

# TGT

TISSUE GROWTH  
TECHNOLOGIES



## Engineering Bioreactors for a Better Tomorrow

### Mechanical Stimulation Bioreactor Systems for Research and Clinical Tissue Engineering

Tissue Growth Technologies is dedicated to providing state-of-the-art bioreactor technology to advance academic and industrial research and development.

DynaGen® bioreactor systems mimic the in vivo mechanical environment in order to:

- condition and engineer developing tissues
- reveal fundamental mechanisms of cell function
- direct stem cell differentiation
- provide an in vitro testbed as an alternative to animal models

TGT employs tissue engineers and biologists, as well as mechanical and controls engineers. Our team develops bioreactors that deliver computer controlled mechanical stimulation profiles to a wide array of constructs. Our DynaGen® Series instruments are standard products that can be customized for your application.



*TGT Mission:*

*To provide technologically advanced bioreactor solutions for creating clinically relevant tissue engineered medical devices and next generation therapies.*

## Company Profile

Tissue Growth Technologies was founded in 1990 as EnduraTEC Systems Corporation. The company charter at that time was to provide material test instruments to the biomedical community. In subsequent years, EnduraTEC introduced many test equipment designs while developing both an in house contract test lab (Medical Device Testing Services) as well as an international customer base.

The technology and expertise required to build material testing equipment is unique. Test instruments are able to generate physiologically relevant stress/strain levels at high frequencies and cycle counts. In the late 1990s it became apparent that the company's core competencies: mechanical, electrical, software, and controls engineering, were applicable to the mechanically stimulated tissue growth market. In 2000, the company began developing a line of bioreactors utilizing motor and control systems that were previously developed for the company's stent testers. Those first systems were purchased by various academic and industrial institutions for vascular tissue engineering applications.

In late 2003 the Bose Corporation approached EnduraTEC with an offer to buy the material testing business and the EnduraTEC name. The transaction was completed in May of 2004 with Bose purchasing the material testing equipment related assets. EnduraTEC's stockholders kept the bioreactor related assets, and MDT Services and changed the company name to Tissue Growth Technologies (TGT) to reflect the company's new charter.

Today, TGT supplies both standard and custom bioreactor equipment solutions to scientists and cell culture environments. These instruments are used to provide mechanical stimulation for conducting research on tissue growth for the development of replacement cells and tissues, including vascular, ligament, bone, cartilage, and skin applications.

Systems for sale into the research market consist of several modular components, typically including at least one bioreactor chamber, a peristaltic pump, and a mechanical stimulator. The systems range from basic, single chamber bioreactors, to integrated systems having six or more bioreactor chambers.

The corporate objectives of the company are separated into two primary areas:

- **Research-** Sales of standardized bioreactor systems to research and educational institutions for use in basic research.
- **Industry-** Development and subsequent sale of bioreactor systems and chambers to industry for volume manufacturing of clinically relevant tissue engineered medical devices.

