The Use of Bone Marrow Stem Cells for Osteoarthritis

Rafael Gonzalez, Ph.D.

Vice President of Research and Development

DaVinci Biosciences, LLC

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Arthritis

- Involves the breakdown of cartilage
- Over 100 forms of arthritis
  -rheumatoid, osteo, lupus, psoriasis, etc
  -Osteo is the most common form
- Affects over 37 million people in the US (1 in 7 people)
  -Estimated 67 million by 2030



- Costs are greater than $128 billion (CDC; 2009)

http://www.cbsnews.com/stories/2007/01/11/health/main2351656.shtml

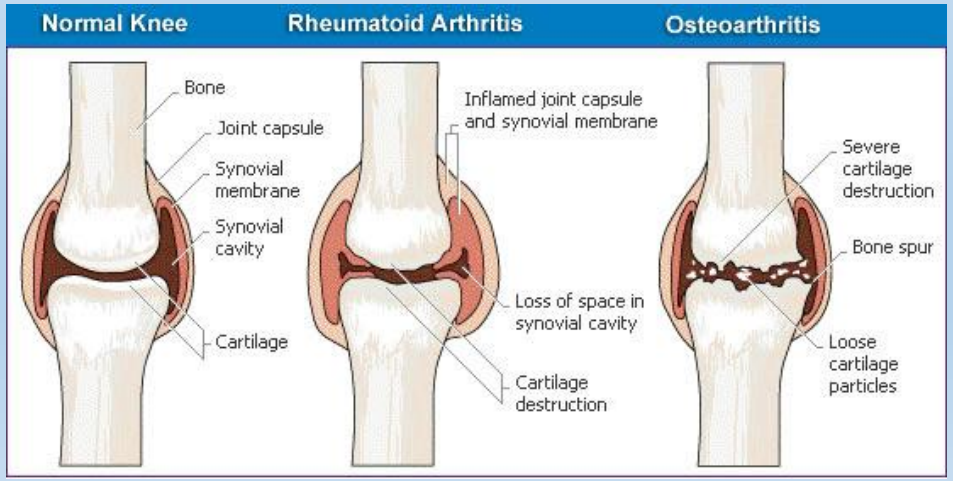
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Arthritis

- Presently no cure
- Standard of care: cortisone therapy, anti-inflammatories, analgesics, small biologics, surgery, physical therapy

  - Described as “inadequate as they only treat symptoms of pain and inflammation”

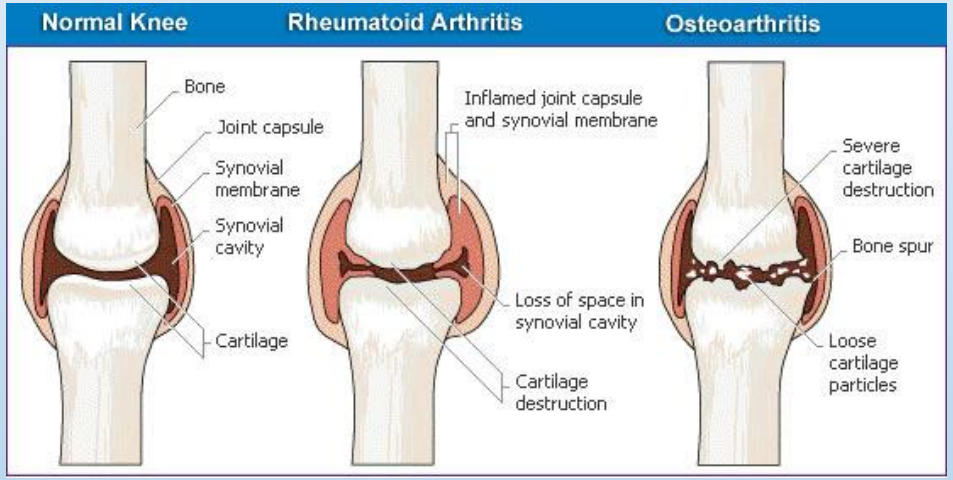
- Alternatives: glucosamine, chondroitin, methysulfonylmethane (MSM), hyaluronic acid



Mobasheri et al., 2009

Arthritis

- Problem 1: an immune response that causes damage most frequently to the joints



- Problem 2: Joints have poor capacity for healing and repair

  -Cartilage regeneration is minimal or incorrectly repaired

Mobasheri et al., 2009

Arthritis and Stem Cells

- Greater than 1300 peer reviewed publications in the field (pubmed.com -2014)
- The most described cell type: Mesenchymal stem cells (MSCs)
  - Multipotent
  - Immunomodulatory and anti-inflammatory properties
  - Trophic support
- Described as early as 1991 with therapeutic technology in mind --- Caplan 1991. Mesenchymal Stem Cells. J Orthop Res.

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MSCs

- Can be isolated from:

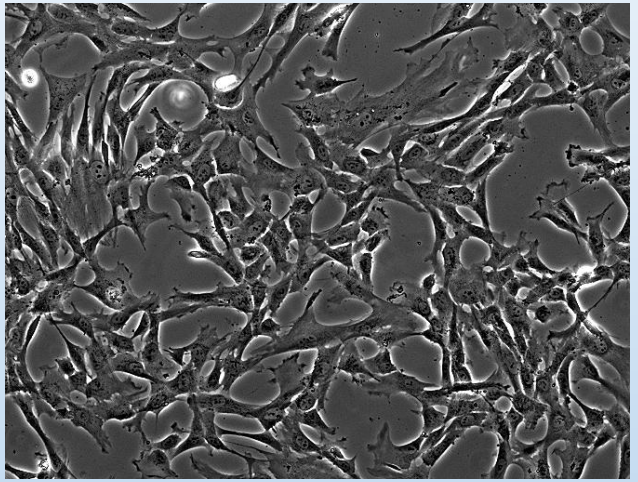
  bone marrow, adipose tissue, dental pulp

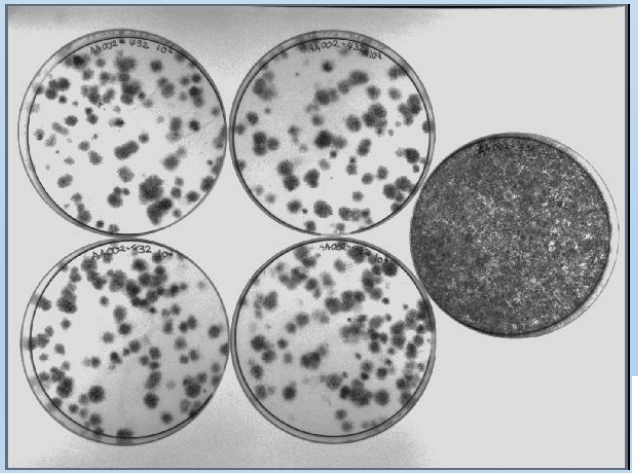
  umbilical cord tissue, synovial, testes, etc

- Highly expandable-without losing ability to differentiate

  -age, disease & culture condition dependent

- Should form CFUs





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MSCs

International Guidelines for MSCs

- Minimum criteria*

  - Plastic adherent
  - (+) CD105, CD73, CD90
  - (-) CD34, CD45, CD14/11, CD19, HLA-DR
  - Differentiate to Mesoderm (osteoblast, adipocytes,chondroblasts)

*Dominci et al., 2006. Minimal Criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4): 315-317

