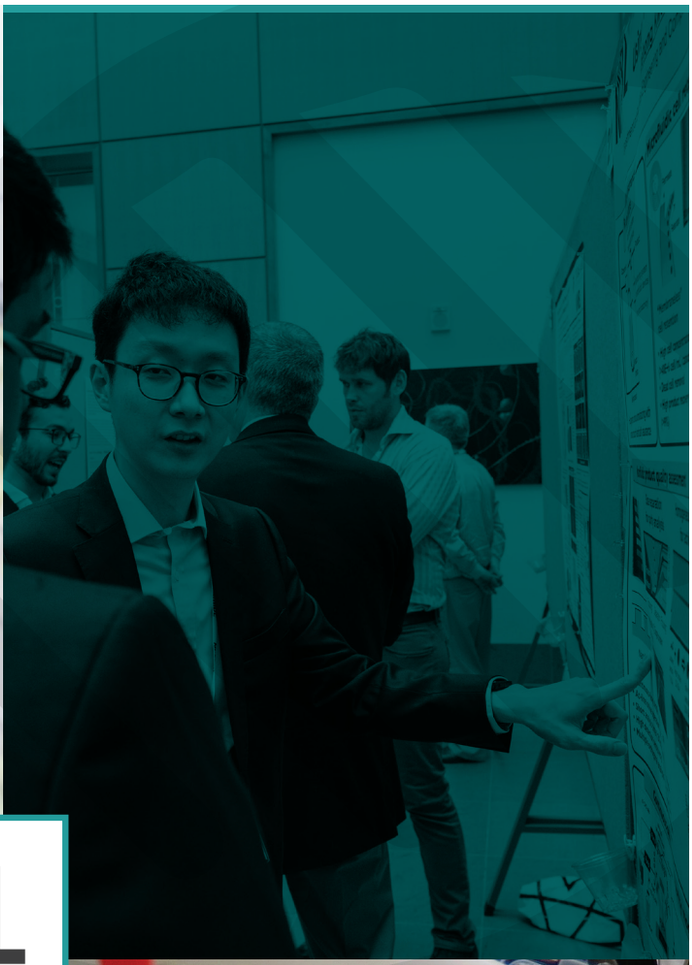

NIMBL

Annual Report

2018/19

THE NATIONAL INSTITUTE FOR INNOVATION IN MANUFACTURING BIOPHARMACEUTICALS

Photo courtesy of BTEC © North Carolina State University

Photo courtesy of BTEC © North Carolina State University

This annual report describes the goals, plans, and accomplishments of the National Institute for Innovation in Manufacturing Biopharmaceuticals during its second year which ran from March 1, 2018 – February 28, 2019.

Cover: Top photos courtesy of NIIMBL, Bottom photos courtesy of BTEC ©North Carolina State University

OUR MISSION

The NIIMBL mission is to accelerate biopharmaceutical manufacturing innovation, support the development of standards that enable more efficient and rapid manufacturing capabilities, and educate and train a world-leading biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry.

OUR VISION

Better lives through a healthy society and a strong economy.

NIIMBL stakeholders participate in a technology roadmapping exercise.

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A MESSAGE From The NIIMBL Team

Dear Colleagues,

An ability to innovate is a defining characteristic of a strong and thriving economy. In particular, innovations in advanced manufacturing turn new ideas and technologies into useful products. The Manufacturing USA® network of institutes reflects our nation's commitment to leadership in advanced manufacturing. It ensures new technologies and products are developed within the U.S. Through its public-private partnership model, Manufacturing USA fosters the ground-breaking research and innovation that solidifies our nation as a global manufacturing leader.

NIIMBL is proud to be a part of the Manufacturing USA network and to join in that commitment. We have convened experts from the biopharmaceutical manufacturing community in a collaborative environment to drive the development of new manufacturing technologies that will strengthen U.S. leadership in advanced biomanufacturing. Our work helps improve patient access to life-saving medicines, bolsters the U.S. economy, and strengthens national security.

Over the last year, NIIMBL has achieved a number of significant milestones and accomplishments such as:

- Expanding our portfolio to more than 40 projects with a cumulative value approaching $50M;
- Growing our membership to 100+ members including the addition of large industry leaders Genentech, Celgene, Merck & Co, Inc., MilliporeSigma/EMD Serono, AstraZeneca, Pfizer, and Sartorius as well as several Small-to-Medium Manufacturers (SMMs);
- Synthesizing the collective expertise of the biopharmaceutical community to publish technology roadmaps for gene therapy, antibody-drug conjugates and bispecific antibodies, and vaccines;
- Introducing the NIIMBL eXperience, a hands-on program designed to give underrepresented students a look into career possibilities in the biopharmaceutical industry;
- Announcing the Global Health Fund to support cost-saving manufacturing technology development for vaccines;
- Promoting partnerships and idea exchange through our technology workshops, Global Health Fund activities, project call summits, and our annual National Meeting.

As we reflect on the achievements of the past year, our excitement continues to grow for future activities including expanding our portfolio of industry-driven technology and workforce projects, introducing the first NIIMBL eXperience student cohort to the biopharmaceutical industry, and moving into NIIMBL's new headquarters, the Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center at the University of Delaware.

All of this is only possible with the dedication and commitment of the NIIMBL community. The Institute's accomplishments are a reflection of the time, energy, and expertise NIIMBL members bring to the Institute. We greatly appreciate all members of our community for your vision and support of NIIMBL.

Our successes are also a result of the support and guidance we receive from our colleagues at the National Institute of Standards and Technology (NIST), the U.S. Department of Commerce, and our partner Manufacturing USA Institutes. We are fortunate to work with colleagues who share a common goal of strengthening U.S. manufacturing competitiveness. In addition, we are also grateful for the relationships we have built with federal agencies including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority (BARDA), National Science Foundation (NSF) and the Department of Defense (DoD).

We thank you all for your continued support and look forward to a bright and innovative future.

Sincerely,

The NIIMBL Team

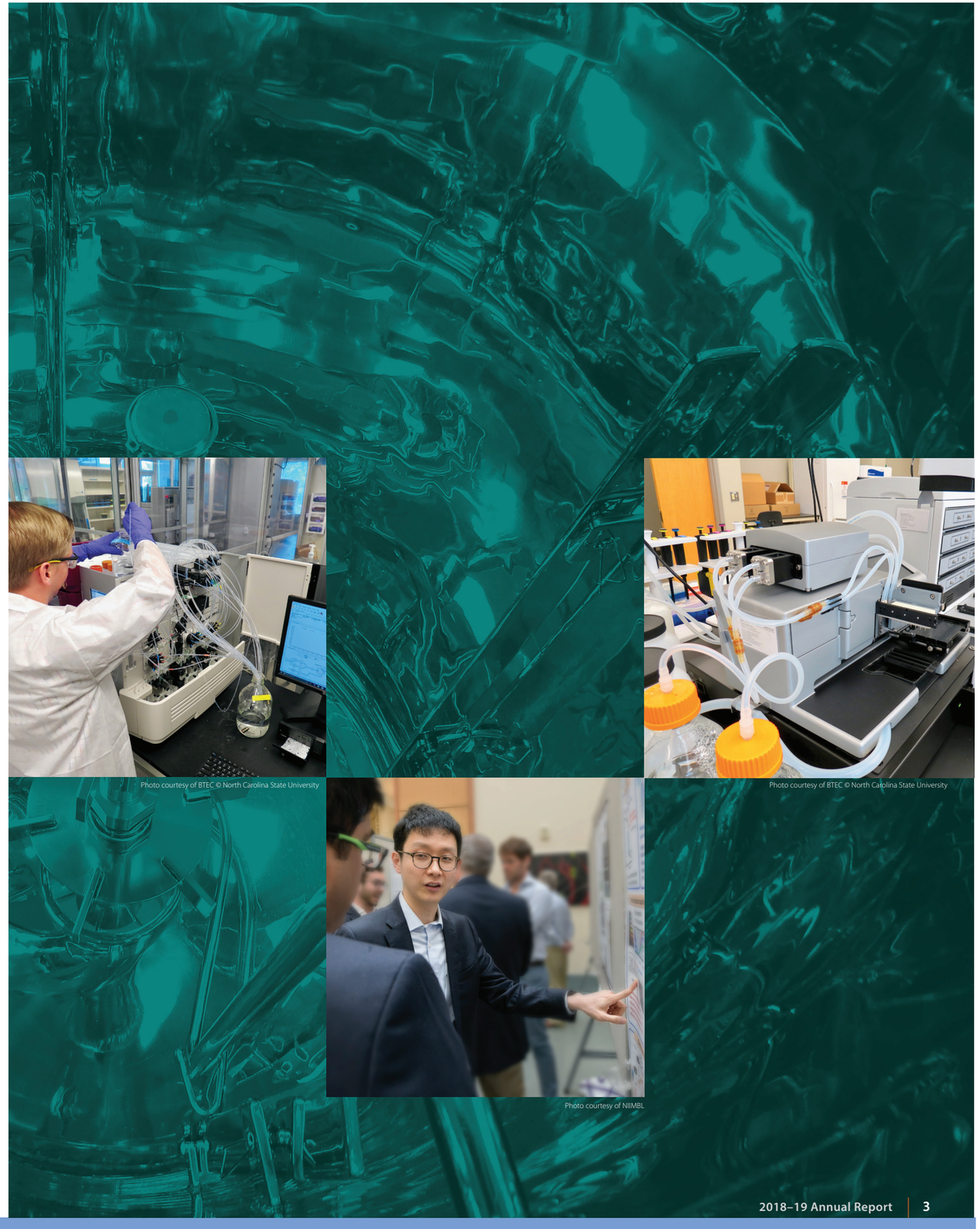


Photo courtesy of BTEC © North Carolina State University

Photo courtesy of BTEC © North Carolina State University

Photo courtesy of NIIMBL

Improving the Competitiveness of U.S. Biopharmaceutical Manufacturing

A Vital Industry with Significant Economic Impact

Over the past 30 years, biopharmaceuticals have made a difference in the lives of people suffering from cancer, diabetes, cardiovascular disease, autoimmune disorders, and other conditions. These products include monoclonal antibodies and other therapeutic proteins, and, more recently cell and gene-based therapies that are saving and improving countless lives.

In addition to improving the health of patient populations, biopharmaceuticals also serve as a significant economic driver. Consider the following impacts of the biopharmaceutical industry on the U.S. economy:

- The industry directly employed over 800,000 people in the U.S. and indirectly supported an additional 3.9 million jobs through supplier and support services. In all, the industry directly or indirectly accounted for more than 4.8 million U.S. jobs in 2015. Workers in biopharmaceutical manufacturing earn $115,000 annually on average.
- The biopharmaceutical industry provides high-quality jobs. Employees earned more than $100 billion in personal income.
- The industry contributed $1.3 trillion in total economic impact, with $558 billion in business revenue and $659 billion in indirect impact and worker spending in 2015.

The Biopharmaceutical Industry: Impacting the U.S. Economy

Source: TECconomy Partners, LLC for the Pharmaceutical Research and Manufacturers of America (PhRMA). Biopharmaceutical Manufacturing in the U.S.: Making Cutting-Edge Medicines Today and Leading the Way on Medicines of Tomorrow, March 2019

4.8M
Direct and indirect jobs supported by the biopharmaceutical industry.

294,422
U.S. jobs in biopharmaceutical manufacturing

802,000
Directly employed by the biopharmaceutical industry

$1.3T
Estimated total impact the biopharmaceutical industry contributes to the U.S. economy

$104B
Combined personal income of individuals directly employed by the biopharmaceutical industry

$115,010*
Average annual wage of biopharmaceutical manufacturing workers

*Source: TECconomy Partners, LLC for the Pharmaceutical Research and Manufacturers of America (PhRMA). Biopharmaceutical Manufacturing in the U.S.: Making Cutting-Edge Medicines Today and Leading the Way on Medicines of Tomorrow, March 2019.

The Biopharmaceutical Industry: Transforming Human Health

Source: PhRMA, 2018 Industry Profile

7,000
Medicines in clinical development globally

1,120
Medicines currently in development to treat cancer

74%
Percentage of medicines in development considered first-in-class treatments

200
Medicines in development for heart disease, the leading cause of death in the United States

A Multifaceted, Coordinated Effort to Improve U.S. Competitiveness

Since recombinant human insulin was launched more than 30 years ago, the U.S. has been a global leader in the discovery and manufacturing of biopharmaceutical products. A number of successes are due to the roles industry-academic partnerships played in drug discovery and development.

More recently, the U.S. has faced increased pressure from a globalized market. Biopharmaceutical manufacturing companies are inherently multi-national entities, with operations strategically placed in other regions around the world. As the ability to innovate is the hallmark of a thriving and growing economy, countries such as Singapore, Ireland, Austria, and South Korea continue to invest in biomanufacturing innovation and workforce development to increase their presence within the sector.

To remain competitive in the increasingly global biopharmaceutical landscape, the U.S. must continue to invest in strategies to drive technology innovation and workforce development in this industry. NIIMBL reflects the U.S.'s commitment to innovation in the biopharmaceutical sector. It leverages the collective investment of its stakeholders, including government agencies and the Institute's 100+ members, to develop the manufacturing capabilities and workforce training programs that will help the U.S. lead the global biopharmaceutical sector.

Improving the Competitiveness of U.S. Biopharmaceutical Manufacturing

A NIIMBL Approach to Improving Biomanufacturing Competitiveness

NIIMBL's public-private partnership model, like that of other Manufacturing USA® institutes, provides a valuable mechanism to facilitate the applied research and innovation needed to advance the industry's interests within the U.S.

NIIMBL's projects, programs, and initiatives are designed to bring stakeholders together to strengthen the nation's position within the global industry and help the U.S. retain the economic benefit from its biopharmaceutical research and development programs. NIIMBL is fostering U.S. leadership in this crucial industry sector through the activities listed below.

- Technology workshops and teaming events: NIIMBL convenes stakeholders from across the ecosystem to collaborate and exchange ideas on potential solutions for shared challenges in a pre-competitive environment.
- Technology projects: The Institute invests in technology projects focused on all areas of the biopharmaceutical manufacturing process including analytical assays, upstream and downstream drug substance, drug product, and approaches used for both existing products as well as the newest modalities such as cell and gene therapy.
- Workforce Development Programs: A growing portfolio of workforce development programs helps to prepare students for successful careers in biopharmaceutical manufacturing, ensures the U.S. has a pipeline of highly-skilled workers, and provides learning development opportunities to support the technical growth of the industry.
- Small-to-Medium Manufacturer (SMM) Engagement: The Institute supports the growth and development of Small-to-Medium Manufacturers (SMMs) who can provide innovations on many fronts.
- Underrepresented Student Outreach: The Institute conducts outreach to underrepresented student populations to introduce talented students to career possibilities in the biopharmaceutical industry.

More information about each of these initiatives can be found within this Annual Report.

Contributing to National Goals and Outcomes

By bringing together the best minds from industry, academia, and government, NIIMBL helps the U.S. lead the global industry through improved manufacturing processes that can increase speed to market and reduce development risks. These efforts have significant impact on national goals and desired outcomes.