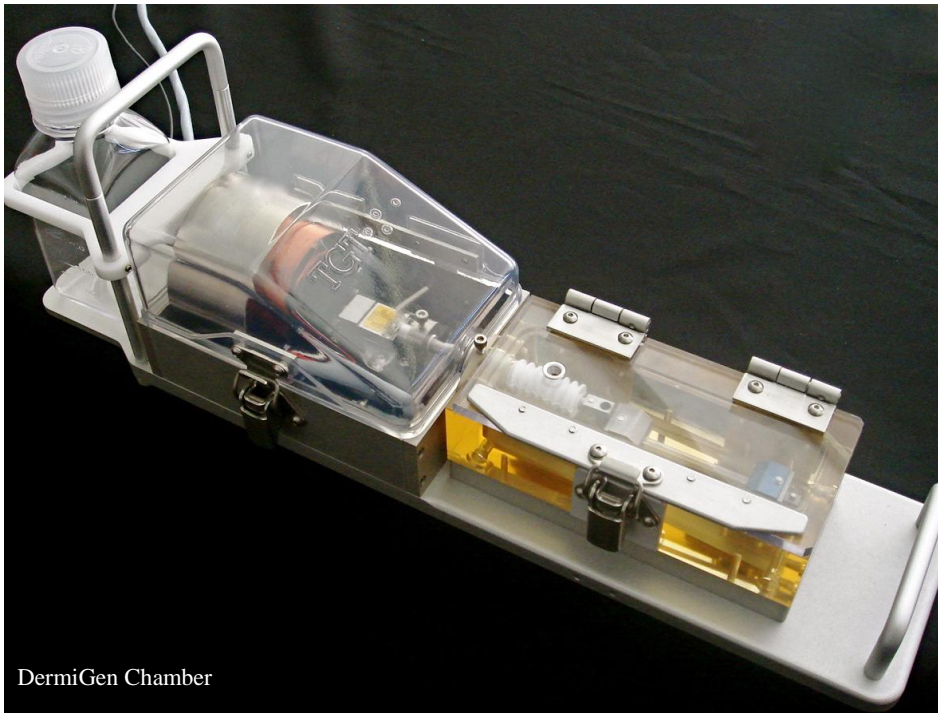
TGT has initiated efforts into both areas. The DynaGen Series bioreactors represent our standard offerings and are sold into the "Research" market

The "Industry" strategy of selling commercial bioreactor TEMP systems and chambers involves close interaction with medical device, biotech, and other development companies. TGT currently has several development projects underway to create commercially viable bioreactors.

TGT possesses several key advantages to ensuring success as a premier supplier of clinically applicable regenerative medicine bioreactors. TGT holds (and has patents pending on) critical intellectual property to protect equipment and process solutions. Although the tissue engineered product market has a high barrier to entry (complex integration of mechanical, electrical, software, regulatory and biological systems), TGT holds the position of "first to market" and potentially sole source supplier for many potential products. Our small size allows us to adapt quickly to the changing market and technical requirements to provide cutting edge solutions. TGT is solely focused on tissue growth; we have multiple projects under development simultaneously, and are constantly increasing our knowledge base. Our dedication to improvement ensures that new knowledge is transferred and translated to subsequent tissue engineering projects. TGT employs mechanical, electrical, and software engineers with over 20 years of experience in tissue engineering who have presented at numerous national and international tissue engineering conferences.

TGT's focus is to apply our resources to enter the worldwide market for regenerative medicine, recently estimated at \$500B.<sup>7</sup> The value of TGT is dependent on the speed at which tissue engineered products enter the marketplace and the ability of TGT to develop critical path equipment solutions to reinforce partnerships/agreements with customers.





DermiGen Chamber

## TGT Bioreactor Chambers

TGT's chambers carry a variety of critical features for tissue growth and 3-D culture, reflecting our product design philosophy.

Our bioreactor chambers are third generation designs, and capture the benefits of customer feedback. Chambers can be tailored to grow/culture different tissues such as: blood vessels, ligaments, cartilage, skin, heart valve and bone by stimulating cell-seeded scaffolds via perfusion or controlled mechanical deformation. Though each has unique features, all retain common design characteristics required to make your experiments productive.

## Custom Chamber Development

We have designed a variety of custom chambers to meet our customers' needs. Examples include:

The patent pending **CartiGen HP** System has been designed as a single or multi-sample bioreactor hydrostatic pressurization system. The chamber can accommodate up to one disc shaped sample up to 50mm diameter x 5mm thick or up to 6 samples that are 30mm diameter X 5mm thick. This system is unlike the other CartiGen Systems in that stress is applied using a high pressure air source. This enables hydrostatic stresses up to 0.5MPa to be applied.

Fabricated from autoclavable materials, each **CartiGen HP - x** chamber is compatible with standard 6, 12, 24, or 96 well tissue culture plates. The standard system can accommodate multiple chambers for increased sample counts. Designed

for placement within a standard incubator, the modular design allows installation of the cell seeded scaffold independent of the stimulation system.

