Cell Characterization and Scalable Manufacturing

Assuring Quality Control and Improving Access for Cell Therapies

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CONSORTIUM

Georgia Tech

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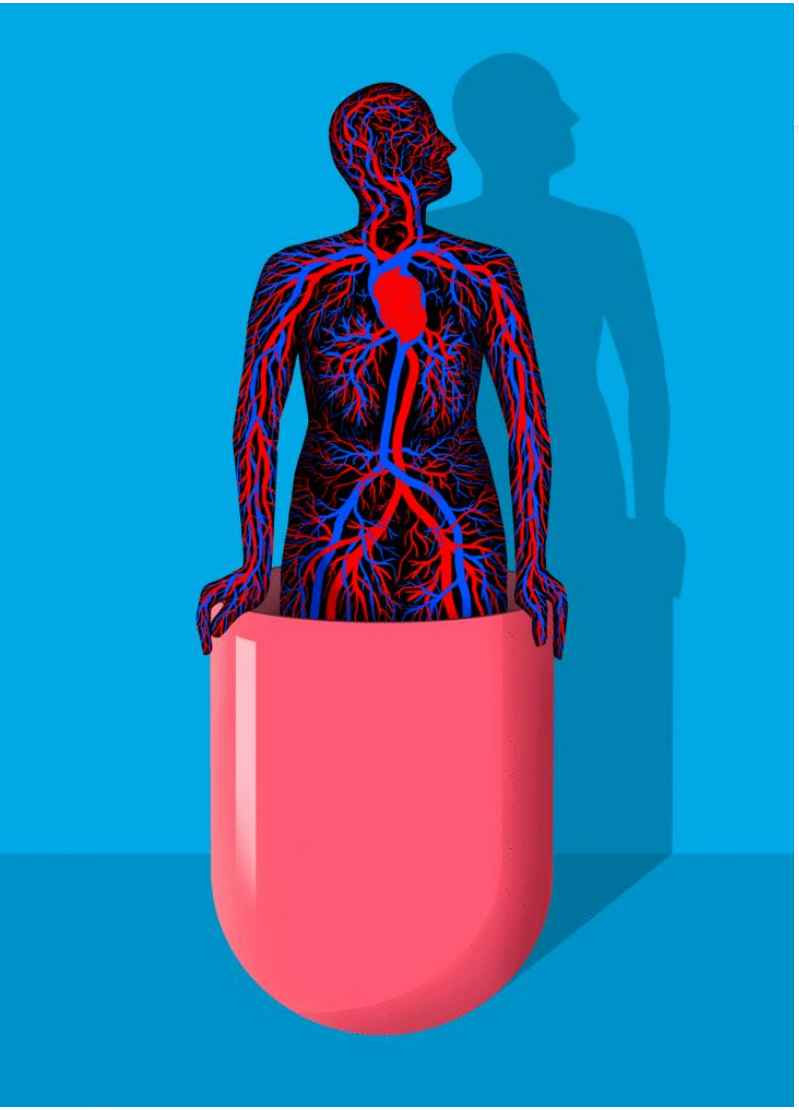


THE NEW YORKER

THE PROMISE AND PRICE OF CELLULAR THERAPIES

New "living drugs"—made from a patient's own cells—can cure once incurable cancers. But can we afford them?

By Siddhartha Mukherjee July 15, 2019

"The estimated cost to manufacture a typical CAR-T infusion is close to six figures. In short, even if CAR-T therapy were offered with no margin of profit, it would still rank with some of the most expensive procedures in medicine."

"Extracting cells from an individual patient, purifying them, genetically modifying them, and expanding their numbers into the millions will never be akin to churning out amoxicillin in a factory."

