Evolving Techniques: Autologous Stem Cells and New Scaffolds

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Los Angeles, California
Disclosure

Consultant - Osiris
Board member – Tissue Banks International
Promotion

ADULT STEM CELLS

I LEARN HOW STEM CELL THERAPY MAY BE USED IN THE FOLLOWING CONDITIONS:

Cardiac - Pulmonary
Congenital Heart Disease
Congestive Heart Failure
Cerebral Palsy
Cerebral Ischemia
Stroke
Orthopedic - Degenerative Arthritis
Degenerative Disc Disease
Spine Stenosis
Orthopedic - Degenerative Arthritis
Degenerative Disc Disease
Spine Stenosis

FREE EDUCATIONAL LECTURES

Wednesday, April 22, 2015
11:00 AM and 1:00 PM
Hampton Inn - Sherman Oaks
8638 Sepulveda Blvd., Sherman Oaks. CA 91411

Tuesday, May 19, 2015
11:00 AM and 1:00 PM
Holiday Inn Express & Suites - Pasadena
3500 E Colorado Blvd, Pasadena, CA 91107

Sunday, May 17, 2015
12:00 PM (noon)
Crossroads Corporate Centre - Irvine
3500 Barranca Pkwy., 3rd Floor, Irvine, CA 92606

Sunday, May 31, 2015
12:00 PM (noon)
Courtyard Los Angeles Westside
8333 Bristol Pkwy, Culver City, CA 90230

Limited Seating - RSVP: (949) 679-3889

Listen to Our Radio Show "The Stem Cell Show" - KABC 790 AM Talk Radio - Sundays @ 4 PM
or "Listen Live" on www.KABC.com (Worldwide)

Irvine Stem Cell Treatment Center - Irvine
3500 Barranca Pkwy, Suite 315
Irvine, CA 92606
www.IrvineStemCellsUSA.com

Thomas A. Gionis MD JD MPH MBA MHA LLM FAHQ
Surgeon-in-Chief, Irvine Stem Cell Treatment Center
United States Fulbright Scholar
Fellow, American Institute for Healthcare Quality
KABC Radio Talk Show Host

Irvine Stem Cell Treatment Center - Westlake
911 Hampshire Road, Suite 2
Westlake Village, CA 91361
www.IrvineStemCellsUSA.com
Internet Influence

New Millennium

World Influence

Facebook/Social Media
Patient Injection Awareness

- Injection based products creating outpatient clinic model.
- #1 sales driver now
Alphabet Soup

BLA  SVF  ANDA
IND  FDA  ASC
NDA  GMP  MSC
ANDA  GTP  BMAC
ASC  BMA
BMA  PRP
HA  361
HCT/Ps  351
510(k)
Where Are We Now

I. FDA Influences/Regulation

II. 4 Autologous Cellular Treatments
   • Bone Marrow
   • Fat
   • PRP
   • Placenta

III. Stem Cells
Regulatory Issues
FDA

State Jurisdiction vs. Federal Law
Interstate Commerce
FDA

Public Safety
GMP / GTP
Consistency, Potency, Purity, Safety, Efficacy

• 1977 Title 21-Human cells, tissues and cellular and tissue-based products-(HCT/Ps)
  • 361: No premarket clinical studies
  • 351: PMA clinical trials with active investigational new drug (IND) application
Human Tissue Classification

361 → Human Allografts

351 → Biologic Drugs/Devices
FDA

- You can **NOT** manipulate cells
- **Non-Homologous Use** – Cells serve a different function than natively in the body
  - BMA cannot be expanded
  - Adipose-derived stem cells (ASCs) cannot be expanded
  - Placenta products into knee???
- **Homologous Use**
  - Placenta products to cover a wound
  - Watch claims: improved healing?
The Food & Drug Administration's (FDA) role is to regulate the sale and distribution of drugs, devices, biologics and combination products, but not how these products are used by physicians.

The surgical procedures conducted by RSI including surgery and bone marrow transplants are not performed as part of any research intended for FDA approval of a product that is under the jurisdiction of the FDA. Therefore, the stem cell procedures conducted by RSI are not under the jurisdiction of the FDA. Rather, the procedures conducted by RSI are considered the "practice of medicine," and is left up to individual surgeons' judgment and experience by the Colorado Board of Medicine.