The **DermiGen D70-1** system is configured as a single sample bioreactor system that is able to support a wide range of cell and tissue growth experiments via user defined stimulation protocols. The chamber's unique design provides an air/media interface to facilitate cell differentiation and the development of skin like products. The chamber provides media perfusion/flow along the underside of the construct while preventing it from migrating onto the topside. Mechanical clamp grips with soft linings provide secure positioning of the sample. This chamber can accommodate a single sample with a gauge lengths between 40-70mm, 20mm width and 0.1 to 2mm thickness. The instrument may be customized to specific research applications.

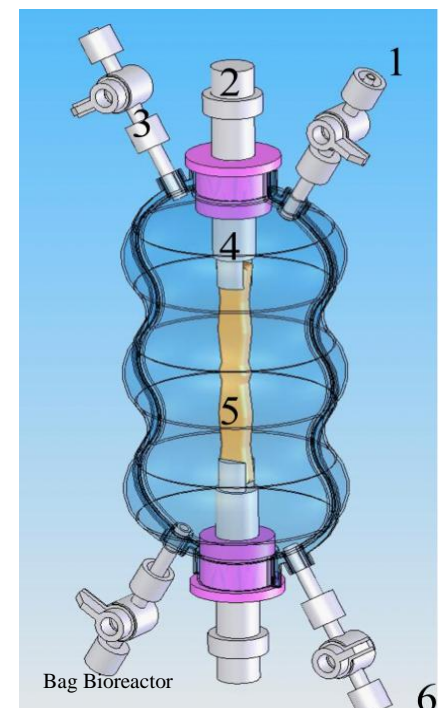
The patent pending **Transportable/Disposable Bag Bioreactor** has been designed to accommodate stimulation for a single construct 30-100mm long. The dual bag system transitions from culture to clinic providing a stable, sterile environment for complete TEMP generation. Bar code or microchip embedding are available for traceability. Samples are installed before the bag is sealed allowing 360 access for sample installation. This novel design also allows combined modes of mechanical stimulation such as axial and torsional deformation, as well as hydrostatic pressure.



CartiGen HP-X



CartiGen HP



Bag Bioreactor

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## TGT Design Philosophy

The Tissue Growth Industry is emerging and much needs to be done in the area of research instrument development. A wide array of bioreactors have been designed by researchers and commercial entities throughout the world requiring an enormous investment in time and resources. A considerable amount of time has been spent refining these designs.

The opportunity to harness "best-in-class" design concepts in convenient, modular designs is available to us by close interaction with customers, partners, and the broader industry. Our mission is to empower your research by providing research tools to you in simple, modular, validated designs. By doing so we enable you to focus on the mechanisms of tissue growth.

### Ingenuity

Modular design allows the researcher to customize the products to fit their needs with the addition of optional features including increased sample number

### Simplicity

Through base designs that are built to stand alone; Higher levels of complexity can be achieved through the addition of additional chambers or optional features.

### Feasibility

Reduced complexity minimizes the part count, easing assembly and sterilization, and minimizing system cost.

### Validity

All incorporated materials are validated for biocompatibility and autoclave durability.

### Adaptability

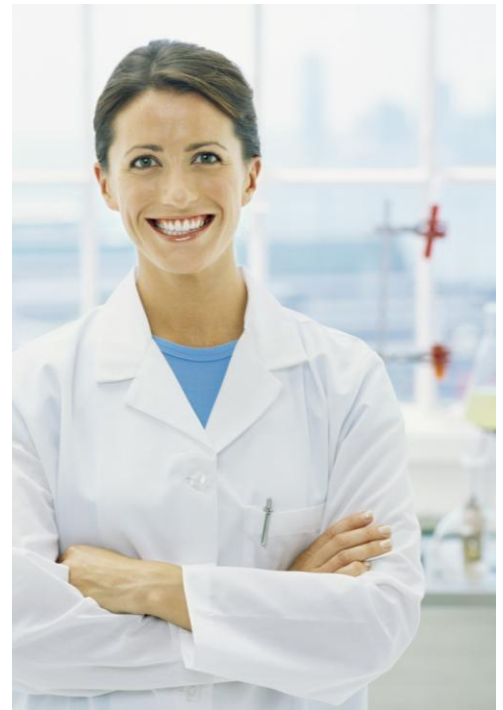
Designs are adaptable to numerous biomaterials applications.

