Quantitative Phase Imaging will offer enhanced cell quality control in the cell therapy manufacturing process

— A Perspective by Phase Holographic Imaging

Introduction

Manufacturing cells for regenerative medicine is a sensitive and demanding process. In addition, cell-based therapies often use patient-derived samples where every cell is precious. Tracking cell quality at every stage of the process would go a long way toward ensuring timely manufacturing, patient safety, and treatment success. Currently, it is still unclear exactly which parameters or cell characteristics need to be monitored for the best outcome. Thus, many different potential quality measurements should be collected to ensure a safe and effective treatment. Continuous cell monitoring at every step in the manufacturing process, along with environmental monitoring, is a way to ensure cell quality. With this approach, the manufacturing process can be adjusted to optimize the outcome as soon as a deviation is detected. With enough data and experience, it may even be possible to predict the outcome of the manufacturing process based on initial readings.

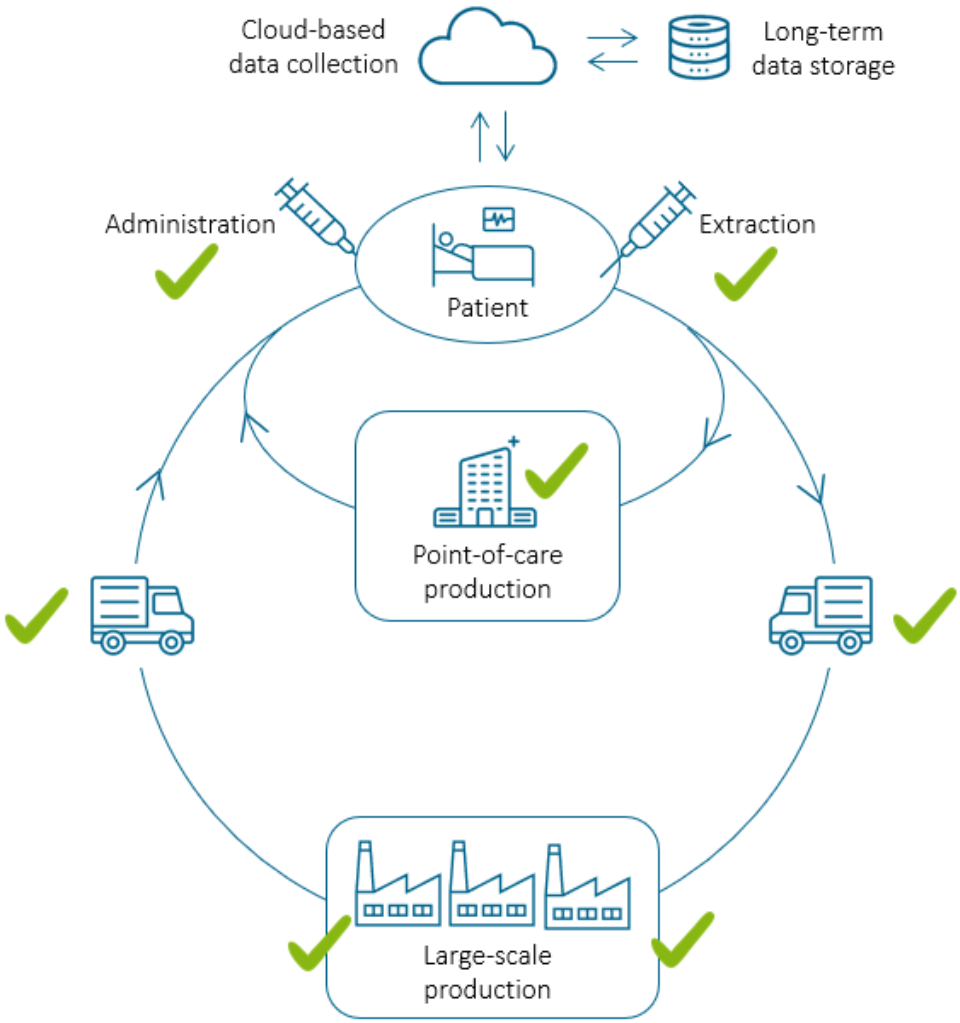
To avoid cell losses in the manufacturing process, an ideal cell quality control method would be cell-friendly and not cause negative side effects on the sample. Additionally, a method that can be applied without removing the cells from the production line would save time and materials. Quantitative Phase Imaging (QPI) utilized to capture images of the cells while growing in their culture vessels will supply cell images that provide extensive data on cell number, phenotype, health, and behavior. Not only will the images show, qualitatively, the appearance of the cell sample, but they will quantitatively describe exactly how many cells there are and how large they are. Moreover, the cell images can be used to assess individual cell morphology that may be predictive of cell quality. Given the low intensity of the light used in QPI, the cells are not harmed by this imaging method and thus can be imaged countless times without any negative effects. Other methods for cell quality control often require cells to be removed from the sample and sacrificed for the analysis.

