Cell Therapy Moving in the Right Direction

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Recently, Biagi et al., 2021 published results of yet another successful demonstration of how hiPSC-derived cardiomyocytes can engraft in rats’ hearts and improve their cardiac function [1]. According to the work, these results are probably due to the segmental improvement in areas where the grafts were found. Importantly, paracrine effects observed in previous studies [2] cannot be ruled out, but specific data on radial and circumferential strain support that structural and contractile implications of the graft presence should reliably account for some of the results.

The publication joins others [3-8] in stating the limitations of the current rat model pointing towards more in depth studies currently being carried out in pigs [9-13] or non-human primates [14-17], two options of more clinically relevant models. However, why should we celebrate and encourage an ever-increasing number of studies in this area? There are many answers to this question, but we will focus on three aspects: i) relevance of the problem, ii) potential of cell-based restorative technology and iii) unidentified critical quality attributes (CQAs) of the proposed cell therapy product and delivery methods.

First, it is hardly a problem to convince anyone of the burden of cardiovascular disease, Heart Failure (HF) specifically, to humanity as a whole and, more particularly, to the health care system everywhere. There are currently around 26 million patients suffering from the disease [18]. Some more conservative studies predict that HF costs more than 108 billion dollars to the health care system worldwide and roughly 40% of this is only in the US [19]. It’s believed that the UK, arguably the most sophisticated public health care system in the world, spends 2% of its entire health care budget on this single disease [20] and the main cause of hospitalizations in South America are due to HF [21]. It has been a while since any relevant medication has been approved for this patient population and everything approved so far is generally focused on palliative rather than restorative care.

This leads to our second point: the potential of cell-based restorative technology. Producing or cultivating cells ex-vivo has always been a money-intensive and challenging process. Complexity around protocols and scaling up challenges has hampered previous attempts and aside from hemopoietic stem cell transplantation, cell sourcing has always been a relevant bottleneck.

However, in the past 15 years, progress in the field such as the advent of induced pluripotent stem cells [22,23], relevant improvements in cultivation systems based on suspension culture bioreactors [24-29], and significant reduction in the cost of media [30] has entirely reshaped the opportunities in the field inviting new possibilities spurring well-founded options to be explored as potentially new curative solutions to decades-old problems.

Never before in the history of humankind were we able to industrially produce meaningful amounts of cells to treat patients by actually replacing their cells. Now we are. In the beginning, we foresee allo- genetic applications being developed, taking advantage of gene-edited universal cells [31-33] profiting from an economy of scale but slowly progressing towards more autologous personalized applications when relevant.

Finally, for all that promise to be realized, we need to tackle the hard questions related to the CQAs of these newly developed potentially curative cell therapies. From a regulatory standpoint, it is vital to clearly understand what matters in a product to be injected into patients. Due to the novelty of the process, it is improbable that one group or team alone would address all the potentially relevant points. Therefore, when analyzed as a whole, several independent efforts would eventually bear more compelling evidence of the beneficial aspects of the therapy. As for delivery methods, the most straight forward approach would be to do transepicardial delivery of cells in patients undergoing CABG procedure and indeed is being pursued in current clinical trials (NCT03763136). We anticipate a move towards more non-invasive methods of delivery such as the ones based on catheter-like devices. This field will definitely take advantage of technology previously developed for adult stem cell therapies [34] and others still yet to be developed.

Additionally, large animal studies are notoriously hard and expensive to undertake and therefore, more extensive sets of tests are welcomed specially coming from independent groups. This increases confidence in the field as a whole and establishes benchmarks for future developments. The potential safety problems associated with arrhythmias arising from engrafting large patches of autonomous cells are also being more closely studied [11,14,15,17] and should be the focus of groups developing such technologies as safety remains the number one priority for regulatory agencies when considering IND applications.

We recognize that these three major points could be extrapolated to several diseases and cell types and not only to HF and hiPSC-derived cardiomyocytes, but this is intentional and speaks to the breath of the ex-vivo cell production technology and its potential applications.
Finally, we also acknowledge numerous potentially relevant efforts to use cells without the need to replace damaged/non-functional tissue, but solely based on its paracrine effect. Even though this is true, we chose to focus on the potential of cell-replacement therapy as a ground for future technologies aiming to replace entire tissues and organs that will eventually emerge as a possibility.

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