Biologics in Spine Surgery: Assessing Evidence and Clinical Value

A Data Driven Approach

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Disclosures

- Research/Institutional Support:
  - NIH, OREF, AOA, AO North America
- Honoraria
  - Medtronic, Innovasis, RTI, Globus Medical, Stryker
- Royalties
  - Medtronic, Stryker
- Stock:
  - Simpirica, Providence Medical

2013-1579-BIVIT-SP-1

Spectrum of Bone Graft Options

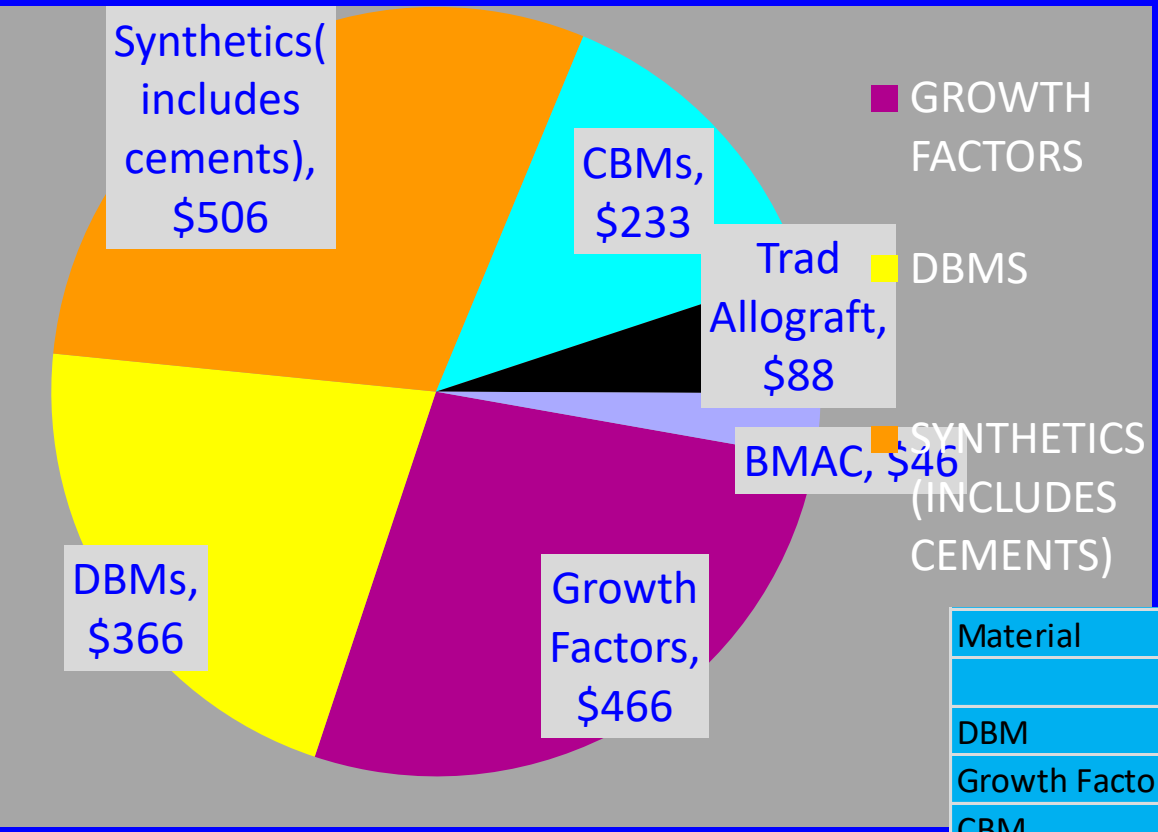
- Bone graft extenders
  - Osteoconductive matrices, Demineralized matrices
- Bone graft enhancers
  - Osteopromotive materials (AGF, PDGF)
- Bone graft substitutes
  - Osteoinductive-
    - Recombinant proteins, Demineralized Matrices
  - Osteogenic-
    - Cell-based technologies with synthetic matrices

Bone Graft Choices

- Characterized by significant variability

US 2015 Market by Technology

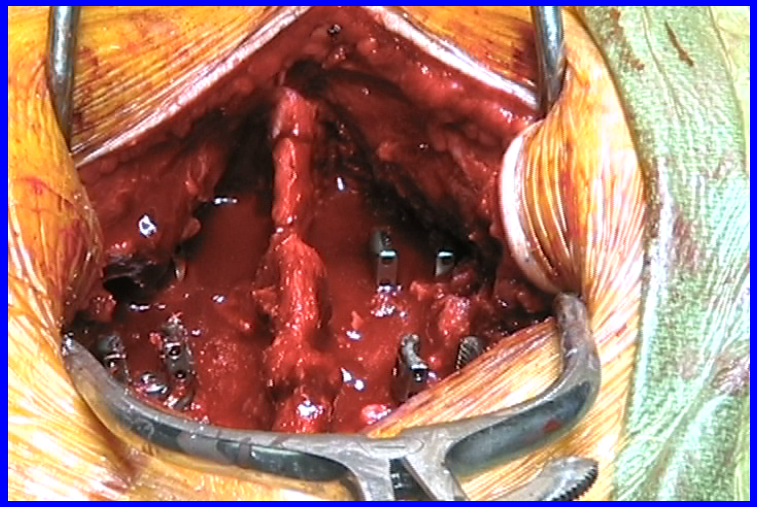
REVENUE IN $MILLIONS



Material	2011	2012	2013	2015
DBM	16%	21%	24%	21%
Growth Factors	55%	47%	39%	27%
CBM	8%	9%	12%	14%
Syntherics	15%	16%	17%	30%
Traditional Allograft	6%	7%	8%	5%
Bone Marrow Aspirate				3%

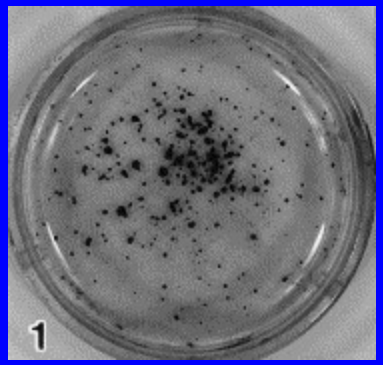
Level of Evidence

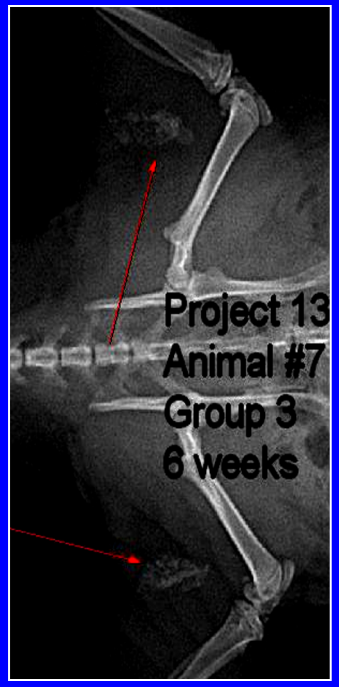
- Supportive Evidence
  - Preclinical studies
- Compelling Evidence
  - Human clinical trials
  - Comparative Studies

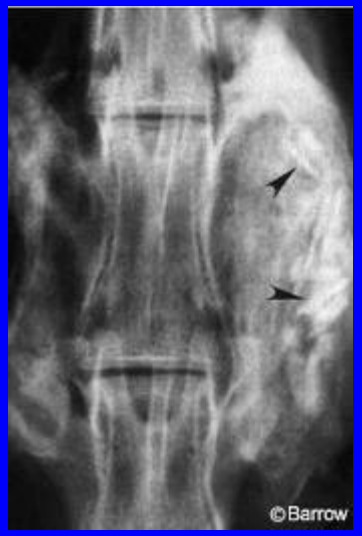


Levels of Proof

- Preclinical
  - In vitro
  - In vivo
- Clinical data

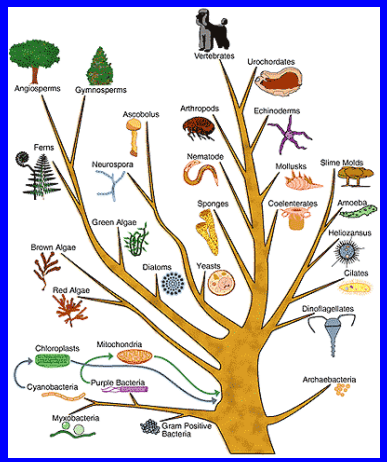


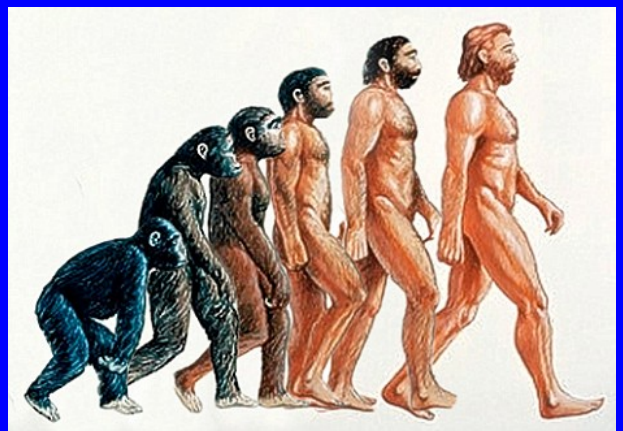


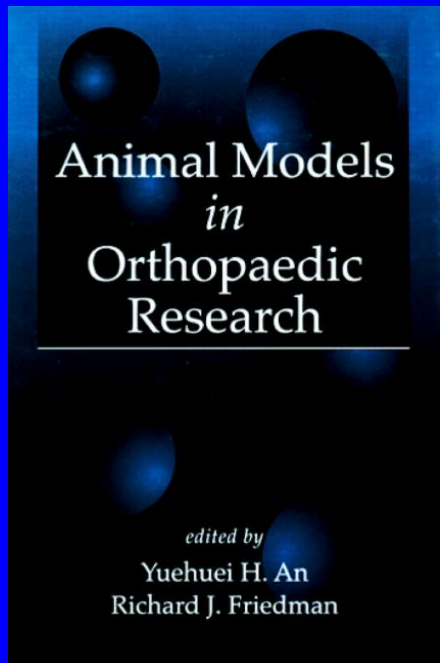


Hierarchy of Evidence

- Progression of evidence
  - Preclinical to Clinical
    - Alkaline phosphatase expression in cell culture to human clinical trials
  - Heterotopic to orthotopic
    - Calvarial defects to posterolateral spine models
  - Phylogenetic progression
    - Eukaryotic cells to human trials

