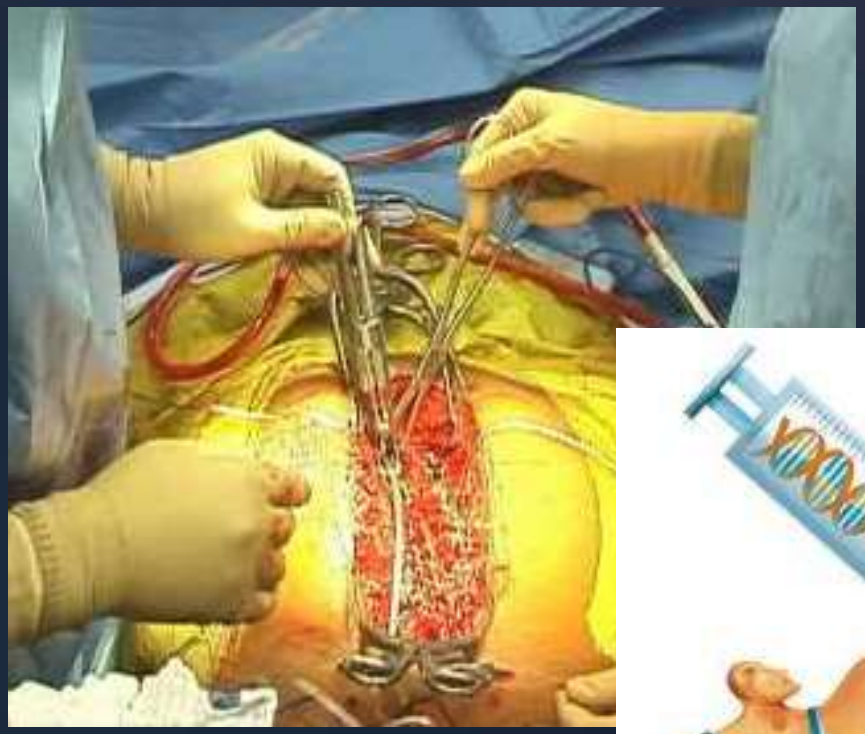
FUTURE BIOLOGICS IN SPINE

Wayne Cheng, MD

Bones and Spine

What Do Patients want:

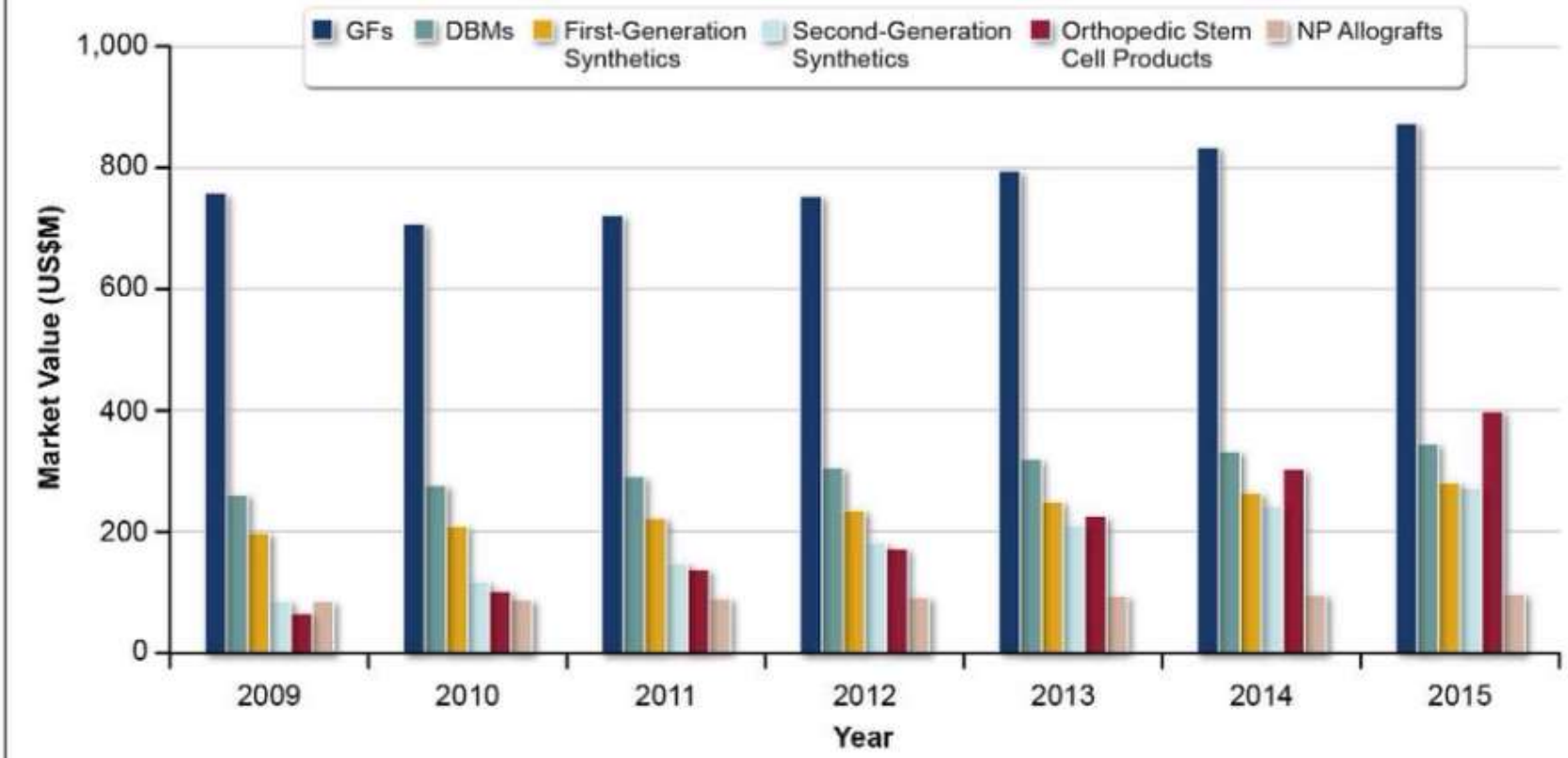


OUTLINE

- ***FUSION BIOLOGICS***
  - BMP
  - MESENCHYMAL STEM CELL
  - NANOSTRUCTURES
- ***DISC REGENERATION***
  - ANTICATABOLICS
  - GROWTH FACTORS
  - STEM CELLS

Where is Market going?

Figure 9: BGS Market, by Material, US (US$), 2009–2015



BMP - Advantages

- 2002
- "It works"

A Prospective, Randomized, Controlled Cervical Fusion Study Using Recombinant Human Bone Morphogenetic Protein-2 With the CORNERSTONE-SR™ Allograft Ring and the ATLANTIS™ Anterior Cervical Plate

David S. Baskin, MD,*† Patrick Ryan, MD,‡ Volker Sonntag, MD,§ Richard Westmark, MD,‖ and Marsha A. Widmayer, MA*

Study Design. A prospective, randomized, pilot clinical trial compared recombinant human bone morphogenetic protein-2 (rhBMP-2) with iliac crest autograft bone for the treatment of human cervical disc disease.

Objective. To examine the safety and effectiveness of using INFUSE™ Bone Graft (rhBMP-2 applied to an absorbable collagen sponge), as compared with an autogenous iliac crest bone graft placed inside the CORNERSTONE-SR™ fibular allograft, in anterior cervical discectomy and interbody fusion.

Summary of Background Data. Recombinant human bone morphogenetic protein-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but it has not been studied in patients with degenerative cervical disc disease.

Methods. For this study, 33 patients with degenerative cervical disc disease were randomly assigned to investigational or control groups. The investigational group received a fibular allograft (CORNERSTONE-SR™ Allograft Ring) with an rhBMP-2-laden collagen carrier inside the graft along with an ATLANTIS™ anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside it, along with an ATLANTIS anterior cervical plate. The patients underwent plain radiographs at 6 weeks, then at 3, 6, 12, and 24 months, and CT scans at 3 and 6 months after surgery. They also completed general health profiles and self-evaluation scales. Adverse events were evaluated for severity, duration, association with the implant, and the need for a second surgical procedure.

Results. All the patients evaluated had solid fusions 6, 12, and 24 months after surgery. There were no device-related adverse events. At 24 months, the investigational group had mean improvement superior to that of the control group in neck disability and arm pain scores ($P < 0.03$ each).

Conclusions. This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine. [Key words: allograft, anterior cervical fusion, anterior cervical plating, bone morphogenetic protein, osteoinduction, radiography] **Spine 2003;28:1219–1225**

From the Departments of *Neurosurgery and †Anesthesiology, Baylor College of Medicine, and Veterans Affairs Medical Center, Houston, Texas, ‡Jackson Hospital, Montgomery, Alabama, §Division of Neurological Surgery, Barrow Neurological Institute, and St. Joseph's Hospital and Medical Center, Phoenix, Arizona, and ‖Clear Lake Regional Medical Center, Webster, Texas.

Sponsored by Medtronic Sofamor Danek.

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The devices and drugs described in this article are being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) or a corresponding national protocol for assessment of safety and effectiveness, as compared with a control implant in the treatment of patients with one level or two adjacent levels of cervical symptomatic degenerative disc disease. The objectives of the protocol are to demonstrate that the surgical treatment of degenerative disc disease with the investigational implant is at least as safe and effective as that of a control implant.

Corporate and industry funds were received to support this work. Although one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript, benefits will be directed solely to a research fund, foundation, educational institution, or other nonprofit organization with which the authors have been associated.

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Anterior cervical discectomy and fusion is an effective and extensively practiced treatment for degenerative cervical disc disease. Smith and Robinson[1] and Cloward[2] first described the technique in the 1950s. Initially, autogenous bone, typically harvested from the iliac crest, was used for the interbody graft. The procedure has developed to include alternatives to autograft. Allograft and interbody fusion devices avoid the pain, scarring, and morbidity associated with autograft harvest, yet maintain high fusion rates. Anterior cervical plating has become an accepted component of the procedure because it has been shown to provide immediate stability, maintain sagittal alignment, and increase the fusion rate.[3,4]

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to initiate osteoinduction and achieve spinal arthrodesis in a nonhuman primate model.[5,6] The application of rhBMP-2 in humans has been explored in a lumbar fusion indication. Human clinical studies have demonstrated that patients treated with rhBMP-2 soaked onto an absorbable collagen sponge and placed into the central cavity of the LT-CAGE™ Lumbar Tapered Fusion Device had consistent and clear osteoinduction.[7,8]

The use of rhBMP-2 in an anterior cervical fusion application was previously unexplored. The authors took part in a prospective, randomized, controlled clin-

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD,* Ensor E. Transfeldt, MD ,† Scott H. Kitchel, MD,‡ Robert G. Watkins, MD,§ and Richard A. Balderston, MD‖

uman Bone Morphogenetic
osterolateral Lumbar Spine

Clinical Pilot Trial
al Studies

, Harvinder Sandhu, MD, and John G. Heller, MD

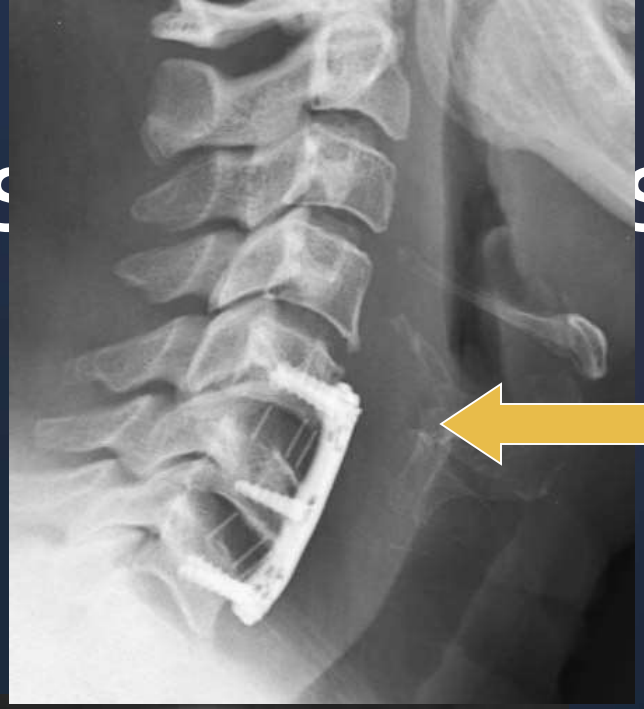
the posterolateral lumbar spine when delivered at a dose of 20 mg per side with or without the use of internal fixation. Patients with spondylolisthesis classified higher than Meyerding Grade 1 or with more than 5 mm of translational motion may still require internal fixation. Some patients did smoke during the postoperative period, and all in the rhBMP-2 groups still obtained solid fusions.

