Bone Graft Materials for Spinal Fusion

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Bone Formation

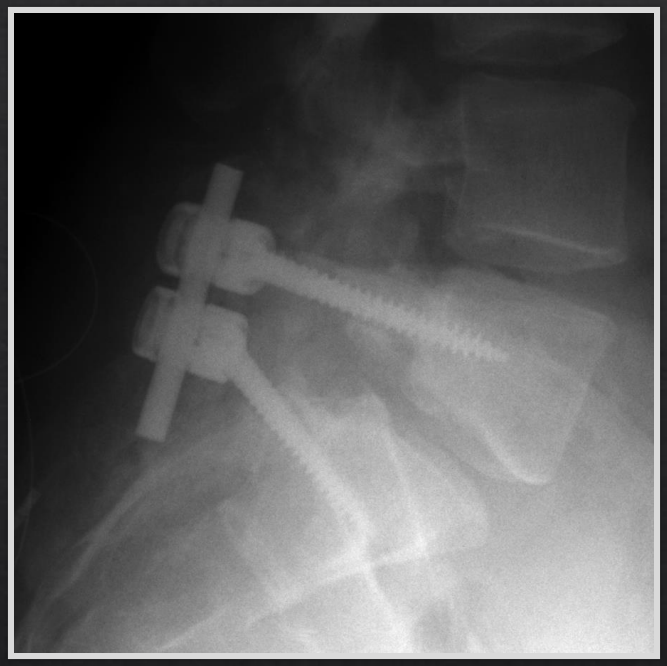
- Complex process involving an intricate cascade of molecular and cellular events
  - Osteogenic cells
  - Osteoinductive growth factors
  - Osteoconductive matrix

Bone Formation

- Success of various orthopaedic procedures dependent upon adequate bone production
  - Fracture consolidation
  - Filling of osseous defects
  - Joint fusions
  - Spinal arthrodesis

Spinal Fusion

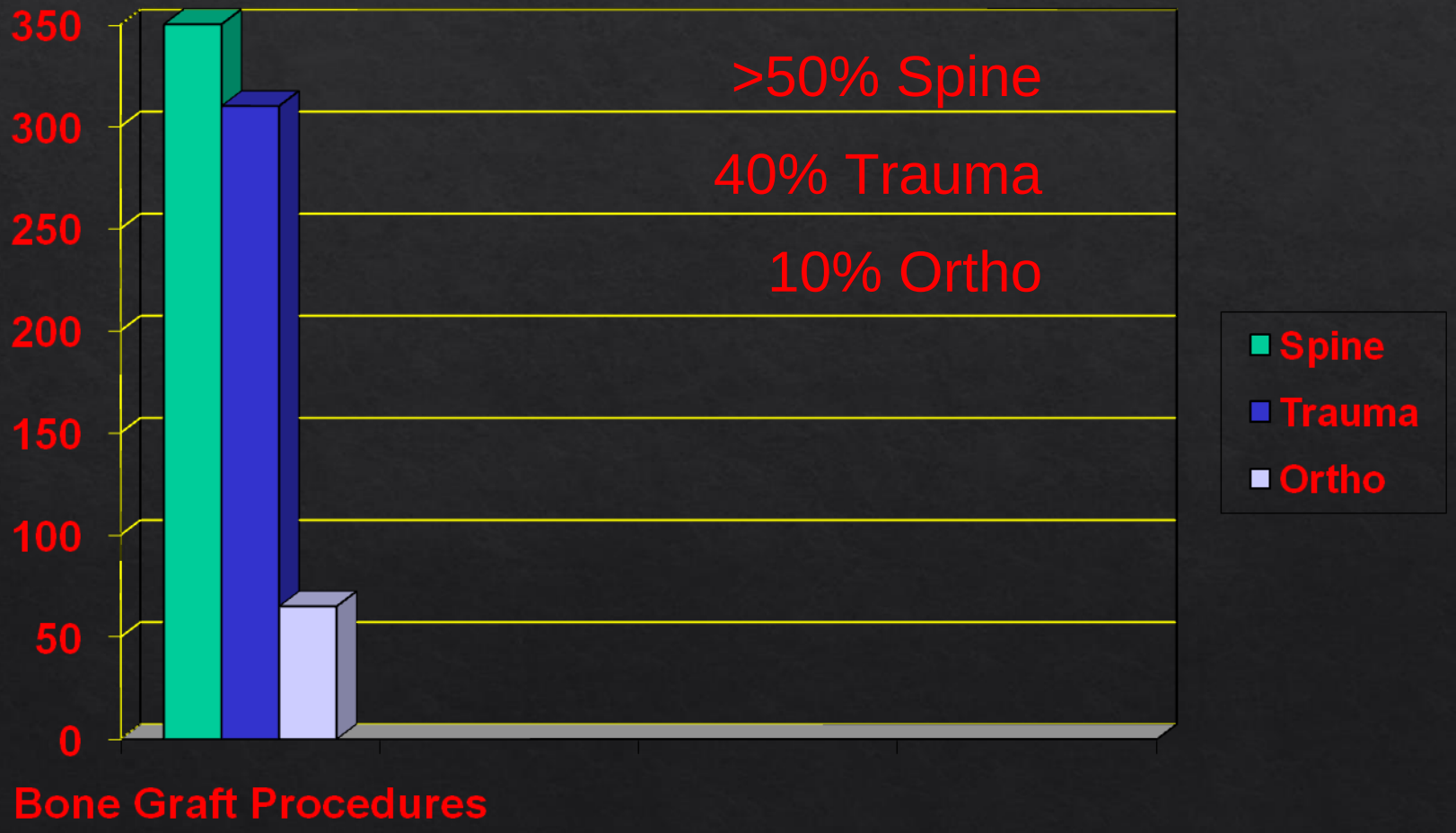
- Factors affecting fusion rate
  - Systemic
  - Local
  - Technical - woodworking
- Incidence of pseudarthrosis following lumbar fusion depending on technique at least 15%