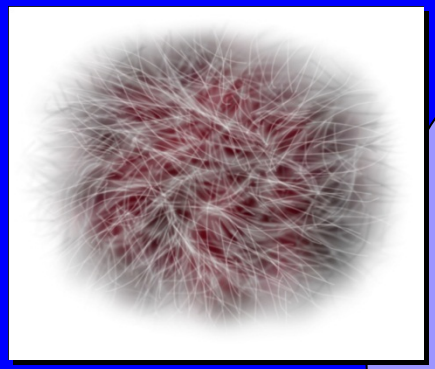






Constituents of a Bone Graft Material

Scaffolds



Growth/Differentiation Factors

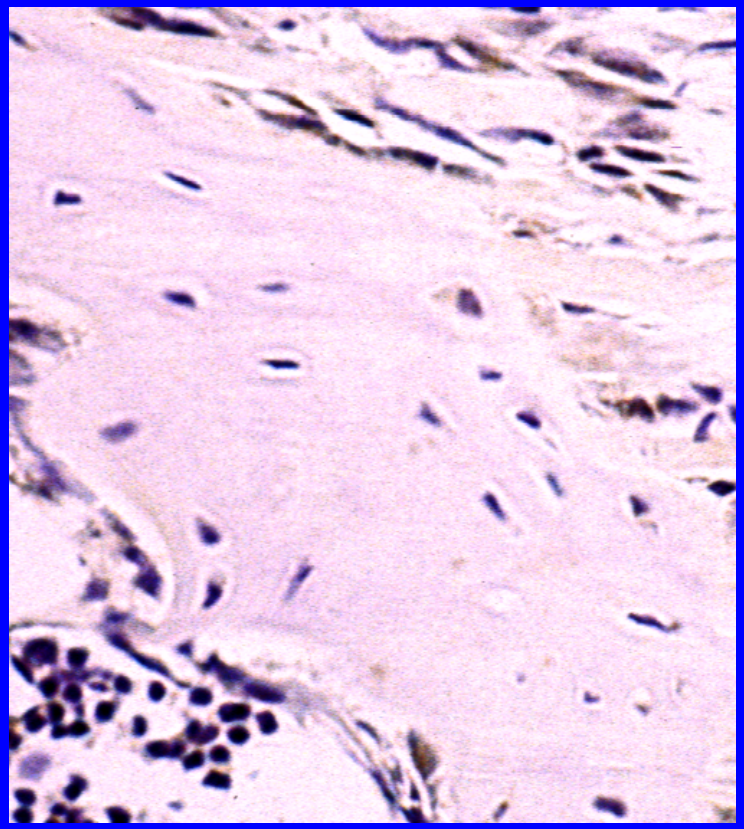
Cells

Composition of the Graft

Cells

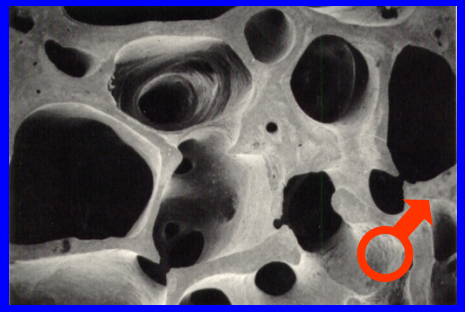
Growth Factors

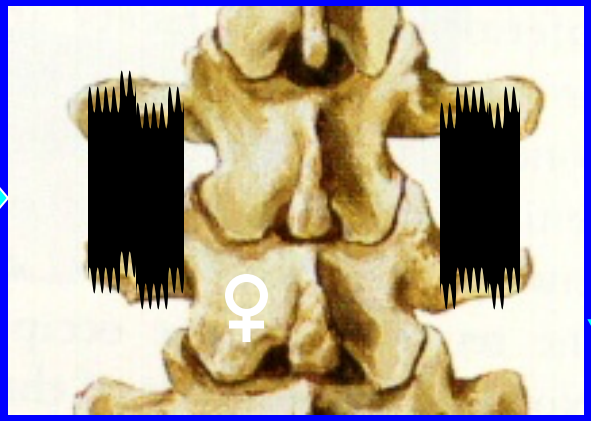
Matrix



Cellular contribution to the Regenerate

- Grafted cells comprise a portion of the final fusion mass
- Grafted cells may also contribute to local inflammation
- Release factors that promote angiogenesis and cellular recruitment