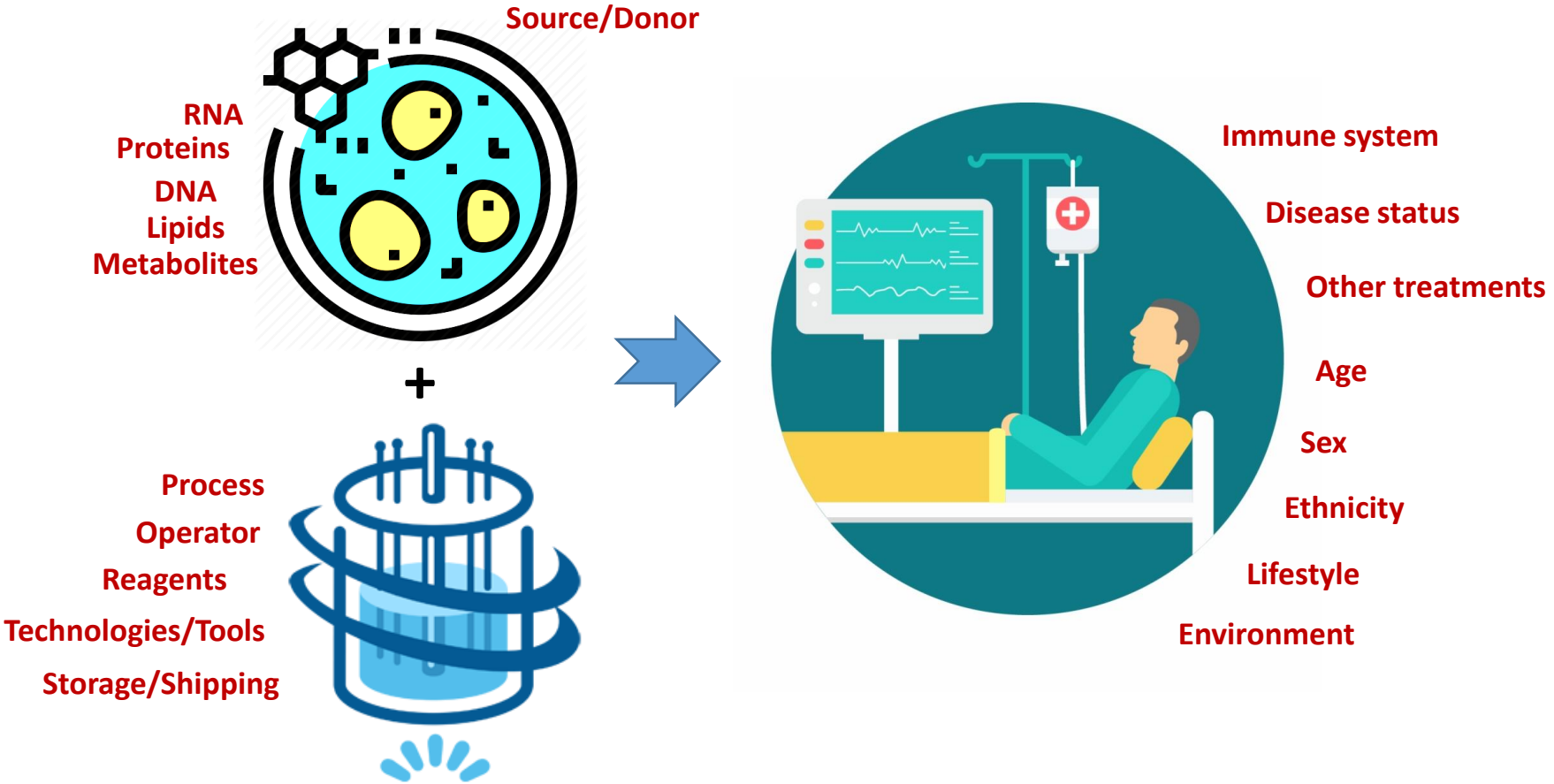
The Major Challenge

Reproducible manufacture of cells at large scale, with consistent, predictive, and therapeutic quality, at low cost

The FUNDAMENTAL Barrier

The product (cell) is a living entity, often a mixture of different cell types with poorly understood function - whose properties can "change" with every manipulation… throughout the manufacturing process

Cell Therapy: Interaction of Multiscale Complex Systems



The Roadmap: Industry-driven, Ambitious, and Detailed

The National Cell Manufacturing Roadmap formally released to public on June 13, 2016 *by the White House Office of Science, Technology and Policy (OSTP)* – ***Updated Summer 2017, Another Update underway***

Complete Roadmap Available at www.cellmanufacturingusa.org

National Cell Manufacturing Consortium

Manufacturing Challenges Faced by the Cell Therapy Industry

Quality

- **Current QC/QA concepts** are mostly unrelated to cell function in patients
- **Mechanisms of Actions (MOAs)** are complex and difficult to ascertain → Especially why, when, and in which patients the therapy might work
- **Critical Quality Attributes (CQAs)** to maximize function (efficacy and safety) are likely to be multivariate and disease/patient specific – and mostly unknown

Quality

- **Critical Process Parameters (CPPS)** that ensures CQAs are met after manufacturing, are complex and difficult to develop – manufacturing a "living" product
- Nascent and very risky **supply chain**
- **Donor and Patient Variability**
- **Product reproducibility and comparability** are often poor
- **Lack of Trained workforce**

Quality

- **QA/QC** is performed at the end of the process – little in-process or real time QC
- **Release assays** are long and often physiologically and functionally irrelevant
- **Standards**, best practices are only starting
- **Rigid** processes and automation
- **TIME and resources**

Opportunities in Cell Manufacturing CMC

Quality

- **Data Science** integration into QC and process, for CQAs, CPPs, custody, design. **HUGE opportunity for BIG DATA, AI, and DATA SCIENCE**
- **Real-time monitoring** and predictive analytics
- **Rapid, physiologically relevant potency assays**
- **Standards**, best practices
- Quality-by-Design (**QbD**) and **Flexible Automation**

Speed

- Develop **faster and more efficient** bioprocesses
- **Lower failure** rate
- **Faster batch release**
- Readily available, highly trained, and diverse **workforce**

Agility

- **"What if" models in supply chain and logistics**
- **Nimble operation and adaptability** to changing science and industry

Cost

- **Lower** failure **risk** and supply-chain risk
- **Reduced** need for **scale-up** through maximizing quality
- Lower cost through **maximizing safety**
- Readily available highly trained, and diverse **workforce**
- **Flexible, Quality-controlled Automation**

Can better Characterization Manufacturing and Control (CMC) improve access?

