Engineering Research Center for Cell Manufacturing Technologies (CMaT)

Georgia Institute of Technology (lead institution)

Working together to enable large-scale manufacturing of high-quality cell therapies

A National Science Foundation Engineering Research Center since 2017

Partner Institutions:

- University of Georgia
- University of Wisconsin-Madison
- University of Puerto Rico at Mayagüez

CMaT's vision is to transform the manufacture of cell-based therapeutics into a large-scale, low-cost, reproducible, and high-quality engineered process for broad industry and clinical use. CMaT will be a visionary and strategic international resource and an exemplar for developing new knowledge, innovative technologies, a diverse workforce, and enabling standards for cell production and characterization processes. This convergent center brings together engineers with wide-ranging expertise including biomedical engineers, chemical engineers, mechanical engineers, electrical engineers, and industrial and manufacturing systems engineers. They will work closely with cell biologists and clinicians as well as ethics, policy, and workforce development experts alongside industry partners to create new fundamental knowledge and to invent and translate new and transformative tools and technologies for affordable, reproducible, and high-quality cell production. Throughout this effort, CMaT will develop and disseminate best practices and standards to all stakeholders in the cell manufacturing ecosystem.

There are three Engineered Systems (Test-Beds) in CMaT:

- Mesenchymal Stromal Cells (MSCs) to repair diseased tissues and organs
- T cell immunotherapies to cure cancer
- Induced Pluripotent Stem Cell-derived Cardiac Cells (iPSC-CMs) to treat heart diseases.

In each of these Test-Beds, CMaT focuses on three synergistic technical innovation thrusts (see Figure 1):

- ***Thrust 1*: Deep cell characterization to determine Critical Quality Attributes (CQAs) – What to measure for quality?
- ***Thrust 2*: Rapid and reliable assessment of CQAs, in-line, during manufacturing – How to measure quality?
- ***Thrust 3*: Process and systems engineering for large scale, reproducible manufacturing of high quality cells – How to scale?

