Osteochondral Allograft Transplantation

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Fundamental Strategies of Cartilage Restoration

• Cell based
  – Induce cells to form (chondral) tissue in situ
  – Marrow stimulation
  – ACI
  – Other cell sources

• Whole tissue based
  – Restore defect with mature tissue
  – Osteochondral autograft (OAT)
  – Osteochondral allograft (OCA)
  – Processed (acellular) allografts
Cartilage is an Ideal Tissue for Transplantation

- Avascular
- Aneural
- Immunopriveleged
- Amenable to storage
- Can be fashioned to fit recipient
Osteochondral Allografting

• Originally introduced as a joint reconstructive procedure for trauma, tumors and arthritis
• Now widely used as a cartilage restoration technique for chondral and osteochondral lesions

Complex reconstruction paradigm
• OCD
• AVN
• Post-traumatic

Cartilage repair paradigm
• Microfracture
• OAT
• ACI
• OCA
Historical Perspective

- **Lexer (1908, 1925)**
  - First published reports of fresh OCA use
  - Partial joints
- **Gross (1970’s)**
  - Post traumatic reconstruction, giant cell tumors
  - Small fragment grafts
- **Meyers, Akeson, Convery, (1980’s)**
  - Osteoarthritis, osteonecrosis, chondrosis
  - Shell allografts
- **Garrett (1994)**
  - Osteochondritis dissecans
  - Dowel allografts
- **Commercialization of fresh graft distribution (2002)**
- **Widespread use in US, programs in development throughout the world**
The San Diego Experience

- IRB approved protocol (1983)
- Tissue bank collaboration
- Clinical outcome data collection
- Retrieval program
- Basic scientific studies
- Multidisciplinary collaboration
Governing Principles for Fresh Allograft Use Cartilage Repair

- Whole tissue transplant
- Viable chondrocytes in mature hyaline cartilage matrix
- No cell or tissue differentiation required
- Maximizing and preserving inherent chondrocyte and matrix properties critical
- Cells within matrix are immunoprivileged
- Allograft chondrocytes survive transplantation and maintain matrix
Governing Principles for Fresh Allograft Use in Cartilage Repair

- Osseous portion is a nonliving scaffold and interface for attachment and integration
- Minimal volume unless osseous reconstruction necessary
- Incorporation by creeping substitution
- Potential site for immunologic response by recipient
- Behavior of osseous component important predictor of clinical success
Indications for Osteochondral Allografts

- Osteochondritis dissecans
- Post traumatic reconstruction
- Osteonecrosis
- Traumatic or degenerative chondral lesions/ OA
- Salvage previous cartilage surgery
- Cartilage lesions associated with subchondral bone abnormality
### “Logistics” of Osteochondral Allograft Transplantation

**Donor (tissue bank)**
- Donor recovery
- Donor suitability evaluation
- Processing and testing
- Graft storage
- Donor and recipient matching
- Final graft release
- Shipping

**Patient (clinic)**
- Evaluation and indication
- Consent and counseling
- Communication with tissue bank
- Anatomic sizing
- Insurance approval
- Patient notification of potential donor tissue
- Surgery
OCA “Types”

- **Dowel**
  - Focal lesions
  - 15-30 mm
  - Femoral condyle, trochlea
  - Humeral head
  - Femoral head

- **Shell graft**
  - Complex, inaccessible lesions
  - Tibial plateau, posterior femoral condyle
  - talus

- **Small fragment**
  - Large or deep lesions
  - Tibia, patella
  - Compartmental grafts
  - ankle
Surgical Principles

- Restore mechanical environment
- Transplant least amount of bone necessary
- Dowels are simplest to perform
- Congruent fit (within 1mm)
- Avoid impact on insertion
- Fixation with pins, darts or screws when necessary
Mechanisms and Consequences of Chondrocyte Injury During Impact Loading and Insertion of Human Osteochondral Grafts


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^Shiley Center for Orthopaedic Research & Education
Scripps Clinic, La Jolla, CA

[Graph showing cell death percentage over time and load culture]
Surgical Technique: Femoral Condyle
Surgical Technique: Femoral Condyle
Surgical Technique: Femoral Condyle
Multiple Grafts
Patellar Allograft
Tibial Plateau and Meniscus
Shell Allograft (Talus)
OCA Clinical Experience in the Knee

- Multiple clinical outcome studies
- Clinical variables
  - Diagnosis
  - Anatomic location
  - Previous surgery
  - Graft types
  - Adjunct procedures (meniscus/ osteotomy)
  - Immunology
  - Failure: revision/ arthroplasty
  - Retrieval analysis
Clinical Evaluation