Meeting the Medical Needs of the Nation

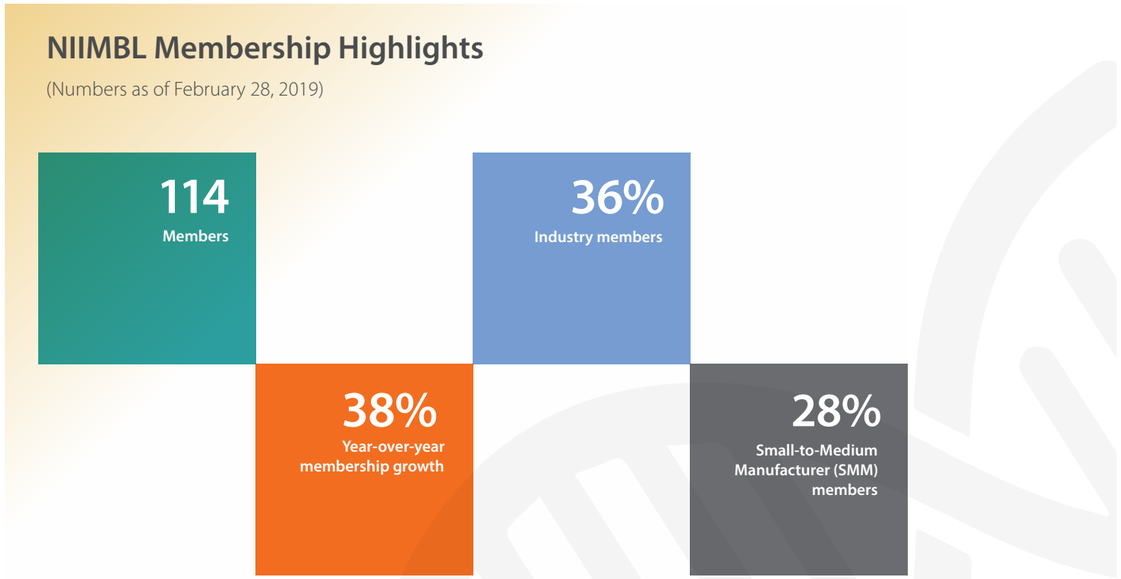
Improved manufacturing platforms can ensure life-saving treatments are readily available to patients. These medicines include therapeutic proteins and monoclonal antibodies targeted for a range of cancers, autoimmune and neurological diseases, and infectious diseases; and include large scale manufacturing as well as small scale manufacturing of precision medicines such as cell and gene therapies.

Contributing to a Thriving Economy

NIIMBL supports job growth by investing in training programs for the next generation of biopharmaceutical workers. These programs will help ensure the best-trained biopharmaceutical workforce resides in the U.S.

Improving National Security and the Domestic Supply Chain

Flexible, adaptive manufacturing platforms allow the U.S. to quickly respond to health crises whether natural or manmade. In addition, NIIMBL's commitment to standards and reference materials will help secure the domestic supply chain, ensuring the efficacy and safety of biologic products.



Leveraging the Power of Community

As the leading biopharmaceutical manufacturing consortium in the world, NIIMBL connects large and small companies, leading research universities, community colleges, nonprofit organizations, and federal agencies to accelerate domestic manufacturing capabilities through new technologies. NIIMBL members include biomanufacturers, suppliers, academic research institutions, community colleges, non-profit organizations, and state governments. The diversity in members brings a wide-range of expertise and capabilities to the community.

A Focus on Membership Growth

During the past year, NIIMBL focused on growing and diversifying the Institute's membership base. By expanding membership, NIIMBL is able to leverage additional investment from member organizations and expand the breadth of knowledge and expertise within the Institute.

As of February 28, 2019, NIIMBL membership included 114 organizations, representing 38% growth from the end of the Institute's first year. The membership increase speaks to the value organizations see from engagement with the NIIMBL community.

Enhanced Membership Offerings

In October, NIIMBL announced new membership options for industry partners. The new offerings give existing members the flexibility to choose their level of engagement in NIIMBL activities. One new benefit rolled out with the enhanced membership options is SMM membership passes, which enable Tier 1 industry partners to select up to three SMMs per year who will have their annual membership fee waived. Large industry partners understand the value small companies bring to the innovation ecosystem through new, disruptive technologies. SMM membership passes allow companies to introduce small companies to the community and encourage collaborations within NIIMBL, greatly benefiting the ecosystem as a whole.

Photo courtesy of BTEC © North Carolina State University

NIIMBL WELCOMES ASTRAZENECA, PFIZER, AND SARTORIUS

This year, NIIMBL welcomed industry leaders AstraZeneca, Pfizer, and Sartorius to our growing member community. The combined insight and expertise these companies bring will enhance the Institute's ability to advance novel technologies in biomanufacturing.

AstraZeneca is an industry leader in biologics research and development. With a robust biologics development portfolio that includes more than 120 products, AstraZeneca focuses on treatments in four key therapeutic areas: oncology; respiratory; cardiovascular, renal and metabolic disease; and infection vaccines.

A global leader in biologic R&D, ***Pfizer's*** products address key therapeutic areas including internal medicine, inflammation & immunology, oncology, rare disease, and vaccines. Its extensive R&D portfolio includes cutting-edge research on the emerging treatments of tomorrow such as gene therapy and precision medicines.

The ***Sartorius Group*** is a leading pharmaceutical and laboratory equipment provider with a broad product portfolio focusing on single-use solutions to help customers produce biologics and vaccines safely and efficiently. The company provides a wide-range of solutions for numerous biopharmaceutical product types including monoclonal antibodies, vaccines, blood and plasma products, bioconjugates, and biosimilars. It's extensive knowledge of process development equipment and innovative solutions promises to benefit the NIIMBL community.

"NIIMBL provides a unique structure for collaboration and innovation through a network of leading researchers from industry, academic and government institutions. Merck is excited to participate in NIIMBL which provides an active forum to enable scientific exchange as our industry seeks to leverage expertise and capabilities to develop disruptive breakthroughs to advance bioprocess."

David Roush
Merck & Co., Inc.

The NIIMBL Ecosystem

NIIMBL engages stakeholders from across the country as the only coordinated, national effort to solve biopharmaceutical manufacturing challenges.

NIIMBL MEMBERS & PARTNERS *as of February 28, 2019*

Industry

- Genentech
- Celgene Corporation
- MilliporeSigma/EMD Serono
- Merck & Co., Inc.
- AstraZeneca
- Sartorius
- Pfizer
- 908 Devices
- AccuGenomics
- Aerosol Therapeutics
- Akron Biotech
- Alcami
- Applied Control Engineering, Inc.
- Applied Materials, Inc.
- Artemis Biosystems
- ChromaTan
- Commissioning Agents Inc.
- Denali Therapeutics
- Fisher Rosemount Systems Inc.
- ILC Dover
- ImmunoGen
- Intabio, Inc.
- LEWA-Nikkiso America
- LigaTrap® Technologies
- Lindy Biosciences
- LumaCyte
- Metalytics
- NewAge® Industries
- Oxford Instruments
- Physical Sciences Inc.
- Potomac Affinity Proteins, Inc.
- ProMechSys-RLP, LLC
- Redbud Labs
- ReForm Biologics
- Repligen
- RoosterBio
- Sudhin Biopharma Co.
- Unum Therapeutics
- Vericel Corporation
- Whirlcell

Academics & Non-Profits

- The Bill & Melinda Gates Foundation
- Carnegie Mellon University
- Clemson University
- Fraunhofer USA
- Georgia Tech Research Corporation
- Johns Hopkins University
- Massachusetts Institute of Technology
- Missouri University of Science and Technology
- National Institute for Pharmaceutical Technology and Education, Inc. (NIPTE)
- New Jersey Innovation Institute
- North Carolina State University
- Northeastern University
- Pennsylvania State University
- Purdue University
- Regents of University of Minnesota
- Rensselaer Polytechnic Institute
- Texas A&M University System
- Thomas Jefferson University
- Tulane University
- University of Delaware
- University of Maryland Baltimore
- University of Maryland College Park
- University of Massachusetts System
- University of North Carolina at Wilmington
- University of Pennsylvania
- Virginia Commonwealth University
- Albany College of Pharmacy and Health Sciences
- Delaware State University
- East Carolina University
- Florida State University
- Gustavus Adolphus College
- North Carolina Central University
- Regents of the University of Colorado (Boulder)
- Sloan Kettering Institute for Cancer Research
- Southwest Research Institute
- The Research Foundation for the State University of New York, on behalf of State University of New York Polytechnic Institute
- University of Georgia Research Foundation
- University of North Carolina, Chapel Hill
- Villanova University
- Worcester Polytechnic Institute
- AABB Center for Cellular Therapies
- American Institute of Chemical Engineers
- Alamance Community College
- BioKansas
- Brunswick Community College
- Bucks County Community College
- Cape Fear Community College
- Center for Entrepreneurial Innovation Maricopa CCCD
- Delaware BioScience Association
- Delaware Technical Community College
- Durham Technical Community College
- Forsyth Technical Community College
- Frederick Community College
- Hagerstown Community College
- International Academy of Automation Engineering
- Life Science Washington
- Massachusetts Life Sciences Center
- Missouri Biotechnology Association
- Montgomery College
- Montgomery County Community College
- North Carolina Biosciences Organization
- North Carolina Biotechnology Center
- North Carolina Community Colleges Systems BioNetwork
- Quincy College
- Shoreline Community College
- Solano College
- Standards Coordinating Body
- The American Society of Mechanical Engineers (ASME)
- Vance-Granville Community College

Manufacturing Extension Partnerships

- Delaware Manufacturing Extension Partnership
- Massachusetts Manufacturing Extension Partnership
- New Jersey Manufacturing Extension Partnership
- North Carolina Manufacturing Extension Partnership

Federal Partners

- National Institute of Standards and Technology (NIST)
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)

NIIMBL interacts with several other federal agencies and institutes.

States

NIIMBL would like to thank the following states for their support of the Institute:

State of Delaware | Commonwealth of Massachusetts (Massachusetts Life Sciences Center)
State of North Carolina | State of Maryland

Stimulating Leadership in Advanced Biopharmaceutical Manufacturing Research, Innovation, and Technology

Leveraging Shared Investment to Address Industry Needs

The biopharmaceutical industry makes a substantial impact on public health, the U.S. economy, and national security. As the industry continues to evolve, it must look to solve several challenges that will help to put life-saving medications in the hands of patients, such as:

- Further industrialization and scale-up of existing products to meet variable market needs and demand as well as improved speed to market and flexibility;
- New small-scale manufacturing platforms for emerging products, such as cell and gene therapies, integrated with robust measurement capabilities;
- New standards and measurement technologies to ensure product consistency, safety, and efficacy throughout the manufacturing process;
- A highly-skilled, biopharmaceutical workforce to produce the products of today and tomorrow.

The biopharmaceutical industry is regulated to ensure products are safe and efficacious for patients and can be consistently manufactured. This regulatory environment can reduce business drivers for industry to adopt and implement new process technologies, as introduction of new technology may delay regulatory approval. Thus, the ability to demonstrate new technologies and assays in the context of an industry-wide public-private partnership helps de-risk these innovations in a precompetitive environment, leading to faster adoption of new technologies and increased economic competitiveness, and ultimately helping provide patients with enhanced access to medicines.

NIIMBL provides an environment where companies can leverage the shared investment of industry, academia, and government to develop the new process technologies and assays that will improve manufacturing capabilities, and increase the global competitiveness of the U.S. biopharmaceutical industry, and help meet the demand for emerging therapies and improve quality of life.

Catalyzing U.S. Leadership

NIIMBL stimulates U.S. leadership in biopharmaceutical manufacturing research, innovation, and technology through:

- Technology Advancement: NIIMBL innovation projects offer a collaborative environment that pools resources and de-risks technology development and adoption. To date, NIIMBL has funded more than 40 technology and workforce projects.
- Workforce Training: The Institute's expanding portfolio of workforce development projects helps to better prepare workers, including students, career-changers, and veterans for lucrative careers in the biopharmaceutical industry. NIIMBL workforce development projects focus on a number of needs including automation training and gene therapy vector manufacturing.
- Idea and Best Practice Exchange: NIIMBL leads discussions and facilitates idea exchange on key topics through our series of workshops, events, and the online Community Portal.
- Technology Roadmapping: NIIMBL's open roadmapping process explores the key technology needs for various product modalities.
- Federal Engagement: Through NIIMBL's engagement with federal scientists, we focus on a collaborative approach that takes into account diverse expertise and interests.
- Support Small Companies: Small companies can be a wellspring of innovation. NIIMBL supports these businesses by exposing their technologies through the SMM Innovation Showcase and a project call process that emphasizes SMM participation.
- Diversity and Inclusion: Through the NIIMBL eXperience program, NIIMBL seeks to connect talented, underserved student populations with career opportunities in the biopharmaceutical industry.

Strengthening the Innovation Ecosystem

One of the fundamental components of ensuring U.S. leadership is to expand and strengthen the biopharmaceutical ecosystem through connections and collaborations that facilitate new technologies and workforce programs. This includes connecting small companies with large biomanufacturers and suppliers who may benefit from their cutting-edge capabilities.

NIIMBL's collaborative approach provides a unique ability to facilitate these interactions. For example, LumaCyte™, a small company that produces equipment to characterize cells, is working on a project with Carnegie Mellon University and Genentech focused on efficiently detecting bacterial and viral contaminates during the manufacturing process.

Supporting Small-to-Medium Manufacturers (SMMs)

Small companies often bring innovative ideas and technologies to the biopharmaceutical ecosystem. NIIMBL is committed to supporting the continued growth of these companies. NIIMBL helps SMMs access sources of business capital, technical expertise, training resources, regulatory guidance, and testbeds at NIIMBL sites where they can test development ideas.

SMM Innovation Showcase

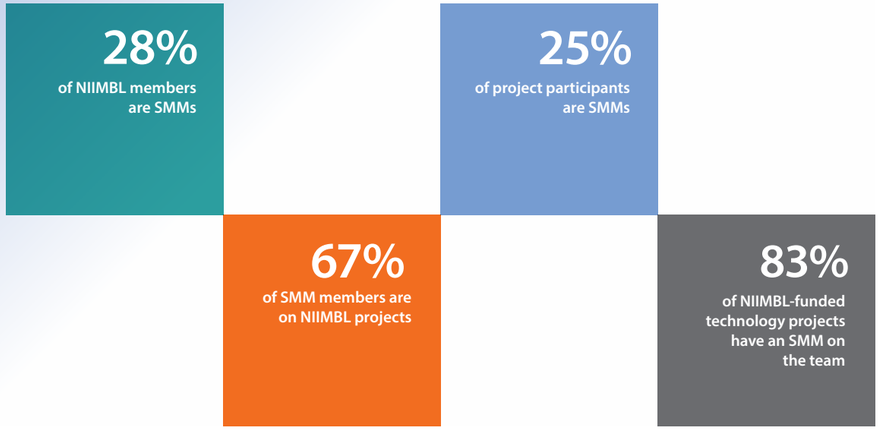
As one of the featured events during our National Meeting, the SMM Innovation Showcase offers small companies the chance to pitch their business to an open audience of several hundred industry stakeholders including NIIMBL members and non-members. At our 2018 National Meeting in May, nearly 30 companies gave presentations. The SMM Innovation Showcase receives positive feedback from presenters and attendees.

NIIMBL/Manufacturing Extension Partnership (MEP) Collaborative Project

NIIMBL actively engages with the Manufacturing Extension Partnership program, funded by NIST. Through an award received by Delaware Technical and Community College, NIIMBL has Manufacturing Extension Partnership (MEP) staff from Delaware, Massachusetts, and North Carolina embedded within the Institute to serve the needs of SMM companies and increase NIIMBL awareness within the biotechnology community. The MEP staff frequently attend conferences and trade shows to forge relationships with SMMs. In addition, MEP staff conduct regular surveys of the current SMM membership to assess their experience with Institute activities.

Through a collaborative environment and shared investment, NIIMBL is positioned to pioneer the development and adoption of new technologies and workforce training that will not only save lives, but also strengthen our Nation's position as the global leader in biopharmaceutical manufacturing.