- **Address cost and access across the world** regardless of socio-economic status or race or country?
- **Extremely high risk product for industry** → can we **reduce risk** by reducing batch failure, predicting efficacy and safety, understanding CQAs and CPPs, and ensuring reproducibility
- **Why do we need billions of cells?** → Quality vs Quantity
- **Reduce COGS** → reproducibility, automation, CPPs, trained workforce, Scale, Allogeneic
- **Should regulatory agencies think differently?** How do we figure out comparability – process and products, without re-doing everything?
- **Standards, best-practices, pre-competitive advancements**

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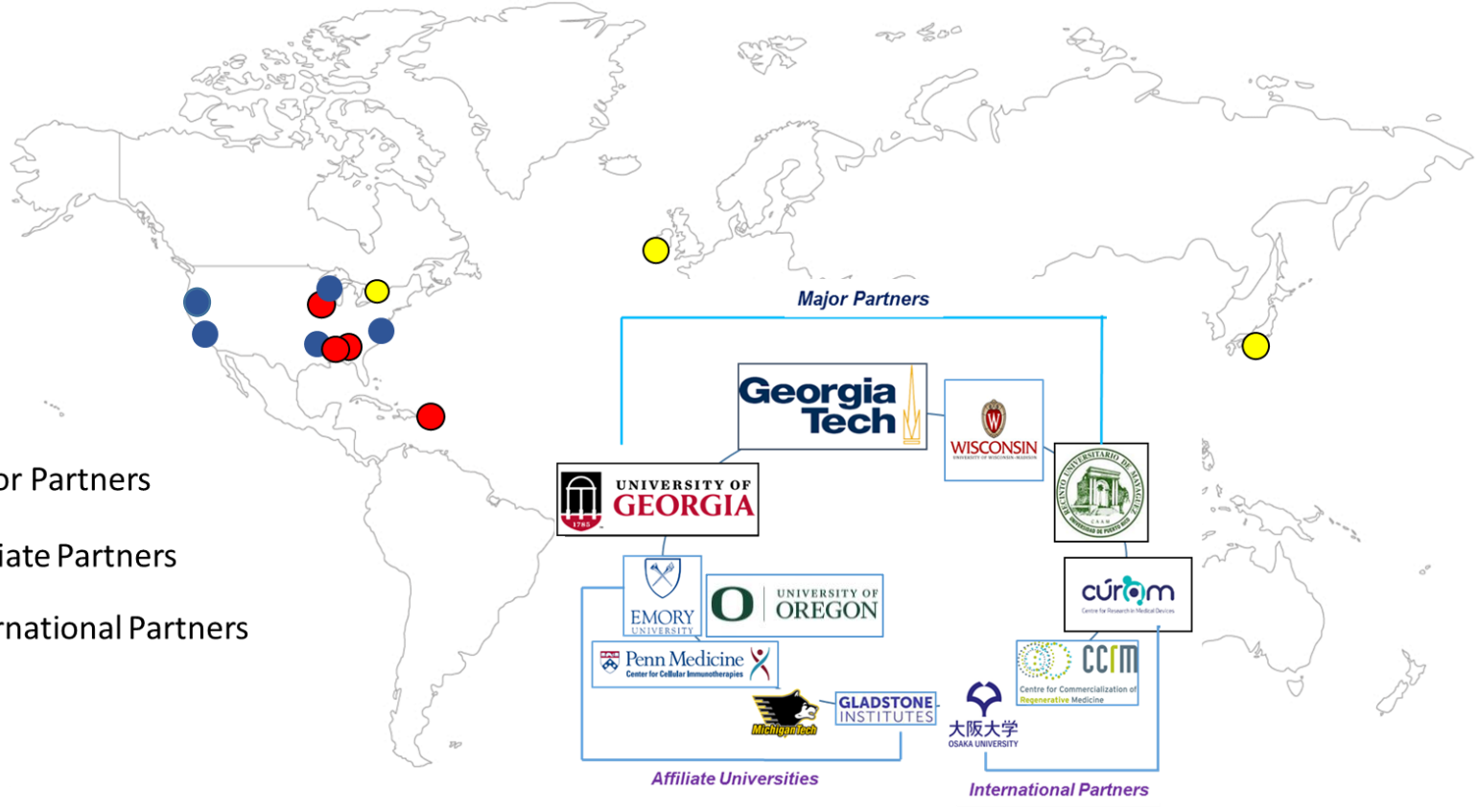
for Cell Manufacturing Technologies

A National Center on Cell Manufacturing Technologies

www.cellmanufacturingusa.org

Up to $40 million over 10 years



At Georgia Tech -
The Philanthropy-funded and State-funded Arm

Georgia Tech **Marcus Center for Therapeutic Cell Characterization and Manufacturing**

www

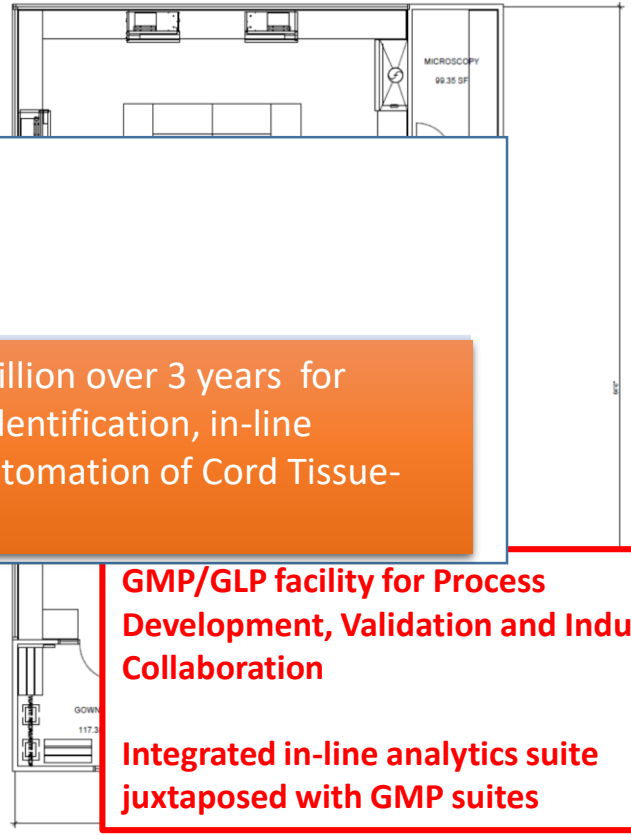
- **Formally**
- Collabora
- **Key Goal** facilitate therapeu
- **$23 milli**
  - **$15.75 million** from the Marcus Foundation
  - **$1 million** from the Georgia Research Alliance
  - **$6.25 million** from Georgia Tech
    - Including **$5 million for new faculty hiring**
- **$5 million State Bond Funding in 2018**

