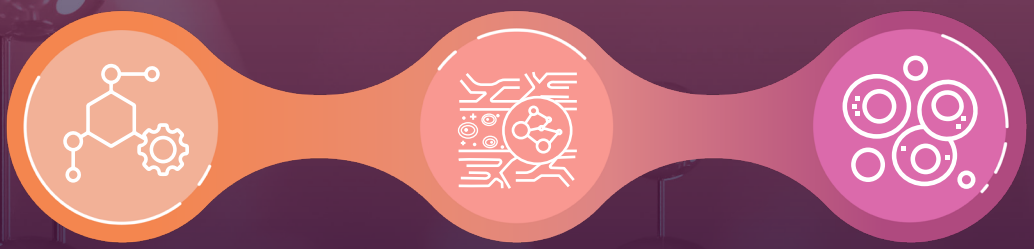
Alliance *for* Regenerative Medicine

Tissue Therapeutics:

The Curative Potential of Combining Cells & Biomaterials



Biomaterials **Tissue Therapeutics** **Cell Therapy**

INTRODUCTION: DEFINING TISSUE THERAPEUTICS AND TISSUE ENGINEERING

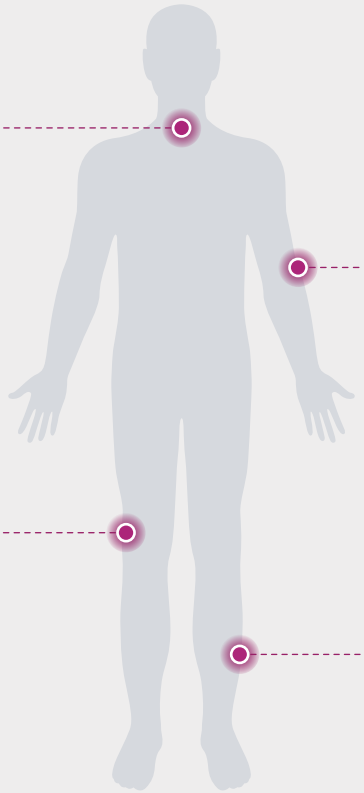
There are many significant areas of unmet clinical need, such as organ or tissue transplants and tissue repair, where conventional biologics or even genetically engineered cell products are not sufficient, as they cannot provide the structural and functional therapy needed to replace, repair, or supplement lost function. By providing structure and enabling more advanced functions, the field can step into indications where there are currently no therapies or only poorly controlled therapies. Alongside the advancement of tissue engineering approaches and technologies, the field is at a point where the design and manufacturing of tissues can address this opportunity. Tissue engineering and tissue therapeutics can be leveraged to create formidable advanced medicinal therapies with the promise of providing long-lasting, durable, potentially curative repair and restoration of function that can currently not be achieved by conventional medicines or cell or gene therapies.

Tissue engineering is a method that describes key principles of manufacturing for tissue therapeutics. The term therapy or therapeutic indicates that a cell-based drug is produced. Importantly, tissue therapeutics comprise a continuum of products that combine biomaterials and cell therapies (Figure 1 & 2). They are typically three-dimensional products that will be implanted, administered locally to the affected tissue, or ectopically to restore lost function. Furthermore, biomaterials are more than mere scaffolds. Advanced understanding of mechanobiology and bio-manufacturing technology allows them to be imbued with instructive properties and guide cell engraftment and functional differentiation. As such, they can augment and drive vascularization, shield the implanted cells from an overactive immune response (i.e., in diabetes), or provide specific therapeutic advantages and functionalities by re-creating three-dimensional organotypic structures.

A diverse array of innovative tissue therapeutic products has emerged, bridging the gap between MedTech devices, traditional biologics, and cell therapy. This advancement in tissue engineering represents a groundbreaking paradigm, combining the strengths of both fields to create a new category of therapies with highly predictable mechanisms of action. By focusing on restoring functional tissue in patients with impaired tissue performance, these novel therapeutics offer the potential to address a wide range of related indications with a single drug platform.