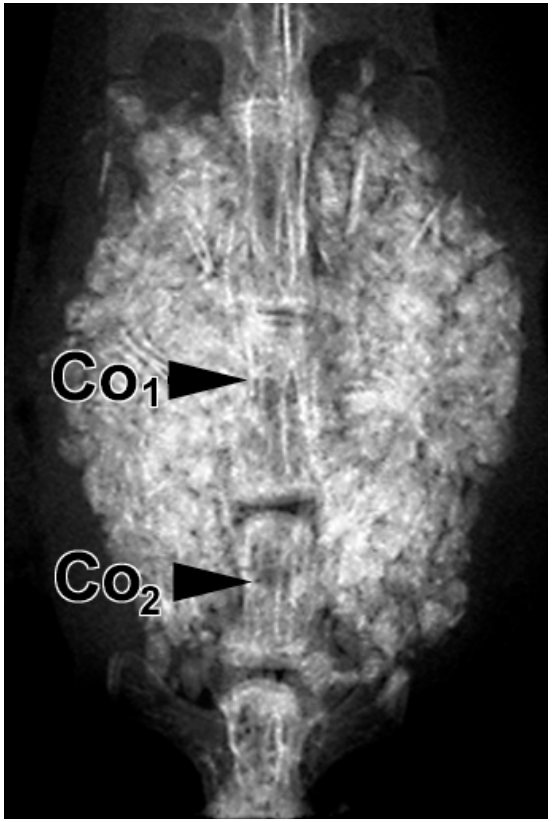


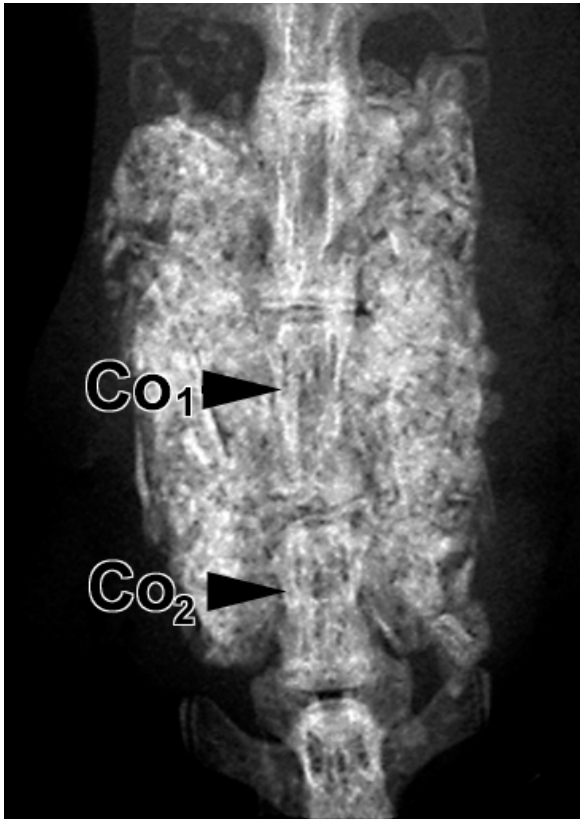


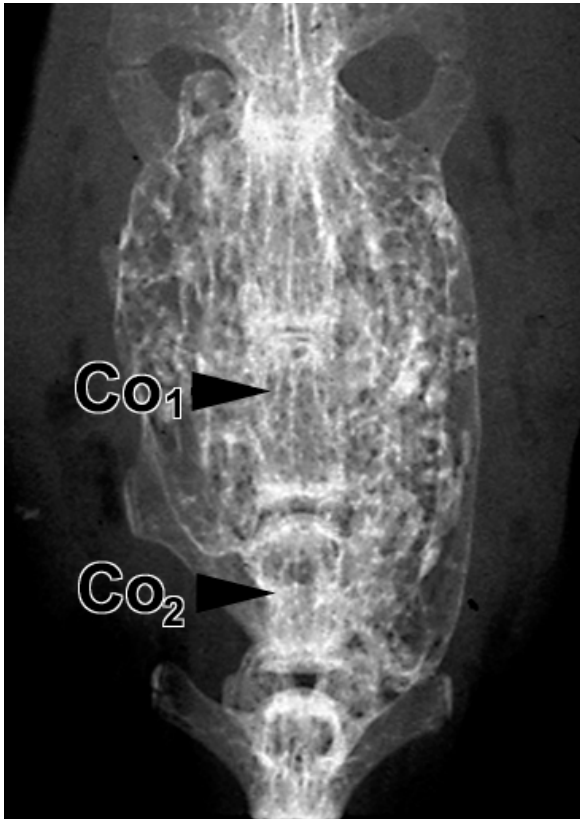
FISH

Track graft derived cells

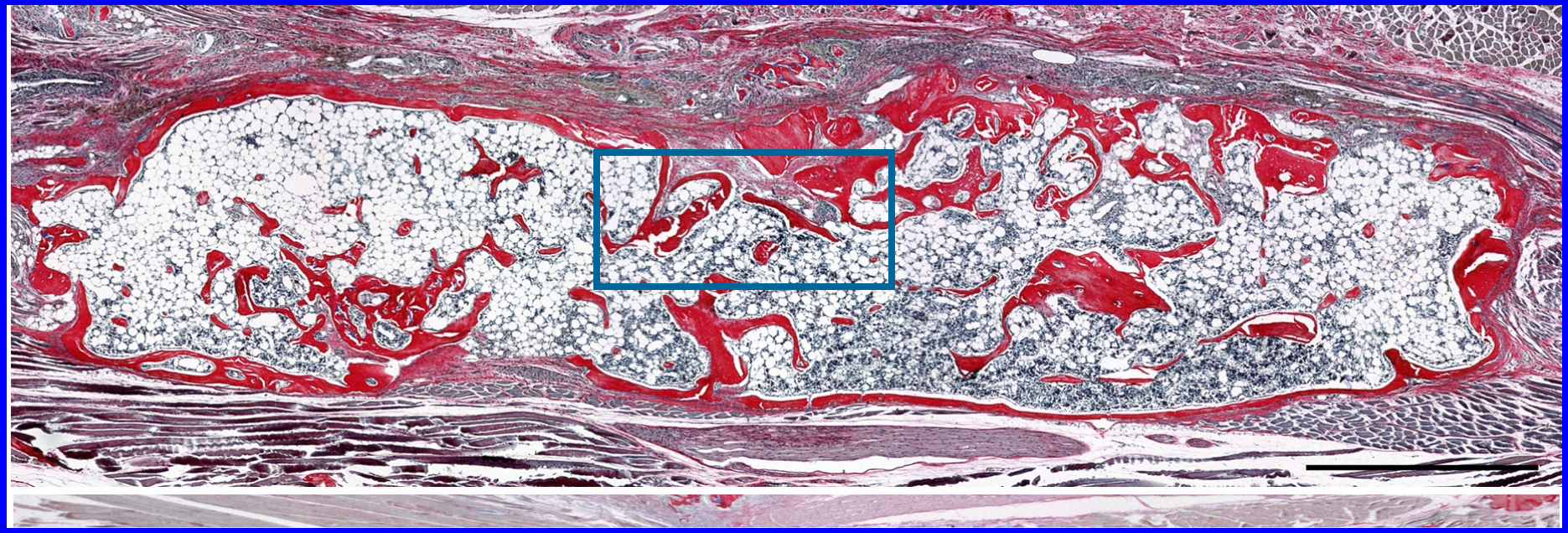
Y-Chromosome


Co1
Co2

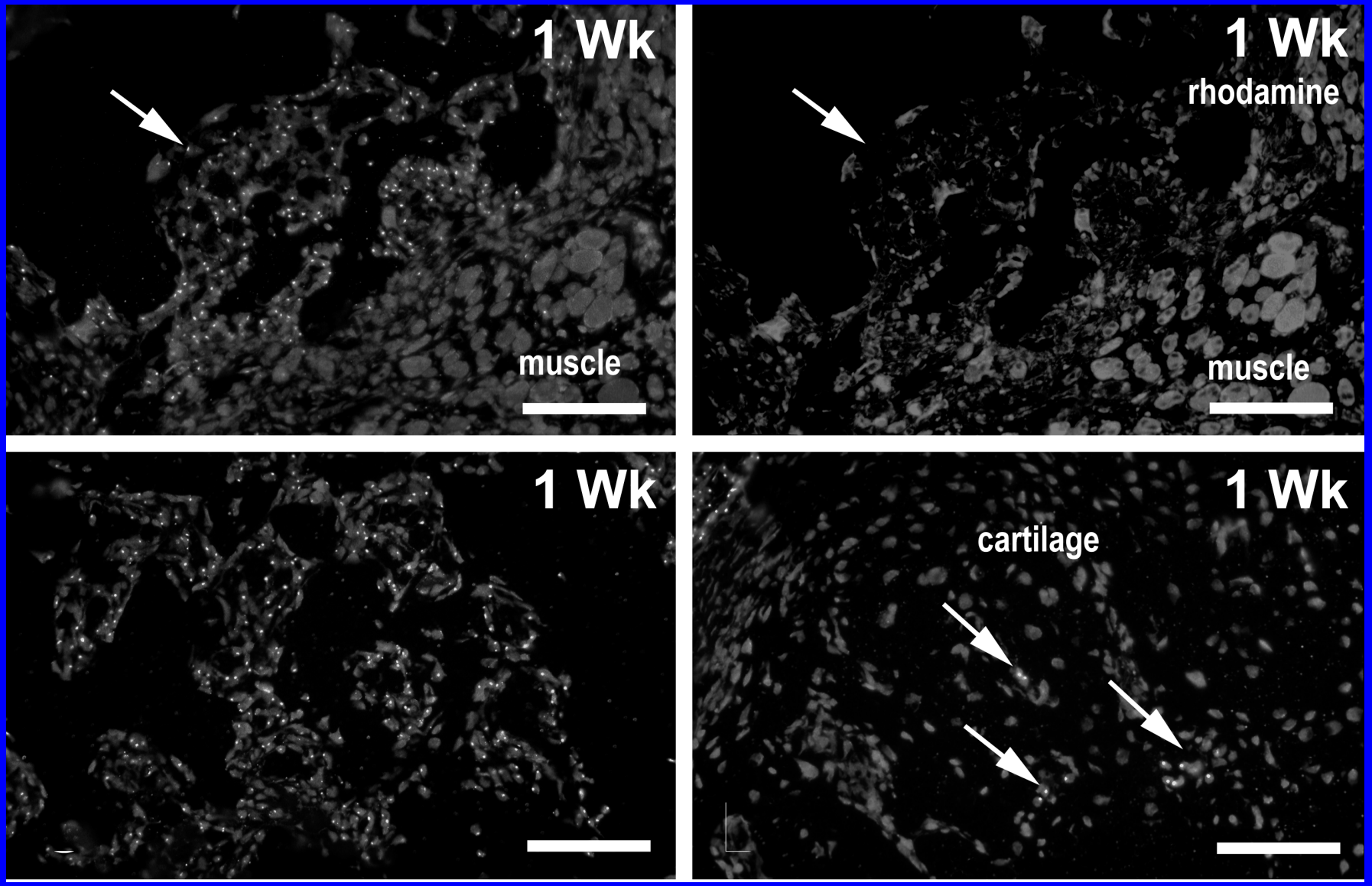

Co1
Co2


Co1
Co2

Murine spinal fusion

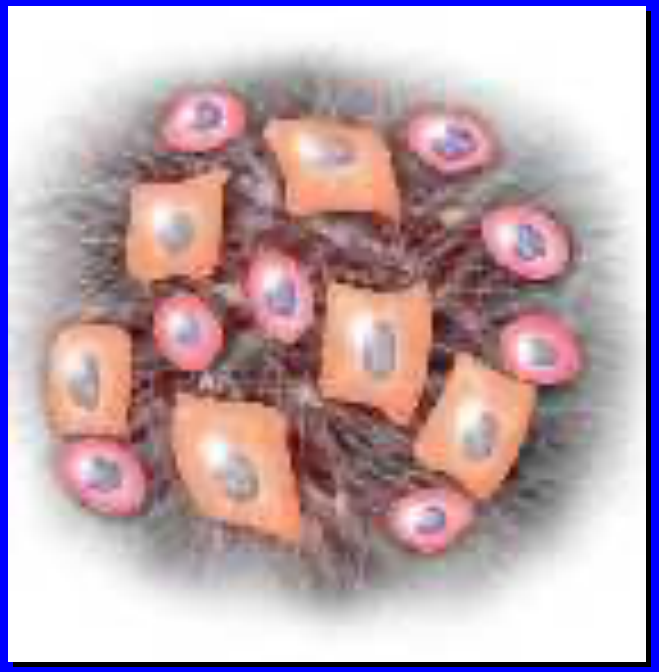


Y-chromosome stain: murine fusion



Cell-based Therapy

- Sources
  - Autogenous
    - Unfractionated Marrow
    - Fractionated Marrow
  - Allogeneic
  - Xenogeneic



- Synchrony
  - Off the shelf
  - Harvest in situ
  - Harvest and process with delayed reimplantation

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

- **Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Products**
  - **Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act**

- be minimally manipulated;
- be intended for homologous use only
- not be combined with a drug or device, except for water, crystalloids, or a sterilizing, preserving, or storage agent
- not have a systemic effect and not be dependent on the metabolic activity of living cells for its primary function
- FDA regulations further define "minimal manipulation" for structural tissue as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

- **Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Products**
  - **Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act**
  - NOT INCLUDED= Drugs and Biologic Products/Compounds
  - CULTURED CARTILAGE CELLS
  - CULTURED NERVE CELLS
  - LYMPHOCYTE IMMUNE THERAPY
  - GENE THERAPY PRODUCTS
  - HUMAN CLONING
  - HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector)
  - UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELLS
  - UNRELATED DONOR LYPHOCYTES FOR INFUSION

Cells

Autogenous

Allogeneic

Xenogeneic

Cadaveric

Live Donor

Bone-derived

Allosource
Trinity
Osteocel
MAP3

Tissue-derived

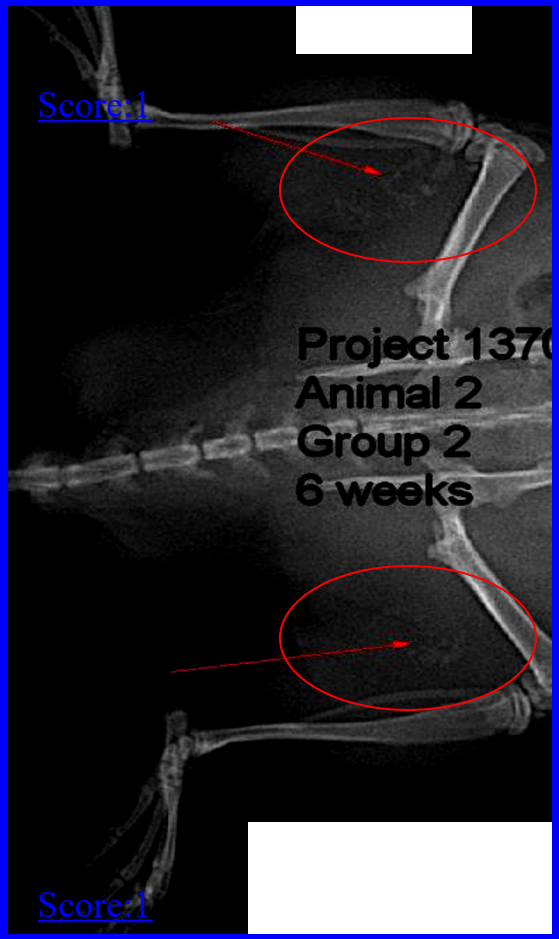
Amniotic Cells- NuCel, Gensano
Placental- Pluristem
Fat- Allosource, Cellerix, Cytori, Tissue Genesis
Umbilical- Gamida Cell, Bio D
Human Embryonic – Aruna, Stemina
Synovial Cell- Puregen

