"AN ALTERNATIVE GRAFT FOR ACL RECONSTRUCTION, BACKGROUND AND RATIONALE"

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CURRENT GRAFT OPTIONS FOR ACL REPLACEMENT

- Surgeon/patient’s three ACL graft options include: autograft, allograft and synthetic graft

- Autograft: (graft from patient’s own patellar tendon or hamstring)
- Allograft: (graft from human cadaver)
- Synthetic Graft: (only available in Europe; Dacron, Gore-Tex, polyester, etc.)

Each treatment option has numerous shortcomings . . .
ARTIFICIAL GRAFT

LIGAMENT AUGMENTATION AND RECONSTRUCTION SYSTEM (LARS):

- MAIN ADVANTAGE: NO GRAFT HARVESTING
- DRAMATIC EXPERIENCE WITH OLD GENERATION ARTIFICIAL GRAFT
SHORTCOMINGS OF AUTOGRRAFTS

- Necessitates a second surgical site
  - Increases operative time
  - Reduces function and causes arthritis at harvest site
  - Increases rehabilitation needed and scarring
  - Increases risk of infection
- Harvested tendons do not grow back; limited number available per patient
## BIOMECHANICAL PROPERTIES

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Ultimate Tensile Load (N)</th>
<th>Stiffness (N/mm)</th>
<th>Cross-sectional Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact anterior cruciate ligament³</td>
<td>2,160</td>
<td>242</td>
<td>44</td>
</tr>
<tr>
<td>Bone-patellar tendon-bone (10 mm)⁶</td>
<td>2,977</td>
<td>620</td>
<td>35</td>
</tr>
<tr>
<td>Quadruple hamstring⁵</td>
<td>4,090</td>
<td>776</td>
<td>53</td>
</tr>
<tr>
<td>Quadriceps tendon (10 mm)²,⁷,⁸</td>
<td>2,352</td>
<td>463</td>
<td>62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Graft</th>
<th>Tensile load (N)</th>
<th>Stiffness (N/mm)</th>
<th>Biologic Incorporation</th>
<th>Method of Fixation</th>
<th>Graft Site Morbidity</th>
<th>Outcomes/Return to Play (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patellar tendon autograft³,⁴</td>
<td>2,977</td>
<td>620</td>
<td>Bone-to-bone healing (6 wks)</td>
<td>Interference screw</td>
<td>Anterior knee pain; larger incision</td>
<td>4-6</td>
</tr>
<tr>
<td>Quadruple semitendinosus/gracilis³</td>
<td>4,090</td>
<td>776</td>
<td>Soft-tissue healing (8-12 wks)</td>
<td>Variable</td>
<td>Hamstring weakness</td>
<td>Increased laxity/6</td>
</tr>
<tr>
<td>Patellar tendon allograft⁶</td>
<td>Similar to patellar tendon autograft</td>
<td>Similar to patellar tendon autograft</td>
<td>Bone-to-bone healing, slow incorporation (&gt;6 mos)</td>
<td>Interference screw</td>
<td>None</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Quadriceps tendon⁷,⁸</td>
<td>2,352</td>
<td>463</td>
<td>Bone-to-bone and soft-tissue (6-12 wks)</td>
<td>Variable</td>
<td>Similar to patellar tendon autograft</td>
<td>Limited data</td>
</tr>
</tbody>
</table>

*West & Harner 2005*
SHORTCOMINGS OF ALLOGRAFTS

- Demand for high quality grafts for ACL replacement significantly outstrips supply
- Procedures are being performed with less-than-ideal allografts
- Variable tissue characteristics (such as length, width, etc.) that can be difficult for the surgeon to adjust for during the procedure
- Allograft products are not FDA-approved; known risk of human disease transmission
- Allografts have limited availability globally
SHORTCOMINGS OF SYNTHETIC (NON-TISSUE) ACLS

- Without the ability to regenerate, many synthetic ACLs quickly wear down and fail
- Often times at the fixation points
- Dacron, carbon fiber, polyester and other chemical fibers have been tried
- Mixed clinical experiences
- High failure rates have resulted in very limited acceptance


Leeds-Keio polyester ligament for ACL replacement
XENOGRAFTS ARE CAPABLE OF MEETING SUCH ACL GRAFT REQUIREMENTS AND ARE ALREADY WELL-ACCEPTED IN OTHER SEGMENTS