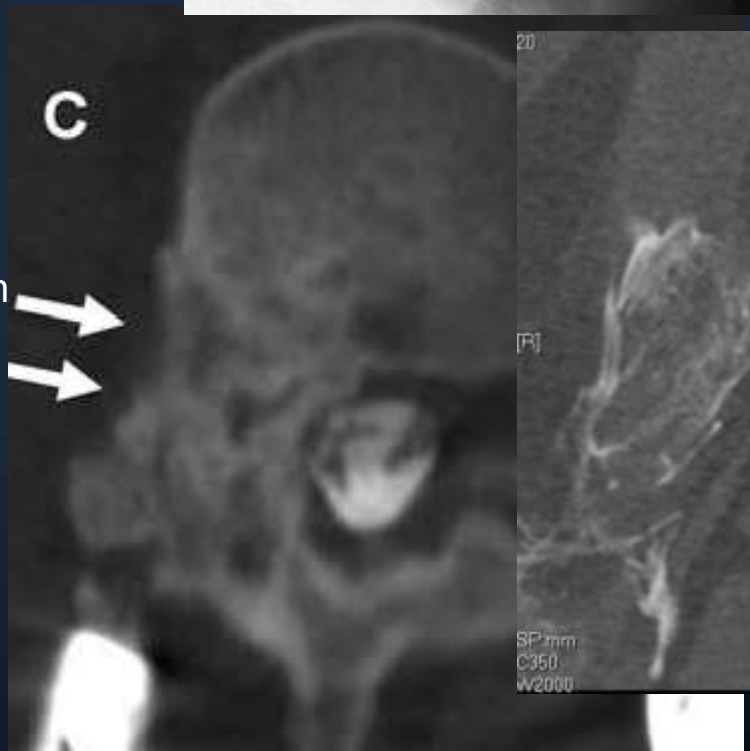
Conclusions. Consistently, rhBMP-2 with the biphasic calcium phosphate granules induced radiographic posterolateral lumbar spine fusion with or without internal fixation in patients whose spondylolisthesis did not exceed Grade 1. Statistically greater and quicker improvement in patient-derived clinical outcome was measured in the rhBMP-2 groups. [Key words: bone morphogenetic protein-2, calcium phosphate, clinical trial, spine fusion] **Spine 2002;27:2662–2673**

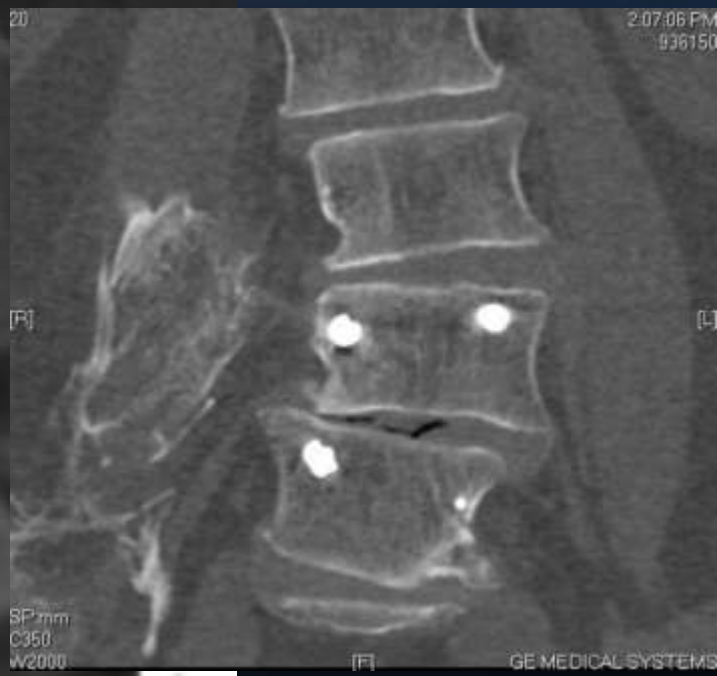
The two primary drawbacks in performing a spinal ar-

BMP - Dis s

- Cost
- Complication
  - Death
  - Radiculitis
  - Seroma
  - Antibody
  - Ectopic bone
  - Osteoclastic resorption
- Medical Legal
- Cancer?





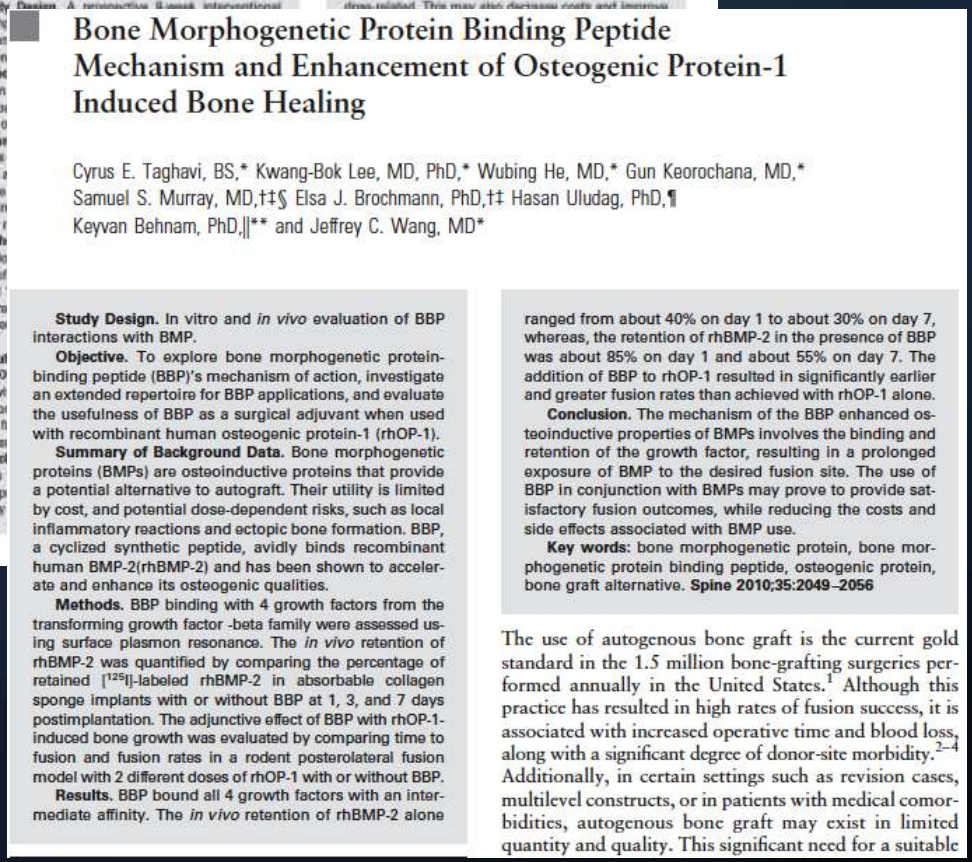


Future of BMP – Faster/higher LESS DOSAGE!

- BBP (BMP binding peptide)
- Retention of bmp2
  - Day 1 (40 to 85%)
  - Day 7 (30 to 55%)
- Decrease dosage?

The Adjunctive Effect of a Binding Peptide on Bone Morphogenetic Protein Enhanced Bone Healing in a Rodent Model of Spinal Fusion

Ahmet Alanay, MD,* ChiHui Chen, MD,† Sang Lee, MD,† Samuel S. Murray, MD,‡§¶ Elsa J. Brochmann, MD, PhD,‡§¶ Masashi Miyazaki, MD,† Antonia Napoli, MD,† and Jeffrey C. Wang, MD†



Bone Morphogenetic Protein Binding Peptide Mechanism and Enhancement of Osteogenic Protein-1 Induced Bone Healing

Cyrus E. Taghavi, BS,* Kwang-Bok Lee, MD, PhD,* Wubing He, MD,* Gun Keorochana, MD,* Samuel S. Murray, MD,†‡§ Elsa J. Brochmann, PhD,†‡ Hasan Uludag, PhD,¶ Keyvan Behnam, PhD,‖** and Jeffrey C. Wang, MD*

Study Design. In vitro and *in vivo* evaluation of BBP interactions with BMP.

Objective. To explore bone morphogenetic protein-binding peptide (BBP)'s mechanism of action, investigate an extended repertoire for BBP applications, and evaluate the usefulness of BBP as a surgical adjuvant when used with recombinant human osteogenic protein-1 (rhOP-1).

Summary of Background Data. Bone morphogenetic proteins (BMPs) are osteoinductive proteins that provide a potential alternative to autograft. Their utility is limited by cost, and potential dose-dependent risks, such as local inflammatory reactions and ectopic bone formation. BBP, a cyclized synthetic peptide, avidly binds recombinant human BMP-2(rhBMP-2) and has been shown to accelerate and enhance its osteogenic qualities.

Methods. BBP binding with 4 growth factors from the transforming growth factor -beta family were assessed using surface plasmon resonance. The *in vivo* retention of rhBMP-2 was quantified by comparing the percentage of retained [^{125}I]-labeled rhBMP-2 in absorbable collagen sponge implants with or without BBP at 1, 3, and 7 days postimplantation. The adjunctive effect of BBP with rhOP-1-induced bone growth was evaluated by comparing time to fusion and fusion rates in a rodent posterolateral fusion model with 2 different doses of rhOP-1 with or without BBP.

Results. BBP bound all 4 growth factors with an intermediate affinity. The *in vivo* retention of rhBMP-2 alone ranged from about 40% on day 1 to about 30% on day 7, whereas, the retention of rhBMP-2 in the presence of BBP was about 85% on day 1 and about 55% on day 7. The addition of BBP to rhOP-1 resulted in significantly earlier and greater fusion rates than achieved with rhOP-1 alone.