- Modified D’Aubigne and Postel (18-point) scale
- Knee Society Score
- IKDC pain and function scores
- KOOS
- Patient satisfaction
- Radiographs
- Serum anti HLA antibodies
Clinical Evaluation

• Reoperations
  – Not directly related to the allograft
  – Failure of allograft
    • Revision or removal
Allograft Database

IRB approved allograft outcomes database 1983-present:

887 OCA

Knee:

692 OCA, 655 primary OCA
## Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (sd) or %</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>34 (11.8)</td>
<td>14-68</td>
</tr>
<tr>
<td>Male</td>
<td>53.1%</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>26.8%</td>
<td></td>
</tr>
<tr>
<td>Degenerative chondral lesion</td>
<td>22.6%</td>
<td></td>
</tr>
<tr>
<td>Traumatic chondral injury</td>
<td>14.7%</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>12.4%</td>
<td></td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Failed osteochondral allograft</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Previous surgery on affected joint</td>
<td>90.7%</td>
<td></td>
</tr>
<tr>
<td>Number of previous surgeries</td>
<td>2.6 (1.8)</td>
<td>1-13</td>
</tr>
</tbody>
</table>
## Graft Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (sd) or %</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral condyle (medial)</td>
<td>35.3%</td>
<td></td>
</tr>
<tr>
<td>Femoral condyle (lateral)</td>
<td>18.4%</td>
<td></td>
</tr>
<tr>
<td>Tibial plateau (medial)</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Tibial plateau (lateral)</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Patella</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td>Trochlea</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>Combination (2 locations)</td>
<td>26.3%</td>
<td></td>
</tr>
<tr>
<td>Combination (3 locations)</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Number of grafts</strong></td>
<td>1.5 (0.7)</td>
<td>1-4</td>
</tr>
<tr>
<td><strong>Total graft area (cm²)</strong></td>
<td>10.1 (7.0)</td>
<td>1.2-57.5</td>
</tr>
</tbody>
</table>
Results

- Average follow-up 86 months (range, 24–309)
- 7.1 years (range, 2-25)
## Modified D’Aubigne and Postel (18-point) Scale

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>--</td>
<td>32.0%</td>
</tr>
<tr>
<td>Good</td>
<td>10.9%</td>
<td>42.3%</td>
</tr>
<tr>
<td>Fair</td>
<td>48.1%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Poor</td>
<td>41.0%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>
IKDC Pain Scores

- Mean pre-op score 6.2 (± 2.3)
- Mean post-op score 3.2 (± 2.7)
- p < 0.001
IKDC Function Scores

- Mean pre-op score 3.4 (± 1.9)
- Mean post-op score 7.3 (± 2.3)
- p < 0.001
Subjective Postoperative Patient Satisfaction

Percentage

- Extremely satisfied: 73%
- Satisfied: 18%
- Somewhat satisfied: 5%
- Somewhat dissatisfied: 3%
- Dissatisfied: 1%
Results: Reoperations

- 29% of “non-failing” knees underwent further surgery
  - Arthroscopy
    - Diagnostic
    - Chondroplasty
    - Meniscectomy
  - Hardware removal
  - ACL reconstruction
  - Osteotomy
Results: Clinical Failure

- 72 of 354 (20%) knees failed at a mean of 40 months (range, 3–165)
  - 41 TKA
  - 23 revision allografts
  - 4 UKA
  - 2 patellectomies
  - 2 knee fusions
Survivorship (Kaplan-Meier)

- 82% at 5 years
- 72% at 10 years
- 70% at 25 years
# Failure Rates by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>21/44</td>
<td>47.7%</td>
</tr>
<tr>
<td>Failed osteochondral allograft</td>
<td>8/25</td>
<td>32.0%</td>
</tr>
<tr>
<td>Tibial plateau fracture</td>
<td>3/12</td>
<td>25.0%</td>
</tr>
<tr>
<td>Other osteochondral fracture</td>
<td>3/13</td>
<td>23.1%</td>
</tr>
<tr>
<td>Degenerative chondral injury</td>
<td>14/80</td>
<td>17.5%</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>5/33</td>
<td>15.2%</td>
</tr>
<tr>
<td>Traumatic chondral injury</td>
<td>7/52</td>
<td>13.5%</td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>11/95</td>
<td>11.6%</td>
</tr>
</tbody>
</table>
Survivorship: OCD vs. OA