NIIMBL SMM Engagement Highlights



Facilitating the Transition of Innovative Technologies into Scalable, Cost-Effective, and High-Performing Manufacturing Capabilities

An Expanding Portfolio of Technology Projects

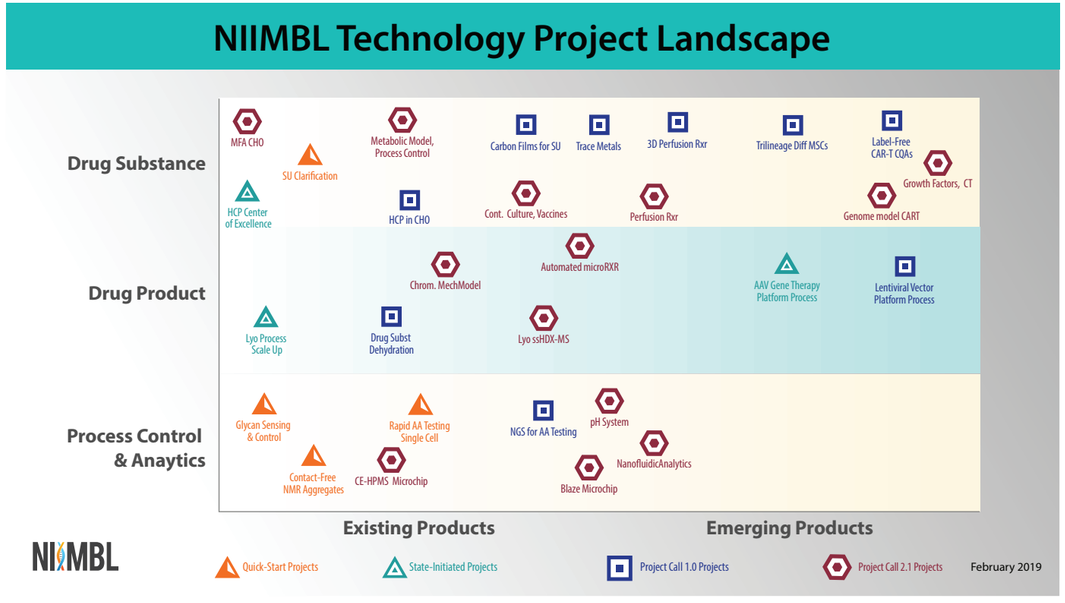
NIIMBL facilitates the development and implementation of new manufacturing capabilities by funding collaborative teams as they advance innovative technologies and solve precompetitive challenges of the industry. As of February 28, 2019, NIIMBL's technology project portfolio includes 28 technology projects with a total estimated value of approximately $35M.

The array of technology projects addresses existing and emerging product types as well as three manufacturing themes paramount to biopharmaceutical manufacturing:

- Drug Substance: Manufacturing and purification of the active therapeutic ingredient
- Drug Product: Formulation and manufacturing of the final dosage form
- Process Control & Analytics: Analyzing the product to ensure product safety, efficacy, and quality at all stages of the process

Below are some examples of the work our members are undertaking to drive innovation:

- Continuous Processing of T-cells for Immunotherapies: Consistent, cost-effective manufacture of T-cell therapies is a challenge for industry due to the need for human interaction with the process stream. Led by Southwest Research Institute with the University of Pennsylvania, this project aims to develop an integrated process to achieve the selection, activation, and gene transduction of T-cells in a single continuous processing system. The project helps ensure product consistency by eliminating human interaction through the process and serves as a critical first step toward automation.



"We have found our membership with NIIMBL to be incredibly valuable as we have been afforded the opportunity to work with some amazing individuals and organizations. LumaCyte's innovative label-free single-cell analysis technology (Laser Force Cytology) has benefited from increased exposure through this industry led consortium, and for an SMM organization focused on driving innovation into a market that has historically been conservative, our membership has proven to be well worth the commitment."

Renée Hart
LumaCyte

- Detecting Viral and Bacterial Contaminants: To ensure patient safety, the manufacturing processes and drug products must be completely free of bacterial or viral contaminants, also known as Adventitious Agents (AAs). Standard industry methods for AA detection are off-line, laborious and take three weeks to be completed. Two NIIMBL projects, led by Carnegie Mellon University and AccuGenomics, focus on advanced methods for rapid AA detection. These efforts intend to create efficiencies in the manufacturing process by allowing manufacturers to quickly identify and eliminate contaminants, ensuring the supply of quality medicines for citizens.
- Software and Hardware Tools for Pharmaceutical Lyophilization Scale-up – Lyophilization, or freeze-drying, is used to stabilize and extend the shelf-life of biopharmaceuticals, ensuring safe and quality products reach the patient. Current lyophilization techniques are costly and add significant time to the manufacturing process. Physical Sciences, Inc., along with Genentech, Merck, University of Massachusetts Lowell, University of Connecticut, Purdue University and the Massachusetts Life Sciences Center, are working to develop software and hardware tools to enable lyophilization process development and scale-up. This project looks to help manufacturers develop higher throughput lyophilization processes which can allow for efficient production of higher quality products with fewer capital resources.
- Preparing for the future: Gene Therapy Vector Production – Gene therapy has shown tremendous promise in treating cancers and other diseases. However, these very new therapies are expensive to produce, in part because of the industry's relative lack of experience with commercial-scale manufacturing processes. North Carolina State University and its partners are tackling this problem by developing a scalable platform process for production, purification, and analysis of adeno-associated virus (AAV) vectors, a delivery vehicle for DNA into a patient's cells. In addition to technology development, the project also aims to strengthen the workforce by developing coursework and training modules for gene therapy vector production. The project includes Sudhin Biopharma Co., and the University of North Carolina Chapel Hill.

NIIMBL's project portfolio is highlighted on page 26.

Project Call Process

NIIMBL issued Project Call 2.1 in May and Project Call 2.2 in November of 2018. These calls solicited cutting-edge project concepts from the NIIMBL community to address critical industry needs.

NIIMBL solicited input from large industry members to help define industrial needs and prioritize topic areas for each project call. In Project Call 2.1 and 2.2, NIIMBL asked for projects in key areas including:

- Process Analytical Technologies (PAT)
- Rapid Release of Drug Substance and Drug Product
- Viral Clearance Technologies
- Cell Line Development and Engineering
- Manufacturing Platforms for Cell Therapy Products
- Drug Substance Manufacturing -Chromatography Technology Development
- Continuous Processing Technology Development –Biologics
- Scale-down Models for Biologics Manufacturing Process Development
- Mechanistic Model Development
- Cost-Effective Gene Vector Production
- Improved Drug Product Stability
- Novel Materials for Biomanufacturing

The community proposed nearly 200 concepts in response to the two calls. Based on feedback from large industry members, select concept teams were invited to submit a full proposal.

NIIMBL selected 22 Project Call 2.1 awardees in October 2018. The Institute plans to announce Project Call 2.2 awardees in mid-2019.

GLOBAL HEALTH FUND

BILL & MELINDA GATES *foundation*

Developing new technologies that will reduce the cost of manufacturing biopharmaceuticals will have a profound impact on patient health in the U.S. and globally. In November 2018, NIIMBL received a $1.5M grant from the Bill & Melinda Gates Foundation to launch the Global Health Fund.

The grant will support the development of innovative technologies to increase speed to market and lower costs for biopharmaceuticals, improving healthcare outcomes for all patients, including those in underserved markets and developing nations, through enhanced access to life-saving medicines and vaccines.

The Foundation will participate in NIIMBL activities including workshops, roadmapping, and committees.

Funds will be awarded to projects that align with the strategic goals and priority topics articulated by NIIMBL and the Foundation. Workshops focused on Global Health Fund priorities are scheduled for 2019.

NIIMBL members and stakeholders gather for the Project Call 2.2 Summit.

Technology Roadmapping

Industry-led roadmaps are a vital tool to understand existing technology needs and formulate plans on how to address those gaps.

In November 2018, NIIMBL published technology roadmaps for gene therapy, antibody-drug conjugates and bispecific antibodies, and vaccines. The roadmaps describe the market drivers, current challenges, and potential solutions for manufacturing challenges associated with these three product classes.

Facilitated by the BioPhorum Operations Group, the year-long roadmapping initiative involved more than 40 organizations including biomanufacturers, equipment makers, suppliers, academic institutions, non-profits and federal agencies. To encourage a broad perspective, the process was open to NIIMBL members, non-members, and federal scientists.

The NIIMBL roadmaps address topics that are not the primary focus of other recently published roadmaps such as NIST-funded efforts in lyophilization and cell therapy. NIIMBL will roadmap in additional topics over the next year.

The NIIMBL roadmaps are publically available at *http://www.niimbl.org/roadmaps.*

Facilitate Access by Manufacturing Enterprises to Capital-Intensive Infrastructure

A rendering of the Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center at the University of Delaware, the future NIIMBL headquarters.

New NIIMBL Headquarters — Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center

The new Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center at the University of Delaware will house the future NIIMBL headquarters and provide a state-of-the art facility for NIIMBL project teams to collaborate and test their ideas. The University of Delaware broke ground on the project in October 2017 and construction has rapidly progressed throughout this year. NIIMBL expects to move into the facility in early 2020.

In addition to NIIMBL headquarters, the $165M building will include other University of Delaware biopharmaceutical discovery and development activities.

NIIMBL will occupy approximately 25% of the building's 200,000 square feet of laboratory and office space. The NIIMBL space will feature shared laboratory space, NIIMBL platform process facilities, showcase laboratory and workforce training facilities.

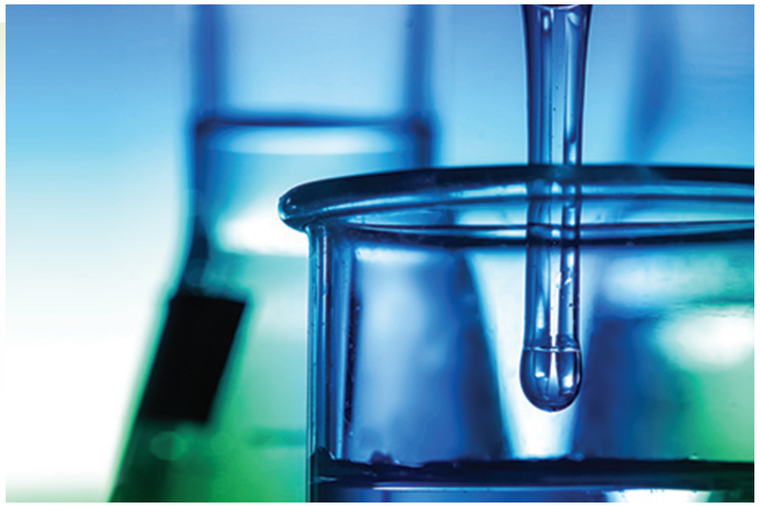
Shared Facilities Network

With 100+ members, the NIIMBL community benefits from an extensive network of facilities and equipment resources. The network provides members with access to facilities and equipment needed for process innovation, technology platform demonstrations, and Good Manufacturing Practices (GMP) production. Facilities within the NIIMBL network include:

- Biopharmaceutical Training and Education Center at North Carolina State University: Offers facilities, equipment, and resources to help NIIMBL members solve challenges of the biopharmaceutical process including process development and analytical technologies.
- MassBiologics at the University of Massachusetts Medical School: Boasts over 25,000 square feet of cGMP space in its FDA licensed manufacturing facility including areas for fill finish and bulk drug substance production.
- Biomanufacturing Education and Training Center at Worcester Polytechnic Institute: Delivers a variety of training and education programs including one-day and week-long programs shaped with input from industry experts as well as contract services.
- National Center for Therapeutics Manufacturing at Texas A&M University: Provides an extensive array of hands-on training programs for upstream and downstream processing biological materials.
- CSL Behring Fermentation Facility at Penn State University: Offers scale up capabilities for the production of biomolecules, analytical characterization and quantification instruments and services to further our understanding of microbial bioprocesses.

"Scientific advances are driving the evolution of next generation platforms, products and methods in biologics manufacturing. NIIMBL has allowed multi-stakeholder collaborations to collectively navigate technical and regulatory hurdles, thereby fostering innovation and accelerating technology implementation."

Audrey Chang
MilliporeSigma



Member Resource Database

Two new tools on the Community Portal provide information the resources available to NIIMBL membership. These tools were launched in November 2018 as part of NIIMBL's expanded and enhanced Community Portal. The database enables members to identify, share, and promote Education & Training Resources as well as Facilities & Equipment Resources.

Members can search based on several criteria including keywords, relevant technologies, and location. The tools are an exclusive benefit for NIIMBL members

A Center of Excellence for Host-Cell Protein Analysis

Several NIIMBL projects also endeavor to provide infrastructural technology capabilities resources for the community. One such project is a Center of Excellence for host-cell protein analysis led by the University of Delaware. Host-cell proteins (HCP) are impurities expressed by the host organism during the manufacturing process. Biopharmaceutical products need to be free of these impurities to ensure they are safe for patients. The Center of Excellence will help biomanufacturers better identify and remove HCP contaminants and it will serve as a NIIMBL core facility for understanding HCPs by providing analyzation services and supporting projects which rely on HCP analysis.

NIIMBL SPECIAL PROJECT — BUFFER STOCK BLENDING SKID

In addition to our standard project call process, we explore ways our robust expertise can contribute to solutions to industry needs. One example is the Buffer Stock Blending Skid project launched in early 2019.

Buffer solutions are key components in a number of upstream and downstream stages of biopharmaceutical manufacturing. However, current buffer preparation processes are expensive, labor-intensive, and have a large footprint at manufacturing facilities.

NIIMBL has partnered with the BioPhorum Operations Group to develop a Buffer Stock Blending Skid that will use concentrated buffer stock solutions in a small, portable device, to greatly reduce manufacturing preparation time, costs, and labor.

The skid is an open-source project, which will allow industry to access plans and specifications in order to build a similar skid suitable for their own manufacturing facilities.

The project includes NIIMBL members Merck & Co., Inc., MilliporeSigma as well as other leading companies from the biopharmaceutical industry. NIIMBL has invested approximately $650K in the project.

Accelerating the Development of an Advanced Manufacturing Workforce

Through curriculum development, hands-on training, digital learning programs, and development of skill standards, NIIMBL develops workforce training and education programs to ensure the U.S. has the most advanced, highly-qualified biopharmaceutical workforce in the world.

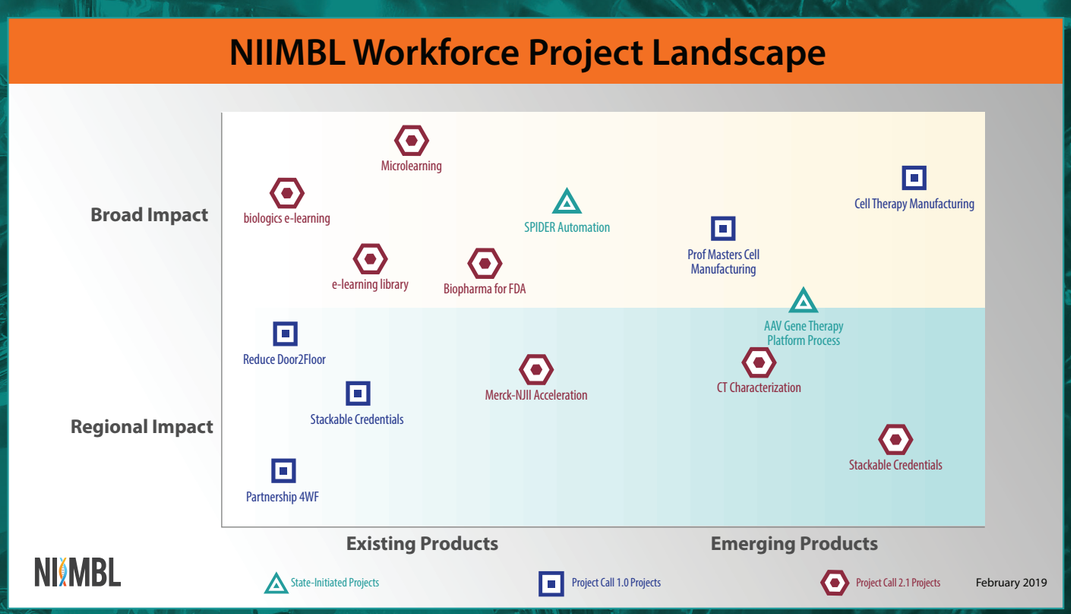

Photo courtesy of the University of Delaware

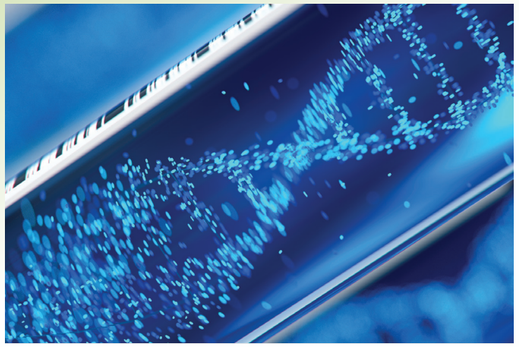
U.S. Senator Chris Coons signs the top beam of the Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center at the University of Delaware on June 25. 2018.