The promise of these products lies in their scientific foundation, drawing from cutting-edge developments in biotechnology while integrating the precision and adaptability of device-based approaches. Through the incorporation of advanced biomaterials and tailored applications, tissue therapeutics is uniquely positioned to revolutionize patient care, addressing unmet medical needs with unparalleled efficacy and precision.

Figure 1: FDA-Approved Products



Immune Reconstitution

Rethymic
(Sumitomo Pharma America, 2021)

Cartilage Repair

Carticel
(Genzyme, 1997)

MACI
(Vericel Corporation, 2016)

Wound Healing, Skin Substitutes

Apligraf
(Organogenesis, 1998 & 2000)

Dermagraft
(Shire, 2001 | Now owned by Organogenesis)

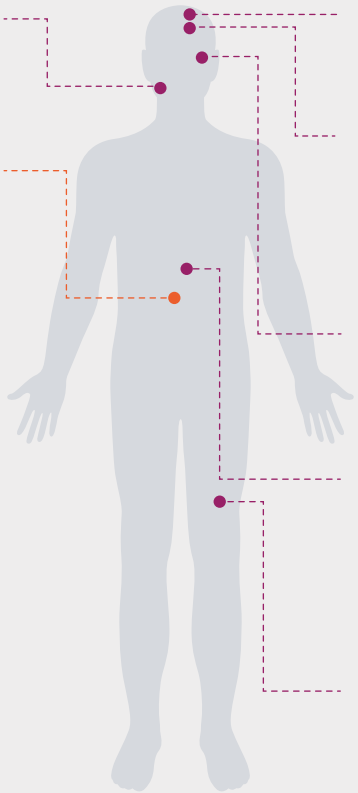
Epicel
(Vericel Corporation, 2007)

Stratagraft
(Mallinckrodt, Stratatech Corporation, 2021)

Vascular repair

Acellular tissue engineered vessel (ATEV)
(Humacyte, 2024)

Figure 2: Tissue Therapeutics In the Pipeline



Individualized Bone Graft

EB-CMF
(EpiBone)

Replacement & Support Organ Function

miroliverELAP, Mirokidney
(Miromatrix, United Therapeutics),

SB-001
(Satellite Bio),

ReLiver ®
(Morphocell),

SR-02
(Seraxis),

Bioprinted Tissue Therapeutics
(BTTs) for diabetes & obesity*, liver disease, and endocrine disorders
*in partnership w/ Novo Nordisk
(Aspect Biosystems)

Liver Failure
(Dimension Inx)

Retina Repair

CPCB-RPE1
(Regenerative Patch Technologies)

Brain Function / Parkinson's Disease

Tissue-Engineered Nigrostriatal Pathway (TE-NSP)
(Innervace)

Microtia

AuriNovo™ – Autologous 3D-printed ear
(PrintBio)

Immune Modulation

AT102
(Avery Therapeutics)

