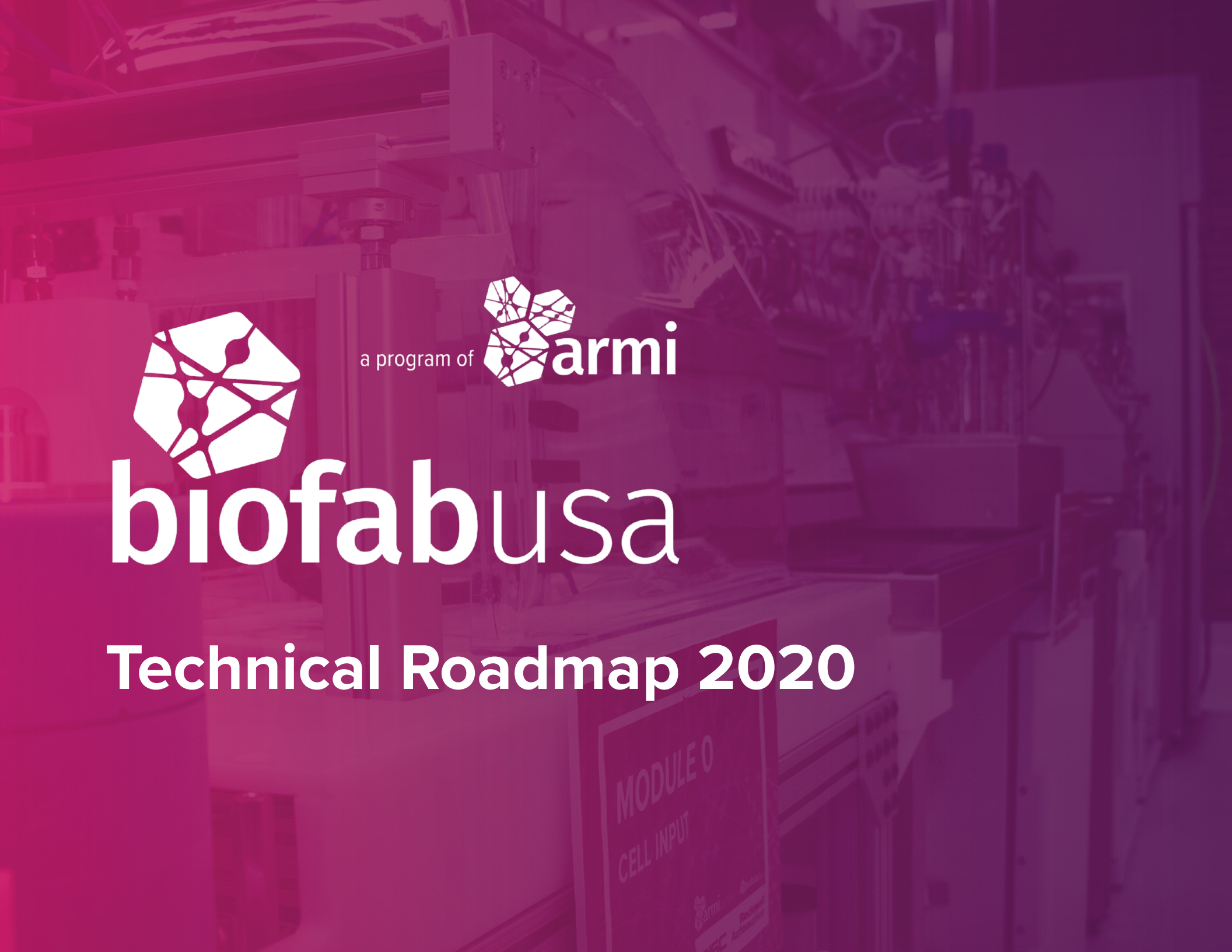
a program of
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biofabusa
Technical Roadmap 2020
MODULE 0
CELL INPUT


Agitator
CWS

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About this Report

BioFabUSA is a Department of Defense-funded Manufacturing Innovation Institute that launched in mid-2017 by the Advanced Regenerative Manufacturing Institute (ARMI). In order to plan its technology strategy for the BioFabUSA program, ARMI, in conjunction with the Tissue Engineered Medical Product (TEMP) ecosystem, developed and published its original Technology Roadmap, entitled "Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of Engineered Tissues" in 2018, and has updated it on an annual basis.

To develop the 2018 technology roadmap, ARMI enlisted the experience of its diverse ecosystem, comprising members of the TEMP industry, academic institutions, non-profit organizations, and government agencies. Gaps were initially identified in a manufacturing needs assessment, and were then refined in a series of workshops published as the inaugural BioFabUSA Technical Roadmap in 2018. To update the draft for 2019, ARMI engaged its four technology working groups representing the stages of the TEMP manufacturing process: cell culture and harvest; scaffold fabrication; tissue maturation and bioreactor culture; and preservation, packaging, and transport.

Following the technology working group evaluation and modifications, the technology development tasks were further prioritized and refined at the ARMI Member Day workshop in the spring of 2019. The updated roadmap, entitled "Scalable, Consistent, Cost-Effective Manufacturing of Tissue Engineered Medical Products" was published to the ARMI on-line portal in mid-2019.

There have been a number of advances in the manufacturing technologies and advances in the scientific understanding required to advance high quality, safe and effective TEMPs since the 2019 technology roadmap update. To capture the changing landscape of TEMP manufacturing, ARMI members aligned with the BioFabUSA program were asked to report any new technologies that addressed technology gaps or bottlenecks identified in the 2019 BioFabUSA Technical Roadmap and any new technology gaps or bottlenecks to the scalable, consistent, cost-effective manufacturing of TEMPs that have emerged as a result of recent advancements. The ARMI technology working groups reviewed member feedback and assessed the existing development items to remove accomplished items, add new gaps, and update language to better reflect current needs.

Working group members were asked to evaluate existing items by:

ORIGIN
Document the source of the need and why it exists

IMPLEMENTATION-FREE
Solution is not prescribed to maximize design flexibility and minimize constraints

SUCCESS CRITERION
Define the criteria that will fulfill the need

UNAMBIGUOUS
Clearly communicate the true need

PRIORITIZED
Determine which of the requirements are most important relative to each other

RELATIONSHIP
Identify synergy or conflict between needs

Following language refinement, members were asked to rank the extent to which addressing this need could improve quality, scalability, consistency, time to market, and cost (impact). Alongside impact, members were asked to assess the appropriate time the development item would take to achieve, considering the urgency, need to act now vs. later. Development items with a high impact and short timeline are considered high priority items for technology development.

