



**IR ROTIUM™**

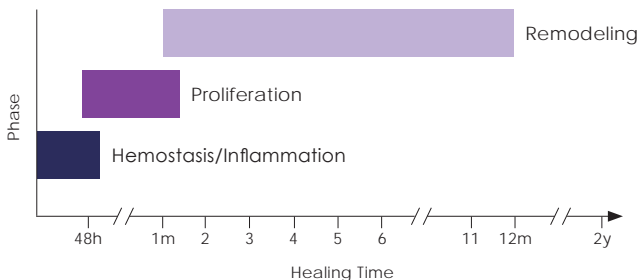
Product Reference Guide

INTERNAL USE ONLY

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## Tendon Phases of Healing



The tendon repair process in humans involves three distinct but overlapping phases:

- Hemostasis/Inflammation
- Proliferation
- Maturation/Remodeling

**Each phase involves a complex cascade of events** involving multiple cellular and molecular players. Phase duration depends on the location and severity of injury.

# Tendon Phases of Healing

## PHASE ONE

### Hemostasis/Inflammation



NEUTROPHILS



TSPCs\*



MACROPHAGES

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**Phase objective:** Stop the bleeding (hemostasis) and clear the injury/repair site of debris, devitalized tissue, and foreign material.

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**ROTIUM is engineered to support the inflammatory phase by providing a temporary scaffold that:**

1. Facilitates vital cell infiltration at the repair site
2. Generates a pro-healing milieu via the known actions of its organic acid degradants
3. Supports the cascade of events that effectively prepares the repair site for the next phase of healing

\*TSPC – Tendon stem/progenitor cell

# Tendon Phases of Healing

## PHASE TWO Proliferation



TENOCYTES



FIBROBLASTS



MACROPHAGES

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**Phase objective:** Initiate the regeneration of new, healthy tissue at the repair site.

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### **ROTIUM is engineered to facilitate proliferation by:**

1. Providing a temporary ECM-like scaffold with increasing pore size that facilitates infiltration by key cellular players
2. Supporting a pro-healing milieu that enables macrophage immunomodulation from pro-inflammatory (M1) to pro-proliferative (M2) phenotype
3. Facilitating the regeneration of new, healthy tissue at the repair site

# Tendon Phases of Healing

## PHASE THREE

### Maturation/Remodeling



TENOCYTES



APOPTOTIC CELLS



MACROPHAGES

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**Phase objective:** Continue to remodel and strengthen new, regenerated tissue at the repair site.

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#### **ROTIUM is engineered to maturation/remodeling by:**

1. Continuing to provide an environment that supports native healing biology
2. Complete resorption within 3-6 months, replaced with native ECM scaffolding and maturing tissue
3. Enabling restoration of the enthesis\* to its pre-injured state

\*Enthesis – The site of attachment of tendon to bone; the tendon-bone interface

## How ROTIUM Works

# The Science of ROTIUM: Structure & Function

### ROTIUM is engineered to:

- Support **cell adhesion, infiltration and proliferation**
- Provide **vital biology** via
  - wicking action (repository for cells and growth factors)
  - morphology (porous structure of bioinductive fibers)
  - actions of degradants
- Support the **natural phases of healing**
  - hemostasis/inflammation
  - proliferation
  - maturation/remodeling
- Enable **M1-M2 macrophage immunomodulation** which
  - harnesses inflammation
  - promotes proliferation
- Promote **angiogenesis**
  - regeneration of new blood vessels, vital to healing
- Facilitate and accelerate regeneration of **native tissue architecture**, including *Sharpey's fibers*, vital to enthesis strength
- Restore **enthesis** (tendon-bone interface) to its pre-injured state

\*Results demonstrated by sheep study and retrospective clinical trial  
[Manuscripts submitted for publication]

How ROTIUM Works  
The Science of ROTIUM:  
Structure & Function



**ECM Morphology**  
biomimetic

**Scaffold Size**  
mimics  
supraspinatus  
footprint

**Fiber Size**  
promotes cell  
adhesion and  
migration

**Pore Size  
and Volume**  
promotes cell  
adhesion and  
migration

**Engineered to regenerate and restore**



How ROTIUM Works  
The Science of ROTIUM:  
Degradants



**Non-Immunogenic  
and Bioresorbed**

**Degradants**  
known to promote healing

**Glycolic  
Acid**

**Lactic  
Acid**

**Caproic  
Acid**

*Continued on page 10*

## How ROTIUM Works

# The Science of ROTIUM: Degradants

### Known actions of degradants:

#### Caproic Acid

- Anti-microbial properties
- Anti-inflammatory properties

#### Glycolic Acid

- Anti-microbial properties
- Anti-inflammatory properties
- Increases fibroblast proliferation and production of collagen & hyaluronic acid

#### Lactic Acid

- Anti-microbial properties
- Provides major fuel source
- Stimulates VEGF\* and collagen gene expression
- Recruits endothelial progenitor cells
- Promotes reparative angiogenesis
- Stimulates reperfusion of ischemic wounds
- Activates collagen factors
- Promotes ECM\*\* deposition
- Accelerates healing

\*VEGF – Vascular endothelial growth factor

\*\*ECM – Extracellular matrix

## How ROTIUM Works

# The Science of ROTIUM: pH

ROTIUM is designed to reduce pH at the repair site.