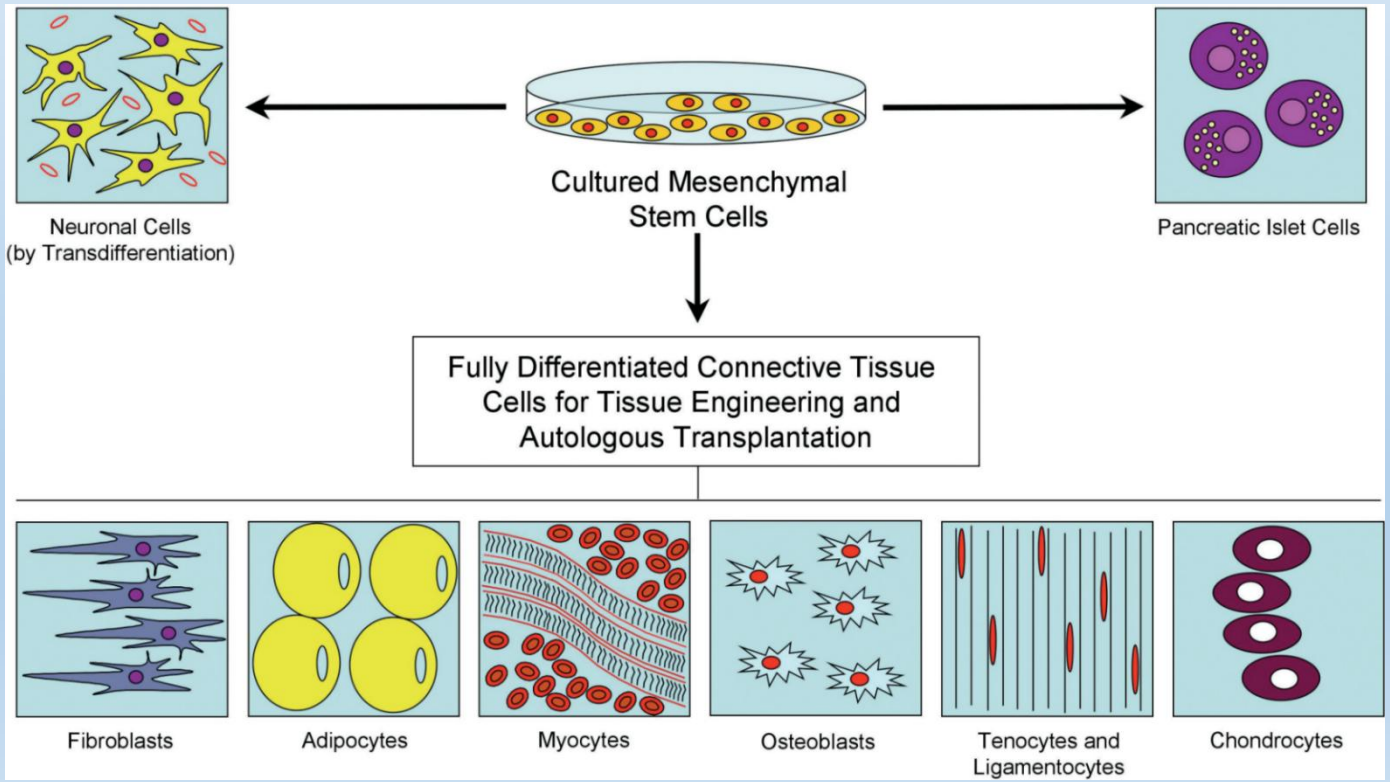
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Why Mesenchymal Stem Cells?

- Mesoderm

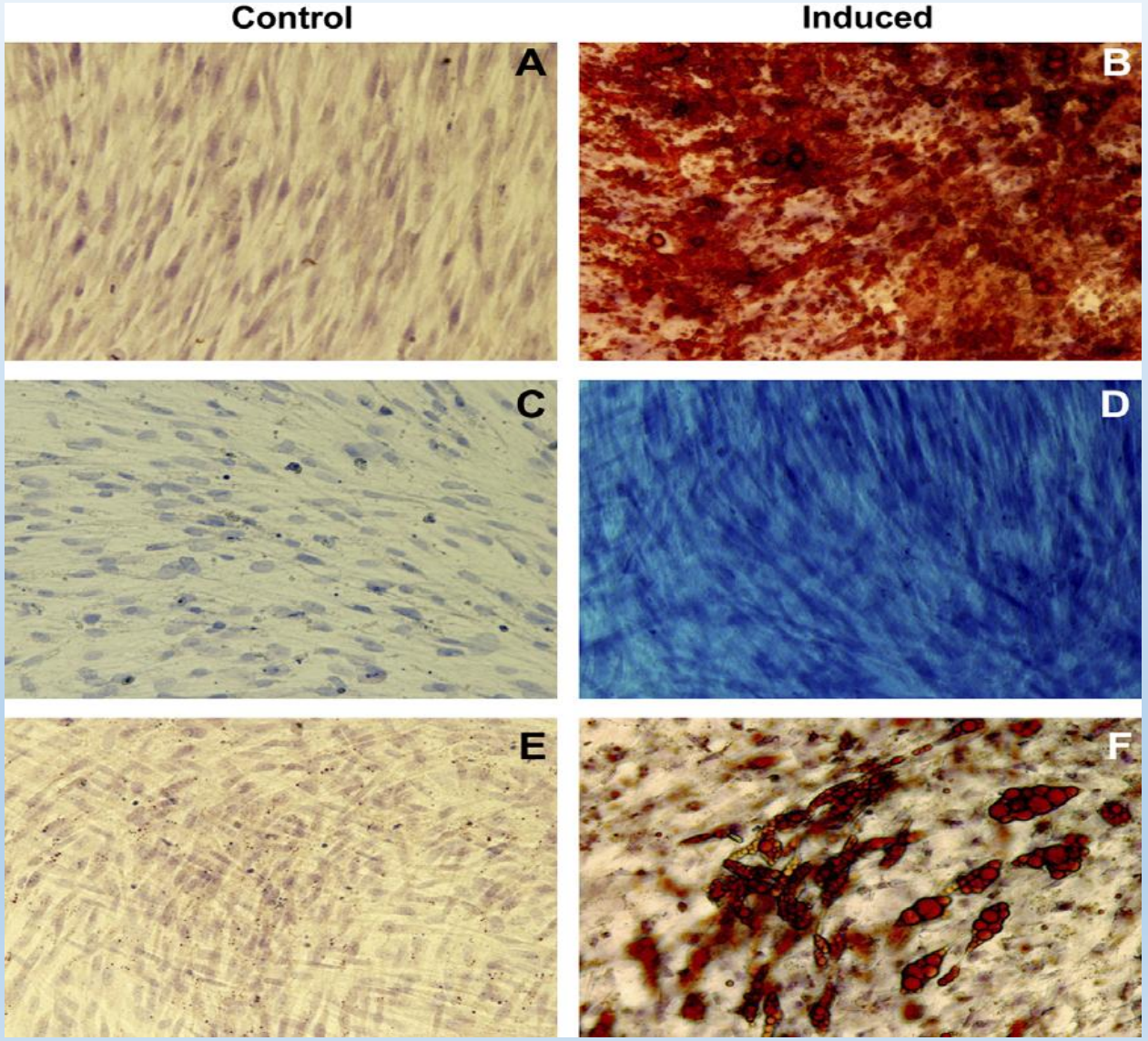
  Mesenchyme (connective tissue)

- Easily differentiate into fat, cartilage and bone



Mobasheri et al., 2009

Why Mesenchymal Stem Cells?



Bone

Cartilage

Adipose

Gonzalez et al., 2007

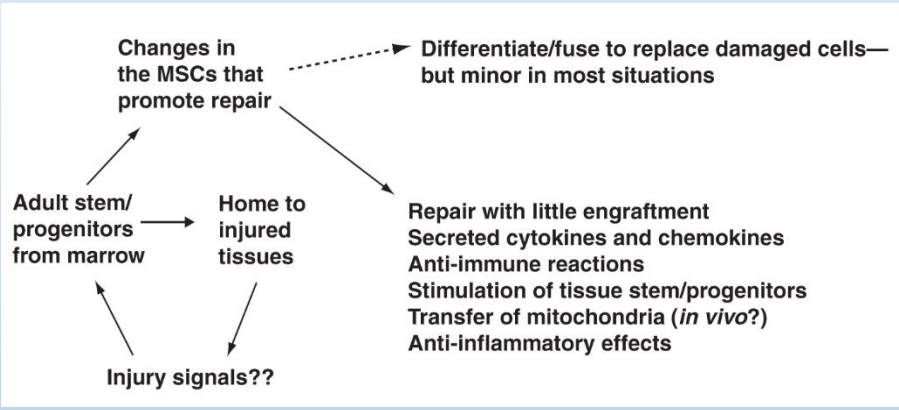
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Why Mesenchymal Stem Cells?

"Stemness" Does Not Explain the Repair of Many Tissues by Mesenchymal Stem/Multipotent Stromal Cells (MSCs)

DJ Prockop[1]

There has recently been an explosion of interest in adult stem/progenitor cells that have the potential to repair tissues, with over 3,000 citations to publications (PubMed) and numerous announcements of clinical trials in which the cells are used to treat individuals with a broad range of diseases. At the same time, the data present a paradox—the cells originally attracted attention because of their stem-cell–like properties, but the cells frequently repair injured tissues without much evidence of either engraftment or differentiation.



Prockop 2007

Why Mesenchymal Stem Cells?