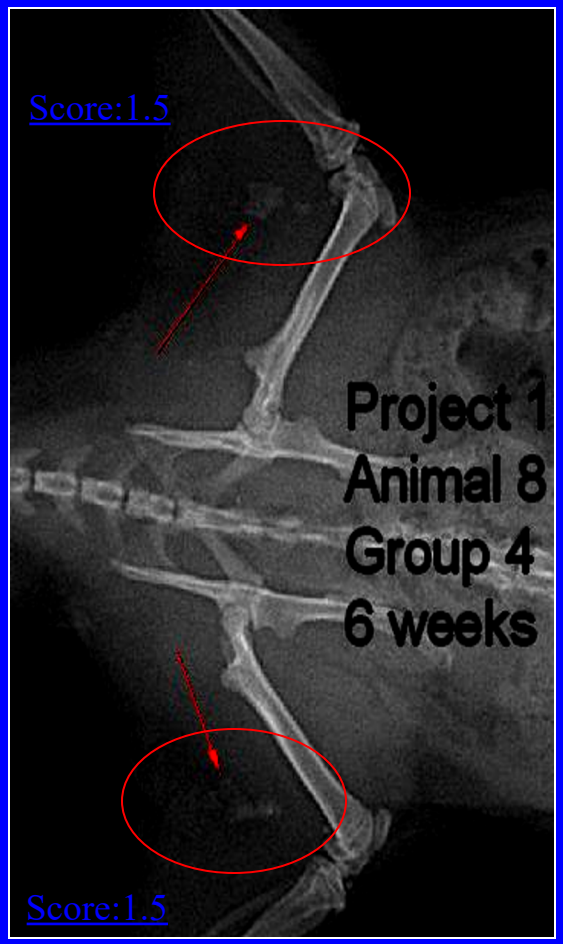
Marrow

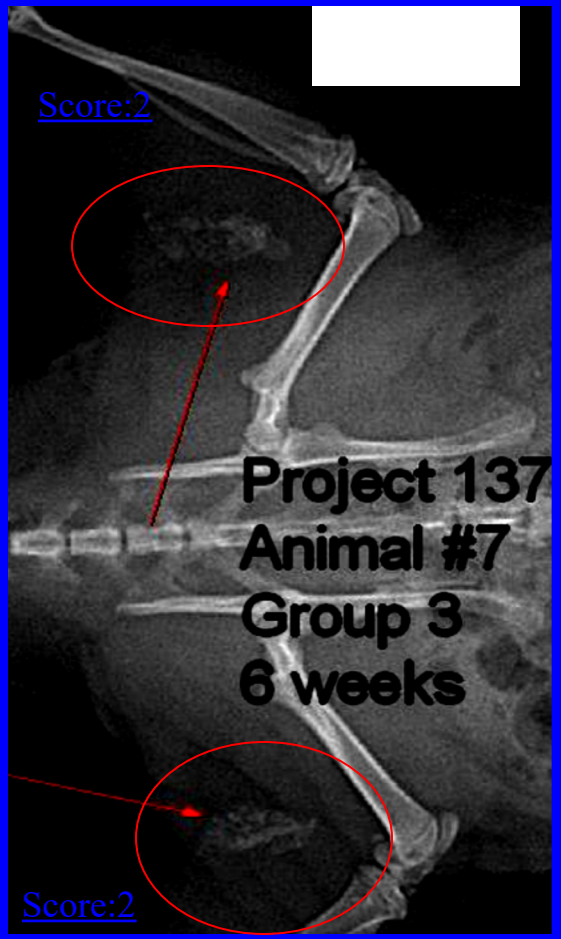
Mesoblast
OsteoAmp

Supportive Evidence

Intramuscular Study: *In-Vivo Study: 6 week results*







BMA* *(with demineralized bone chips)*

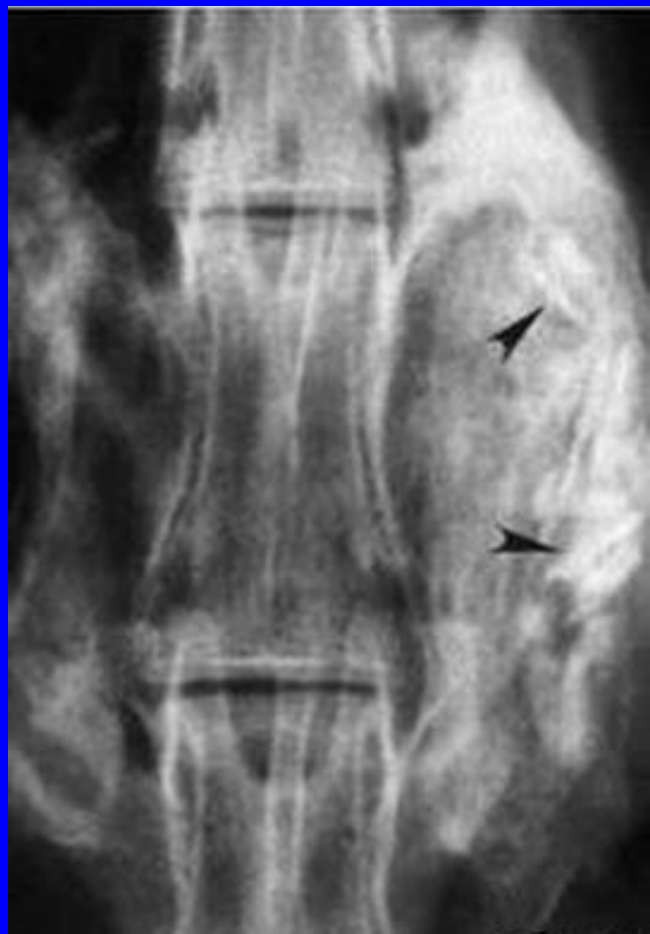
MSC* *(with demineralized bone chips)*

Osteoprogenitor cells *(with demineralized bone chips)*

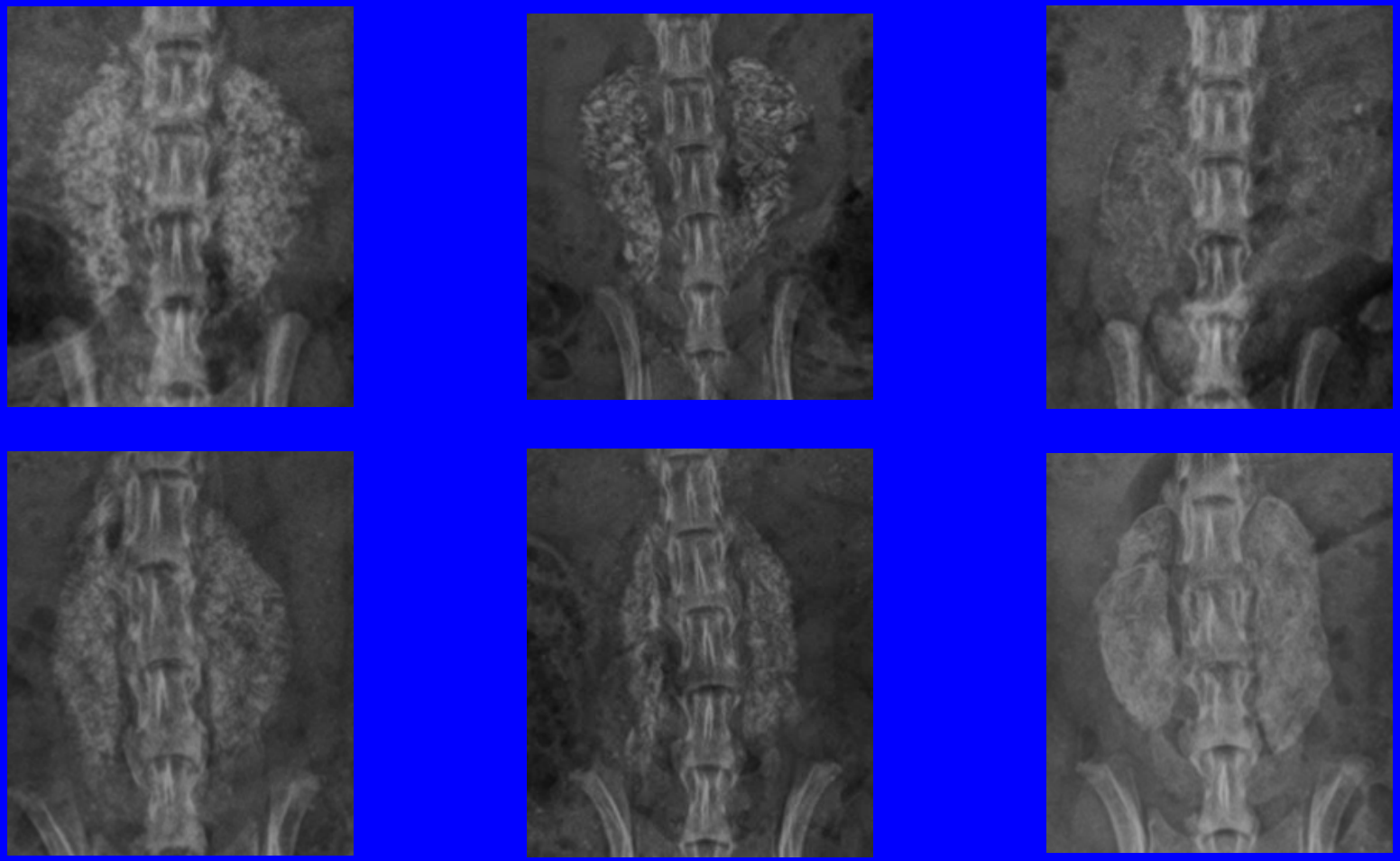
**Note: College Age Donor*

Athymic Rat 2-Level Posterolateral Fusion Model

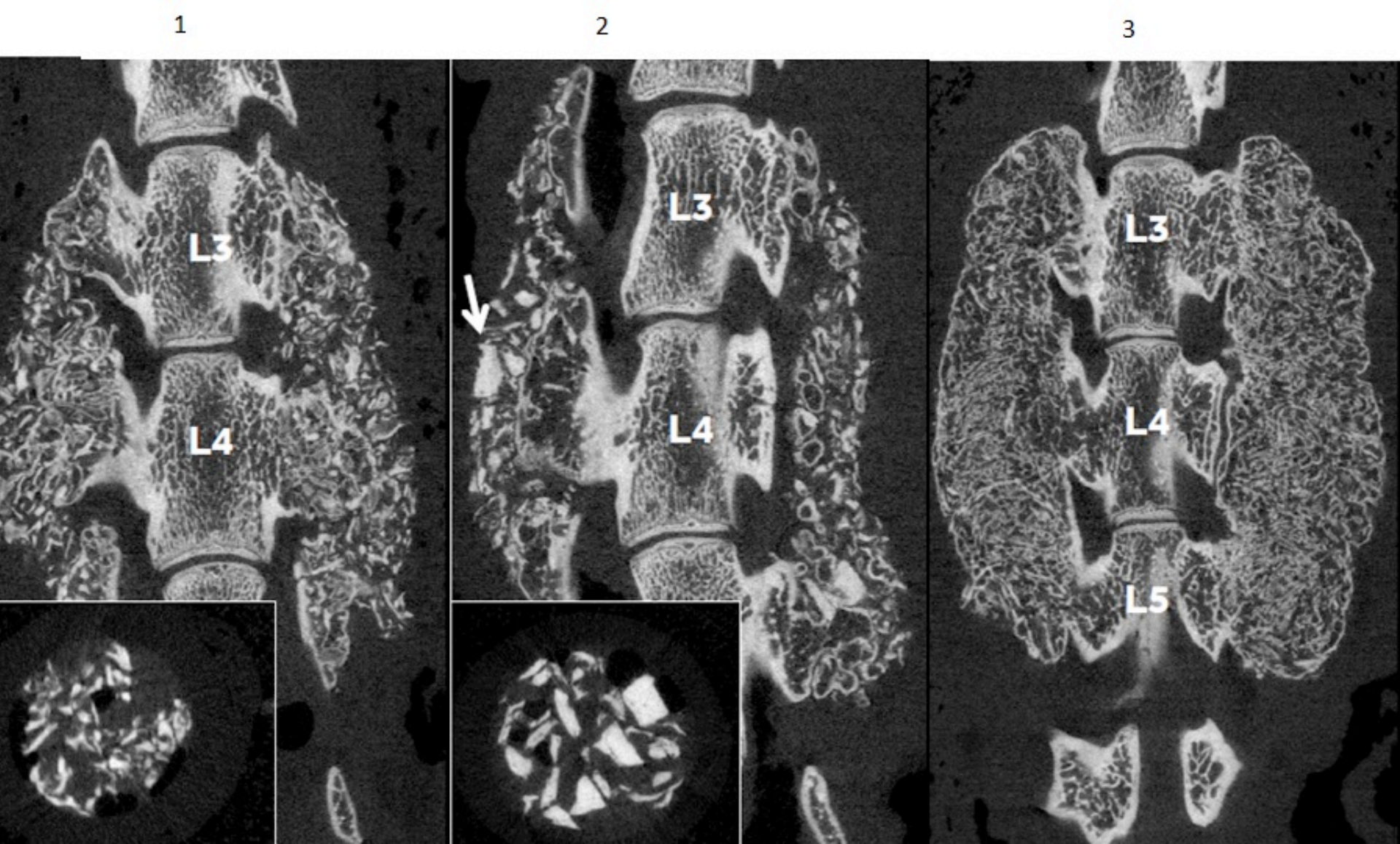
- Direct Comparison of Cell-based DBM preparations and non-cell based DBM