Bone Grafts for Spinal Fusion

- Graft material used to enhance bone healing and reduce the risk of nonunion
- Fusion process influenced by the cellular, biochemical and mechanical properties of the bone graft substance

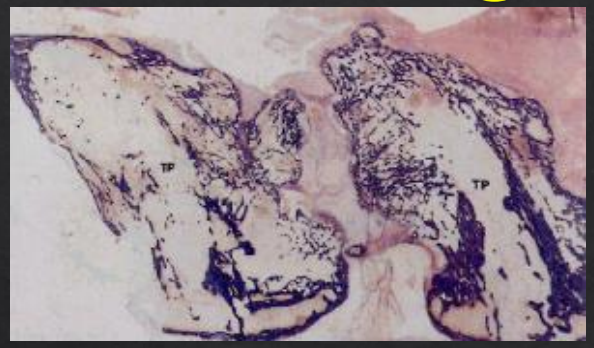
Bone Grafting Procedures

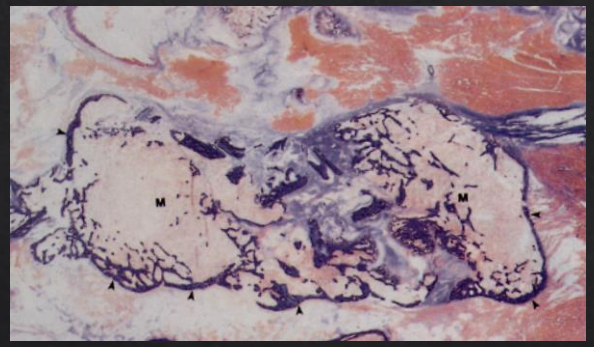


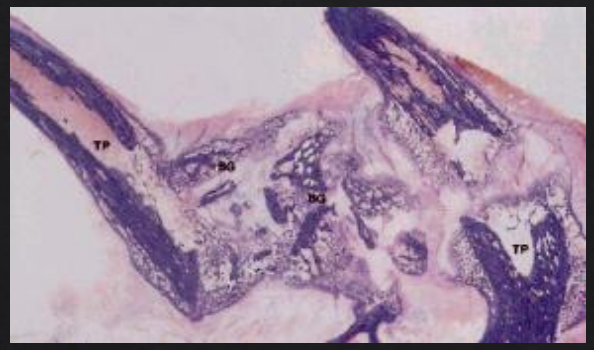
Autogenous Bone Graft

- "Gold standard" graft material for spinal fusion
  - Osteogenic cells
  - Osteoinductive factors
  - Osteoconductive scaffold
- Cancellous – provides most potent osteogenic signal
- Cortical – resistant to compressive forces

Autogenous Bone Graft



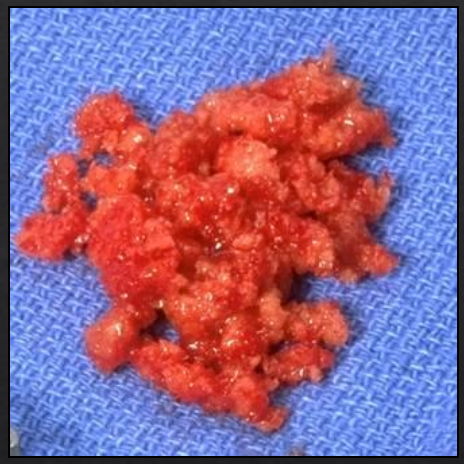




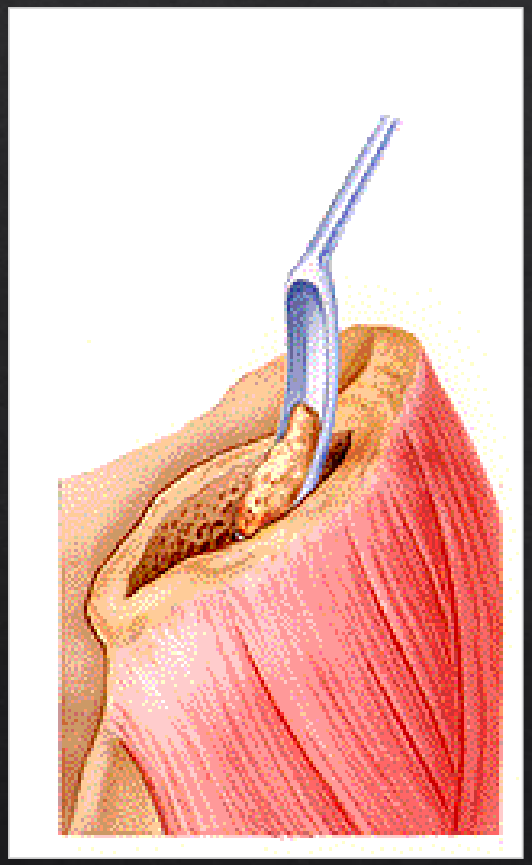
- Graft incorporation
  - Hemorrhage
  - Inflammatory response
  - Neovascularization
  - Host bone formation
  - Graft remodeling

Disadvantages of Autograft

- Available in limited quantities
  - Children
  - Multilevel procedures
  - Revision surgeries
- Significant donor site morbidity
  - Separate incision
  - Increased operative time/blood loss