This document is intended to update the existing BioFabUSA Technical Roadmap Update 2019. The technology roadmap will continue to be updated annually to reflect progress on technology development tasks and highlight new technology needs as the industry continues to evolve.

Executive Summary

The goal of the BioFabUSA program is to enable the scalable, consistent, and cost-effective manufacturing of tissue engineered medical products (TEMPs) by:

- Removing existing hurdles to reproducible tissue biomanufacturing
- Producing modular and scalable Good Manufacturing Practice (GMP)-compliant manufacturing processes and integrated technologies
- Developing and standardizing manufacturing practices across the industry
- Closing the skills gap in tissue and organ manufacturing by providing training opportunities from “K to gray”
- Disseminating knowledge and technologies to enable continued innovation

Essential targets for technology development efforts by ARMI | BioFabUSA:

- Development of advanced cost-effective technologies and flexible manufacturing processes
- Understanding the link between a product’s Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical Material Attributes (CMAs)
- Technology projects that culminate in a TEMP manufacturing platform that is scalable, modular, automated, and closed

The following activities that cross-cut the TEMP manufacturing process were identified as strategic priority areas for the industry:

- Tighten control over raw materials
- Develop equipment and software that enables automation of manual or high-risk process steps
- Advance development of automation that minimizes process variability and labor costs
- Design and implement measurement technologies that integrate with technologies and methods to store, manage, and integrate large volumes of data
- Advance technologies and processes for the preservation, packaging, and transport of material intermediaries and final product
- Demonstrate and promote a Quality-by-Design-based (QbD) approach to manufacturing process development and decrease the difficulty with which a quality system is implemented for Cell Therapies and TEMPs
- Support the development of relevant standards

The following report outlines and describes a consensus-based list of technology development tasks aimed at achieving the vision for scalable, consistent, and cost-effective manufacturing of TEMPs.

Purpose and Scope

There has been significant scientific progress in the field of tissue engineering over the last several decades. However, only a very small percentage of this progress has been translated into commercialized TEMPs. The lack of commercially available TEMPs is largely attributed to the challenges of manufacturing these products consistently, cost-effectively, and at scale. BioFabUSA, an industry-led public private partnership, was created to address these challenges. This Manufacturing Innovation Institute has created a collaborative community that includes TEMP developers and tool manufacturers from commercial firms and academia, who conduct interdisciplinary, advanced manufacturing research and development (R&D). These R&D activities aim to develop common, modular manufacturing platforms and associated processes, standards, and know-how to de-risk and lower the cost of developing and executing robust manufacturing for any TEMP.

To accomplish this mission, BioFabUSA is focused on the following goals aimed toward achieving scalable, consistent, cost-effective manufacturing of Tissue Engineered Medical Products:

- Remove existing hurdles to reproducible TEMP biomanufacturing
- Produce modular and scalable GMP-compliant manufacturing processes and integrated technologies
- Develop and standardize manufacturing practices across the field
- Close the skills gap in tissue and organ manufacturing by providing training opportunities from “K to gray”
- Disseminate knowledge and technologies to enable continued innovation

In previous roadmaps, BioFabUSA identified the raw material, equipment, measurement, automation, logistics, and big data analytics challenges that need to be overcome to support the scalable, consistent, and cost effective manufacturing necessary to deliver sufficient numbers of safe, effective, and affordable TEMPs to the wounded warfighter and the nation. BioFabUSA funds co-investment projects to overcome these challenges. Furthermore, BioFabUSA is developing a series of integrated platform technologies, including the Tissue Foundry and the Deep Tissue Characterization Center (DTCC). The Tissue Foundry is a model for a scalable, modular, automated, and closed manufacturing system. The DTCC focuses on supporting robust, Quality-by-Design-based TEMP process development by performing deep cell and tissue characterization and leverage the power of big data analytics. BioFabUSA-supported technical advancements are accessible by all members so that they can increase the speed at which TEMPs reach the market and patients in need.

This roadmap expands upon the technical accomplishments of the program and details the advanced research and development tasks needed to carry out the technical goals of the BioFabUSA program. A separate roadmap, which focuses on education and workforce development (EWD) activities, is available as a separate document through BioFabUSA. Additionally, BioFabUSA will not serve as a standards development organization (SDO), however, BioFabUSA and its members will identify gaps that can be addressed by a standard and collaborate with SDOs as needed to develop standards in the Tissue Engineering and Regenerative Medicine (TERM) field.

Technology Working Groups

Technology Working Groups are composed of ARMI members and convene a diverse set of cross cutting expertise representing small and large industry, academia, non-profit organizations and the federal government to discuss the challenges and innovations they are experiencing and implementing in their own work. In 2019-2020, ARMI's 4 technical working groups comprised 147 members.

Technology Groups:

Cell Culture and Harvest

Scaffold Fabrication

Tissue Maturation and Bioreactor Culture

Preservation, Packaging and Transport

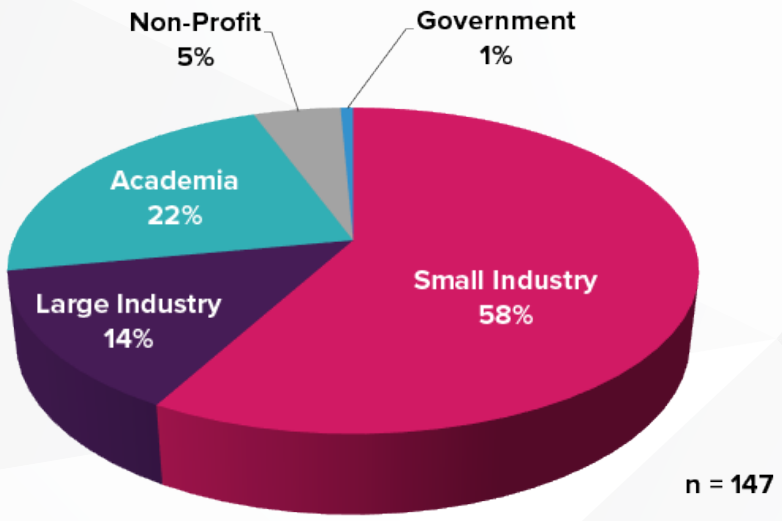


Figure 1: Breakdown of roadmap participation by organization type. Large Industry defined as >500 employees.