Rat 8 Week 2-Level Spine Fusion



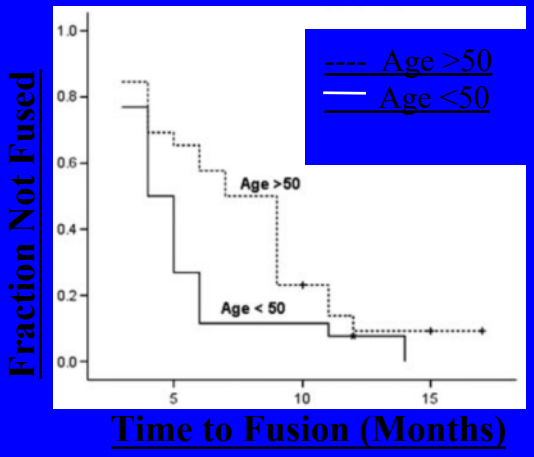
Direct Comparison of bone formation

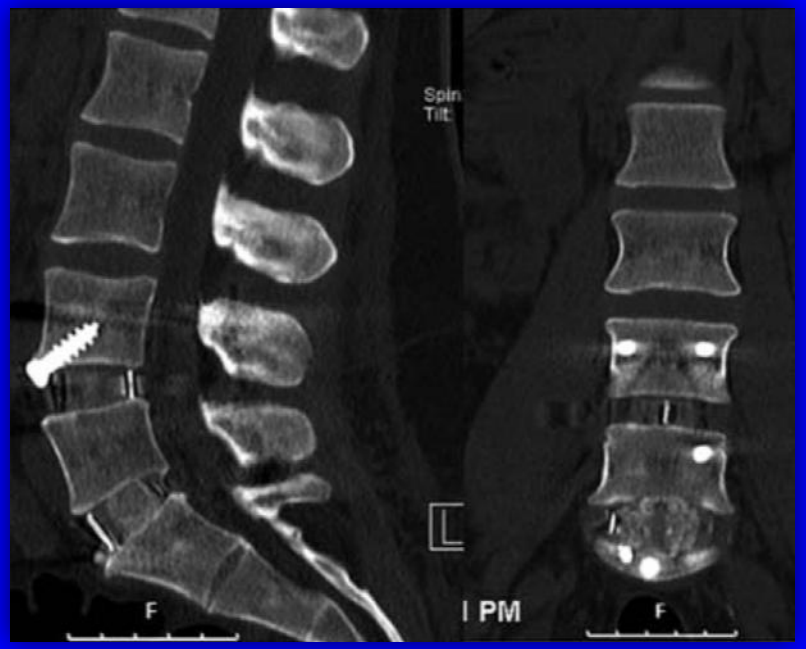


Osteocel® Plus in Lumbar Spinal Fusions

- 52 consecutive lumbar fusion patients[1]
  - Mean age - 50 years old
  - 43% - Smokers; 21% - Previously Failed Fusions

- High union rate: 92.3%
- Median union time: 5 months
- No graft rejection
- 1 wound infection complication: 1.9%





CT Scan of Osteocel Plus Fusion

"Osteocel allograft is safe and effective"

[1]*Kerr, et al., Journal of Surgical Orthopaedic Advances (2011) 20(3); 193-197*

Osteocel Plus Cellular Allograft in Anterior Cervical Discectomy and Fusion

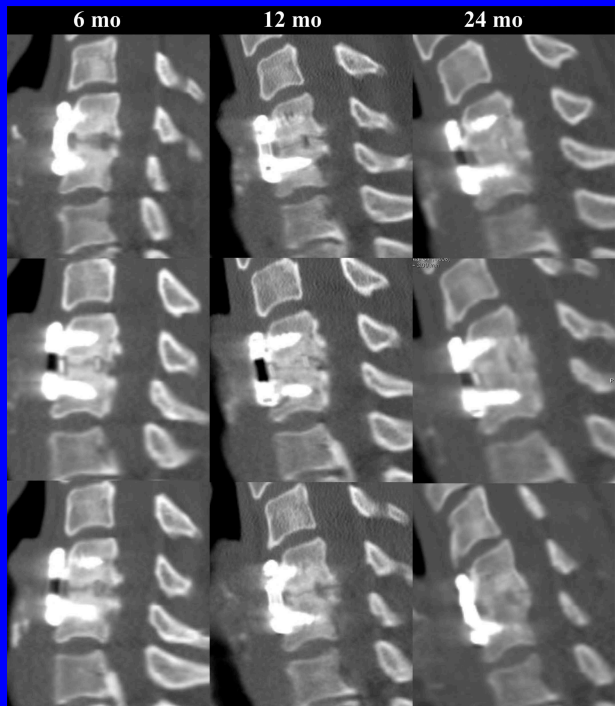
SPINE Volume 39, Number 22, pp E1331-E1337 ©2014

Evaluation of Clinical and Radiographic Outcomes From a Prospective Multicenter Study

Robert K. Eastlack, MD,* Steven R. Garfin, MD,† Christopher R. Brown, MD,‡ and S. Craig Meyer, MD§

- Prospective Multicenter Study, Single Arm
- Fusion rates and clinical outcomes comparable with IDE trials of ACDF vs CDR

Levels in 1-Level Constructs	24-mo Radiographic Results
ROM <3°	95% (76/80)
ROM <5°	100% (80/80)
Solid bridging	89% (75/84)
All Treated Levels	**24-mo Radiographic Results**
ROM <3°	92% (148/161)
ROM <5°	99% (160/161)
Solid bridging	82% (138/169)



Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution® Viable Cellular Bone Matrix) in patients undergoing two-level anterior cervical discectomy and fusion

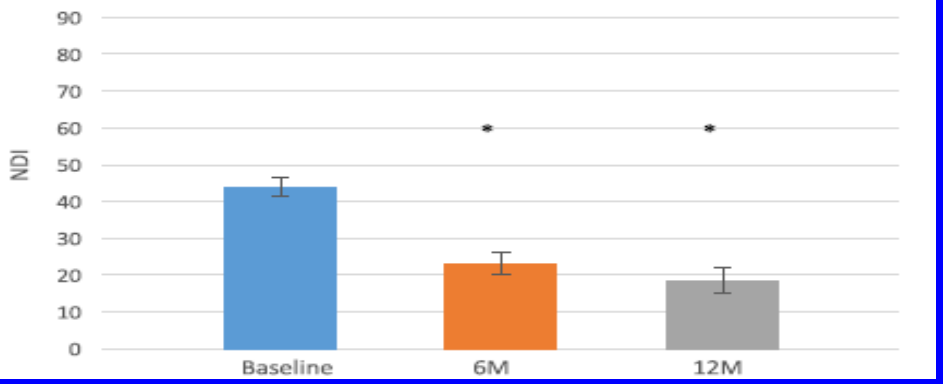
Journal of Orthopaedic Surgery and Research (2017) 12:67

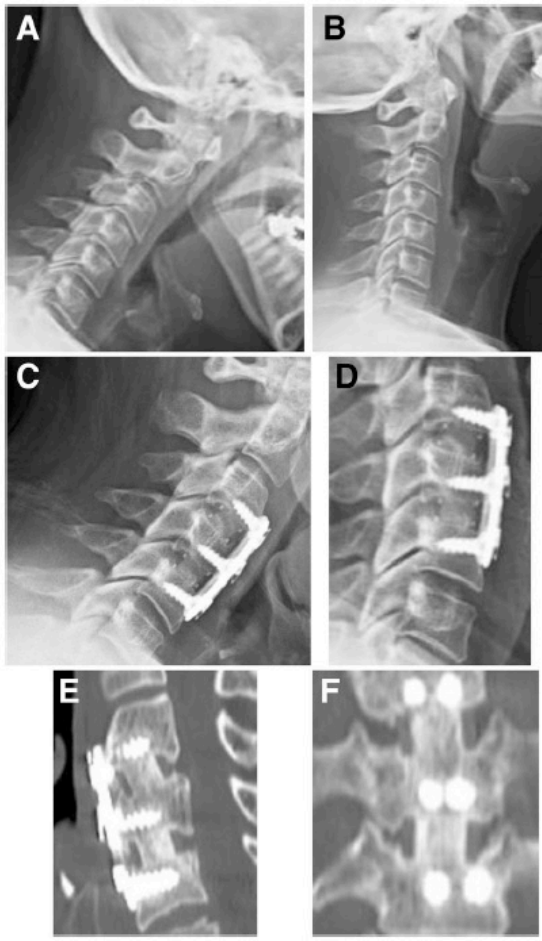
Timothy A. Peppers[1], Dennis E. Bullard[2], Jed S. Vanichkachorn[3], Scott K. Stanley[4], Paul M. Arnold[5], Erik I. Waldorff[6], Rebekah Hahn[6], Brent L. Atkinson[7], James T. Ryaby[6] and Raymond J. Linovitz[8*]

- Multicenter prospective study
- 40 consecutive patients

Table 2 Fusion rates at 6 and 12 months

	Per subject fusion		Per level fusion	
Time (M)	6	12	6	12
Fused *N* (%)	23 (65.7)	34 (89.4)	38 (54.3)	71 (93.4)
Not fused *N* (%)	12 (34.3)	4 (10.6)	32 (45.7)	5 (6.6)





Cellular bone matrices: viable stem cell-containing bone graft substitutes

Branko Skovrlj, MD[a], Javier Z. Guzman, BS[b], Motasem Al Maaieh, MD[b], Samuel K. Cho, MD[b], James C. Iatridis, PhD[b], and Sheeraz A. Qureshi, MD, MBA[b,*]

Spine J. 2014 November 1; 14(11): 2763–2772

Conclusion

Cellular bone matrices may be a promising bone augmentation technology in spinal fusion surgery. Although CBMs appear to be safe for use as bone graft substitutes, their efficacy in spinal fusion surgery remains highly inconclusive. Nonindustry sponsored studies evaluating the efficacy of CBMs are required. Without results from such studies, surgeons must be made aware of the potential pitfalls of CBMs in spinal fusion surgery. Furthermore, CBMs come with a premium price because of the claim that the MSCs within them have the ability to produce bone. However, with the current lack of evidence showing that MSCs can survive in a fusion bed posttransplantation, no such claim can be made. With the currently available data, there is no sufficient evidence to support the use of CBMs as bone graft substitutes in spinal fusion surgery.

