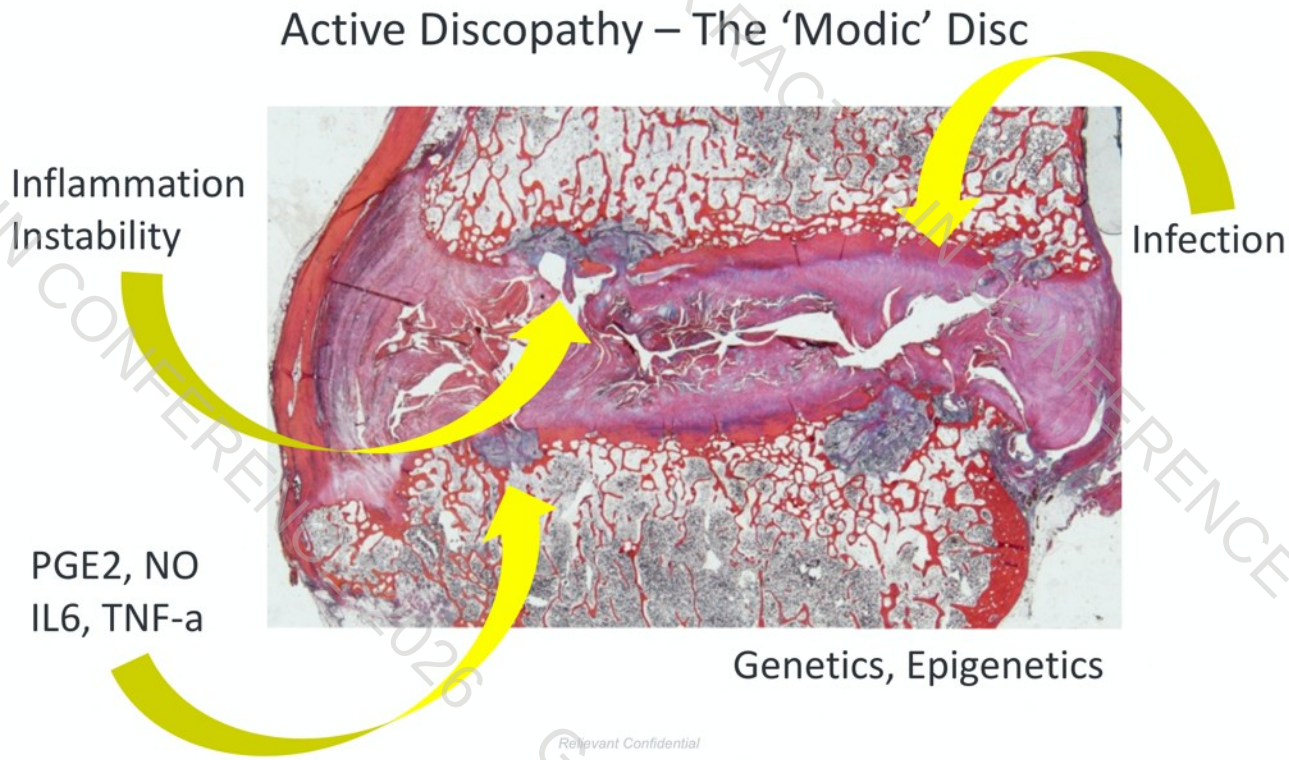




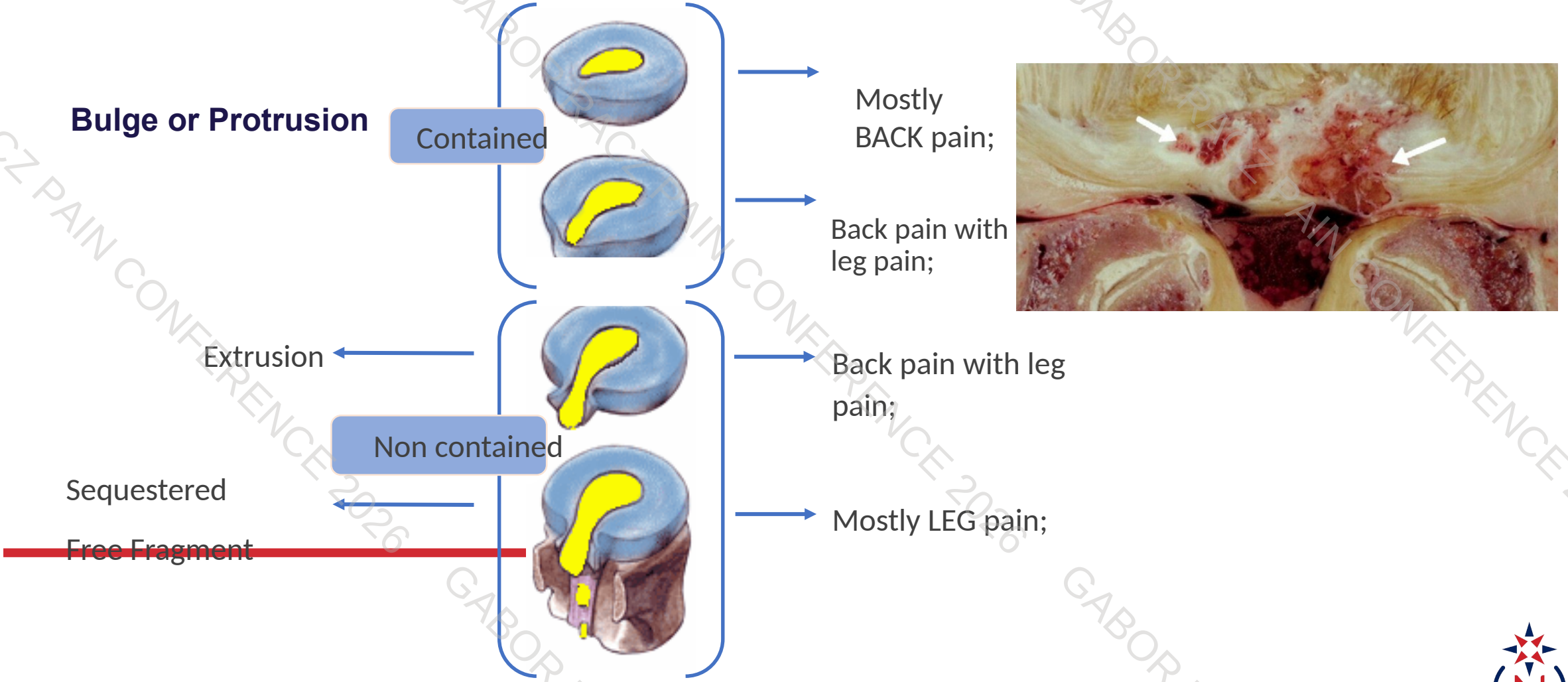
Mechanisms of Discogenic Pain

- **Mechanical**:
  - Increased intra-discal pressure sensitizes nerve ingrowth, resulting in pain and disc bulging

- **Chemical**:
  - The disc becomes more acidic due to degeneration, irritating the newly ingrown nerves and causing pain.