Roadmap Progress and Activities

ARMI's BioFabUSA supports the production of scalable, consistent, cost-effective TEMPs through the development of advanced cost-effective technologies and flexible manufacturing processes. This technology roadmap outlines a series of technologies and processes that will work in concert to achieve a manufacturing process that is scalable, modular, automated, and closed. Roadmap development tasks span end-to-end manufacturing of TEMPs, from the point of cell or scaffold harvest as a raw material input to the final product transportation to the patient bedside (Figure 2).

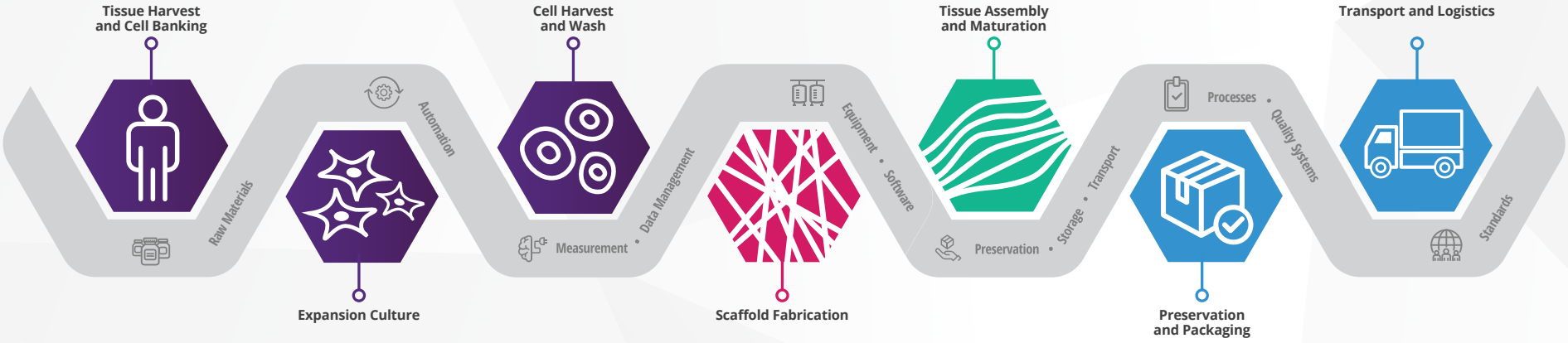


Figure 2: Roadmap organization by manufacturing modules with crosscutting technology areas

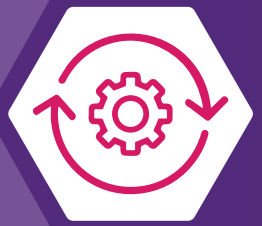
Development items address key cross-cutting technology development areas underlying the manufacturing process steps:

RAW MATERIALS

The materials required to produce TEMPs are often living cells and animal-derived components leading to a high degree of supply chain insecurity plagued by high product costs and variability. The production of a robust and redundant supply chain will lead to more cost-effective manufacturing and consistent product. The roadmap focuses on three areas of raw materials—cells, biomaterials, and reagents.

EQUIPMENT AND SOFTWARE

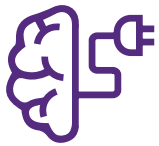
Equipment used for manufacturing of TEMPs needs to be fit for stringent environmental conditions and able to scale-up or -out. Software accompanying equipment should utilize sensor and tracking technology, process models, data analytics, and adopt simplified processes that permit assembly in controlled, non-classified (CNC) spaces. Development of manufacturing appropriate equipment that includes sensors for real-time monitoring and feedback control mechanisms will lead to more consistent, high-quality TEMPs.



AUTOMATION

Existing TEMP manufacturing processes use multiple manual unit operations that are often conducted in open environments with variable environmental conditions, uncontrolled manipulations, and increased contamination risk. In addition, much of manufacturing of TEMPs relies on a fixed process control strategy to mitigate variability. A fully closed and automated biomanufacturing system with automation technology would reduce error and minimize contamination risk, thereby reducing overall costs and helping to ensure a quality product.

MEASUREMENT AND DATA MANAGEMENT



The development of on-line and non-destructive technologies that permit in-process testing and release of final product in real time will improve the monitoring of in-process quality attributes and critical process parameters. Using an integrated platform, sensors and measurement data can be leveraged by machine learning, artificial intelligence to generate predictive models describing the multifactorial relationships between CPPs and CQAs. Development and application cost-effective and easy-to-use measurement and sensors combined with real-time data analytics, will drastically improve process control and increase process efficiency.

PRESERVATION, STORAGE AND TRANSPORT

Preservation, storage, and transport of TEMPs and biologic input materials requires the maintenance of the product's CQAs and a user-friendly process. Further development of preservation and shipping technologies will improve TEMP preservation and increase flexibility in logistics design for the storage and transport of TEMPs.

PROCESSES AND QUALITY SYSTEMS

Quality should be designed into a product. A QbD-based approach will lead to accelerated development of highly-reproducible and scalable manufacturing processes, faster paths to FDA approval, a significantly mitigated risk of raw material supply chain variability, fewer batch failures, and lower manufacturing costs.

STANDARDS

The development of standards reduces the barriers to innovation, increases safety and reliability, improves review process efficiency, and decreases overall costs of therapies. Under the coordination of the SCB, the development of TEMP standards will increase the consistency of technology and processes across the ARMI ecosystem.

Overarching Themes

Roadmap development tasks work towards the development of advanced cost-effective technologies and flexible manufacturing processes, understanding the link between a product's Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical Materials Attributes (CMAs), and the culmination of a TEMP manufacturing platform that is scalable, modular, automated, and closed.