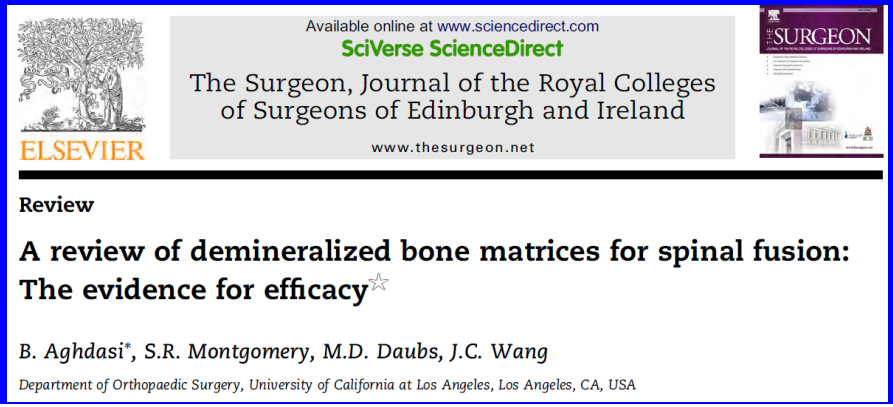
Currently available CBMs (all data is shown exactly as reported by the individual companies; no extrapolations have been made)

Product	Osteocel Plus	Trinity Evolution	Cellentra VCBM	AlloStem	Ovation
Manufacturer	NuVasive, Inc. (San Diego, CA, USA)	Orthofix (Lewisville, TX, USA)	Biomet (Warsaw, IN, USA)	AlloSource (Centennial, CO, USA)	Osiris Therapeutics, Inc. (Columbia, MD, USA)
Source of MSCs	Cadaveric bone	Cadaveric bone	Cadaveric bone	Cadaveric adipose tissue	Live donor placenta chorion layer
Average donor age at harvest (y)	18–44	30	n/a	50	n/a
Total cellular concentration (cells/cc)	3,000,000	≥250,000	≥250,000	66,255	≥400,000
MSC Concentration (MSCs/cc)	n/a	≥1,000	n/a	66,255	n/a
% MSCs	68	n/a	n/a	100	0.0001
Storage temperature	−80°C±5°C *−75°C to −45°C	−80°C	≤−70°C	−80°C	−85°C to −75°C
Shelf life (mo)	60 *3	60	18	60	24
Cell viability once defrosted (h)	≤6	≤2	≤4	n/a	≤1
Osteoinductive cytokines	Naturally occurring in bone	Naturally occurring in bone	BMP-2, 4, 7; VEGF, TGF-β, PDGF; IGF-1; FGF	Naturally occurring in bone	BMP-2, 7; PDGF; VEGF; FGF; IGF-1; TGF-β; PIGF
Osteoconductive carrier	Cancellous bone chips	Demineralized bone	Cancellous bone matrix	Demineralized bone	None (product can be added to any carrier)

CBM, cellular bone matrix; VCBM, viable cell bone matrix; n/a, not available; MSC, mesenchymal stem cell; BMP, bone morphogenetic protein; VEGF, vascular endothelial growth factor; TGF, tissue growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PIGF, placental growth factor; FGF, fibroblast growth factor.

Review of DBM Products

- Systemic Review of MEDLINE using PubMed and Cochrane, CINAHL, and Google Scholar databases
- Articles appraised utilizing the 27-point PRISMA checklist
- 108 articles identified with search terms
- 43 articles meet the inclusion criteria
- Preclinical and clinical articles included



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ELSEVIER

Review

A review of demineralized bone matrices for spinal fusion: The evidence for efficacy☆

B. Aghdasi, S.R. Montgomery, M.D. Daubs, J.C. Wang*
Department of Orthopaedic Surgery, University of California at Los Angeles, Los Angeles, CA, USA

Key points

- DBM has been studied as a bone graft extender, enhancer, and substitute in animal models and human clinical trials.
- Animal models have demonstrated significant intra- and inter-product variability in DBM performance.
- In the cervical spine, a number of case series have demonstrated good results with DBM, but few prospective controlled trials have been performed.
- In the lumbar spine, prospective controlled trials using DBM in posterolateral fusion support the use of DBM as a graft extender.

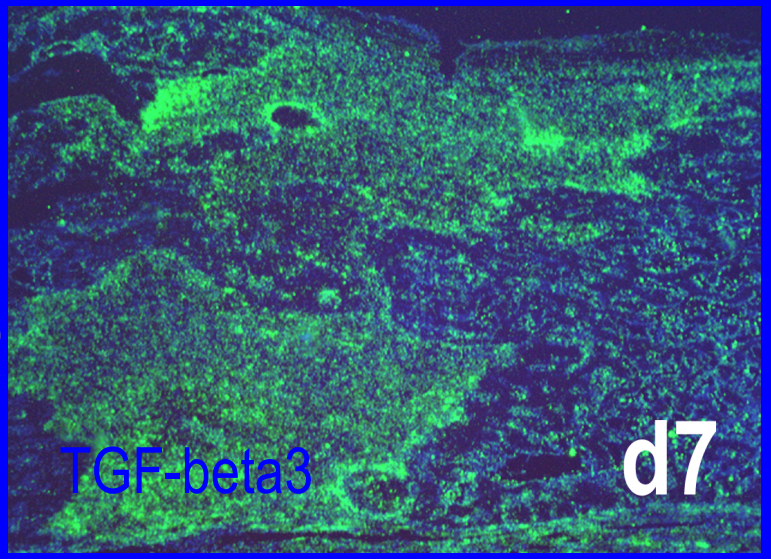
- Aghdasi, et.al. A review of demineralized bone matrices for spinal fusion: The evidence of efficacy. E Surgeon II (2013) 39-48 PMD018671-2.0

Composition of the Graft

Cells

Growth Factors

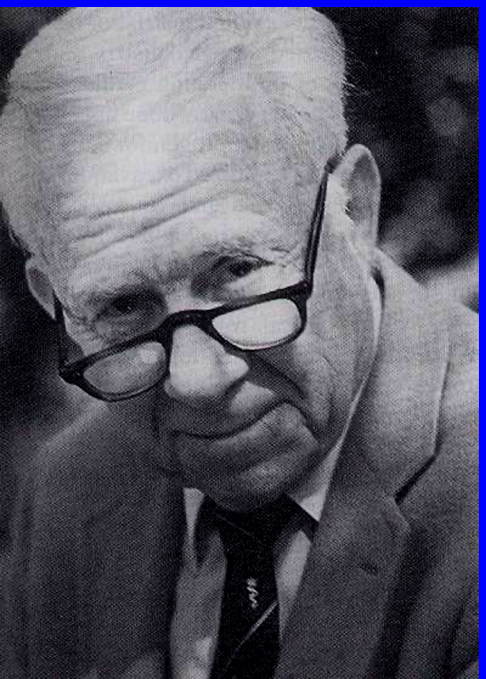
Matrix

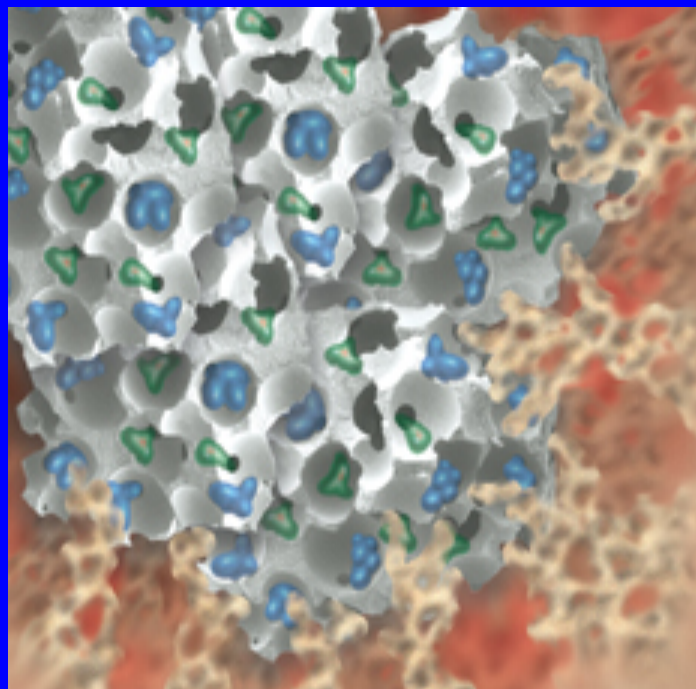


Bone: Formation by Autoinduction

MARSHALL R. URIST
Department of Surgery, University of California Center for Health Sciences, Los Angeles 90024