FDA In Brief: FDA awards grants to foster innovation for advanced manufacturing technology as part of the agency's efforts to ensure a robust and reliable supply of biological products

SHARE TWEET LINKEDIN PIN IT

September 20, 2018

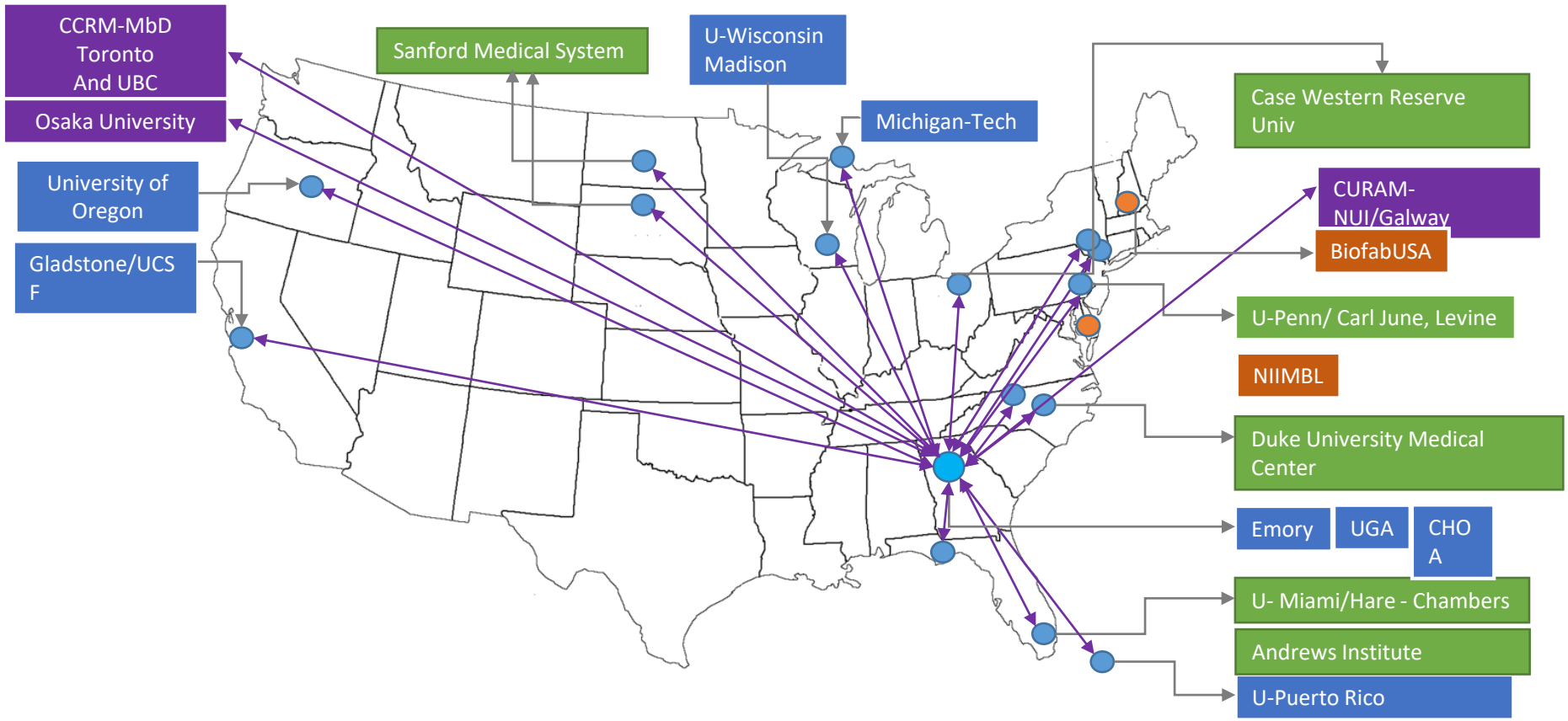
New R01 from FDA, $1.8 million over 3 years for scalable production, CQA identification, in-line monitoring, and process automation of Cord Tissue-derived MSCs



