Smith & Nephew
REGENETEN

Kerrin Rennie Award Submission
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</table>
The REGENETEN BioInductive Implant is a highly porous, highly aligned, highly purified collagen scaffold that is disrupting the current treatment pathways for Rotator Cuff Disease.

The implant is both an Inductive and Conductive scaffold that rapidly induces the growth of new tendon like tissue.
Criteria 1
Innovation
**REGENETEN™ Bioinductive Implant**

First To Clinically Demonstrate Tendon Tissue Induction

Rotator Cuff Disease Progressions¹

*Rotator cuff inflammation and pain is caused by excessive micro-strains in the tendon.*

*Excessive micro-strains lead to partial-thickness tears which often progress to full-thickness tears that require major surgical intervention.*

Hypothesis

*Inducing a layer of new tendon-like tissue on the bursal side of the tendon will reduce the micro-strains in the tendon.*

- Reduced micro-strains will reduce inflammation and relieve pain
- Reduced micro-strains will slow or stop tear progression

Biological Augmentation – new tissue adds strength*²

*In contrast, competitive approaches use implant to add strength to massive tears – mechanical augmentation only.*

Conduction vs. Induction

*The REGENETEN Bioinductive Implant is also conductive.*

- A **conductive** implant “allows” a **general** biological response to occur³
- An **inductive** implant “causes” a **particular** biological response to occur⁴

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Current State

Current State RC Disease Treatment

Severe Tendinosis/Low-Grade Partial-Thickness Tears (PTT) – Failed Conservative Treatment

• Chronic rotator cuff tendinosis has been identified as a primary cause of rotator cuff tears\(^1\)
• ~44% have been reported to progress to full-thickness tears\(^7\)

Subacromial Decompression (SAD):
Inconsistent results, limited long-term efficacy\(^2\)

High-Grade Partial-Thickness Tears

• Up to 80% of PTTs increase in size within 2 years\(^3\)
• ~10% have been reported to progress to full-thickness tears\(^4\)

Take down/repair and trans-tendon approach:
Both have challenges and neither is an ideal treatment option\(^5\)

Full-Thickness Tears (FTT)

• Small tears progress over time, eventually requiring surgical repair\(^6,8\)
• Larger tears requiring repair tend to re-tear over 40% of the time\(^9,11\)

Repair:
High rate of revision/retear\(^11\)

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Our Hypothesis

The Problem

• While the biologic potential for healing may exist\(^1\), several factors, such as subacromial impingement, may adversely affect this process
• Growing belief that the reason rotator cuffs do not heal on their own is a biomechanical issue – excessive stress and strain on the tendon inhibits the natural healing process*\(^2\)

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Based on Finite Element Modeling.
Our Hypothesis

The Solution:

Hypothesis:

The induction of a layer of new tendinous tissue on the bursal side of the supraspinatus tendon could reduce micro-strains within the tendon and could:

- **Provide an optimized, mechanical environment for tendon healing**
- **Inhibit, or arrest, tear propagation**

<table>
<thead>
<tr>
<th>Bursal Surface Tear(^1)</th>
<th>Articular Surface Tear(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47% reduction in peak strain(^2)</td>
<td>40% reduction in peak strain(^2)</td>
</tr>
</tbody>
</table>

REGENETEN™ Bioinductive Implant
What is it?

A collagen implant derived from bovine Achilles tendon, with highly purified, highly porous, highly oriented design

Stimulates the body’s natural healing response to support new tendon growth and disrupt disease progression¹,²

Clinically proven to reliably induce new tendon-like tissue and promote tendon healing¹,²

Gradually absorbs within six months, leaving a layer of new tendon-like tissue to biologically augment the existing tendon³

“[REGENETEN is the] first regenerative pathway to stimulate angiogenesis and be restorative, not reparative. If you believe in biology, this is a big step.”¹-⁴

- Felix "Buddy" Savoie III, MD, Tulane University School of Medicine, New Orleans, LA

Criteria 2
Technical Excellence
REGENETEN™ Bioinductive Implant
Harnessing the Biology of the Body

A highly porous, precisely oriented reconstituted collagen implant made from thoroughly purified, bovine type I collagen

Stimulates the body’s natural healing response to support new tendon growth and disrupt disease progression\(^1,2\)

Clinically proven to reliably induce new tendon-like tissue and promote tendon healing\(^1,2\)

Gradually absorbs within six months, leaving a layer of new tendon-like tissue to biologically augment the existing tendon\(^3\)

REGENETEN™ Bioinductive Implant

How does it work?

