Because we are committed to limiting uncertainty, Integra continues to develop new products in regenerative technology.

- Integra LifeSciences has leveraged over 30 years of science and innovation in the development of collagen technology.
- Integra LifeSciences’ extensive collagen purification process, advanced bio-engineering proficiency, and manufacturing experience add value to our products designed for protection, regeneration and repair of human tissue in various clinical applications.
- Ultra Pure Collagen™ is the base material of implants used successfully in over 10 million procedures worldwide.
- Ultra Pure Collagen™ has been used in general surgery, burn surgery, neurosurgery, plastic and reconstructive surgery, peripheral nerve/tendon surgery & orthopedic surgery.

Specifications

- An established product line with proven results.
- Outstanding safety profile.
- Implanted in over 900,000 patients.
How was Integra LifeSciences’ Collagen Matrix Created?

For over thirty years, Integra LifeSciences has been a leader in developing and manufacturing high quality collagen implants.

In the early 1970’s, John F. Burke, MD, chief of Trauma Services at Massachusetts General Hospital and Shriners Burns Institute, identified the need to improve skin restoration of severely burned patients. While patient related donor skin was an option, immunorejection was a critical issue. Dr. Burke theorized that an artificial means to cover the skin might offer positive results without the potential for donor skin rejection.

Dr. Burke collaborated with Dr. Ioannas Yannas, a professor at MIT with a specialization in material sciences and physical chemistry, to develop a biocompatible product to improve wound healing. With Dr. Burke’s expertise in wound management and Dr. Yannas’ knowledge of collagen, a collagen matrix was created. Initial experimentation with the matrix not only resulted in improved wound healing, but also supported the regeneration of the dermis. These findings confirmed the concept of tissue regeneration using a collagen based matrix.

This creation of a biocompatible, porous collagen matrix by Integra LifeSciences, led to an evolution in the science of collagen processing and manufacturing. Thirty years and over ten million implantations later, Integra LifeSciences continues to develop innovative collagen implant solutions for a number of clinical applications including general surgery, burn surgery, neurosurgery, plastic and reconstructive surgery, oral surgery, and peripheral nerve/tendon surgery.

What Makes Integra LifeSciences’ Collagen Unique?

Integra LifeSciences is the only company to manufacture its products from Ultra Pure Collagen™.

Ultra Pure Collagen

Reduces uncertainties concerning product safety.
- Limits the risk of foreign body reaction
- Reduces the chance of encapsulation by fibrous tissue
- Mitigates the possibility of immunological response

Collagen Sourcing
Each Integra LifeSciences product is made with collagen derived from bovine deep flexor tendon, which is used specifically for its highly collagenous composition (95% collagen). Bovine tendon is known to be one of the purest sources of Type I collagen that is commercially available.

Collagen Purification
After a mechanical breakdown, the collagen is further purified using proprietary treatments to ensure an ultra pure base material.

Advanced Bioengineering
The Ultra Pure Collagen™ matrix is specifically engineered for each clinical application.

Developing and Manufacturing
Each Integra LifeSciences collagen product is purified, engineered, and manufactured by Integra LifeSciences.

What Makes Integra LifeSciences’ Collagen Ultra Pure™?
Integra LifeSciences’ ultra purification method follows established and proven protocols for the removal of antigenic materials and the inactivation/destruction of potential viral and bacterial contaminants.

Purification Process
Integra LifeSciences places its collagen through a proprietary purification process which deactivates viruses and bacteria, substantially reducing the risk of transmission of bovine spongiform encephalopathy (BSE) and mitigating the risk of inflammatory response. Integra LifeSciences’ collagen products are processed 40 times longer than bFarm recommendation thus resulting in substantially mitigation of the probability of viral or other disease transmissions.

Integra LifeSciences Ultra Pure Collagen™ technology

Bio-engineering with Ultra Pure Collagen™
Integra LifeSciences controls the physical and chemical composition to ensure each product is designed with attributes critical for ideal biological/physiological activity.
- Pore Size
- Crosslinking
- Pore Volume
- Degradation Rate

Processing and Manufacturing the Ultra Pure Collagen™ matrix
With over three decades of processing and manufacturing experience, Integra LifeSciences has the ability to take a product from concept to commercialization. Integra LifeSciences has complete ownership and control of the design and manufacturing to ensure consistent, reliable, and safe products.
Ultra pure collagen  
Regenerative medicine

Integra Lifesciences’ Collagen Timeline*

1996
Burn surgery
Integra® Dermal Regeneration Template
A resorbable collagen and glycosaminoglycan (GAG) implant that provides a scaffold for skin replacement.