SCALABLE

Manufacturing technologies must enable manufacturing from research scale to commercial production, such that process output can be increased with minimal impact to product quality and low demand for expensive comparability studies. Additionally, scale is highly dependent on the process. Autologous and allogeneic approaches present unique challenges that need to be considered when designing manufacturing solutions.

CONSISTENT

TEMP products are historically plagued by challenges in reducing batch-to-batch variability and maintaining a consistent product. While some variables are extremely difficult to identify and control, development of manufacturing technologies that control for process-related variability will help increase product consistency and eliminate potential sources of product variability.

COST-EFFECTIVE

The high cost of materials, equipment, and labor is a major barrier to return on investment and patient access. While not explicitly stated, roadmap development items aim to reduce the cost of manufacture while maintaining product quality.

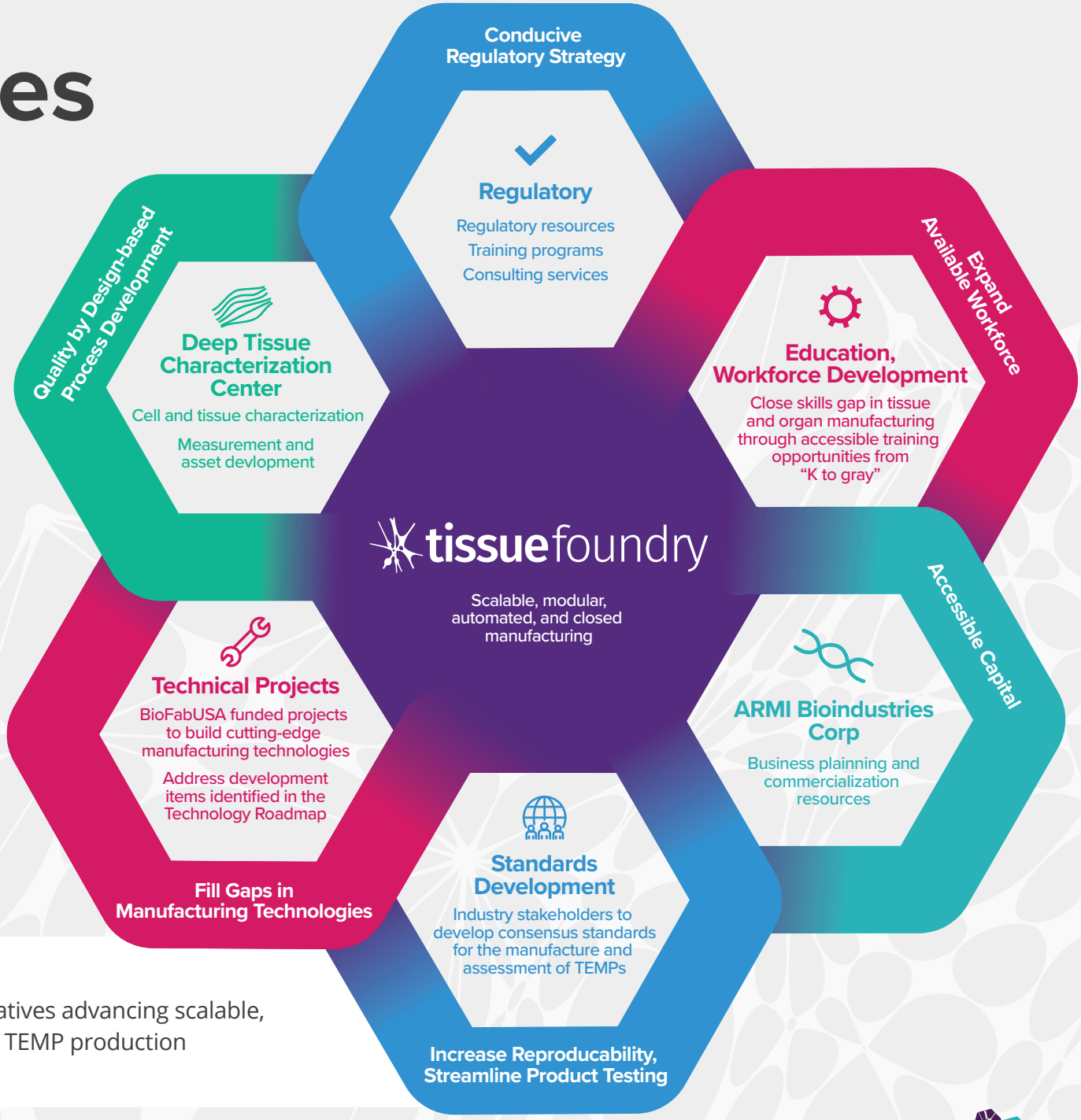
ON-LINE, NON-DESTRUCTIVE AND REAL-TIME SENSING

Sensing technologies must be on-line, non-destructive and real-time to detect and evaluate quality attributes in a material or system without impacting the overall process, and continuously record data at a response time that is small in comparison to the process dynamics, and enable continuous process control.

QUALITY BY DESIGN

The development of manufacturing processes will be based on the principles of QbD. This process development approach begins with the development of a Quality Target Product Profile (QTPP). The QTPP involves an in-depth characterization of the end product to understand its CQAs. QbD is used to develop a scientific understanding of the link between a product's CQAs and how the variability in important process parameters (i.e., CPPs) and material attributes (i.e., CMAs) affects the CQAs. The development activities outlined in this roadmap will therefore be underpinned by QbD principles.