- Immunomodulatory and anti-inflammatory properties:
  1. prostaglandin E2, TGF-β1, HGF, SDF-1, nitric oxide, IL-4, IL-6, IL-10, indoleamine 2,3-dioxygenase and others
  2. prevents function proliferation of inflammatory cells
     -both innate and adaptive immune responses
  3. Cause transitions of Th1 to Th2 response (balance)
     -cartilage regeneration (Tidball et al., 2010)
     -autoimmune diseases (Kong et al., 2009)
     -anti-diabetic effect (Ezquer et al., 2012)

Table 2 Anti-inflammatory mechanisms of MSCs

Target cell	*Mechanism*	*Primary effect*	*Secondary effect*
Dendritic cells	PGE2/direct contact	↓ TNF-α, IL-12, differentiation and activation	Impairs effect on resting NK cells ↓ T-cell proliferation ↓ INF-γ by T_H1 cells[a]
	PGE2, IL-6, IL-8 and SDF-1	↑ IL-10	↑ IL-4 by T_H2 cells[a]
Immature Dendritic cells	PGE2	↑ IL-10	↑ Treg production, ↑ IL-10 by Treg cells
T cells (CD4+, helper T cells)	PGE2, IDO, HGF, TGF-β1 and NO	↓ CD4+ T-cell proliferation by S-phase entry block and Go/G1 phase arrest Inhibits T-cell functions	↓ B-cell proliferation ↓ Ig antibody production by B cells
	IL-10	Inactivate T_H1 cells	
T cells (CD8+, cytotoxic T cells)	sHLA-G5	↓ cytotoxicity	
Treg cells	IL-10	↑ Treg production ↑ IL-10 by Treg cells	
	sHLA-G5	↓ Treg differentiation	
B cells	PGE2, HGF, TGF-β1, IDO, NO and PD-L1	↓ B-cell proliferation by Go/G1 phase arrest ↓ Ig antibody production by B cells, ↓ B-cell chemotaxis	
NK cells	PGE2, IDO, sHLA-G5, HGF, TGF-β1	↓ INF-γ ↓ NK cell proliferation ↓ cytotoxicity	
Monocytes	PGE2	↓ Monocyte proliferation by Go/G1 phase arrest ↓ Monocyte difference to DC	
Macrophages	IL-6	↓ TNF-α	
	TSG-6	↓ NF-kB	↓ TNF-α and IL-1 ↓ MMP synthesis
	PGE2	Converts M1 (pro-inflammatory) type to M2 (anti-inflammatory) type macrophages	↓ IL-10 ↓ IL-12 ↓ TNF-α
Neutrophils	IL-6	↓ respiratory burst ↓ apoptosis	
No specific target	VEGF	Pro-angiogenic	Increased nutrient, O_2 and waste transport
	IL-1Ra	Antagonizes IL-1	
	sTNF-R	Inhibits TNF-α production	↓ T-cell proliferation, ↓ INF-γ by T_H1 cells[a]

Abbreviations: HGF, hepatocyte growth factor; HLA, human leukocyte antigen; IDO, indoleamine 2,3-dioxygenase; IL-1Ra, IL-1 receptor antagonist; INF, interferon; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; NK, natural killer; NO, nitrous oxide; PD-L1, programmed cell death ligand-1; PGE2, prostaglandin 2; SDF-1, stromal cell-derived factor-1; sTNF-R, soluble TNF-α receptor; TGF, transforming growth factor; TNF, tumor necrosis factor; TSG, tumor necrosis alpha-stimulating gene; VEGF, vascular endothelial growth factor.
[a]Promotes $T_H1 \rightarrow T_H2$ T-cell transition.

Murphy et al., 2013

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Why Mesenchymal Stem Cells?

- Immunomodulatory and anti-inflammatory properties:
  4. Express negligible amounts of MHC II; mid levels MHC I
  5. Fail to induce activation of adaptive immune responses
  6. Used for GVHD

Table 1 Mesenchymal stromal cell trials in acute graft versus host disease*

Authors	Phase	n	Dose	CR (%)	PR (%)	NR (%)	OS	Donor source
Ringden et al[65]	I	8	Variable	6 (75)	–	2 (25)	5 2–3 years	2 HLA ID siblings, 6 haploidentical family members
Fang et al[66]	I	6	1×10^6/kg × 1	5 (83)	–	1 (16.7)	4 40 months	Third party
Le Blanc et al[50]	2	55	Variable	30 (54.5)	9 (16.40)	16 (29.1)	52% for CR 16% for PR, NR	Third party
Von Bonin et al[67]	I	13	0.9×10^6/kg × 2	2 (15)	5 (38)	6 (46)	31% at 257 days	Third party
Kebriaei et al[68]	2	31	2 versus 8×10^6/kg × 2	24 (77)	5 (16)	2 (6.5)	NS	Third party
Perez-Simon et al[69]	I	10	2×10^6/kg × variable	1 (10)	6 (60)	3 (30)	20% at final follow-up	Various
Herrmann et al[63]	I	12	2×10^6/kg × 2–4	7 (58)	4 (38)	3 (30)	55% at 36 months	Haploidentical family members or third party
Muroi et al[70]	I	14	2×10^6/kg × 8	12 (86)	1 (7)	1 (7)	57% at 24 months	Third party

Notes: *Published trials of mesenchymal stromal cells in acute graft versus host disease in peer-reviewed journals. Compassionate use reports are not included.
Abbreviations: NS, not stated; CR, complete response; OS, overall survival; PR, partial response; NR, no response; HLA ID, human leucocyte antigen identical.

Table 2 Mesenchymal stromal cell trials in chronic graft versus host disease*

Authors	Phase	n	Dose	CR (%)	PR (%)	NR (%)	OS	Donor BM source
Zhang et al[71]	I	12	Various × 3	3 (25)	6 (50)	3 (25)	77.7 at 2 years	Various
Weng et al[72]	I	19	0.6×10^6/kg × 1	4 (21)	10 (57.6)	5 (28.8)	75% (NS)	Third party
Zhou et al[57]	I	4	$1–2 \times 10^6$/kg × 4–8	0	4 (100)	0	100% at 14–23 months	Third party
Perez-Simon et al[69]	1/2	8	2×10^6/kg × variable	1 (12)	4 (37)	4 (50)	2/8 at 5–12 months	Various
Herrmann et al[63]	I	7	2×10^6/kg × various	1 (12)	3 (43)	4 (57)	50% at 8 months	Various

Note: *Published trials of mesenchymal stromal cells in chronic graft versus host disease in peer-reviewed journals.
Abbreviations: BM, bone marrow; NS, not stated; CR, complete response; OS, overall survival; PR, partial response; NR, no response.

Herrmann and Sturm 2014

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Why Mesenchymal Stem Cells?

- Trophic Support via release of GFs and chemokines:
  - TGF-α, TGF-β, HGF, EGF, FGF-2 and IGF-1 all potent mitogens
  - VEGF, IGF-1, EGF and angiopoietin-1 to recruit endothelial lineage cells and initiate vascularization
  - Paracrine effect of local cells secreting KGF, SDF-1 and MIP1 α & β

Reduction of scar tissue formation

Table 1: Detection of secreted factors from human mesenchymal cells under normoxic and hypoxic conditions. Relative concentration between normoxic and hypoxic conditions are expressed from 1–5 with 1 being the lowest concentration and 5 being the highest [52].

Secreted factors	Normoxia	Hypoxia	Biological function
Activin A	3	2	Cell proliferation, differentiation, apoptosis, and immune response
Epiregulin	3	3	Remodeling
Endothelin	4	4	Cytoprotection, cell proliferation
Glypican-3	3	3	Cell proliferation
IGFBP-7	4	5	Cytoprotection, cell migration, and contractility
IL-15 alpha	2	1	Immune response
LRP-1	2	1	Cell migration
LRP-6	4	1	Cell migration
Osteoprotegrin	4	5	Bone development
sFRP-4	3	4	Development, apoptosis
Smad4	3	2	Vessel maturation, cell proliferation
Smad7	2	2	Vessel maturation, cell proliferation
Thrombospondin-1	3	5	Cell migration, apoptosis
TIMP-1	4	5	Cell migration, remodeling
TIMP-2	4	5	Cell migration, remodeling
VEGF	3	4	Cytoprotection, proliferation, migration, and angiogenesis

Burden et al., 2011

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Why Mesenchymal Stem Cells?

- Trophic support

  - TGF-β1 and IGF-1 amongst others cause chondrogenic differentiation

  - TGF-β1 most commonly used *in vitro*

  - Endogenous tissue repair or engrafted cells?