### Customization

Design engineers can modify standard products to support unique specimen growth protocols

#### TGT Customer List

- Advanced Technology & Regenerative Medicine
- Children's Mercy Hospital
- Cleveland Clinic
- Cook Biotech
- Debakey Institute
- Drexel University
- Gel Del Technologies
- Keele University
- NanoMatrix
- National Research Center of Canada
- North Carolina State University
- Ohio State University
- Rensselaer Polytechnic Institute
- Scripps Research Institute
- Stanford University
- University of California, Los Angeles
- Wake Forest Health Sciences Medical Center
- University of Liverpool
- University of Manchester
- University of Michigan
- University of Hong Kong
- State University of New York at Buffalo
- State University of New York at Stony Brook
- Sunnybrook University
- Thomas Jefferson University
- Queens University
- Queensland University



## Tissue Engineered Medical Products (TEMPS)

*TGT is dedicated to providing state of the art enabling technology to transition from the bench to the bedside*

### Members of ASTM

ASTM working group F2211 formed to outline the aspects of TEMPS that will be developed as standards.

### FDA Contacts

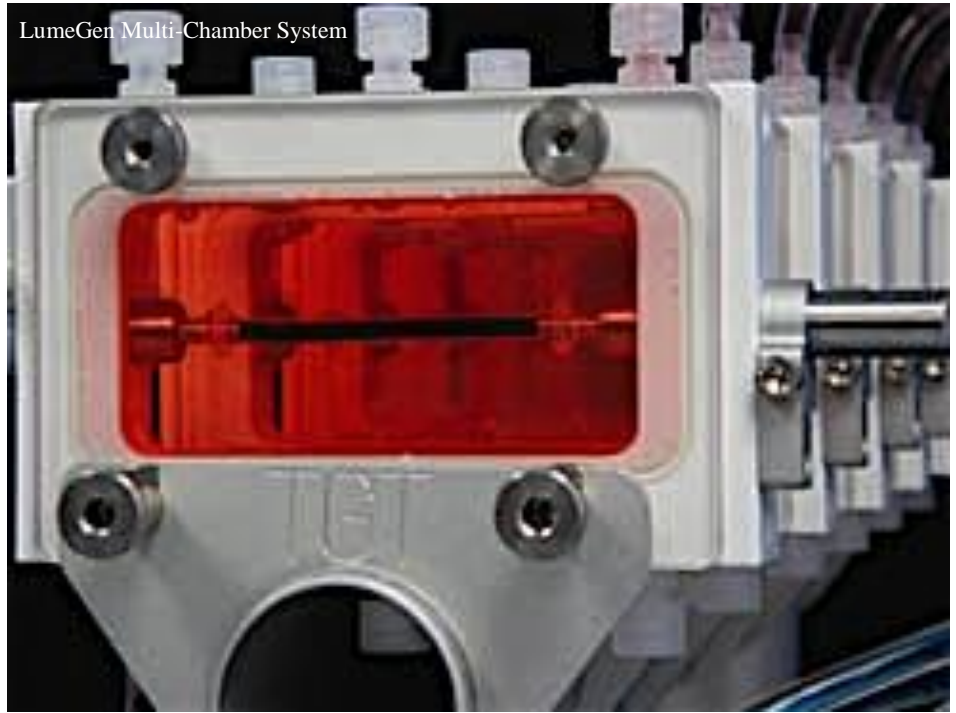
The FDA's Center for Biologics Evaluation and Research (CBER) regulates an array of diverse and complex biological products, both investigational and licensed, including; human tissues and cellular products and xenotransplantation products.