2000
General surgery
Helitene™ Absorbable Collagen Hemostatic Agent
An absorbable collagen hemostatic agent used to help control bleeding in surgical procedures.

2003
Peripheral Nerve surgery
NeuraGen® Nerve Guide
An absorbable collagen tube designed for the repair of peripheral nerve discontinuities.

2005
Neurosurgery
DuraGen Plus™ Adhesion Barrier Matrix
An optimized resorbable dural graft that protects against CSF leakage and provides a scaffold for Regenerative medicine.

2005-2007
Neurosurgery
Neurosurgery
DuraGen Plus™ Adhesion Barrier Matrix
An optimized resorbable dural graft that protects against CSF leakage and provides a scaffold for Regenerative medicine.

Peripheral Nerve surgery
NeuraWrap™ Nerve Protector
An absorbable collagen implant that provides a non-constrictingencasement for injured peripheral nerves for protection of the neural environment.

Orthopaedic
Integra Mozaik™ Osteoconductive Scaffold
A scaffold composed of collagen and tricalcium phosphate that is intended for use as a bone void filler.

Integra Flowable Wound matrix:
an injectable scaffold to treat tunneled and undermined wounds.

IDRT SL Thin combines the proven technology of Integra Dermal Regeneration Template Single Layer with a versatility of a thinner scaffold for one-step surgical procedures.
Normal Wound

Healing Process

Damage to skin triggers inflammatory cascade.

Granulation tissue

Fibroblasts enter & differentiate into contractile myofibroblasts.

Myofibroblasts align and contract to close the open wound.

Wound is repaired with contraction and scar formation. (20-30% of original size)

Integra® Dermal Regeneration Template

Healing Process

Damage to skin triggers inflammatory cascade.

Silicone layer Collagen/GAG

Fibroblasts enter collagen/GAG, bio-degrade it and produce normal dermal tissue.

INTEGRA® matrix inhibits myofibroblast activation and actions to block contraction.

Neodermis is regenerated with little or no scar formation.
**Histological results**

A histological analysis performed on 131 patients demonstrated that an intact dermis was achieved with no scar found in any of the 336 serial biopsies (from 7 days to 2 years after application of the template).¹

With early excision of in the burn patient, the resultant clinical need was a product that could cover the large open wound after excision. Key characteristics and requirements of a skin substitute are shown in the following 2 tables.²

### Biological Characteristics

**Objective: Cellular compatibility and control of contraction and scarring**

<table>
<thead>
<tr>
<th>Critical graft properties</th>
<th>Desired events in graft lifetime</th>
<th>Clinical functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biodegradable rate</td>
<td>Migration rate of non-inflammatory cells</td>
<td>Infection control</td>
</tr>
<tr>
<td>Concentration of metabolites</td>
<td>Metabolic dispersal of graft</td>
<td>Fluid loss control</td>
</tr>
<tr>
<td>Antigenicity</td>
<td>Synthesis of neodermis tissue</td>
<td>Contracture control</td>
</tr>
<tr>
<td>Pore volume fraction</td>
<td></td>
<td>Scar control</td>
</tr>
<tr>
<td>Mean pore size</td>
<td></td>
<td>Cellular compatibility</td>
</tr>
<tr>
<td>Thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood compatibility</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Physical Requirements

**Objective: Membrane for single-application closure of full-thickness skin wounds with control of infection and fluid loss**

<table>
<thead>
<tr>
<th>Critical graft properties</th>
<th>Clinical properties of graft/wound interface</th>
<th>Clinical functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bending rigidity</td>
<td>Wetting</td>
<td>Infection control</td>
</tr>
<tr>
<td>Surface energy</td>
<td>Peel strength</td>
<td>Fluid loss control</td>
</tr>
<tr>
<td>Moisture flux rate</td>
<td></td>
<td>Viable tissue</td>
</tr>
<tr>
<td>Blood compatibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tear strength</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Three main components in the design of IDRT

Collagen
• It is the Primary Extracellular Matrix component.
• A Hydrophilic polymer capable of biodegradation at a rate that can be controlled by crosslinking.
• Has a Young’s modulus that can be varied by a factor of at least 10⁵ which allows for design flexibility.