Injured Tendon

- Stress and Strain Are Decreased*4
- Favorable Biomechanics, Tendon heals1-4

REGENETEN™ Induces New Tissue, Increasing Tendon Thickness1-3

New Tissue Integrates with Native Tendon and Bone, Shares the Load, Decreasing Load on Native Tendon1-4

Implant placed over bursal surface of RCT
Proprietary implant design creates an environment conducive to healing2

Implant induces new host tissue onto tendon by 12 weeks
Within 3 months, implant facilitates the formation of new tendon-like tissue5

New tissue integrates and remodels into the healed tendon
Strength comes from patient’s own induced tissue, not the implant, which completely absorbs within 6 months5

REGENETEN™ Bioinductive Implant
How does REGENETEN stimulate healing using no growth factors?

By taking advantage of the body’s normal healing process and orchestrating this process to produce new tendon tissue.

1. The reconstituted collagen scaffold is highly porous and highly purified, which avoids any adverse inflammatory response

2. Immediately after surgery the collagen scaffold becomes saturated with blood

3. The patient’s own platelets undergo degranulation due to contact with the collagen scaffold, resulting in the release of growth factors that initiate the healing process

4. The growth factors released by the platelets attract the ingrowth of fibroblasts and blood vessels into the collagen scaffold

5. The fibroblasts produce new tissue and remodel the tissue according to the strain environment created by the collagen scaffold properties

Blood

- Platelet aggregates
- Growth Factors
- Red blood cells and fibrin

Fibroblasts and Blood Vessels

- Rapid ingrowth of new fibrovascular tissue (H&E 100x)

Fibroblasts and new collagen

- Fibroblasts remodel new tissue into structure of normal tendon (H&E 50x)

Strain Signal to Fibroblasts

- Fibroblasts remodel new tissue into structure of normal tendon (H&E 50x)

Collagen scaffold

- Collagen scaffold is completely absorbed during the remodeling process

Oriented collagen fibers with interconnected porosity (H&E 50x)

Blood growth factors

- Platelet aggregates
- Red blood cells
- Fibrin

Oriented collagen fibers

- Interconnected porosity (H&E 50x)

Fibroblasts and new collagen

- Collagen scaffold
- Rapid ingrowth of fibrovascular tissue (H&E 100x)
- Fibroblasts remodel new tissue into structure of normal tendon (H&E 50x)

References:
REGENETEN™ Bioinductive Implant
Harnessing the Biology of the Body

1. Injured Tendon

2. REGENETEN® Induces New Tissue, Increasing Tendon Thickness\(^1-3\)

3. New Tissue Integrates with Native Tendon and Bone, Shares the Load, Decreasing Load on Native Tendon\(^1-4\)

4. Stress and Strain Are Decreased\(^4\)

5. Favorable Biomechanics, Tendon heals\(^1-4\)

Implant placed over bursal surface of RCT
Proprietary implant design creates an environment conducive to healing\(^2\)

Implant induces new host tissue onto tendon by 12 weeks
Within 3 months, implant facilitates the formation of new tendon-like tissue\(^5\)

New tissue integrates and remodels into the healed tendon
Strength comes from patient’s own induced tissue, not the implant, which completely absorbs within 6 months\(^5\)

References:
Criteria 3

Significant contribution to improving patient outcomes by improving quality of life
Criteria 3  Significant contribution to improving patient outcomes by improving quality of life

The REGENETEN BioInductive Implant has shown through published clinical data and a REBUILD registry to significantly improve patient outcomes post operatively from Rotator Cuff Repair Surgery.

These outcomes have been based on previously proven clinical measurement systems as well as patient specific outcomes that have been deemed relevant to life post surgery.