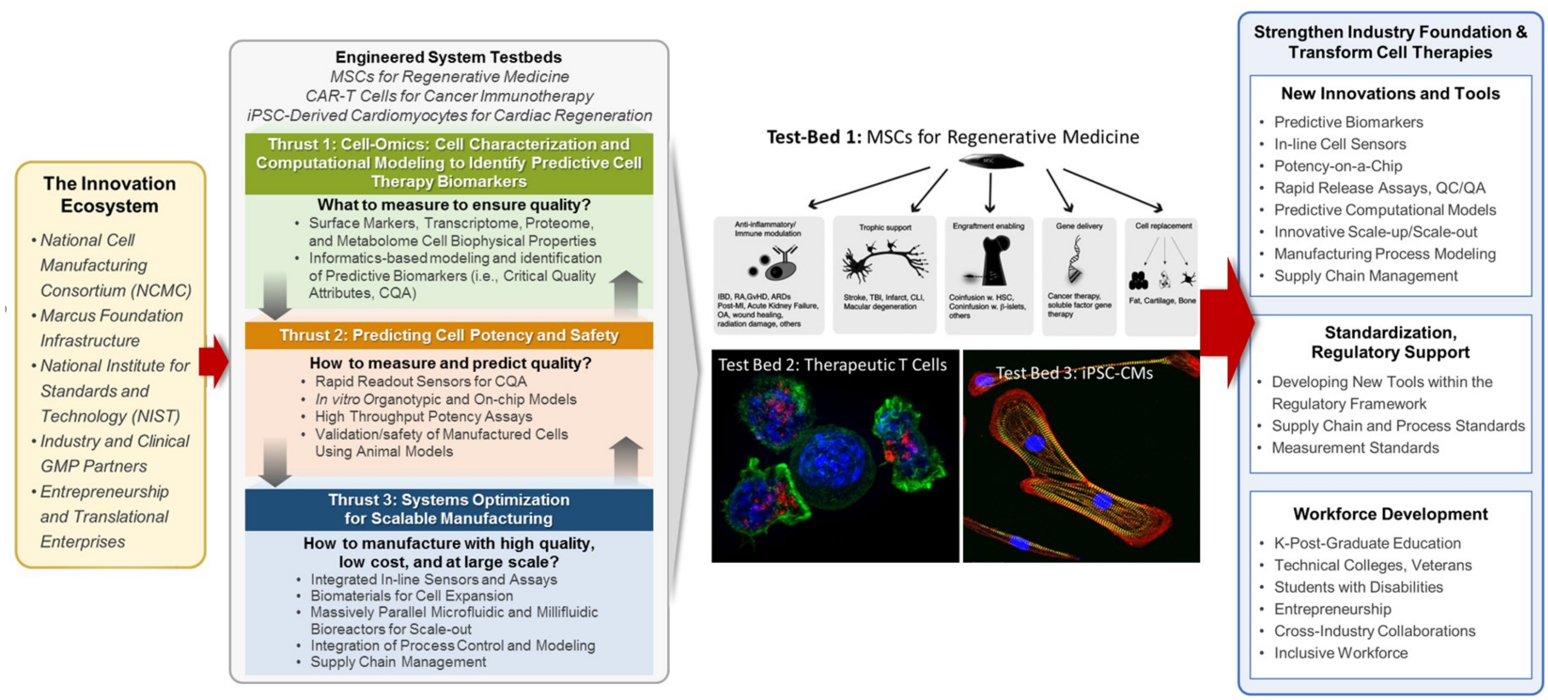

Figure 1: The Ecosystem, Overall Strategic Plan, and Outcomes of CMaT

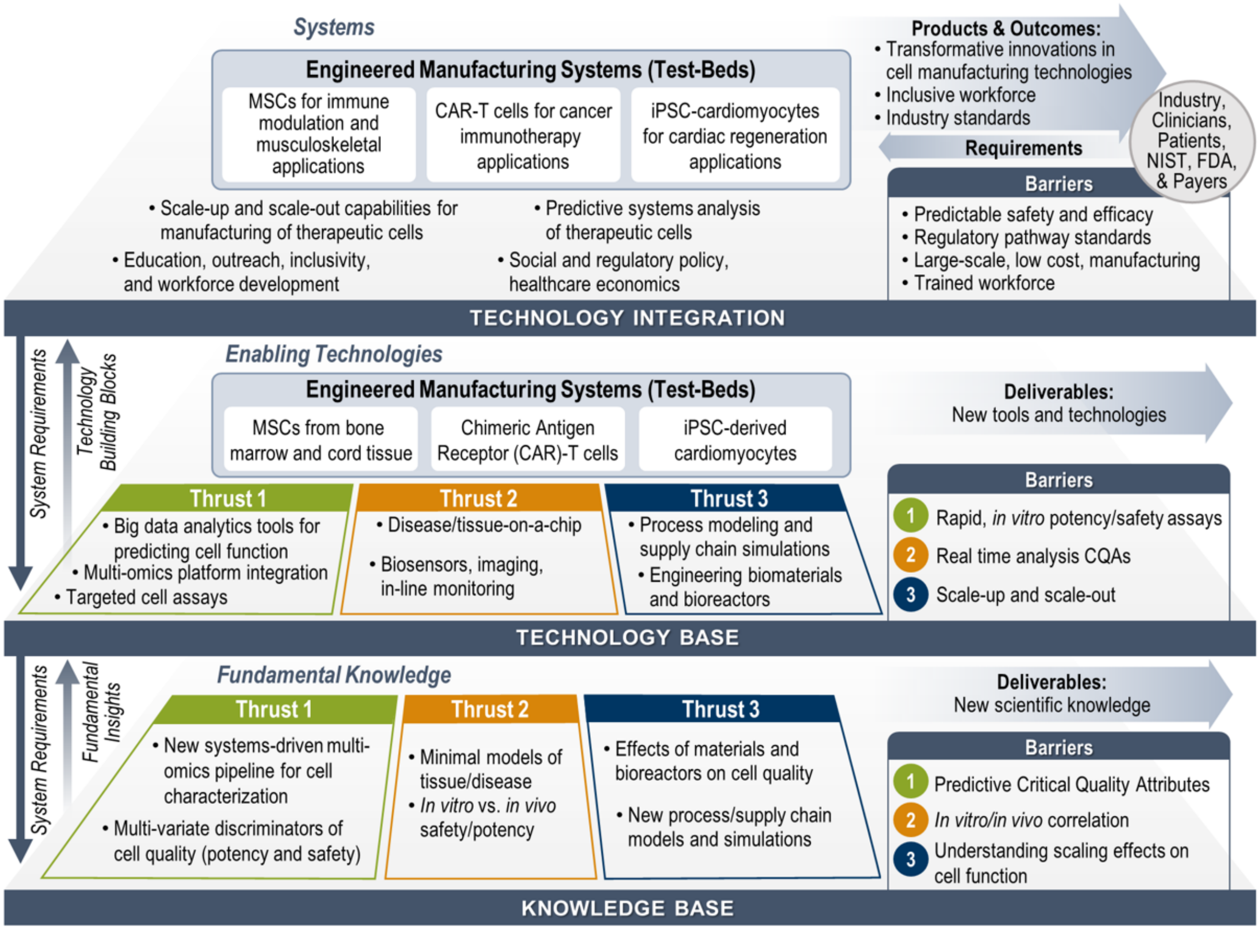

Figure 2: CMaT's ERC 3-Plane Chart

A key need for industry and practitioners in cell manufacturing is a diverse, well-trained workforce—both entry-level trainees and advanced-degree trainees. CMaT's workforce development program is designed to achieve four overarching goals:

1. Train a diverse group of undergraduate and graduate engineers with key technical and professional skills
2. Prepare technical college and pre-college students for careers in biomanufacturing industry
3. Use excitement surrounding cell therapies to stimulate interest in research career pathways
4. Expand the education of students from underrepresented non-normative groups (e.g., veterans, students with disabilities).

Research Scientist Sommer Durham and Research Technician Naima Djeddar set up and initiate process steps for automated cell culture on the AMBR 15 micro-bioreactor in the Krone Engineered Biosystems Building at Georgia Tech. (Credit: Rob Felt, Georgia Tech)

Researchers work in the cell manufacturing laboratory of Krishnendu Roy at Georgia Tech. Shown (R-L) are NSF Graduate Research Fellow Joscelyn Mejias, Research Experience for Undergraduates (REU) Program student Angela Jimenez, (background) Postdoctoral Fellow Randall Toy, Georgia Tech Research Institute TAG-Ed High School Intern Gita Balakirsky, and Project ENGAGES High School Intern Ayanna Prather. (Credit: Rob Felt, Georgia Tech)

Research

In pursuit of CMaT's transformative vision, new knowledge will be gained to catapult scalable cell manufacturing, especially in areas of Critical Quality Attributes (CQAs) and process optimization. A major barrier to the success of cell therapies, as well as their reproducibility across clinical centers and industry, is the lack of reliable CQAs