Conclusion. The mechanism of the BBP enhanced osteoinductive properties of BMPs involves the binding and retention of the growth factor, resulting in a prolonged exposure of BMP to the desired fusion site. The use of BBP in conjunction with BMPs may prove to provide satisfactory fusion outcomes, while reducing the costs and side effects associated with BMP use.

Key words: bone morphogenetic protein, bone morphogenetic protein binding peptide, osteogenic protein, bone graft alternative. **Spine 2010;35:2049–2056**

The use of autogenous bone graft is the current gold standard in the 1.5 million bone-grafting surgeries performed annually in the United States.[1] Although this practice has resulted in high rates of fusion success, it is associated with increased operative time and blood loss, along with a significant degree of donor-site morbidity.[2–4] Additionally, in certain settings such as revision cases, multilevel constructs, or in patients with medical comorbidities, autogenous bone graft may exist in limited quantity and quality. This significant need for a suitable

Bmp-Reduce dose

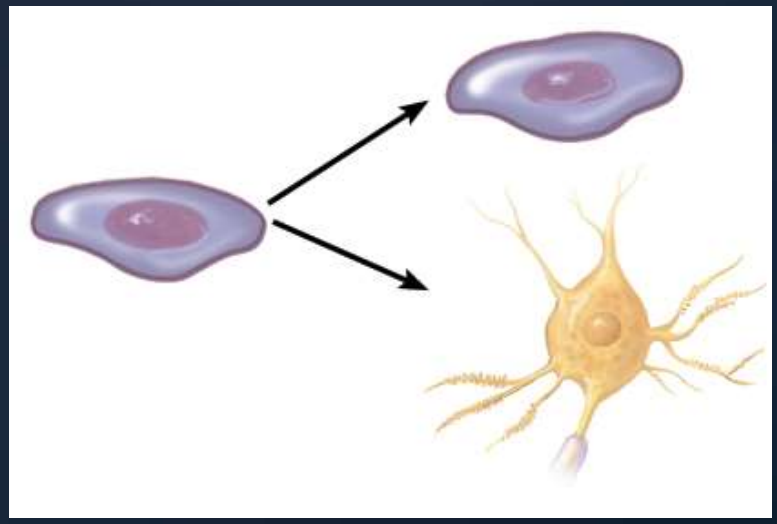
- Adding DBM
- SAS11. R. Delamarter.

STEM CELLS

- NIH REPORT 2001
- BY RUTH KIRSCHSTEIN MD.

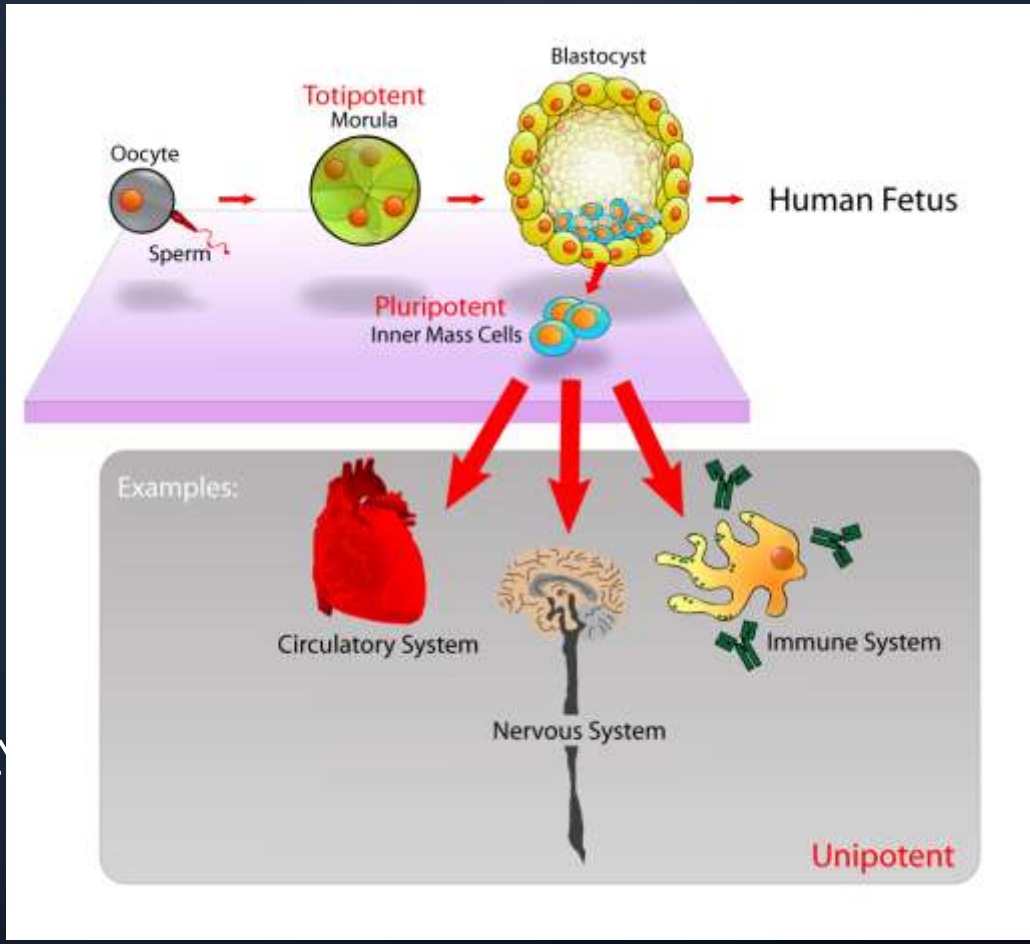
What is Stem cell?

- **Self-renewal**: Cells capable of making identical copies
- **Differentiation**: Give rise to specialized cell

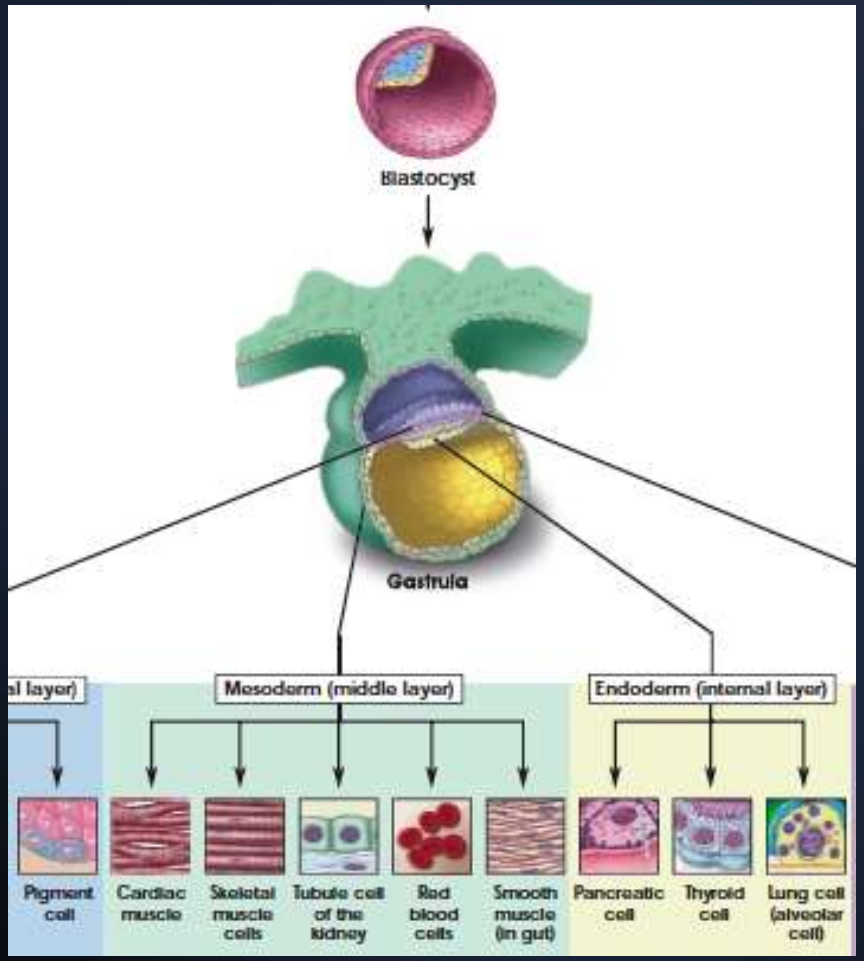


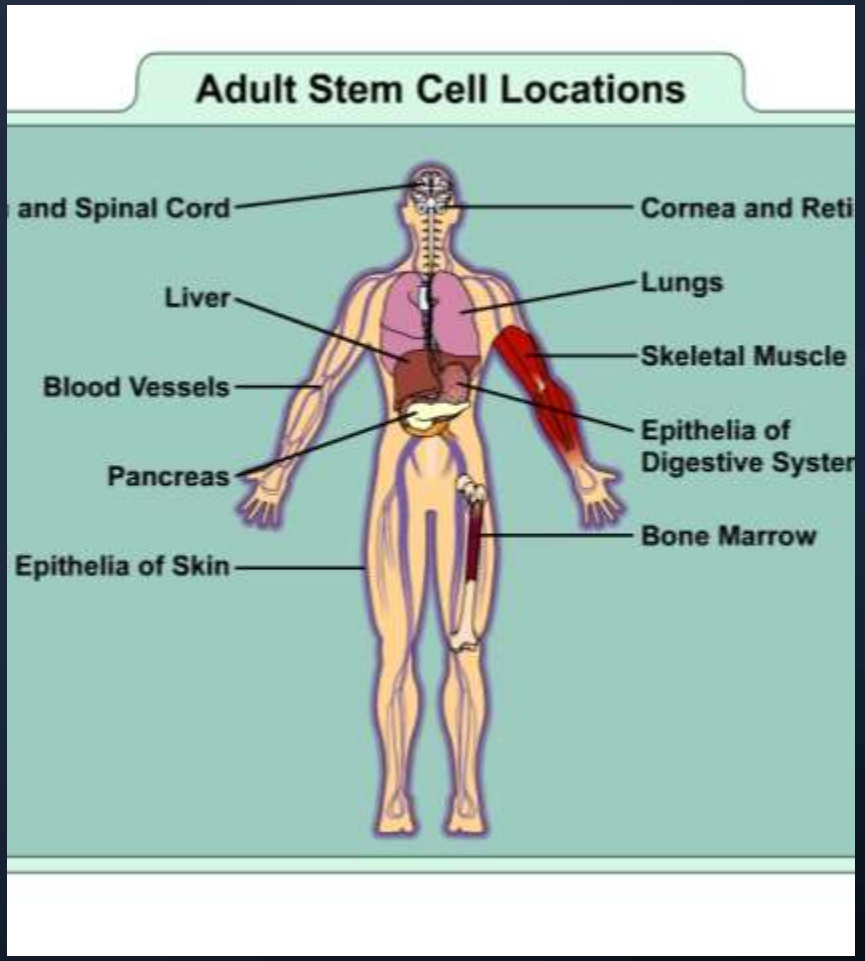
POTENCY DEFINITIONS

- ***TOTIPOTENT***
  - DIFFERENTIATE INTO ALL CELL TYPE
- ***PLURIPOTENT***
  - THREE GERM LAYERS
- ***MULTIPOTENT***
  - CLOSEDLY RELATED FAMILY OF CELLS