Disadvantages of Autograft

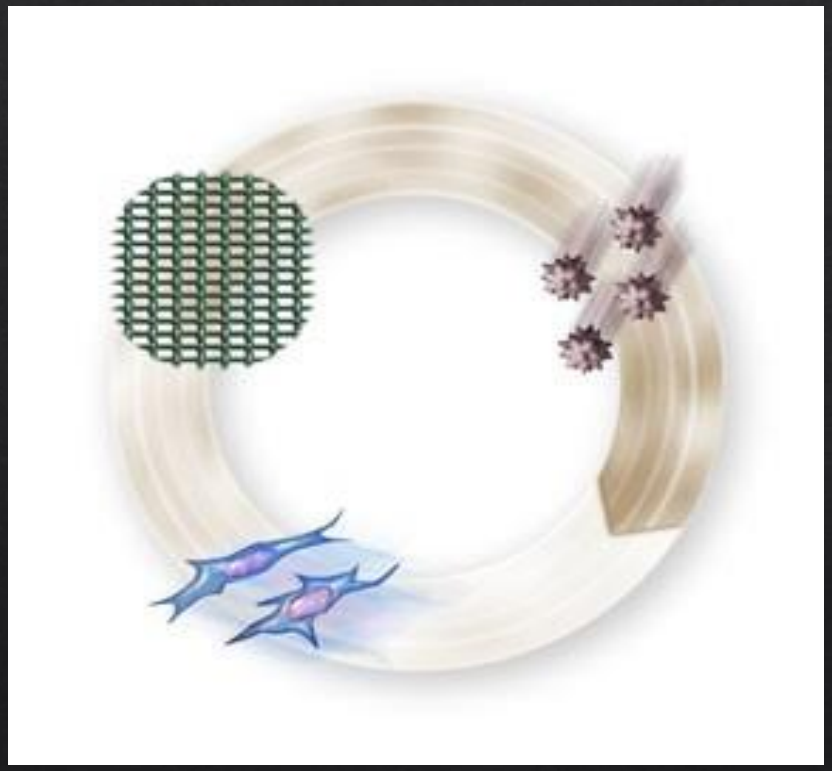


- Postoperative complications
  - Fracture/pelvic instability
  - Hematoma/seroma
  - Infection
  - Neurovascular injury
  - Intractable pain

Alternatives to Autograft

- Various materials have been developed as alternatives to autograft for spinal fusion
  - Extenders – combined with autograft
  - Substitutes – implanted without autograft
- Efficacy of each substance dependent upon the clinical application for which is it being used
  - Interbody fusion vs. posterolateral fusion

“Ideal” Bone Graft Material



- Osteogenic cells
- Osteoinductive factors
- Osteoconductive matrix
- Structural support

“Ideal” Bone Graft Material

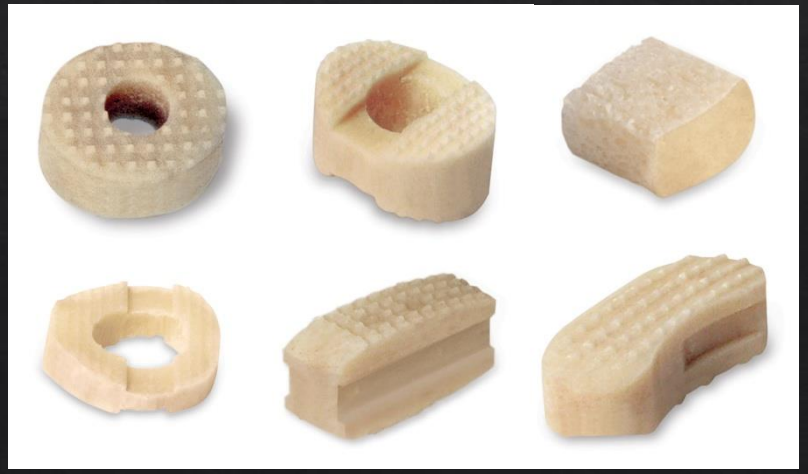
- Fusion rates equal to autogenous bone
- Eliminate donor site morbidity
- Minimal risk of disease transmission
- Unlimited supply
- Inexpensive to procure
- Easy to store and apply

Graft Materials for Spinal Fusion

- Allograft
- Osteoconductive scaffolds
- Demineralized bone matrices
- Bone marrow aspirates/stem cells
- Autologous platelet concentrate
- Recombinant growth factors
- Stem cells

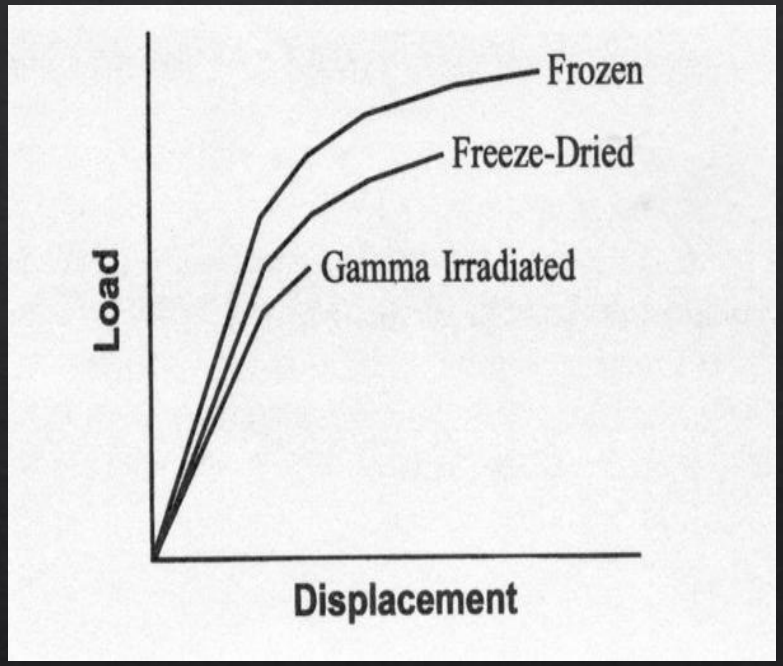
Allograft

- Most widely used substitute for autograft
- Primarily osteoconductive with minimal osteoinductive potential
  - Not a source of osteogenic cells