Centeno-Scultz Clinic
Cayman Islands

LEGAL PRECEDENCE
### Systematic Review

**Umbilical Cord Tissue Offers the Greatest Number of Harvestable Mesenchymal Stem Cells for Research and Clinical Application: A Literature Review of Different Harvest Sites**

C. Thomas Vangsness Jr., M.D., Hal Sternberg, M.D., and Liam Harris, B.S.

September 2015

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>MSCs/ml or Content</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>317,400 MSCs/ml</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>1.55 million MSCs/ml</td>
<td>20%</td>
</tr>
<tr>
<td>Umbilical Cord</td>
<td>10,0005 MSCs/ml-4,700,0006 cells/cm of cord</td>
<td>2%</td>
</tr>
<tr>
<td>Amniotic Fluid</td>
<td>3 MSCs/cc</td>
<td>0.03%</td>
</tr>
<tr>
<td>Amniotic Membrane</td>
<td>1-4 million MSCs/amnion</td>
<td>1.4-8%</td>
</tr>
</tbody>
</table>
BONE MARROW ASPIRATE
“BMA” “BMAC”

- Similar Issues to PRP
- More Difficult Access
- “Safe”
- Centrifuged
- Growth Factors
- # Stem Cells?
- Increasing Popularity
- Level V

• $$$
FAT ASPIRATION

- Primarily Adipose Stem Cells (ASC)
- Numbers Greater
- Centrifuged
- FDA
- Level V
- $$\text{AdiStem}$$
FAT ASPIRATION

- FDA... “Fat transplant”
- Enzyme breakdown
  - no
- Mechanical breakdown
  - yes
Fat vs. Bone Marrow MSC

ASCs better for clinical application

- Numbers
- Proliferative capacity

Differences:
- Efficiency
- Immunosuppression
- Long-term stability
PLATELET-RICH PLASMA

- Common
- Costly
- Centrifuged
- Confusing (Evidence?)
- Consecutive Admin
- Cash
NO STEM CELLS
PRP PROBLEMS: The Literature

A. EBM
   1. Lacking
   2. Early Science - Infancy

B. Study Designs
   1. What Are You Injecting?
   2. Where Are Your Injecting?
   3. Standardization of Pathology
   4. Dose/ Number/ Time Interval

C. Reproducibility
   1. “DOSE”??
PRP

Orthogen Germany

- Orthokine/Regenokine
  - Weekly Injections....6 in 3 weeks
  - IRAP Blocks IL-1

- 2 Clinics in USA

- FDA – ACS

- Dose Measurement

- Cash

- NO STEM CELLS
Orthopaedic Placental/Cord Products

• Ovation- Osiris (Chorionic Membrane)
• Neox Flo Particulate Matrix-Amniox Medical
• Amniofix-MiMedX (Amniotic Membrane)
• Whartons Jelly Stem Cells-Cambridge BioScience (Wharton’s Jelly)
• AmnioPur- Aurora (Amniotic Membrane)
• Trinity Elite – Orthofix. (Amniotic Membrane)
• Applied Biologics – FloGraft (Amniotic Fluid-Derived Allograft)
• PLX- Pluristem Therapeurics (‘Placental Tissue’) Still in Trials
• BioD Factor – BioD (Amniotic Membrane)

No Clinical Studies
"361"
Placental Tissue

Literature databases and Internet resources

- Use of amnion, chorion, amniotic fluid and umbilical cord tissue
- Most tissue processing methods result in devitalized/decellularized allografts
  - No biological activity
- Information very difficult to obtain from company websites
- Lack of level 1 clinical studies
FDA

- Homologous vs. non-homologous
- Ovation – pulled from market
- NuTech (ReNu) – allowed to proceed w/ RCT

- Grafix™
  - Allograft-fetal
  - MSCs
    - 200K/cm²
  - Growth factors
  - Extracellular matrix

- April 2016 Review
STEM CELLS

- Many In Vitro and In Vivo Animal Studies

Few Human Studies

“Utility Infielder… Or Quarterback?”
Stem Cells - Expanded

Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy
A Randomized, Double-Blind, Controlled Study

2014

C. Thomas Vangsness Jr., MD, Jack Farr II, MD, Joel Boyd, MD, David T. Dellaero, MD, C. Randal Mills, PhD, and Michelle LeRoux-Williams, PhD