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MSCs and Arthritis Case Studies

Osteoarthritis and Cartilage (2002) **10**, 199–206
© 2002 OsteoArthritis Research Society International
doi:10.1053/joca.2001.0504, available online at http://www.idealibrary.com on IDEAL®
1063–4584/02/030199+08 $35.00/0

Osteoarthritis and Cartilage
Journal of the OsteoArthritis Research Society International

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees

S. Wakitani*, K. Imoto†, T. Yamamoto†, M. Saito†, N. Murata† and M. Yoneda‡
*Department of Orthopaedic Surgery, Sinshu University School of Medicine, Japan
†Department of Orthopaedic Surgery, Osaka-Minami National Hospital, Japan
‡Center for Sports medicine, Osaka Kosei-Nenkin Hospital, Japan

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MSCs and Arthritis Case Studies

- Wakitani et al. 2002:

  -**24 patients diagnosed with OA** (12 controls-membrane alone)

  -autologous bone marrow derived MSCs (culture expanded)

  -**MSCs (1.3 x 10^7; mean**) seeded onto collagen type I membrane

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MSCs and Arthritis Case Studies

- Wakitani et al. 2002 outcomes:
  -**Significantly higher hyaline cartilage formation** in treated
  -**Clinical improvement not significantly different**
  -**arthroscopic and histological grading score significantly higher**
  Wilcoxon signed rank tests

- Unable to determine if it was the cells or endogenous cartilage growth

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MSCs and Arthritis Case Studies

Case Report

Increased Knee Cartilage Volume in Degenerative Joint Disease using Percutaneously Implanted, Autologous Mesenchymal Stem Cells

Christopher J. Centeno, MD[1,2], Dan Busse MD[1], John Kisiday, PhD[3], Cristin Keohan[1,2], Michael Freeman, PhD[4], and David Karli, MD[5]

Centeno et al., 2008. Pain Physician 11:3:343-353

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MSCs and Arthritis Case Studies

- Centeno et al 2008:
  - **1 case with OA** presented
  - Autologous bone marrow derived MSCs
  - **2.4 x 10^7 cells** in PBS intraarticular by 1 ml of nucleated cells from bone marrow (BMC from 50 ml) in 10% platelet lysate
  - Patient returned for 2 additional 10% platelet lysate injections

    1 & 2 week post transplantation

Centeno et al., 2008. Pain Physician 11:3:343-353

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MSCs and Arthritis Case Studies

- Centeno et al 2008 results:
  - **Statistically significant cartilage and meniscal growth**
  - **increased range of motion**
  - **Decreased modified VAS pain score**

- Unable to determine if it was the cells or endogenous cartilage growth

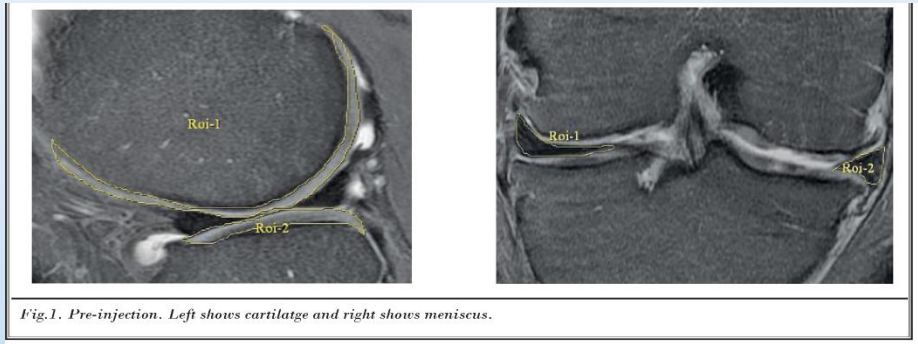


Fig.1. Pre-injection. Left shows cartilatge and right shows meniscus.

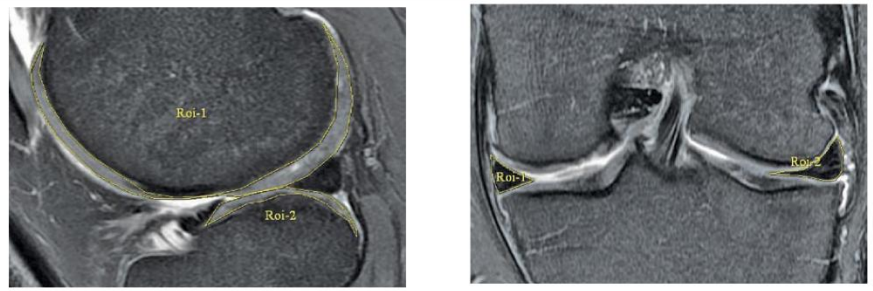


Fig.2. Six months post-injection. Left shows cartilatge and right shows meniscus.

Table 4: Cartilage volume analysis in mm3.

Image	Area of Measurement	Volume (n = 3)	STDEV	SE	% Change from Pre-Injection
Pre-injection	Cartilage surface	4020	12.1	6.99	
	Meniscus	5178	164.57	95.13	
1 month	Cartilage surface	4924	149.01	86.13	**22.49**
	Meniscus	5647	453.57	262.18	**9.06**
3 months	Cartilage surface	4795	113.5	65.61	**19.28**
	Meniscus	6661	146.47	84.67	**28.64**

Centeno et al., 2008. Pain Physician 11:3:343-353

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MSCs and Arthritis Case Studies

Autologous Bone Marrow–Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation

An Observational Cohort Study

Hossein Nejadnik,* MD, James H. Hui,*† MBBS, FRCS, FAMS, Erica Pei Feng Choong,‡ Bee-Choo Tai,§ PhD, and Eng Hin Lee,* MD, FRCS

*From the *Department of Orthopedic Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, ‡National University Hospital, National University Health System, Singapore, and the §Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*

Nejadnik et al., 2010.Am J Sports Med 38 (6) 1110-1116

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MSCs and Arthritis Case Studies

- Nejadnik et al 2010:
  - **72 patients**
  - **36 patients with Chondrocytes; 36 patients with BMSCs**
  - Chondrocytes and BMSCs (**10-15 million cells**) transferred in sheets
  - Placed in a periosteal patch and secured with fibrin glue
  - Various time points up to 24 months
  - ICRS evaluation package to include Short form health survey, knee evaluation form, Lysholm knee scale and Tegner activity level scale

Nejadnik et al., 2010.Am J Sports Med 38 (6) 1110-1116

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MSCs and Arthritis Case Studies

- Nejadnik et al 2010 results:
  - **Significant improvement in short form QoL** in both groups
  - **No difference in groups clinical outcomes except in physical role functioning which was better in BMSC group**
  - **No difference in groups for knee evaluation form, Lysholm knee scale and Tegner activity level scale**
  - **Under 45 year old patients did better** then older in **chondrocyte group**
  - **No difference in benefit with age in BMSC group**
- BMSC is as effective and less invasive as it requires one less knee surgery

Nejadnik et al., 2010.Am J Sports Med 38 (6) 1110-1116

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MSCs and Arthritis Case Studies

- The 3 studies all used autologous cells-cultured or not
  -many more of these published
- All demonstrate clinical improvements

- All demonstrate structural changes through MRI based evidence

- None are the same

- However…….they made a difference

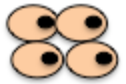
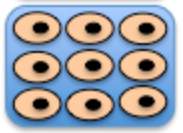
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Are MSCs an Ideal Cell Source for Cartilage Repair?

- There are several reports of MSCs used for chondrogenic differentiation, however most of these are based on micromass pellet culture or 3-D culture of these cells.
- The objective of this study was to develop a condition where monolayer MSCs could be induced towards chondrogenesis, there by these cells could be lifted off the culture dish and directly injected into the injury sites.
- MSCs were treated with different conditions (TGF β 3, TGF β3 +IGFI, TGF β3 + TGF β 1, TGF β3 +FGF) for various times and tested for chondrogenic gene and protein expression.

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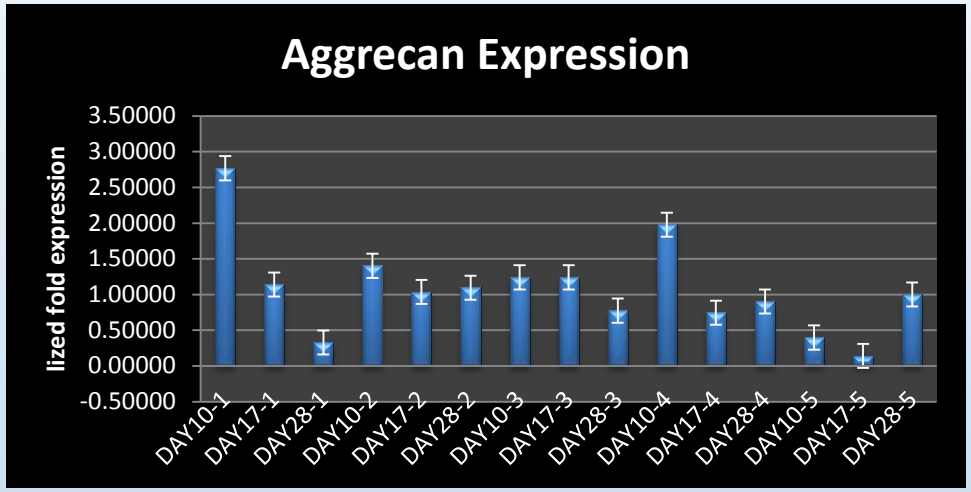
Different Stages of Chondrogenesis