Activities



ARMI programs and initiatives advancing scalable, consistent, cost-effective TEMP production

Progress Updates

TISSUE FOUNDRY

- 7 newly awarded projects for Tissue Foundry development for TEMPs related to repair of skeletal muscle, pancreatic islets, skin, heart, retina
- Development of a bioreactor system compatible with bioprinting and tissue exercise during culture

TECHNICAL PROJECTS

- 26 active technical projects
- 6 newly awarded projects in 2019 and 4 newly awarded projects in 2020
- Completed project to develop an off-the-shelf, baseline quality system with standard operating procedure for common operations and assays for TEMPs

DEEP TISSUE CHARACTERIZATION CENTER

- Began build out of DTCC with mass spectrometry, mechanical testing capabilities, and a data management system

REGULATORY

- Provided regulatory guidance to members, related to strategy, manufacturing, preclinical, and clinical trial design
- Delivered an educational workshop on the basics of FDA regulation of TEMPs
  - Obtained feedback in a workshop to assist in the development of a TEMP-specific quality system

STANDARDS

- Engaged with members and stakeholders to support standards development to address industry needs
- Alongside SCB, coordinated efficient development of meaningful and relevant TEMP standards across SDOs (ASME, ASTM, IEEE, and ISO)
- Led standard development efforts for characterization of Type I collagen, rapid microbial testing methods for TEMPs, bioprinting, and alignment of TEMP lexicon

KEY = Raw Materials = Equipment and Software = Automation = Measurement and Data Management = Preservation, Storage and Transport = Processes and Quality Systems = Standards

BioFabUSA projects advancing manufacturing technologies and addressing roadmap development tasks:

✓ = Awarded Project(s) Addressing Development Item(s) ○ = Area Without Projects Addressing Development Items ▭ = No Development Items to be Addressed

Recent Industry Advancements

- Automated image analytics for cell counting, confluence, and characterization
- Defined and xeno-free media and cell culture reagents
- Large-scale bioreactor cell expansion using 3D microcarriers
- In-line, non-destructive sensors; particularly for temperature, pH, and dissolved oxygen
- Artificial intelligence and machine learning
- Novel formulations and production methods for hydrogels, bioinks, 3D printable materials, other scaffold materials
- Electronic Master Control Batch Record and Manufacturing Execution Systems
- Closed system manufacturing platforms and data analyses

SECTIONS OF THE BIOFABUSA TECHNICAL ROADMAP

Cell Culture and Harvest

Scaffold Fabrication

Tissue Maturation and Bioreactor Culture

Preservation, Packaging, and Transport

Cell Culture and Harvest

Living cells are a critical component of most TEMP processes. Cells are commonly used as the foundational building block to produce, maintain, and remodel the tissue matrix and can be considered a key contributor to the regenerative properties of a TEMP. Variabilities exist in the cell source, attributed to factors such as donor source, processing steps, preservation, and manual handling. This variability can be better understood and controlled by developing technologies that monitor CPPs non-invasively, non-destructively, and in real-time as well as by establishing process standards and removing human-factors through automation.

Current technologies are not sufficient to produce TEMPs at the manufacturing scale required to meet the clinical need. Cell culture and harvest technologies must advance to consistently produce quality cellular products using methods that are scalable and cost-effective. Pertinent processes to obtaining cells of sufficient quantity and potency for TEMP manufacture include cell isolation and banking, expansion culture, and cell harvest, wash, and concentration.

CURRENT PROJECTS

PROJECT DESCRIPTION	CROSSCUTTING AREA(S)
Biomanufacturing of Cells in the Neuroectodermal Fate Space	
A Bioreactor for Large-Scale Culture of Anchorage-Dependent Cells with Hollow Microcarriers	
A Novel, Single-Use, and Scalable Bioreactor for Anchorage-Dependent Cell Expansion	
Cell Growth Capsules for High-Speed Bioreactor Culture	
Automated Coating of Cell Culture Surfaces with Growth Factor-Releasing Polyelectrolyte Multilayers	
Development of a Platform for Label-Free High-Throughput Single-Cell Authentication of Induced-Pluripotent Stem Cell Derived Transplants	
Real-time and Label-free Monitoring of Critical Quality Attributes of Engineered Tissues	
Electrochemical Sensors for Process Monitoring of Bioreactors	
Adaptable Multi-Modality Nanoprobes for Non-Invasive Real-Time Monitoring of Engineered Tissues	
Monitoring Tissue Growth Attributes with Bioimpedance Imaging	
Fully Automated Non-Invasive Monitoring System for Validation of Biofabricated Tissues	
An automated High-Throughput Multiplexed Detection Platform for Real-Time Monitoring of Engineered Tissues	
Smart Bioreactor with Wireless, Integrated Soft Hybrid Sensors and Electronics	
Wireless Electrochemical Sensor Capsules for Real-Time Monitoring of Cell Secretomes and Culture Media in Tissue Growth Bioreactors	
Multi-Analyte In-line Sensor for Biomanufacturing Applications Based on Analyte-Responsive Smart Hydrogels	

Core Challenges

- Lack of analytic tools and standards for characterizing raw materials to support supply chain control and flexibility as well as ensure product consistency
- Limited availability of advanced systems and real-time analytic sensors that enable in-process monitoring and adaptive process control
- High cost of goods, particularly media and reagents
- Lack of materials and equipment that enable precise control of physical, biological, and chemical influences during cell culture and harvest processes

HIGH PRIORITY DEVELOPMENT TASKS

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Advance systems and real-time analytic technologies that can identify the phenotypic attributes of adherent cells, and can enrich the intended cell population.	
Develop non-destructive and minimally-invasive methods and technologies to accurately assess CPPs and CQAs in real-time throughout the cell expansion process to support in-process monitoring and control.	
Develop culture platforms that integrate technologies for continuous in-process monitoring of specific CPPs and CQAs of cells.	
Develop technologies to remove undesirable components, maximize cell yield, and concentrate desired cell population during downstream processing (concentrate, wash, and re-suspend cells).	
Develop and implement simple to use, re-usable, and sterile connection systems that can be used in controlled non-classified spaces with standardization as an end goal.	
Develop automated technologies for cell recovery from 2D or 3D culture substrates during harvest that maximizes yield of intended cell populations while maintaining CPPs and CQAs (viability, purity, potency, identity, sterility).	
Develop an automated, cost-effective platform that can be used to culture and expand sufficient quantities of pluripotent, primary, progenitor, and terminally-differentiated cell types for the intended use.	
Develop methods or engineer materials (e.g. surface substrates, chemically defined media, and synthetic growth factors) that reduce the time, increase the repeatability, and decrease the cost of goods required for the differentiation and expansion of homogenous populations of target cell types from primary cell isolates, pluripotent progenitors, or multipotent progenitors.	
Develop low cost, xeno-free methods for the dissociation of adherent cells from tissue culture surfaces that do not affect CQAs.	
Develop label-free, minimally -invasive, and non-destructive adventitious agent (microorganism, mycoplasma, viruses, and endotoxin) in-process monitoring that is as accurate and sensitive as current compendial or rapid sterility tests.	
Develop quantitative methods and technologies to accurately assess cell health, identity, viability, density, number, growth rate, and confluence in real-time throughout the expansion process in 3D culture.	