### Manufacturing Partners

TGT has cultivated working relationships with local and global vendors to provide GMP certified equipment to produce TEMPS



LumeGen Multi-Chamber System



## Commercial Chamber Development

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We are pleased to provide engineering services to produce commercial and clinical bioreactor chambers. The generic format of this product development is as highlighted below:

- Discovery
- Concept Development & Refinement
- Engineering Development & Prototype
- Delivery of Alpha System
- Production Development
- Production Enablement
- Packaging & Sterilization

TGT expects to take a stepped approach towards each program, with budgets in place prior to beginning each next stage. We will assign a full time program manager to drive inter-company communications, schedules and cost models as well as product deliverables.

The following page chronicles the design, development, and production processes used by TGT to deliver a clinical and commercial solution.

# Clinical & Commercial TEMP Bioreactor Development Process

Phase	Sub Phase	Description
<b>Design</b>	Discovery: Review of Existing Design, Initiation of a Users Requirements Document, Generation of Verification and Validation Matrix	Time and attention are spent in the front end to ensure that fabrication and eventual production is correct and meets all necessary requirements for customer and commercial production. TGT & Customer visits are often included to share capabilities, regulatory concerns and current research protocols which should be included in the final product.
	Concept Development & Refinement: Generate Flow in 2D Format – Flow chart to demonstrate chamber and system process	Further Development of sketches and specifications into full fledged concepts for review by customer in preparation for engineering development.
<b>Engineering</b>	Engineering Development and Prototype	TGT Engineers develop chosen concept into working prototypes. These may include chambers, stimulators, and other accessory components. Deliverables 1) Rapid Prototypes 2) Results of verification testing per TGT's verification and validation matrix.
	Delivery of Alpha System	The first system (machined or rapid prototype – not molded) is delivered to the customer for validation.
	Review of Alpha System	TGT and Customer review the Alpha system and design and operation. TGT incorporates changes identified during validation.
<b>Production</b>	Production Development	TGT initialized production. Tooling is fabricated and tested for disposable chamber manufacturing. This phase can overlap with the Alpha delivery; however, quick review of the Alpha system will be necessary in order to make tooling modifications.
	Production Enablement	The production network is finalized and first units off of the tooling are validated.
<b>Packaging &amp; Sterilization</b>	Packaging: Package design is developed, fabricated, and tested.	TGT designs and initializes sterilization testing for the disposable items. This phase can overlap with production development. However, significant changes to the chamber during production will negatively affect package and sterilization time lines. Deliverables 1) Package prototype 2)Final sterile package.

# Publications: TGT in Current Literature

## Patents:

Instrumented bioreactor with material property measurement capability and process-based adjustment for conditioning tissue engineered medical products. US pat no 7410792. August 12, 2008

Bioreactor with plurality of chambers for conditioning intravascular tissue engineered medical products. US pat no 7348175. March 25, 2008

## Peer Reviewed Publications:

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Voge CM, Kariolis M, MacDonald RA, Stegemann JP. Directional conductivity in SWNT-collagen-fibrin composite biomaterials through strain-induced matrix alignment. *J Biomed Mater Res A*. 2008 Jul;86(1):269-77. PubMed PMID: 18428799.

## Presentations:

Christopher M. Voge, Mihalis Kariolis, Rebecca A. MacDonald, Jan P. Stegemann, Directional Conductivity in Protein-Nanotube Biomaterials through Strain-Induced Matrix Alignment. 8th World Biomaterials Congress. Amsterdam, Netherlands, June 2008.

S Saber. Stanford University Medical Center, Department of Plastic Surgery, Flexor Tendon Tissue Engineering: Cyclic Strain Increases Construct Strength and Tendon Architecture. Plastic Surgery Research Council. Springfield, Illinois, May 2008. Also presented at the California Society of Plastic Surgeons, Dana Point, California, June 2008.

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