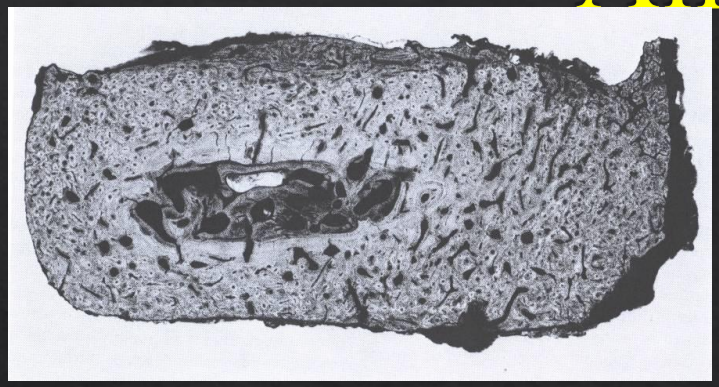


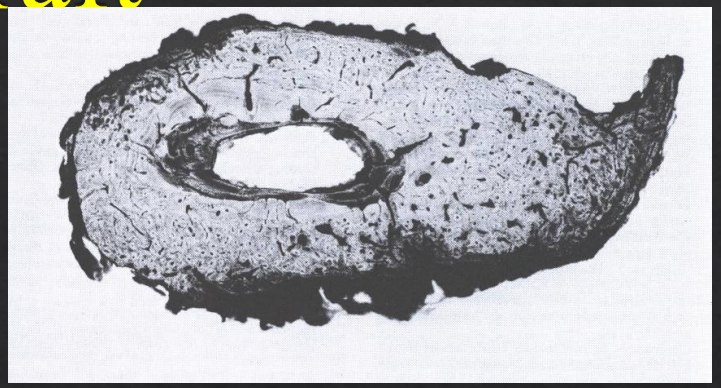
Allograft

- Tissue processing
  - Freezing
  - Lyophilization (freeze-drying)
  - XRT/ethylene oxide
- Risk of disease transmission
  - Hepatitis
  - HIV risk < 1:1,000,000



Allograft

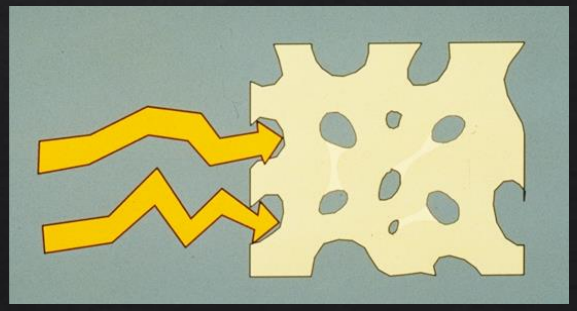


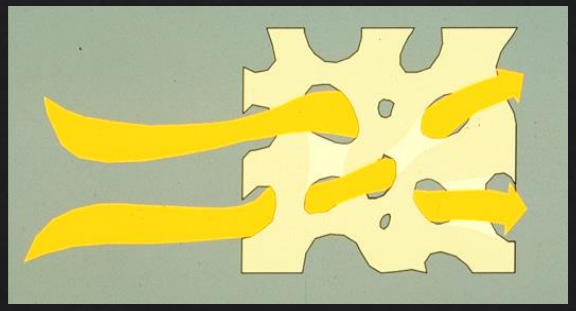


- Graft incorporation similar to autograft
  - Occurs more slowly and is less complete
  - Greater resorption of graft material
- Particulate – incorporates more rapidly
- Cortical – provides structural stability

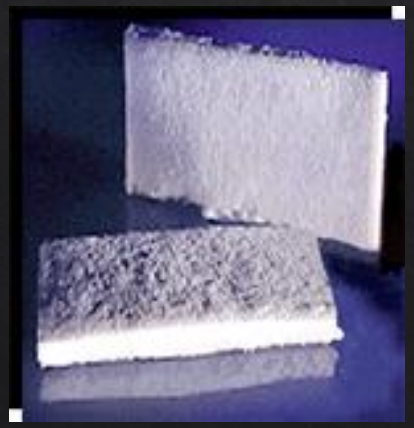
Osteoconductive Scaffolds

- Promotes bone formation by supporting angiogenesis and facilitating cellular adhesion
- Optimal pore size between 100 – 500 μm
- Purely osteoconductive
  - No osteogenic cells or osteoinductive factors
  - Generally used as part of a composite graft





Osteoconductive Scaffolds



- Ceramics
- Coralline matrices
- Calcium sulfate (plaster of Paris)
- Mineralized collagen
- Acid polymers
- Porous metals

Osteoconductive Scaffolds

- Advantages
  - Biocompatible
  - No inherent risk of infection
  - Available in unlimited quantities
- Disadvantages
  - Poor mechanical properties
  - Variable rates of bioabsorption
  - Cost

Demineralized Bone Matrices

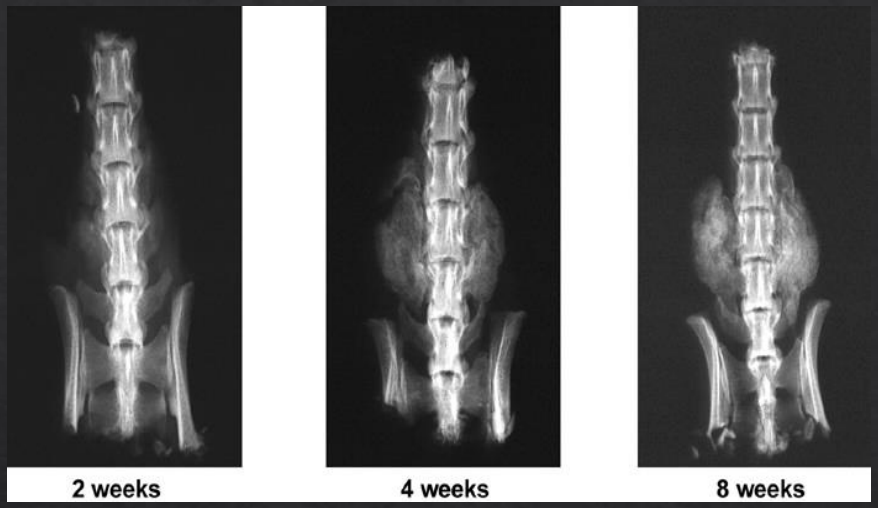
- Osteoinductive with variable osteoconductive properties
- Acid extraction of allograft bone
  - Demineralized matrix (type I collagen)
  - Noncollagenous proteins

