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"What really is a healthy donor?" asked the organizers of the ISCT New Orleans Virtual Annual Meeting. This question led to a very interesting discussion in the session chaired by Dr. Dominic Clarke (Hemacare, NC, USA). Indeed, cell sourcing and biological variability are critical right at the start of the production flow. Inconsistent access to the correct donors, inappropriate handling and/or unreliable quality of the starting materials may lead to the failure of batch release or missed production deadlines.

As opposed to other types of drugs (i.e. small molecules or biologicals) the raw materials needed for allogeneic cell therapies cannot be manufactured on demand, but instead, rely on volunteer donors, each one with their unique physiological characteristics, thus introducing great variability from the outset. But what defines a healthy donor and how extensive a health checkup or blood test should be considered sufficient to ensure the success in the production of safe and efficacious cell-based medicines? There will be a chance to answer this question if we fully understand the entire bioprocess and the links between critical quality attributes (CQA) of the starting material, specifications of the final drug product and the ultimate clinical effect (in terms of safety and efficacy). And that's not trivial, at least not for most cell-based therapies.

However, some starting materials, such as apheresis, are relatively well understood. Besides many factors (i.e. cell subset composition, phenotype, presence of inflammatory or stress-related factors), a simple parameter such as initial counts of viable white blood cells (WBC) are known to impact directly on downstream processing and, eventually, on reaching the target dose of cells for treatment. But WBC yields also vary significantly with age, gender, body mass index (BMI), ethnicity, lifestyle habits and medical history (EBMT).

On other cell types, genetic variability between donors has shown a bigger impact on reprogramming efficiency and differentiation potential of induced pluripotent stem cells (iPSC) than the parental cell type source (1, 2). Another example is illustrated by inconsistent results from clinical trials targeting Graft versus Host Disease (GvHD), in which mesenchymal stromal cells (MSC) were prepared in different facilities by following different manufacturing protocols, thus supporting that A) not all MSC preparations are equivalent and B) specific manufacturing protocols influence therapeutic success (3). Alternative approaches, such as the establishment of current Good Manufacturing Practice (GMP)-compliant banks of MSC generated from pooled starting materials of multiple donors has been proposed recently to circumvent donor-to-donor variability (4).

Testing of starting materials for specific acceptance criteria may prevent spending resources in the production of batches that could not meet release criteria for clinical use. And again, the importance of defining suitable specifications and, when possible, the development of relevant potency assays. This is a challenge provided that potency assays often fail to faithfully recapitulate the biological processes involved in the expected therapeutic activity of the cell-based

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medicine. Therefore, A) discerning which CQA are most relevant and B) selecting quality control assays that accurately assess these attributes throughout process development and manufacturing are critical for the successful manufacture of the cell-based drug product. Understanding the optimal operating limits of critical reagents and methods can speed process adaptation and product re-validation if starting materials are changed at any time.

Other weaknesses exist beyond donor-to-donor variability and acceptance criteria for donated tissues and cells. The supply chain, in particular, is critical due to the unique biological nature of such living materials. Not to mention, donor center capacity, donor network access, sample handling, storage, shipping, automation, use of closed-loop systems, adequate quality controls, and overall quality management systems in compliance with pharmaceutical standards. In fact, the integration of cell collection with GMP-compliant preliminary processing will ensure that starting material meets strict quality criteria consistently. This provides the benefit of regulatory compliance and assured quality upstream in the bioprocess.

As developers of allogeneic MSC-based therapies, our Cell Therapy Service decided to realize the huge potential of the existing cord blood network of maternities coordinated from our institution (Blood and Tissue Bank, Barcelona, Spain) and started to use umbilical cord tissue and blood as a source of cells in compliance with generic (i.e. ISO9001) and specific quality standards (i.e. JACIE, FACT) and other local regulations for the derivation of MSC and induction of iPSC (6-8). But again… *what constitutes a healthy donor, or healthy enough?* Umbilical cord, as a newborn tissue, is apparently free of co-morbidities, is routinely tested for infectious pathogens and Human Leukocyte Antigen (HLA) typed by next-generation sequencing (NGS) technologies. Would that be sufficient? If not, (multi-)omics approaches may be a powerful tool for deeper understanding of biological processes on these cells. However what data are relevant when so often the mechanisms of action of cell-based therapies are not understood for specific indications? Could novel tools such as Artificial Intelligence (AI) assist us in the processing of data (i.e. including that from registries of donors, medical histories and quality controls from biological samples)? Besides, what about the bioprocess itself, which transforms the starting material into the desired final product? Even minor changes in a manufacturing platform can have a significant impact on MSC production and possibly also on its pharmacological activity (9). Would a robust bioprocess design compensate donor-to-donor variation of the starting materials? In any case, a better understanding of the cells in the manufacturing setting would help us to design production platforms to maintain product consistency across multiple processing steps and, ideally, multiple manufacturing sites.

Finally, close collaboration between donor centers and manufacturing centers may contribute to integrate and coordinate efforts early in the development process and ensure regulatory and quality compliance of the starting materials. To achieve this goal, we believe that the donation process needs to adapt to new developments by incorporating a pharmaceutical mindset and pursue a process of constant innovation in order to offer a competitive and useful catalogue of starting materials for the production of the next generation of cell-based medicines.

The debate is open!

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Other resources:

- ISCT2021-On demand
- https://www.biopharminternational.com/view/aceto-to-acquire-cascade-chemistry