Workforce Development Projects

To date, NIIMBL has elected to fund 15 workforce development projects with an estimated value of nearly $10M. These projects touch on the diverse training needs of our industry members. Examples include:

- Preparing for the Future: A Gene Therapy Vector Production Platform: Gene therapy is a revolutionary new approach for treating cancers and other diseases. However, the therapies are expensive to produce due to a lack of commercial-scale manufacturing processes. North Carolina State University, Sudhin Biopharma Co., and the University of North Carolina Chapel Hill are developing a platform process for the production, purification, and analysis of adeno-associated virus (AAV) vectors, the delivery vehicle for DNA into a patient's cells. Another primary component of the project is the development of coursework and training for gene therapy vector production. The team piloted the course with a small group of post-doc students in early 2019 with resounding results and positive feedback on the curriculum and coursework. The Biomanufacturing Education and Training Center (BTEC) at North Carolina State opened registration for the course titled *Hands-On cGMP Biomanufacturing of Vectors for Gene Therapy.* Due to high demand for the first course scheduled for May 2019, a second session has been scheduled for August 2019.
- Partnership for Workforce Development in the Biopharmaceutical Industry: A team consisting of the University of North Carolina Wilmington, Alcami Corporation, Cape Fear Community College, and Brunswick Community College have partnered on a project to strengthen the skills of new graduates so they are better prepared to enter the biopharmaceutical workforce. The program includes lectures and coursework as well as a capstone internship program. The curriculum emphasizes GMP, quality and risk analysis, and advanced manufacturing technologies. The project kicked off with an initial internship cohort in the summer of 2018, followed by a lecture course during the fall. Despite significant challenges in the North Carolina area stemming from Hurricane Florence, 16 students completed the course and will move on to the laboratory portion of the curriculum in the spring of 2019.
- S.P.I.D.E.R. Network for Automation Training: There are significant efforts in advanced manufacturing to automate processes. Several NIIMBL members are working on a project to develop automation test beds and training for implementation at several NIIMBL sites. The S.P.I.D.E.R Network test beds will consist of sensors and software, process control, data analysis, process evolution, and reporting. The test beds will be used to train personnel on automation aspects related to biomanufacturing through a hybrid of online courses and hands-on learning. The S.P.I.D.E.R. team will launch the courses with events at the University of Maryland, Worcester Polytechnic Institute, and North Carolina State University in April and May 2019.





"NIIMBL is enabling development of training programs related to the manufacture of important new therapeutic modalities, like gene therapy. The resulting training opportunities will benefit patients by accelerating the path of these innovative medicines to the clinic."

Gary Gilleskie
Biomanufacturing Training and Education Center at North Carolina State University

The NIIMBL eXperience

In September 2018, NIIMBL and the National Society of Black Engineers announced the NIIMBL eXperience program. The NIIMBL eXperience gives freshman students from HBCUs, historically underrepresented minority-serving institutions, and historically underrepresented minority students at NIIMBL member academic institutions a glimpse into the exciting possibilities of a career in the biopharmaceutical industry. Over the course of one week, students will visit several biopharmaceutical companies and federal agencies. Students will have the opportunity to learn about each organization, interact with current employees, tour facilities, and participate in simulated work activities.

NIIMBL began accepting applications in the Fall of 2018. In February, the first cohort of students was selected. The students will embark on their eXperience journey in June 2019. Host sites include Amgen, AstraZeneca, Merck & Co. Inc., RoosterBio, and NIST.

U.S. Senator Chris Coons, NIST Director Walter Copan, and NIIMBL Institute Director Kelvin Lee visit the site of the Carol A. Ammon and Marie E. Pinizzotto Biopharmaceutical Innovation Center at the University of Delaware on March 31, 2018.

Focusing on Industry's Workforce Needs

Our workforce development group works with our industry members to assess their needs and identify gaps. These insights help NIIMBL shape its project calls and focus areas for workforce development initiatives.

In October 2018, NIIMBL convened a workshop of large industry members. The purpose of the meeting was to come to a consensus on priority topics for NIIMBL's Project Call 2.2 in November.

In 2019, NIIMBL will convene large industry members and academic representatives in a second workshop to continue discussions around workforce priorities. The purpose of this workshop is to provide strategic direction to NIIMBL's workforce development group with respect to actionable strategies, activities, and projects that add value to our members and the biopharmaceutical manufacturing industry as a whole.

In 2019, NIIMBL will launch a workforce assessment survey developed with the help of large industry members. The in-depth survey takes a deep dive into issues related to the recruitment and retention of talent, training and professional development, as well as the skills and experiences necessary to support the next generation of biopharmaceutical workers. The survey results will serve as a key resource in driving NIIMBL's workforce development priorities.

Facilitating Peer Exchange of Best Practices to Address Advanced Biomanufacturing Challenges

Innovation is born from conversation. One of the defining benefits of NIIMBL is our ability to convene conversations among a variety of biopharma stakeholders. These conversations bring about partnerships, lead to innovation that improves our ability to manufacture medicines for the benefit of all patients, and bolsters the Nation's position as the world-leader in biomanufacturing.

Project Call Summits

To bolster collaboration opportunities during the project call process, NIIMBL introduced the Project Call Summit. The two-day Summit gives proposers the chance to showcase their concept to an audience of NIIMBL members and federal scientists through oral and poster presentations. Based on feedback from industry members, selected proposers are invited to move on to the next phase of the project call process and submit a full proposal.

The Project Call 2.1 Summit took place in June 2018. In February 2019, NIIMBL hosted the Project Call 2.2 Summit. In total, NIIMBL members presented nearly 200 concepts.

The Summit not only provides proposers the opportunity to present their ideas to evaluators, but it also gives ample opportunities to network, exchange ideas, and find partners among the NIIMBL community.

Technology Workshops

NIIMBL partners with our members to host topic-focused technology workshops. The workshops are open to NIIMBL members and federal stakeholders and are designed to promote idea exchange and teaming amongst the NIIMBL community.

In 2018, NIIMBL held four technology workshops addressing topics of interest in biomanufacturing. The workshops featured presentations from industry and academic thought-leaders and federal agencies, breakout sessions, poster presentations, and networking opportunities. The focused discussions and breakout sessions helped attendees generate ideas for future project calls.

More than 300 representatives from nearly 50 organizations in total, attended the technology workshops in 2018.

Presentations and breakout session reports are available as a resource to members on the Community Portal at **http://www.niimbl.org.**

2018 NIIMBL TECHNOLOGY WORKSHOPS

Date	Topic	Host
April 23, 2018	Process Innovations for Biologics	Genentech, South San Francisco, CA
May 17, 2018	Process Analytical Technologies, Modeling and Simulation	NIIMBL National Meeting, Washington DC
August 6, 2018	Cell Therapy Manufacturing Innovation	Celgene Corporation, Summit, NJ
October 22, 2018	Adventitious Agent Detection Methods & Controls	Merck & Co., Inc., Kenilworth, NJ

Member Forum

As projects mature, NIIMBL has been expanding ways to highlight project progress to members. In October 2018, we held our first Member Forum, a monthly webinar series open to NIIMBL members and federal stakeholders. Each month, one or more project teams give a brief overview of their project and its progress. Attendees are invited to pose questions to the project team and they are also able to learn more about other NIIMBL activities.

NIIMBL members explore process analytical technologies at a Technology Workshop held May 17, 2018.

"NIIMBL provides us the opportunity to work closely with industry, to find out what industry needs, and hopefully come up with practical technologies industry can use."

Bruce Yu
University of Maryland

2018 NATIONAL MEETING – CELEBRATING, EXPANDING, AND STRENGTHENING THE NETWORK

The spirit of innovation, collaboration, and community was prevalent as NIIMBL convened its second National Meeting in Washington D.C. on May 16 and 17, 2018.

With an emphasis on celebrating, expanding, and strengthening the NIIMBL network, the National Meeting brought together over 300 representatives from NIIMBL member organizations, the biopharmaceutical community, and government agencies to celebrate NIIMBL's first year achievements and look towards future opportunities to advance U.S. leadership in biomanufacturing.

The May 16, 2018 agenda was open to the public and included talks from FDA leadership, Celgene Corporation CEO Mark Alles and MilliporeSigma CEO Udit Batra, which emphasized the impact the NIIMBL public-private partnership can have in addressing technology gaps and enhancing patient access to life-saving therapies. A panel discussion with industry leaders focused on biomanufacturing innovation and its influence on patient health. Remarks from Johnathan Holifield, Executive Director of the White House Initiative on Historically Black Colleges and Universities, and Gail Drake, For Inspiration and Recognition of Science and Technology (FIRST) mentor, addressed developing the next generation of professionals through diversity, inclusion, and mentorship initiatives. The agenda also featured the popular SMM Innovation Showcase in which small companies highlighted their technologies to the biopharmaceutical community to promote visibility and partnerships.

On May 17, 2018, NIIMBL members gathered for project updates, a Technology Workshop focused on Process Analytical Technologies, and sessions devoted to maximizing membership benefits.

"The event is a great opportunity for the community to get together and build momentum for the coming year. We are grateful for the enthusiastic participation and look forward to building upon our National Meeting year after year," said Barry Buckland, NIIMBL Executive Director.

MilliporeSigma CEO Udit Batra presents at the National Meeting on May 16, 2018.

Photos courtesy of NIIMBL.

Photos courtesy of NIIMBL.

Celgene CEO Mark Alles speaks at the NIIMBL National Meeting on May 16, 2018.

The NIIMBL Project Portfolio

Technology Projects

NIIMBL Projects At A Glance

43
Number of Technology and Workforce Development Projects

65
Unique Organizations on Technology and Workforce Projects

>$44M
Total Value of Technology and Workforce Projects

NIIMBL Technology Projects

28
Number of Technology Projects

44
Unique Organizations on Technology Projects

>$35M
Total Value of Technology Projects

NIIMBL Workforce Development Projects

15
Number of Workforce Development Projects

36
Unique Organizations on Workforce Development Projects

>$9M
Value of Workforce Development Projects

PROJECT HIGHLIGHT: ENSURING THE SAFETY OF MEDICINES THROUGH CONTINUOUS IN-LINE MONITORING DURING MANUFACTURING

A considerable part of the cost to manufacture biopharmaceuticals is high because current technologies rely on batch processing rather than continuous processing. To help the field achieve the benefits of continuous processing, it is critical to have "process analytical technology" (PAT) that can monitor the manufacturing of medicines to ensure that the product stream is producing appropriate and safe medicines. NIIMBL members at the University of Maryland Baltimore and ChromaTan are pioneering an in-line approach to measuring contaminants in process streams that should enhance patient access to medicines by shortening the time needed to manufacture and reducing the cost.

The project uses water proton NMR (nuclear magnetic resonance) for in-line monitoring during the downstream purification process. This in-line PAT is noninvasive, reducing the need for interaction with the product stream that may lead to contamination or errors. It also monitors in real-time, allowing for continuous manufacturing which has the potential to significantly reduce manufacturing times.

The team has made significant progress to date. It has been able to demonstrate the applicability and sensitivity of Flow-water NMR as a contact-free, real-time, in-line PAT for continuous biomanufacturing, as it has the ability to detect concentration changes of a protein under a wide-range of flow conditions. The project enters its next phase during NIIMBL's third year.

Technology Projects

PROJECT HIGHLIGHT: MAINTAINING PRODUCT QUALITY AND ENHANCING MANUFACTURING SPEED THROUGH GLYCOSYLATION STANDARDS, MEASUREMENT AND CONTROL

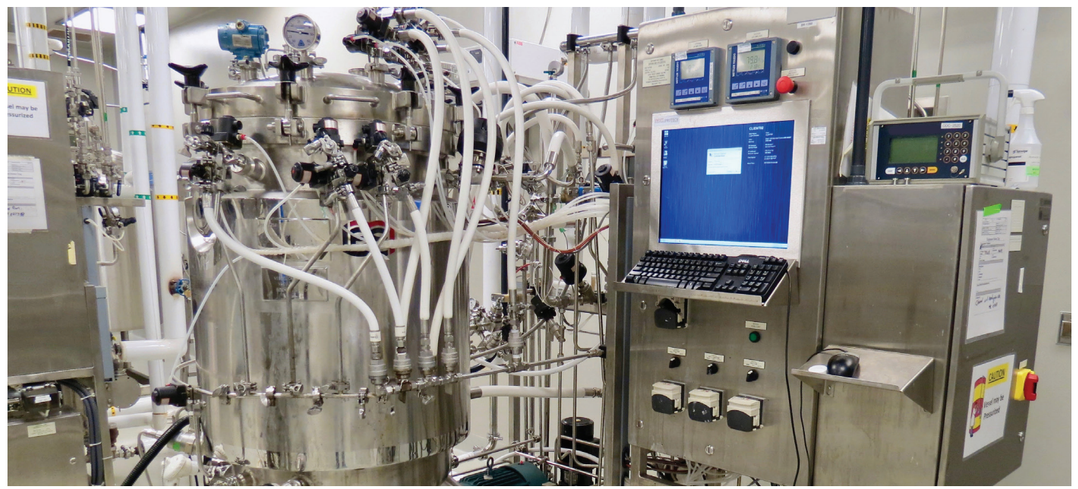
After a cell synthesizes a protein, post-translational modifications may be made that affect the function of the protein. One such modification is glycosylation, or the addition of carbohydrate groups (glycans) to a therapeutic protein. Glycosylation patterns can affect therapeutic protein half-life, immunogenicity, and function within the body. A project led by Carnegie Mellon University aims to help industry more fully control glycosylation on therapeutic proteins through development of standards, improved measurement technologies, and process control.

The team is creating antibody glycan standards, which are not currently commercially available, that will be used for development of more rapid glycan measurement methods.

Current processes used to measure glycosylation are time-intensive, often requiring days to receive results. This project is developing multiple approaches to improve measurement times. At-line rapid-response sensors are being developed to measure glycans on antibody products. The team is also working to improve at-line profiling of glycans using UPLC and MS technologies. The ability to more quickly measure glycans on the order of minutes to hours will help manufacturers more quickly assess and control product quality in their processes.

Using the newly developed measurement technologies, the team is also working on new control systems to culture conditions in bioreactors to achieve the desired glycan profiles. This technology enables manufacturers to make adjustments during the process to maintain and ensure product quality.

The project shows tremendous promise as so far the team has been able to establish the necessary standards and has progressed to perfecting the measurement technologies. The team has also begun preliminary work on the control algorithms that will be used as soon as the sensors and measurement techniques become available.