Demineralized Bone Matrices

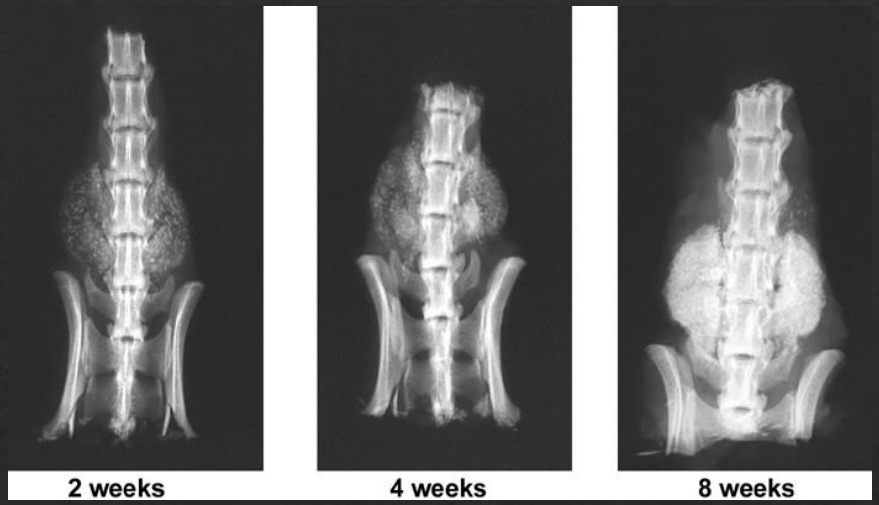
- Significant variability in osteoinductive potentials
  - Differences in BMP content – < 0.1% of all proteins
  - Inherent properties of allograft
- DBMs now regulated by FDA

Demineralized Bone Matrices

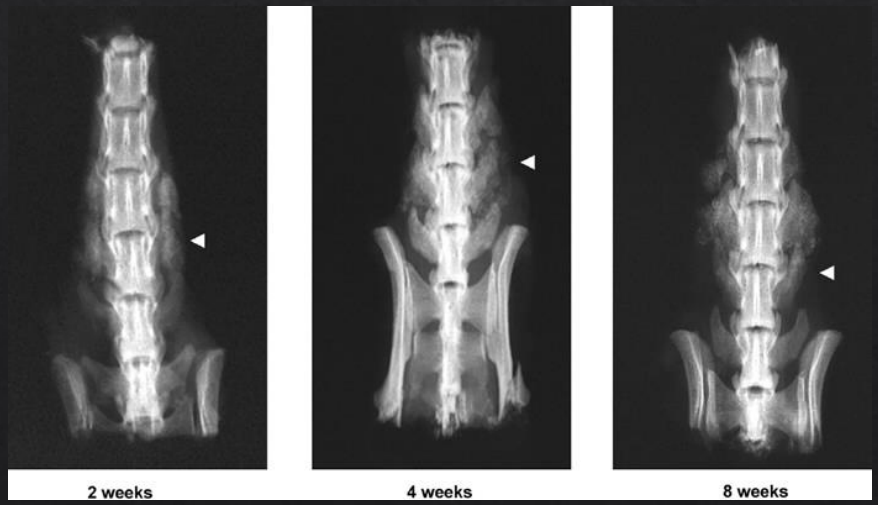
- Peterson B, Whang PG *et al*., J Bone Joint Surg Am 2004; 86:2243-2250
  - Compared osteoinductive potentials of three commercially available DBMs
  - Grafton (Osteotech), DBX (MTF), AlloMatrix (Wright Medical)
  - Intertransverse spinal fusion in athymic rats
  - Radiographic, biomechanical and histologic evaluation



