Stem Cells in Pain Management
Ramon Go, MD
Assistant Professor Anesthesiology and Pain Medicine
History of Stem Cell Research

1974: Congress bans all fetal tissue research, a year after Roe vs Wade.

1981: Martin Evans (Cambridge) isolates stem cells in mice

1961: James Till and Ernest McCulloch identify stem cells

1994: HHS Secretary Donna Shalala lifts ban on Fed Funding of hESC research. 1995 Dickey Wicker amendment reverses this (hESC’s may not be destroyed)

1995: Dickey Wicker amendment reverses this (hESC’s may not be destroyed)

1997: Dolly the Sheep. 1st animal clone. Nucleus from udder cell to embryonic cell

1998: James Thompson (U. Wisconsin) & John Gearhart (Hopkins), isolate hESC

2001: George W Bush: Federal funding limited to established hESC

2006: Yamanaka (Kyoto Univ.) creates induced pluripotent stem cells from adult tissue

2009: B. Obama lifts restrictions from 2001 on new cell lines

2013: Mitalipov (Oregon): Somatic cell nuclear transfer to human embryo
hESCs should have been derived from human embryos:

1. that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose;

1. that were donated by individuals who sought reproductive treatment ...and for which all of the following can be assured and documentation provided, such as consent forms, written policies, or other documentation, provided:

All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment. No payments, cash or in kind, were offered for the donated embryos.
Stem Cell Research Policies around the World 2009

Dhar & Ho 2009
Stem Cell Research: *Current Clinical Trials for Pain Related Disorders*

<table>
<thead>
<tr>
<th>Country</th>
<th># of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>8</td>
</tr>
<tr>
<td>Korea</td>
<td>2</td>
</tr>
<tr>
<td>Spain</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
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<tr>
<td>China</td>
<td>1</td>
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<td>India</td>
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<td>Iran</td>
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<td>Egypt</td>
<td>1</td>
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<td>Vietnam</td>
<td>1</td>
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<tr>
<td>Austria/Germany</td>
<td>1</td>
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</tbody>
</table>

**#1 Knee OA**  
DJD, DDD, Rotator cuff, Lumbar OA, diabetic neuropathy, amputation pain

2012:  
$1.4$ Billion dollar awarded by NIH for stem cell research

Vs

2008: $938$ Million dollars

*Chakravarthy et al 2017*

*NIH.gov*
Stem cell definitions

- **Totipotent cells**: Gives rise to ALL cell types (fertilized egg)
- **Pluripotent cells**: Can give rise into nearly ALL cell types (placenta and amniotic sac excluded)
- **Multipotent cells**: Develops into family of related cell types (Mesenchymal Stem Cells)
Stem cell sources

Embryos

Adults

Umbilical

Bone marrow
Adipose
Blood
Joint Tissue

CD29, CD44, CD105

Mesenchymal Stem Cells

Chondrocytes
Smooth Muscles
Cardiac Muscle
Skeletal Muscle
Adipocyte
Osteoblasts

Rosenbaum 2008
Some studies suggest bone marrow stem cells have better potential for osteogenesis and chondrogenesis than adipose derived stem cells.

Rosenbaum 2008

<table>
<thead>
<tr>
<th>Stem cell sources</th>
<th>CD29, CD44, CD105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Umbilical</td>
<td></td>
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<tr>
<td>Bone marrow</td>
<td></td>
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<tr>
<td>Adipose</td>
<td></td>
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<tr>
<td>Blood</td>
<td></td>
</tr>
<tr>
<td>Joint Tissue</td>
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<tr>
<td>Mesenchymal Stem Cells</td>
<td></td>
</tr>
<tr>
<td>Chondrocytes</td>
<td></td>
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<tr>
<td>Smooth Muscles</td>
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<tr>
<td>Cardiac Muscle</td>
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<tr>
<td>Skeletal Muscle</td>
<td></td>
</tr>
<tr>
<td>Adipocyte</td>
<td></td>
</tr>
<tr>
<td>Osteoblasts</td>
<td></td>
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</tbody>
</table>

Rosenbaum 2008
Stem cell in pain management

Only a small proportion of MSC’s will actually be incorporated into injured tissues. Benefits likely indirect and depend on paracrine activity of MSC’s

Chakravarthy et al. 2017
Stem Cells for Neuropathic Pain
Anti-inflammatory effects of mesenchymal stem cells

**In Vitro Model**

- Mesenchymal stem cells down regulate the expression of inflammatory mediators
- Inhibition of pro-inflammatory molecules may prevent degradation of extracellular matrix.