- Xenografts are biologic/tissue-based and do not have supply issues
- Porcine xenografts have been successfully commercialized for many years
- Currently sold examples of porcine xenografts include:

  - Porcine heart valve
  - Porcine patch
  - Porcine collagen
IMMUNOLOGICAL CHALLENGE

Pig to Human Discordant Transplantation

- Lower species produce specific carbohydrates antigenic to old world monkeys and humans
- 1% of circulating human antibodies are anti-Gal
- Galili et al, PNAS 1987
**IMMUNOLOGICAL CHALLENGE**

- **Gal Epitope**
  - Anti-gal antibody causes hyperacute rejection
  - 95% of rejection response
  - Old world primates and humans

- **Secondary Epitopes**
  - Less critical response
  - Attenuated with crosslinking

Lower mammalian cells or ECM components
IDEAL ORTHOPAEDIC XENOGR AFT

- FUNCTIONAL AT TIME OF IMPLANTATION
- BIOCOMPATIBLE/IMMUNOCOMPATIBLE
- ASSURED STERILITY
- ASSURED VIRAL SAFETY
- CELLULAR INGROWTH SCAFFOLD
- GRADUAL REMODELING
The Z-Lig is an engineered porcine tendon that has been “humanized” to allow the tissue to be turned into an off-the-shelf scaffold device that can be used by surgeons to replace a ruptured anterior cruciate ligament (ACL) in the knee.

femoral bone tunnel showing graft to host bone integration and new bone formation around the edge of the tunnel
The Z-Process deactivates both α-gal and no-gal antigens on the xenograft: an enzyme is used to cleave the terminal galactose of the gal antigen so that the carbohydrate chain remaining on the animal tissue is the same in its structure as the carbohydrate chains present in humans.
ABI’s Proprietary Technology

Xenograft (Cells + ECM)

Z-process

Implantation

Host Remodeling
### STRUCTURAL PROPERTIES

<table>
<thead>
<tr>
<th></th>
<th>Porcine Patellar Tendon-treated (n=10)</th>
<th>Human Patellar Tendon (n=10)</th>
<th>Human ACL (16-26yrs) (n=6)</th>
<th>Human ACL (48-86yrs) (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultimate Load (N)</strong></td>
<td>1889 252</td>
<td>1387 299</td>
<td>1730 660</td>
<td>734 266</td>
</tr>
<tr>
<td><strong>Yield Load (N)</strong></td>
<td>1437 256</td>
<td>1101 397</td>
<td>1170 750</td>
<td>622 283</td>
</tr>
<tr>
<td><strong>Ultimate Displacement (mm)</strong></td>
<td>20.5 5.5</td>
<td>15.1 4.5</td>
<td>11.8</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Yield Displacement (mm)</strong></td>
<td>14.0 4.3</td>
<td>11.7 3.6</td>
<td>6.9</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Stiffness (N/mm)</strong></td>
<td>184.2 34.8</td>
<td>181.9 79.5</td>
<td>182 56</td>
<td>129 39</td>
</tr>
</tbody>
</table>
Z-Lig Biomechanics

Z-Lig vs. Human Allograft Load

Age of Human Donor

Z-Lig EUSA Clinical Trial (Mean = 1356 N)
SURGICAL TECHNIQUE

- Anatomic SB ACL rec. (femoral half tunnel from the AM portal)

- Preconditioning (5 min at 80N)

- Fixation with screws (titanium screws on femur and absorbable on tibia) and sometimes a staple on the tibia if the tendon is long enough and if the quality of host bone not strong enough
THE UNPACKED Z-Lig GRAFT
THE PREPARED Z-Lig GRAFT
PEARLS

- ready to use (no harvesting, no long graft preparation)
- good handling properties (a little bit elastic: there is the need for preconditioning)
- the bone quality of Z-Lig is better compared to allograft (less risk of breakage of the bone plug)
- good bone-tendon interface
**REHABILITATION**

- 2 weeks return to partial then full load bearing (with full-extension brace)
- 4 weeks return to activities of daily living
- 6 weeks return to work
- 8 months return to physical activity/sports
- 12 months return to pre-injury activity levels.
Z-LIG MULTICENTER STUDY
SITE 01 - ITALY

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, MULTICENTER CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE Z-LIG MEDICAL DEVICE COMPARED TO ALLOGRAFT FOR THE RECONSTRUCTION OF RUPTURED ANTERIOR CRUCIATE LIGAMENTS

Site Representative: Stefano Zaffagnini, Maurilio Marcacci
Site Coordinator: Giulio Maria Marcheggiani Muccioli
Other Co-Investigators: Marco Nitri, Tommaso Bonanzinga, Alberto Grassi

Institution: Istituto Ortopedico Rizzoli – Bologna, Italy

Number of ACLs/year by group: 350
Standard ACL technique: Hamstring plus lateral plasty or anatomical DB; fixation device: staples, interference screws.