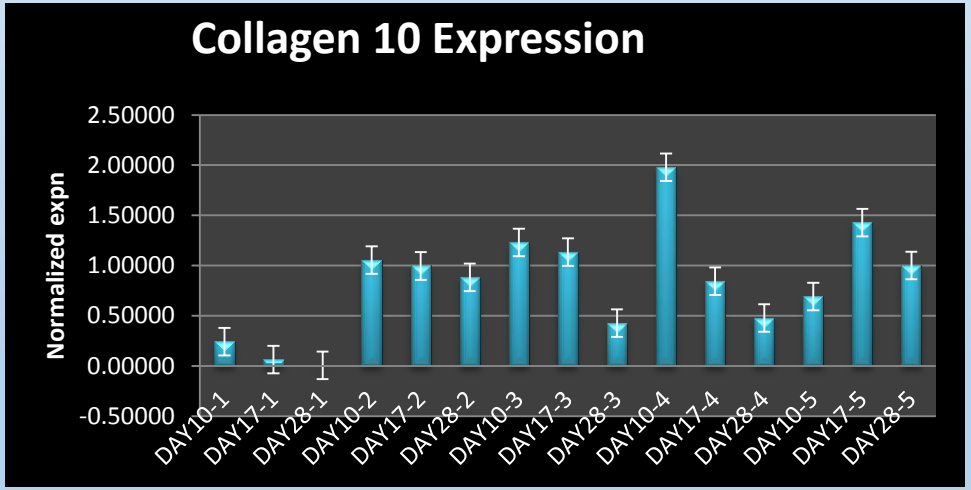
Differentiation step	Extracellular matrix markers	Regulatory markers		Growth and differentiation factors
Chondrogenic Mesenchymal cells	*Col1a1*	*Sox9, Runx2*		Shh, TGF-β
Prechondrocytes	*Ncam1, Tnc*	*Sox9, Sox5, Sox6*		TGF-β Wnt-3A, Wnt7A FGF-2,4,8,10 BMP-2,4,7
Early chondroblasts	*Col2a1, Acan, Crtl*	*Sox9, Sox5, Sox6*		IGF-1 FGF-2/ FGFR2 BMP-2,4,7,14
Columnar chondroblasts	*Col2a1, Acan, Crtl1 Comp, Crtm*	*Sox9, Sox5, Sox6*		FGF-18,FGFR-3 BMP-2,7
Prehypertrophic chondrocytes	*Col2a1, Acan, Crtl1 Comp, Crtm*	*Pthr1, Ihh*		VEGF FGF-2,FGF-R1 Wnt14/β-catenin
Hypertrophic chondrocytes	*Col10a1*	*Runx2, Runx3*		
Terminal chondrocytes	*Mmp13, Spp1*	*Runx2, c-Maf*		

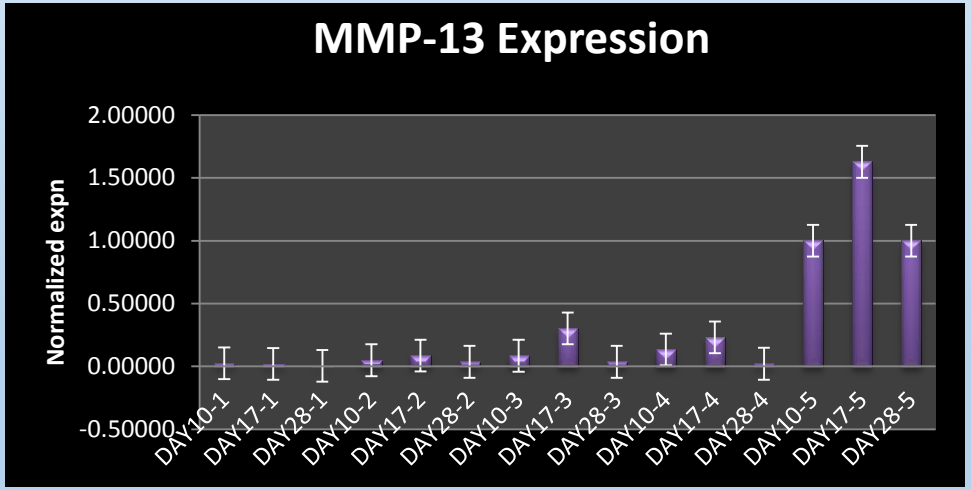
A schematic representation of the different stages of chondrogenesis showing the temporal pattern of extracellular matrix markers, transcription factors, and growth and differentiation factors. Modified from Lefebvre and Smits (2005).

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Gene Expression Profile of MSCs post GF Addition



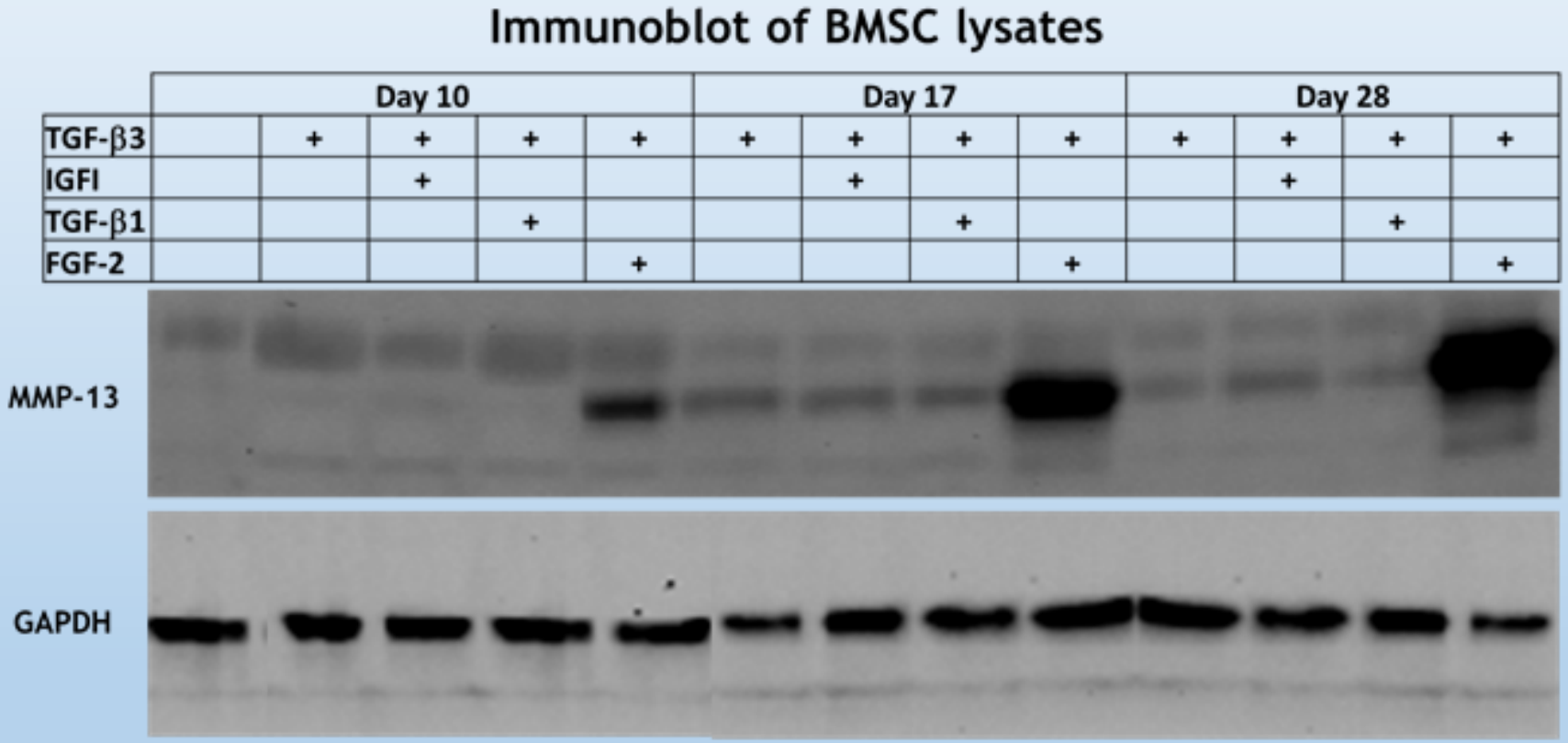




1. Control
2. TGF β 3
3. β3 +IGF-1
4. β3 + β 1
5. β3 +FGF-2

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Immuno blot for MMP-13 & GAPDH expression



Expression of MMP-13 (hypertrophic condition) is induced by synergistic action of TGF-β3 and FGF-2

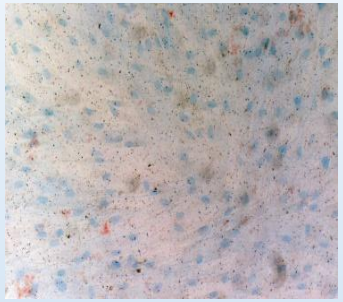
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Effect of Synovial Fluid on *in vitro* chondrogenesis

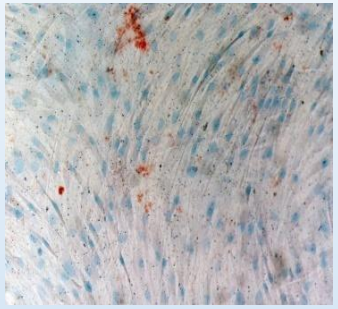
- To evaluate the effect of different types of human Synovial fluids (AR, OA, RA) mimicking *in vivo* conditions on chondrogenic differentiation of BMSCs.