Glycosaminoglycans
• Inhibit myofibroblasts
• The degradation and co-precipitation of collagen with several GAG is eventually slower because such collagen–GAG membranes are significantly more resistant to collagenase degradation than collagen membranes without GAG.
• Collagen–GAG membranes have a significantly higher moduli of elasticity and need a higher energy to fracture; allow for a more open pore structure.
• Crosslinking with GAG does not affect the triple-helical structure of collagen
• The use of precipitation of collagen with GAG at acid pH is meant to adjust the blood clotting properties of the membrane. This control could conceivably be used to prevent generation of a weak boundary layer of blood clots.

Temporary epidermis
Silicone layer for protection and scar prevention.

3D Matrix Layer
• Cross-linked collagen and glycosaminoglycan (chondroitin-6-sulfate)
• Functions as an extracellular matrix
• Promotes cellular growth and collagen synthesis
• Biodegrades while being replaced by autologous dermal tissue
INTEGRA® Dermal Regeneration Template - INTEGRA® Meshed Dermal Regeneration Template

Indications for use
Integra Template is indicated for the postexcisional treatment of full-thickness and partial-thickness injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient. Integra Template is also indicated for use in reconstruction of postexcisional, full-thickness defects of the integument where there is, in the opinion of the treating surgeon, a potential benefit to the patient by improving the reconstructive outcome or decreasing their mortality/morbidity.

Contraindications
Use of Integra Template is contraindicated in patients with known hypersensitivity to bovine collagen, chondroitin sulfate derived from shark cartilage, or silicone materials.
Integra Template should not be used on clinically diagnosed infected wounds.
When using Integra Meshed Dermal Regeneration Template with Negative Pressure Wound Therapy, follow contraindications for the specific Negative Pressure Wound Therapy device utilized, such as in the presence of:
- Exposed arteries, veins, organs, anastomotic sites, or nerves
- Malignancy in the wound
- Untreated osteomyelitis
- Untreated malnutrition
- Necrotic tissue (with or without eschar present)
- Non-enteric and unexplored fistulas
- Sensitivity to silver (if silver dressings are used)

INTEGRA® Dermal Regeneration Template Single Layer - INTEGRA® Dermal Regeneration Template Single Layer (Thin)

Indications for use
Integra Single Layer Template is indicated for the postexcisional treatment of full-thickness and partial-thickness injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.
Integra Single Layer Template is indicated for use in reconstruction of postexcisional, full-thickness defects of the integument where there is, in the opinion of the treating surgeon, a potential benefit to the patient by improving the reconstructive outcome or decreasing their mortality/morbidity.

Contraindications
Use of Integra Single Layer Template is contraindicated in patients with known hypersensitivity to bovine collagen or chondroitin sulfate derived from shark cartilage.
Integra Single Layer Template should not be used on clinically diagnosed infected wounds.

INTEGRA® Flowable Wound Matrix

Indications for use
INTEGRA® Flowable Wound Matrix is indicated for the treatment of tunneling and/or undermined wounds including surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence) and diabetic ulcers of both partial and full-thickness varieties. The device is intended for one-time use.

Contraindications
This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials. The device is not indicated for use in third degree burns.

NeuraGen®

Indications for use
NeuraGen® is indicated for the repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity.

Contraindications
NeuraGen® is not designed, sold or intended for use except as described in the indications for use and is contraindicated for patients with a known history of hypersensitivity to bovine derived materials.

NeuraWrap®

Indications for use
NeuraWrap nerve protector is indicated for the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue.

Contraindications
NeuraWrap nerve protector is not designed, sold or intended for use except as described in the indications for use and is contraindicated for patients with a known history of hypersensitivity to bovine derived materials.
Availability of these products might vary from a given country or region to another, as a result of specific local regulatory approval or clearance requirements for sale in such country or region.

- Non contractual document. The manufacturer reserves the right, without prior notice, to modify the products in order to improve their quality.
- Warning: Applicable laws restrict these products to sale by or on the order of a physician.

Consult product labels and inserts for any indications, contraindications, hazards, warnings, precautions, and instructions for use.

Products mentioned in this document are CE class III devices. Please contact Integra customer service should you need any additional information on devices classification. All the medical devices mentioned on this document are CE marked according to European council directive 93/42/EEC on medical devices and its relatives, unless specifically identified as “NOT CE MARKED”.

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