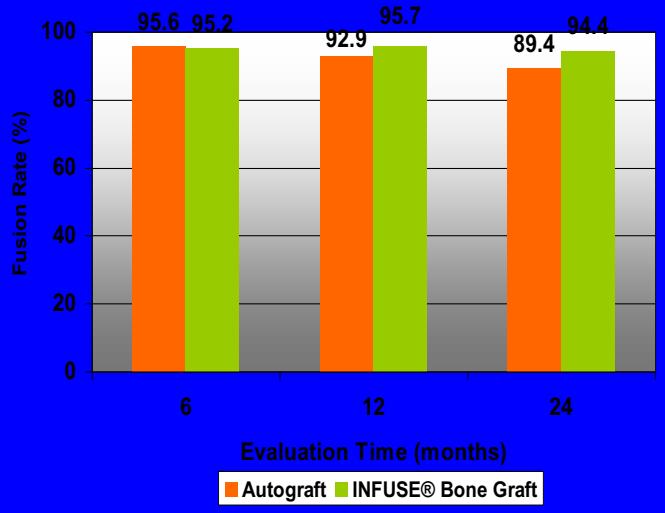
12 NOVEMBER 1965



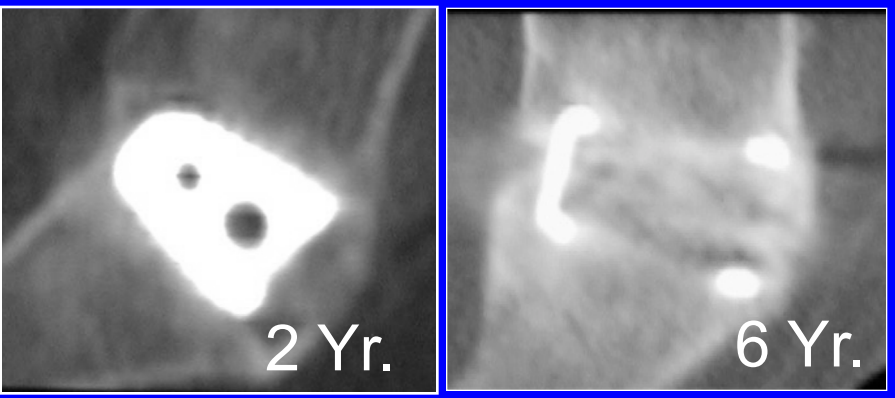


Indication: rhBMP-2/ACS in Anterior Lumbar Fusion

Autograft Control



- 679 total patients
- Postoperative outcomes
  - Eliminate graft donor site pain (>30% @ 2 years) - no ICBG Harvest
  - Improved fusion at 24 months (p= 0.022)
  - Improved clinical outcomes (ODI @2 yrs; p<0.001)
  - Median return to work reduced by 55 days (p<0.02)
- 6-Yr Followup (146 Patients)
  - High fusion success
    - 98% at 6 years
  - ODI, back pain, leg pain Improvements Maintained



Burkus *et al.*, *J Spinal Dis*, 2003

PMD018671-2.0

JB&JS

Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, Matthew F. Gornet, Thomas C. Schuler, Thomas J. Kleeman and Thomas A. Zdeblick
J Bone Joint Surg Am. 2009;91:1181-1189. doi:10.2106/JBJS.G.01485

REVIEW | Annals of Internal Medicine

Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion

A Systematic Review and Meta-analysis

Rongwei Fu, PhD; Shelley Selph, MD; Marian McDonagh, PharmD; Kimberly Peterson, MS; Arpita Tiwari, MHS; Roger Chou, MD; and Mark Helfand, MD, MS

- 13 RCTs and 31 Prospective Cohort Studies
  - Similar Fusion Rates and Overall Success
  - Similar adverse events
  - BMP-2 associated with increased cancer rate
    - Small numbers and heterogeneous tumors
  - Early disclosure of all data would have better informed physicians and public than original trial publications did

Annals of Internal Medicine

REVIEW

Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion

A Meta-analysis of Individual-Participant Data

Mark C. Simmonds, PhD, MA; Jennifer V.E. Brown, MSc, BA; Morag K. Heirs, MSc, MA; Julian P.T. Higgins, PhD, BA; Richard J. Mannion, PhD; Mark A. Rodgers, MSc, BSc; and Lesley A. Stewart, PhD, MSc, BSc

Figure 4. Meta-analysis of adverse events at or shortly after surgery in 11 Medtronic trials.

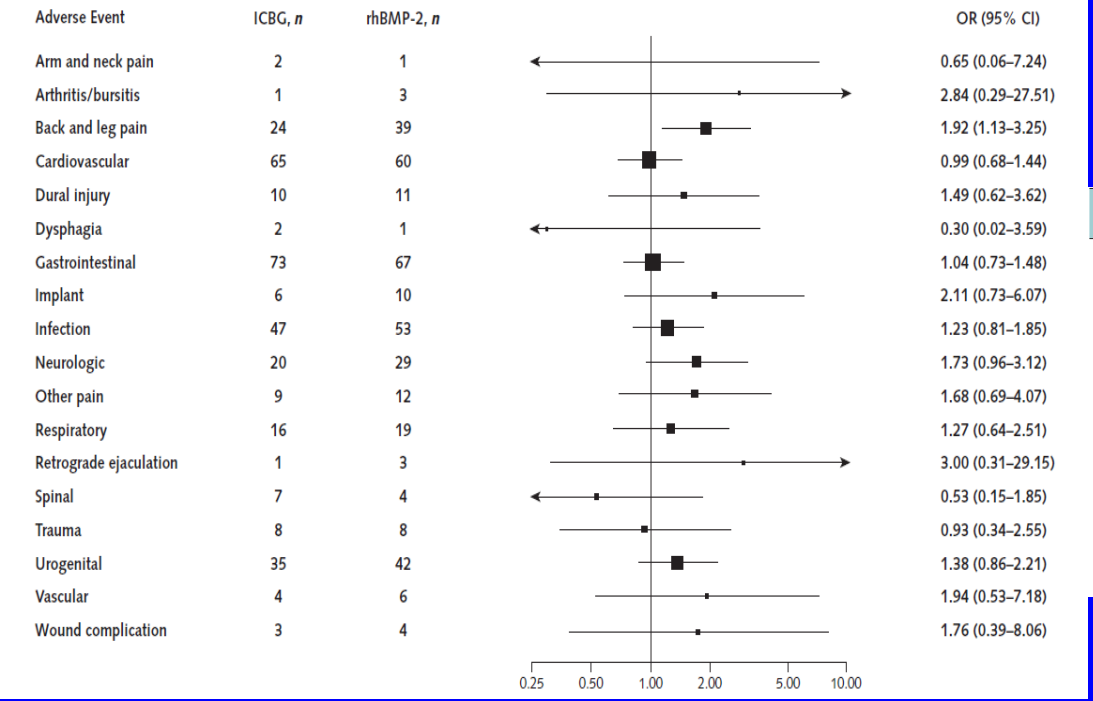
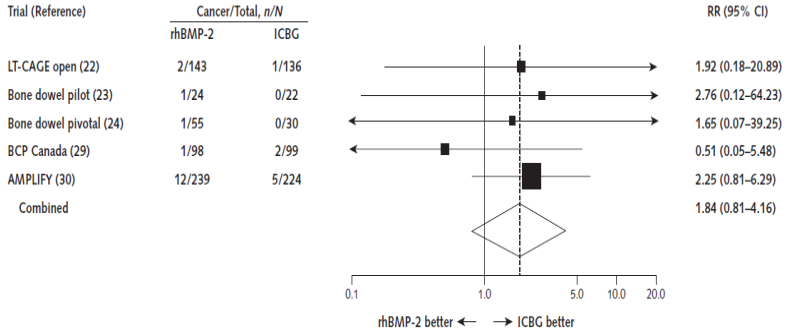


Figure 5. Forest plot of cancer incidence in the Medtronic trials.

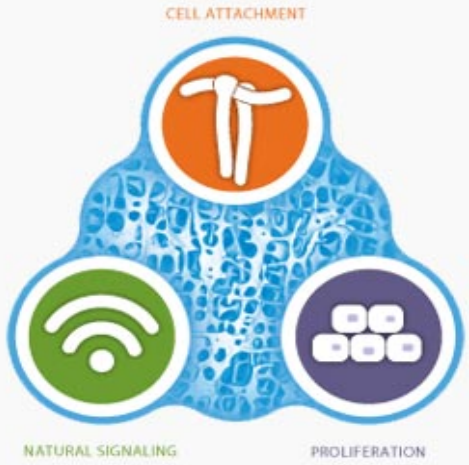


i-Factor

- i-Factor is a composite bone substitute material consisting of the P-15 synthetic collagen fragment adsorbed onto anorganic bone mineral and suspendedin an inert biocompatible hydrogel carrier.

CERAPEDICS

Enhancing the Science of Bone Repair



Efficacy of i-Factor Bone Graft *versus* Autograft in Anterior Cervical Discectomy and Fusion

Results of the Prospective, Randomized, Single-blinded Food and Drug Administration Investigational Device Exemption Study

SPINE Volume 41, Number 13, pp 1075–1083 2016

Paul M. Arnold, MD,* Rick C. Sasso, MD,† Michael E. Janssen, MD,‡ Michael G. Fehlings, MD, PhD,§ Joseph D. Smucker, MD,† Alexander R. Vaccaro, MD, PhD,¶ Robert F. Heary, MD,‖ Ashvin I. Patel, MD,** Benoit Goulet, MD,†† Iain H. Kalfas, MD,‡‡ and Branko Kopjar, MD, PhD§§

- Multicenter prospective randomized study comparing Local Allograft with iFactor in cortical ring allograft in ACDF
- Control subjects received a cortical allograft ring filled with autograft bone collected from osteophytes and endplate preparation during the procedure. Investigational subjects received a cortical allograft ring filled with an average of 0.78 cc (range 0.15–4.0 cc) of i-Factor

Non-inferiority

Test Parameter	i-Factor (n = 161)		Autograft (n = 152)		P
	Least Squares Mean	95% Confidence Intervals	Least Squares Mean	95% Confidence Intervals	
VAS					
Neck pain	4.45	4.00–4.90	4.39	3.96–4.82	0.8257
Arm pain	4.89	4.44–5.34	4.85	4.40–5.30	0.9010
SF-36v2					
Physical health component	10.02	8.39–11.66	9.95	8.25–11.65	0.9520
Physical function	9.22	7.60–10.84	9.58	7.97–11.19	0.7497
Physical role limitation	13.52	11.57–15.46	13.56	11.47–15.65	0.9756
Bodily pain	14.67	12.96–16.38	13.90	12.16–15.64	0.5373
General health	1.10	−0.49 to 2.70	0.73	−0.78 to 2.25	0.7381
Mental health component	8.33	6.66–10.01	8.21	6.48–9.95	0.9204
Emotional well-being	7.93	6.40–9.46	7.80	6.18–9.42	0.9101
Emotional role limitation	10.02	7.88–12.16	10.27	8.27–12.27	0.8651
Social functioning	12.12	10.23–14.02	11.69	9.75–13.63	0.7478
Energy/fatigue	8.94	7.32–10.55	8.78	7.04–10.52	0.8976
Odom criteria	P-15 Putty (n = 129)	%	Autograft (n = 129)	%	0.9929*
Excellent	80	62.0%	80	62.0%	
Good	25	19.4%	25	19.4%	
Fair	16	12.4%	15	11.6%	
Poor	8	6.2%	9	7.0%	