Flow Water Proton NMR as Contact-Free Real-Time In-Line PAT for Continuous Biomanufacturing

PARTICIPANTS

University of Maryland Baltimore

SUPPORTING PARTICIPANT

ChromaTan

ABSTRACT

This project develops a contact-free real-time in-line process analytical technology (PAT) for biomanufacturing. The technology, flow-wNMR, is based on the nuclear magnetic resonance signal of water. Because water is the solvent in all biomanufacturing processes, flow-wNMR has wide applicability. Flow-wNMR has no contact with the process stream, therefore probe fouling, a fundamental limitation of existing in-line PATs, is eliminated. The focus of this project is to integrate flow-wNMR with a continuous protein purification system --- countercurrent tangential chromatography. The simplicity, flexibility, affordability and sturdiness of flow-wNMR make it easily adoptable to various floor conditions in biomanufacturing plants.

IMPACTS

- In-line, non-invasive monitoring of soluble protein aggregates in downstream process steams at 1-10% levels
- Enabling PAT for continuous manufacturing and reduced time for product release

At-line Detection of Viral and Bacterial Contaminants in Mammalian Cell Culture Using High Affinity Probes and Label-free Single-cell Analysis

PARTICIPANTS

Carnegie Mellon University

SUPPORTING PARTICIPANTS

LumaCyte

Genentech

ABSTRACT

We propose to design and implement a combination of laser force cytology cell analysis and sorting and capillary electrophoresis (CE)-based methods to screen for viral and bacterial contamination, along other process parameters. Detection will be accomplished using a rapid, gel-free analysis platform ("micelle-ELFSE") and high affinity unnatural nucleic acid probes. A laser force cytology system will be developed for label-free detection of virus and bacteria. The two systems will be integrated with the goal of at-line or in-line detection along with assessment of final product purity.

IMPACTS

- Rapid at-line detection of viral contaminants
- Allows for process troubleshooting and screening of raw materials, cell banks and bulk harvest materials

Technology Projects

Adaptive Process Control and Advanced Sensing for Robust mAb Glycan Quality

LEAD PARTICIPANT

Carnegie Mellon University

SUPPORTING PARTICIPANTS

Johns Hopkins University
University of Maryland College Park
University of Delaware

ABSTRACT

This project focuses on key post-translation modification impacting product quality of biotherapeutics, specifically the carbohydrate groups (glycans) that affect antibody function, stability, immunogenicity, and plasma half-life. The goal of this multidisciplinary, multi-institute initiative is to implement enhanced glycan sensors with control algorithms to produce consistent, desirable glycosylation patterns. Lectin arrays generating quantitative electrical and fluorescence signals will be tested against antibody standards and samples from bioreactors and then integrated with nested glycan and nutrient control during fed-batch culture. A bioprocess performance platform producing near real-time control of critical glycan attributes will be ready for pilot scale implementation by completion of the 18-month project.

IMPACTS

Improved process efficiency and reduced batch-to-batch variability

Fully Automated Micro-Bioreactor

LEAD PARTICIPANT

ProMechSys
WHERE INTELLIGENCE INNOVATES

(ProMechSys-RLP, LLC)

SUPPORTING PARTICIPANTS

Genentech
Johns Hopkins University
MilliporeSigma/EMD Serono

ABSTRACT

Manual laboratory trials in biotechnology have high labor and time demand, which leads to prolonged R&D time and to increased capital investment for biotechnology projects. Current automation solutions are very expensive and not customizable. Especially SMEs and start-ups, and research institutes fall back upon manual methods, which lead them to fall behind in the highly competitive biotechnology market. The aim of this project is to develop a proof-of-concept for modular microbioreactor system especially for Biotech Industry by tackling mechatronic, electronic and bioprocess engineering challenges. The identification of critical specifications, target application, implementation of the design, system validation and bio-validation are the main tasks of the project. By the end of the project, safety, robustness, repeatability and performance of the Alpha prototype will be ensured. It is intended to provide a low cost, highly modular solution for automation of laboratories with a high-throughput micro bioreactor for the cultivation of wide range of cells. This is going to reduce CAPEX and OPEX and speed-up (up to 200 times) the R&D projects such as development of bio-molecules and industrial cell lines.

IMPACTS

- Low cost, highly modular automated micro bioreactor for cultivation of a wide range of cells.
- Reduce CAPEX and OPEX as well as reduced biopharmaceutical development timelines.

Software and Hardware Tools for Pharmaceutical Lyophilization Scale-up

LEAD PARTICIPANT

PSI Physical Sciences Inc.

SUPPORTING PARTICIPANTS

Genentech
Merck & Co., Inc.
University of Massachusetts Lowell
NIPTE-University of Connecticut
Purdue University
Massachusetts Life Sciences Center

ABSTRACT

This project aims to develop and test hardware and software tools that will harmonize pharmaceutical lyophilization process development and scale-up. These manually operated tools (spreadsheets, procedures and sensors) are targeted for application by research and development scientists. These tools enable application of rapid and standardized procedures for Quality by Design (QbD)-based process development and process scale-up for pharmaceutical companies that possess lyophilization expertise and also for those companies that have limited experience in freeze drying. In addition to standardizing lyophilization process development, the development of comprehensive knowledge of the process design space enables the development of higher throughput processes, saving time, money and enabling more efficient production of higher quality products using fewer capital resources.

IMPACTS

- Development of modeling tools and sensors to enable process development and scale-up

A Multiscale Metabolic Model for Fed Batch Culture Process Control

LEAD PARTICIPANT

(Regents of the University of Minnesota)

SUPPORTING PARTICIPANTS

MilliporeSigma/EMD Serono
Merck & Co., Inc.
Matalytics

ABSTRACT

Glucose metabolism plays a central role in cell physiology. Cells in culture have a high flux of glucose consumption and convert a large portion of the consumed glucose to lactate. In the late stage of fed-batch culture, the high flux metabolism may switch to low flux. The occurrence, or the lack thereof, of metabolic shift in fed-batch cultures affects the productivity and quality of therapeutic proteins. However, the behavior of such a metabolic shift varies among different production cell lines, and in some cases, even among manufacturing runs using the same production cell line. This project will develop a mechanistic model of cell metabolism that can be integrated with a multiscale cell growth model to predict of metabolic behavior in fed-batch culture. The metabolic profile of three cell lines will be characterized to determine the kinetic parameters and cell specific model will be established for the three cell lines. The model will allow for a rational design of fed-batch processes to increase process robustness. The technology is currently at MRL3 and will be at level 4 upon the completion of the project.

IMPACTS

- Development of a systems model for fed-batch cell culture, which can enable rational process design and increase process robustness.

Center of Excellence in Host-Cell Protein Analysis

LEAD PARTICIPANT

UNIVERSITY OF DELAWARE

ABSTRACT

The analysis of host-cell proteins (HCPs) is a route to more fine-grained insights into cell culture and purification of existing products and is likely to aid development of new modalities such as cell therapies. Proteomics technologies, particularly liquid chromatography – mass spectrometry (LC-MS) approaches, enable HCP analysis, and their availability allows more routine characterization of HCPs that may pose challenges to the industry and development of new methods for HCP analysis. Delaware is creating a NIIMBL Center of Excellence in HCPs that will support the development and testing of state-of-the-art and emerging methods for HCP analysis using mass spectrometry. Such a Center will also serve as a NIIMBL "core facility" for performing HCP analysis in support of NIIMBL projects and organizations. Such support may include, but is not limited to: A) providing HCP analysis services to partners (e.g. academic, Tier 3 industry, etc.) on a fee-for-service mechanism, which is likely to require significantly less expense than third-party analyses; B) supporting projects that rely on HCP analysis (where analyses will be done by the Center of Excellence or as a complement and benchmark to such analyses from partners); C) testing various methods that may be applicable to emerging LC-MS approaches; and D) developing methods that will be leveraged in defining standards for routine testing in the industry. Moreover, such a Center will serve as a repository for identified HCPs, which will lead to the creation of either a NIIMBL-specific, or a publicly-available, database of all identified HCPs and their significance in bioprocessing. This activity will also leverage the University of Delaware's role in maintaining the CHO and Chinese hamster reference genomes. This activity will be led by Prof. Bramie Lenhoff.

IMPACTS

- Standardized mass spectrometry-based methods for HCP detection
- Support for routine HCP analysis

Use of Carbon Thin Films to Reduce Leachable Contamination

LEAD PARTICIPANTS

NC STATE UNIVERSITY

SUPPORTING PARTICIPANTS

Genentech

ILC Dover

ABSTRACT

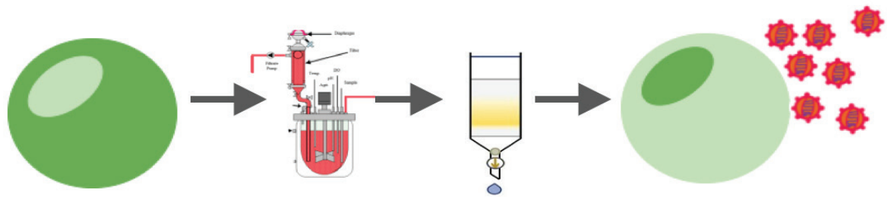
This project seeks to minimize the release of leachables from single-use vessels used in biopharmaceutical manufacturing by depositing hydrogenated diamond like carbon coatings on the interior surfaces of these vessels. NC State University, ILC Dover, and Genentech will work together to evaluate diamond-like carbon coatings in a GLP laboratory environment using industry-relevant samples and standards (i.e., MRL 4 project activities). An overall approach described by U.S. Pharmacopeia that involves material screening, controlled extraction (simulation), and product assessment steps will be utilized. In the materials screening steps, surface resistivity studies, mechanical assessment studies, oxygen transmission studies, protein adsorption studies, and in vitro biological studies will be performed. The controlled extraction (simulation) study will simulate the release of leachables from the diamond-like carbon coated vessels under worst case parameters. The product assessment step will involve the measurement of leachables in a biopharmaceutical therapeutic product under commercial biopharmaceutical manufacturing conditions. If the proposed project is successful, then the biopharmaceutical industry will have an optimized approach for applying diamond-like carbon coatings to vessels that are used in biopharmaceutical manufacturing. A report describing the performance of the diamond-like carbon coated vessel will be prepared, which will facilitate implementation of diamond-like carbon coating technology in biopharmaceutical manufacturing.

IMPACTS

- Develop a standardized approach for depositing diamond like carbon coating on single use vessels to minimize the release of leachables
- Minimize the need for extensive functional tests typically required for disposable vessels

Technology Projects

Improved Lentiviral Vector Biomanufacturing for Cell and Gene Therapy Applications



Improved LV Production and Scalability

LEAD PARTICIPANTS

UMASS · JOHNS HOPKINS UNIVERSITY

SUPPORTING PARTICIPANTS

Artemis Biosystems
Rensselaer Polytechnic Institute
Repligen
Massachusetts Life Sciences Center
Unum Therapeutics

ABSTRACT

Lentiviral vectors are critical to the growing field of cell and gene therapy, in which the lentiviruses are used to deliver life-saving genes into a patient's own cells. Unfortunately, current production processes, in which host mammalian cells are used to generate lentivirus, are inefficient, resulting in low yields, lack of scalability, and high biomanufacturing costs. With clinical trials and FDA approval of T-cell immunotherapy, efficient lentiviral production processes appropriate for large scale manufacturing are needed. The aim of this project is to provide the industry with a lentivirus production process that yields large quantities of highly potent vector with fast facility turnaround times. Specifically, upstream challenges will be addressed using high-throughput studies to optimize host cell growth and increase lentivirus production. These findings will be used to develop a cell culture process using transient transfection of high density HEK293 cells. Downstream purification will be enhanced by advanced chromatographic separations and screening media reagents. These findings will be used to replace existing lentivirus purification processes with fast, high yielding flow through mode chromatography processes. In parallel, analytical technologies will be developed to enable manufacturers reduced feedback time for in-process samples as well as increased accuracy and precision of viral and infectious titer measurement. Ultimately, an integrated process including optimized bioreactor operations and downstream purification will be developed appropriate for scale-up. This NIIMBL academic-industrial collaboration will define and modify key factors with the goal of improving lentiviral production in a process appropriate for large scale biomanufacturing.

IMPACTS

- Development of a platform process to mitigate lentiviral vector supply shortages for cell and gene therapy
- Improved viral vector production process yield, processing times, and measurement accuracy

At-Biorecator Trace Metal Quantification and Statistical Process Control in CHO Cell-culture Production

LEAD PARTICIPANT

CLEMSON UNIVERSITY

SUPPORTING PARTICIPANTS

FDA
Merck & Co., Inc.
University of Massachusetts (Lowell)

Liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma integrated with an Advion Compact Mass Spectrometer (CMS) for at-reactor elemental analysis.

ABSTRACT

While there are relationships between CHO cell growth/productivity and the metals composition of the medium, studies to date have not yielded universally applicable conclusions. Once quantified accurately and in real-time, metals composition could become a useful control parameter. To this end, researchers at UMass Lowell along with US FDA (CDER) are studying the roles of trace metals, (Cu, Mn, Se, and Zn) in CHO cell culture production and are developing an offline assay for trace-metal quantification. In order to closely monitor and control critical trace metals in cell-culture production, real-time (or near real-time) instrumental methods need to be in place that provide such analyses, preferably on simplified platforms that can be implemented at-reactor. This can be particularly useful in continuous processing environments. Clemson University has developed the liquid sampling-atmospheric pressure glow discharge (LSAPGD) microplasma as a simple, sensitive ionization source for elemental analysis. Uniquely, the device can be implemented on small-footprint LC-MS platforms. As such, the need for "remote" or off-line analyses on core facility ICP-MS systems may be alleviated. Proof of concept has been demonstrated in collaboration with Merck laboratories on a Waters (Billerica, MA) QDa platform, but other manufactures also offer systems which could be readily implemented on the production floor.

IMPACTS

- At-line measurement of trace metals in near real time to enable process consistency and control

Technology Projects

Next Generation Sequencing (NGS) Internal Controls for Adventitious Agent Testing to Ensure Sensitivity for All Targets in Every Sample

LEAD PARTICIPANT

AccuGenomics
STANDARDIZED MOLECULAR DIAGNOSTICS

SUPPORTING PARTICIPANT

North Carolina State University

ABSTRACT

Adventitious agent testing of Master and Working cell banks is one critical aspect of purity testing as it minimizes risk of upstream contamination. Adventitious agent testing is moving away from the use of animal models to more in vitro tests such as cell culture and PCR-based methods. This project will develop a test kit—AccuKit— that streamline adventitious agent screening while directly ensuring every target is measured with the required sensitivity. AccuKits will incorporate PCR primers specific for 22 known adventitious viruses and bacteria for high throughput NGS screening assays. Our kit will contain a mixture of competitive templates for every adventitious agent spiked into every sample as internal sensitivity controls; the expected test result for contamination should be positive for every spike-in target and negative for the native targets. The platform allows for additional primer sets to be added to the AccuKit to meet future adventitious agent detection needs. In collaboration with our partners at North Carolina State University, Celgene Corporation, and Merck we will advance our MRL-4 level technology to MRL-6. Our project will increase the efficiency of adventitious agent detection by providing the missing quality controls to ensure a sensitive biosafety testing package for any biopharmaceutical product.