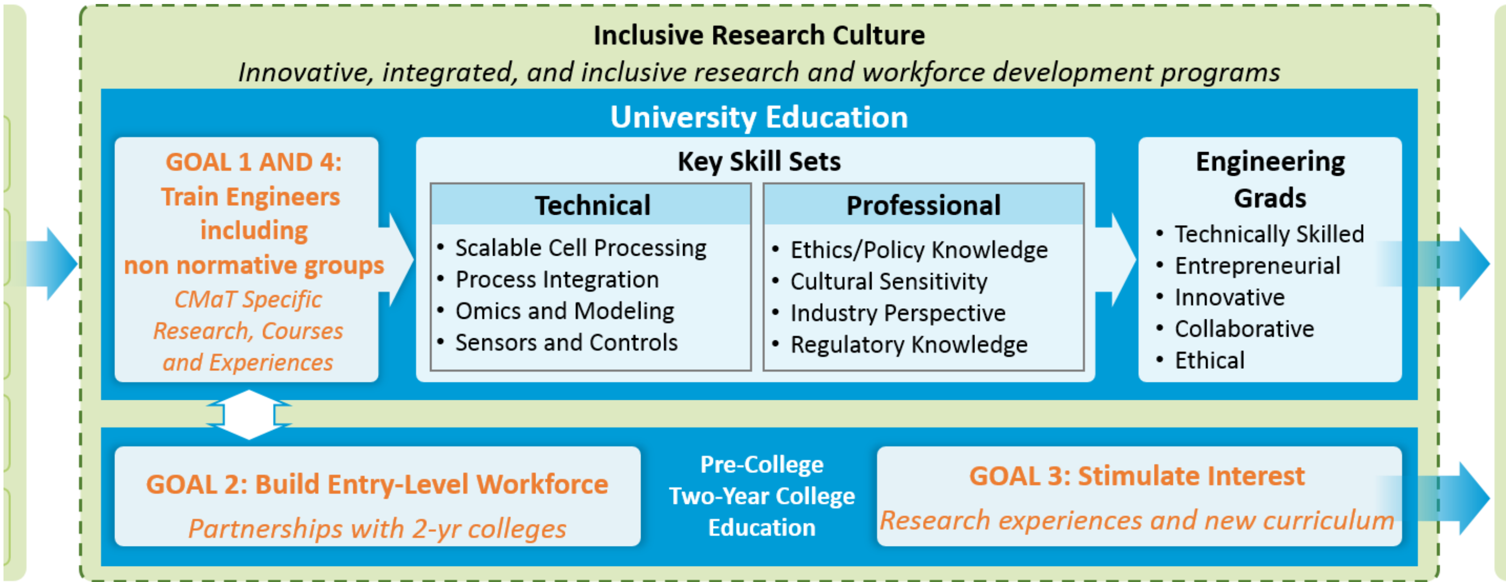

Figure 3: Overall Strategic Plan of CMaT's Engineering Workforce Development

and our ability to measure them longitudinally throughout the manufacturing process. There is also little correlation between *in vitro* and *in vivo* potency-safety measurements and between lab-scale and industry-scale production parameters.

CMaT will develop new enabling tools and technologies that will be broadly applicable to all Test-Bed cell types as well as other cell therapies and biomanufacturing platforms. At the Engineered Systems level (Figure 2), CMaT will address key barriers: predicting safety and efficacy on industry relevant Test-Beds; large-scale, low-cost manufacturing; lack of industry standards; and the lack of a trained workforce with broad training not only on technical skills but also on regulatory and social policies. CMaT will nurture an inclusive, industry-academia-clinician-government ecosystem to achieve its goals.

The goal of Thrust 1 is to work synergistically with Thrusts 2 and 3 to develop robust, reproducible, and predictive analytical measurements and models that will ensure reproducible manufacturing of the highest quality of cells—in terms of both safety and potency. CMaT will use both non-targeted and targeted analyses of cell characteristics and take a multiomics-driven big-data approach to (a) develop multi-variate classifiers as putative CQAs and (b) understand how process parameters influence CQAs—with the eventual goal of identifying critical process parameters (CPPs) for robust and reproducible manufacturing. The large data set generated for each cell type as a function of process variables and stage of manufacturing will be subjected to big-data analytics and predictive modeling to identify CQAs and CPPs that are most predictive of product quality.

Thrust 2 will focus on engineering robust and reproducible measurement and assay technologies that enable batch and continuous monitoring of both process conditions and cell state during manufacturing across all three Test-Beds. These goals will be achieved through the development of non-destructive, in-line, closed-system analysis tools that enable real-time CQA measurements as well as "Potency-on-a-chip" approaches using on-chip organoid models to study cell potency and safety.

Thrust 3 will focus on developing new technologies for scale-up/scale-out of therapeutic cells. In this Thrust, information about "what to measure" (Thrust 1) and "how to monitor" (Thrust 2) will be combined using technologies such as new bioreactors/biomaterials, integration of process control based on real-time feedback from sensors, and creation of models for supply chain management and reduction of product variability and cost.

