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Summary of the National Institute of Standards and Technology and US Food And Drug Administration cell counting workshop: Sharing practices in cell counting measurements

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Abstract

The emergence of cell-based therapeutics has increased the need for high-quality, robust and validated measurements for cell characterization. Cell count, being one of the most fundamental measures for cell-based therapeutics, now requires increased levels of measurement confidence. The National Institute of Standards and Technology (NIST) and the US Food and Drug Administration (FDA) jointly hosted a workshop focused on cell counting in April 2017 entitled "NIST-FDA Cell Counting Workshop: Sharing Practices in Cell Counting Measurements." The focus of the workshop was on approaches for selecting, designing and validating cell counting methods and overcoming gaps in obtaining sufficient measurement assurance for cell counting. Key workshop discussion points, representing approximately 50 subject matter experts from industry, academia and government agencies, are summarized here. A key conclusion is the need to design the most appropriate cell counting method, including control/measurement assurance strategies, for a specific counting purposes. There remains a need for documentary standards for streamlining the process to develop, qualify and validate cell counting measurements as well as community-driven efforts to develop new or improved biological and non-biological reference materials.

Key Words: *cell characterization, cell counting, quality attributes, reference materials, standards*

Introduction

Cell-based technology is a fundamental pillar of modern biotechnology. Cells are used in drug discovery and validation, in the production of life-saving medicines and high-value materials and, more recently, as the therapeutic product itself, often referred to as cell therapy products (CTPs). With the development of CTPs, there is an increased need for high-quality, robust and validated measurements for cell characterization. Seemingly routine cell measurements now require refinement and, in some cases, redevelopment. One such example is the cell counting measurement. Cell count, defined here as the discrete number of cells typically expressed as cell concentration or area density of cells, is one of the most fundamental metrics of a cell sample. This measurement, conducted routinely for over a century, underpins key decisions in the manufacturing and commercialization of cell-based products. For example, Figure 1 illustrates the important role of cell counting in each of the unit operations of a manufacturing pipeline for a hypothetical induced pluripotent stem cells (iPSCs) to a genetically engineered cardiomyocyte manufacturing process.

The translation of cell counting measurements from research to manufacturing settings has shifted the way the cell counting measurement is considered. While cell counting was once considered a routine and well-established measurement, the emergence of CTPs has required a greater understanding of and appropriate means to specify measurement quality. For example, this may include an increased level of requirement in precision, accuracy and robustness of cell counting to enable manufacturing control and product release.

The National Institute of Standards and Technology (NIST) has been working to develop strategies to improve the confidence of cell measurements critical for the translation, manufacturing and commercialization of CTPs [1,2]. Cell counting, including total cell counting and counting of cell subpopulations (e.g., viable cells), is a fundamental and often underappreciated measurement that needs improvements as noted by the cell therapy community [3]. Cell counting is arguably the simplest cell characterization