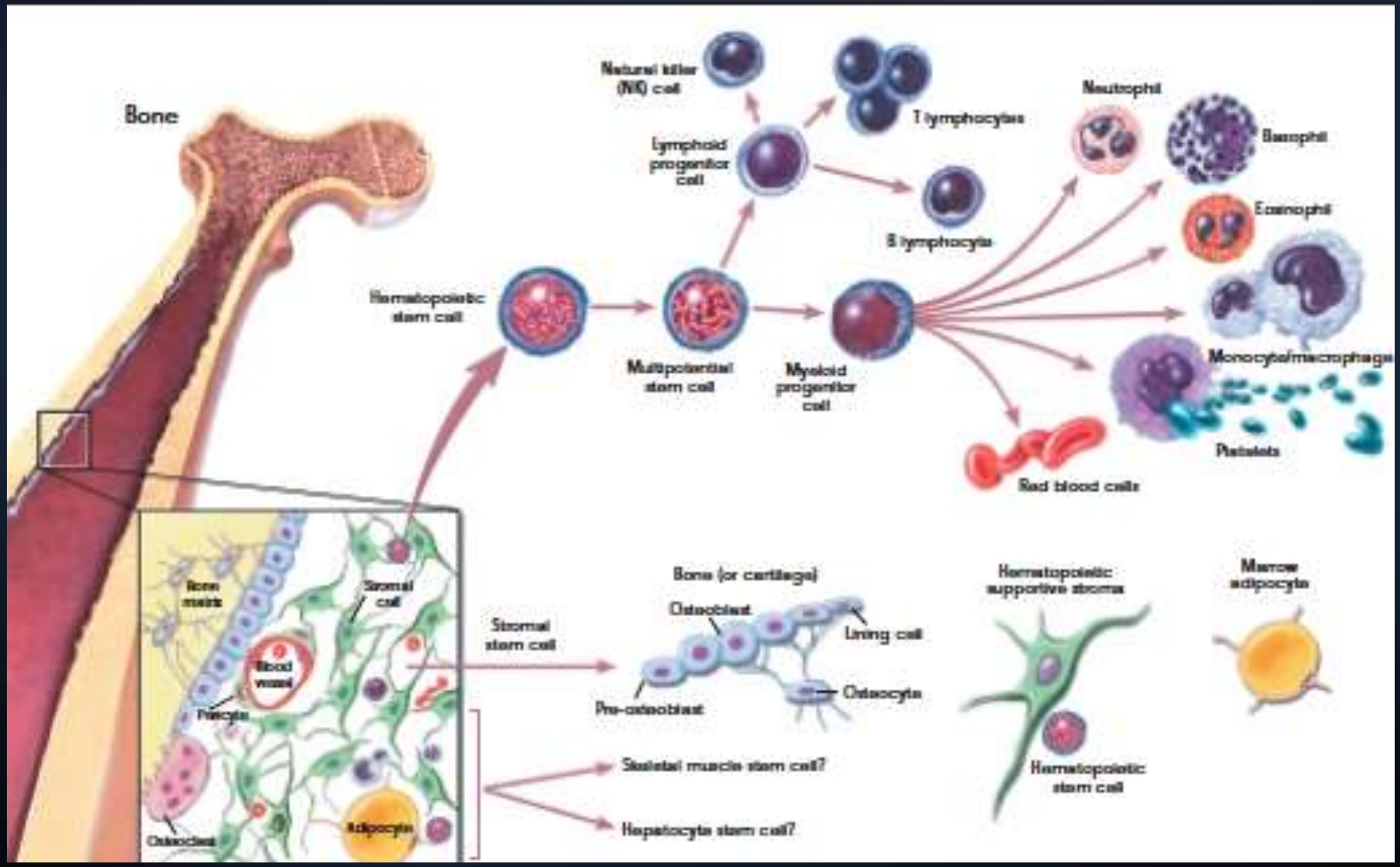


EMBRYONIC Vs. ADULT STEM CELL

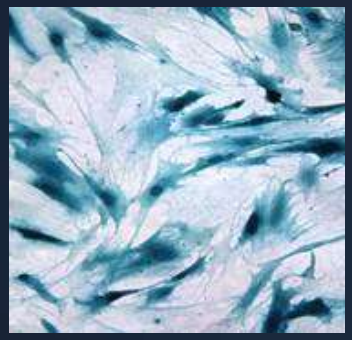




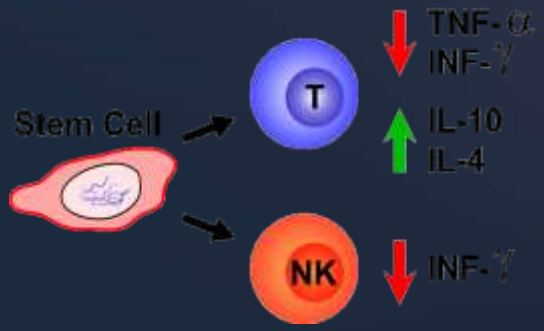
Adult Stem Cells (bone Marrow)



Mesenchymal Stem Cell (Stromal Stem Cells) Properties

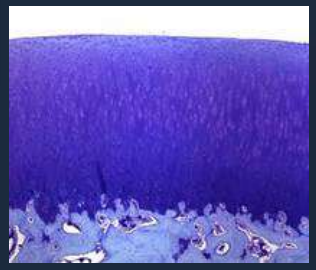


Mesenchymal Stem Cell



Cytokine Factories

- Cytokine Production
- Regulate immune system
- Growth Factor Production



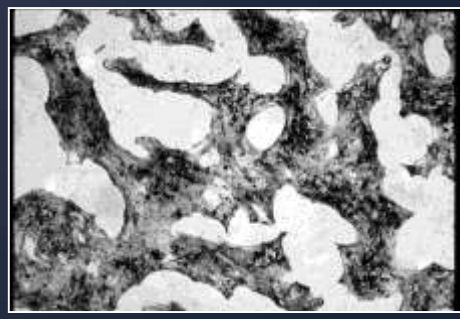
Multipotential

- Regenerate Tissue
- Bone, Cartilage, Tendon, etc.

Multilineage potential of adult human mesenchymal stem cells. *Science 1999, 284:143-147.*

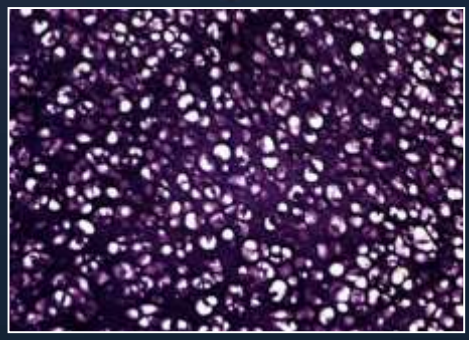
Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR:

10% FBS
dexamethasone
ascorbate 2-P
β-GP



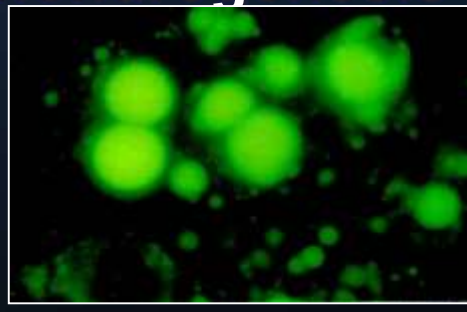
Osteogenesis

ITS+
dexamethasone
TGF-β
ascorbate 2-P



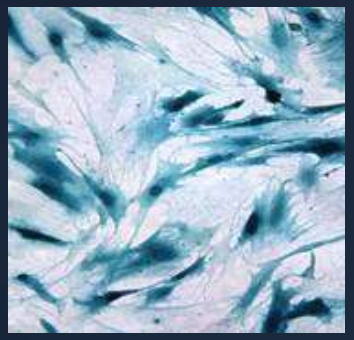
Chondrogenesis

10% FBS
dexamethasone
insulin
IBMX
indomethacin

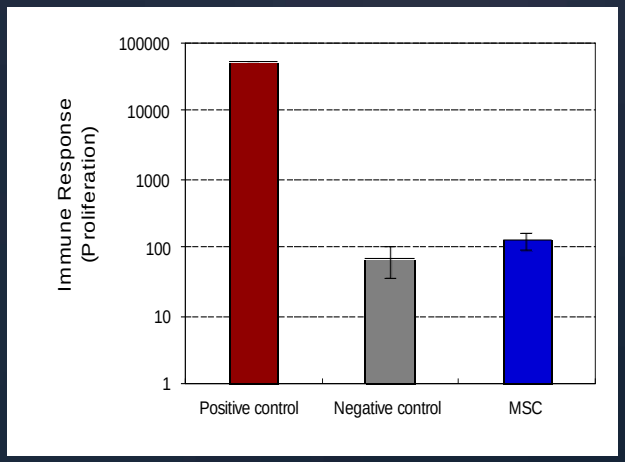


Adipogenesis

Mesenchymal Stem Cell Properties



Mesenchymal Stem Cell



Immune privileged

- **Absence of Class II antigens & co-stim. molecules**
- **No HLA matching required for allogeneic use**

MSC Process

Harvest bone marrow from young donors

- Highly selective of donors
- Immediate processing

Depletion of HSC (cd45+)

- Preserve MSC
- Preserve osteoprogenitor cells

Cryopreservation

- -80C
- -180C

Evidence ?