- OCD: 84% at 25 years
- OA: 35% at 15 years
Logistic Regression Analysis

- Clinical variables:
  - Sex
  - Age
  - Diagnosis
  - Graft anatomic location
  - Graft size
  - Number of grafts
# Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reference Group</th>
<th>Odds Ratio in comparison to reference group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Male</td>
<td>2.02</td>
<td>0.041</td>
</tr>
<tr>
<td>Age 30-40</td>
<td>Age &lt;30</td>
<td>2.33</td>
<td>0.085</td>
</tr>
<tr>
<td>Age &gt;40</td>
<td>Age &lt;30</td>
<td>3.33</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCI / DCI</td>
<td>OCD</td>
<td>0.89</td>
<td>0.824</td>
</tr>
<tr>
<td>Fracture</td>
<td>OCD</td>
<td>0.89</td>
<td>0.887</td>
</tr>
<tr>
<td>AVN</td>
<td>OCD</td>
<td>1.02</td>
<td>0.981</td>
</tr>
<tr>
<td>OA</td>
<td>OCD</td>
<td>1.20</td>
<td>0.788</td>
</tr>
<tr>
<td>Failed OCA</td>
<td>OCD</td>
<td>2.47</td>
<td>0.220</td>
</tr>
<tr>
<td><strong>Graft location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial plateau (M/L)</td>
<td>Femoral condyle (M/L)</td>
<td>0.27</td>
<td>0.280</td>
</tr>
<tr>
<td>Trochlea</td>
<td>Femoral condyle (M/L)</td>
<td>0.52</td>
<td>0.559</td>
</tr>
<tr>
<td>Patella</td>
<td>Femoral condyle (M/L)</td>
<td>1.76</td>
<td>0.385</td>
</tr>
<tr>
<td>Combination (2 locations)</td>
<td>Femoral condyle (M/L)</td>
<td>1.86</td>
<td>0.354</td>
</tr>
<tr>
<td>Combination (3 locations)</td>
<td>Femoral condyle (M/L)</td>
<td>10.83</td>
<td>0.065</td>
</tr>
<tr>
<td><strong>Graft size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium (5-10 cm²)</td>
<td>Small (&lt;5 cm²)</td>
<td>1.62</td>
<td>0.403</td>
</tr>
<tr>
<td>Large (&gt;10 cm²)</td>
<td>Small (&lt;5 cm²)</td>
<td>4.89</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Number of grafts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.10</td>
<td>0.884</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.57</td>
<td>0.527</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.06</td>
<td>0.077</td>
</tr>
</tbody>
</table>
Risk Factors for Failure

- After controlling for other variables in the logistic regression model:
  - Gender, age and total graft size all predicted clinical failure
    - Female: 2X
    - Age > 40: 3.3X
    - Graft size > 10 cm²: 4.9X
  - Diagnosis, graft location or number of grafts did not predict outcome
  - Revision OCA study: Risk = burden of degenerative disease
Factors in Allograft Survival

- Biological
  - Alignment
  - Ligaments
  - Menisci

- Mechanical

- Surgical

- Immunology???
• 42% of patients develop anti-HLA cytotoxic antibodies
• Most clinical failures are antibody positive
• Antibodies are associated with inferior appearance on MRI
• Histology rarely shows immune phenomena
Allografting of Other Joints

• Ankle
  – OLT
  – Osteoarthritis
  – AVN

• Shoulder
  – AVN
  – Chondral or osteochondral lesions

• Hip
  – AVN
  – Trauma

• Small joints
Fresh Allograft
Recovery and Processing

• Before 2002
  – Institution associated tissue banks
  – “Exceptional release criteria”
  – IRB, independently developed recovery, processing and release protocols
  – Recovery to implantation < 7 days

• After 2002
  – Commercial distribution by national tissue banks
  – Standardized protocols, FDA oversight
  – Recovery to implantation > 14 days
Fresh Allograft Paradigm: Chondrocyte Viability

- Living chondrocytes are the fundamental basis for fresh allografting
- Maintenance of intact hyaline cartilage matrix
- Long term graft function
Media Optimization for the Storage of Osteochondral Allografts
Basic Science Collaboration

David Amiel, PhD
Connective Tissue Biochemistry Lab
Department of Orthopedics, UCSD

Robert Sah, MD, ScD
Cartilage Tissue Engineering Lab
Department of Bioengineering, UCSD
Allograft Storage Studies

FBS versus SFM: Viability by Layer

Day 1 Control   Day 28 SFM   Day 28 FBS

- Superficial
- Middle
- Deep

% Viability

Day 1 Control: Higher viability compared to Day 28 SFM and Day 28 FBS, especially in the superficial layer.

Day 28 SFM: Lower viability than Day 1 Control, with a slight increase in the middle layer.

Day 28 FBS: Similar viability to Day 28 SFM, with slight increases in the middle and deep layers.