- Synovial fluids were added to BMSCs and after fixed time intervals cells were stained using Alcian blue dye solution, counter stained by Nuclear Fast Red.

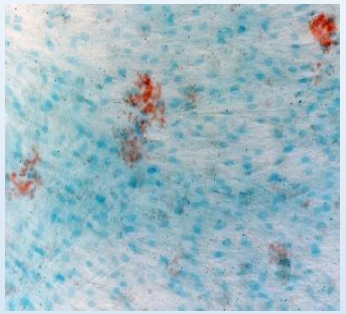
Alcian Blue Staining to visualize proteoglycan conter



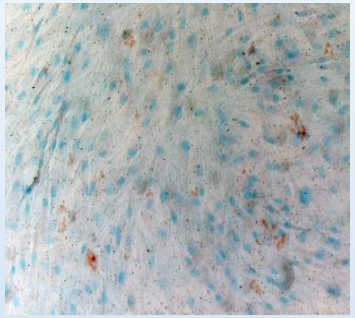
D10-C



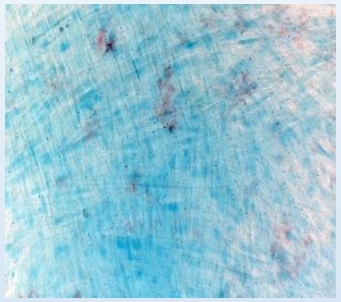
D10-AR



D10-OA



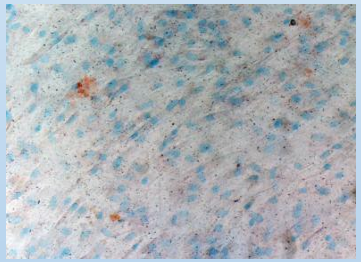
D10-RA



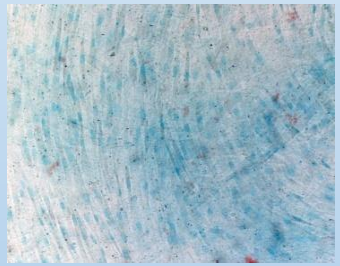
D10-TGFβ3



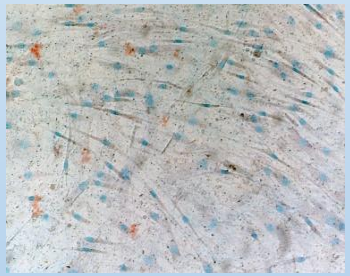
D28- C



D28- AR



D28- OA



D28- RA



D28-TGFβ3

Cells cultured in synovial fluid from OA or TGFβ3 appear to have more detectable proteoglycans

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Conclusions from these set of experiments

- Culturing monolayer MSCs with **TGFβ3+FGF-2, induced hypertrophic condition** of MSCs as seen by very high expression of Collagen10 and MMP-13 genes and proteins.

- Alcian blue staining, showed **increased proteoglycan content in OA (Osteoarthritis) synovial fluid** treated MSCs. Implying **monolayer MSCs when exposed to their in vivo condition, may move towards chondrogenesis**.

- MSCs in **monolayer culture did not express Collagen type II**, one of the main early differentiation markers of chondrogenesis.

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Clinical Application

- 5 patients with Osteoarthritis
- BMC: IV and intraarticular
- MSCs: 1.0 x 10^8 cells IV; 5.0 x 10^7 cells intraarticular
- Assess:

  Blood for safety

  WOMAC

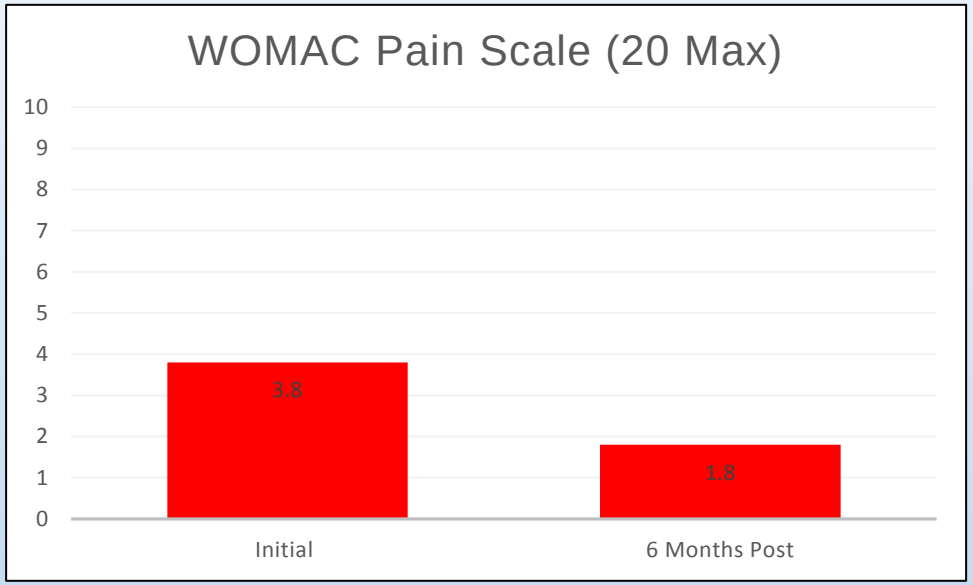
  Knee evaluation form

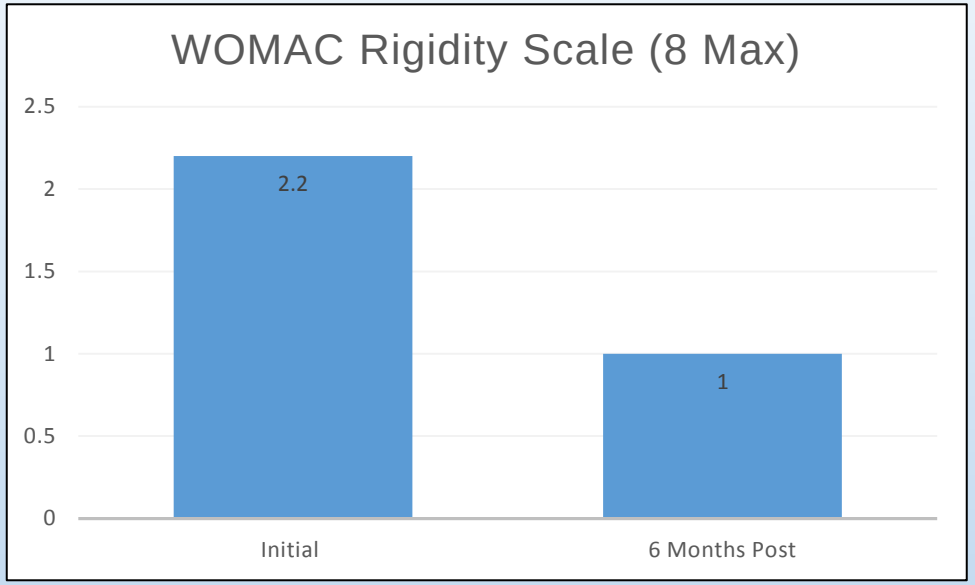
  Knee Society Clinical Rating System (KSCRS)