Types of Disc Herniation

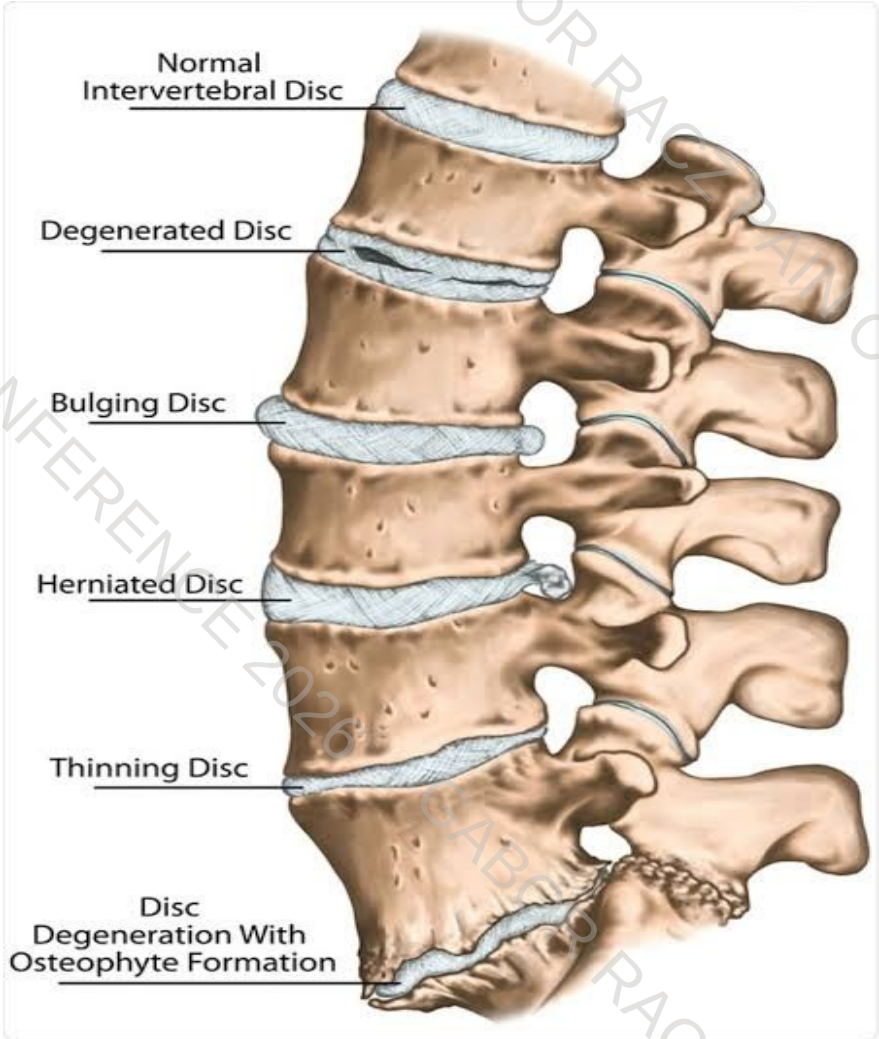


Mechanisms of Discogenic Pain

- **Mechanical**:
  - Increased intra-discal pressure sensitizes nerve ingrowth, resulting in pain

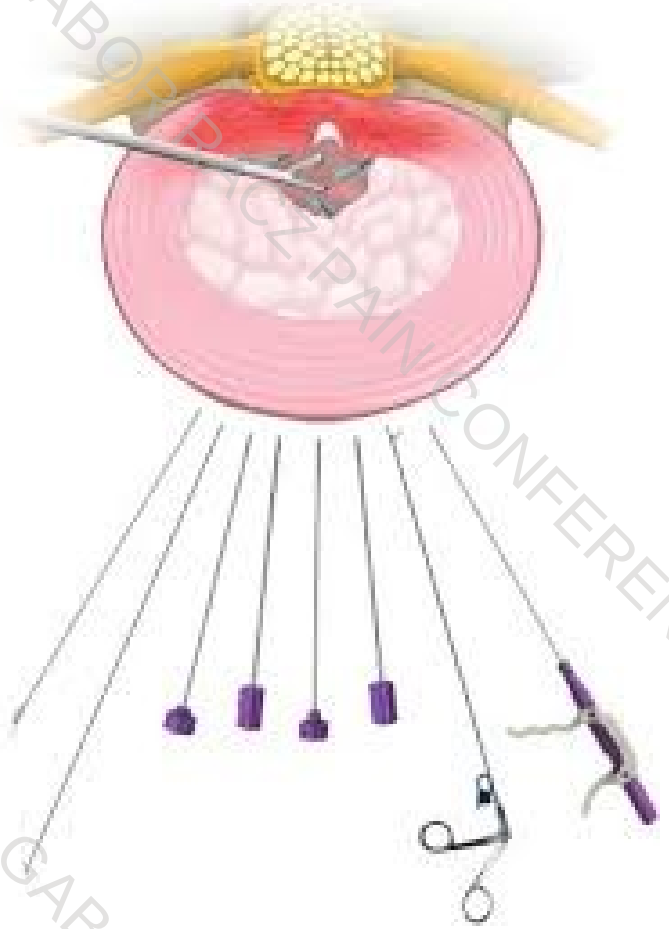
  - End Plates/Modic I and II Changes – Inflammatory response with microfractures

- **Chemical**:
  - The disc becomes more acidic due to degeneration, irritating the newly ingrown nerves and causing pain.



Traditional Treatments 2.0 Medicine

- Traditional approaches (Medicine 2.0):
  - Treatments like IDET, nucleoplasty, lumbar fusion, and disc arthroplasty, BVNA
- These treatments have a 50-60% success rate due to their failure to consider the complexity of the spinal anatomy and the overall health of the patient.