Vascular repair

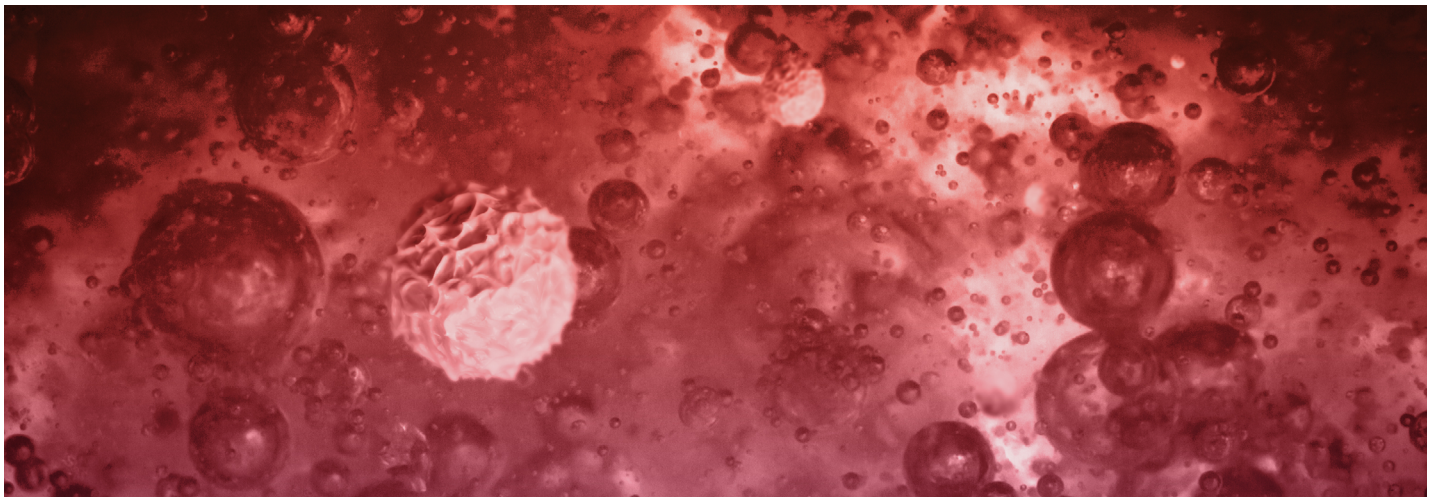
P-TEV
(VERIGRAFT)

01 The Power of Tissue Therapeutics

Tissue therapeutics are more than a cell therapy or a biomaterial. They are advanced combination products that have been designed for a durable, potentially curative outcome that can only be achieved via a functionally active product. Depending on the indication and therapeutic mode of action, they can elicit a physiological response, respond to physio-chemical cues, and restore balance in immunologically inflamed or un-balanced scenarios. It is precisely their multifaceted function that allows them to achieve the efficacious response needed for long-lasting tissue repair, function restoration, and rebalancing. Tailored to the anatomic location within the patient and type of indication, tissue therapeutics can either be highly personalized or provided in an off-the-shelf (allogeneic) format. Because the therapeutically active component consists of living cells, their functionality is already built in at an immediate and higher-order level than biologics, small molecules, or gene therapies.

When comparing clinical trial success rates, the field is expecting those for tissue therapeutics to be higher compared to biologics or devices. The improved success rates have already been observed in the field of CAR-T therapies (NEWDIGS data). This comparative analysis suggests durable CGTs for orphan diseases and hematological cancers are 2-3.5 times more likely to succeed than other therapeutic modalities for similar conditions or compared to the entire drug pipeline. This improved correlation is likely due to the mechanistic hypothesis for tissue therapeutics being stronger than that of a single-target traditional therapeutic.

For some tissue therapeutics, cells play a minor and rather supportive role. In these scenarios, e.g., for VERIGRAFT's product P-TEV, the non-cellular components are responsible for providing functionality, and cells enable functional engraftment with the recipient tissue. The biomaterials used in these combination products offer more than a structural component since they can also provide environmental and immune protection to the cells and facilitate functional integration for engraftment and longevity of the product. The site-specific response that the implanted products deliver in response to their microenvironment, combined with the interdependent synergy between the cellular and non-cellular components, is the basis for the transformative nature of tissue therapeutics.



Pioneering Products

The concept of tissue engineering and its promise was first explored in a basic research setting over four decades ago, resulting in early product success in skin wound healing, such as Apligraf and Dermagraf, as the most straightforward and achievable first application (see Figure 1). Early approved products were pioneers paving the way for a new wave of products in the pipeline. There are currently eight products on the market for use in both inpatient and outpatient settings. Product launch prices range from 25k to over $2 million (see Table 1). These products have provided the foundation for more advanced tissue therapeutics targeting cardiovascular, bone, ocular, and whole organs (see Figure 2).