After 30,000 -

35,000

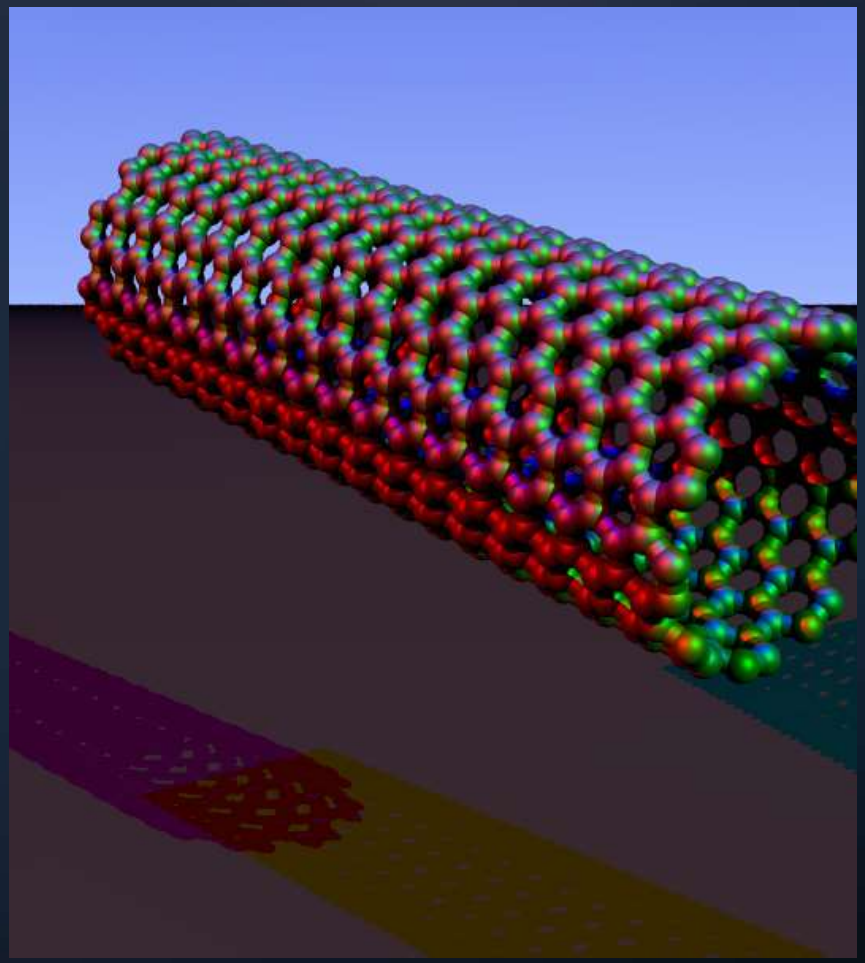
patients

Clinical Trials

- ***TRINITY EVOLUTION***
  - ACDF
- ***OSTEOCEL PLUS***
  - XLIF
  - ALIF

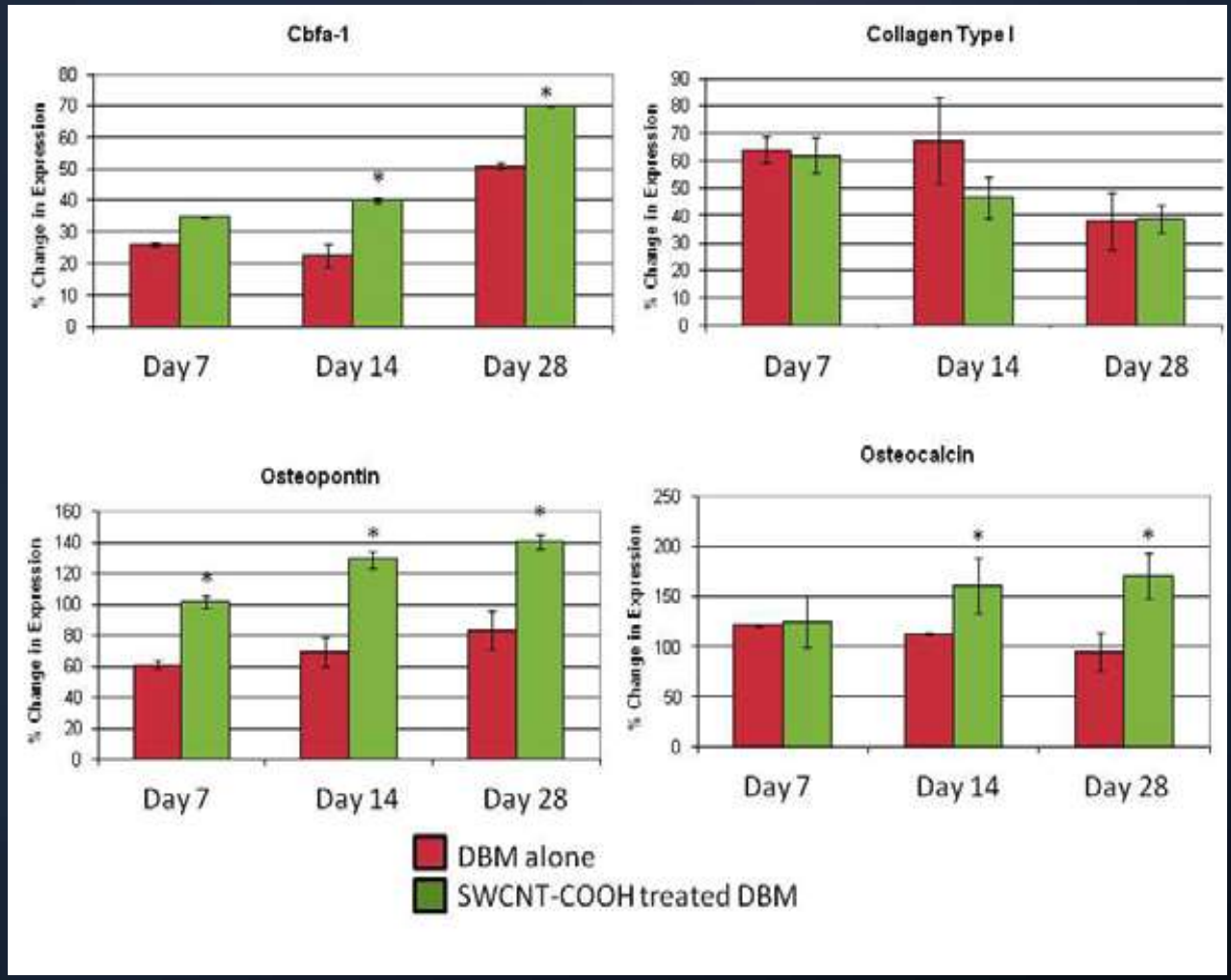
CARBON NANOTUBES

- ALLOTROPES OF CARBON
- STRONGEST MATERIAL KNOWN
- LENGTH : DIAMETER
  - 132 BILLION : 1



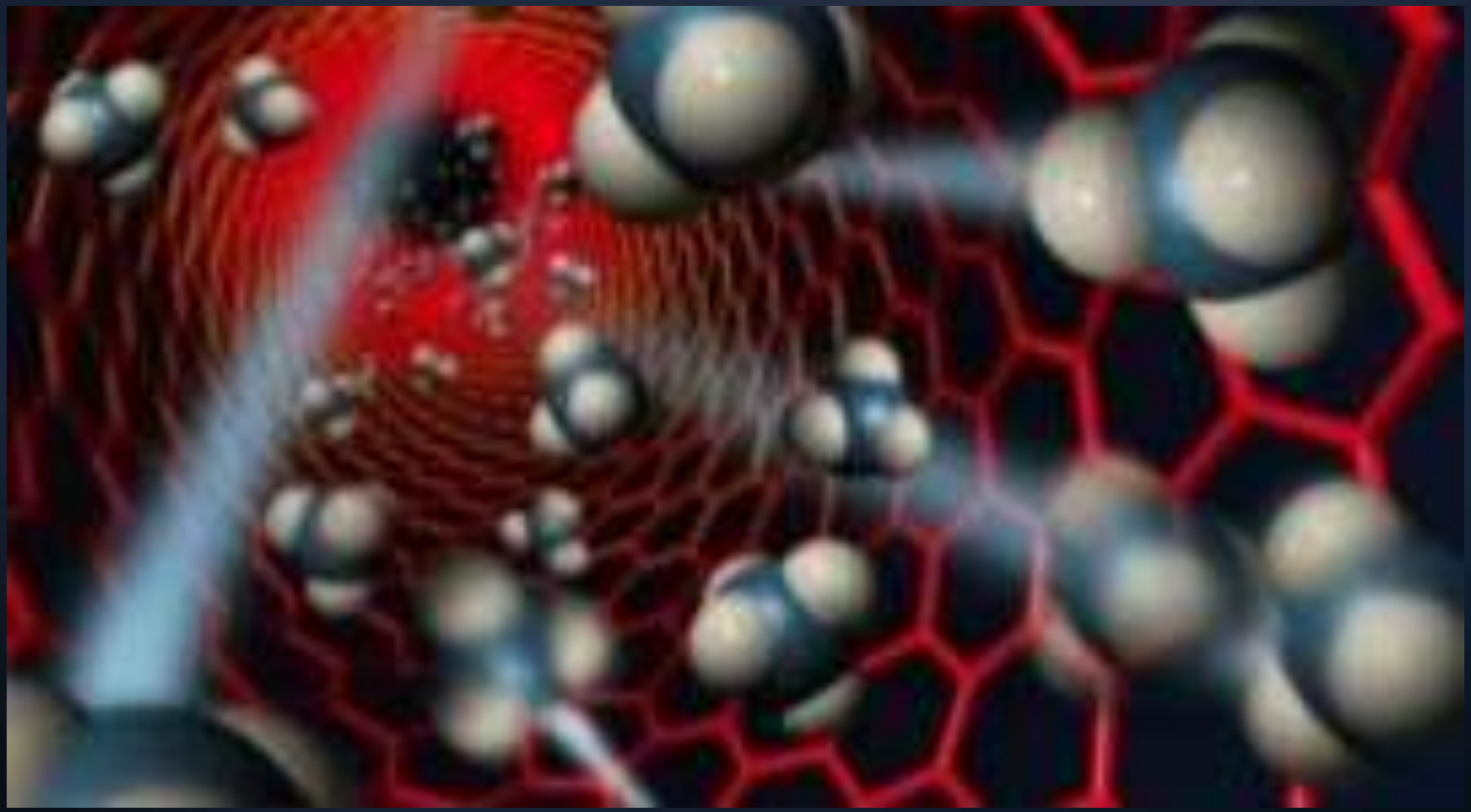
DBM with CNT

- Expression of osteoblastic markers



Zanello LP, Sharma P, Corzano R, Hauschka P 2008 Osteogenic induction of single-walled carbon nanotube scaffolds. NSTI Nanotechnology 1, 75-78

