The Use of Bone Marrow Stem Cells for Osteoarthritis

Rafael Gonzalez, Ph.D.
Vice President of Research and Development
DaVinci Biosciences, LLC
DaVinci Family of Companies

- Cutting-Edge Adult Stem Cell Research
- Stem Cell Therapy Centers
- Adult Stem Cell Storage
- Research Tools for Drug Discovery
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)

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
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

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
International Guidelines for MSCs

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

Why Mesenchymal Stem Cells?

• Mesoderm
  Mesenchyme (connective tissue)

• Easily differentiate into fat, cartilage and bone

Mobasheri et al., 2009
Why Mesenchymal Stem Cells?

Gonzalez et al., 2007

Bone

Cartilage

Adipose
Why Mesenchymal Stem Cells?

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

DJ Prockop

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.
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

<table>
<thead>
<tr>
<th>Target cell</th>
<th>Mechanism</th>
<th>Primary effect</th>
<th>Secondary effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cells</td>
<td>FG2 direct contact</td>
<td>TGF-β, IL-10, differentiation and activation</td>
<td>Impair effect on starting NK cells</td>
</tr>
<tr>
<td>Immature Dendritic cells</td>
<td>FG2</td>
<td>IL-10</td>
<td>TGF proliferation, IL-6 by T-cell and IL-10</td>
</tr>
<tr>
<td>T cells (CD4+, helper T cells)</td>
<td>FG2, IL-6, HGF, SDF-1, IL-10, IL-12, TGF-β1, IL-21</td>
<td>CD69, T cell proliferation, IL-10, Th1 cytokines, IL-12, Th2 cytokines</td>
<td>IL-10 production by Th cells</td>
</tr>
<tr>
<td>Th cells</td>
<td>IL-10</td>
<td>Th1 cytokines, Th2 cytokines</td>
<td>IL-10 production by Th cells</td>
</tr>
<tr>
<td>B cells</td>
<td>FG2, HGF, SDF-1, IL-10</td>
<td>B-cell proliferation, IL-10, TGF-β1, Th1 cytokines</td>
<td>IL-10 production by Th cells</td>
</tr>
<tr>
<td>NK cells</td>
<td>FG2, IL-6, IFN-γ, HGF, SDF-1, IL-12, IL-18</td>
<td>NK cell activation, Th1 cytokines, Th2 cytokines</td>
<td>Th1 cytokines, Th2 cytokines</td>
</tr>
<tr>
<td>Monocytes</td>
<td>FG2, IL-10</td>
<td>Monocyte proliferation, IL-10, Th1 cytokines, Th2 cytokines</td>
<td>Th1 cytokines, Th2 cytokines</td>
</tr>
<tr>
<td>Macrophages</td>
<td>TH1, TH2</td>
<td>TH1, TH2</td>
<td>TH1, TH2</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>IL-12, IFN-γ</td>
<td>respiratory burst</td>
<td>increased oxygen consumption</td>
</tr>
<tr>
<td>Macrophages</td>
<td>TH1, TH2</td>
<td>TH1, TH2</td>
<td>TH1, TH2</td>
</tr>
</tbody>
</table>

Murphy et al., 2013
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

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>n</th>
<th>Dose</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>OS</th>
<th>Donor source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringden et al(^a)</td>
<td>1</td>
<td>8</td>
<td>Variable</td>
<td>6 (75)</td>
<td>-</td>
<td>2 (25)</td>
<td>5-2-3 years</td>
<td>2 HLA ID siblings, 6 haploidentical family members</td>
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<tr>
<td>Fang et al(^a)</td>
<td>1</td>
<td>6</td>
<td>1 x 10^6/kg x 1</td>
<td>5 (83)</td>
<td>-</td>
<td>1 (16.7)</td>
<td>4.0 months</td>
<td>Third party</td>
</tr>
<tr>
<td>Le Blanc et al(^a)</td>
<td>2</td>
<td>55</td>
<td>Variable</td>
<td>30 (54.5)</td>
<td>9 (16.0)</td>
<td>16 (29.1)</td>
<td>52% for CR</td>
<td>Third party</td>
</tr>
<tr>
<td>Von Bonin et al(^a)</td>
<td>1</td>
<td>13</td>
<td>0.9 x 10^6/kg x 2</td>
<td>2 (15)</td>
<td>5 (38)</td>
<td>6 (46)</td>
<td>31% at 257 days</td>
<td>Third party</td>
</tr>
<tr>
<td>Kebriaei et al(^a)</td>
<td>2</td>
<td>31</td>
<td>2 versus 8 x 10^6/kg x 2</td>
<td>24 (77)</td>
<td>5 (16)</td>
<td>2 (6.5)</td>
<td>NS</td>
<td>Third party</td>
</tr>
<tr>
<td>Perez-Simon et al(^a)</td>
<td>1</td>
<td>10</td>
<td>2 x 10^6/kg x variable</td>
<td>1 (10)</td>
<td>6 (60)</td>
<td>3 (30)</td>
<td>20% at final follow-up</td>
<td>Various</td>
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<tr>
<td>Herrmann et al(^a)</td>
<td>1</td>
<td>12</td>
<td>2 x 10^6/kg x 2-4</td>
<td>7 (58)</td>
<td>4 (38)</td>
<td>3 (30)</td>
<td>55% at 36 months</td>
<td>Haploidentical family members or third party</td>
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<tr>
<td>Murakami et al(^a)</td>
<td>1</td>
<td>14</td>
<td>2 x 10^6/kg x 8</td>
<td>12 (86)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>57% at 24 months</td>
<td>Third party</td>
</tr>
</tbody>
</table>