Table 1: List of FDA-approved Tissue Therapeutics and their Applications

Product (Manufacturer)	Indication	Launch Price	Setting of Care	Info on Reimbursement
Aurix (Nuo Therapeutics)	FDA has cleared Aurix for use on exuding wounds (link)		Inpatient treatment and outpatient monitoring	Medicare NCD (link) (APC) 5054 (Level 4 Skin Procedures)
Apligraf (Organogenesis Inc. & Novartis AG)	FDA approved Apligraf on May 22, 1998, to treat venous leg ulcers and on May 2000, to treat diabetic foot ulcers (link)	$25,370 (link)	Outpatient	HCPCS: Q4101 Claims 100% commercial and Medicare coverage
Dermagraft (Organogenesis)	Approved by FDA for use in the treatment of full-thickness diabetic foot ulcers of >6 weeks duration (link)	$24,552 (link)		HCPCS: Q4101
Epicel (Vericel)	Authorized by the FDA for use in patients with burns that cover at least 30% of their body (link)	$13,000 per 1% of body surface treated (link) indication is a minimum 30% burns	Inpatient	Humanitarian device approval HCPCS: Q4100 C9399 No product specific ICD-10-PCS codes
Matrix Associated Chondrocyte Implantation (MACI) (Vericel)	FDA approved MACI on December 13, 2016, for repair of cartilage defects in the knee of adult patients (link)	$50,000+ (link)		

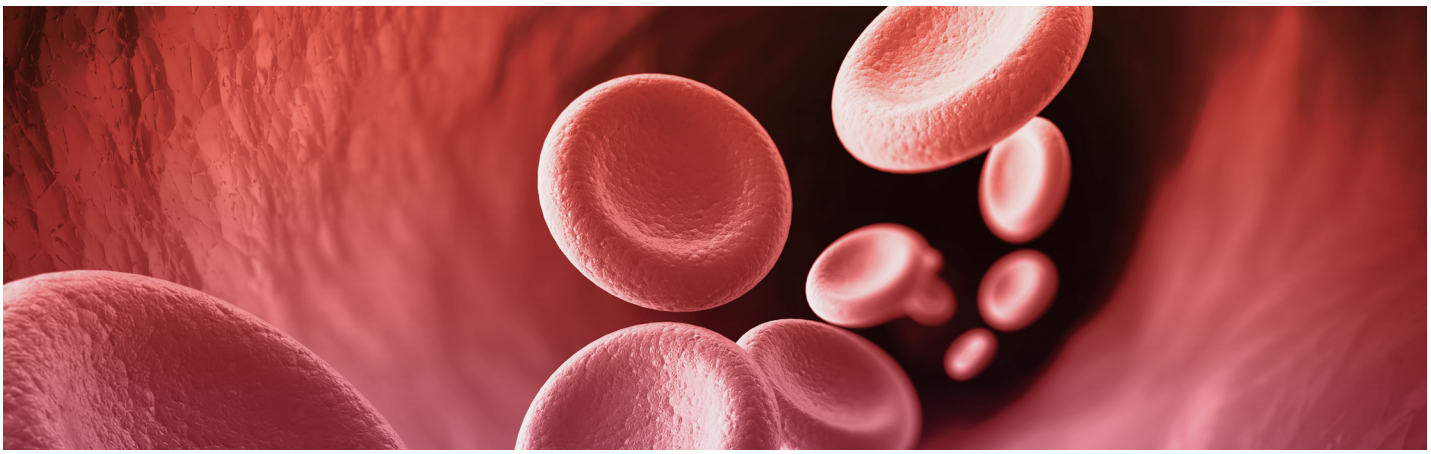
Product (Manufacturer)	Indication	Launch Price	Setting of Care	Info on Reimbursement
Rethymic (Sumitomo Pharma, Enzyvant Therapeutics)	On Oct 8, 2021, the FDA approved this tissue-based treatment for congenital athymia. It is engineered to help children develop an immune system sufficient to fight infections (link)	$2,729,500 per implant (link)	Inpatient (only at Duke)	Commercial coverage policy (link)
Stratagraft (Mallinckrodt)	FDA approved StrataGraft on June 15, 2021, for the treatment of adult patients with deep partial thickness burns. (link)		Inpatient	NTAP for 2022: $44,200
Transcyte (Organogenesis)	FDA approved TransCyte, a temporary skin substitute for treating burn wounds, on Dec 15, 2003. (link)	$46,000 (link)		HCPCS: Q4182

As capabilities and knowledge improved in the field, more advanced and complex health challenges have been successfully addressed in the last decade with tissue therapeutics products such as Carticel for cartilage repair and ATEV (Acellular Tissue Engineered Vessel) for vascular repair.