Ultimate Scaffolds

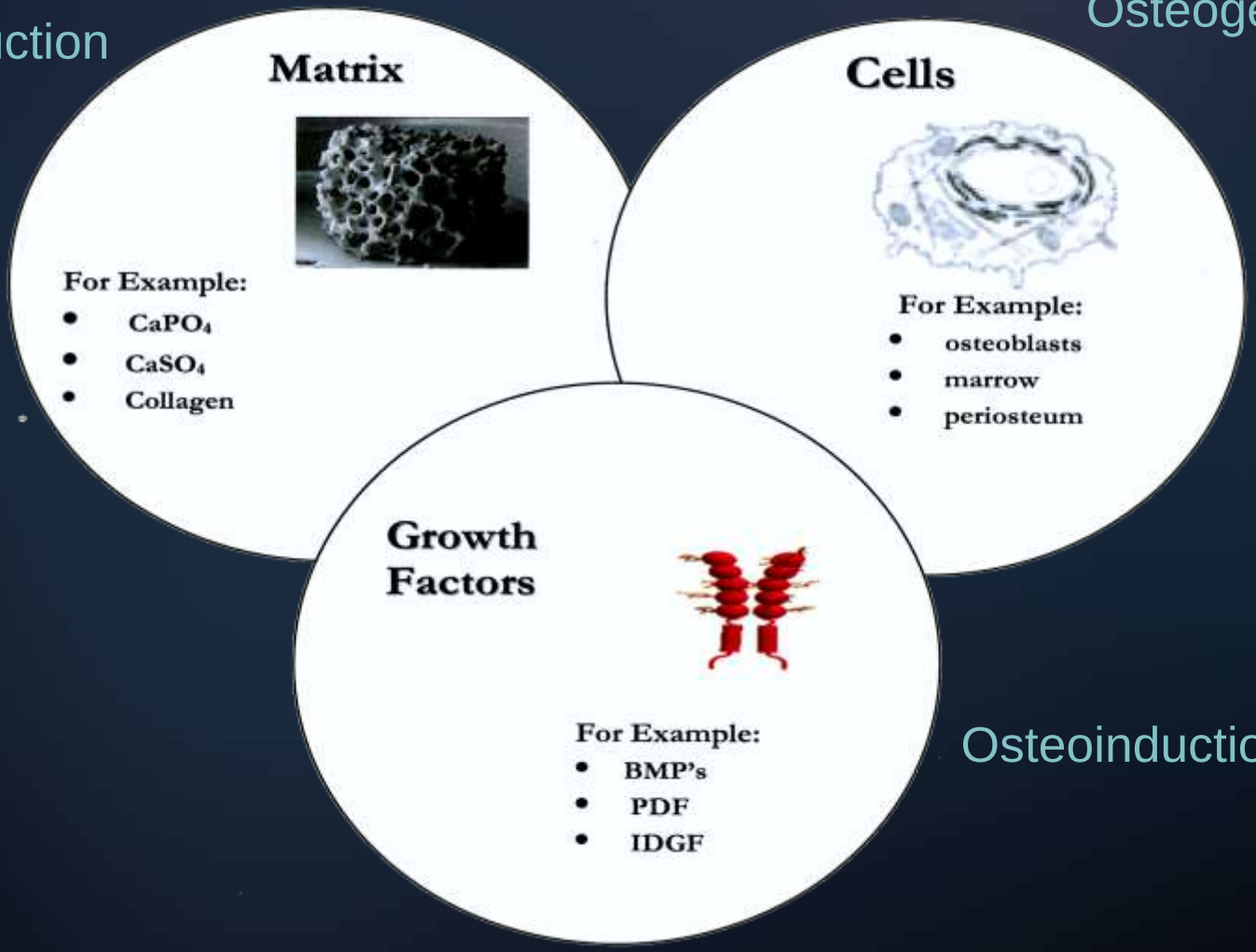


Triad of Bone Regeneration

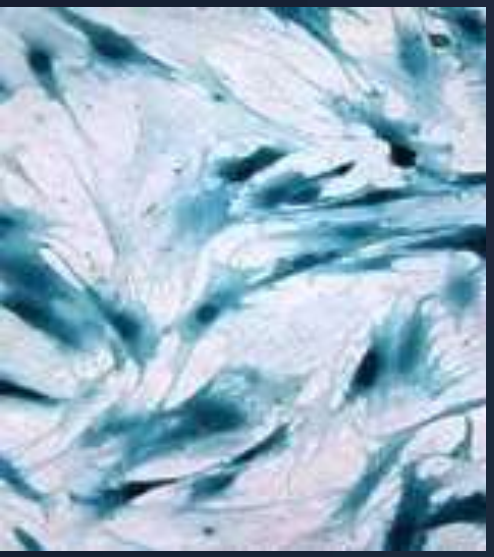
Osteoconduction

Osteogenesis

Osteoinduction



Future



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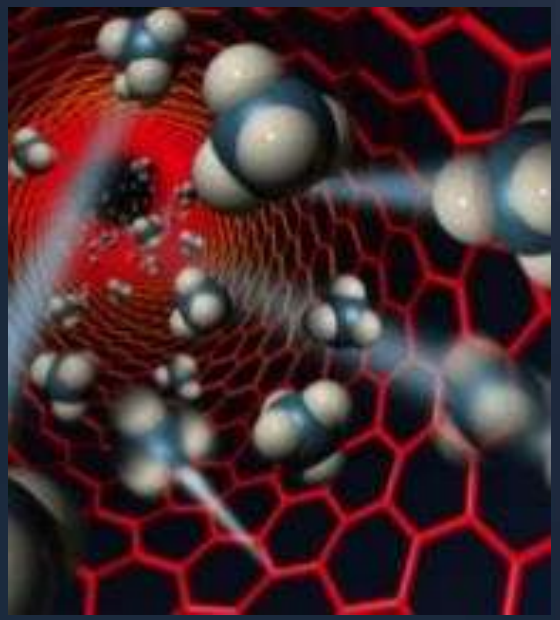

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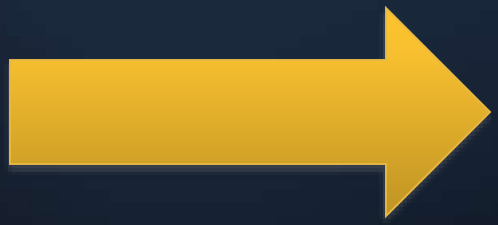
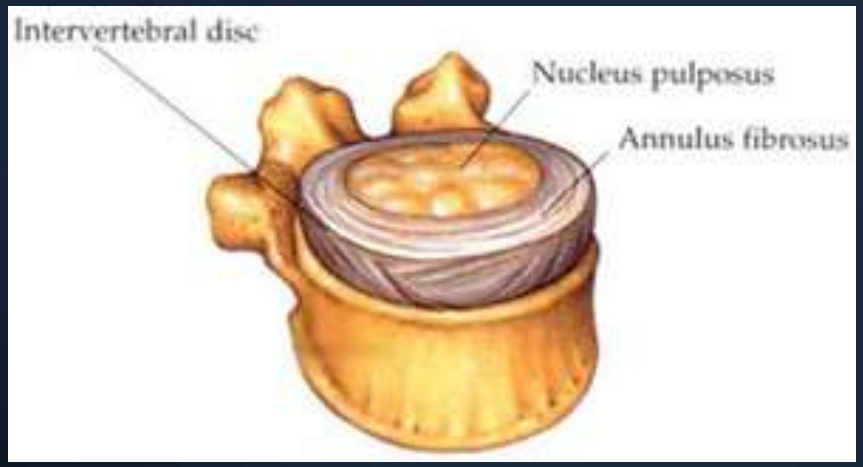


Disc

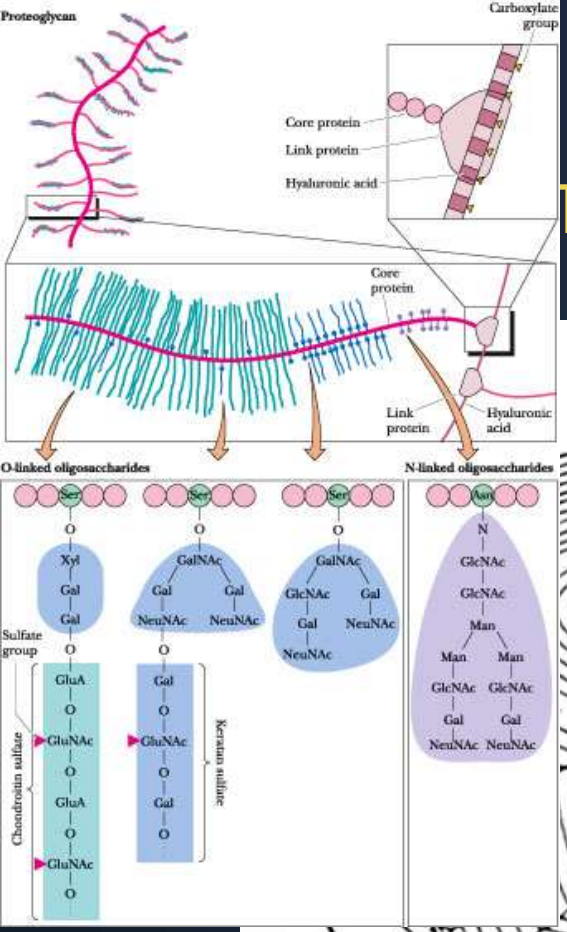


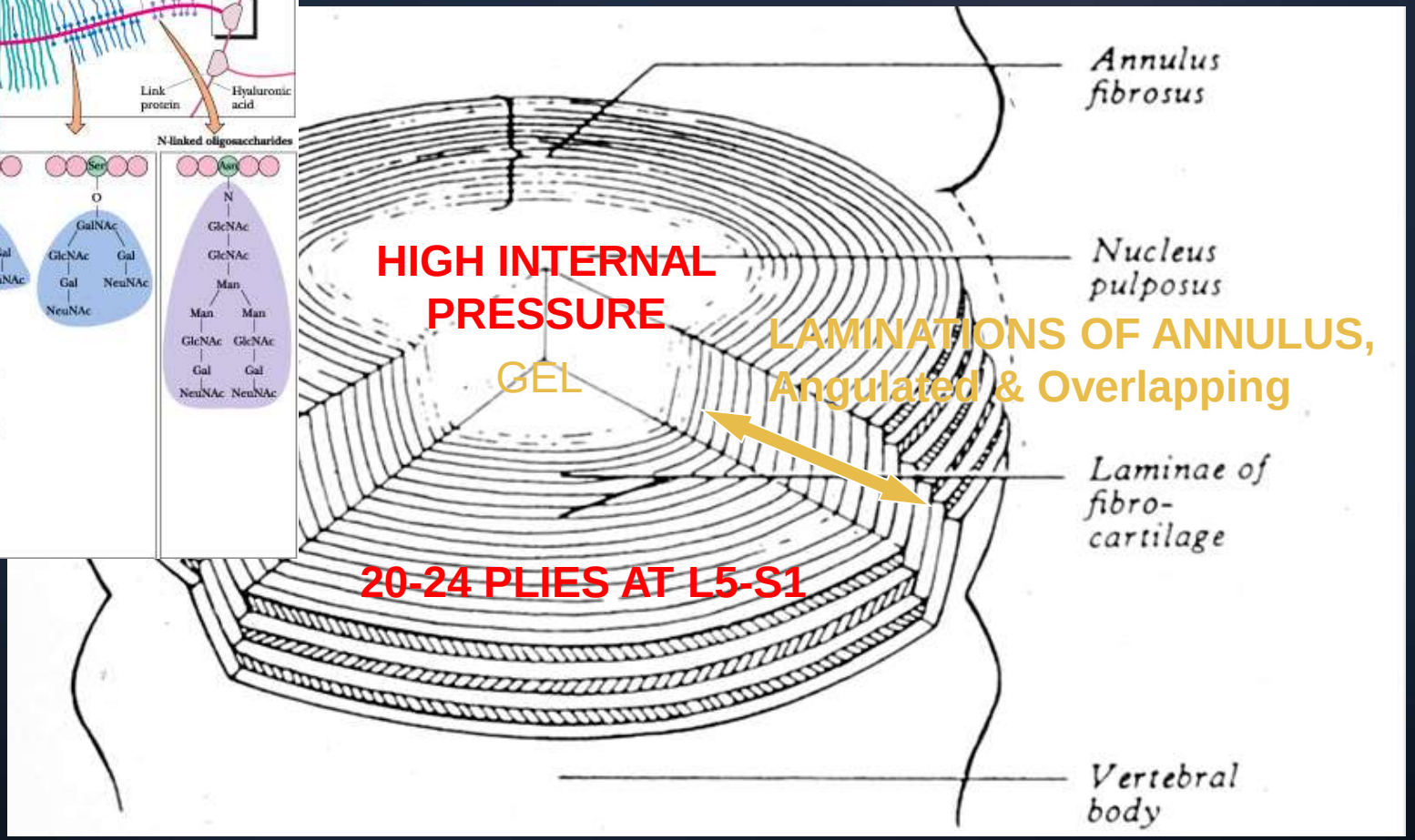
Part 1- ANULUS

LAMINATED CONSTRUCTION OF THE ANNULUS RESISTS MECHANICAL FORCES YET PRESERVES SEGMENTAL MOTION (THE AUTOMOBILE TIRE, WITH ITS HIGH INTERNAL PRESSURE IS QUITE SIMILAR.)