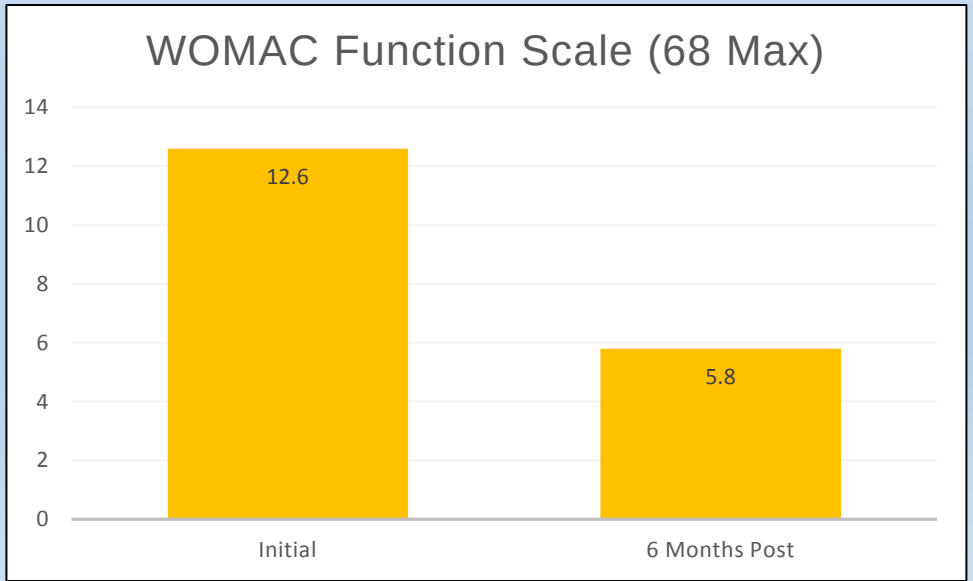
  MRI using Q Metrics Imaging Software

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Clinical Application



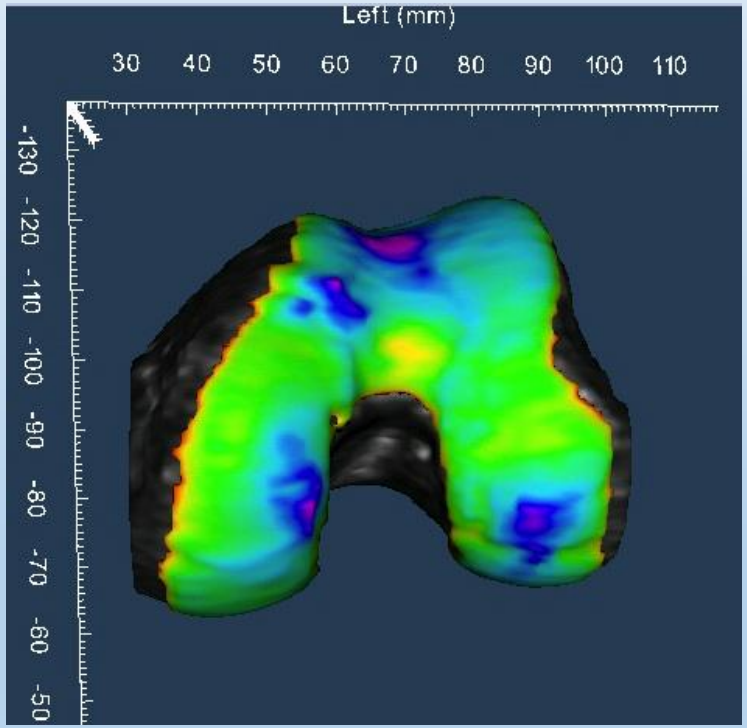




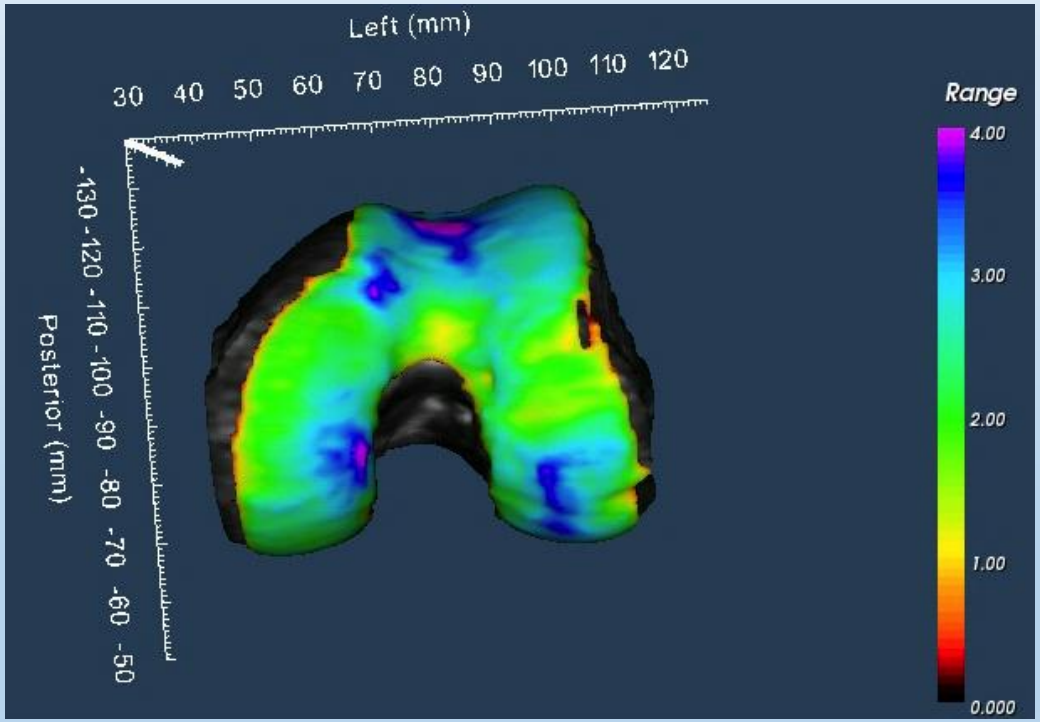
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Femur Cartilage Thickness Maps

S3_CAP: 20130925 (Baseline)



S3_CAP: 20140414 (Month 6)

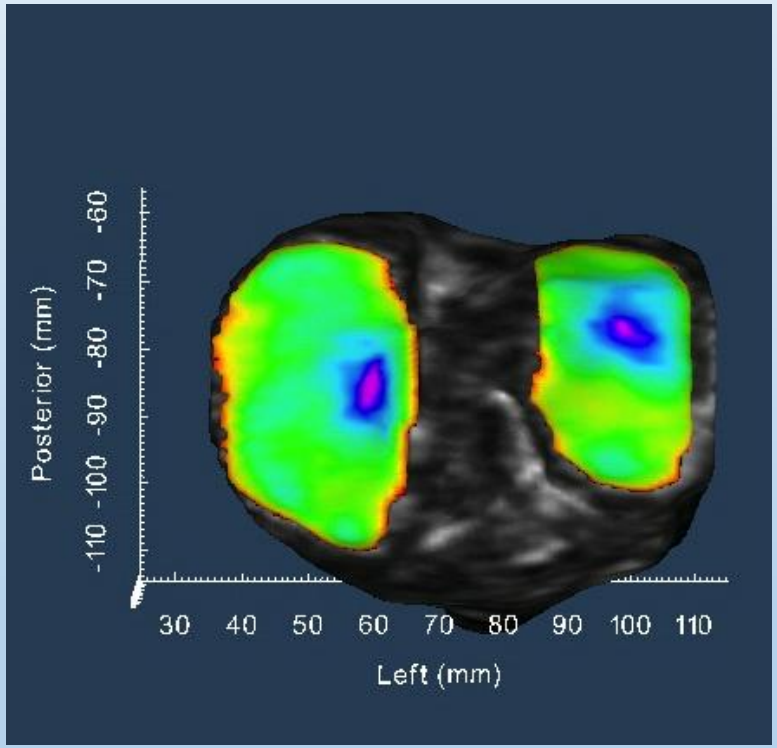


Qmetrics TECHNOLOGIES

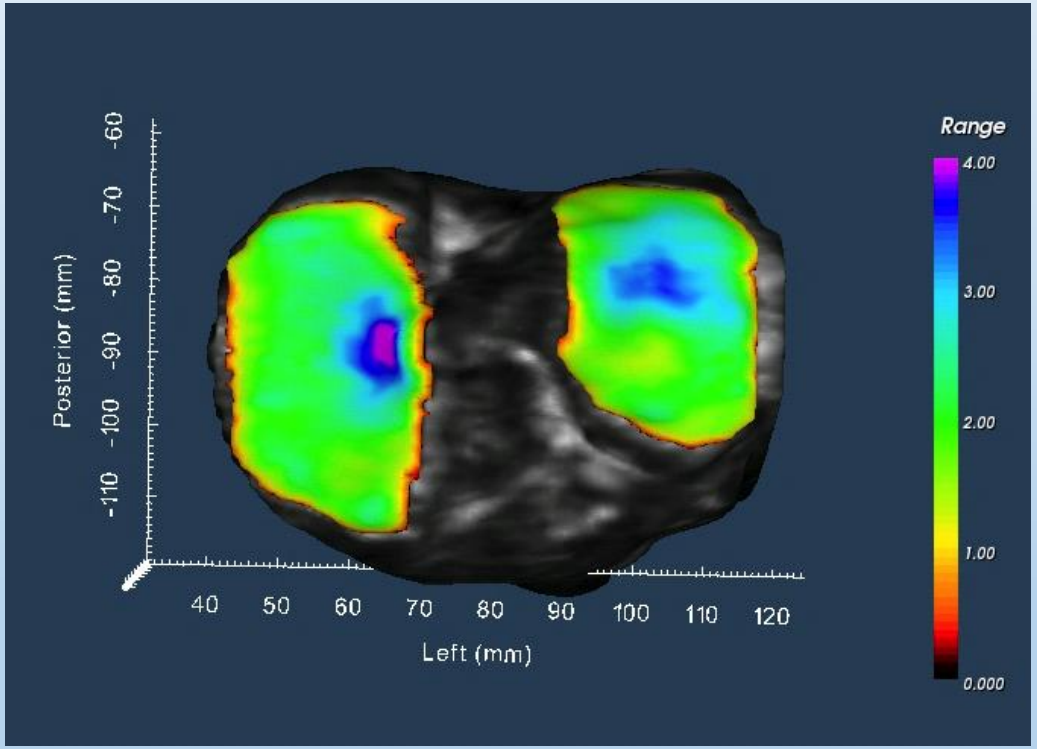
DaVinci biosciences

Tibia Cartilage Thickness Maps

S3_CAP: 20130925 (Baseline)