Graft preference in primary ACLs:
• 80% autograft vs 20% allograft
• allograft preference fresh frozen not-irradiated Achilles Tendon

Graft preference in revision ACLs:
• 50% autograft vs. 50% allograft
• allograft preference fresh frozen not-irradiated Achilles Tendon
STUDY GROUPS

Willem van der Merwe, M.D. (Cape Town, South Africa)
Maurilio Marcacci, M.D., Stefano Zaffagnini, M.D., (Bologna, Italy)
Martin Lind, M.D., Ph.D (Aarhus, Denmark)
René Verdonk, MD, Ph.D; Peter Verdonk, M.D., Ph.D; Fredrik Almqvist, M.D., Ph.D. (Gent, Belgium)
Kees van Egmond, M.D.; ET al. (Zwolle, Netherlands)
Ramon Cugat, M.D.; ET al, (Barcelona, Spain)
Pedro Guillen, MD, PhD; Et al. (Madrid, Spain)
# PATIENT DEMOGRAPHIC DATA

<table>
<thead>
<tr>
<th></th>
<th>Allo (n = 34)</th>
<th>Xeno (n = 32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Surgery (mean ± sd, yrs)</td>
<td>30.5 ± 9.6 (18 - 52)</td>
<td>31.6 ± 8.8 (18 - 52)</td>
<td>0.517</td>
</tr>
<tr>
<td>Gender N(%)</td>
<td>22 (64.7%)M</td>
<td>12 (35.3%)F</td>
<td>27 (84.4%)M</td>
</tr>
<tr>
<td>Side N(%)</td>
<td>13 (38.2%)R</td>
<td>21 (61.8%)L</td>
<td>15 (46.9%)R</td>
</tr>
<tr>
<td>Time from injury to surgery (mo)</td>
<td>10.7 ± 18.7</td>
<td>13.8 ± 21.9</td>
<td></td>
</tr>
<tr>
<td>Follow-up interval (mo)</td>
<td>25.8 ± 1.8 (24.0 - 32.7)</td>
<td>25.8 ± 8.7 (2.1 - 38.0)</td>
<td>0.098</td>
</tr>
<tr>
<td>Mechanism of initial injury N(%)</td>
<td>24 (70.6%)</td>
<td>26 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>Sports</td>
<td>4 (11.8%)</td>
<td>3 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>ADL</td>
<td>3 (8.8%)</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Motorbike</td>
<td>1 (2.9%)</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td>2 (5.9%)</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>
## OBJECTIVE LAXITY EVALUATION

### No statistical significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivot Shift N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equal</td>
<td>4 (12.9)</td>
<td>1 (4.8)</td>
<td>29 (93.5)</td>
</tr>
<tr>
<td>Glide</td>
<td>11 (35.5)</td>
<td>8 (38.1)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Clunk</td>
<td>15 (48.4)</td>
<td>11 (52.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gross</td>
<td>1 (3.2)</td>
<td>1 (4.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>KT-1000 (mean ± sd, range)</td>
<td>5.7 ± 2.2 (1 - 9)</td>
<td>5.9 ± 3.7 (0 - 14)</td>
<td>1.7 ± 2.5 (-2 - 9)</td>
</tr>
<tr>
<td>Lachman's Test N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1 to 2mm</td>
<td>0 (0)</td>
<td>1 (4.3)</td>
<td>27 (87.1)</td>
</tr>
<tr>
<td>3 to 5mm</td>
<td>10 (32.3)</td>
<td>8 (34.8)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>6 to 10mm</td>
<td>16 (51.6)</td>
<td>9 (39.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt; 10mm</td>
<td>5 (16.1)</td>
<td>5 (21.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
SUBJECTIVE EVALUATION

NO STATISTICAL SIGNIFICANT DIFFERENCES BETWEEN GROUPS
Z-Lig Composite Endpoint – ITT Subjects at 6, 12 and 24 Months