PART 2 - NULEUS

T COMPRESSION TO 8X BODY WEIGHT

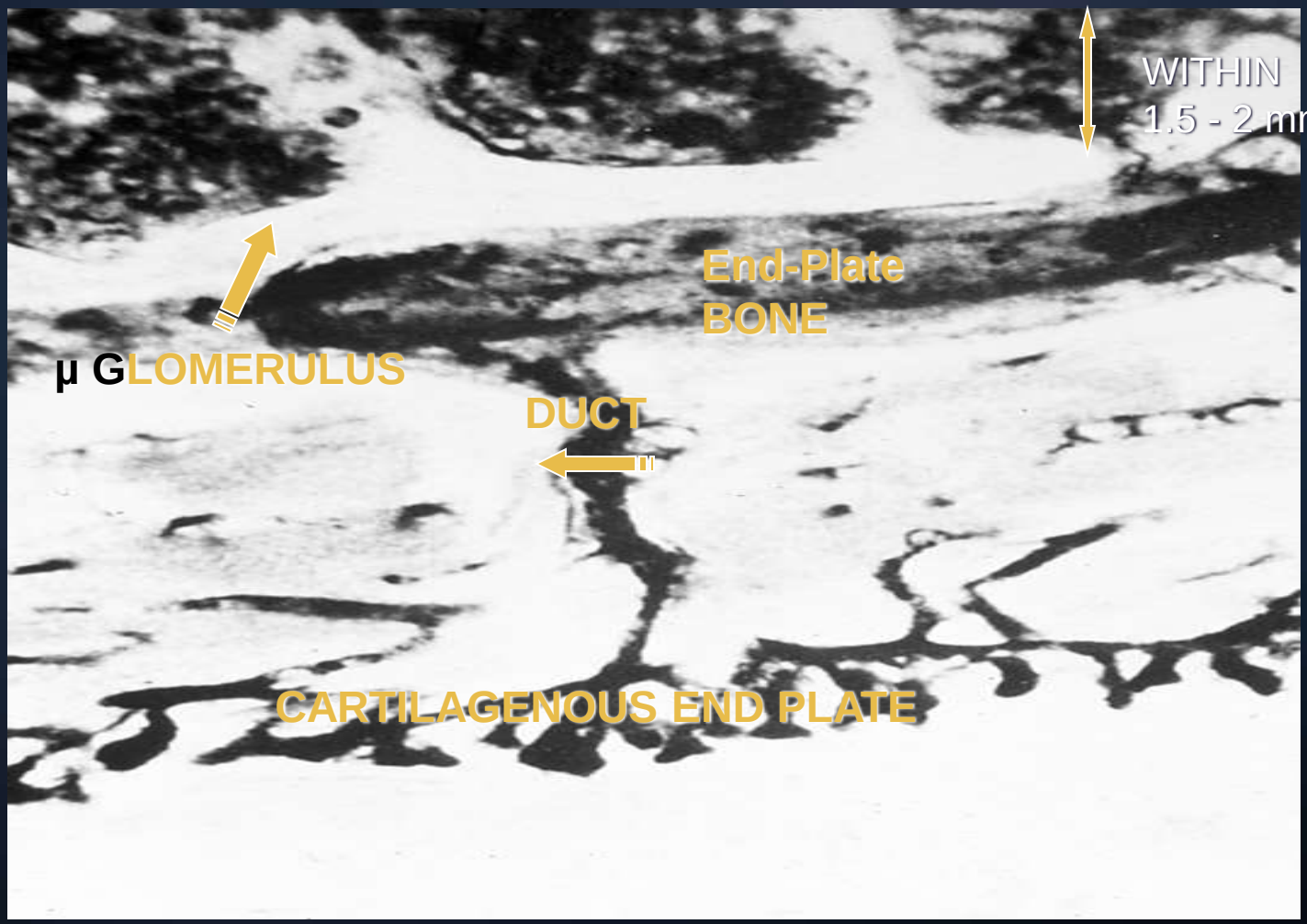




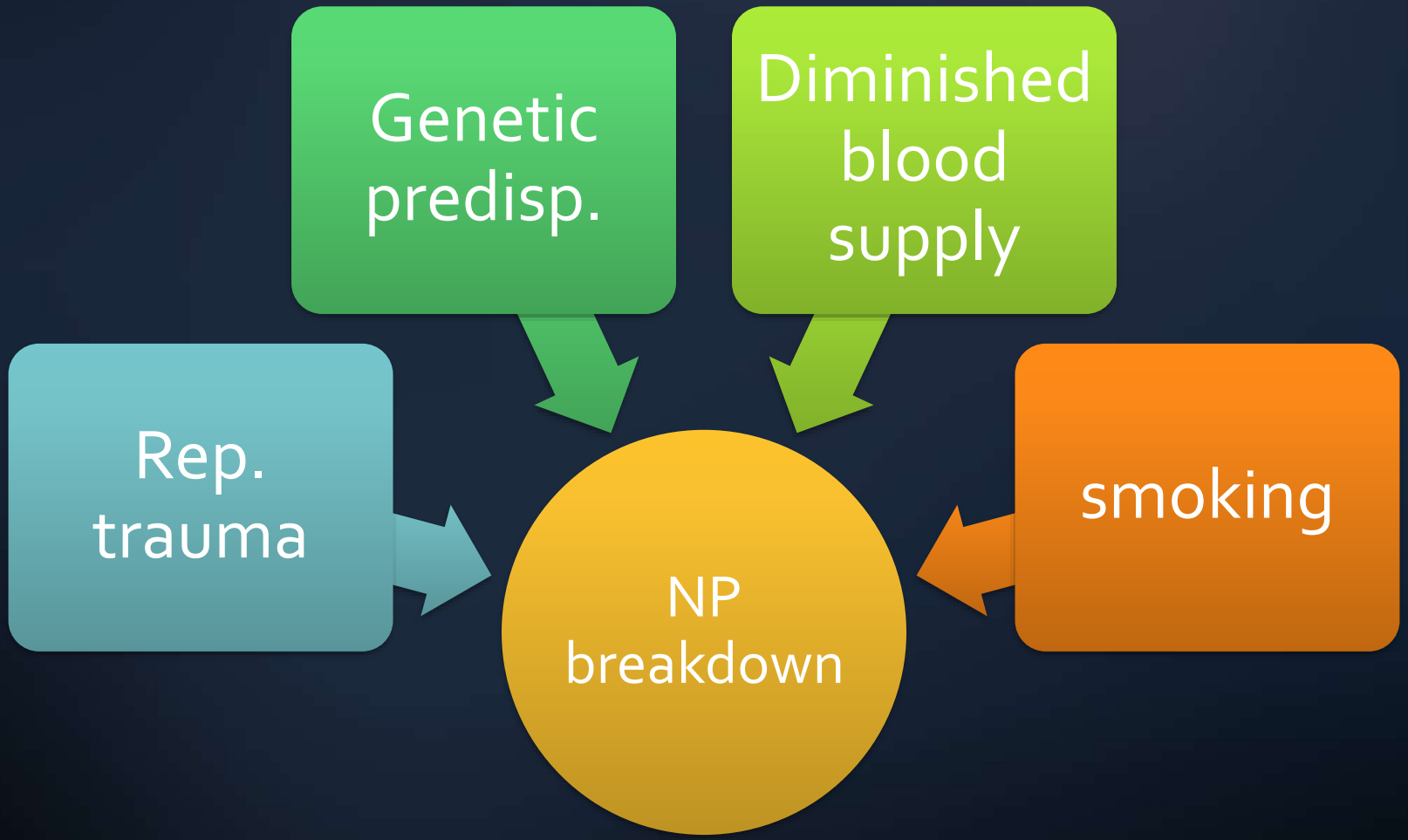
PART 3- ENDPLATE /VASCULAR: ENDPLATE FILTRATION SYSTEM

For

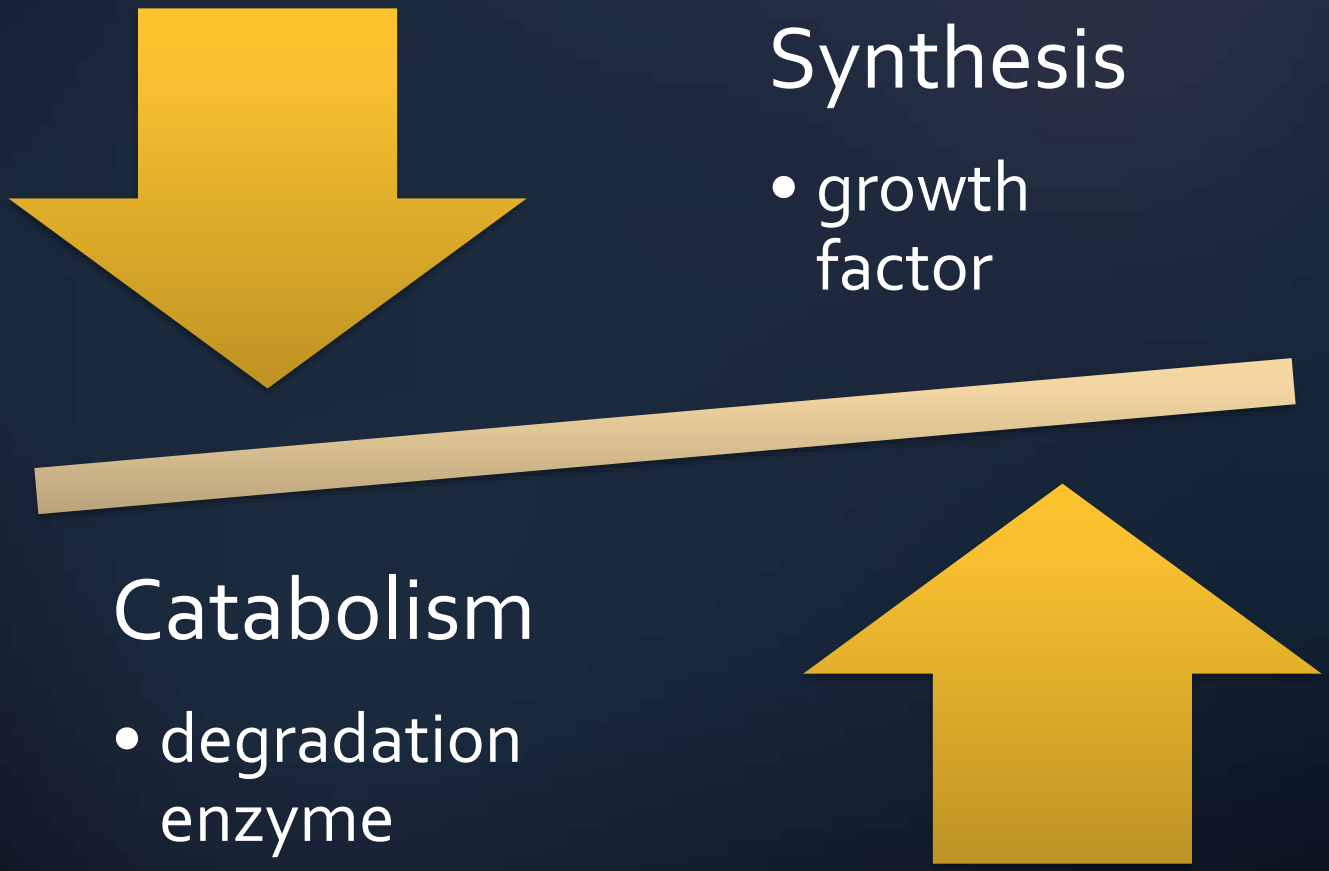
Transfer of Nutrients and Waste Removal



Associated factors



Disc Matrix (proteoglycan/collagen)



