Adipose-Derived Cells: How Does That Translate?

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JM Gimble MD PhD
Pennington Biomedical Research Center
Baton Rouge, LA, USA
gimblejm@pbrc.edu

Disclosures: Co-founder-LaCell LLC, Consultant-ATRM/Johnson & Johnson
Overview

• How Does Adipose Tissue Stack Up Against Bone Marrow As A Stromal/Stem Cell Source?
• What Do We Need To Translate Adipose-Derived Cells To The Clinic?
Adipose-derived Cell Types

- Stromal Vascular Fraction (SVF) Cells
  - Freshly isolated
  - Heterogeneous
  - Suspended, not adherent

- Adipose-derived Stromal/Stem Cells (ASC)
  - Culture expanded
  - Plastic adherent
  - Relatively homogeneous relative to SVF cells
Adipose vs. Bone Marrow - Pros & Cons

ASC
• Abundant
• Accessible
• $>10^2$ to $10^3$ Superior Yield per Unit Tissue Volume
• Replenishable
• Clinical Trials – 36*

BMSC
• Well Characterized
• Multi-Potent
• Allogeneic Transplantation
• Regulatory Approval
• Manufacturing Know How
• Clinical Trials – 143*

*www.clinicaltrials.gov
BMSC vs ASC Antibody Gallery
Gray Filled = BMSC
Black line = ASC

ASC vs. BMSC Cytokine Profile: Similar, Not Identical

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<th>Flt3L</th>
<th>G-CSF</th>
<th>GM-CSF</th>
<th>HGF</th>
<th>IL-1α</th>
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Adapted from Kilroy G et al. J Cell Physiol 212:702, 2007
ASC vs. BMSC

- Overlapping but Distinct Immunophenotypes
- Overlapping but Distinct Cytokine Profiles
- Similar Immunomodulatory Function
- Differentiation Profiles
  - BMSC Reported to Exhibit Superior Osteogenesis
  - ASC Reported to Exhibit Superior Adipogenesis
  - Could epigenetic mechanisms account for fidelity to tissue of origin?

Clinical Osteogenic ASC Application

Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells


REGEA Institute, Tampere, & University of Helsinki, Finland
Clinical Approach

- 65 yr old male 28 months post hemimaxillectomy for keratocyst
- Harvest autologous adipose tissue and expand ASC in autologous serum
- Mix with HA/TCP and BMP2 inside titanium cage
- Implant in rectus abdominis muscle above epigastric artery for 6-8 months
- Transfer as free flap to repair palatal defect with anastomosis to facial artery
- Subsequent dental implants
- Success out to 1.5 year follow up
Repair of Soft Palate Defect

Before

After

Adipose vs. Bone Marrow

Conclusion(s)

• Separate But Equal –
  – Cells From Both Tissue Sources Have Unique Advantages & Limitations
  – Optimal Culture and Processing Conditions May Be Tissue Specific
  – Development of Consensus Specifications for ASC and SVF Cells May Facilitate Future Product Development, Standardization & International Harmonization
Moving to the Clinic - Do We Need A Dictionary For Translation?

- Adipose (English – US)
- Adipose (English – UK)
- Vet (Dutch)
- Adipeux (French)
- Adiposo (Spanish)
- Fettvävnad (Swedish)
- Lihava (Finnish)
- (Arabic)
- (Hebrew)
- (Chinese)
- (Japanese)
- Жировой (Russian)
- Λιπώδης (Greek)
- Tłuszczowej (Polish)

Translations Courtesy of Google translate
Or Do We Need A Roadmap?
Travel Destinations

Regulatory Based
• EMEA/FDA
• Closed System Devices
• Donor Specifications
• Reagent Sourcing
• Collagenase Enzyme Classifications

Assay Dependent
• Product Acceptance Criteria
• Shipping Studies
• Sterility Testing Criteria
• Cryopreservation
• Tumorigenesis
• Serum Substitutes
• Xenoprotein Free

Gimble et al. Stem Cells  29:749, 2011
Closed System Devices

Harvest fat (adipose) tissue → Separate and concentrate regenerative cells → Return cells / tissue to same patient in approximately one hour

Cytori Therapeutics/GE Celution™ 700
Tumorigenesis

• In vitro cultured ASC have been found to undergo transformation
    • Retraction Cancer Research 70:6882, 2010
Animal Protein Free Reagents

• Non-porcine sources of trypsin

• Human serum culture medium
  – Bieback et al. Stem Cells 27:2331, 2009

• Xenoprotein-free culture medium
Ra et al. *Safety of Intravenous Infusion of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Animals and Humans*

- Korean biotech report of regulatory pre-IND & IND studies:
  - Isolation, immunophenotype & multi-lineage differentiation
  - Karyotype & single nucleotide polymorphism analyses
  - Survival/viability/stability in cold storage for 72 hrs
  - Toxicology & tumorigenicity studies in vivo
- Phase I clinical safety trial for spinal cord injury

*Stem Cells & Develop 2011 (epub)*
Setting the course...

• Continue to promote peer reviewed publications of academic & biotech pre-IND & IND experience (both success & failure)
• Development of international guidelines & standards describing SVF cells & ASC by ISCT, IFATS, & other societies reflecting the highest scientific, manufacturing & regulatory standards

Gimble, Bunnell, Chiu & Guilak
Stem Cells & Develop 2011 In Press
Evidenced Based Medicine Approach

• Prepare the literature for future meta-analyses validating the efficacy & safety of adipose-derived cell products
• Advance to Level 1 & 2 studies

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<th>Level</th>
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<tr>
<td>5</td>
<td>Expert opinion without support from physiological bench science or first principles</td>
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<tr>
<td>4</td>
<td>Poorly controlled case series</td>
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<td>3</td>
<td>Individual case controlled study</td>
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<td>Retrospective cohort study</td>
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<td>Randomized case controlled prospective trial</td>
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Thanks for your attention!
Questions?