S3_CAP: 20140414 (Month 6)

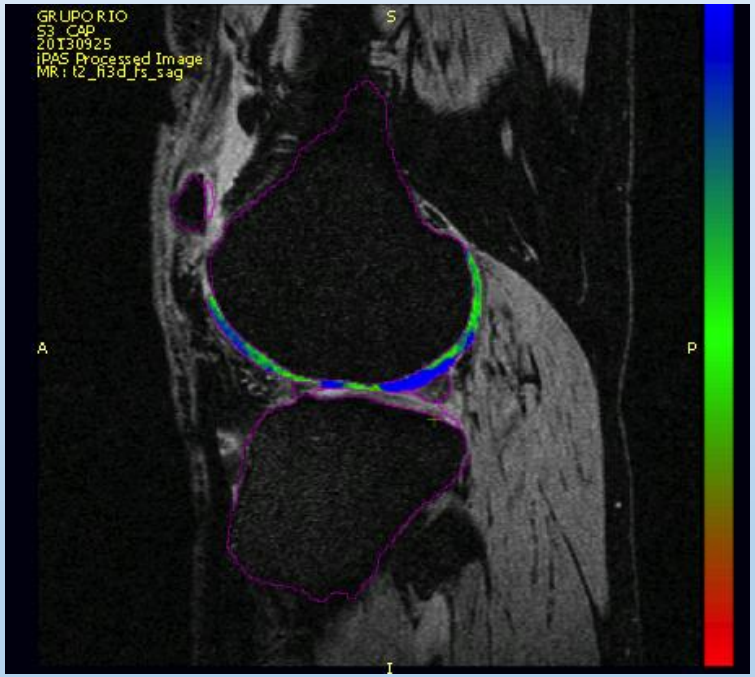


Qmetrics TECHNOLOGIES

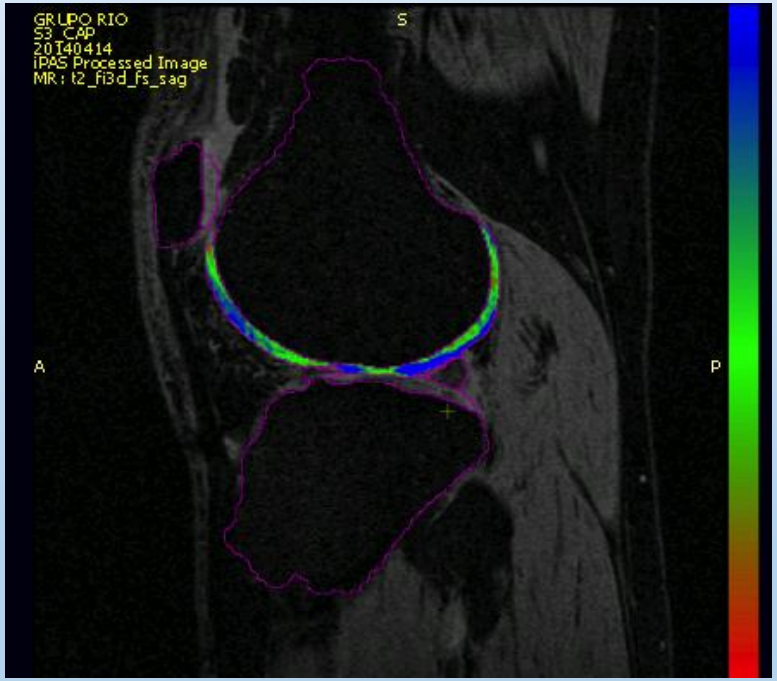
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T2 Image

S3_CAP: 20130925 (Baseline)



S3_CAP: 20140414 (Month 6)



Qmetrics TECHNOLOGIES

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Measurements=Data

		Medial Tibia															
ID	Timepoint	Volume	BCI Area	Thickness				Curvature		T2							
				Mean	Standard Deviation	95% Percentil	5% Percentil	Mean	Standard Deviation	Whole T2 Mean	Whole T2 STD	Top T2 Mean	Top T2 STD	Middle T2 Mean	Middle T2 STD	Bottom T2 Mean	Bottom T2 STD
		mm^3	mm^2	mm	mm	mm	mm	1/mm	1/mm	ms	ms	ms	ms	ms	ms	ms	ms
S1_FAP	20130925	2613.650	1044.204	2.463	0.726	3.736	0.971	-0.012	0.036	49.508	6.370	52.286	9.202	48.082	7.767	51.069	9.523
S1_FAP	20140318	2511.275	1092.106	2.402	0.631	3.320	0.917	-0.012	0.048	51.161	6.909	52.112	8.656	47.995	7.943	57.426	11.747
S2_MBG	20130925	2000.700	1052.812	1.965	0.660	3.369	0.789	-0.014	0.050	159.779	222.217	108.142	246.119	146.522	251.666	209.062	226.164
S2_MBG	20140319	1820.325	1066.340	1.717	0.594	3.118	0.619	-0.013	0.042	142.852	190.365	103.652	208.985	130.029	212.341	188.139	193.856
S3_CAP	20130925	2233.075	1020.214	2.098	0.547	3.347	0.959	-0.011	0.040	54.922	8.025	50.972	14.376	48.662	9.438	69.933	15.218
S3_CAP	20140414	2305.550	1128.551	2.156	0.662	3.864	0.910	-0.012	0.042	50.516	11.319	57.117	29.849	46.668	9.739	52.303	11.747
S4_JCS	20130925	2837.900	1007.092	2.742	0.786	4.258	1.023	-0.003	0.041	54.374	8.432	60.318	19.420	51.421	9.491	57.140	13.127
S4_JCS	20140317	3017.300	1025.320	2.797	0.797	4.216	1.028	-0.004	0.045	54.553	7.957	55.293	13.536	49.295	9.785	66.118	15.950
S5_MTF	20130925	1733.875	853.383	1.977	0.696	3.547	0.903	-0.005	0.054	53.601	9.174	59.451	23.672	50.280	9.058	55.655	12.762
S5_MTF	20140321	1650.025	805.863	1.985	0.656	3.461	0.866	-0.006	0.047	57.648	32.384	77.692	96.961	52.659	18.626	48.835	14.386

Qmetrics TECHNOLOGIES

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MSCs and Arthritis

- Allogeneic products offer a possible “off the shelf”



PRELIMINARY COMMUNICATION

ONLINE FIRST

Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy

The POSEIDON Randomized Trial

- Safe with varying improvements in both groups

Hare et al., 2012

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MSCs and Arthritis

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An Efficient Approach to Isolation and Characterization of Pre- and Postnatal Umbilical Cord Lining Stem Cells for Clinical Applications

R. Gonzalez,* L. Griparic,* M. Umana,* K. Burgee,*
V. Vargas,* R. Nasrallah,* F. Silva,* and A. Patel†

*DaVinci Biosciences LLC, Costa Mesa, CA, USA
†Cardiovascular Center, University of Utah, Salt Lake City, UT, USA

Patent # 13/668,138

MSCs and Arthritis

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ORIGINAL RESEARCH REPORT

Human Umbilical Cord Mesenchymal Stem Cell Therapy for Patients with Active Rheumatoid Arthritis: Safety and Efficacy

Liming Wang,[1*] Lihua Wang,[2*] Xiuli Cong,[3] Guangyang Liu,[3] Jianjun Zhou,[1] Bin Bai,[1] Yang Li,[1] Wen Bai,[1] Ming Li,[1] Haijie Ji,[3] Delin Zhu,[3] Mingyuan Wu,[4,5] and Yongjun Liu[3,5]

MSCs and Arthritis-Summary

- MSCs are safe
- MSCs decrease symptoms of arthritis
- MSCs increase cartilage formation
- MSCs may be used as an allogeneic product
- Better controlled studies are needed
- May need to apply MSCs more than once as shown in many studies

  -cryopreservation is ideal for this

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Dr Jesus Esparragoza

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Catalina Martinez

Marcela Escudero

Quality and supporting staff

Daniel Spurgin

Erin Sairafe

Tony Delamaza

Juan Jose Duran

Marty Killian

Delaney Ware

Slavenska Stockwell

Katrina Fernandez

Gabriela Salgado

Jesus Eduardo Esparragoza

Maria del Carmen Guevara

Raul Plaza

Maria del Carmen Fernandez

The Isaias family

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