ATREON
ORTHOPEDICS

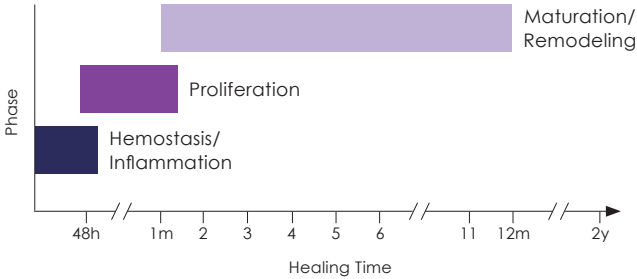
ROTIUM™

Product Reference Guide

INTERNAL USE ONLY

Contents

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

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

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

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

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

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

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**
  - neovascularization is 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

ROTIUM

a bioinductive scaffold

ECM Morphology
biomimetic

Scaffold Size
mimics supraspinatus footprint

Fiber Size
promotes cell adhesion & migration

Pore Size and Volume
promote cell infiltration & proliferation

Engineered to regenerate and restore

How ROTIUM Works

The Science of ROTIUM: Degradants

ROTIUM
a bioinductive scaffold

Non-Immunogenic and Bioresorbed

Degradants
promote healing

Glycolic Acid	Lactic Acid	Caproic Acid

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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

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 **A**merican **S**houlder and **E**lbow **S**urgeons 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.

Glossary

Chronic Injury	A chronic injury develops and worsens over an extended period of time; often overuse injuries.
Cytokines	Small, secreted proteins released by cells that mediate interactions and communications between cells. **Cytokine types:** • Pro-inflammatory • Anti-inflammatory • Homeostatic
Degradation/ Degradants	**Degradation** 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 **degradants**.
Enthesis	Site of attachment of tendon, ligament, fascia, or capsule to bone. *Sharpey's fibers*, found in the enthesis, strengthen the attachment of tendon to bone.

Glossary

Extracellular matrix (ECM)	Non-cellular component present throughout all tissues and organs. Provides essential physical scaffolding for cellular constituents, initiates vital biochemical & biomechanical cues required for tissue development, maintenance & regeneration.
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.

Glossary

SEM Imagery	Extremely high magnification images achieved with a **S**canning **E**lectron **M**icroscope.
Sharpey's Fibers	Collagen fibers of a tendon that insert into bone at the attachment site (known as the *enthesis*), 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. **Tenocytes** are responsible for maintaining tendon homeostasis; **TSPC**s 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.

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