Miguelez-Rivera 2017
Stem cell in neuropathic pain: Trigeminal Neuralgia

Pilot study (n = 10) w/ trigeminal neuralgia

- Patients failed conservative treatment
- Autologous adipose MSCs injected into trigeminal nerve
- Pain Intensity and Use of neuropathic agent

Findings:

No adverse effects

Pain score improvement at all time points 1 week, 3 months, and 6 months

Trend in decreased neuropathic drug dosage
Stem cell in neuropathic pain: Pudendal Neuralgia

Pilot study (n = 15) w/ pudendal neuralgia

- Patients failed medical therapy
- Autologous adipose MSCs injected into trigeminal nerve
- VAS, SF-36, and pudendal nerve latency

Results:
3 lost to follow up, 2 with no improvement in pain,
10 with significant improvement in pain
VAS : 3.2 vs 8.1

Significant improvement in quality of life

QOL significantly improved

Table 2: SF36 Health Survey questionnaire in preoperative evaluation and during 12-month follow-up in 10 patients with pudendal neuralgia submitted to pudendal nerve lipofilling (data expressed as mean ± SD)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Preoperative n = 10</th>
<th>3 months n = 10</th>
<th>6 months n = 10</th>
<th>12 months n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations: physical activities</td>
<td>15.5 ± 3.3</td>
<td>13.4 ± 2.0</td>
<td>10.7 ± 1.7</td>
<td>11.3 ± 1.8</td>
</tr>
<tr>
<td>Limitations: social activities for physical, or emotional problems</td>
<td>4.8 ± 0.6</td>
<td>5.1 ± 0.7</td>
<td>6.5 ± 0.6</td>
<td>6.4 ± 0.7</td>
</tr>
<tr>
<td>Limitations: usual role activities for physical problems</td>
<td>6.2 ± 1.3</td>
<td>6.4 ± 1.5</td>
<td>7.9 ± 1.5</td>
<td>7.8 ± 1.4</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>5.1 ± 1.0</td>
<td>3.7 ± 0.6</td>
<td>1.0 ± 0.3</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>General mental health</td>
<td>5.4 ± 1.2</td>
<td>4.9 ± 0.9</td>
<td>3.3 ± 0.6</td>
<td>3.4 ± 0.8</td>
</tr>
<tr>
<td>Limitations: usual role activities for emotional problems</td>
<td>4.4 ± 0.7</td>
<td>5.1 ± 0.8</td>
<td>5.9 ± 1.3</td>
<td>5.8 ± 1.2</td>
</tr>
<tr>
<td>Vitality</td>
<td>32.2 ± 4.4</td>
<td>31.0 ± 4.0</td>
<td>29.0 ± 3.7</td>
<td>29.6 ± 3.8</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>11.4 ± 2.2</td>
<td>10.6 ± 2.1</td>
<td>9.3 ± 1.9</td>
<td>9.5 ± 2.0</td>
</tr>
<tr>
<td>Total</td>
<td>85.0 ± 4.5</td>
<td>80.2 ± 3.9</td>
<td>73.6 ± 3.7</td>
<td>75.5 ± 4.1</td>
</tr>
</tbody>
</table>

* A repeated measure variance analysis was used. F was 15.99, with P < 0.0001.
Stem Cells for Knee and Hip Pain
Stem cell for knee pain

Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A 2-Year Follow-up Study.

Jo CH¹, Chai JW², Jeong EC³, Oh S⁴, Shin JS⁵, Shim H⁶, Yoon KS¹.

Autologous Adipose Derived MSC injected

N = 18 patients with knee OA
3 doses of ADMSC (Low, Medium, High)

Measurements: Knee injury and Osteoarthritis Outcome Score (KOOS), WOMAC, VAS

Findings: Improvement in KOOS, VAS, WOMAC scores at 6, 12, and 24 months as compared to baseline in all three groups.

Structurally:
Significant change in cartilage defect at 24 months
No difference in cartilage volume at 24 months.

50% improvement in knee function
57% improvement VAS
70% improvement in WOMAC score
Stem cell for knee pain

The effect of intra-articular injection of autologous bone marrow stem cells on pain and knee function in patients with osteoarthritis.

Ganay-Mendoza D1, Villareal-Martinez L2, Garza-Rodilla A2, Pérez-Garza DH2, Acosta-Olivo C1, Vílchez-Cavazos F1, Diaz-Hutchinson C1, Gómez-Almaguer D2, Jaime-Pérez J2, Manciel-Guerra C2.