Diversity and Inclusion

CMaT will be a "best-in-class" role model by infusing the values of diversity and inclusion at each educational level and across all program components. The CMaT diversity and inclusion mission will be achieved by focusing on the following objectives across the whole CMaT ecosystem:

Objective 1: Ensure that CMaT's leadership and researchers represent a diverse group across ALL partners, and promote a welcoming and inclusive culture in all we do.

Objective 2: Leverage and share individual institutional strengths to train under-represented minority, women, and disabled students in cell manufacturing engineering from the pre-college through post-doctorate pipeline.

Objective 3: Identify, train, and mentor non-normative groups of students who could be successful in manufacturing careers.

The above objectives will be met by the following initiatives/programs:

Implicit Bias and Cultural Competency Training: All members of the CMaT consortium will be engaged in ongoing training to support a culture of inclusion. Training will focus on aspects of activities most susceptible to influences of implicit bias—for example, in student evaluation and selection, classroom and lab interactions, mentoring and hiring.

Diversity and Inclusion Educational Pipeline: CMaT will infuse in and expand existing educational programs (pre-college, REUs, technical college training, veterans) at each institution to enhance reach to and access for underrepresented minority students.

Sharing and Leveraging Strengths (SLS): All CMaT institutions have existing exemplar programs, including NSF LSAMP programs

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and institutional programs, that will be shared and developed at other CMaT institutions.

Representation: CMaT will proactively work towards gender, ethnicity, expertise, and rank diversity across all participants.

Reach and Access: CMaT will focus on engaging, recruiting, retaining, and training non-traditional and underrepresented students in cell manufacturing.

Education

CMaT will contribute to a new innovative, diverse, and skilled engineering workforce through the following programs (Figure 3).

Graduate Training: CMaT graduate students will enroll in new CMaT-designed courses and will complete mentored research experiences focused on cell manufacturing barriers as part of a program designed to train them in the key skill sets prioritized by our industry and clinical "good manufacturing practices" partners.

Undergraduate Training: Undergraduate students at each institution will participate in multi-year, mentored research experiences in CMaT labs. In addition, faculty and graduate students from all partners will jointly develop educational modules for integration into existing undergraduate engineering courses and capstone design courses. CMaT will also provide annual training opportunities for undergraduate students—drawn primarily from non-CMaT institutions—to participate in mentored summer research projects.

Global Experiences: Three international partners will provide opportunities to launch new collaborative research projects that will present CMaT graduate and undergraduate students with opportunities for research experiences abroad. CMaT institutions will also host visiting student researchers and faculty from our partners.

Pre-college and Technical College: CMaT will provide deep and enriching opportunities, grounded in fundamental engineering education research, for pre-college students and teachers to engage in learning activities using the ideas and practices of cell manufacturing to help build an inclusive, innovative engineering workforce. CMaT will build on existing partnerships among GT, UGA, U-Wisc, and local 2-year colleges to help address the shortage of skilled workers. We will partner with the Technical College System of Georgia and Madison Area Technical College to develop and implement a curriculum and create a new 12-month, part-time cell manufacturing internship for students pursuing 2-year degrees at colleges near GT and UGA.

Non-Normative Groups: CMaT has identified opportunities for members of groups that are currently under-represented in STEM fields, including veterans and students with disabilities, to contribute to the biomanufacturing workforce.

Innovation Ecosystem

CMaT builds on a strong partnership started though Georgia Tech's leadership in the National Cell Manufacturing Consortium, which brought together 30 industry partners, 16 universities, as well as regulatory and funding agencies, to create a 10-year roadmap for the field (see cellmanufacturingusa.org). The vision of CMaT's innovation ecosystem is to achieve global intellectual leadership, national industrial competitiveness, and lasting economic impact. The mission is to pioneer a vibrant environment for collaboration and entrepreneurship, effective knowledge transfer, and value exchange based on mutually beneficial partnerships.