Examples of early pioneer products approved by the FDA's CDRH include Apligraf, Dermagraft, and Carticel, while Stratagraft was reviewed and approved by the FDA's CBER. For example, products that utilize a decellularization and recellularization step, e.g., Miromatrix's products, are regulated by CBER. Similarly, CBER regulates products that embed cells within a biomaterial, e.g., hydrogel or other polymeric scaffold, to create an implantable tissue-like product that replaces function (but not typically structure), e.g., those developed by Satellite Bio, Aspect Biosystems, Avery Therapeutics, and Dimension Inx. Other products in the tissue therapeutics space are closer to traditional tissue transplants that mimic or replace the native tissue in both function and structure, e.g., those developed by VERIGRAFT and EpiBone.

Outlook: Reimbursement Pathways for CGTs and Tissue Therapeutics in the US

- In the US, most tissue therapeutics will likely be for Medicare-eligible patients, and currently, coverage exists for certain treatments. Overall, tissue therapeutics are typically covered under Medicare National Coverage Determinations (NCD). Medicare NCDs are formal policies developed through an evidence-based process and are commonly applied to certain items and services that are, among other characteristics, considered expensive compared to current usage.
- DRGs, or Diagnosis-Related Groups, are a system used by Medicare to classify hospital cases into groups that are expected to have similar hospital resource use. Each DRG is associated with a fixed payment amount, which helps to standardize reimbursement for hospitals. As an example, CMS created a new DRG titled "MS-DRG 018: CAR-T Cell Immunotherapy," moving CAR-T cases from the previously assigned DRG-016. This new grouping offered a much higher relative weight for high-cost CAR-T therapies and has since been expanded to include "& Other Immunotherapies." In 2024, the unadjusted base payment rate is $248,925, which is the highest base payment rate of any current DRG. However, this rate is often still insufficient for such high-cost therapies.
- Since DRG-018's inception, more non-CAR-T, high-cost therapies have come to market. However, because there are insufficient DRGs for these products to map to, many attempt to be classified under DRG-018 to ensure the highest reimbursement possible and to increase the likelihood of utilization by healthcare providers.
- New Technology Add-On Payments (NTAP) were created through a statutory provision that allows Medicare to provide additional reimbursement for new and innovative medical technologies. NTAP is a useful tool to demonstrate a higher likelihood of commercial uptake. This program aims to encourage the adoption of advanced therapies by enhancing administrators' ability to receive adequate payment for the use of these products. By securing NTAP status, developers of tissue therapies support a hospital's ability to secure adequate reimbursement for these unique, high-cost treatments and facilitate their adoption in clinical practice. The additional reimbursement can encourage research and development in the field of tissue engineering by providing financial incentives for hospitals to implement new therapies.



- NTAP is capped at 65% of the product cost. For example, if a new product costs $200,000, the maximum NTAP reimbursement on top of the MS-DRG payment would be $130,000. The NTAP period is phased out over two or three years, CMS then has a more robust set of claims data for future rate-setting to include tissue therapies. Manufacturers will generally apply for NTAP before products are approved to come to market to ensure a smaller timeframe without the additional payment. A recent example is Vertex Pharmaceutical's CASGEVY, which is indicated for use in patients with sickle cell disease; this product was approved in December 2023 and received NTAP starting October 2024.
- In the past five years, there has been only one tissue therapeutic to be awarded NTAP, which is Stratagraft by Mallinckrodt. As new products are commercialized in the inpatient care setting, we expect to see more manufacturers apply for NTAP. With adequate reimbursement through NTAP, more patients may gain access to cutting-edge therapies, ultimately improving patient outcomes and advancing healthcare practices. NTAP can be a critical mechanism for promoting the adoption of tissue therapeutics within Medicare, helping to bridge the gap between innovative treatments and their practical use in healthcare settings.

