UNIVERSITY OF TORONTO

BIOMANUFACTURING WORKSHOP REPORT

April 28th, 2021

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UNIVERSITY OF TORONTO

SUMMARY

The tremendous health and economic impact of COVID-19 has demonstrated the need for a more robust and innovative biomanufacturing sector to bring Canadian biotechnologies rapidly to market. Recent advances in biological characterization, gene editing, and digital manufacturing provide an opportunity to modernize and improve the productivity of the Canadian biomanufacturing sector while building capacity.

In this context, the University of Toronto (U of T) organized a workshop on April 28, 2021, inviting participants from organizations focused on enhancing Canada's biomanufacturing capacity. The goals of this workshop were to (1) identify the key training and knowledge gaps that must be overcome to advance the Canadian biomanufacturing sector and (2) enhance linkages between U of T's vast expertise and the other players in the biomanufacturing ecosystem.

Participants identified the critical need for a highly skilled workforce in order to keep up with the advancing pace of innovation. Employee training is critical to developing highly qualified personnel with up-to-date expertise in process engineering, biological sciences and data sciences. Furthermore, this talent pool must understand the diversity and complexity of biomanufacturing processes in the era of ubiquitous sensing and automation. Participants also identified the opportunity presented by research and development in areas such as digital characterization of bioprocesses, digital twins for scale-up modelling, and the use of process analytics and data-driven operation to improve efficiencies. The lack of large, high-quality, open representative datasets was seen as an impediment to the development of the machine learning algorithms required to improve processes.

Based on the enthusiastic response to this workshop, U of T is committed to working with interested organizations to develop a Biomanufacturing Training and Innovation Institute that will address the identified gaps, improve academic-industry collaboration, and support a robust and innovative biomanufacturing sector in Canada. This Institute would have the following objectives:

- **Talent Creation** – Provide students with expertise in bioprocess engineering, artificial intelligence (AI), data analytics and modelling, fundamental biology, regulatory and quality control issues, and the professional skills & rigour required to support industrial R&D; provide the existing biomanufacturing workforce with professional training courses and programs to reskill with the proficiencies required to digitize biomanufacturing processes and leverage advancements in automation and machine learning.
- **Research & Innovation** – Conduct research with institute partners to advance the state-of-the-art in biomanufacturing and promote industrial adoption of the latest advancements in engineering biology and digital manufacturing.
- **Knowledge Translation Programs** – Facilitate the transfer of highly qualified personnel and technologies from academic to industry partners.
- **Infrastructure** – Develop and provide partners with access to infrastructure for training and innovation. Infrastructure will include modular, flexible biomanufacturing facilities for training and process improvement, automated platforms for discovery, and pilot facilities for process scale-up and commercialization.

WORKSHOP GOALS

1. To identify **key training and knowledge gaps** that must be overcome to advance the Canadian biomanufacturing sector
2. To **enhance linkages** between U of T's vast expertise and the other players in the biomanufacturing ecosystem

20

Organizations

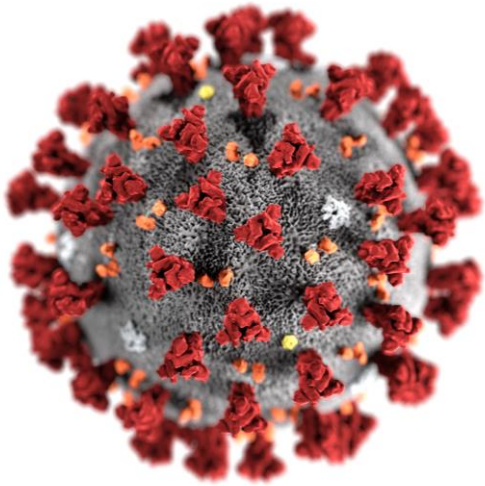
81

Attendees

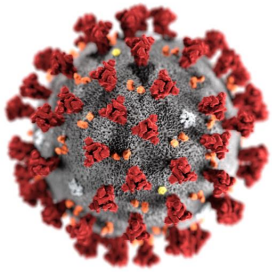
NEXT STEPS

Develop a biomanufacturing training and innovation institute to produce a highly trained workforce and research innovations to support a robust biomanufacturing centre.