Dilemma 1!!

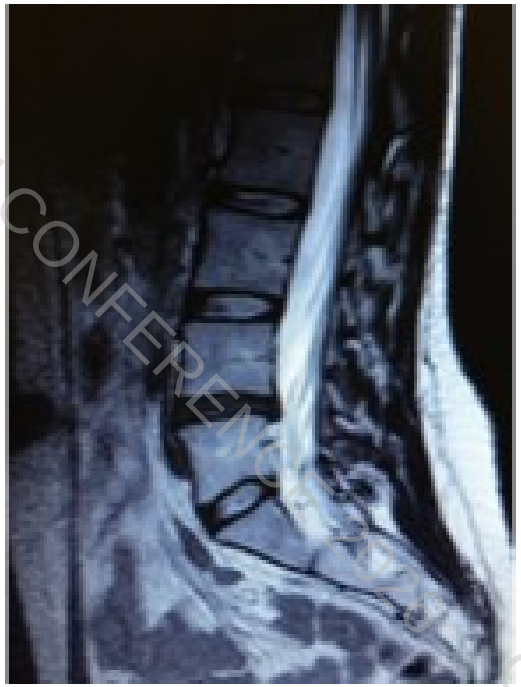
- A multifactorial disease treat how??
  - Treat the cause?
  - Treat Just the disc?
  - Inject what?

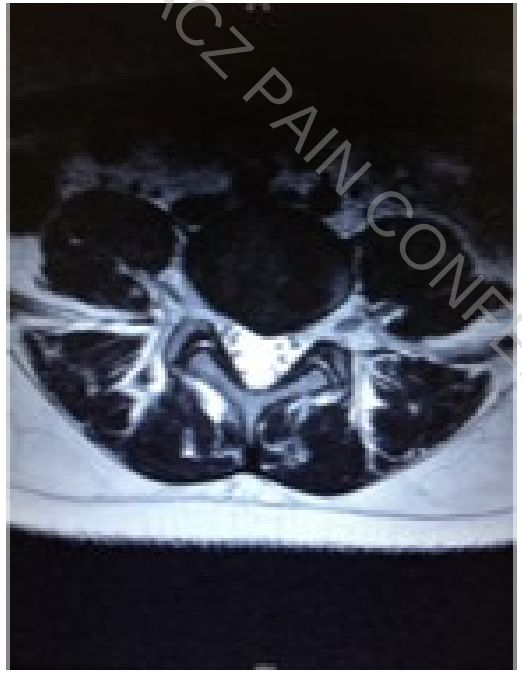
Dilemma 2!!

- We single out the disc! Ok!

- What kind of disc do we inject?
  - Anatomical Disc
  - Early degeneration/Late?

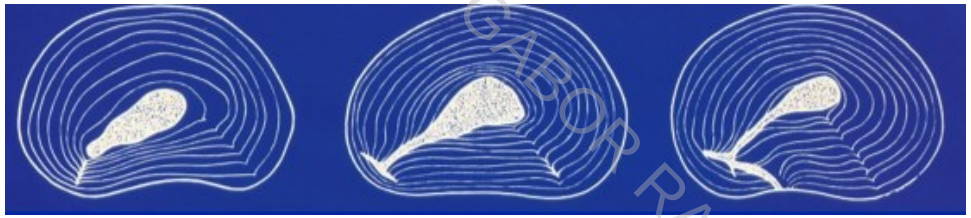
    - What disc height
    - Contained or not
    - Operated or not?

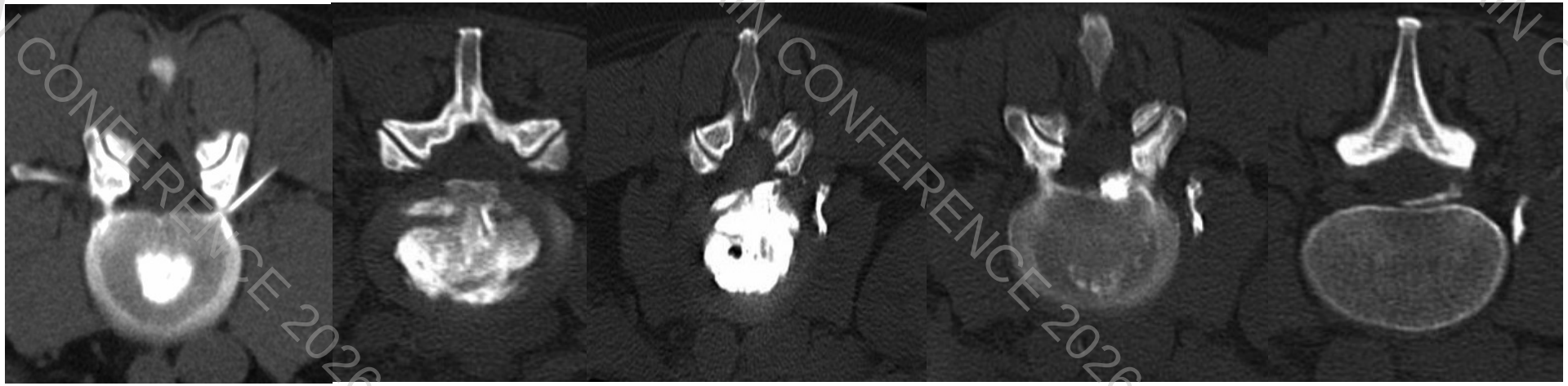




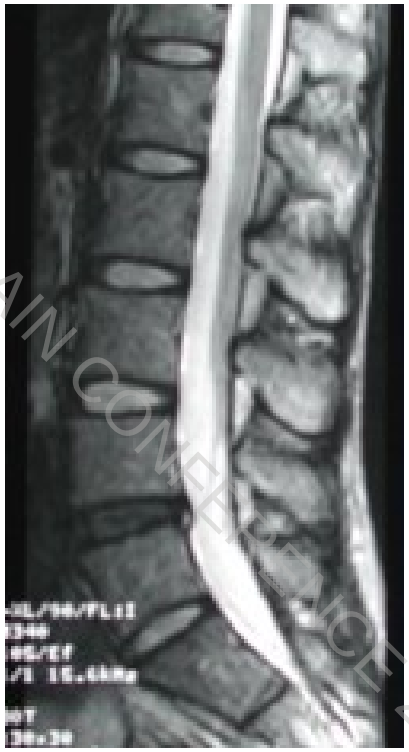
Dilemma 3!!