02 Regulatory Pathways to Approval

The promise of tissue therapeutics is becoming a reality with a growing pipeline of clinical-stage tissue therapeutics products in development and increasing investment in relevant manufacturing capabilities in cell therapies, bioprinters, and advanced biomaterials. This also ties in with the forward-leaning nature of the FDA's CBER, as emphasized by the recently reorganized Super Office OTP and the office's leadership's vision.

Tissue therapeutics are neither devices (regulated by FDA's CDRH) nor cell or gene therapies (regulated by FDA's CBER). Historically, products were reviewed and approved by CDRH but then re-homed to CBER since manufacturing is often similar to CGTs and biologics.

Comprehensive reviews of the regulatory pathways and requirements for tissue therapeutics are available here. Of note, not all tissue therapeutics are combination products as some may rely more on the material/scaffold-nature while others focus on the cellular component of the product. However, due to the increasing complexity inherent in these products, CBER's OTP has regulatory oversight for tissue therapeutics today. A non-exhaustive overview of tissue therapeutics currently in the pipeline to approval is provided in Figure 2.

Existing regulatory pathways, including the RMAT designation, are available to sponsors and frequently requested per the FDA's annual summaries. ARM encourages newly formed teams at OTP to embrace their mandate and employ flexibility and long-range thinking when interpreting guidance for use with tissue therapeutics. Future topics to be addressed will need to include regulation of clinical trials in n=1 applications (a setting similar to rare disease trials). In addition, the approach to CMC release and potency testing is unique for tissue therapeutics and different from those for Cell and Gene therapies due to the combinatorial effect of the cells and biomaterial as well as the intended applications. The importance of quality and release assays has become the focus of many regulatory discussions, and results are being incorporated into novel guidance and Q&A documents.

In the EU, advanced therapy medicinal products (ATMPs) are classified into somatic cell therapy medical products, gene therapy medical products, tissue-engineered products, or combined advanced therapy medicinal products (CATMPs), according to Article 2 of the Regulation (EC) No. 1394/2007. According to this classification, tissue-based Products are defined in the EU as TEPs (Tissue Engineered Products) or CATMPs, depending on whether a medical device has been incorporated or not.

Japan's Pharmaceuticals and Medical Devices Act (PMD Act) includes a conditional and time-limited approval system specifically designed for regenerative medical products. This framework aims to expedite patient access to innovative therapies while ensuring safety and efficacy. It also includes post-marketing studies and informed patient consent. As of August 31, 2023, Japan has approved 20 regenerative medical products under the Pharmaceuticals and Medical Devices Act (PMD Act) (Reference). Of these, four products have been granted conditional and time-limited approval, allowing for earlier patient access while requiring further post-marketing studies to confirm their safety and efficacy.

Key features of conditional approval framework

Expedited Approval:
Regenerative medical products can receive conditional, time-limited approval based on preliminary evidence of safety and efficacy. This allows patients earlier access to promising treatments.

Post-Marketing Obligations:
Manufacturers are required to conduct further clinical studies after approval to confirm the product's safety and effectiveness. These post-marketing studies are essential for transitioning from conditional to full approval.

Patient Consent:
Patients must be informed about the conditional approval status of the regenerative medical product, including its expected risks and benefits, before consenting to treatment.

Time-Limited Authorization:
Conditional approval is granted for a specific period, during which the required post-marketing data must be collected and submitted for review.

03 Manufacturing from pilot-scale to automation

The complexity of manufacturing is still a hurdle, but automation and learnings from previous decades of experience and pioneer products help advance the field. Still, human intervention and interpretation are required in manufacturing, quality control (QC), and quality assurance (QA). The safety and efficacy of products are paramount to regulators and developers entering clinical trials. The goals in production for the cellular component(s) are shared with the field of cell therapy: Sponsors need to produce a sufficient number of cells along with a sufficient level of viability to ensure short- and long-term engraftment of the cells into the recipient. Common manufacturing pathways can be employed, and bioprocessing methods and devices from the advanced cell therapy area can be leveraged. In addition, proven methods for sourcing cells include the use of human blood itself as the cellular component for tissue therapeutics.