**Chi-square for statistical difference between P-15 Putty and autograft.*

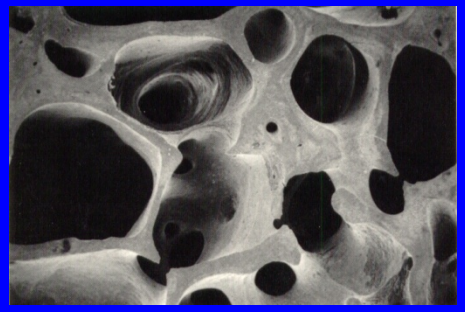
- Overall success rate consisting of fusion, NDI, Neurological, Success and Safety Success was higher in i-Factor subjects than in autograft subjects (68.75% and 56.94%, p=0.0382)

Composition of the Graft

Cells

Factors

Matrix



Bone Graft Matrices

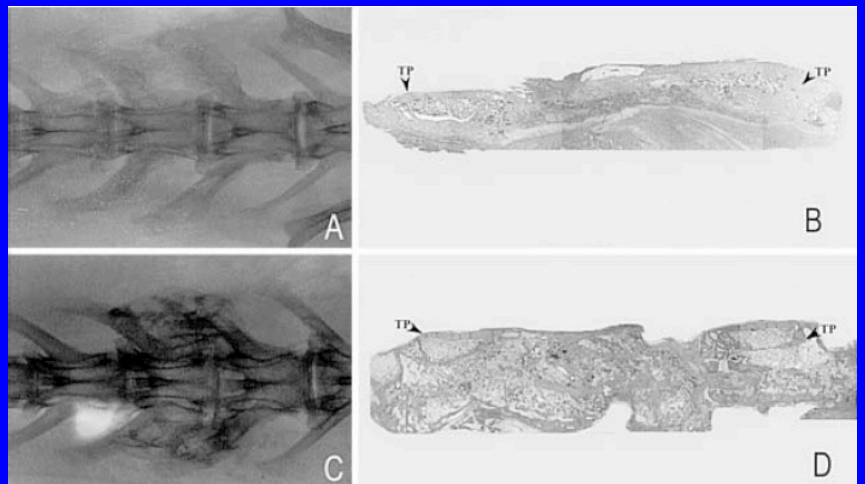
- Allograft
- Demineralized Bone Matrices
- Collagen
- Coralline Hydroxyapatite
- Synthetic Matrices
  - Calcium Sulfate
  - Hydroxyapatite
  - Tricalcium Phosphate
  - Nanochrystalline Hydroxyapatite
  - Bioglass

Sigurd Berven
Bobby K.B. Tay
Frank S. Kleinstueck
David S. Bradford

Eur Spine J (2001) 10 : S169–S177

Clinical applications of bone graft substitutes in spine surgery: consideration of mineralized and demineralized preparations and growth factor supplementation

- Synthetic matrices mimic the inorganic phase of bone
- Advantages of ceramic matrices include low immunogenicity and toxicity, stability at physiologic pH levels, and the ability to withstand sterilization procedures without losing structural integrity.



Matrix Properties

- Resorption rate
- Cell adherence
- Osteoconduction
  - Cell adherence/migration assays
- Osteoactivation
  - Alkaline phosphatase/Osteocalcin expression

Spine
SPINE Volume 36, Number 20, pp E1328–E1334

LITERATURE REVIEW

The State of Lumbar Fusion Extenders

Kalil G. Abdullah, BS,*†‡ Michael P. Steinmetz, MD,*†‡ Edward C. Benzel, MD,*†‡ and Thomas E. Mroz, MD*†‡§

- Fusion Extenders Reviewed:
  - DBM
  - Calcium Phosphate
  - Calcium Sulfate

Spine
SPINE Volume 36, Number 20, pp E1328–E1334

LITERATURE REVIEW

The State of Lumbar Fusion Extenders

Kalil G. Abdullah, BS,*†‡ Michael P. Steinmetz, MD,*†‡ Edward C. Benzel, MD,*†‡ and Thomas E. Mroz, MD*†‡§

- Calcium phosphate is the most supported of the lumbar fusion extenders.
- These formulations are supported by these initial studies but in some cases need to be better examined with regard to side effect profiles.

Spine

SPINE Volume 37, Number 16, pp E993–E1000

LITERATURE REVIEW

Osteoconductive Bone Graft Extenders in Posterolateral Thoracolumbar Spinal Fusion

A Systematic Review

Khalid A. M. Alsaleh, MBBS, FRCSC,*† Caroline A. Tougas, MD,*‡ Darren M. Roffey, PhD,*§ and Eugene K. Wai, MD, MSc, FRCSC*§‖

- Overall quality of studies very low
  - Cochrane Risk of Bias 4.8 (3-6)

"Caution should be taken in interpreting these findings, given the low quality of the studies and the heterogeneity in the results. Randomized controlled studies using blinded assessments are required to help elucidate more conclusive evidence."

Systematic Review of Stem Cells in Spine Fusion

Table 2: studies included for key question 1.

Reference	Design	Patients number	Diagnosis	Region	Fusion type	Study group 1	Study group 2	Control group	Fusion rates	Level of evidence
Kitchel 2006	RCT	25	Degenerative	Lumbar	PLF+IF	Mineralized collagen +BMA		ICBG	Study: 80% Control: 84% IF: 92%	II
Neen 2006	Case control	50	NS	Lumbar	PLF/TLIF/ 360	Collagen/HA + BMA		ICBG	Study: IF=85%, PLF=93% Control: IF=92%, PLF=93%	III
Niu 2009	Prospective cohort	21	Degenerative	Lumbar	PLF	LBG+BMA	CaSu+BMA	ICBG	Study1: 85.7% Study2: 45% Control: 90.5%	III
Vaccaro 2007	Prospective cohort	73	Degenerative	Lumbar	PLF	DBM+BMA	DBM+ICBG	ICBG	Study1:63% Study2: 70% Control: 67%	III

RCT: randomized controlled trial, PLF: postero-lateral fusion, IF: inter-body fusion, TLIF: trans-formainal lumbar inter-body fusion, BMA: bone marrow aspirate, HA: hydroxyapatite, LBG: local bone graft, DBM: demineralized bone marrow, CaSu: calcium sulfate, ICBG: iliac rest bone graft.

Selective Application

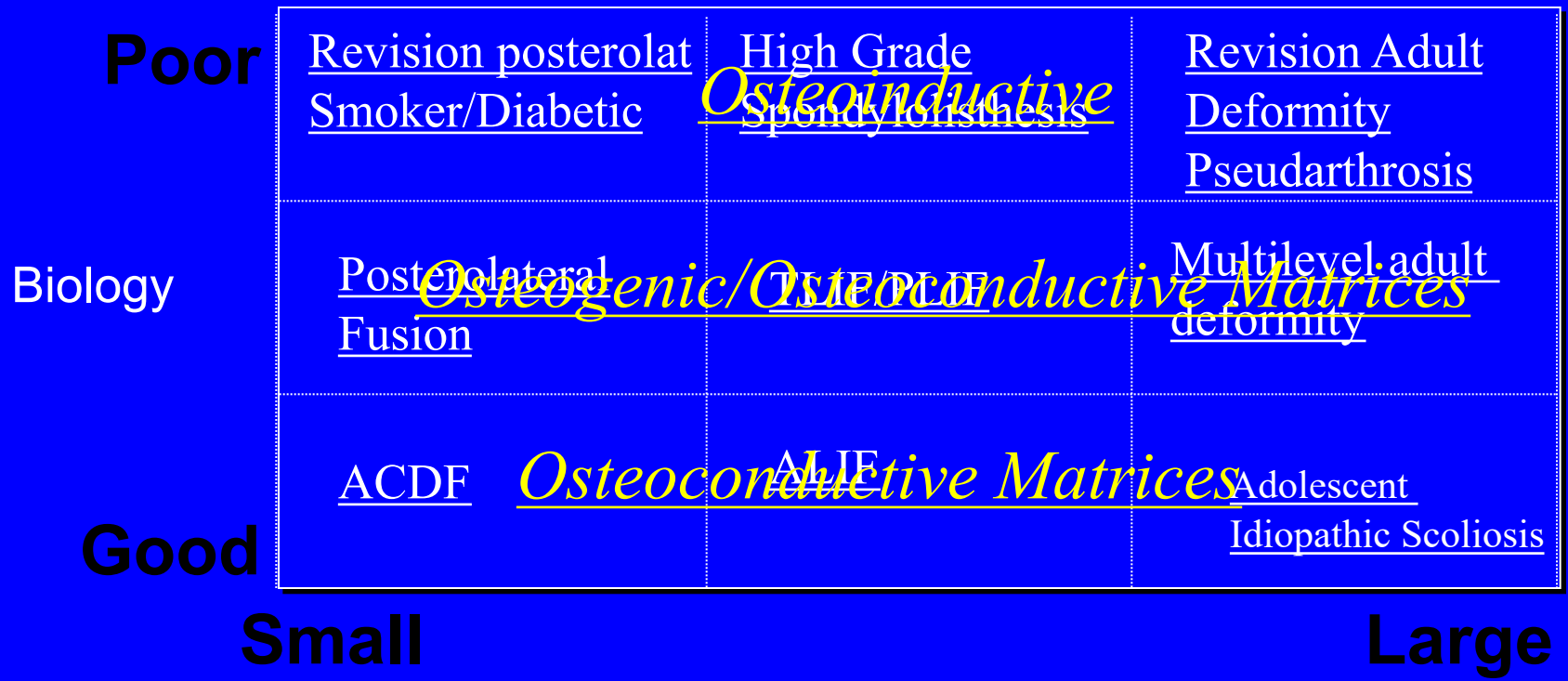
- When do we need our most potent osteobiologics?
- When are more potent osteobiologics inappropriate?
  - Clinical efficacy
  - Cost
  - Complication profile

Biologics Applications:

Biology	Small		Large
Poor	Revision posterolat Smoker/Diabetic	High Grade Spondylolisthesis	Revision Adult Deformity Pseudarthrosis
	Posterolateral Fusion	TLIF/PLIF	Multilevel adult deformity
Good	ACDF	ALIF	Adolescent Idiopathic Scoliosis

Bone defect size

Biologics Applications:



Conclusion

- There is tremendous variability in the choice of bone graft substitutes for common spine applications
- Decision-making on bone graft materials is often made with incomplete data
- Matching graft choice with patient need may provide a framework for informed choice
- Future use of Incremental Cost Effectiveness Analysis to evaluate utility of osteobiologics in the spine may lend insight into cost-effective solutions

Thank You

UCSF Center for Outcomes Research