6 Months

- Success: 96%
- Failure: 4%

12 Months

- Success: 92%
- Failure: 8%

24 Months

- Success: 91%
- Failure: 9%

Demonstrated success when compared to “standard of care” as described in the literature.
POST-OPERATIVE MRI 36-month FU
ANTIBODY RESPONSE CURVES

(A) Antibody results for anti-Gal and anti-non Gal were the following in a representative allograft patient;

(B) anti-Gal levels for the patients implanted with the xenograft device

(C) anti-non Gal antibody response for the xenograft patients.
ADVERSE EVENTS

6 xenograft subjects received Ralstonia pickettii contaminated grafts resulting in graft removal. This is an unusual contamination. Ralstonia pickettii is a waterborne organism that creates biofilms associated with membranes commonly found in high purity water systems. The small size of Ralstonia pickettii makes it a sentinel organism to challenge 0.2 micron aqueous filters. The combination of water source and the use of 0.2 micron filters in the sponsor’s manufacturing water supply was determined to be the root cause of the contamination.

Corrective actions implemented by the sponsor included installation and validation of a water for injection quality purification system with 0.05 micron filters and additional decontamination procedures during tissue procurement and monitoring procedures during processing.

After this corrective action Z-Lig obtained the CE mark.
## ADVERSE EVENTS

- § non-device related events (yellow)
- * subject received device associated with water-based pathogen (green)
- ° device related events (white)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Study Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2F §</td>
<td>Xenograft</td>
<td>□ Surgical site stitch abscess</td>
</tr>
<tr>
<td>2O *</td>
<td>Xenograft</td>
<td>□ Device infection requiring graft removal</td>
</tr>
<tr>
<td>2AE °</td>
<td>Xenograft</td>
<td>□ Persistent effusion and pain</td>
</tr>
<tr>
<td>4D *</td>
<td>Xenograft</td>
<td>□ Post-op septic arthritis □ Persistent effusion requiring graft removal</td>
</tr>
<tr>
<td>4F *</td>
<td>Xenograft</td>
<td>□ Synovitis, tibial tunnel osteomyelitis requiring graft removal</td>
</tr>
<tr>
<td>7A *</td>
<td>Xenograft</td>
<td>□ Persistent inflammation and surgical site fistula □ Tibial screw removal □ Tibial tunnel osteomyelitis □ Persistent inflammation, surgical site fistula requiring graft removal</td>
</tr>
<tr>
<td>7D °</td>
<td>Xenograft</td>
<td>□ Persistent pain</td>
</tr>
<tr>
<td>7E §</td>
<td>Xenograft</td>
<td>□ Traumatic ACL re-rupture</td>
</tr>
<tr>
<td>7I §</td>
<td>Allograft</td>
<td>□ Myocardial infarction</td>
</tr>
<tr>
<td>7N*</td>
<td>Xenograft</td>
<td>□ Synovitis □ Persistent inflammation, surgical site fistula requiring graft removal □ Surgical site septic arthritis, post graft removal</td>
</tr>
<tr>
<td>8B *</td>
<td>Xenograft</td>
<td>□ Traumatic ACL re-rupture</td>
</tr>
</tbody>
</table>
Key Clinical Takeaways

- Key endpoint met for non-inferiority evaluation by Notified Body

- Compelling 6, 12 and 24 month safety and performance data versus “standard of care” – control well above historical results

- Objective measurements - stability, ROM

- Functional - one legged hop

- Subjective - SF-36, Tegner

- All of study subjects have met 24 month milestone, most are beyond 36 months and continue trend of successful performance

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Clinical Analysis

Five subjects suffered SAEs deemed related to device—external experts confirm all device-related SAEs caused by infection—remedied by review and improvement of manufacturing process

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Z-Lig performed extremely well and demonstrated success at 6, 12 and 24 months
CE Mark

• CE Mark certification received on 16 April 2014 – Z-Lig™ Device for multiligament and revision ACL reconstruction surgeries
  
  – Logical place to initiate clinical use due to immediate clinical need for a graft option

• Broader indication requires additional data on 20-30 patients with 12 month follow-up

• Approval include commitment to post-market Registry on 100 patients
  
  – Provides additional data on safety and performance
  
  – Provides data for reimbursement activities
  
  – Sites participated in Z-Lig study or countries with existing ACL registries
INDICATIONS

The Z-Lig is the only CE-Marked non-human biologic device for revision and multiligament ACL knee reconstruction to be approved anywhere in the world.
THANK YOU

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