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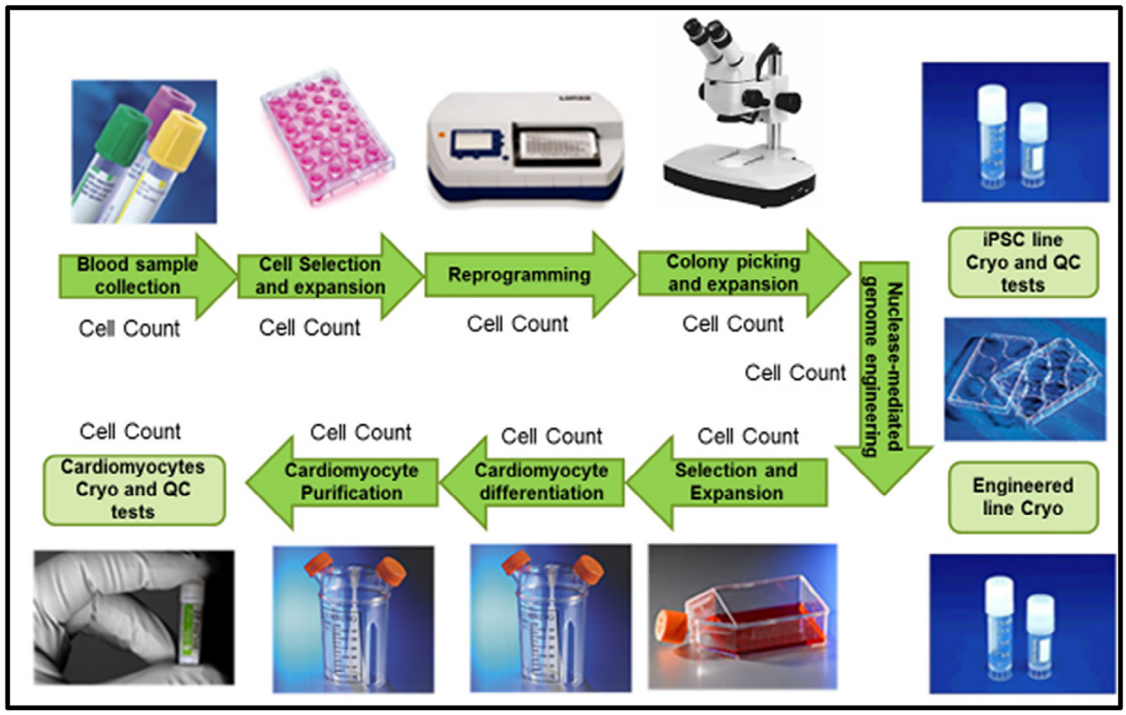

Figure 1. Example manufacturing process for the development of genetically engineered cardiomyocytes from iPSCs, highlighting the need for cell counting at each step (courtesy of Cellular Dynamics International [CDI]). iPSCS, induced pluripotent stem cells; QC, quality control.

method, yet it is subject to many of the same sources of measurement variability as more complex characterization methods. In response, NIST has recently established a research program specifically designed to evaluate the quality of cell counting measurements, identify and mitigate sources of variability and develop measurement controls. Additionally, NIST is leading the development of two International Organization for Standardization (ISO) standards on cell counting within ISO/TC 276 Biotechnology [4] and participating in many other standardization efforts related to CTPs.

As part of these efforts, NIST and the US Food and Drug Administration (FDA) jointly hosted a workshop focused on cell counting in April 2017 entitled "NIST-FDA Cell Counting Workshop: Sharing Practices in Cell Counting Measurements." NIST and FDA are actively collaborating on projects and standards activities that address regulatory and measurement challenges for regenerative medicine products and advanced therapies. These collaborations leverage NIST expertise in measurement sciences to address specific analytical and scientific challenges as well as FDA regulatory science, research and review expertise in regenerative medicine products to ensure that the science and standards developed address significant regulatory challenges that recur across the field. The focus of the workshop was on approaches for selecting, designing and validating cell counting methods and overcoming gaps in obtaining sufficient measurement assurance for cell counting, with a focus on cell therapy applications. Workshop agenda and presentation slides can be found at www.nist.gov/news-events/events/2017/04/nist-fda-cell-counting-workshop-sharing-practices-cell-counting.

General workshop summary

The workshop brought together approximately 50 experts representing cell counting device manufacturers, device users (CTP developers, contract manufacturing organizations and academic translational centers), and government agencies, including the FDA, which provided regulatory perspectives, and NIST, which discussed ongoing measurement assurance and standards efforts. Key discussion points raised by each group are summarized in Figure 2 and are further elaborated within this workshop report.

An overarching theme was the need for fit-for-purpose measurements depending on the properties of the cell samples and purpose and requirements for the cell count measurement. For example, counting of cells in a panel for drug screening may differ significantly from counting cells during the manufacturing or release of a CTP. Fit-for-purpose in this