To deepen the understanding of cell expansion and manufacturing as well as for traceability, it would be beneficial to store as much data as possible during the entirety of the patient's lifetime. The great challenge here would be to make data retrieval possible through the years, making it accessible for future data analysis tools. At present, it is not possible to know which data will be important going forward, making it desirable to store as much data as possible.

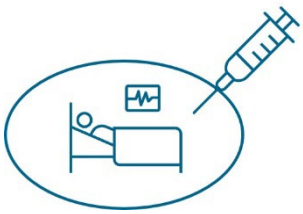
PHI is currently heading a project for Smart Manufacturing at the Wake Forest Institute for Regenerative Medicine (WFIRM) in Winston Salem, NC, USA, in cooperation with the Regenerative Medicine Development Organization (ReMDO), SAS, BioSpherix, and QIAGEN. The goal is to set up a system for cell quality control and data storage. The project aims to develop a tool called the Cell Report Card, where QPI cell quality data, as well as omics information, is stored and will accompany the cell sample throughout the lifetime of the cells and the patient. The project also looks into the possibility of predicting the outcome of the expansion process already at the earlier stages of the expansion, based on QPI data.

The manufacturing process

The first step in the manufacturing process is to extract cells. They can either be extracted from the same patient they will be used for, i.e., autologous, or the cells can be extracted from a donor to be used for the patient, i.e., allogenic. After extraction, the cells must be sufficiently expanded and treated to produce the desired therapeutic effect in the patient. To ensure maximum product efficacy, potency, and safety throughout the entire process, it is beneficial to collect and analyze cell growth and quality data continuously. Using QPI for cell quality control, a vast amount of data could be collected at all steps in the process, ideally supplemented by other methods to ensure process and end product quality.



Extraction



The first step of the manufacturing process is to extract cells from the patient. It would be ideal to assess the cells as soon as possible after extraction to ensure they are of sufficient quality to go through the manufacturing process. Data gathering and analysis could be performed immediately while the patient is waiting in case a new sample must be extracted if the first sample was not of sufficient quality.

To achieve this, a suitable QPI setup for analysis must be developed. Cooperative efforts with the right partners are needed to develop cell carriers, data handling, storage, and analysis. In addition, establishing processes and protocols for every step would be necessary, e.g., how to extract the cells for maximum quality, how to perform the quality analysis and store the data or how to interpret the cell quality data.

Point-of-care production

For some treatments, production adjacent to the healthcare facility could be efficient and speed up the process. Closed production systems with a constantly controlled and monitored growth environment, where QPI monitors the cell quality and expansion rate, could contribute to consistently high-quality production. More in-depth controls, such as RNA, DNA, or protein analysis, may be advantageous when determining the success of cell expansion and manufacture.

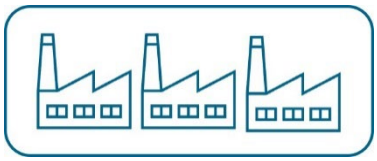
To achieve this, QPI setups, cell carriers, data handling, storage, and analysis aimed at decentralized facilities would need to be developed. Creating protocols for every step of the expansion and manufacturing process would be necessary, e.g., how to propagate the cells, how to perform the different types of analysis and store the data or how to interpret the quality data.

Transport

Cells can be transported either frozen or at normal growth conditions. Frozen cells may be sufficient for some processes, while other processes require cells to be transported at their normal growth conditions. The benefit of freezing the cells would be that their transport and subsequent use would not be time-critical, although it could affect the cells' growth and development in unpredictable ways. On the other hand, transporting cells at their optimal growth conditions would allow the sample to arrive unaffected at the manufacturing plant, ready to be processed, or at the patient facility, ready to be administered. Transportation of living cells is challenging, as an unbroken chain of a controlled and monitored environment with a closely regulated temperature and gas composition is needed.

To achieve this, partnerships with expert shipping companies that would develop suitable transporting equipment, including environmental monitoring, would be needed. Data handling, storage, and analysis processes during transport would have to be developed. If beneficial, a QPI system for monitoring the cells during transportation could be developed.

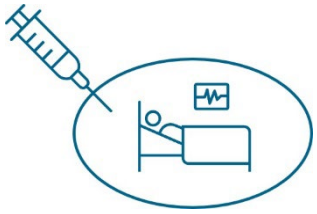
Large-scale production



Large-scale manufacturing plants often require automated control and monitoring of the manufacturing process. These processes must be tailored for each facility. Closed production systems with a constantly controlled and monitored growth environment, where QPI monitors the cell quality and expansion rate, could contribute to consistently high-quality production.