**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.

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>n</th>
<th>Dose</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>OS</th>
<th>Donor BM source</th>
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<tr>
<td>Zhang et al(^a)</td>
<td>1</td>
<td>12</td>
<td>Various x 3</td>
<td>3 (25)</td>
<td>6 (50)</td>
<td>3 (25)</td>
<td>77.7 at 2 years</td>
<td>Various</td>
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<tr>
<td>Weng et al(^a)</td>
<td>1</td>
<td>19</td>
<td>0.6 x 10^6/kg x 1</td>
<td>4 (21)</td>
<td>10 (57.6)</td>
<td>5 (28.8)</td>
<td>75% (NS)</td>
<td>Third party</td>
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<tr>
<td>Zhou et al(^a)</td>
<td>1</td>
<td>4</td>
<td>1-2 x 10^6/kg x 4-8</td>
<td>0</td>
<td>4 (100)</td>
<td>0</td>
<td>100% at 14-23 months</td>
<td>Third party</td>
</tr>
<tr>
<td>Perez-Simon et al(^a)</td>
<td>1/2</td>
<td>8</td>
<td>2 x 10^6/kg x variable</td>
<td>1 (12)</td>
<td>4 (37)</td>
<td>4 (50)</td>
<td>2/8 at 5-12 months</td>
<td>Various</td>
</tr>
<tr>
<td>Herrmann et al(^a)</td>
<td>1</td>
<td>7</td>
<td>2 x 10^6/kg x various</td>
<td>1 (12)</td>
<td>3 (43)</td>
<td>4 (57)</td>
<td>50% at 8 months</td>
<td>Various</td>
</tr>
</tbody>
</table>

**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.
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>
<thead>
<tr>
<th>Secreted factors</th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Biological function</th>
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<td>Activin A</td>
<td>3</td>
<td>2</td>
<td>Cell proliferation, differentiation, apoptosis, and immune response</td>
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<tr>
<td>Epiregulin</td>
<td>3</td>
<td>3</td>
<td>Remodeling</td>
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<tr>
<td>Endothelin</td>
<td>4</td>
<td>4</td>
<td>Cytoprotection, cell proliferation</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>3</td>
<td>3</td>
<td>Cell proliferation</td>
</tr>
<tr>
<td>IGFBP-7</td>
<td>4</td>
<td>5</td>
<td>Cytoprotection, cell migration, and contractility</td>
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<tr>
<td>IL-15 alpha</td>
<td>2</td>
<td>1</td>
<td>Immune response</td>
</tr>
<tr>
<td>LRP-1</td>
<td>2</td>
<td>1</td>
<td>Cell migration</td>
</tr>
<tr>
<td>LRP-6</td>
<td>4</td>
<td>1</td>
<td>Cell migration</td>
</tr>
<tr>
<td>Osteoprotegrin</td>
<td>4</td>
<td>5</td>
<td>Bone development</td>
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<tr>
<td>sERP-4</td>
<td>3</td>
<td>4</td>
<td>Development, apoptosis</td>
</tr>
<tr>
<td>Snail4</td>
<td>3</td>
<td>2</td>
<td>Vessel maturation, cell proliferation</td>
</tr>
<tr>
<td>Snail7</td>
<td>2</td>
<td>2</td>
<td>Vessel maturation, cell proliferation</td>
</tr>
<tr>
<td>Thrombospondin-1</td>
<td>3</td>
<td>5</td>
<td>Cell migration, apoptosis</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>4</td>
<td>5</td>
<td>Cell migration, remodeling</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>4</td>
<td>5</td>
<td>Cell migration, remodeling</td>
</tr>
<tr>
<td>VEGF</td>
<td>3</td>
<td>4</td>
<td>Cytoprotection, proliferation, migration, and angiogenesis</td>
</tr>
</tbody>
</table>