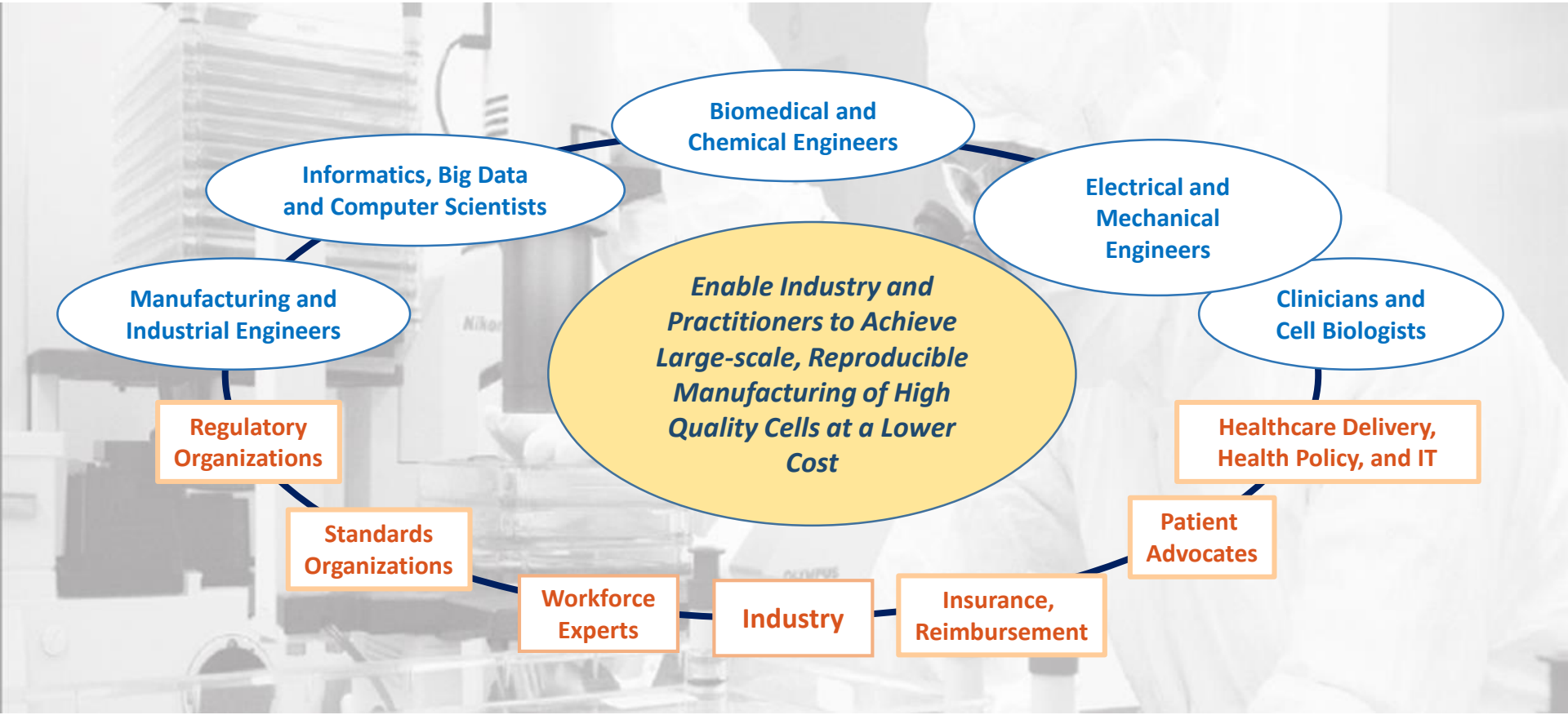
GMP/GLP facility for Process Development, Validation and Industry Collaboration

Integrated in-line analytics suite juxtaposed with GMP suites

Building an Internal Coalition of Academic and Clinical R&D Partners: CMaT + Marcus Center



Working Together – Without Boundaries



CMaT and MC3M: The Overall Vision

Engineered System Testbeds
MSCs for Regenerative Medicine
CAR-T Cells for Cancer Immunotherapy
iPSC-Derived Cardiomyocytes for Cardiac Regeneration

Thrust 1: Cell-Omics: Cell Characterization and

low cost, and at large scale?
- Integrated In-line Sensors and Assays
- Biomaterials for Cell Expansion
- Massively Parallel Microfluidic and Millifluidic Bioreactors for Scale-out
- Integration of Process Control and Modeling
- Supply Chain Management

Test-Bed 1: MSCs for Regenerative Medicine

The Innovati… Ecosystem
- *National Cell Manufacturing Consortium (NC…*
- *Marcus Founda… Infrastructure*
- *National Institu… Standards and Technology (NI…*
- *Industry and Cl… GMP Partners*
- *Entrepreneursh… and Translation… Enterprises*

NSF Feedback Advisory Boards FDA, SCB, NIST State Investments Professional Societies NIIMBL / BioFabUSA

Strengthen Industry Foundation & Transform Cell Therapies

New Innovations and Tools
- Predictive Biomarkers
- In-line Cell Sensors
- …
- …says, QC/QA
- …tational Models
- …p/Scale-out
- …cess Modeling
- …agement

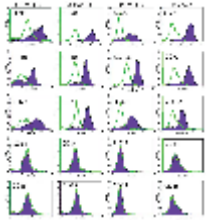
…ization, … Support
- …ools within the …work
- …Process Standards
- …ndards

…evelopment
- …t-Graduate Education
- Technical Colleges, Veterans
- Students with Disabilities
- Entrepreneurship
- Cross-Industry Collaborations
- Inclusive Workforce

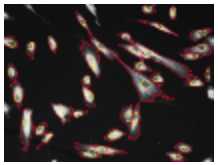
Research Strategic Goal: *To achieve (a)* ***Quality-by-Design (QbD)-enabled, lower-cost manufacturing****, and (b)* ***robust, lower-risk supply chain logistics*** *for cell-based therapeutics at an industrial scale.*

Deep characterization: “Cell Fingerprint”