Grafton



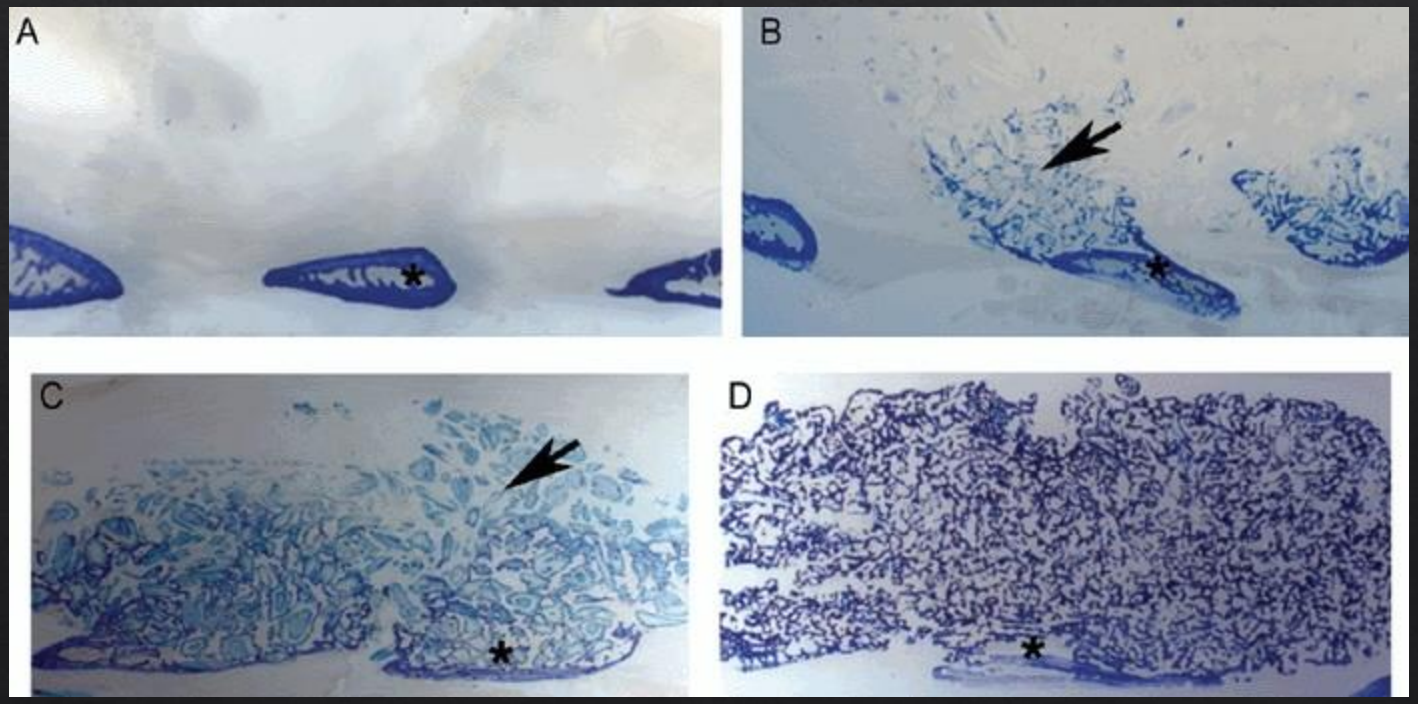
DBX



AlloMatrix

Treatment Group	No. of Fusions* (N = 6)			
	Two Weeks	Four Weeks	Eight Weeks	P Value†
I: Grafton Putty	0	5	6	0.001
II: DBX Putty	0	2	3	0.091
III: AlloMatrix Injectable Putty	0	0	0	NS
IV: Decortication alone	NA	NA	0	

*NA = not applicable. †Compared with the control value at eight weeks. NS = not significant.

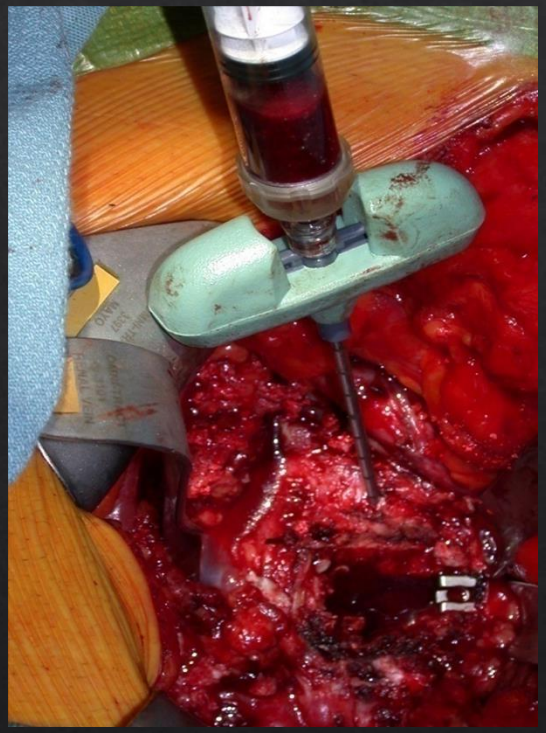


Bone Marrow Aspiration

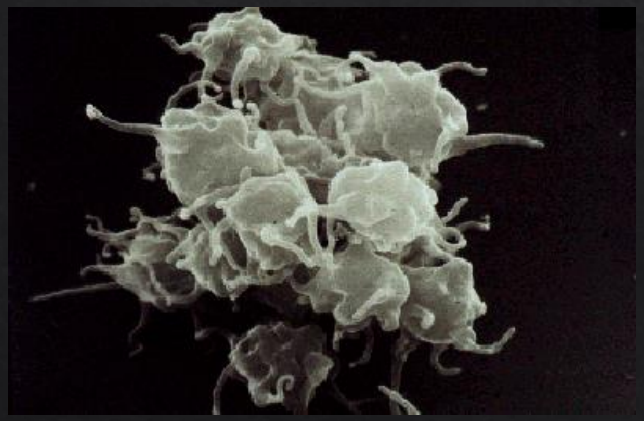
- Source of osteogenic cells and osteoinductive growth factors
- Autologous tissue
- Minimal morbidity compared to autograft
  - Iliac crest
  - Vertebral bodies
- Combined with carrier to form composite graft

Bone Marrow Aspiration

- Unfractionated bone marrow exhibits only moderate osteogenic potential
  - Healthy adult – 1 stem cell/50,000 nucleated cells
  - Only 2 cc should be harvested from a single site to avoid dilution with peripheral blood
- Systems have been developed to concentrate osteogenic cells



Autologous Platelet Concentrate



- Activated platelets release multiple factors that may enhance bone formation
  - PDGF
  - TGF-β
  - VEGF
- Not osteoinductive
  - BMPs not released by platelets

Autologous Platelet Concentrate

- Platelet-rich plasma filtered from autologous blood and concentrated in fibrinogen matrix
- Combined with osteoconductive scaffold and/or osteogenic cells to form composite graft

Autologous Platelet Concentrate

- Multiple studies have demonstrated that platelet gels may fail to improve[1] or even inhibit bone formation[2]
- Efficacy for promoting spinal arthrodesis remains unsubstantiated

[1] Carreon LY *et al*., Spine 2005;30:E243-6

[2] Weiner BK and Walker M. Spine 2003;28:1968-70

Efficacy of Platelet-Rich Plasma for Bone Fusion in Transforaminal Lumbar Interbody Fusion

- Kubota et al.
  - 400 mL of peripheral venous blood was taken from each patient for PRP preparation. The blood was processed using a two-stage centrifugation method
  - 9 patients PRP and local bone, 11 patients control local bone only
  - 91 % fusion in PRP group and 77% fusion in control

Small number of patients with inconsistent local bone graft

Table 3. Literature review about the effect of PRP based on the human spinal fusion studies.