DEVELOPMENT TASKS

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Engineer scalable culture platforms that automatically monitor, store, and balances specific media components based on feedback from sensors that monitor in-process CPPs and CQAs.	
Engineer technologies that enable precision control of the physical, biological, and chemical parameters impacting cell characteristics during culture and expansion.	
Engineer technologies that enable precision control of the physical, biological, and chemical parameters impacting cell characteristics during cell harvest and concentration.	
Develop automated technologies for cell recovery from tissues that maximize yield of intended cell populations while maintaining CPPs and CQAs (viability, purity, potency, identity, sterility).	
Develop automation that can be used for consistent and high-efficiency reprogramming for the generation of induced Pluripotent Stem Cell (iPSC) lines.	
Engineer technologies capable of filtration and replacement to remove media waste and supplement depleted media components.*	
Enable high-throughput screening of chemically-defined media formulations that generate cell cultures with defined CQAs and reflect cell performance in an in vivo 3D environment.	
Develop an analytical platform and statistical tools that enable rapid identification and validation of CPPs and CQAs to support adaptive process control and predictive modeling.	
Study the effects of common unit operations (e.g., cell concentration) on the CPPS and CQAs in cell culture, especially those that might change during scale-up, scale-out or development of closed processes.	
Develop a standard content and layout for certificate of analysis documents for raw materials (cell, biomaterials, media and reagents) used in the TEMP process.	
Create an informational resource for reference cell lines, including terminally differentiated and progenitor cell types.	
Develop a standard guidance document for evaluating functional bioequivalence of media components (e.g. growth factor and cytokine activities) for replacing animal- and human-derived products.	
Establish standard guidance document(s) for the creation of pluripotent, primary, progenitor, and terminally-differentiated cell banks.	
Establish standards for manufacturing subsystem (e.g., cell isolation, cell culture and expansion, cell harvest and wash) crosstalk and software compatibility.	
Develop modular programming guidelines for biomanufacturing automation systems.	
Develop a standard software platform for automation technologies to ensure quality across multiple TEMPs and reduce overall costs.	

*** = New Task**

Scaffold Fabrication

Biomaterial scaffolds are used as a structural mechanical support and provide cells with mechanical and biochemical cues that guide the behavior of cells residing in or recruited into the biomaterial. The consistency, purity, cost, and safety of the source materials used as the input for the scaffold fabrication process can have a profound impact on downstream performance of the final TEMP. Methods and standards for characterization and production of biomaterials are a baseline requirement for a robust supply chain and efficient quality control for transferable and scalable processes. Pertinent processes for scaffold fabrication include material production/ fabrication, material characterization, and methods for cell incorporation.

Current Projects

PROJECT DESCRIPTION	CROSSCUTTING AREA(S)	
Automated Assembly of Tissues and Organs		
Creation and Characterization of a Biopolymer-Bioink Hybrid Tissue Engineered Vascular Graft		
Bioprocessor Platform for Decellularization & Recellularization		

Progress and Community Update

In collaboration with the Standards Coordinating Body (SCB), ARMI members are participating in standards development for bioprinter hardware (ASME), bioinks (ASTM), bioprinter software (IEEE-SA), fiber-based constructs (ASTM), type I collagen (ASTM), and TEMP terminology (ASTM).

- ASME New Guide for Use of Bioprinters
- New Guide for Bioinks Used in Bioprinting of Tissue Engineered Medical Products (TEMPs)
- ASTM WK72274 - New Test Method for Printability of Bioinks for Extrusion-based Bioprinting
- IEEE-SA P2864 - Guide for a Software Change Control System for Three-Dimensional (3D) Bioprinting of Tissue-Engineered Medical Products (TEMPs)
- ASTM WK70847 - Revision of F2212-11 Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)
- ASTM WK65476 - New Guide for Characterizing Fiber-Based Constructs for Tissue Engineered Medical Products
- ASTM WK71984 - Revision of F2312-11 Standard Terminology Relating to Tissue Engineered Medical Products

Core Challenges

- Minimal availability of high quality raw materials that are well-characterized and consistent batch to batch
- *In situ* process control consideration of mechanical, biological, and chemical properties of the biomaterial throughout the manufacturing cycle
- Predicting *in vivo* scaffold performance
- Development of functionally closed equipment that can be operated in controlled non-classified spaces and is easily interoperable with up- and down-stream processes

HIGH PRIORITY

Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Develop cost-effective methods and toolsets to reliably and reproducibly manufacture purified, well-characterized GMP-grade extracellular matrix (ECM) components for scaffold manufacturing.	
Develop cost-effective methods and toolsets to reliably and reproducibly manufacture complex scaffold from naturally derived sources with known quantifiable bioactive components.*	
Develop terminal sterilization, cost-effective isolator technologies, or aseptic processes to reduce the need for clean-room manufacturing of acellular scaffolds.	
Develop cost-effective isolator technologies or aseptic processes to reduce the need for clean-room manufacturing of cell-containing scaffolds.	
Develop tools and methods for physical manipulation of fragile scaffolds without damaging cells or negatively impacting scaffold properties during production handling.*	
Develop and implement simple to use, reusable, and sterile connection systems for development purposes that can be used in controlled non-classified spaces with standardization as an end goal.	
Launch and maintain an accessible database, analyze and assemble a comprehensive list of physical, biological, and chemical properties of commercially available biological cGMP complaint scaffold materials.*	
Establish standard methods for determination of the mechanical, dimensional, and physiochemical characteristics of biomaterials and biomaterial scaffolds to fill existing standards gaps.	
Develop a standard content and layout for certificate of analysis documents for raw materials (cells, biomaterials, media and reagents) used in the TEMP process.	