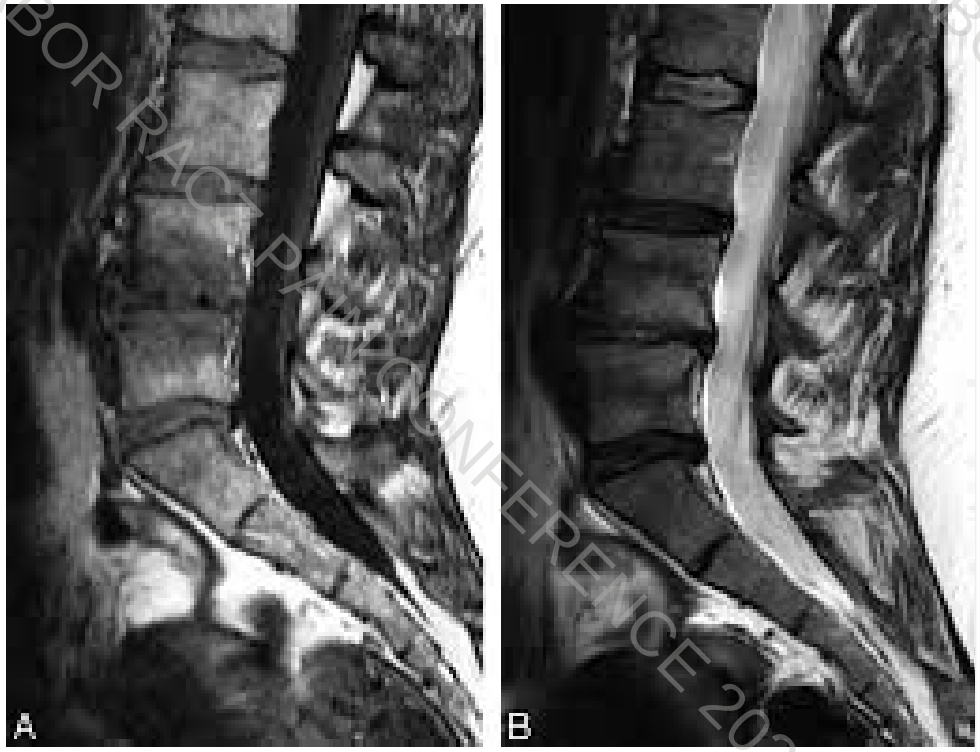
- Ok we focus on disc ONLY!
- What kind of disc do we inject?
  - Symptomatic or not?
  - Or Both?

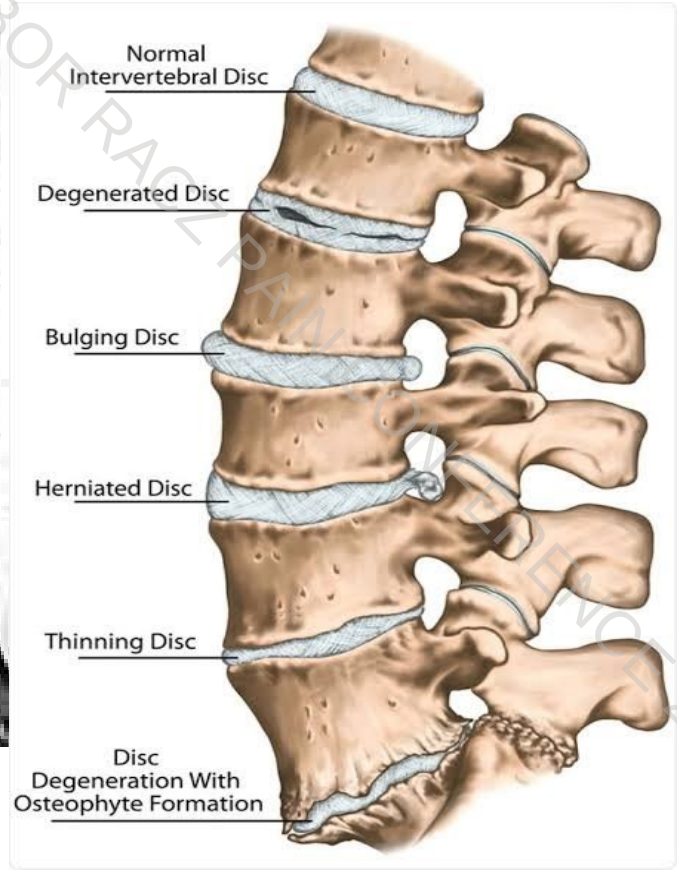




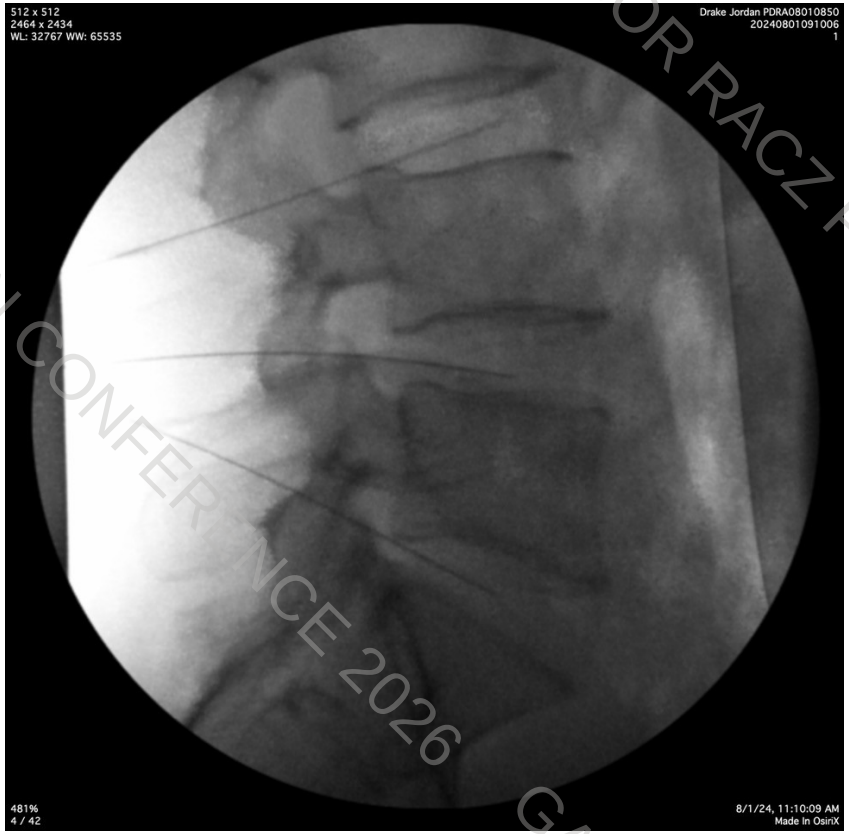
Which Disc is good for Mesenchymal cells?