IMPACTS

- Development of a platform process to mitigate lentiviral vector supply shortages for cell and gene therapy
- Improved viral vector production process yield, processing times, and measurement accuracy

A Novel Perfusion-based 3D Bioreactor for Effective Selection, Activation, and Transduction of T-cells for Immuno-Gene Therapy

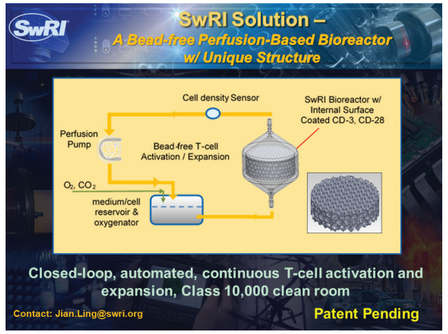
LEAD PARTICIPANT

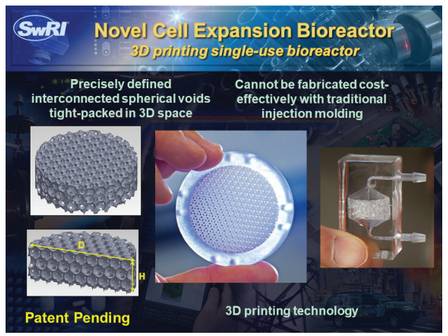
SwRI®

(Southwest Research Institute)

SUPPORTING PARTICIPANT

University of Pennsylvania





ABSTRACT

Adoptive T cell immunotherapy has become an important approach to cancer therapy with two therapies, tisagenlecleucel and axicabtagene ciloleucel, achieving FDA approval in 2017. Manufacturing of T cell-based therapies both consistently and cost-effectively remain major challenges in the field. Current approaches such as microbead-based selection and activation require multi-stage, open processes with significant human interaction, which contributes to the high-cost for cGMP manufacturing of these therapies. This application will focus on development of an integrated process/platform development based on a novel perfusion-based, microbead-free 3D bioreactor to achieve the selection, activation, and gene transduction of T cells in a single continuous processing system. This beads-free, closed-loop system is expected to simplify the manufacturing process and form the foundation for achieving full automation. In addition, this system is designed to facilitate scaling for different applications that can be applied across a broad array of T-cell based applications to reduce the development cost, shorten the transition time from discovery to manufacturing, and have high impact to the immunotherapy of cancer, and bring benefits to the patients. The technology will start at MRL 4 and end at MRL 5 for this application.

IMPACTS

- The goal of the project is to develop a superior process / platform for selection, activation and lentiviral vector transduction of human T-cells using perfusion bioreactor system
- The project will enable continuous processing of T-cells in a closed environment and reduce process costs

Identification, Characterization and Removal of Host-Cell Proteins (HCP) in Chinese Hamster Ovary (CHO) Monoclonal Antibody Biomanufacturing Processes

LEAD PARTICIPANT

University of Delaware

SUPPORTING PARTICIPANTS

Genentech
Merck & Co., Inc.
North Carolina State University
Rensselaer Polytechnic Institute
Repligen Corporation

ABSTRACT

We propose to develop a consistent, comprehensive approach to identify and clear problematic HCPs in mAb biomanufacturing. Our starting point will be to determine the identities and levels of HCPs in representative mAb bioprocesses based on CHO cells, which will serve as the foundation for a CHO HCP knowledge base that will include biophysical properties and downstream process characteristics for individual HCPs. This knowledge base can support a wide variety of related activities; among which we will pursue two avenues. First, our analysis of clearance of individual HCPs will allow identification of a set of HCPs that are not easily cleared, and these problematic HCPs will be identified as such in the database. Second, we will develop a novel approach to bioprocessing by using a tailored mixture of peptide ligands (PepMix) designed to capture the broad spectrum of HCPs secreted by CHO cells. The approaches to be used will be primarily at MRL 4 or above; the database to be developed will be applicable to both process development and analytics (e.g., general HCP reagent for conserved HCPs) and processes currently in manufacturing, while the new bioprocessing component is expected to reach MRL 5---6 by the end of the project.

IMPACTS

- Develop a database of CHO host cell proteins (HCPs) and their biophysical properties, particularly those that are difficult to remove during manufacturing.
- Database will include characterization of HCP interactions with mAb products and typical resins.
- Improved PepMix(es) for capturing a broad spectrum of HCPs from CHO cell lines, including the clearance of problematic HCPs.

Quantitative Trilineage Differentiation Assays for cGMP Cell Manufacturing of Human Mesenchymal Stem Cells

LEAD PARTICIPANT

RoosterBio

SUPPORTING PARTICIPANT

Tulane University

ABSTRACT

Human Mesenchymal Stem Cells (hMSCs) are currently associated with over 800 clinical trials (clinicaltrials.gov). As these studies progress to Phase 2 trials and beyond, more rigorous cGMP operations become required. Many investigators will then need to transfer their production and testing processes to contract manufacturing and testing organizations (CMOs and CTOs). In the production of clinically relevant hMSCs, one limiting obstacle is the lack of objective quantifiable protocols for evaluating trilineage differentiation, a critical attribute of these stem cells. Currently, the standard assessment of osteogenic, adipogenic, and chrondrogenic differentiation is based on qualitative staining. In order for this critical quality attribute to be able to shift from a "for information only" characterization to a product release specification, GMP compliant assays for differentiation need to be developed. Over the course of this effort, an analytical method will advance from MRL 4 to MRL 7.

IMPACTS

- GMP compliant assays for human mesenchymal stem cell (hMSCs) differentiation.
- CQAs for product release specification rather than "for information only."
- Methods developed will be used to draft standards for differentiation with the Standards Coordinating Body for the entire field of adult stem cell research.

Technology Projects

Low-cost Production and Purification of Cytokines and Growth Factors for Cell Therapy Products

LEAD PARTICIPANT

Potomac Affinity Proteins

SUPPORTING PARTICIPANT

University of Maryland College Park

ABSTRACT

Cellular therapeutics would greatly benefit from standard synthetic cell culture media. Cytokines and growth factors are critical and expensive components in synthetic media and are needed to support cell growth, survival, and differentiation. Potomac Affinity Proteins has developed an E. coli expression system and affinity-tag purification method that can provide great simplicity, reliability, and economy in the production of cytokines and other growth factors. We will develop stable and well-controlled processes for producing and purifying IL-2 and FGF2. IL-2 is a cytokine used in Adoptive T-Cell Therapy (ACT). Basic-Fibroblast Growth Factor (FGF2) is used in the cultivation of Mesenchymal Stem Cells and Induced Pluripotent Stem (ISP) Cells. The two main technical objectives are: 1) Scale-up and standardized manufacture of a low-cost purification medium for capturing tagged-proteins and releasing the tag-free proteins. 2) Scale up and standardize economical purification of IL-2 and FGF2 and validate the purity, biophysical properties, and biological activity in each purification run. Over the 18-month project, the processes will advance from the laboratory scale (MRL 3-4) to a process capable of manufacturing quantities of IL-2 and FGF2 for large-scale use in cell culture (MRL7-8). We also expect that the cost of growth factor will decrease by >10-fold.

IMPACTS

- Reduce the cost of growth factors (by 10 fold) for cell therapy manufacturing
- Develop a novel low-cost purification technology to purify difficult to express tag-free proteins

Use of Metabolic Flux Analysis (MFA) to Expedite Media Selection and Optimization of CHO

LEAD PARTICIPANT

MilliporeSigma

SUPPORINT PARTICIPANT

Metalytics

ABSTRACT

This NIIMBL project seeks to build an expedited process for media selection and optimization for biomanufacturing. Current approaches to identify appropriate media formulations for CHO cell factories are lengthy, costly, and labor-intensive. Thus, there is an industry need to improve media selection processes and speed time to production. In this regard, MilliporeSigma has partnered with Metalytics, Inc. to integrate metabolic flux analysis (MFA) into a diagnostic kit that can be used to quickly and effectively identify best media composition for a given CHO cell line. To achieve this, we will stratify a diverse set of CHO lines into distinct groups, each characterized by its own set of nutritional requirements. We will use MFA characteristics of these CHO clonal groups to rationally design and optimize media and process for each group. Finally, we will utilize our findings to create a diagnostic tool-kit that can be utilized by end users to pair each clone with a "best fit" media formulation that will maximize metabolism of raw ingredients into pharmaceutical product. At completion of this project, our technology will be at an MRL level of 7. These studies stand to have significant impact on the biomanufacturing industry, leading to shorter development timelines and measurable labor and cost savings.

IMPACTS

- Create a guided metabolic profiling toolkit to streamline identification of optimal CHO cell media formulations.
- Reduce media development screening costs by using a predicted "best fit" medium formulation for CHO cell clonal groups.

Technology Projects

Improving Lyophilization of Recombinant Proteins with ssHDX-MS

LEAD PARTICIPANT

PURDUE UNIVERSITY

SUPPORTING PARTICIPANTS

Genentech

Lindy Biosciences Inc.

ABSTRACT

More than 40% of protein drugs approved by the FDA in the past decade are sold as solid powders. Most are produced by lyophilization, a manufacturing process that is effective but slow and inefficient. Developing or improving a lyophilization process requires stability studies to ensure product quality. In a stability study, the product is stored at controlled conditions and analyzed over time for drug degradation. Because degradation is usually slow, stability studies can take months or even years to complete. This increases time-to-market for new drugs and slows manufacturing improvements for existing drugs. This project will evaluate a novel analytical method, called solid-state hydrogen deuterium exchange with mass spectrometric analysis (ssHDX-MS), as an alternative to stability studies for proteins in solid powders. ssHDX-MS takes just days to complete and the results are highly correlated with formulation-induced stability changes. This NIIMBL project will relate changes in lyophilization process to ssHDX-MS and protein stability on storage, testing whether ssHDX-MS can be a surrogate for stability studies. The project will also evaluate ssHDX-MS for novel drying methods being developed as alternatives to lyophilization. The ssHDX-MS method is currently TRL 4 and will be advanced to TRL 6-7 in this project.

IMPACTS

- Evaluation of ssHDX-MS as a potential tool to rapidly determine the stability of lyophilized drug products during process development and formulation.
- Decrease the risk of post-approval CMC changes and enable high-resolution evaluation of novel drying technologies for recombinant proteins.

A Transcriptome-based model for improved CAR-T Therapy

LEAD PARTICIPANT

VILLANOVA UNIVERSITY COLLEGE OF ENGINEERING

NovaCell CENTER FOR CELLULAR ENGINEERING

SUPPORTING PARTICIPANTS

Merck & Co., Inc.

Redbud Labs

ABSTRACT

An estimated 10-20% of CAR-T batches fail due to slow growth rates of Tcells during the expansion step of the process. Furthermore, the starting material for every batch differs in many ways including the distribution of phenotypes in the Tcell population, yet the final product specification is fixed. Tcell growth rates can be affected by levels of cytokines and different Tcell phenotypes respond differently to growth factors. This project then aims to evaluate how levels of key cytokines affect the growth rate of important Tcell phenotypes, so as to promote a more consistent final product. To accomplish this, a properly scaled-down "bioreactor" must be used. Preliminary work will evaluate the capabilities of Redbud Technologies' magnetic posts for providing mixing and improved oxygen transfer to Tcells growing on 96 well plates. With a cost per treatment of approximately $500K, preventing 20 batches per year from failing protocol growth specifications could result in a cost avoidance of $10M. The proposed approach of using microbioreactors and a transcriptomics-based mathematical model to optimize levels of cytokines for CART patients is at MRL level of 4-5 now and will proceed to level 6-7 with the hand-off to clinicians at the end of this project.

IMPACTS

- Screen CAR-T patients' cells for enhanced growth prior to start of the clinical batch using a transcriptome-driven mathematical model and scaled-down bioreactor.
- Reduce number of failed batches of CAR-T cells due to slow growth or incorrect phenotype distribution.

Technology Projects

Development of a Microchip CE-HPMS Analyzer for Bioreactor Monitoring

LEAD PARTICIPANT

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

SUPPORTING PARTICIPANTS

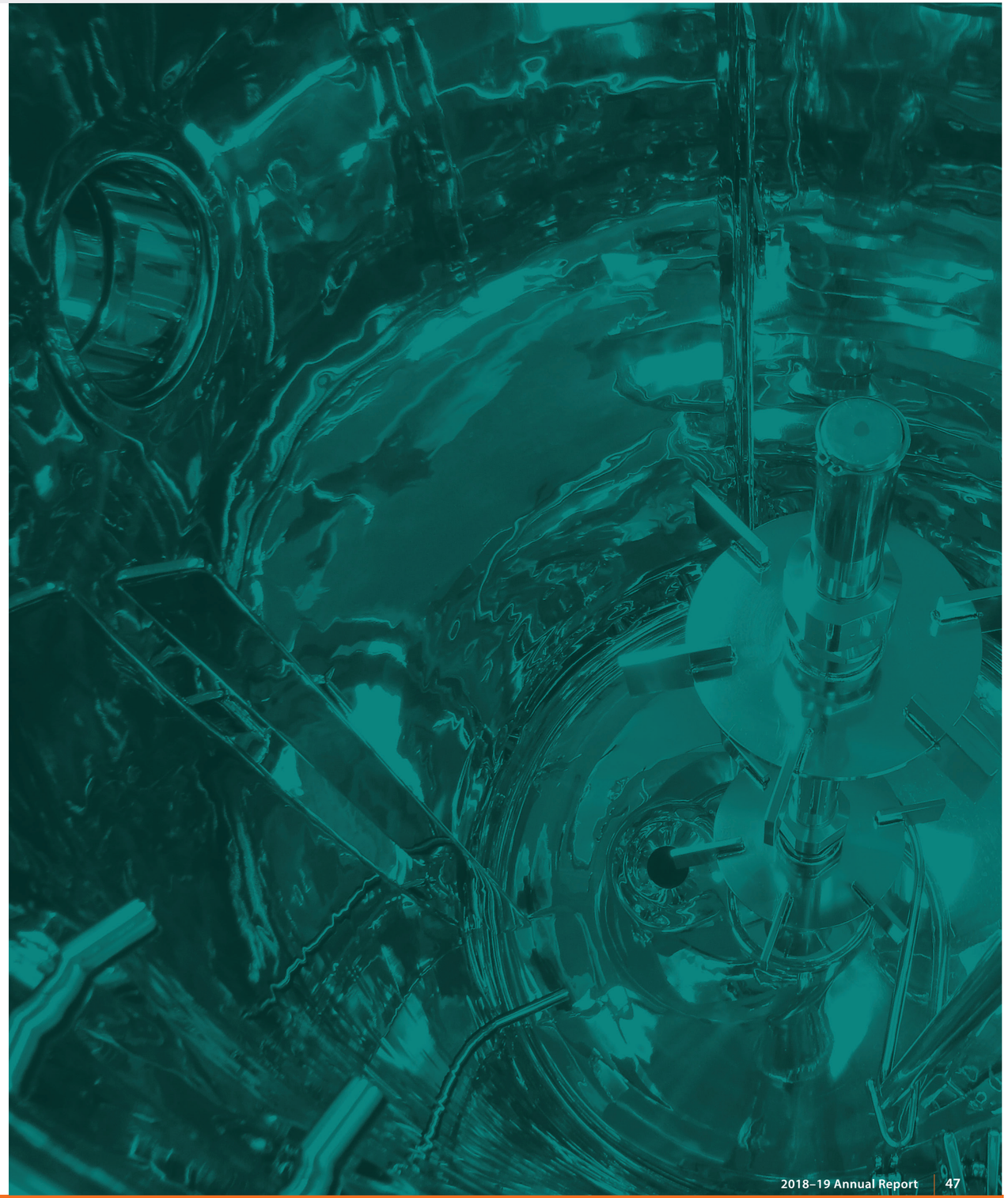
908 Devices Inc.
Celgene Corporation
MilliporeSigma/EMD Serono
North Carolina State University

ABSTRACT

We propose the development of a compact microchip-¬based capillary electrophoresis-¬high pressure mass spectrometer (CE-¬HPMS) analyzer for near real-¬time monitoring of the nutrients and cell metabolites involved in the biomanufacturing process. An analyzer capable of monitoring cationic species will first be demonstrated followed by the addition of anionic molecules. The system offers the benefit of high separation efficiencies with MS detection in a small footprint that can be located on manufacturing floors or cell culture labs. The rapid feedback would improve bioreactor control and thus product quality and yield. The proposed tool builds off two commercial technologies; the first is the ZipChip CE separation platform that uses commercial mass spectrometers and can analyze small molecules up to intact proteins in less than 3 minutes. The second is the MX908 handheld HPMS used for chemical, explosive, drug, and toxic industrial chemical monitoring. Both core technologies are fully commercialized products at MRL 10. The integration of both into a single platform has been demonstrated in the laboratory and is at the MRL 5/6 level. It is expected that within 18 months, the cation analyzer will advance to MRL 8, and incorporating the anion capabilities will be at MRL 7.