*** = New Task**

Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Develop GMP compliant, clean-room ready, functionally closed fabrication equipment for cell containing scaffolds.*	
Formulate cytocompatible bioinks and biomaterials that can be used independent of the additive manufacturing platform.	
Assemble an atlas of tissue characteristic reference ranges in the native environment.*	
Produce a list of ISO-certified manufacturers of polymers and resins suitable for TEMP scaffold manufacturing.	
Develop non-destructive quantitative tools to assess ECM quality.	
Develop real-time, non-destructive technologies to assess the biological properties during the manufacturing process of a scaffold produced from a biological source (e.g. residual cellular content).	
Establish surrogate methods for in vivo testing of biomaterial degradation and new tissue formation.	
Develop reliable, high-throughput methods to determine accelerated aging of biomaterials that can be used in lieu of real-time aging.	
Establish quality and performance standards for biomaterials and bioinks used in TEMP manufacturing.	
Establish standards for manufacturing subsystem (e.g., cell isolation, cell culture and expansion, cell harvest and wash) crosstalk and software compatibility.	
Develop modular programming guidelines for biomanufacturing automation systems.	
Develop a standard software platform for automation technologies to ensure quality across multiple TEMPs and reduce overall costs.	

*** = New Task**

Tissue Maturation and Bioreactor Culture

Maturation of TEMPs *in vitro* prior to implantation necessitates recreating a complex biological environment outside the body. Due to the complexity of culturing specific tissues, tissue bioreactors are often custom-made for each individual product and challenging to scale up or out. Conducting multi-omic analysis and following QbD principles helps to empirically identify a product's CQAs and draw correlations to CPPs that need to be monitored and controlled during the tissue maturation process. This will encourage the maturation of technologies for sensing, monitoring, and streamlining of process development.

Tissue bioreactor technologies need to be scalable and utilize sensor and tracking technology, process models, data analytics, and adopt simplified processes that permit assembly in CNC spaces. Developing a platform technology for tissue culture bioreactors that includes sensors for real-time and non-destructive monitoring and feedback control mechanisms will lead to more consistent, high-quality engineered tissues. Pertinent processes for tissue maturation and bioreactor culture include bioreactor seeding and tissue assembly, tissue maturation culture, and tissue monitoring.

Current Projects

PROJECT DESCRIPTION	CROSSCUTTING AREA(S)
Generalized Biomanufacturing Platform for Dynamic Vascularized Tissues	
Advanced Liver 3-D Tissue Models for Drug Development Applications to Support Toxicology, Drug Metabolism, Target ID, & Pharmacology	
Centralized Fluid Management and Culture Control System	
Opto-Mechanical Characterization of Engineering Tissues for Non-Contact In-Line Process Monitoring	
Non-Destructive Monitoring for Quality Control of Engineered Tissues	
Real-Time and Label-Free Monitoring of Critical Quality Attributes of Engineered Tissues	
Electrochemical Sensors for Process Monitoring of Bioreactors	
Adaptable Multi-Modality Nanoprobes for Non-Invasive Real-Time Monitoring of Engineered Tissues	
Monitoring Tissue Growth Attributes with Bioimpedance Imaging	
Fully Automated Non-Invasive Monitoring System for Validation of Biofabrication	
An Automated High-Throughput Multiplexed Detection platform for real-time Monitoring of Engineered Tissues	
Smart Bioreactor with Wireless, Integrated Soft Hybrid Sensors and Electronics	
Wireless Electrochemical Sensor Capsules for Real-Time Monitoring of Cell Secretomes and Culture Media in Tissue Growth Bioreactors	
Multi-Analyte In-line Sensor for Biomanufacturing Applications Based on Analyte-Responsive Smart Hydrogels	
Differentiation and Monitoring of Mature Liver Organoids for Drug Testing	

Core Challenges

- Understanding the CQAs for engineered tissues and determining CPPs and CMAs that correlate to CQAs
- Integration of in-process analytics capable of monitoring tissue content, structure and function
- Reducing the cost of goods and increasing supply chain security
- Available materials and equipment that enable precise control of physical, biological, and chemical influences during tissue maturation

HIGH PRIORITY

Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Develop a scalable and automated tissue manufacturing platform that maintains sterility but allows for functional modularity such as the integration of in-process analytics, artificial intelligence, and monitoring.	
Develop platform technologies to overcome diffusion limited feeding (e.g. nutrients, oxygen, growth factors) and waste removal.	
Develop non-destructive and non-invasive mechanical testing methods to assess the function of tissues as they mature.	
Develop measurement capabilities for sensing functional biomarkers within the TEMPs.*	
Develop an analytical platform and statistical tools that enable rapid identification and validation of CPPs and CQAs to support adaptive process control and predictive modeling.	

* = New Task

Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Engineer a bioreactor with modularity for use with multiple tissue types and can provide the necessary biological, chemical and physiological stimuli to mature TEMPs.	
Develop bioreactor technologies that are compatible with storage and shipping solutions while supporting sterile transfer.	
Develop and implement simple to use, reusable, and sterile connection systems that can be used in controlled non-classified spaces with standardization as an end goal.	
Develop multiplexed and multimodality sensor platforms for long-term, sensitive, and accurate detection of secreted biomarkers for tissue maturation (e.g., metabolites, lipids and proteins, volatile organic compounds).	
Engineer technologies that permit non-destructive monitoring of viability, cell function, and cell identity in TEMPs.	
Gather and obtain data from multi-omic analysis that supports the development of general bioprocess models that identify process bottlenecks, cost drivers, and space and supply chain constraints.	
Adapt and coordinate storage, management, processing, and big data analytic tools to facilitate the adoption of QbD principles during all stages of process development and product lifecycle management.	
Adopt Failure Mode and Effect Analysis (FMEA) principles for TEMPs.	
Develop a standard content and layout for certificate of analysis documents for raw materials (cell, biomaterials, media and reagents) used in the TEMP process.	
Establish standards for manufacturing subsystem (e.g., cell isolation, cell culture and expansion, cell harvest and wash) crosstalk and software compatibility.	
Develop modular programming guidelines for biomanufacturing automation systems.	
Develop a standard software platform for automation technologies to ensure quality across multiple TEMPs and reduce overall costs.	

*** = New Task**

Preservation, Packaging, and Transport

A living tissue needs to maintain the CQAs throughout preservation, packaging, and transport to the patient. Cryogenic processes are commonly used, however, this presents challenges in maintaining cell viability and tissue structural integrity. Furthermore, cryogenic preservation requires stringent control over logistics and is susceptible to transient warming and accidental temperature excursions. Preservation at ambient and non-freezing temperatures is considered to be lower risk and more cost-effective.