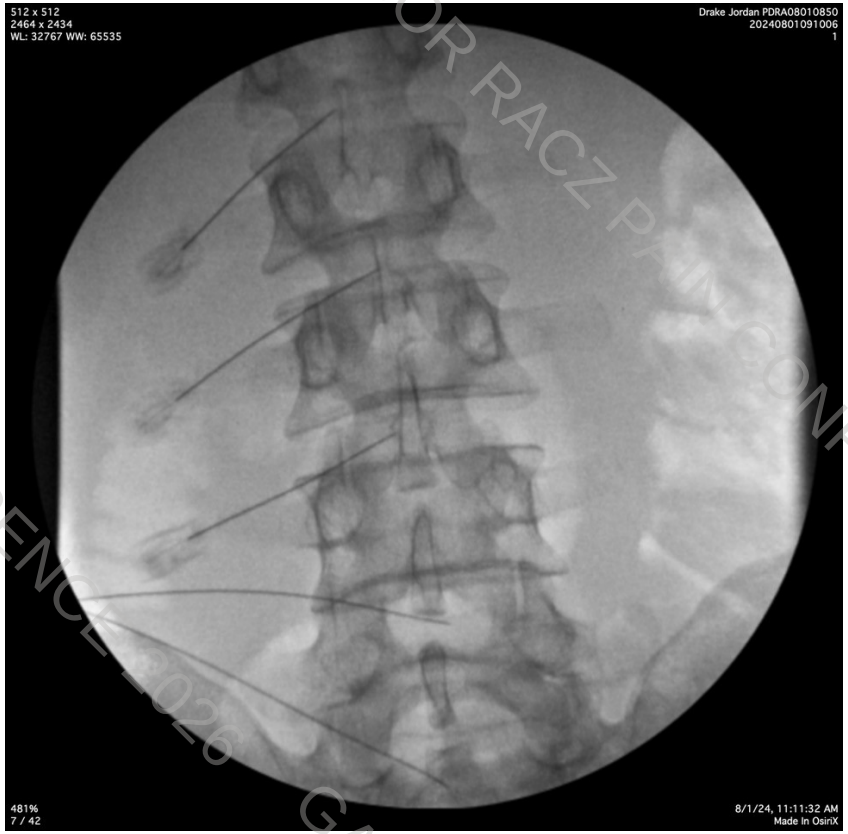






One thing is sure ... technique for one's is not a challange! :)





A major bottleneck: cell survival and retention

- Injected cells may be exposed to hypoxia, acidity, inflammatory mediators and mechanical stress.
- Poor retention can reduce the effective local dose.
- Survival is not equivalent to functional integration.
- Delivery vehicles are therefore becoming as important as the cell itself.

Why MSC injection alone may not be enough

MSC injection

+ biological signal

BUT

– limited retention
– no structural scaffold
– no restoration of lamellar architecture
– limited mechanical support

Scaffold / hydrogel

+ retention
+ defect filling
+ mechanical support

BUT

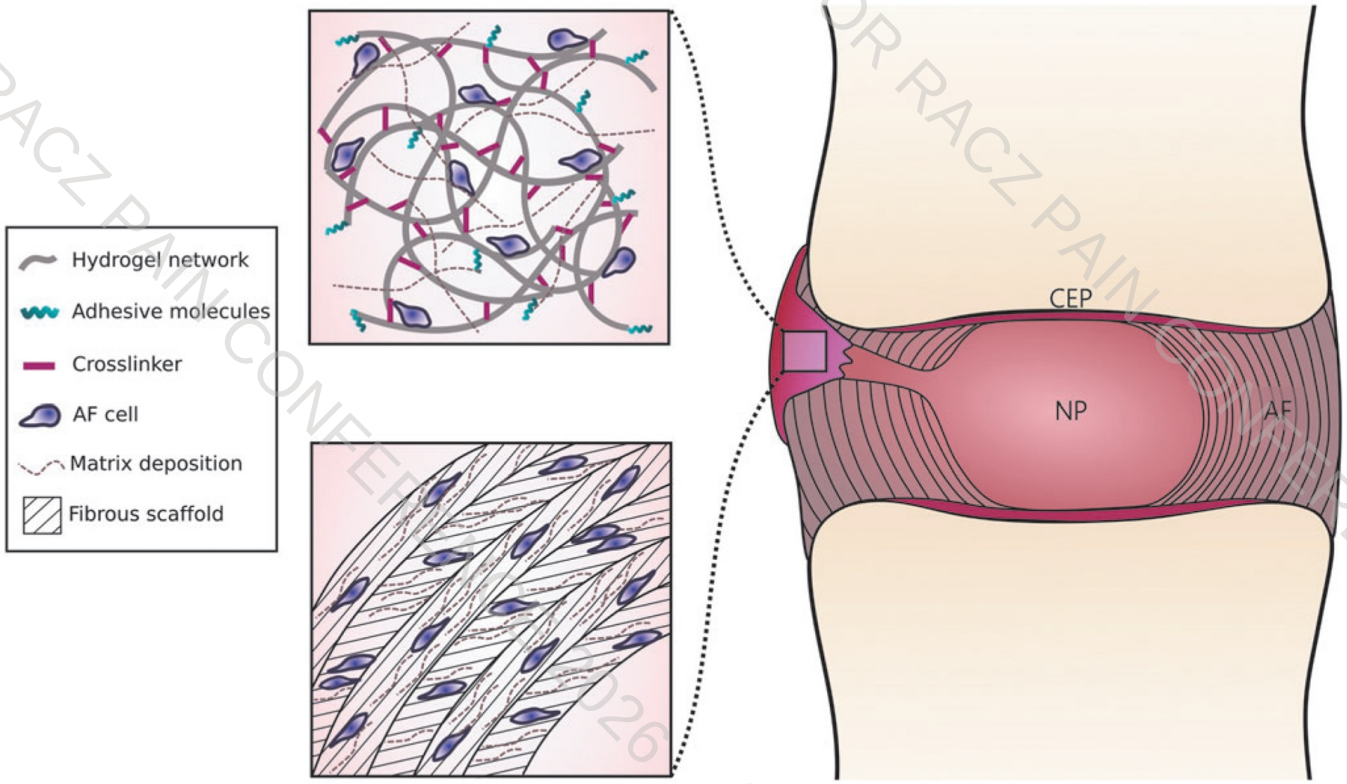
– may lack regenerative signals

Combination

MSC + biomaterial + bioactive cues

→ biological repair
→ structural integration
→ mechanical restoration

Emerging strategy: hydrogel–fibrous scaffolds



Hydrogel provides a hydrated 3D niche.