Error bars indicate the variability in viability measurements.
Proteoglycan Synthesis

$^{35}\text{SO}_4$ Uptake

<table>
<thead>
<tr>
<th>Day</th>
<th>CPM/mg Cartilage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
</tr>
<tr>
<td>7</td>
<td>Moderate</td>
</tr>
<tr>
<td>14</td>
<td>Moderate</td>
</tr>
<tr>
<td>28</td>
<td>Low</td>
</tr>
</tbody>
</table>

Williams et al., JBJS Am 2003
Biomechanics Results:
Indentation Stiffness [IRHI]

7 Day
57.2 ± 10.9

28 Day
61.0 ± 10.2

Not significant
Results:
GAG Content [% hexosamine/dry wt]

<table>
<thead>
<tr>
<th>Time</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Day</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>7 Day</td>
<td>4.1 ± 1.3</td>
</tr>
<tr>
<td>14 Day</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>28 Day</td>
<td>4.2 ± 0.5</td>
</tr>
</tbody>
</table>
Gene Expression in Stored Allografts

Figure 1: RNA is obtained from cartilage, reverse transcribed, amplified, and hybridized to the array. Band intensity is then quantified and analyzed.

Intensities are quantified.
Gene Array Results
Up Regulated Apoptosis Genes

Robertson, et al. CORR 2006
Mechanism of Cell Death

Apoptosis Pathway
Goat Allografts Stored in Media at 4°C
Role of Etanercept
(AJSM 2012)

Baseline With Etanercept Without Etanercept

10% Superficial
50% Middle
40% Deep

4 Weeks
The 37°C storage of OCA supports long-term chondrocyte viability, especially at the vulnerable surface and superficial zone of cartilage.
Storage Studies: Conclusions

- 28 day storage does not significantly affect cartilage matrix or biomechanical properties.
- Cell viability, cell density and cell metabolism decreased with increasing storage time.
- Optimum storage conditions not yet defined
- In vivo studies are needed to determine the effect of storage on in vivo performance of osteochondral allografts.
In Vivo Studies


Allograft Efficacy May Be Dependent on Viable Chondrocytes & Mechanical Stability

- retrieved fresh grafts
  - patients required revision/TKA $\rightarrow$ bias
  - contain viable cells up to 29 yrs after implant\(^1\)
  - failures demonstrate:\(^2\)

- low \# chondrocytes
- ↑ surface roughness
- necrotic bone

- pannus-like covering, subchondral irregularities\(^3\)

Experimental Design & Methods

DONOR PREPARATIONS

FROZEN 4°C/14d

FRESH 4°C/28d

ALLOGRAFT SURGERY

0 12 months

RETRIEVAL

n=15 adult goats

\( \varnothing = 8 \text{ mm} \)
\( h = 5 \text{ mm} \)

NON-OP

LT MFC

OP

LT MFC

STRUCTURE

COMPOSITION

FUNCTION

gross score

Mankin histopathology score

PROX DIST

Saf-O HE-\( \mu \)CT cellularity

indenter tip

depth

stiffness

load

time

Aim 1
Systematic, multi-scale, and inter-disciplinary analyses (1) validated a large animal model of OCA, and (2) demonstrated the superiority of Fresh vs. Frozen grafts.
Decreased cellularity, as a result of 4°C storage, detrimentally affects repair outcomes. Surface cellularity may be essential for long-term repair efficacy.
Secretion of the lubricant proteoglycan-4 (PRG4) may not only be a useful marker of OCA performance, but also a biological process protecting the articular surface of grafts following cartilage repair.
Biological & Structural Properties of OCA Affect Functional Repair Through Mechanobiological Mechanisms

**Integrate** Bone-Bone Interface
- Bone Biology & Structure
- ScB & Basal Cysts

**Maintain** Articular Surface
- *In Vitro* Articular Surface Biology
- *In Vivo* Cartilage Repair Structure

**Preserve** Bone-Cartilage Interface
- ?bone metabolism?

- extend 4°C storage paradigm → ↓ *in vivo* performance
- enhance OCA biological performance
- provide insight into bone cyst pathogenesis
- develop & apply integrative, multi-scale analysis that highlights relationship between cartilage & bone *in vivo*
Clinical Summary: Fresh Osteochondral Allografts

- Useful treatment for a wide spectrum of joint pathology
  - Clinically important objective and subjective improvement
  - High rate of patient satisfaction

- Significant reoperation and revision rate
  - Similar to other cartilage restoration procedures

- Many interesting and important clinical and scientific questions remain to be answered
Future Allograft Innovations

- Changes in tissue banking paradigm
- Storage or cryopreservation technology
- Physical/ Molecular manipulation
- Allografts as scaffolds for cell based technologies
- Allografts as a cell source for tissue engineered repair
- Joint fabrication
Thank You
Thank You