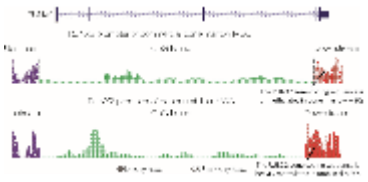
Surface Markers



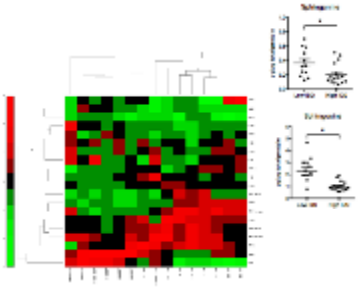
Morphology and
High-content Imaging



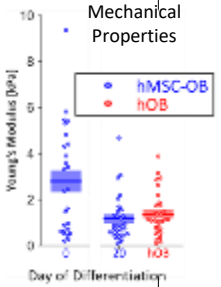
Epigenome

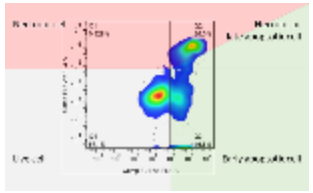


Lipidome



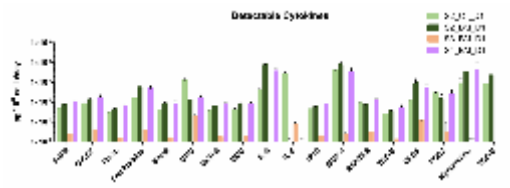
Mechanical
Properties



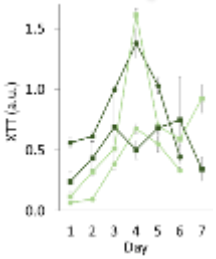


Apoptotic/Necrotic Marker
Viability

Surrogate Potency

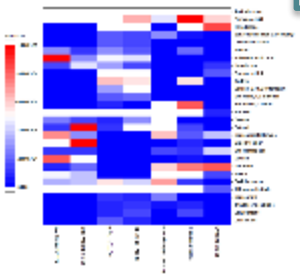


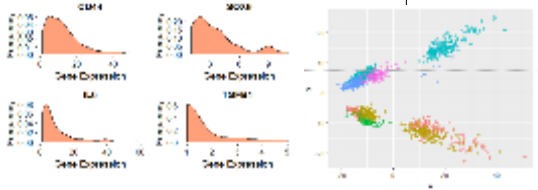
Secretome/Proteome



Metabolic activity

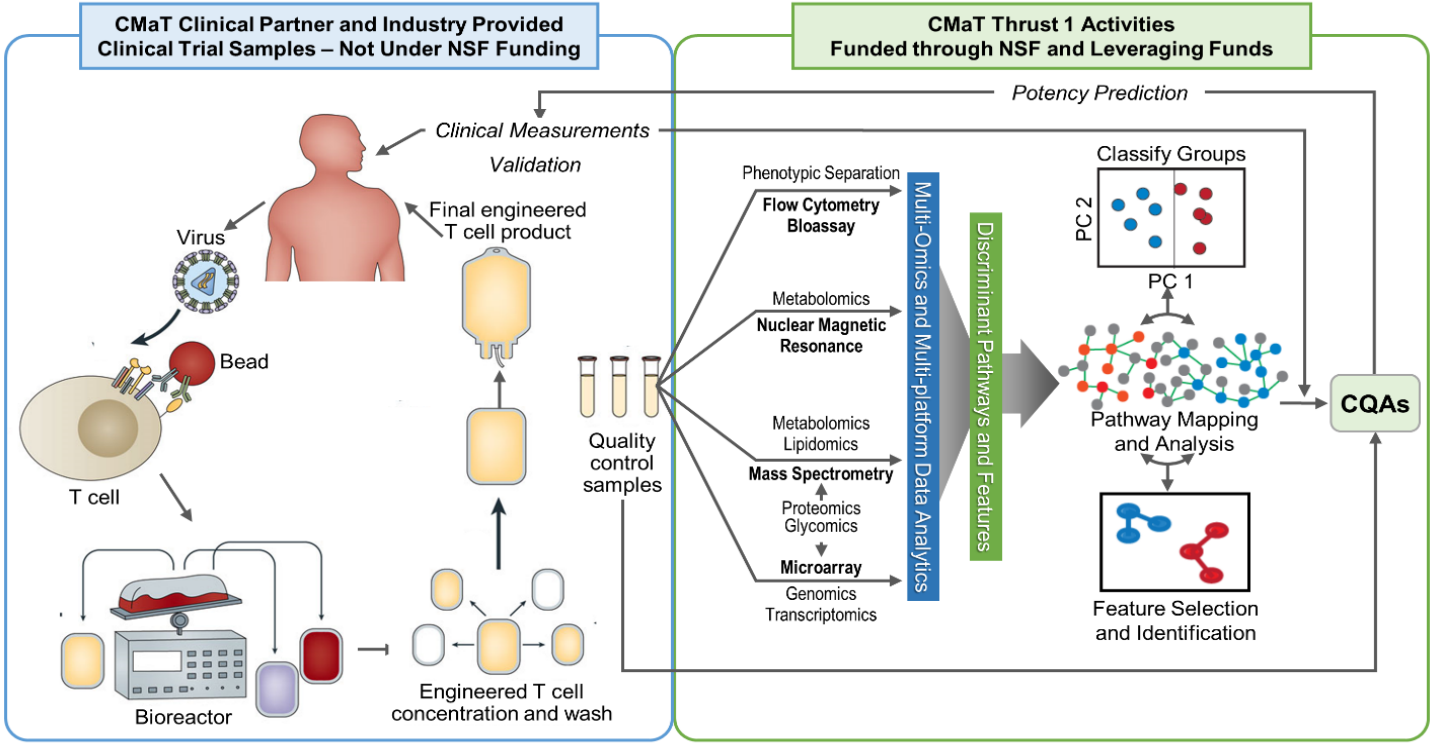
Metabolome





Single cell transcriptome

Getting to CQAs and CPPs for Cell Manufacturing: The Big Data Approach, "Fingerprinting" the cells