Control (Paracetamol): n = 25 w/ Grade II or III OA
BM-MSC injection: n = 26 w/ Grade II or III OA

**VAS 6 months:** $0.92 \pm 1.29$ VS $4.64 \pm 2.43$
$(P < 0.0001)$

**WOMAC 6 months:** $91.73 \pm 9.45$ VS $72.96 \pm 15.04$
$(P < 0.0001)$

Figure 2 Graph showing visual analogue (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores: Group 1 versus Group 2.
Stem Cells for Hip Pain


**Outcome of childhood leukaemia survivors and necrosis of the femoral head treated with autologous mesenchymal stem cells.**

de Rojas T1, Martinez-Alvarez S2, Lerma-Lara S3, Diaz MÁ1,4, Madero L1,4, Ramirez M1,4.

**Author information**

1 Paediatric Oncology Hematology and Stem Cell Transplant, University Hospital Niño Jesús, Av. Menéndez Pelayo, 65, 28009, Madrid, Spain.

-Pilot study mesenchymal Stem Cells for bilateral HIP AVN:

-Two patients with history of acute lymphoblastic leukemia w/ steroid induced osteonecrosis

-Autologous mesenchymal stem cell implantation

-Improved pain, ambulation, overall function (Rojas et al 2017)

-No significant change based on MRI and XRAY of hip joint morphology
Stem Cells for Hip Pain

Mesenchymal stem cell therapy in the treatment of hip osteoarthritis.

Mardones R³, Jofré CM³, Tobar L³, Minguiél Julián³.

Author information

1 Centro de Traumatología y Ortopedia, Clínica Las Condes, Santiago, Chile Centro de Terapia Regenerativa Celular, Clínica Las Condes, Santiago, Av Las Condes 11283, 302B, Las Condes, CP 7550000, Santiago, Chile.

-Pilot Study mesenchymal Stem cell for HIP OA
10 patients w/ pain from Hip OA;

- Inclusion: ≥ 60 years; Radiological evidence of OA, pain levels (refractory to analgesics and/or hyaluronic acid or cortisone injection treatment) ≥ 40 (Visual Analog Scale of 100 mm)

- Exclusion: intra-articular space ≤ 1 mm, indication of cartilage’s loss of volume (by MRI) and/or failure to complete the protocol’s established number of cell infusions.

- Intervention: 3 injections of autologous mesenchymal cells

- Findings: minimal radiological improvements;
 Improvement in pain score and mobility

<table>
<thead>
<tr>
<th>Hip scores</th>
<th>Pre-infusion values</th>
<th>Post-Infusion values</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>4.2±0.5</td>
<td>1.1 ± 0.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>WOMAC</td>
<td>34.5 ± 8.2</td>
<td>19.2 ± 6.1</td>
<td>0.15</td>
</tr>
<tr>
<td>HHSM</td>
<td>61.9 ± 6.1</td>
<td>85.7 ± 3.9</td>
<td>0.003</td>
</tr>
<tr>
<td>VAIL</td>
<td>61.2 ± 4.5</td>
<td>78.2 ± 5.2</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Stem Cells for Shoulder Arthroscopy

-A cohort study: arthroscopy (35 patients) VS arthroscopy + MSC (35 patients) - adipose-derived MSCs loaded in fibrin glue - Patients matched (age, sex, lesion size) - Outcomes: VAS, ROM, functional measures (Constant score and UCLA shoulder rating scale), and tendon structural integrity (MRI) at 12 months.

Findings: Both groups improved after surgery. VAS, ROM, function – no difference at final follow up (28 months). Re-tear rate was statistically significant: lower in stem cell group (14.3%) vs conventional (28.5%), P < 0.001.
Stem Cells for Back Pain
Mesenchymal stem cells reduce fibrosis and facilitate repair

-Collagen fibril disorganized in degenerative disc disease; fibrotic Nucleus Pulposes (NP)

-Rabbit model with puncture induced degenerative disc disease

-Bone marrow MSC were isolated from rabbits and grown in culture

-MSC vs Saline injected into NP

**Findings:**

-Reduced fibril production w/ MSC injection

-Decreased stiffness in the animal spine model

-Disc heights did not change

-Delay not arrest disc degeneration

Leung et al 2014
Mesenchymal stem cells reduce fibrosis and facilitate repair

- Collagen fibril disorganized in degenerative disc disease; fibrotic Nucleus Pulposes (NP)

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- MSC vs Saline injected into NP

**Findings:**

- Reduced fibril production w/ MSC injection

- Decreased stiffness in the animal spine model

- Disc heights unchanged

- Disc degeneration delayed NOT arrested with MSC

Leung et al 2014
Stem Cells for Discogenic Pain

Intervertebral Disc Repair by Autologous Mesenchymal Bone Marrow Cells: A Pilot Study

Lluis Orozco, Robert Soler, Carlos Morera, Mercedes Alberca, Ana Sánchez, and Javier García-Sanchez

Transplantation, 2011 Oct 15;92(7):822-8

Pilot study (n = 10) w/ DDD

- Patients failed conservative treatment
- Autologous MSCs injected into intervertebral disc NP
- Pain and Function assessed by VAS and ODI

Findings:

Analgesia: 71% improvement
Function: Significantly improved
Anatomy: No improvement in disc height (MRI)
Problem: Discectomy results in loss of tissue and disc height.