To achieve this, large-scale QPI setups would need to be developed, as well as suitable cell culture environments and cell carriers. Data handling, storage, and analysis processes would need to be developed specifically for each facility. As with the point-of-care production, protocols for every step in expansion and manufacturing would need to be created, e.g., how to propagate the cells, how to perform the different types of analysis and store the data or how to interpret the cell quality data.

Administration



Depending on the type of treatment, it may be beneficial to assess the cells after transport, just before administration, to confirm that the cell quality would be sufficient for patient health and safety, as well as therapeutic effect.

To achieve this, cooperative efforts would be needed to develop suitable QPI devices and cell carriers. Data ought to be created that would fit into the same system for handling, storage, and analysis as all other data. As with the extraction step, establishing processes and protocols for every step would be needed, e.g., how to perform the quality analysis and store the data, how to interpret the cell quality data, and how to administer the cells for maximum safety and efficacy.

Cloud-based data collection

All manufacturing process steps will generate large amounts of data, comprising QPI images and data, omics information, temperature measurements, gas composition data, process and handling data, patient data, etc. Collecting and compiling all pertinent data in the cloud would make it available for in-process data analysis, allowing for immediate feedback on the collected data. This would allow for fine-tuning the manufacturing process in real-time, thus optimizing cell health, growth, potency, and quality, ensuring product safety and efficacy.

To achieve this, cooperation would be needed to develop suitable data handling protocols ensuring patient data integrity, as well as to determine which data would be pertinent for the process and how to use it for analysis and feedback.

Data depository

To enhance patient health and safety and deepen the understanding of the cell manufacturing process, it would be beneficial to store all data safely, at least during the patient's lifetime. As time passes, it ought to be possible to add to the data in the same way that a report card follows a pupil through all school classes.

Cooperative efforts would be needed to develop suitable data storage protocols and facilities, data handling processes for data safety and patient integrity, and determine which data to save.

Summary

QPI stands out for producing extensive data on cell number, phenotype, health, and behavior that can be immediately analyzed or stored for future use. As a quantitative and non-destructive analysis method, it has the potential to become a possible standard in ensuring the quality of future cell therapies. QPI used for cell quality control could universally add value at every manufacturing step without undesirably stressing or sacrificing precious cells. When using QPI for cell quality control, the setup should be tailored to fit the requisites of the different stages in the manufacturing process. When extracting cell samples from the patient or administering cell therapy to a patient, QPI systems would need to be small and user-friendly, providing a quick insight into cell sample quality. For point-of-care production, medium-sized systems with medium throughput would be needed, while large-scale production facilities would require high-throughput QPI systems customized for the processes. In both cases, using QPI information, it could be possible to determine cell viability, cell proliferation, cell morphology, cell motility and other cell parameters, allowing for an in-depth understanding of the process dynamics, as well as allowing for immediate feedback on and fine-tuning of the process.

A main concern going forward is the storage and retrieval of all pertinent data to ensure a lifetime of data accessibility and patient safety. Currently, the knowledge regarding what data is needed is limited, making it imperative to store as much raw data as possible, thus making it available for later analysis. The ongoing Smart Manufacturing project proposes to evaluate a comprehensive and flexible model for data storage.

In addition to developing QPI to fit into the cell manufacturing process, cooperative efforts will be necessary to develop suitable cell carriers, transport techniques, data storage, and analysis methods, establish processes and protocols, and evaluate the processes.

Our vision for QPI in regenerative medicine

As part of the medical arsenal, regenerative medicine will play a pivotal role in the landscape of medical therapies. When regenerative medicine is accessible to all, QPI for quality control would be needed in all regional hospitals and small- and large-scale manufacturing plants. We envision QPI as a standard method for cell quality control, which will contribute to making cell therapies affordable, accessible and safe for everyone.

Remark

All the information regarding QPI in this document is not specific to PHI's products. QPI is a well-published and commonly available method and has been used in hundreds of scientific publications for cell monitoring and cell analysis.

Suggestions for further reading

A-Cell — A case study-based approach to integrating QbD principles in Cell-based Therapy CMC programs by ARM | https://alliancerm.org/manufacturing/a-cell-2022/

Quantitative Phase Imaging: Recent Advances and Expanding Potential in Biomedicine, Nguyen *et al.*, 2022, ACS Nano 2022 Aug 23;16(8):11516-11544 | https://doi.org/10.1021/acsnano.1c11507

Cytocentric measurement for regenerative medicine, Henn *et al.*, 2023, Front. Med. Technol., 27 April 2023, Sec. Regenerative Technologies Volume 5 - 2023 | https://doi.org/10.3389/fmedt.2023.1154653

More information regarding

- WFIRM https://school.wakehealth.edu/research/institutes-and-centers/wake-forest-institute-for-regenerative-medicine
- ReMDO https://remdo.org/
- SAS https://www.sas.com/en_us/home.html
- BioSpherix https://biospherix.com/
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