Key Features

- **Multivariate quality discriminators** rather than universal biomarkers
- **Non-linear Models, Machine learning, Deep learning and AI to extract CQAs and CPPs from "Cell Fingerprints" and outcome data**
- **Clear integration of clinical partners** and samples in discovery process
  - In CMaT
  - Marcus Network

Research Focus: New Enabling Technologies

Assays and Sensors for Non-destructive Evaluation (NDE) of Cell Properties

- **Imaging-based sensors** → Machine Learning /AI; Combining with Lipidomics
- Rapid, small-sample assays for potency-relevant markers → Single Cell Assays, Single Cell-cell interaction assays
- In-line, real time monitoring of cells in culture – **Flexible Electronics Sensors**
- **How to automate these** and **build these in-line with the manufacturing process**

Efficacy and Safety assays that better mimic human organs and diseases

- **Organ-on-a-chip or Tissue-on-a-chip** using patient-derived cells
- 3D, Mimics human physiology and immunology
- Can make patient-specific tissues
- Validate using animal experiments and clinical trial data

Research Focus: Automation

Regardless of Point-of-care manufacturing, distributed manufacturing, or centralized

- **CQA and Potency driven Automation**
- **Built-in Sensors/Measurements**
  - Rapid, non-destructive or minimally destructive (small samples), near real-time analyses
- **Feedback Control of Process**
  - NOT just a closed system device, a CLOSED LOOP device
- **FLEXIBLE AUTOMATION → Adjust process according to quality**
- **Live cell transport with continuous quality monitoring?**

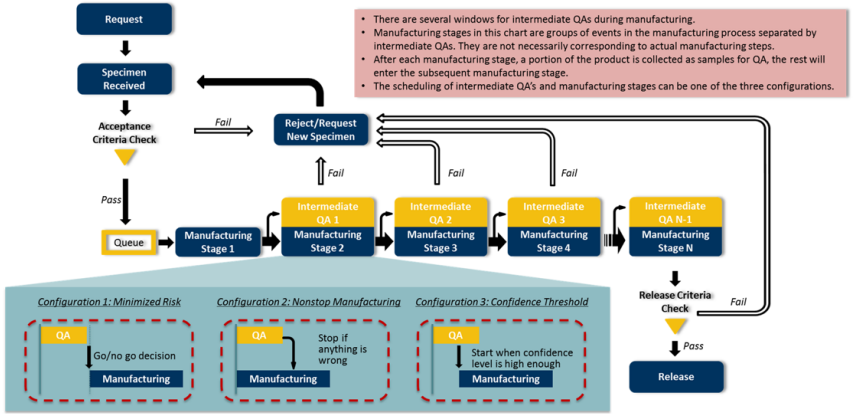
Ultimately as we understand the process, need for measurements/sensors goes down or becomes unnecessary; further reducing cost without compromising quality → Enabling QbD

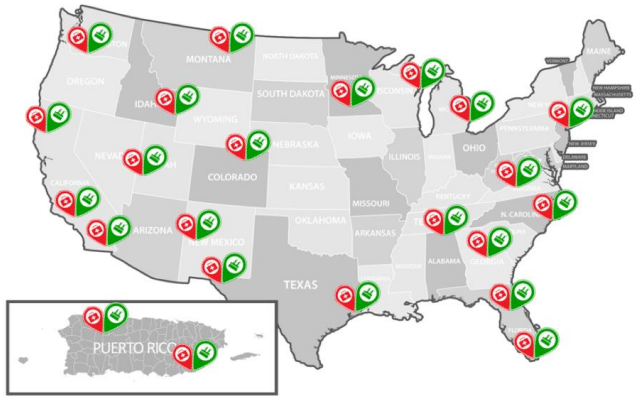
Research Focus Areas: Scalability

Rapid, large scale, low cost, high quality

- **Bioreactor Technologies and Biomaterials**
  - Learn from the body → Physiologically driven designs
- **Supply-Chain Management**
  - Critical to reduce raw material variability
- **Manufacturing Process Development**
  - Increase efficiency and workflow
- **Data-driven Manufacturing**
  - Continuous feedback of process parameters into models for improvement
  - Integration of data from end-to-end (needle-to-needle)
  - Big data processing techniques
  - Chain of custody

Unique Supply Chain Models





Developing Standards and International Policies

- **Standards Coordinating Body (SCB) for Cell Therapies and Regenerative Medicine → Industry, Academia, NIST and other stakeholders**
  - **https://www.standardscoordinatingbody.org**

STANDARDS COORDINATING BODY

  - **ISO, ASTM Activities**
  - **FDA-NIST → 21st Century CURE Act**
- **Newly-formed National Academies' Forum on Regenerative Medicine → Industry, Academia, Patient Advocates, Policy Experts, FDA, NIST, NIH**
- **Vatican Conference on Cell Therapies -** Presentation on Barriers and Solutions for Cell Manufacturing
- **Numerous Industry Forums**