Fibrous scaffold guides cell alignment.

Adhesive cues can improve cell attachment.

Goal: reproduce the architecture and matrix environment of native AF.

Figure: PMC10799291

Strategy: biomaterial design must match the annulus

Design targets

High tensile integrity

Controlled elasticity

Porosity for cell migration

Strong tissue integration

Predictable degradation

Manufacturing approaches

Electrospinning

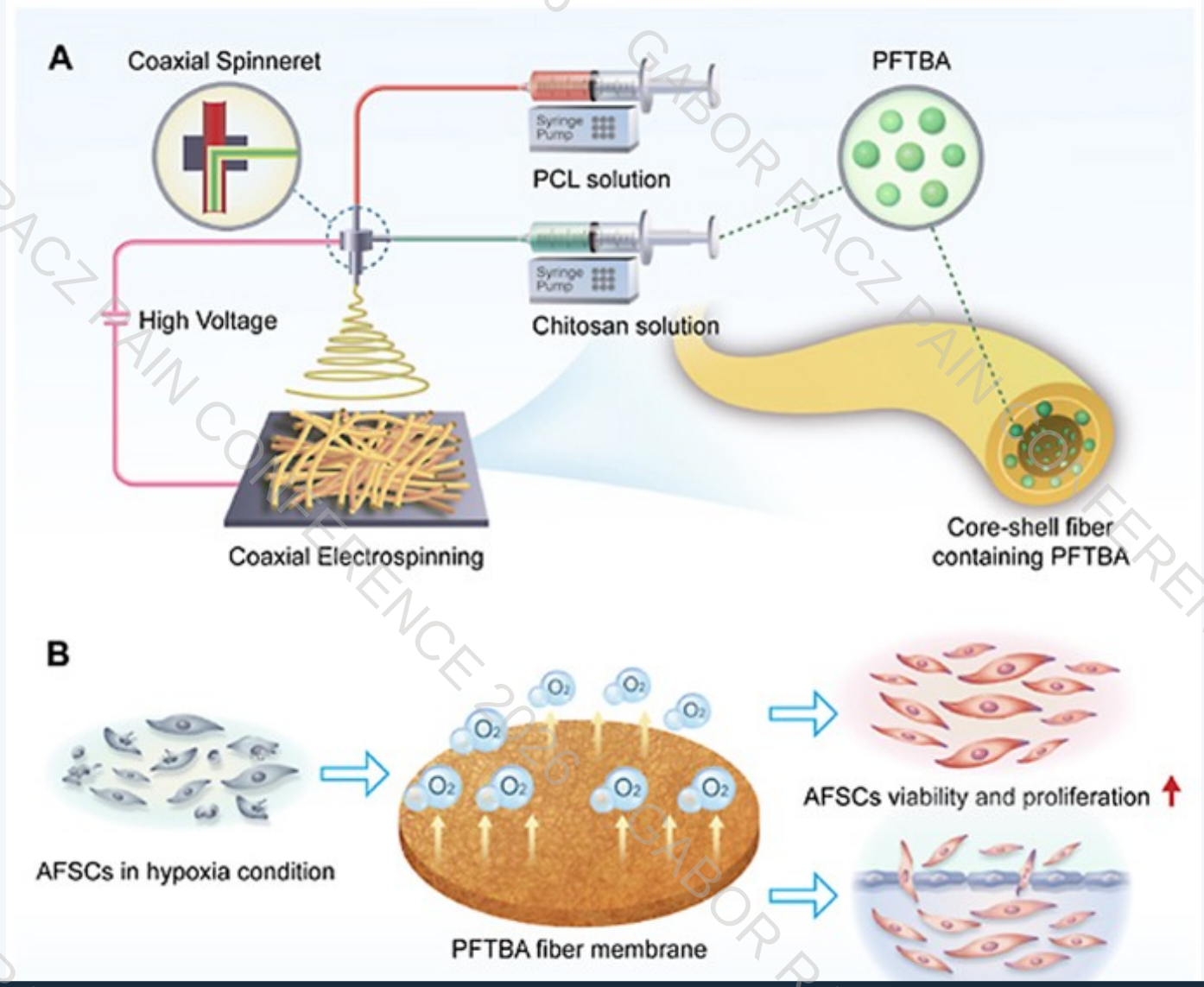
3D printing

Hybrid scaffolds

Injectable hydrogels

Composite fiber–gel systems

Strategy: engineer the microenvironment



Oxygen-releasing biomaterials are being explored to improve cell survival.

Preclinical work shows potential effects on viability, proliferation and migration.

Microenvironment engineering may be necessary before MSCs can perform effectively.

Figure: PMC9841168

Strategy: direct AF-like differentiation

Biochemical cues: growth factors and matrix-derived signals

Mechanical cues: controlled tension, compression and shear

Topographic cues: aligned fibers and anisotropic architecture

Goal: type I collagen-rich, organized AF-like matrix rather than nonspecific scar.