-Multicenter RCT: Single level micro-discectomy vs micro-discectomy + Autologous disc chondrocyte transplantation (ADCT)

-N= 28 patients (16 micro-discectomy only; 12 micro-discectomy w/ ADCT; followed for 24 months

Findings:

-Greater pain reduction at 2 years

-Micro-discectomy w/ ADCT – Trend to decrease in disability scores

-No difference in disc height between groups

-No adverse events
Long term benefit?

N = 26 patients w/ DDD surgical candidates for spinal fusion
- Injected with 2ml of autologous BMC and followed for 36 months

Findings:
- 6 patients proceeded to surgery
- Statistically significant improvement in ODI and VAS
### Clinical Trials Using Biologic-based Therapies for Degenerative Disc Disease

<table>
<thead>
<tr>
<th>Primary Researcher</th>
<th>Biologic Therapy</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Follow-Up (M)</th>
<th>Findings</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meisel, et al.</td>
<td>Autologous Disc Chondrocyte Transplantation (EuroDisc)</td>
<td>Multicenter prospective, randomized, controlled, non-blinded study</td>
<td>28</td>
<td>24</td>
<td>Patients who received ADCT had lower pain scores as tabulated by the OPDQ than control. Patients who received ADCT had retention of better hydration of the disc than control, but no change in disc height</td>
<td>EuroSpine J 2006, 2008</td>
</tr>
<tr>
<td>Orozco, et al.</td>
<td>Autologous Bone Marrow Mesenchymal Cell</td>
<td>Pilot Study/ Case Series</td>
<td>10</td>
<td>Improvement in pain, disability, and disc hydration</td>
<td>Transplantation 2001</td>
<td></td>
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<td>Yoshikawa, et al.</td>
<td>Autologous Bone Marrow Mesenchymal Cell</td>
<td>Pilot Study/Case Series</td>
<td>2</td>
<td>24</td>
<td>Both patients showed improvement in pain? And intensity of T2-weighted MRIs</td>
<td>Spine 2010</td>
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<tr>
<td>Haufe SMW, et al.</td>
<td>Hematopoietic Stem Cell</td>
<td>Pilot Study/Case Series</td>
<td>10</td>
<td>12</td>
<td>No improvement in back pain</td>
<td>Stem Cells Dev. 2006</td>
</tr>
<tr>
<td>Corio D, et al.</td>
<td>Allogeneic Juvenile Chondrocytes (NuQs)</td>
<td>Pilot Study/Case Series</td>
<td>15</td>
<td>12</td>
<td>ODI, NRS SF 36 improvement from baseline with 89% of patients showing some improvement on MRI</td>
<td>JNS 2013</td>
</tr>
<tr>
<td>Ruan, et al.</td>
<td>Total Disc Replacement with Allogeneic IVD</td>
<td>Pilot Study/Case Series</td>
<td>5</td>
<td>60</td>
<td>The allograft engrafted the disc space without apparent immunoreaction; 4 out 5 implanted disc spaces preserved their range of motions after disc implantation</td>
<td>Lancet 2007</td>
</tr>
<tr>
<td>Pettine, et al.</td>
<td>Injection of Autologous Bone Marrow Concentrate Cells</td>
<td>Pilot Study/Case Series</td>
<td>26</td>
<td>12</td>
<td>Improvement in pain scores prominently in patients with higher CFU-F concentrations. Rehydration of the discs observed (n=8)</td>
<td>Stem Cells 2015</td>
</tr>
</tbody>
</table>

Pennicooke et al 2016
Risks

- Invitro studies show ability to foster tumor growth

- MSC’s secrete cytokines which may suppress immune system by down regulating MHC class II, CD40, and CD86 molecules
Review of 844 patients
- 4 serious adverse events
  1 Bone marrow site infection
  1 Pulmonary embolism
  2 Tumors at 21 months
Retinal detachment after stem cell injection
Summary

History of Stem Cells Research and Policy in US

Studies are limited but promising

Adverse effects for now seem low in autologous stem cells

Risk of tumorigenicity needs further assessment
Thank you for your attention