Author	Fusion model	Study design	FU	Evaluation	Fusion rates
Weiner and Walker[24]	Lumbar PLF	ABG iliac + PRP ($n = 32$), ABG iliac ($n = 27$)	12	Radiograph	NSD
Carreon et al.[25]	Lumbar PLF	ABG iliac + PRP ($n = 76$), ABG iliac ($n = 76$)	24	Radiograph, CT	NSD
Tsai et al.[26]	Lumbar PLF	ABG lamina + PRP ($n = 33$), ABG lamina ($n = 34$)	24	Radiograph, CT	NSD
Kubota et al.[27]	Lumbar PLF	ABG lamina + PRP ($n = 25$), ABG lamina ($n = 25$)	24	Radiograph, CT	SD
Tarantino et al.[28]	Lumbar PLF	Heterologous bone + PRP ($n = 20$), Heterologous bone ($n = 20$)	12	CT	NSD
Jenis et al.[29]	Lumbar PLF	Allograft bone + PRP ($n = 15$), ABG iliac bone ($n = 22$)	24	Radiograph, CT	NSD
Sys et al.[30]	Lumbar IF only	CA + ABG iliac + PRP ($n = 19$), CA + ABG iliac ($n = 19$)	12	Radiograph, CT	NSD
Hee et al.[31]	Lumbar IF with PLF	CA + ABG iliac + PRP ($n = 23$), CA + ABG iliac ($n = 111$)	24	Radiograph	NSD
Hartmann et al.[32]	Lumbar or thoracic IF with PLF	CA + ABG fracture + PRP ($n = 15$), CA + ABG fracture ($n = 20$)	8	CT	NSD
Feiz-Erfan et al.[33]	Cervical IF	Cortical allograft bone + PRP ($n = 42$), Cortical allograft bone ($n = 39$)	24	Radiograph	NSD

FU: follow-up period (months); PLF: posterolateral fusion; IF: interbody fusion; ABG: autogenous bone graft; CA: cage; PRP: platelet-rich plasma; CT: computed tomography; NSD: no significant difference; SD: significant difference.

Bone Morphogenetic Proteins

- Members of the TGF-ß family of growth factors
- Bind to receptors on surface of osteoprogenitor cells and activate various intracellular signal transduction cascades
- Stimulate osteoblastic differentiation of pluripotential stem cells

Recombinant BMPs

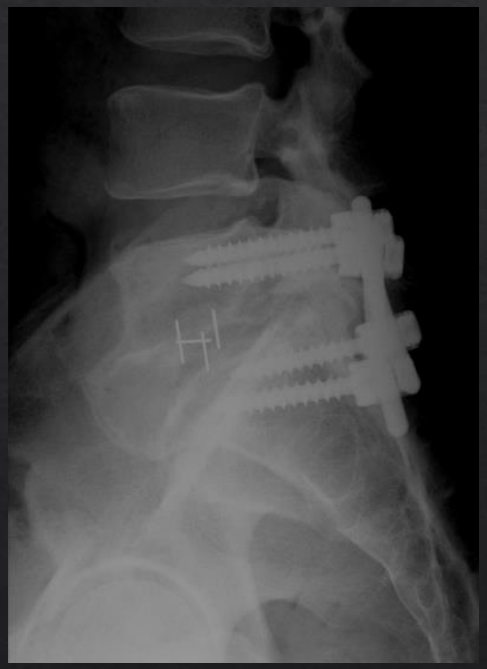
- Genes encoding several BMPs have been identified, sequenced and cloned
- Mass production of specific BMPs
  - rhBMP-2 (INFUSE, Medtronic Sofamor Danek) – single level lumbar interbody fusion
  - rhBMP-7 (OP-1 Putty, Stryker Biotech) –

Recombinant BMPs

- Combined with osteoconductive carrier to form composite graft
  - Supports cellular adhesion, angiogenesis
  - Restricts diffusion of soluble factors away from fusion site
  - Ideal carrier may be dependent upon the specific clinical application
- Osteogenic cells must also be present

Recombinant BMPs

- Supraphysiologic concentrations of BMPs necessary to induce spinal fusion
- Potential safety concerns
  - Heterotopic ossification
  - Osteolysis
  - Toxicity
  - Host immunologic response



Bone Morphogenetic Proteins

- Ong KL et al. *Spine* 2010;35:1794-1800
  - Epidemiologic study assessing the utilization patterns of rhBMP
  - 4.3x increase between 2003 and 2007
  - 92.8% of procedures were spinal fusions
  - 85% of cases involved off-label applications

Bone Morphogenetic Proteins

Table 1. Breakdown (by Principal Procedure) of All Procedures (Including Nonspine Fusion) Using BMP (Total n = 340,251) From October 1, 2002 to December 31, 2007

Procedure	Percent of All Principal Procedures With BMP
Primary PLIF/TLIF	30.0%
Primary PSF	20.4%
Primary ALIF	16.6%
Primary cervical fusion	13.6%
Primary thoracolumbar fusion	3.9%
Revision PSF	2.7%
Revision PLIF/TLIF	1.6%
Revision cervical fusion	1.0%
Revision ALIF	1.0%
Revision thoracolumbar fusion	0.6%
Others	8.6%

PLIF indicates posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; PSF, posterolateral spine fusion; BMP, bone morphogenetic protein; ALIF, anterior lumbar interbody fusion.