Standards Development
CMaT and MC3M Involvement

*CMaT and MC3M are **working with key standards organizations and NIST** to develop best practices, white papers, documents, and early standards in the field.*

STANDARDS COORDINATING BODY

STANDARDS ADVANCEMENT PROJECT

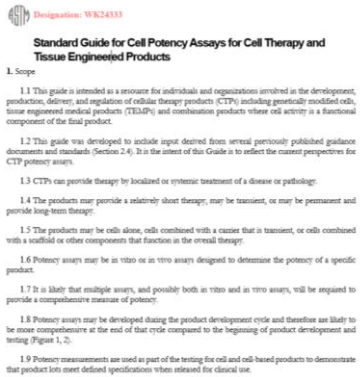
Anticipated Availability: November 2020

Characterization of Human Cells for Therapeutic Use

Project Partners: ISO/TC 276 U.S. Working Group 3 (WG3), National Institute of Standards and Technology (NIST)

The manufacturing of cell therapy products requires a complex mix of not only living cells but also active or inactive media and ancillary materials. Assessing and characterizing the critical quality attributes—identity, purity, biological activity, and viability—of all aspects of a cell preparation can offer greater insight into how these components will interact, as well as greater predictability of the impacts of processing changes throughout the manufacturing process on the final product. Developing standards for this characterization will allow product developers to create analytical tools optimized for assessing cell quality and consistency, thereby ensuring the safety and efficacy of cell therapy products.

SCB is coordinating U.S. efforts to develop an ISO documentary standard on the characterization of cell therapy products that defines relevant cell characterization terms, processes to define critical quality attributes, and approaches to select and design fit-for-purpose measurements.



Designation: WK24333

Standard Guide for Cell Potency Assays for Cell Therapy and Tissue Engineered Products

1. Scope

1.1 This guide is intended as a resource for individuals and organizations involved in the development, production, delivery, and regulation of cellular therapy products (CTPs) including genetically modified cells, tissue engineered medical products (TEMPs) and combination products whose cell activity is a functional component of the final product.

1.2 This guide was developed to include input desired from several previously published guidance documents and standards (Section 2.4). It is the intent of this Guide is to reflect the current perspectives for CTP potency assays.

1.3 CTPs can provide therapy by localized or systemic treatment of a disease or pathology.

1.4 The products may provide a relatively short therapy, may be transient, or may be permanent and provide long-term therapy.

1.5 The products may be cells alone, cells combined with a carrier that is transient, or cells combined with a scaffold or other components that function in the overall therapy.

1.6 Potency assays may be in vitro or in vivo assays designed to determine the potency of a specific product.

1.7 It is likely that multiple assays, and possibly both in vitro and in vivo assays, will be required to provide a comprehensive measure of potency.

1.8 Potency assays may be developed during the product development cycle and therefore are likely to be more comprehensive at the end of that cycle compared to the beginning of product development and testing (Figure 1, 2).

1.9 Potency measurements are used as part of the testing for cell and cell-based products to demonstrate that product lots meet defined specifications when released for clinical use.

STANDARDS COORDINATING BODY

STANDARDS ADVANCEMENT PROJECT

Anticipated Availability: 2021-2023

Rapid Microbial Testing Methods (RMTM)

Project Partners: National Institute of Standards and Technology (NIST), BioFabUSA, the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), ISO/TC 276, ASTM International Committee F04, and the SCB Cell Therapy Sector Working Group

Current methods for detecting the presence of viable microbes in a commercially manufactured cell or gene therapy product have a number of limitations, including requiring too much time to yield relevant results, an inability to detect certain microbes, and unsuitability for large product volumes due to high cost and time requirements. While rapid microbial test methods are critical for assessing the quality and safety of regenerative medicine products, many are not suitable for testing cell and gene therapies. Developing standards for identifying and validating fast, efficient, and reliable testing methods will help manufacturers better assess the quality and safety of products and allow treatments to be administered more quickly.

SCB established an RMTM working group and is coordinating its support of three separate standards advancement efforts. There are 27 individuals in the working group, representing 5 academic institutions, 3 government institutions, and 11 industry organizations.

STANDARDS COORDINATING BODY

STANDARDS ADVANCEMENT PROJECT

Anticipated Availability: December 2021

Requirements for Cell Therapy Manufacturing Equipment

Project Partners: ISO/TC 276 U.S. Working Group 4 (WG4), National Institute of Standards and Technology (NIST), and the SCB Cell Therapy Sector Working Group

Variations in manufacturing equipment and processing techniques across regenerative medicine advanced therapies development make it difficult to evaluate and ensure consistent product quality and safety. Minimum technical and operational requirements and general considerations for cell therapy manufacturing systems—including hardware and software—will allow product developers to assess the impact of manufacturing changes or innovations on their products and will enable cross-comparison of products developed in different locations or by different companies.

SCB is coordinating the U.S. effort to develop an ISO documentary standard that defines relevant cell therapy manufacturing terms, minimum equipment requirements, and general considerations for equipment involved in cell procurement, isolation/selection, expansion, washing and volume reduction, in-line monitoring, and cryopreservation.

ASTM INTERNATIONAL

CMaT and MC3M to host the ASTM E55 Fall 2019 Meeting in Atlanta with focus on cell therapy standards