The strategic goals are to:

- Engage a diverse group of innovation leaders, entrepreneurs, industry, and practitioners in all aspects of the ERC
- Partner with stakeholders to ensure that engineering innovations happen in the context of current regulatory policies and reimbursement frameworks, and that they are relevant and translatable
- Nurture the ecosystem through a series of enriching meetings and programs that foster two-way exchange of knowledge and value across all stakeholders
- Enable students and faculty with skills necessary to be entrepreneurs and create ecosystem for new start-ups
- Develop sustainable partnerships and business models for CMaT to flourish.

CMaT has established a fee-based membership program where participating industry members contribute financial and in-kind support. Semi-annual Industry Practitioner Advisory Board (IPAB) meetings will provide a forum for collective advice to CMaT leadership on past performance and future strategic plans. IPAB members are expected to: 1) be actively engaged in CMaT; 2) help solicit, review, and select research projects, provide insights on research gaps, and lend expertise in manufacturing, validation, design, regulations, economic evaluation, and technology transfer; 3) contribute to workforce programs by providing guidance on the desired skill sets needed for success in industry and, when appropriate, teaching; 4) provide students with industry perspective by mentoring and hosting internships; and 5) assist in establishing a culture of innovation and inclusion.

Facilities

Georgia Tech's extensive, world-class core facility is managed by the Petit Institute for Bioengineering and Biosciences and spans two buildings, including the brand new Krone Engineering Biosystems Building. There are 13 cores within this infrastructure, all centrally funded and each managed by full-time staff. There are also extensive core facilities at the Georgia Tech Manufacturing Institute for prototyping and process validations. In addition, the recent $15.75 million gift from the Marcus Foundation provides new space and facilities for cell manufacturing.

U-Wisc's Stem Cell and Regenerative Medicine Institute and Waisman Biomanufacturing have extensive core and GMP facilities; UGA's Regenerative Biosciences Center has an extensive state-of-the-art facility for proteomics and metabolomics and big-data analytics, cell processing, and animal studies; UPRM's Chemical Engineering Department and College of Engineering have extensive core facilities for cell and material research; Emory and U-Penn both have world-renowned GMP cell manufacturing facilities; Gladstone has one of the world's premier stem cell core facilities, and Michigan Tech will provide full core facility access through its College of Engineering.

Center Configuration, Leadership, Team Structure

Georgia Tech (GT) is the lead Institute of CMaT. The University of Wisconsin (U-Wisc), the University of Puerto Rico-Mayaguez (UPRM), and the University of Georgia (UGA) are the major partners. For each Thrust and Test Bed, senior and junior faculty from different universities have been paired as co-leaders. CMaT's structure ensures that research, workforce, innovation, and inclusive leadership teams have broad experience in engineering and cell therapy research and in clinical sciences, social sciences, policy, workforce development, systems and enterprise innovation, and industry collaboration. UPRM is the major partner institution that serves primarily underrepresented minorities. In addition, UPRM has strong, nationally recognized engineering programs and an emerging bioengineering program, with several faculty leveraging this critical crosscutting expertise in the proposed research. Puerto Rico is also a major hub for the biomanufacturing industry and related workforce.

Academic organizations affiliated with CMaT include Emory University, Gladstone Institutes, the Abramson Cancer Center at the University of Pennsylvania, and Michigan Technological University. Each of these partners brings highly complementary sets of expertise and infrastructure. GT, UGA, and Emory are integrated in research and education and work closely in several major statewide initiatives. Emory brings key expertise in cell manufacturing research and clinical translation. The Abramson Cancer Center at U-Penn is one of the world's foremost authorities in T cell immunotherapies. The Gladstone Research Institute is a renowned Center of Excellence in stem cell research and biology.

CMaT's international partners are the Center for Research in Medical Devices (CÚRAM) at The National University Ireland (NUI) Galway; Osaka University; and the Center for Commercialization of Regenerative Medicine (CCRM) and the Medicine by Design program at the University of Toronto—adding world-leading complementary infrastructure and researchers.

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