The Journal of Bone & Joint Surgery

USC
Improvement in VAS Pain Score through 2 years post meniscectomy surgery in patients with evidence of cartilage degeneration on MRI. Control: HA; Group A: 50 x 10^6 hMSCs; Group B: 150 x 10^6 hMSCs.
1. No stem cell company makes money
2. No stem cell drug has been approved to date in the USA – Prochymal (Mesoblast)
3. 1 Level I study in Orthopaedic literature – Safety study
4. Illegal to remove cells, manipulate and insert into body
5. Very little clinical trials in Orthopaedic Surgery to date
6. Extensive public curiosity / Misinformation
Conclusion

1. Confusion Persists For Surgeon
2. Future Research and Understanding
3. Improved Systems For Separation and Counting
4. Increase in Clinical Use
5. Education
   “Learn the Alphabet”
Future

- Biologic Injections / Clinics
- Improvement/Definitions with Cell Injections
- Call for Level I Studies
- FDA
- Insurance Companies
- Use Will Increase – Safety?
- Cash
Thank you
Mesenchymal Stem Cell Levels of Common Tissues

Mean
• Adipose
  • 286,909 MSCs/ml
• Bone Marrow
  • 54,570 MSCs/ml
• Whartons Jelly
  • 800,142 MSCs/cm

Median
• Adipose
  • 1,000,000 nucleated cells/ml
  • 333,333 MSCs/ml
• Bone Marrow
  • 269.3MSCs/10^6nucleated cells
  • 13,400,000 nucleated cells/ml
  • 3,606 MSCs/ml
• Wharton’s Jelly
  • 950,000 nucleated cells /cm
  • 650,000 MSCs/cm
Mesenchymal Stem Cell Levels of Common Tissues

- Adipose Tissue
  - 1,000,000 nucleated cells/ml of tissue
  - 333,333 MSCs/ml of tissue

- Bone Marrow
  - 13,400,000 nucleated cells/ml of tissue
  - 3,606 MSCs/ml of tissue

- Wharton’s Jelly
  - 950,000 nucleated cells/cm of Cord
  - 650,000 MSCs/cm of Cord
# Mesenchymal Stem Cell Levels of Common Tissues

## Cell Levels by Tissue

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<thead>
<tr>
<th>Tissue</th>
<th>Nucleated Cells/ml</th>
<th>MSCs/ml</th>
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<tr>
<td>Adipose Tissue</td>
<td>1,000,000</td>
<td>333,333</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>13,400,000</td>
<td>3,606</td>
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<td>Wharton’s Jelly</td>
<td>950,000/cm of Cord</td>
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</tr>
</tbody>
</table>

## Considerations

- Wide variation in harvest levels by technique and anatomic location
- Higher ratio of MSCs:Nucleated cells in Wharton’s Jelly and Adipose

## References

Adipose Offers Higher Levels of cells/ml of Tissue

Adipose Tissue

• Harvest ranges 4,737-1,550,000 cells/ml\(^1,2\)
• Typical Yields range from 150,000-400,000 cells/ml\(^3,4\)
• 60ml of harvested adipose tissue yields \(9.0 \times 10^6 – 2.4 \times 10^7\) MSCs
  • Harvest and purification techniques rapidly evolving

Bone Marrow

Harvest ranges from 30-317,400 cells/ml\(^3,5\)

• Typical Yields range from 1,000 – 10,000 cells/ml\(^7,8\)
• 60ml of harvested bone marrow yields \(6.0 \times 10^4 – 6.0 \times 10^5\) MSCs
  • Yields vary considerably by harvest site and subject age

1. Strem et al. 2005
2. Yoshimura et al. 2006
3. De Ugarte et al. 2003
4. Aust et al. 2004
5. Sakaguchi et al. 2004
6. Pierini et al. 2013
Hernigou et al. 2013
FDA

- Oversight / Regulation
  - Assumed GTP
  - Inspection
    - Limited in Past
    - Strong Increase in 2005
  - F/U, Infections
  - **Warning Letter**
  - Recall / Shutdown
Clinical Use
Knee Injection Theory