Strategy: cell-free MSC-derived products

Extracellular vesicles / exosomes

Carry proteins, lipids and regulatory RNAs

Potentially reproduce paracrine effects

Potentially easier to standardize than living cells

Remaining questions

Potency assay

Dose and delivery

Target tissue exposure

Manufacturing consistency

Long-term biological effect

Strategy: combination therapy

MSC

SCaffold

Growth factors

Exosomes

Mechanical conditioning

Integrated biologic–mechanical platform → cell survival + matrix formation + structural repair

Mechanical closure vs biological regeneration

Mechanical repair

Suture

Annular closure devices

AF patches

Immediate containment

Risk: incomplete biological integration

Biological repair

Cells / progenitors

Scaffolds + bioactive cues

Matrix regeneration

Potential long-term integration

Risk: slower and less predictable

The key concept: mechanical + biological repair

1
CONTAIN

Prevent nucleus extrusion and stabilize the defect

2
REGENERATE

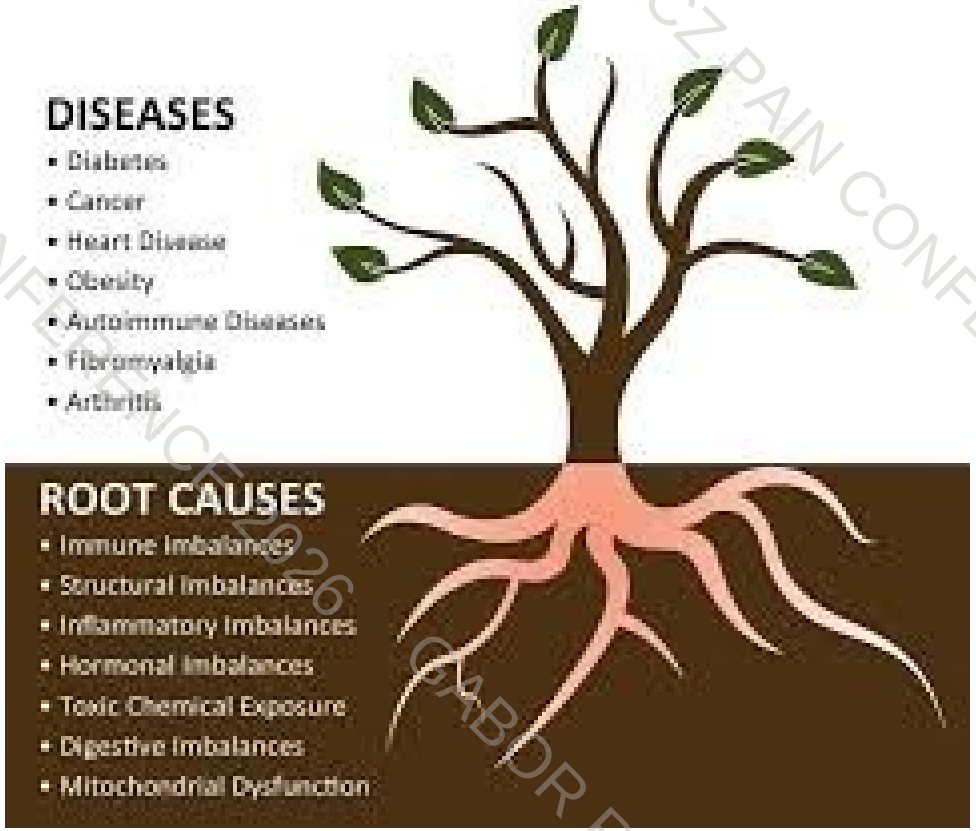
Replace damaged ECM and restore cell–matrix signaling

3
REMODEL

Restore organized lamellae and load transfer

Dilemma nr 4! The Biggest!

- We want to assess Medicine 3.0 by Medicine 2.0 standards!



Preclinical evidence: what looks promising?

Animal studies demonstrate improved defect closure, matrix deposition and disc structure with selected biomaterial/cell combinations.

Hybrid scaffolds are increasingly favored because they address both biological and mechanical requirements.

However, animal defect size, disc geometry and outcome measures vary substantially between studies.

Song et al., Prog Biomed Eng, 2026

Dilemma nr. 5! What should a successful annular repair actually measure?

STRUCTURE
MRI / histology / defect closure

BIOLOGY
ECM composition / inflammation

MECHANICS
Stiffness / load transfer / energy dissipation

CLINICAL
Pain / ODI / function

DURABILITY
Reherniation / reoperation / long-term MRI

Human clinical evidence: promising, but heterogeneous

Clinical trials of intradiscal MSC therapy have generally focused on degenerative disc disease and discogenic low back pain

Symptom improvement has been reported in several studies

Structural MRI changes are less consistent

Evidence specifically for defined AF tears or post-discectomy annular defects remains much more limited.

Medicine 2.0 - DREAM study: an important reality check

RANDOMIZED
DOUBLE-BLIND
PHASE IIB

MSC vs SHAM

Moderate–advanced multilevel degeneration

Main message

Safe / feasible, but no clear clinical superiority over sham at the primary follow-up

Important implication: biological plausibility does not guarantee clinical efficacy.

Patient selection, disease stage, cell product, dose and endpoint choice may determine success.

Annular repair may require a more mechanically targeted strategy than intradiscal cell injection alone.

DREAM Study, J Spine Surg, 2025

Who might be the ideal patient?

Potential candidate

Contained annular defect

Early–moderate degeneration

Discogenic pain phenotype

Preserved segmental stability

Failure of appropriate conservative care

Poor candidate / caution

Severe collapse

Major instability

Severe stenosis needing decompression

Large uncontained extrusion

Advanced facet-driven pain

Post-discectomy annular repair: a particularly attractive target

Discectomy removes the herniated fragment but may leave a structural defect in the annulus.

An ideal repair would seal the defect, integrate with native tissue and tolerate physiologic loading.

Adding regenerative cells or cell-derived products could potentially convert a passive closure into an active biologic repair.

Clinical trials specifically targeting post-discectomy defects are needed.

Could biologic annular repair reduce recurrent herniation?

DISCECTOMY

ANNULAR DEFECT

REPAIR

Hypothesis: stronger biologic integration may improve containment and reduce recurrence.

But recurrence prevention requires mechanical competence, not just MRI appearance.

Large, well-designed comparative trials are needed before this becomes a clinical standard.

Safety and regulatory considerations

Cell identity, potency and manufacturing consistency must be defined.

Risks include infection, inflammatory reactions, ectopic tissue formation and unexpected biologic effects.

Long-term follow-up is essential because disc regeneration is intended to be durable.

Cell-free products may simplify some manufacturing issues but introduce their own potency and dosing challenges.