Known wound healing properties of acidic pH:

- Restores **protease/protease-inhibitor balance** (MMP/TIMP\*)
- Increases **tissue oxygenation** via Bohr-effect
- Promotes **angiogenesis**
- Reduces **toxicity** of bacterial enzymes/metabolites
- Increases **resorption** of defective collagen
- Increases **macrophage & fibroblast** activity

\*MMP – Matrix metalloproteinase

TIMP – Tissue inhibitor of metalloproteinase

## Product Specifications

Thickness	0.6mm
Pore Structure	~ 85% porous
Size/Geometry	20 x 20 mm
Composition	Patented & proprietary combination of electrospun PGA* and PLCL** fibers
Degradation	Degrades to natural metabolites over 3 to 6 months
Disposition	Replaced by regenerated native tissue
Shelf life	2 Years
Storage	Room temperature, shelf storage.

\*PGA – Polyglycolic acid

\*\*PLCL – Poly(lactide-co-caprolactone)

## Glossary

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Acute Injury	An acute injury occurs suddenly due to trauma, surgery, or rapidly spreading infection. An acute injury has the potential to become a chronic injury.
Allogenic	Tissues or cells that come from the same animal species.
Apoptotic cell	Cell programmed for death and clearance as part of normal tissue development and maintenance.
ASES Shoulder Score	Standardized, 17-question, patient survey developed by the <b>American Shoulder and Elbow Surgeons</b> society. Focuses on two dimensions: pain and activities of daily living. Provides a standardized method of assessing pre-surgery condition & post-surgery healing progress.
Biomimetic	Designed to imitate the structure and function of native biological systems.

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## Glossary

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Chronic Injury	A chronic injury develops and worsens over an extended period of time; often overuse injuries.
Cytokines	<p>Small, secreted proteins released by cells that <u>mediate interactions and communications between cells</u>.</p> <p><b>Cytokine types:</b></p> <ul style="list-style-type: none"><li>• Pro-inflammatory</li><li>• Anti-inflammatory</li><li>• Homeostatic</li></ul>
Degradation/ Degradants	<p><b>Degradation</b> is the process by which a chemical substance/ material is broken down to smaller molecules (in the case of ROTIUM, via hydrolysis). The resulting smaller molecules are the <b>degradants</b>.</p>
Enthesis	Site of attachment of tendon, ligament, fascia, or capsule to bone. <i>Sharpey's fibers</i> , found in the entheses, strengthen the attachment of tendon to bone.

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## Glossary

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Extracellular matrix (ECM)	Non-cellular component present throughout all tissues and organs. <u>Provides essential physical scaffolding</u> for cellular constituents, <u>initiates vital biochemical &amp; biomechanical cues</u> required for <u>tissue development, maintenance &amp; regeneration.</u>
Hydrolysis	Chemical breakdown of a compound due to reaction with water.
Immunogenic/ Non-immunogenic	Immunogenic materials evoke sustained inflammatory immune response. Non-immunogenic materials do not.
Morphology	Refers to size, shape, and structure.
PGA	Poly-glycolic acid. Fast-degrading polymer that breaks down in water (hydrolysis) to its glycolic acid monomers.
PLCL	Poly-lactide-co-caprolactone. Slower-degrading polymer that breaks down in water (hydrolysis) to its caproic acid & lactic acid monomers.

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## Glossary

SEM Imagery	Extremely high magnification images achieved with a <b>Scanning Electron Microscope</b> .
Sharpey's Fibers	Collagen fibers of a tendon that insert into bone at the attachment site (known as the <i>enthesis</i> ), strengthening the attachment of tendon to bone.
Simple Shoulder Test (SST)	Patient survey containing 12 yes/no questions about the function of the involved shoulder. Provides a standardized method of recording shoulder function before and after treatment.
Tendon Stem/Progenitor Cell (TSPC)	Two major cell types in tendons are tenocytes & TSPCs. <b>Tenocytes</b> are responsible for maintaining tendon homeostasis; <b>TSPCs</b> replenish tendon cells via self-renewal and differentiation.



## Glossary

Tenocyte	[Various cells, including neutrophils, monocytes/macrophages and TSPCs are attached to the site of injury or repair by pro-inflammatory cytokines.]
Xenogenic	Tissues or cells that come from a different animal species.