Anti – IL-1 / TNF

Interleukin Receptor Antagonist Protein (IRAP)
INFLAMMATION PROCESS COMPLEX

M1 VS M2
(CATABOLIC VS ANABOLIC)
“That Rooster/Chicken Stuff”

Weekly Injections
Hyaluronic Acid

• 6 products
• Variable weight/size/# of injections
• Approaching $1 billion business
• 20-30% responders
• 20-30% placebo
Summary of Recommendations: Conservative Treatments

1. Exercise (STRONG)
2. Weight Loss (MODERATE)
3. A. NO acupuncture (STRONG)
   B. Electrotherapy (INCONCLUSIVE)
   C. Manual therapy (INCONCLUSIVE)
4. Medial compartment unloader (INCONCLUSIVE)
5. NO Lateral wedge insoles (MODERATE)
6. NO glucosamine or chondroitin (STRONG)
Summary of Recommendations: Pharmacologic therapy
6. NSAIDs (STRONG)
7. Tylenol, Opioids, Pain Patches (INCONCLUSIVE)

Summary of Recommendations: Procedures
8. Intra-articular steroids (INCONCLUSIVE)
9. NO Hyluronic Acid (STRONG)
10. PRP (INCONCLUSIVE)
11. NO needle lavage (MODERATE)

Meaningful clinical difference
PLATELET-RICH PLASMA

- Common
- Costly
- Centrifuged
- Confusing (Evidence?)
- Consecutive Admin
- Cash
PROBLEMS
The Literature

EBM
  Lacking
  Early Science - Infancy
Study Designs
  What Are You Injecting?
  Where Are Your Injecting?
Standardization Of Pathology
Dose/ Number/ Time Interval
Reproducibility
  “DOSE”??
Current Status: 2015
ClinicalTrials.gov

- Stem Cell: 4,284 (2867)
- Orthopaedic Surgery: 1552 (843)
- Stem Cells – Orthopaedic Surgery: Only 26 studies (12)
- Rheumatology (969)
- Stem Cells and Rheumatology (15)
MSK CLINICAL TRIALS

- BONE CYST - 2
- OA HIP - 2
- SPINE - 10
- KNEE - 4
- FOOT - 2
- OTHER - 4

U.S., SPAIN, INDIA, EGYPT
Current US Status

- No stem cell company makes money
- Only one drug approved to date by FDA
  - Prochymal
  - Extended access permission
- “Soft Products”
  - Allografts-Active Cells
    - NuVasive: Osteocel Plus, Osteocel Pro
    - Orthofix: Trinity Evolution, Trinity Elite
    - Biomet: Cellentra
    - Allosource: Allostem
    - Stryker: Bio4
    - Depuy/Synthes: Vivigen
  - Ovation
Current Concepts: The Role of Mesenchymal Stem Cells in the Management of Knee Osteoarthritis


Jesse I. Wolfstadt, MD, Brian J. Cole, MD, MBA, Darrell J. Ogilvie-Harris, MD, FRCSC, Sowmya Viswanathan, PhD, and Jaskarndip Chahal, MD, MSc, FRCSC

- Level III
- Unclear if ASCs are more effective than BM-MSCs
- Few studies define dosing/frequency
- Imaging is uncommon
One-Step Cartilage Repair with Bone Marrow Aspirate Concentrated Cells and Collagen Matrix in Full-Thickness Knee Cartilage Lesions: Results at 2-Year Follow-up

Cartilage

Alberto Gobbi, Georgios Karnatzikos, Celeste Scotti, Vivek Mahajan, Laura Mazzucco, and Brunella Grigolo

- 1 step surgery with BMAC injection is viable
- Grade IV knee osteoarthritis
- Limited numbers (n=15)
Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee


Jae-Do Kim, Gun Woo Lee, Gu Hee Jung, Cheung Kue Kim, Taehun Kim, Jin Hyung Park, Seong Sook Cha, Young-Bin You

- BMAC with ASCs are effective in treating grade I-III OA
- n=41
- Short term follow up (6 months)
- No dosing
Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis

Knee Surgery, Sports Traumatology, Arthroscopy.

Yong-Gon Koh, Yun-Jin Choi, Sae-Kwang Kwon, Yong-Sang Kim, Jee-Eun Yeo

- Level IV – case series study
- Grade II-III OA
- MSCs and PRP during arthroscopy
- Lacks quantitative data