Burden et al., 2011
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?
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
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
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
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, MD¹, Dan Busse MD¹, John Kisiday, PhD³, Cristin Keohan¹,², Michael Freeman, PhD⁴, and David Karli, MD⁵

Centeno et al., 2008. Pain Physician 11:3:343-353
MSCs and Arthritis Case Studies

- Centeno et al 2008:
  - 1 case with OA presented
  - Autologous bone marrow derived MSCs
  - $2.4 \times 10^7$ 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
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

Table 1: Cartilage volume analysis (in mm³)

<table>
<thead>
<tr>
<th>Image</th>
<th>Area of Measurement</th>
<th>Volume (mm³)</th>
<th>STDDEV</th>
<th>SE</th>
<th>% Change from Pre-Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injector</td>
<td>Cartilage surface</td>
<td>4020</td>
<td>12.1</td>
<td>6.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meniscus</td>
<td>81.78</td>
<td>104.07</td>
<td>96.13</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>Cartilage surface</td>
<td>4924</td>
<td>119.01</td>
<td>86.13</td>
<td>22.99</td>
</tr>
<tr>
<td></td>
<td>Meniscus</td>
<td>56.47</td>
<td>455.37</td>
<td>262.18</td>
<td>9.86</td>
</tr>
<tr>
<td>3 months</td>
<td>Cartilage surface</td>
<td>4795</td>
<td>113.35</td>
<td>65.61</td>
<td>19.28</td>
</tr>
<tr>
<td></td>
<td>Meniscus</td>
<td>50.61</td>
<td>146.47</td>
<td>85.67</td>
<td>28.24</td>
</tr>
</tbody>
</table>
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*

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 periosteaal 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
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
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
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, thereby 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 β 3 +IGFI, TGF β 3 + TGF β 1, TGF β 3 +FGF) for various times and tested for chondrogenic gene and protein expression.
Different Stages of Chondrogenesis

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).
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
Immuno blot for MMP-13 & GAPDH expression

**Immunoblot of BMSC lysates**

<table>
<thead>
<tr>
<th></th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β3</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IGF1</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TGF-β1</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>FGF-2</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

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

Cells cultured in synovial fluid from OA or TGFβ3 appear to have more detectable proteoglycans.
Conclusions from these set of experiments

• Culturing monolayer MSCs with $\text{TGF}{\beta}_3+\text{FGF-2}$, 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.
Clinical Application

- 5 patients with Osteoarthritis
- BMC: IV and intraarticular
- MSCs: $1.0 \times 10^8$ cells IV; $5.0 \times 10^7$ cells intraarticular
- Assess:
  - Blood for safety
  - WOMAC
  - Knee evaluation form
  - Knee Society Clinical Rating System (KSCRS)
  - MRI using Q Metrics Imaging Software
Clinical Application

**WOMAC Pain Scale (20 Max)**

- Initial: 1.8
- 6 Months Post: 1.2

**WOMAC Rigidity Scale (8 Max)**

- Initial: 2.2
- 6 Months Post: 1.0

**WOMAC Function Scale (68 Max)**

- Initial: 12.6
- 6 Months Post: 5.8
Femur Cartilage Thickness Maps

S3_CAP: 20130925 (Baseline)

S3_CAP: 20140414 (Month 6)
Tibia Cartilage Thickness Maps

S3_CAP: 20130925 (Baseline)  
S3_CAP: 20140414 (Month 6)
T2 Image

S3_CAP: 20130925 (Baseline)  S3_CAP: 20140414 (Month 6)
<table>
<thead>
<tr>
<th>ID</th>
<th>Timepoint</th>
<th>Volume</th>
<th>BCI Area</th>
<th>Thickness</th>
<th>Curvature</th>
<th>T2 T1 Mean</th>
<th>T2 STD</th>
<th>T2 Top Mean</th>
<th>T2 Top STD</th>
<th>T2 Middle Mean</th>
<th>T2 Middle STD</th>
<th>T2 Bottom Mean</th>
<th>T2 Bottom STD</th>
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<tr>
<td>S1_FAP</td>
<td>20130925</td>
<td>2613.650</td>
<td>1044.204</td>
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<td>0.036</td>
<td>49.508</td>
<td>6.370</td>
<td>52.286</td>
<td>9.202</td>
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<td>S1_FAP</td>
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<td>2511.275</td>
<td>1092.106</td>
<td>2.402</td>
<td>0.631</td>
<td>3.320</td>
<td>0.917</td>
<td>-0.012</td>
<td>0.048</td>
<td>51.161</td>
<td>6.909</td>
<td>52.112</td>
<td>8.656</td>
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MSCs and Arthritis

• Allogeneic products offer a possible “off the shelf”

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
MSCs and Arthritis

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
MSCs and Arthritis

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 Liu³,⁵
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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The Isaias family