See below the definitive data.
## REGENETEN™ Bioinductive Implant: Published Clinical Studies

<table>
<thead>
<tr>
<th>Study Author(s)-Publishing Journal</th>
<th>Title</th>
<th>N</th>
<th>Key Results</th>
</tr>
</thead>
</table>
| Bokor DJ et al.6                  | Evidence of healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a collagen implant: a 2-year MRI follow-up | 13 | • The implant induced significant (p<0.0001) new tissue formation in all patients by 3 months (mean increase in tendon thickness 2.2 ± 0.26 mm).  
• This tissue matured over time and became radiologically indistinguishable from the underlying tendon.  
• No tear progression was observed by MRI in any of the patients at 24 months.  
• Clinical scores improved significantly (p<0.01). |
| Bokor DJ et al.14                 | Preliminary investigation of a biological augmentation of rotator cuff repairs using a collagen implant: A 2-year MRI follow-up | 9  | • There was a significant (p < 0.01) increase in mean tendon thickness in all subjects at 3 months when compared to published values  
• No re-tears were observed  
• Clinical scores improved significantly (p<0.001). |
| Arnoczky SP et al.12              | Histologic Evaluation of Biopsy Specimens Obtained After Rotator Cuff Repair Augmented with a Highly Porous Collagen Implant | 7  | • Biopsies of collagen implants retrieved from human rotator cuff repair subjects revealed cellular incorporation, tissue formation and maturation, implant resorption, and biocompatibility.  
• The histologic observations from these clinical biopsies support the biocompatibility of this implant and its ability to promote new connective tissue with the histological appearance of tendon over the surface of the native cuff tendon. |
| Schlegel T et al.5                | Radiologic and clinical evaluation of a bioabsorbable, collagen implant to treat partial-thickness tears: a prospective multi-center study | 33 | • Mean tendon thickness increased significantly by 2.0 mm (p<0.0001).  
• Eight patients demonstrated MRI evidence of complete healing, 23 demonstrated considerable reduction in defect size, and 1 lesion remained stable.  
• Clinical scores improved significantly (p<0.0001) at one-year follow-up.  
• No serious adverse events related to the implant were reported. |
REGENETEN™ Bioinductive Implant:
Consistent Excellence in Clinical Evidence and Patient Outcomes

- **Histological Evidence**
- **MRI Evidence**
- **Patient Outcomes**

→ **Improvement in Clinical Scores**
→ **Increase in Tendon Thickness**
# REGENETEN™ Bioinductive Implant – The Evidence: Claims and Sources

<table>
<thead>
<tr>
<th>CLAIM</th>
<th>SOURCES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reduces strain at tear site</td>
<td>✓</td>
</tr>
<tr>
<td>- First bio-inductive implant to address tendon disease progression</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Disruptive technology that prevents disease progression</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Reverses disease progression in partial thickness tears/fill in defect (mri)</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Newly generated tendon-like tissue biologically augments host tissue</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Clinically proven to induce healing response</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Significantly improves clinical scores</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Improves patient outcomes (sling time, return to work, pt sessions, etx)</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Induces tendon-like tissue growth in all disease stages</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- No foreign body reaction</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Resorbs within 3 to 6 months</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>- Expands treatable patient population (diabetes, smoker)</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
</tbody>
</table>

*Sources included in Appendix.
**Pre-Clinical Sheep Study**

**Baseline:**
Implantation of Bioinductive Implant

**Month 3:**
Increased collagen formation, maturation, and orientation

**Month 6:**
Dense, regularly-oriented newly-regenerated connective tissue; implant fully absorbed

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**Human Biopsy Study**

**Week 5:**
Host cell ingrowth with early collagen production and alignment

**Month 3:**
Increased collagen formation, maturation, and orientation

**Month 6:**
Dense, regularly-oriented newly-regenerated connective tissue; implant fully absorbed
**REGENETEN™** Bioinductive Implant – The Evidence: fMRI Evidence