Maintaining ambient and non-freezing conditions presents challenges in controlling cellular metabolism and activity, and in maintaining cellular identity and viability. Cell recovery following preservation processes is highly variable as a result of a large number of manual processes, as well as custom preservation media and protocols. Preservation, packaging and transport would benefit from a resource on best practices as well as process automation where applicable. Pertinent processes for preservation, packaging, and transport include tissue processing, preservation, storage, packaging, shipping, and logistics design.

Current Projects

PROJECT DESCRIPTION	CROSSCUTTING AREA(S)
Cryopreservation Systems to Preserve Manufactured Tissue Function	 
Supply Chain and Process Modeling Algorithms, Methods, and Tools for Tissue Bio-fabrication and Distribution	

Core Challenges

- Development of standardized package, storage and shipping solutions streamlined for the unique needs of tissue manufacturers and clinical end users
- Controlling and tracking active physiologic conditions during storage and shipping in TEMP-appropriate containers
- Logistically flexible preservation technologies that maintain TEMP critical quality attributes
- Increasing product stability in non-cryogenic solutions
- Identification and validation of alternative biopreservation solutions and reagents that can improve TEMP viability and function

KEY = Raw Materials = Equipment and Software = Automation = Measurement and Data Management = Preservation, Storage and Transport = Processes and Quality Systems = Standards

HIGH PRIORITY
Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Conduct a gap assessment of current best practices and available technologies for packaging and shipping tissues.*	
Identify user requirements and methods for biopreservation that enhance stability, consistency, and recovery of TEMPs that can be reliably executed by clinical personnel receiving and processing for patients.	
Establish standard guidelines for the preservation, transport, storage, and post-preservation processing of engineered tissue.	

* = New Task

Development Tasks

DEVELOPMENT TASKS	CROSSCUTTING AREA(S)
Develop packaging for ambient to physiologic transport capable of controlling physical conditions (perfusion, fluid movement, and mechanical load) and monitoring cell viability and tissue quality during shipping.	
Develop bioreactor technologies that enable TEMP maturation in a system that is compatible with sterile storage and shipping and requirements from the end user and point of care use.	
Develop an automated process for packaging of TEMPs that can be completed in controlled non-classified spaces.	
Identify and validate non-toxic, chemically-defined preservation media formulations and methods of use.	
Develop methods and formulations for preservation and storage of cells and TEMPs at ambient temperature that maintain final product CQAs.	
Screen for molecules that regulate the metabolic rate of cells during preservation.	
Identify biophysical, chemical, and biological factors for cell and tissue cryotolerance to direct the development of preservation methods.	
Develop a standard format for certificate of analysis documents for raw materials used in the TEMP process.	
Establish standards for manufacturing subsystem (e.g., cell isolation, cell culture and expansion, cell harvest and wash) crosstalk and software compatibility.	
Develop modular programming guidelines for biomanufacturing automation systems.	
Develop a standard software platform for automation technologies to ensure quality across multiple TEMPs and reduce overall costs.	

Appendix

ABBREVIATIONS

ARMI: Advanced Regenerative Manufacturing Institute

CFC: Counterflow Centrifuge

CNC: Controlled Non Classified

CPP: Critical Process Parameter

CQA: Critical Quality Attribute

DoD: Department of Defense

EWD: Education and Workforce Development

FMEA: Failure Mode and Effects Analysis

GMP: Good Manufacturing Process

iPSC: induced Pluripotent Stem Cell

ISO: International Organization for Standardization

IT: Information Technology

QbD: Quality by Design

QTPP: Quality Target Product Profile

R&D: Research and Development

RMAT: Regenerative Medicine Advanced Therapy

SDO: Standards Development Organization

TEMP: Tissue Engineered Medical Product

TERM: Tissue Engineering and Regenerative Medicine

GLOSSARY OF TERMS

Biomaterial: Any substance (other than a drug), synthetic or natural, that can be used as a system or part of a system that treats, augments, or replaces any tissue, organ, or function of the body.

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. [1]

Critical Quality Attribute (CQAs): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[1] E.g. properties or characteristics that affect viability, purity, activity, identity, sterility.

Culture vessel: Container used for the culture and expansion of cells, e.g. tissue culture flask, hyper-stack, stir-tank bioreactor, vertical-wheel bioreactor.

Impact: The extent to which addressing this need could improve quality, scalability, consistency, time to market, and cost.

Minimally invasive test: Method or technique used to detect and evaluate quality attributes in a system. Method or technique may make contact with the material or system but would not expose the system to contamination risk during use. Method or technique would not disturb or invade the operation of the system. E.g. sterilizable in-line sensors and sterile sample extraction to an at-line sensor, electrochemical sensor

Non-destructive test: Method or technique used to detect and evaluate quality attributes in a material or system without impacting the overall process.[2] The measurement will not destroy the sample; as such one can continue with further processes or activities.

Non-invasive test: Method or technique used to detect and evaluate quality attributes in a material or system with no interaction between the sensor and the sample. E.g. optical, impedance measurement

Quality by Design: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. [1]

Reagents: Defined broadly to include all substances needed to harvest, culture, and expand cells and tissues, as well as any substances used in the manufacture of biomaterials.

Real-time measurement: A measurement occurring immediately, without delay, or at a high enough frequency that provides the current dynamics of the system being measured. A measurement occurring on demand or immediately.

Timeline: Cost and the time that it will take to complete; considering the urgency, need to act now vs. later.

Tissue bioreactor: Container used for the culture and maturation of a biological tissue, e.g. tissue loader, tissue mounting or fixation system, fluid transport or exchange system.

Tissue Engineered Medical Product (TEMP): A medical product that repairs, modifies or regenerates the recipient's cells, tissues, and organs or their structure and function, or both. [3]

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[1] International Council for Harmonization. "Pharmaceutical Development: Q8(R2)," 2009.
[2] Modified from ASTM Nondestructive Testing Standard. Retrieved from https://www.astm.org/Standards/nondestructive-testing-standards.html
[3] ASTM International Designation F2312-11. "Standard Terminology Relating to Tissue Engineered Medical Products"

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