IMPACTS

- Development of a compact microchip-based capillary electrophoresis-high pressure mass spectrometer (CE-HPMS) analyzer for near real-time monitoring of the nutrients and cell metabolites involved in the biomanufacturing process.
- Reduced reliance on the "centralized laboratory" model, decreased capital and facility costs in next-generation facilities.



Workforce Development Projects

PROJECT HIGHLIGHT: REDUCING DOOR-TO-FLOOR: IMPROVING READINESS OF NEW HIRES THROUGH CGMP HANDS-ON BIOPHARMACEUTICAL TRAINING

Project Highlight: Reducing Door-to-Floor: Improving Readiness of New Hires Through cGMP Hands-on Biopharmaceutical TrainingaGetting new hires to the point of self-sufficiency on the manufacturing floor is often a time-consuming and costly process for biopharmaceutical manufacturers. Texas A&M University with partners Vericel Corporation and Akron Biotechnology, LLC are addressing this challenge by developing a "Door-to-Floor" training program designed to adequately prepare college students and career changers for jobs in the biopharmaceutical industry.

The program creates a pipeline of workers with bioprocess experience and reduces the costs and time required for companies to train new hires.

Students complete 16 hours of online training combined with 80 hours of hands-on training. The online curriculum begins with introductory courses on biopharmaceutical manufacturing, cGMP procedures and documentation, and facility operations and safety. Hands-on training focuses on upstream and downstream biomanufacturing processes.

In February 2019, the first of four student cohorts completed the course. Additional cohorts are scheduled to begin in April, July, and November 2019. Several biopharmaceutical companies in the region have reached out to the trainees for interviews.

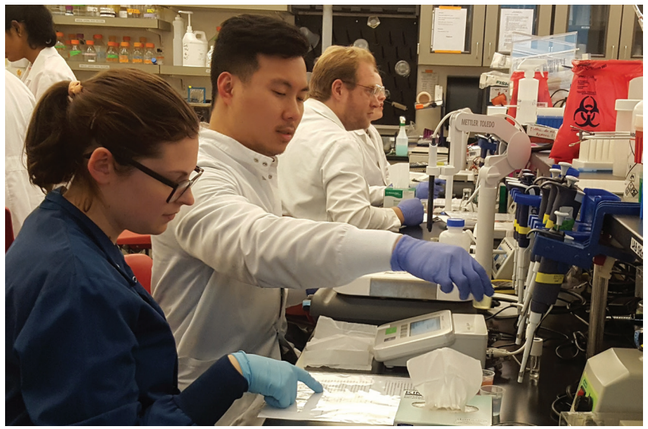
Stackable Credentials for Biotechnology Workforce Development

LEAD PARTICIPANT

Shoreline COMMUNITY COLLEGE
Engage. Achieve.

SUPPORTING PARTICIPANTS

Life Science Washington
Celgene Corporation



ABSTRACT

36,000 workers. Yet the region's competitiveness and long-term growth is challenged by the lack of a skilled workforce. In this project, Shoreline Community College (PI: Guy Hamilton), Juno Therapeutics (Co-PI: Snehal Patel), and Life Science Washington aim to alleviate workforce shortages by establishing guided academic pathways for students and workers seeking careers in biomanufacturing. Working with industry partners, Shoreline seeks to align curriculum with industry workforce needs. After identifying a set of technical knowledge and activities, modules and courses will be created by the team to train students in those skills. Students who complete modules will gain industry-vetted, stackable credentials. To develop a workforce pipeline, the team plans to conduct an engagement campaign with high school and community college students and workers in need of retraining. The team will make all course materials nonproprietary and openly accessible to allow for scalability.

This is the first phase in a long-term objective to establish national standards through a national certification organization.

IMPACTS

- Create stackable credentials and certificates that are scalable for the biomanufacturing and biopharmaceutical sectors.
- Create a workforce pipeline for the biomanufacturing industry via a marketing and communications plan targeting students, teachers, and parents.

Workforce Development Projects

SPIDER Network for Automation Training

LEAD PARTICIPANT

NC STATE UNIVERSITY

SUPPORTING PARTICIPANTS

Worcester Polytechnic Institute

University of Maryland, College Park

Commissioning Agents, Inc.

International Academy of Automation Engineering

Genentech

Merck & Co., Inc.

ABSTRACT

Automated bioprocess test beds will be designed and implemented across three sites. Each test bed will consist of process **S**ensors and software for **P**rocess control, **I**ntegration, **D**ata analysis, process **E**volution, and **R**eporting. The test beds in the SPIDER Network will be used for training that addresses automation topics relevant to engineering, validation, operations, and quality assurance personnel. The team will develop an introductory course that can be delivered in hybrid format: online lectures and hands-on automation activities to apply new learning. In the future, the test beds will support additional courses and can also be used by research teams to facilitate innovation of new process analyzers, software, production processes, and data analysis models.

IMPACTS

- Skilled workforce in automated bioprocesses enables process efficiency and product consistency

Reducing Door-to-Floor: Improving Readiness of New Hires through cGMP Hands-on Biopharmaceutical Training

LEAD PARTICIPANT

TEXAS A&M UNIVERSITY

SUPPORTING PARTICIPANTS

PBS Biotech

Vericel Corporation

ABSTRACT

To address the significant pipeline deficiency of a readily-available skilled workforce in the biopharmaceutical manufacturing industry, Texas A&M Engineering Experiment Station (TEES) will train forty (40) university and community college students, career changers, and military veterans to become biomanufacturing professionals. "Door-to-Floor" is a Manufacturing Readiness Level (MRL) 7 project with the goal to significantly diminish the time it takes for a new hire to add value in their job as biologics manufacturing technicians and engineers. We will immerse trainees in a rigorous digital and hands-on training program, comprised of more than one hundred (100) hours of cGMP- and regulatory-based curricula, including aseptic cell processing using fixed and single-use fermentation and purification systems, quality management systems, proper documentation practices, and advanced cell therapy bioprocessing curriculum developed in conjunction with PBS Biotech. Participants will complete five (5) asynchronous online courses, and then participate in two (2) full weeks of hands-on training at the National Center for Therapeutics Manufacturing (NCTM) in College Station, Texas. Upon completion, the "Door-to-Floor" project will be at MRL 8, and its technically-skilled graduates will be ready for immediate employment with National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) industry partners.

IMPACTS

- "Door-to-floor" will significantly reduce the time for new hires to add value to their biopharmaceuticals manufacturing job.
- In addition to coursework, trainees will gain hands-on experience in current and emerging technologies through two weeks of training at the National Center for Therapeutics.

Workforce Development Projects

Preparing for the Future: A Gene Therapy Vector Production Platform

LEAD PARTICIPANT

NC STATE UNIVERSITY

SUPPORTING PARTICIPANT

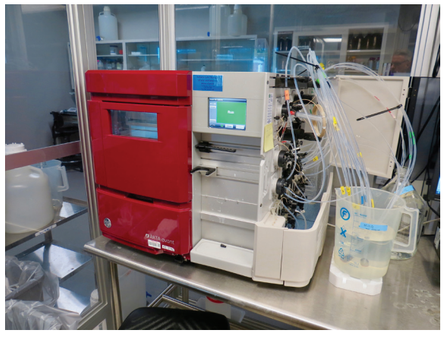
Sudhin Biopharma, Co.

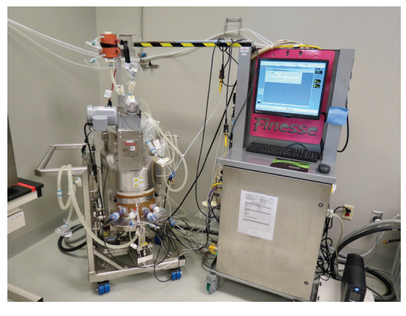
ABSTRACT

The emergence of commercial gene therapy products will require a transition from bench-scale production of gene therapy vectors to manufacturing-scale operations. This project develops a scalable platform process for production, purification, and analysis of adeno-associated virus (AAV) vectors used in gene therapy. This resource will be available for use throughout the NIIMBL network, and enable (1) development of hands-on courses in the area of gene therapy vector production and (2) development and testing of new process and analytical technologies for vector production. In addition to these broad project goals, the following specific objectives will be met:

IMPACTS

- Develop and offer a hands-on short course in gene therapy vector manufacturing that would be offered to NIIMBL members and the broader biopharmaceutical community.
- Test Sudhin Biopharma's inclined settler technology for separation of cells and cell debris from liquid streams in the vector production process.
- Advancement of gene therapy manufacturing through platform process and skills training for adeno-associated virus vectors





Single-use Center of Excellence Based on a Simulated-GMP Process for mAb Production

LEAD PARTICIPANT

NC STATE UNIVERSITY

ABSTRACT

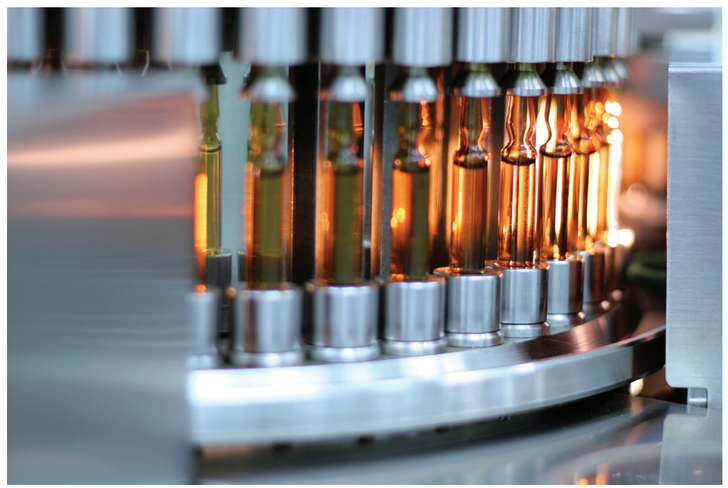
Single-use technology has been widely adopted in the biopharmaceutical industry. Results from a 2015 survey reported in BioPharm International show that 87% of respondents to a "manufacturing trends and outlook" survey reported using single-use components in their processes[1]. Despite the wide adoption of single-use technology, the availability of hands-on training opportunities, particularly those that incorporate an actual bioprocess, are limited.

This is the first phase of a larger project that will assemble the single-use equipment and develop a process for monoclonal antibody (mAb) production in CHO to be used for education/training and development projects. The project would lead to the first dedicated single-use mAb production process for education, training, testing and development of which we are aware.

IMPACTS

- Development of the first dedicated single-use mAb production process for education, training, testing and development

[1] R. Peters, *"Technologies and Practices Must Evolve to Meet Demand,"* BioPharm International, Vol **28** (1) 2015



Workforce Development Projects

Blended Learning for Training of Cell Therapy Manufacturing Personnel

LEAD PARTICIPANT

Massachusetts Institute of Technology

SUPPORTING PARTICIPANTS

Celgene Corporation
Massachusetts Life Sciences Center
Unum Therapeutics Inc.
Vericel Corporation
Worcester Polytechnic Institute

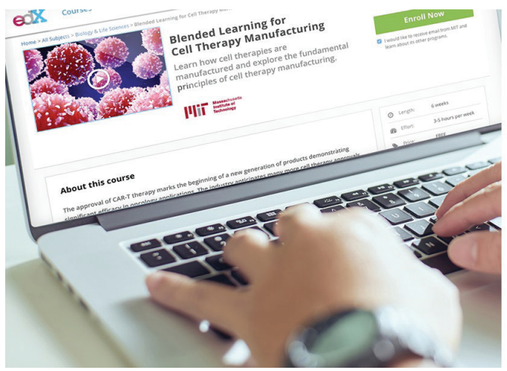
ABSTRACT

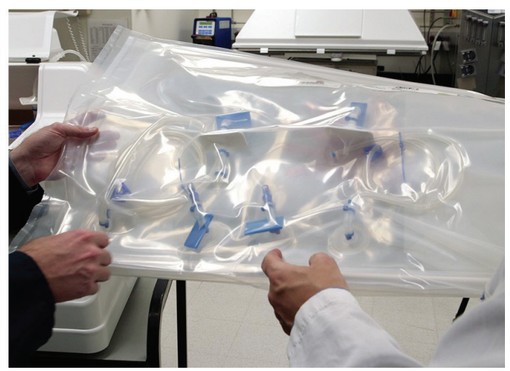
The goal of this project is to create an online course on the fundamentals of cell therapy manufacturing that is coupled to a companion hands-on training component. Such a blended learning course currently does not exist anywhere for cell therapy manufacturing. Currently, there are few, if any, formal training programs for cell therapy manufacturing and training of individuals in the basics is carried out on an ad hoc basis by company subject matter experts when need arises. Given the clinical successes and recent licensing approvals of CAR-T cell therapy products, there is a growing need for a well-trained workforce to deliver these lifesaving therapies. The development of an online resource that teaches important fundamental concepts, which is also tied into a hands-on training component, would accelerate the training of all levels of the cell therapy manufacturing workforce and decrease the resources required to bring new hires up to speed. Additionally, this type of blended learning environment modernizes learning such that the online component of the training will "immortalize" concepts so that they are available on demand, either to train individuals as they are hired or to review important concepts as needed.

IMPACTS

- This project will create a formalized training program to help individuals transition from traditional biotechnology fields to cell therapy development and manufacturing.
- First-of-its-kind modernized blended learning environment with online, self-paced learning coupled with periodic hands-on training for cell therapy manufacturing.

PC1.0-007 Blended learning for cell therapy manufacturing will combine online (left) and hands-on training





Partnership for Workforce Development in the Biopharmaceutical Industry

LEAD PARTICIPANT

UNCW®

(University of North Carolina Wilmington)

SUPPORTING PARTICIPANTS

Brunswick Community College
Cape Fear Community College
Alcami Corporation

ABSTRACT

Lack of regional hands-on training for beginning and existing personnel is a major issue to the biopharmaceutical industry. Students graduate without a skill-set relevant to succeed in industry. The biopharmaceutical industry has identified recruitment of experienced technical staff as their top priority, followed by acquisition, training, and retaining of experienced graduates. While online lectures and materials are valued, it is imperative that lectures are supplemented with local hands-on experiences. Keying on the needs of the biopharmaceutical industry, we designed training and capstone internships with emphasis on GMP, quality and risk analysis, analytical methods, automation, validation, and advanced manufacturing technologies. Lectures are provided in person but videotaping will capture lectures to build an online classroom with refresher and supplemental modules to supplement course and hands-on training. Lectures will be supplemented with a coordinated applied technology class and professional internships at industrial and translational biopharmaceutical science labs with ongoing relevant MRL 4 projects. We leverage networks of existing activities including preparatory introductory biotechnology and med-tech programs at community colleges, GLP/GMP lecture and laboratory courses taught in partnership with Alcami, industry and UNCW MARBIONC summer internships for community college and undergraduates, to build a comprehensive cross-institution program pipelined through a NIST-sponsored public/private building.

IMPACTS

- Targeted biopharmaceutical workforce training program with emphasis on GMP, quality and risk analysis and advanced manufacturing technologies.
- In addition to expanding current course offerings, the program offers a formal internship as a capstone experience.