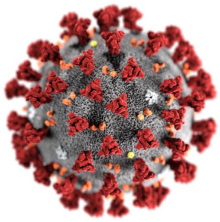
CONTEXT



The COVID-19 pandemic demonstrated the critical importance of robust biomanufacturing capacity to rapidly develop biotechnologies (diagnostics, therapies, and vaccines) that ensure Canada's health and economic wellbeing. Beyond health, biomanufacturing capacity and expertise are essential to support high-priority sectors, including agri-food and cleantech. Robust biomanufacturing capacity allows companies to scale locally and anchors firms and their associated intellectual property and talent in the domestic ecosystem. Accordingly, the Canadian government has recently made significant investments in biomanufacturing infrastructure at the National Research Council and at a number of Canadian companies to support our nation's health security and capture the value of local biomedical research. However, to be sustainable and internationally competitive, Canada's biomanufacturing sector will require a skilled workforce and access to innovative technologies.



Biomanufacturing is complex, inherently stochastic, and must be monitored closely at every step by highly trained technicians using expensive equipment and instrumentation. Furthermore, scaling new biologics from the bench to the manufacturing scale is unpredictable, time-consuming, and costly. Fortunately, we are at the confluence of three interrelated advances – Industry 4.0, digital biology, and engineering biology – that offer an opportunity to accelerate progress. New technologies such as the Internet of Things, big data, and AI have given rise to Industry 4.0 which takes advantage of ubiquitous sensing, centralized data collection, and automation to facilitate rapid, dynamic, and autonomous process development and optimization. Simultaneously, the high-throughput instrumentation, automated characterization, and enhanced understanding of living systems are enabling digital biology tools such as rigorous data-driven models of biological processes. Finally, new gene-editing techniques have enhanced our ability to engineer biology to accelerate discovery and facilitate the production of a wide range of bioproducts. Together, these breakthroughs offer an unprecedented opportunity to advance the state-of-the-art in biomanufacturing and decrease the time, cost, and failure rate of scaling the manufacturing of bio-based products. Canadian companies can lead globally in the development, integration, and adoption of these technologies to revitalize the domestic biomanufacturing sector. Strengthening Canada's biomanufacturing capacity will fundamentally advance its manufacturing competitiveness, improve its population's health security, and increase the local retention of Canadian biotechnology innovations.



BREAK-OUT SESSION SUMMARY

TALENT GAPS

Knowledge. There are insufficient graduates holding advanced degrees to work in biomanufacturing – most have undergraduate degrees focusing on process engineering, and few understand both fundamental science and process engineering. Individuals who can develop practical solutions to industrial bioprocessing challenges are required. Developing these individuals requires training at the convergence of **fundamental biology, applied bioprocess engineering, data sciences and automation, and regulatory frameworks (especially Good Manufacturing Practice, GMP).** Critically, a deep understanding of scientific nuance and awareness of regulatory, quality control and systems-level coordination that happen in production environments are necessary.

There is a lack of graduates holding advanced degrees with expertise in process engineering and understand fundamental biological sciences

Technical Skills. Graduates must be able to apply technical skills to the delivery of core biomanufacturing concepts. The lack of specific training and the diversity (and complexity) of processes in the biomanufacturing sector has dramatically **increased the requirement for on-the-job training**. Industry requires individuals who possess a broad, holistic (big picture) understanding of the whole biomanufacturing workflow (upstream and downstream) and can apply this understanding to navigate specific, specialized processes.

Soft Skills & Industry Mindset. Graduate training often focuses on individual discreet projects that progress slowly with small budgets. In industry, staff tend to work in teams toward larger goals with aggressive timelines. The ability to work in coordination with others to reach these goals is essential. Qualities of effective collaboration and the ability to prioritize, adapt, manage projects, and communicate effectively must be emphasized in graduate training. The need for reproducible, high-quality data generation at both the lab and production scale should be emphasized.

Upskilling & Retraining. The diversity and complexity of biomanufacturing processes and the addition of Industry 4.0 technologies is making the role of employee training increasingly important. Programs, including microcredentialing, for regulatory and quality assurance compliance, GMP, data science, machine learning, automation, etc., are required.

INFRASTRUCTURE GAPS

Training – Demonstration and commercial-scale infrastructure for hands-on experience with full-scale manufacturing facilities

Discovery – High-throughput automated platforms to accelerate discovery and process development

Digitization and automation - Infrastructure that allows for the high-quality generation of data for modelling processes and accelerates process development

Modular, flexible facilities – For the rapid adoption of new platforms and processes.