Automation is a very important facilitator for pivotal and registrational trials. The Advanced Regenerative Manufacturing Institute (ARMI), a nonprofit organization advancing biomanufacturing, offers pilot production capabilities for tissue therapeutics, but a gap exists in the availability of automated "conductor belt"-type manufacturing - akin to automotive manufacturing with robotic arms instead of human technicians -needed to support the number of products intended to serve the large pool of patients expected for tissue therapeutics.

04 Shaping the Future for Patient Care

While public and private investors currently have the opportunity to participate in shaping a bold new future for patient care, there are funding innovations that can help advance this class of therapies to patients. These include new incentives to reduce costs and expanding infrastructure for bio-manufacturing.

The pioneers in this field have demonstrated groundbreaking innovation and IP that has laid the foundation for new bioeconomy and biomanufacturing capabilities. The early approved products were pioneers, paving the way for a new wave of products in the pipeline, which are coming to fruition now. ARPA-H and similar early-stage funding opportunities exist, but don't go beyond pilot-stage or proof-of-concept. Tissue therapeutics would likely benefit from novel governmental funding support mechanisms to bridge clinical trial progression until regulatory approval. This may not necessarily be risk capital but rather governmental support mechanisms that can be leveraged by all developers in this sector.

Figure 3: Outlook - Steps for enabling success in critical areas of need

Embrace Simplicity

Bringing greater simplicity to tissue therapeutics (TT) product design, manufacturing and QC will be crucial for successful TT approvals in the future. Inherent complexities in combining cells and biomaterials need to be minimized during development to ensure tissue therapeutics can be manufactured reproducibly at high quality

Quality by Design

Development should proceed in a phase appropriate manner to ensure process, facilities, and personnel can scale at the right time. Preliminary manufacturing plans should be considered early on to provide a roadmap to commercialization and forecast expected costs and subsequent investments needed.

Scalable Manufacturing

Focus on developing scalable manufacturing and analysis of cells, biomaterials and tissue therapeutic products to reduce future costs. Novel analytical technologies, in-line testing, AI/ML and rapid microbial testing can reduce some of the major contributors to cost and need to be streamlined while enabling high degrees of quality control from raw materials to final product release testing.