Workforce Development Projects

Stackable Credentials to Strengthen the Pipeline to Biopharma

LEAD PARTICIPANT

North Carolina Central University

SUPPORTING PARTICIPANTS

Forsyth Technical Community College

North Carolina Community Colleges Systems BioNetwork

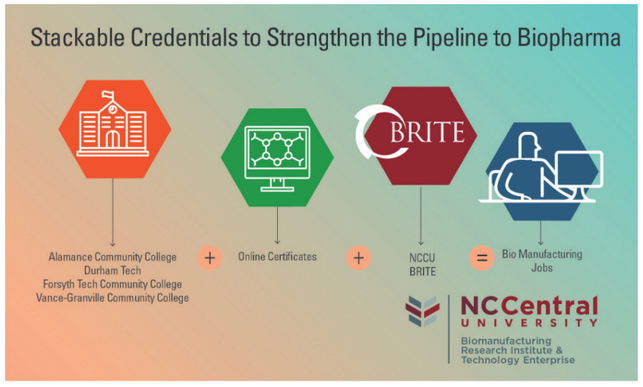
Alamance Community College

Durham Technical Community College

ABSTRACT

North Carolina Central University developed Stackable Credentials to better prepare community college students for entry into the university's biomanufacturing baccalaureate program, as well as give industry employees a chance to gain skills and certifications. The program creates a strong employee pipeline for companies engaged in biopharmaceutical research and manufacturing and gives students practical training for careers in the industry.

The Stackable Credentials program is based in the Biomanufacturing Research Institute and Technology Enterprise (BRITE) on NCCU's campus in Durham. BRITE offers the only university-level biotechnology program in North Carolina and places a heavy emphasis on research. The university offers a B.S. in pharmaceutical sciences, with concentrations in bioanalytical chemistry, protein separation sciences and molecular cloning. Nearly 100 percent of the teaching faculty has direct industry experience.



Online certification programs are active or under development in the following areas: Big Data Sciences for Biopharma; Project Management for Biopharma; FDA Regulations; Manufacturing Sciences; and Good Laboratory Practices.

The Stackable Credentials program also facilitates agreements with community colleges to ensure that all coursework is transferable into NCCU's pharmaceutical sciences program. Community college partners confirmed during the first year of the program include Durham Technical Community College, Forsythe Community College, Alamance County Community College and Vance-Granville Community College. Students on track to complete their education in pharmaceutical sciences at NCCU may be offered summer externship opportunities at BRITE. A student from Alamance County Community College completed the program's first externship in 2018.

IMPACTS

- The Biomanufacturing Research Institute and Technology Enterprise (BRITE) aims to create complimentary stackable credentials to prepare students in the North Carolina Community College Consortium for jobs in the biopharmaceutical industry.
- Certifications that will be developed include: Big Data Science for Biopharma, Project Management for Biopharma, Regulatory Sciences, Manufacturing Sciences and Good Laboratory Practice.

Development of Course Modules for Certificates and Professional Masters Degree Programs in Manufacturing Leadership for Excellence in Cell Manufacturing

LEAD PARTICIPANT

Georgia Tech Research Corporation

SUPPORTING PARTICIPANTS

Akron Biotechnology

Merck & Co., Inc.

RoosterBio

University of Georgia Research Foundation

University of Pennsylvania

Unum Therapeutics

ABSTRACT

Georgia Tech, University of Georgia, and University of Pennsylvania together with industry partners, Merck, Akron Biotechnology LLC, RoosterBio and Unum Therapeutics are working on a collaborative NIIMBL project addressing one of the most pressing needs for biomanufacturing workforce development. The program will focus on developing and beta testing ten course modules in cell and gene therapy manufacturing, including cell-based biologics manufacturing. The comprehensive set of industry-need driven course modules, available via both distance and on-site learning, will equip trainees with the following specific skills: 1) technical knowledge such as cell processing, viral transductions, cell preservation, large-scale cell culture, GMP-skills, cell analytics, quality engineering concepts, and supply chain logistics; and 2) professional skills including best manufacturing practices, regulatory compliance, regulatory filing processes, IP management, revenue models, cultural sensitivity, and policy awareness. The proposing team will incorporate the latest learning methodologies and technologies including active learning and virtual reality to enhance the learning effectiveness. These course modules will be geared towards student trainees, teachers from two-year colleges, and current industry professionals. The team will assess needs and iteratively develop contents with industry and clinical-GMP partners. These courses could form the basis of new certificate programs and professional master's degrees at participating universities.

IMPACTS

- Workforce training for technical knowledge and professional skills that spans the breadth of the biomanufacturing industry using state-of-the-art methodologies and technologies

Photo courtesy of Akron Biotech

Workforce Development Projects

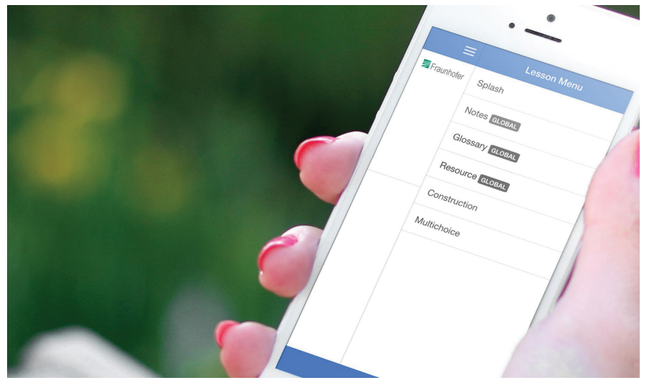
A Microlearning Capability for a Busy Biopharmaceutical Workforce

LEAD PARTICIPANT

Fraunhofer

SUPPORTING PARTICIPANT

University of Maryland College Park



ABSTRACT

Workforce development programs tend to use a learning approach modeled after the traditional classroom-based course. This involves identifying a large body of material, pulling students out of work, and using lectures, assignments, and feedback over long periods of time to teach that material. This is true even when delivering education via an online platform. One well-documented problem with this approach is that training courses and individual lessons are too long for busy, distracted employees. Training becomes a chore, leading employees to put off training programs or to start but then drop out of them. Also, long, comprehensive education offerings delivered away from the work environment often end up being *one-size-fits-many* and disconnected from employee's specific concerns, leading employees to see training program content as irrelevant.

The result is that companies spend substantial resources for few enduring gains in employee skill. To address this issue, we will build a microlearning capability, comprising a flexible, online education delivery architecture aimed at delivering small (2-to 5-minute educational "nuggets") in a just-in-time fashion. This capability will be demonstrated with educational content that covers the main topics in the manufacturing process.

IMPACTS

- On-demand, interactive, employee-driven training for the busy employee
- Reduced costs and improved specificity and relevance of biopharmaceutical training offerings for a better trained, more engaged workforce

Biopharmaceutical Manufacturing for the FDA

LEAD PARTICIPANT

UNIVERSITY OF MARYLAND

SUPPORTING PARTICIPANT

North Carolina State University

ABSTRACT

The necessity of FDA reviewers and auditors to possess comprehensive knowledge of the manufacturing process is vital to pharmaceutical approvals with all manufacturing processes being verified and validated. The emergence of gene therapy, cell therapy, advanced automation, and other bioprocess innovations poses potential challenges for FDA personnel who must keep abreast of industry innovations. This project is focused on the planning of a comprehensive training solution. The project team will evaluate existing training facilities, existing FDA training programs at these facilities, as well as input from FDA and industry to 1) identify training gaps and 2) develop a plan for aligning training resources and developing curriculum material to fill these gaps and establishing a national standard for FDA training.

IMPACTS

- Assessment of existing training opportunities and identification of gaps and unmet needs in regulator training opportunities
- Identification of potential in advanced cell and gene therapy manufacturing training for the regulatory workforce

Workforce Development Projects

Merck-NJII Biopharmaceutical Training Acceleration Proposal (BTAP)

LEAD PARTICIPANTS

New Jersey Innovation Institute
An NJIT Corporation

SUPPORTING PARTICIPANT

Merck & Co., Inc.

ABSTRACT

The purpose of the Merck-NJII Biopharmaceutical Training Acceleration Proposal (BTAP) is to provide funding for the development of a training program to enable incumbent employees in the biopharmaceutical industry to acquire competencies in the bioprocess development and manufacturing operations related to the biologics field. The proposal is led by Haro Hartounian, Ph.D. of the New Jersey Innovation Institute. He will serve as both the PI and the Project Manager. Steve Dziennik, Ph.D. and Kelly Woltornist of Merck will serve as co-PIs.

IMPACTS

- Training plan and curriculum that is vetted by industry for setting industry training standards
- Rapid retraining of incumbent employees to prepare them to move across multiple technical areas
- Establishment of proficiency levels for development and technology professionals in each modality

Online Lyophilization Short Course

LEAD PARTICIPANT

PURDUE UNIVERSITY

SUPPORTING PARTICIPANTS

Merck & Co., Inc.

North Carolina State University

ABSTRACT

In a two-year technology roadmapping process, the Advanced Lyophilization Technology Consortium ("LyoHUB") has identified an unmet need for online educational programs in pharmaceutical lyophilization. This project will develop an online lyophilization course to meet this need. Operators, scientists and engineers with limited lyophilization experience are the target audience; some components will also be accessible to non-technical personnel. Building on existing content from LyoHUB's "Lyo101" course, currently delivered in an in-person format, this NIIMBL project will create eight online learning modules, together with assessment tools and instructions for a virtual laboratory exercise. Using professional production and graphics, the online course will blend voice-over PowerPoint presentations, video recordings of lecturers and of lyophilization equipment, and machine graded assessments. The course will be beta-tested by LyoHUB members, modified if needed, then posted in open-access form on the pharmaHUB website. The project will contribute to NIIMBL's goal of educating and training a world-leading workforce in biopharmaceutical manufacturing and will address an unmet need for online work force training in lyophilization.

IMPACTS

- Online course in pharmaceutical lyophilization including eight online learning modules, virtual laboratory exercise and assessment.
- Course will feature video recordings by leading experts in lyophilization and be posted in open-access form on the pharmaHUB website.
- The goal is to address an unmet need in online educational programs for workforce training in lyophilization.

Workforce Development Projects

Development of an e-Learning Library for New Biotech Employees

LEAD PARTICIPANT

UNIVERSITY OF MARYLAND

SUPPORTING PARTICIPANT

Merck & Co., Inc.

ABSTRACT

This project aims to develop and deliver a library of interactive e-learning modules focused on protein structure and function and upstream/downstream manufacturing steps for entry level employees working in biopharmaceutical process development. This e-learning library will address a significant training deficit, providing learning opportunities for employees with a scientific background who are lacking specific experience in biopharmaceutical production, broadening the potential pipeline of entry level employees. Approximately six hours of content will be delivered through 5-20 minute modules through a combination of narrated slides, short animations, process equipment videos and expert video introductions. Articulate 360 will be used to deliver the content both as a self-contained online platform and individually exported modules for integration into a learning management system. By completing relevant modules, employees will gain a better scientific understanding of their laboratory work, improving engagement and enabling greater scientific agency. Relieving managers of this training burden enables them to focus more on company specific procedures and strategy rather than spending time teaching biopharmaceutical fundamentals to every new employee. In addition to these immediate impacts, this project will create a flexible platform which can be used to deliver online learning modules on additional topics in the future.

IMPACTS

- A library with approximately six hours of content, with each online training module lasting between 5 and 20 minutes, will be designed to educate new employees on the fundamentals of protein structure and function and upstream/downstream manufacturing steps.

Characterization of Cell Therapy Products by Flow and Laser Force Cytometry

LEAD PARTICIPANT

Rensselaer

SUPPORTING PARTICIPANTS

Celgene Corporation

LumaCyte

ABSTRACT

This project addresses a key *Topic of Interest* identified by the Workforce Activities Committee (Cell Therapy). The goal is to develop a 3 day short course (**"Characterization of Cell Therapy Products by Flow and Laser Force Cytometry"**) targeting multiple levels of current and future workforce. The course is designed to provide the fundamentals of two cell characterization technologies (flow cytometry, laser force cytology) in relation to cell therapy. This course has two main components: "Lectures" and "Hands-on Experiments" (approximately 50/50) and is designed to offer a curriculum heavily weighted towards a hands-on approach, and focused on biomanufacturing and QA needs. The course content will place special emphasis in the fundamentals of flow cytometry, the controls needed to draw more reliable and valuable conclusions, color compensation and how it affects the quality of the data being generated, qualification and validation, as well as troubleshooting with the instrumentation and samples. It will also introduce a novel and complimentary cell characterization technology from LumaCyte that captures cell properties (size, shape, deformability) by applying pressure. With the strong fundamental understanding this course offers, the workforce can apply these techniques more effectively and efficiently to applications currently being developed in their industries.

IMPACTS

- Training course for the current and future biopharmaceutical workforce on technologies used for cell characterization in biomanufacturing.

Our Project Pipeline

NIIMBL has authorized funding on additional projects set to begin in 2019.

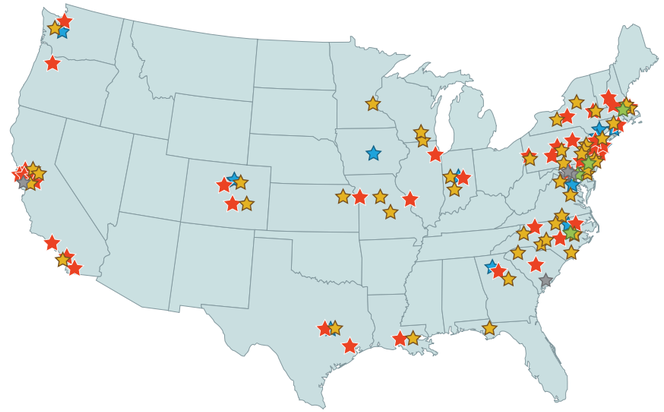
- Label-free Critical Quality Attributes of CAR T-Cell Products
- Novel Dehydration Technology to Streamline Drug Substance Processing and Preservation
- Continuous Cell Culture for Viral Vaccines
- Small-scale Membrane-less Perfusion Bioreactor System for High-throughput Cell line Development and Process Optimization
- Nanofluidic Analytics Platform for Multi-Modal Bioprocess Monitoring and Real-Time Product Release
- In-line Self-calibrated pH Monitoring System with Hyperspectral Imaging and Deep Learning
- Blaze™ Microchip System for Real-Time Characterization of Intact Biopharmaceutical
- Mechanistic Modeling for Enhanced Chromatographic Productivity

About NIIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) is a public-private partnership dedicated to advancing biopharmaceutical manufacturing innovation and workforce development. NIIMBL is one of 14 institutes in the Manufacturing USA network. Each institute focuses on a different technology, but share one common goal — to drive U.S. leadership in advanced manufacturing.

NIIMBL is funded through a $70 million cooperative agreement with the National Institute of Standards and Technology (NIST) in the U.S. Department of Commerce and leverages additional commitments from our partners from industry, academic institutions, non-profit organizations, and the states of Delaware, North Carolina, Maryland, and the Commonwealth of Massachusetts.

NIIMBL is a national network of members and is administratively headquartered in Newark, DE with staff also located in Raleigh, NC.



Membership Information

NIIMBL members are revolutionizing the biopharmaceutical manufacturing industry through technology innovation and workforce training.

KEY Industry State Nonprofits Academia Federal agencies

As a NIIMBL member, your organization will collaborate with leading biomanufacturers, suppliers, academic institutions, non-profits, and government agencies to solve critical manufacturing challenges and train the next generation of biopharmaceutical workers. Your organization's commitment will help enhance patient access to safe and efficacious medicines, promote U.S. economic development, and strengthen our national security.

Membership Benefits

- De-risked technology development through a collaborative environment
- Access to the diverse expertise of fellow NIIMBL members to foster creative solutions
- Participation on NIIMBL-funded projects
- Intellectual Property benefits derived from NIIMBL committees
- Access to the NIIMBL Community Portal, an online resource for partnering and collaboration

For more information on how your organization can get involved, please contact us at **membership@niimbl.org** or visit **http://www.niimbl.org.**

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