Disposable and continuous processes – New reactor designs to improve bioprocess efficacy and yield

Scale-up – Pilot facilities to support academics and start-ups to translate technologies

Successfully bringing the worlds of AI/Deep Learning together with a strong (bio)engineering culture will be extremely powerful

RESEARCH AND INNOVATION GAPS

AI, MODELING, & DATA ANALYTICS

- **Lack of high-quality, openly available and standardized data.** The diversity of enzymatic reactions is huge; therefore, thousands of data points are needed to train and test AI applications. Without standardized datasets that have become commonplace in AI subdomains, like image classification, benchmarking the performance of new algorithms or use cases is not possible. This standardized data set must be an accurate representation of real-world data, but must also have robust, but anonymous, characteristics such as high signal/noise ratios and depersonalization.
- **Data management.** The amount of data that can be collected is huge, in the Terabyte range. Companies require centralized, high-throughput data acquisition platforms and methods to clean, label and standardize data. How is data management and the use of AI/modelling handled from a compliance and regulatory perspective?
- **Lack of expertise.** Data analytical skills are broadly lacking in the workforce.
- **Process Optimization.** Advancements in sensors and machine learning can significantly improve process efficiencies. Digitization will allow bioprocesses to be modelled (digital twinning) and facilitate optimized bioprocess design. Using Industry 4.0 technologies for real time data collection from advanced nano and biosensors will facilitate process analytics technology (PAT) to improve operational efficiencies through the collection, analysis, and control of the manufacturing process in real-time.
- **Modelling whole-cell systems.** Biology is complex, and living cells have thousands of reactions. New digital models are required that can handle this biological complexity and track changes (such as temporal phenotype tracking) over time.

UPSTREAM AND HARVESTING (MICROBIAL/CELL/BIOPROCESS)

- **Industry-academia collaboration gap.** There are opportunities for industry to work more closely with academic labs to gain awareness, and accelerate the development, of new technologies and processes. How can we streamline the up-front effort to establishing these types of collaborations including identifying experts, establishing a legal framework around intellectual property development & confidentiality requirements, and recruiting interns & new hires?
- **Technical challenges.** These include improving protein solubility and expression levels, developing cell lines for mammalian/animal culture systems, process intensification, reducing media costs, and developing portable “bed-side” manufacturing platforms.
- **Policy issues.** New expression systems fall into a domain with unclear governmental policy and regulatory issues, often hampering innovation. Can we establish a more nimble framework for collaborating with our government partners?
- **Reproducibility & quality control.** Can machine learning be used to reduce process deviations?
- **Scale-up and -down models**. Models to accelerate the scale-up of bioprocesses such as dimensional analysis to translate lab-scale conditions to large-scale reactors and statistical computer modelling to extend observations at lab-scale to large-scale performance.

DOWNSTREAM (SEPARATIONS, FORMULATION & ADJUVANT / FORMULATION AND STABILITY)

- **Stability in mRNA and cell therapy products is an issue.** Products should be stable over a two- to three-year shelf life. Analytical assays are required to understand product behaviour over time. A better understanding of the biophysical characteristics (structural and functional characterization) and how this relates to stability and potency are required. The problem is decentralized – the sample is shipped, processed, purified, formulated, then directed back to the patient. Can modelling (mechanistic models or AI) be used to better predict stability? Can microfluidics for mixing and packaging mRNA in lipid nanoparticles be produced and scaled?
- **Automation and machine learning**. There are significant opportunities to improve the automation of downstream processes and collect data to improve process optimization through machine learning. Can automation, synthetic biology and machine learning be used to drive improvements in separations?
- **Analytics.** Complex matrices in vaccine production with multiple components, adjuvants, often in low concentrations, is a challenge for quality control and maintaining potency. Can better analytical equipment and data collection help?
- **Adenovirus/lentivirus.** Tools are needed to purify lentivirus for applications in cell/gene therapy.
- **Robustness of process and yield.** How can downstream processes be improved to increase robustness to input deviations and product yield?
- **Develop more platform technologies.** Antibody platform technologies exist, some new modalities are behind and represent opportunities.

Industry and academia should be more intentional about partnering opportunities. Both have indicated an appetite for enhanced collaboration, where priorities and expertise can be readily aligned and deployed to add mutual benefit.

RECOMMENDATIONS

As described in the break-out session report, workshop participants identified (A) opportunities to improve training for students and employee upskilling; (B) promising areas of research and development; and (C) the need to improve knowledge transfer from academic to industry.