A future clinical pathway

PHENOTYPE
Pain generator + degeneration stage

CHARACTERIZE
Defect morphology + containment

SELECT
Cell / vesicle / scaffold platform

DELIVER
Image-guided defect-targeted therapy

PROTECT
Early mechanical unloading / rehab

MONITOR
Clinical + MRI + mechanical endpoints

Selected references — 2025–2026

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Crosslinking stabilization strategy for AF defects with hBMSCs and hydrogel. Materials Today Bio. 2025;31:101625.

Zhao W, et al. Application of Endogenous Stem Cells in the Repair of Annulus Fibrosus Injury. 2025.

Lv S, et al. Mesenchymal stem cell-derived extracellular matrix for musculoskeletal tissue regeneration. Commun Biol. 2026.

Key visual sources used in the presentation

Goodman Campbell Spine Anatomy — intervertebral disc anatomy illustration.

PMC10799291 — hydrogel–fibrous scaffold schematic for disc repair.

PMC9841168 — oxygen-releasing core–shell fibers for annulus fibrosus repair.

Figures are used here for educational presentation purposes; retain the source attribution when presenting publicly.

Take home message 1

- MSC therapy is biologically compelling, but annular repair is fundamentally a mechanical + biological problem.
- The future is likely to involve integrated cell–material–molecule platforms.
- Clinical symptom improvement is more established than structural regeneration.
- Mechanical competence and durability should be central endpoints.
- Targeted post-discectomy annular repair may be one of the most clinically relevant applications.

Take home message 2

- Regenerative Medicine treats not just the disc but also all supporting ligamentous structures.

- Typically, the treatment focuses on multiple segments above and below the problem area, including the ligamentum flavum, interspinous and supraspinous ligaments, facet joints, and sacroiliac joints.

Conclusions we don't like

- Regenerative Medicine offers a holistic approach to treating lumbar pain by addressing both the spinal anatomy and patient health.
- Success requires careful patient selection, precise diagnosis, and proper delivery of regenerative solutions.
- The success of this treatment is not measured just in short term relief of pain but also in terms of prevention of re-occurrence.
- **Evidence base medicine is hard to find in Medicine 3.0 – it is rather a concept that the patient needs to assume and take charge of himself**
- **Regenerative medicine alone is not the Holly Grail! You need a full integrated approach with significant life style changes**

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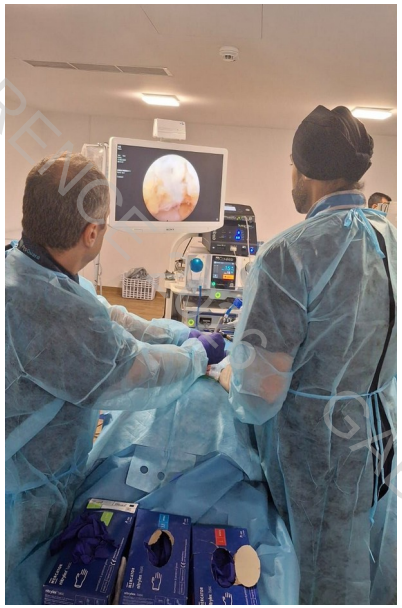

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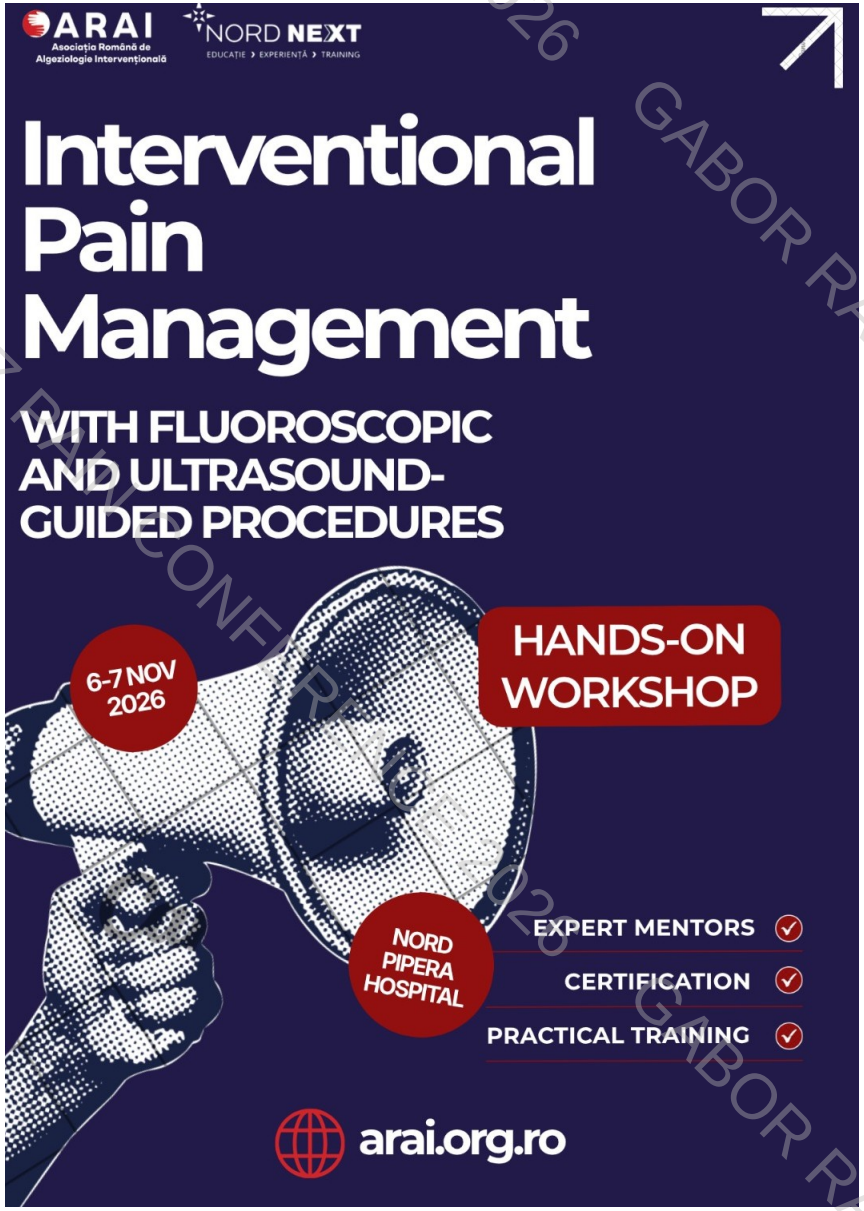

Thank you!

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