**Partial Thickness Tear**

- **Pre-Op:**
  - 8x12mm tear
  - High-grade bursal tear

- **12 Months:**
  - Maturation of new tissue and tendon; tear filled-in

**Full Thickness Tear**

- **Pre-Op:**
  - 8x12mm tear

- **Month 3:**
  - Newly induced inhomogeneous tissue

- **Month 12:**
  - Better tissue quality; still somewhat amorphous
REGENETEN™ Bioinductive Implant – The Evidence: f
Outcomes – US Partial Thickness Tear Study (Schlegel)⁵

Supports the fact that the radiological images correlate to improved patient outcomes (12 month data):

**Radiological Evidence**
- 24% of defects completely filled in
- 70% showed reduction in size
- Tendon increased an average of 5.2mm

**Outcomes**
- ASES combined scores improved from 57 to 89.1 (P<.0001)
- CMS scores improved from 57.1 to 81.4 (P<.0001)
- ZERO dissatisfied patients
## Patient Outcomes Measures

### Constant-Murley Score (CMS)
- Physical exam component = 65%
  - 40% ROM
  - 25% strength testing
- Patient-reported functional assessment = 35%
  - 15% pain
  - 20% function with activities of daily living (ADLs)

### ASES Score
- Society of American Shoulder and Elbow Surgeons
- Surgeon-rated and patient-rated sections
- Score broken down into 50% pain and 50% function

### Single Assessment Numerical Evaluation (SANE)
- “On a scale of 1-100, how would you rate...”

### Pain Visual Analog Scale (VAS)
- Similar to the SANE, but uses visuals:
REBUILD Registry

REBUILD (Rotation MEdical BioindUctive ImpLant Database) is a prospective, non-randomized, multicenter registry designed to collect patient reported outcomes, including shoulder function, pain and quality of life after receiving the Bioinductive Implant.

Interim results of the first 200 patients presented by Dr. Louis McIntyre at the 2017 Arthroscopy Association of North America (AANA) Annual Meeting, showed:

- Reduction in post-operative pain
- Decreased narcotic use
- Less sling time
- Faster return to function
- Improved overall shoulder rating

The study will follow up to 500 patients across 20 study centers

No exclusion of any patients over the age of 18

<table>
<thead>
<tr>
<th>Patients</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.6 ± 10.0 (Range: 24.0 to 80.0)</td>
</tr>
<tr>
<td>History of Symptoms (months)</td>
<td>26.2 ± 52.0 (Range: 0 to 540.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58%</td>
</tr>
<tr>
<td>Female</td>
<td>42%</td>
</tr>
<tr>
<td>Type of Injury</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>32%</td>
</tr>
<tr>
<td>Acute-on-Chronic</td>
<td>17%</td>
</tr>
<tr>
<td>Chronic</td>
<td>51%</td>
</tr>
<tr>
<td>Diabetes</td>
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</tr>
<tr>
<td>Yes</td>
<td>11%</td>
</tr>
<tr>
<td>No</td>
<td>89%</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12%</td>
</tr>
<tr>
<td>No</td>
<td>88%</td>
</tr>
<tr>
<td>Worker's Comp</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10%</td>
</tr>
<tr>
<td>No</td>
<td>90%</td>
</tr>
<tr>
<td>Chronic Narcotic/Opioid Use</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11%</td>
</tr>
<tr>
<td>No</td>
<td>89%</td>
</tr>
</tbody>
</table>
REBUILD Registry: Significant Reduction in Pain

Average VAS Pain (0-10): Partial-thickness/No Repair Cohort

Change in Average VAS Pain from Pre-Surgery: Partial-thickness/No Repair Cohort

*Data shown represents partial-thickness/no takedown repair cohort. REBUILD Registry data on file as of 2017 AANA Meeting, with enrollment and follow-up ongoing.
REBUILD Registry: Additional Patient Benefits

Benefits of Biological Augmentation in Partial-thickness/No Repair Cohort

- Sling Time (Biceps Surgery): 11.1
- Sling Time (No Biceps Surgery): 42.0
- Return to Driving: 21.0
- Return to Work: 60.0
- Narcotic Use: 24.7

*REBUILD Registry data on file as of 2017 AANA Meeting, with enrollment and follow-up ongoing.

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