Leverage Unique Properties

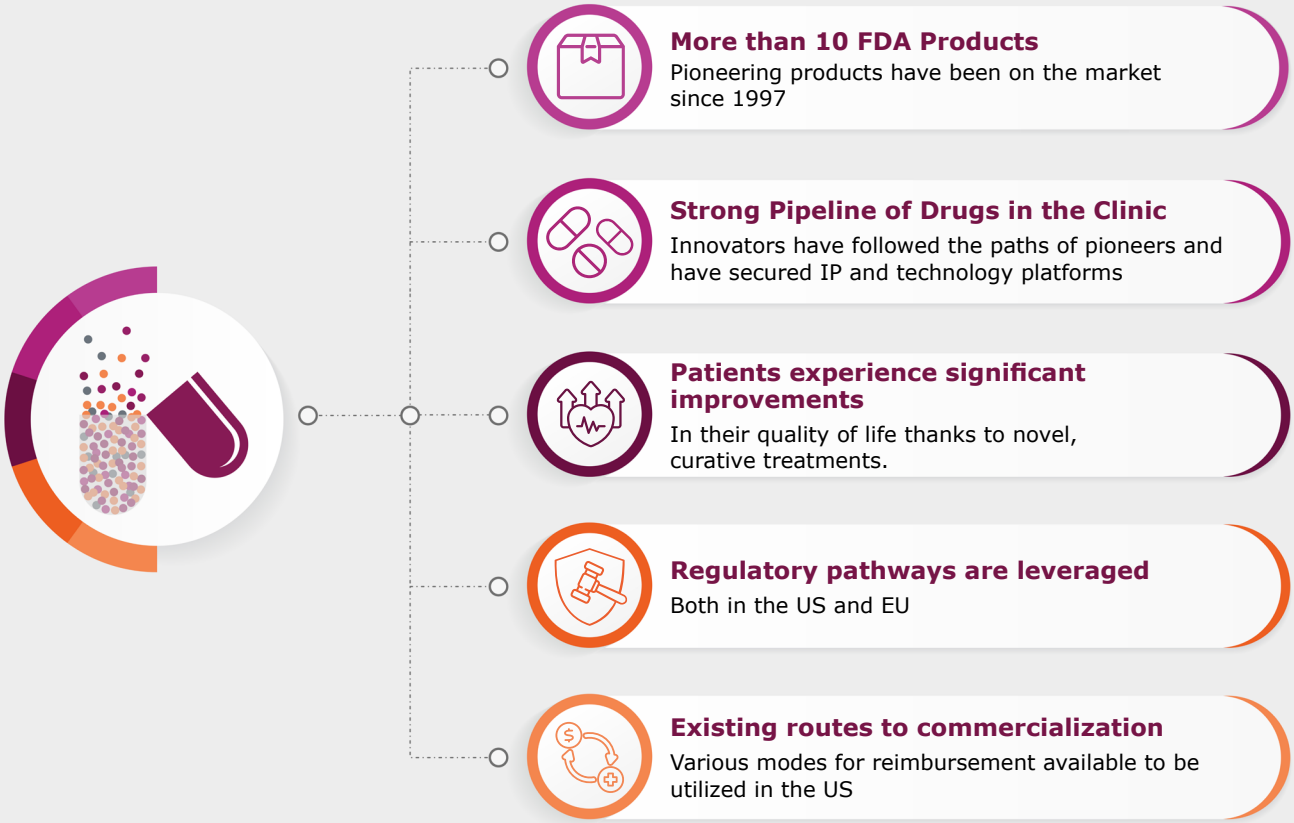
Develop products that leverage the unique ability of tissue therapeutics to address unmet patient needs and allow for significant increases in quality of life for patients. This in turn will translate to significant decreases in healthcare system costs and justifiable reimbursement strategies that will encourage investment.

CONCLUSION: TISSUE THERAPEUTICS IS USHERING IN A BOLD NEW CLASS OF PATIENT CURES

Many tissue therapeutics have entered the clinic, and patients who are treated see a significant improvement in their quality of life (Reference 1, Reference 2). For example, controlled clinical studies have shown that Apligraf® is more effective and economical at healing chronic venous leg ulcers and diabetic foot ulcers compared to standard wound care therapy alone (Reference). A second well-known product in the field, MACI® (autologous cultured chondrocytes on porcine collagen membrane) was approved by the FDA based on the SUMMIT study, a two-year prospective, multicenter, randomized, open-label, parallel-group study which demonstrated a statistically significantly greater improvement in KOOS (Knee Injury and Osteoarthritis Outcome Score) pain and function scores in the MACI group compared to the microfracture group at two years (Reference).

Global access and commercialization pathways are being created by pioneers in the field and the next generation of developers. The field is seeing increased levels of interest and deal activity from pharma companies looking to provide novel treatments and care modalities to patients with unmet needs. This is a very positive trend that has the potential to stimulate investment from both private and public sources to drive innovation.

Figure 4: The Power of Tissue Therapeutics



To ensure patient access to these life-changing advanced therapies, sponsors and investors can leverage existing regulatory and manufacturing paths that have been created in the cell and gene therapy sector, as well as existing routes to commercialization and reimbursement for devices and transplantation.

There is a huge unmet need for providing curative therapies that will impart a vast improvement in how patients lacking alternative options get treatment. By advancing tissue therapeutics that can replace or repair lost function, the opportunity to treat disease at the root cause and prevent a myriad of downstream impacts is a real possibility.

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