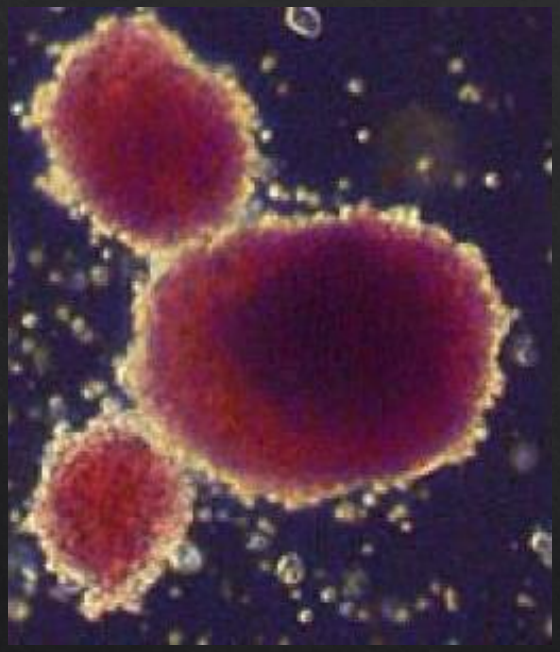
Recombinant BMPs

- Adverse events with “off-label” indications
  - Anterior cervical – swelling/dysphagia
  - Posterolateral lumbar – HO, transient bone resorption, radiculitis, seroma formation
- Complications may be related to excess concentration or “overstuffing” with collagen sponge

Recombinant BMPs

- FDA public health notification regarding "life-threatening complications of rhBMP in cervical spine surgery" Black box warning
  - At least 38 incidents during a 4 years
  - Swelling resulting in compression of airway and/or neurologic structures
  - Usually occurred 2-14 days after surgery
  - May require intubation, tracheostomy, secondary surgical procedures

Stem Cells



- MSCs are a renewable population of undifferentiated cells, resident within their niche in most adult tissues, which can give rise to the various types of mature cells of that tissue
- May have the potential to differentiate into osteoblasts
- Delivered within a carrier matrix

Clinical Studies in Spinal Fusion Displaying Fusion Rates Across Studies.

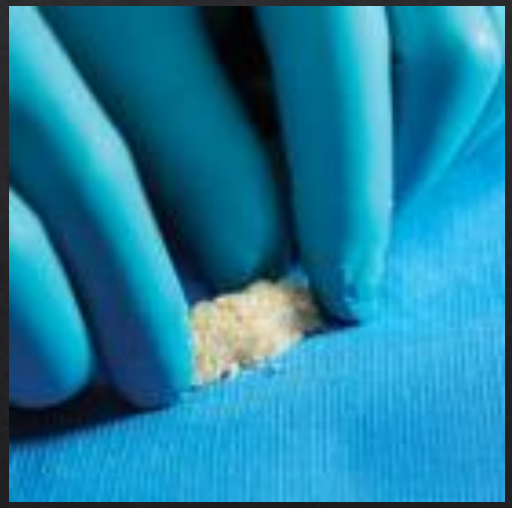
Study	No. of Patients	Approach	End Point	Assessment	Conditions (if Available)	Fusion (%)
Prospective, multicenter, nonrandomized						
Eastlack et al (2014)[57]	182	ACDFP; 1-2 levels	24 mo	CT	Osteocel + PEEK interbody cage and anterior plating	1 level: 92 Overall: 87
Prospective clinical, nonrandomized						
Gan et al (2008)[61]	41	Posterior spinal fusion for DDD or TLF	24 mo	CT	Enriched BMA + βTCP	95.1
Retrospective chart review						
Hostin et al (2013)[62]	22	AIBF	12 mo	CT	Col + BMA in carbon fiber cage	87
Ammerman et al (2013)[56]	23	MITLIF	12 mo	X-ray	Osteocel + DBM	91.3
McAfee et al (2013)[65]	25	XLIF	24 mo	CT	Autograft/Osteocel	85
Caputo et al (2013)[64]	30	XLIF	12 mo	CT	Osteocel + DBM	89.6
Tohmeh et al (2012)[59]	40	XLIF	12 mo	FGX (39) or CT (1)	Osteocel + DBM	90.2
Kerr et al (2011)[58]	52	360 fusion, ALIF, TLIF	5-8 mo	X-ray and CT	Osteocel	92.3
Systematic review						
Khashan et al. (2013)[55]		Comparing BMA with ICBM or LBG				
1 Kitchel (2006), randomized controlled	25	PLF and IF	24 mo	CT	Col + BMA ICBG	80 84
2 Neen et al (2006), prospective case control	50	PLF/TLF/360	24 mo	X-ray	Col/HA + BMA: ICBG	IF 85, PLF 93 IF 92, PLF 93
3 Niu et al (2009), prospective cohort	21	PLF	24 mo	CT	LGB + BMA ICBG	85.7 90.5
4 Vaccaro et al (2007), prospective cohort	73	PLF	24 mo	X-ray	DBM + BMA ICBG	63 67

Abbreviations: AIB, anterior interbody fusion; ACDFP, anterior cervical discectomy and fusion with plating; BMA, bone marrow aspirate; BCP, biphasic calcium phosphates; Col, collagen; DBM, demineralized bone matrix; DDD, degenerative disc disease; FGX, fluoroscopy-guided level-by-level radiography; HA, hydroxyapatite ICBG, iliac crest bone graft; LBG, local bone graft; PLF, posterolateral fusion; TCP, tricalcium phosphate; XLIF, extreme lateral interbody fusion.

- Robins et al. Global Spine J. 2017

Stem Cells

- Concerns about safety and cell viability
- Paucity of published data establishing efficacy of this technique
- Cost issues



Economic Concerns

- Utilization of bone graft materials continues to increase
- Single treatment may cost thousands of dollars
- Cost-effectiveness of many of these products have yet to be definitively established

Conclusion

- Autogenous bone remains the “gold standard” graft material for promoting bone formation
- Alternative materials have been developed as bone graft extenders or substitutes
- Additional prospective clinical studies and economic analyses will need to be performed to establish evidence-based guidelines for orthopaedic applications
- They all work and they all don’t work

Thank You!