TALENT

The rapidly advancing pace of digital manufacturing, digital biology and bioengineering demands a highly skilled workforce that is functionally literate in process engineering, biology, and data sciences. A combination of dedicated undergraduate and graduate courses/programs that leverage a diversity of academic disciplines, short courses and continuing education, professional training, along with the intentional recruitment of specific skill sets, can be strategically leveraged to develop the ideal, multi-skilled talent pool.

Enhanced University and College Training Programs

- Develop undergraduate and graduate programs that provide process engineers with expertise in fundamental biology, data sciences and automation, and quality assurance and regulatory frameworks
- Develop programs that provide graduate students developing biotechnologies with exposure to bioprocess engineering and awareness of quality assurance and regulatory frameworks
- Develop courses/programs with an emphasis on data science, machine learning, and modelling for bioprocess engineering
- Acquire industrially relevant, flexible, and modular biomanufacturing infrastructure to provide students with hands-on training
- Ensure that students have the soft skills required to effectively work in industry - effective collaboration and the ability to prioritize, adapt, manage projects, and communicate effectively
- Create & promote educational pathways for undergraduates with biology and related degrees to apply for graduate programs in chemical engineering with an emphasis on biomanufacturing and bioprocess automation

Upskilling & Retraining

- Leveraging collaborations between universities, colleges and organizations such as BioTalent, CellCAN, etc. to develop courses and microcredentialing for workers to gain expertise in areas such as regulatory and QA compliance, GMP, data science, machine learning, and automation.

Opportunities

- Enhanced graduate training
- Upskilling/retraining
- Big data, AI, digitization, and automation
- Scale-up & -down modeling
- Improving reproducibility and quality control
- Improved product purification and yield
- Enhanced industry / academic collaborations

RESEARCH AND INNOVATION

The rise of digital manufacturing (Industry 4.0), digital biology (genomics), and gene editing has created an unprecedented opportunity to advance the state-of-the-art in biomanufacturing and an opportunity to revitalize Canada's biomanufacturing sector. Advancements in automation, high-throughput instrumentation, advanced gene-editing, and synthetic biology platforms have ushered in the era of digital biology. At the same time, the digital revolution is transforming manufacturing – Industry 4.0 is leveraging real-time monitoring, centralized analytics, automation, modelling, and AI to facilitate rapid, dynamic, and autonomous process development and optimization.

Research Opportunities

- **Big data and AI** – Development of large high-quality open representative datasets of industrial bioprocesses; the creation of data acquisition platforms and algorithms for data cleaning and standardization; and development of machine learning algorithms to improve processes.
- **Digitization –** Digital characterization of bioprocesses and creation of models and digital twins; process analytics, data-based operation (PAT), and process modeling to improve efficiencies.
- **Scale-up and -down models** – Models to accelerate the scale-up of bioprocesses, such as applying dimensional analysis to translate lab-scale conditions to large-scale reactors.
- **Engineering biology** – Development of new therapeutics, improving protein expression levels and solubility, cell line development for mammalian/animal culture systems, and reduction of cell media cost.
- **Automation** – Leverage robotics to improve automation, and data collection to improve process optimization through the application of machine learning.
- **Biomanufacturing platforms** – Cell free systems, disposable bioreactors, continuous bioreactors, etc.
- **Reproducibility (QC)** – Utilization of machine learning and digitization to reduce process deviations.
- **Stability in mRNA and cell therapy** - Analytical assays to understand product behaviour over time and a more complete understanding of the biophysical characteristics (structural and functional characterization).
- **Quality control analytics** - Better analytical equipment, data collection and analysis to improve quality control in complex matrices.
- **Better purifications** – Improving yield of purification processes including adenovirus/lentivirus for cell and gene therapy applications.
- **Scale-up and piloting** – Flexible modular biomanufacturing infrastructure, along with digital twins, at multiple scales to test new processes and commercialize technologies.
- **Improving collaborations** – More effective methods for adopting new technologies by promoting industry internships, hosting industry researchers at the university, and reducing the transaction cost of collaborations (pre-defined agreements).
- **Reducing regulatory burden -** Working towards more effective regulations and policies that address the complex regulatory and intellectual property issues that come with new expression systems.

In the past, companies had one or two people working on modelling; now there are entire departments, growth in this area is accelerating, and demand for labour will be high.