Synthesis

- growth factor

Catabolism

- degradation enzyme

Disc regeneration

Growth factors

- BMP 2, 7, 13(GDF-6)
- TGFB
- LINK N
- Sox-9

Antagonist to Catabolic factors

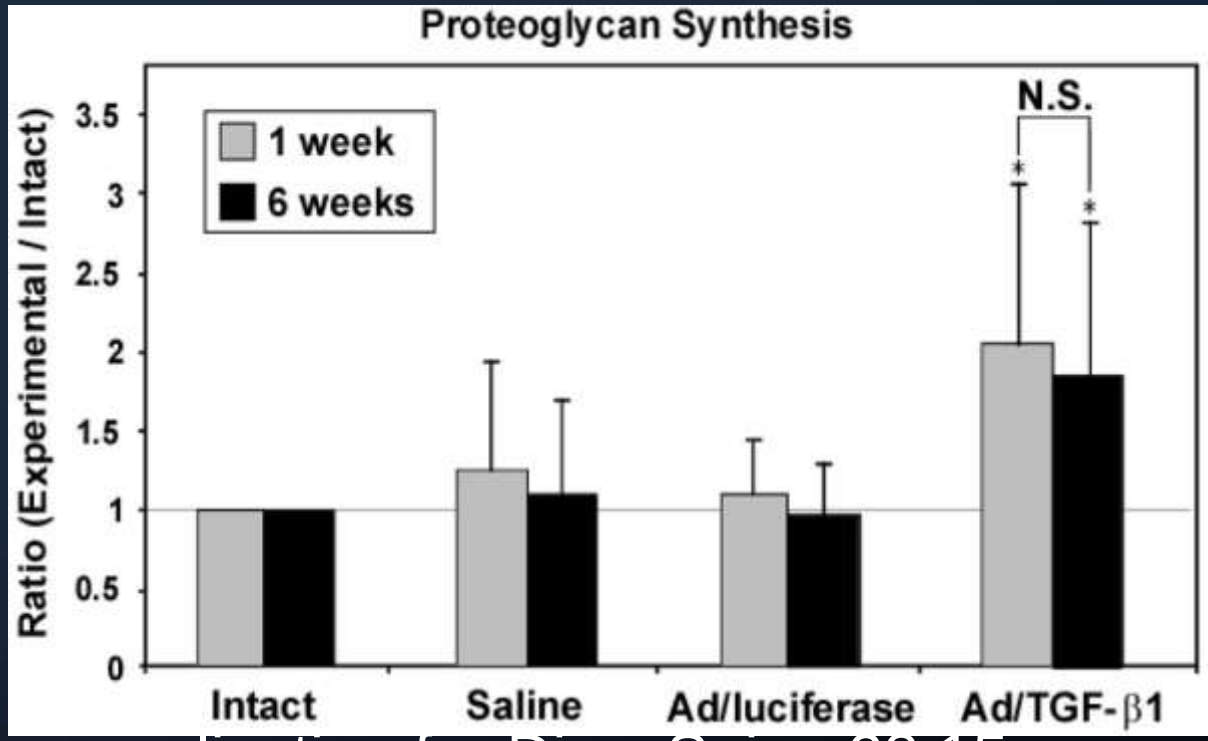
- MMP
- TNF
- PGE2
- IL-6

Stem Cells

- Mesenchymal cells

Growth factor: TGF-B

- Rabbit disc cell transduced with adenoviral TGF-B1 vector



Corey et al. Gene therapy application for Disc. Spine 28:15s

Mesenchymal Stem Cells

- MSC + TGF-b decrease disc degeneration in rabbit by slow down disc ht loss.

ELSEVIER

The Spine Journal 10 (2010) 802–810

THE SPINE JOURNAL

Basic Science

Transplanted mesenchymal stem cells with pure fibrinous gelatin-transforming growth factor-β1 decrease rabbit intervertebral disc degeneration

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Abstract

BACKGROUND CONTEXT: Disc degeneration is a major reason for low back pain and can be caused by apoptosis. The prevention of apoptosis using mesenchymal stem cells (MSCs) may lead to new treatments for low back pain. Previous studies have reported that transplanted MSCs can proliferate and differentiate into cells expressing some of the major phenotypic qualities of nucleus pulposus cells. However, the effects of MSC transplantation on the disc height index (DHI) and apoptosis inhibition have not yet been thoroughly investigated.

PURPOSE: The present study evaluates the effects of MSC transplantation on DHI and its potential to inhibit apoptosis.

STUDY DESIGN/SETTING: Random, controlled, animal experiment study.

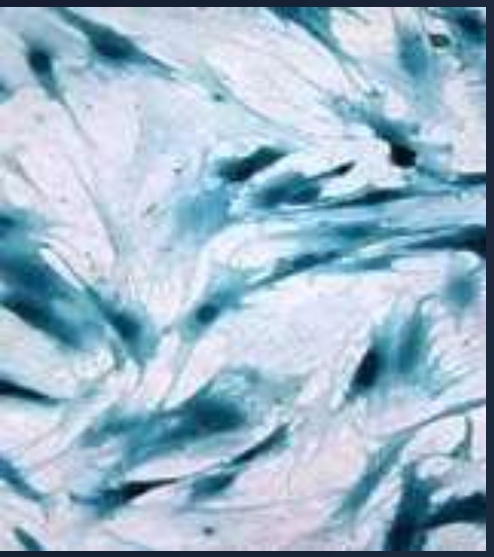
METHODS: The annulus fibrosus of 54 white New Zealand rabbits was punctured with a 21-gauge needle, and the nucleus pulposus tissue from the intervertebral discs was aspirated. The degenerative disc model was produced in each rabbit, which were then randomly divided into three groups: degenerative model group; pure fibrinous gelatin-transforming growth factor-β1 (PFG-TGF-β1) transplanted group; and MSC-PFG-TGF-β1 transplanted group. Computed radiography imaging, magnetic resonance imaging, and histological examinations were performed at Weeks 4, 8, and 12.

RESULTS: The transplanted MSCs inhibited apoptosis and slowed the rate of decrease in DHI. Magnetic resonance imaging results showed that the MSC-PFG-TGF-β1 group had less degeneration and a slower decrease in DHI compared with both the degenerative model and PFG-TGF-β1 groups. An increased quantity of nucleus pulposus and type II collagen content and a decrease in the rate of cell apoptosis were noted in the MSC-PFG-TGF-β1 group.

CONCLUSIONS: Mesenchymal stem cells can slow the rate at which the DHI decreases. This effect may be because of the inhibition of apoptosis by MSCs. Published by Elsevier Inc.

Keywords: Intervertebral disc degeneration; Mesenchymal stem cells; Nucleus pulposus; Disc space height index; Apoptosis

Future



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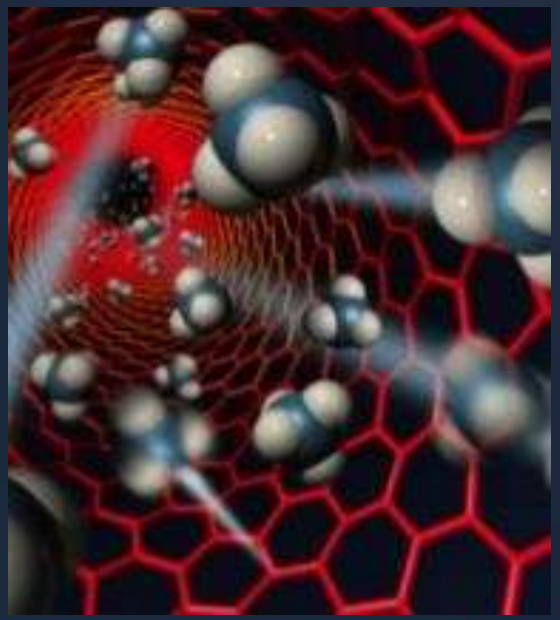

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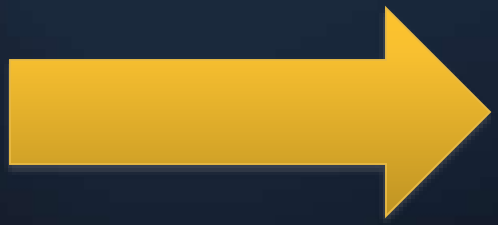
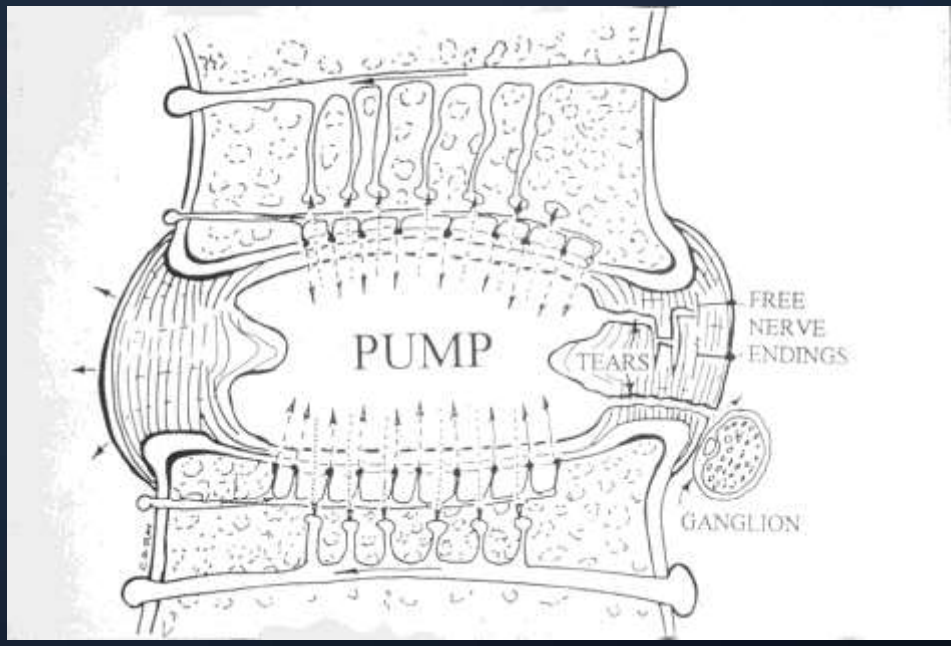


Caution

- Endplate?
- DDD needle puncture model?
- Human are not rabbits?
- How long can it stay?
- Indication? When do we intervene?



THANK YOU!