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Stem Cell Reprogramming - The New Avenue for Stem Cells Therapeutics

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ABSTRACT

The breakthrough finding of the differentiation factors that allow the creation of human iPSCs (hiPSCs) paved the way of novel stem cells-based therapeutics from cell reprogramming. Heavily committed to enhance methods to design and build human stem cells are deriving in new, effective and affordable production systems and bio manufacturing methods that are leading to a new conception of disease management based on both regenerative medicine and drug discovery and development. The switch of a somatic cell to an induced Pluripotent Stem Cell (iPSC) in a previous stage to its differentiation into one of many diverse cell types is known as stem cell reprogramming. Cell reprogramming technologies have introduced a paradigm shift in therapeutics development.

Keywords: Regenerative medicine, Stem cells, Gene editing, Cell reprogramming, Cell therapy, Gene therapy, Three dimensional bioprinting, Nanotechnology, Induced pluripotent stem cells, Tissue engineering

TECHNOLOGIES EMPOWERING CELL REPROGRAMMING INTERVENTIONS

Introduction to reprogramming technologies

Novel cell reprogramming techniques, such as for instance, direct reprogramming, enable the conversion of a somatic cell from one type to another via either *in vitro* or *in vivo* techniques, just utilizing the optimal transcription factors. Direct cell reprogramming allows generating autologous neural precursor cells, which can be utilized as the starting material to treat a variety of diseases [1].

Although many attempts to perfect the methods for reprogramming have gained increasing attention during the past decade, most techniques use vectors to integrate DNA into the cell genome. Potential issues must be taken into account, such as insertional mutagenesis and residual expression of reprogramming factors in cellular progeny [2]. Furthermore, such integrating vectors are not able to preserve the original genomic integrity of the somatic cell. This fact limits the therapeutic potential of iPSC. As a result, life scientists started to work on non-integrating vectors, leveraging many different strategies. The most remarkable innovations based on non-integrating reprogramming systems are: 1) episomal vectors, 2) Sendai virus vectors; and 3) mRNA transfection technology.

Episomal vector reprogramming utilizes components of the Epstein-Barr virus to enhance the delivery of reprogramming factors into somatic cells. Thereby, iPSCs from Peripheral Blood Mononuclear Cells (PBMCs) and fibroblasts can be generated. Moreover, reprogramming vectors are rapidly eliminated from the cells so that, the resting non-viral content does not require a category II tissue culture laboratory. The final product consists of reprogrammed cell lines, which can be used to advance research goals.

Non-pathogenic to humans, the Sendai virus cannot be integrated into the host cell genome. Its use also enables the obtention of iPSCs from PBMCs and fibroblasts with a high success rate of reprogramming. Exhibiting low aneuploidy, Sendai virus vectors would provide a more efficient method to get iPSCs than episomal vector reprogramming. mRNA transfection technology utilizes mRNA rather than DNA to release reprogramming factors into somatic cells. Although the procedure presents greater complexity in comparison with episomal and Sendai virus vectors, mRNA transfection technology is significantly more efficient. The most algid point is related to the design of the mRNA, which must limit activation of an innate immune response to foreign nucleic acids. In addition, this technology requires recapped administration due to the short half-life of mRNA.

Groundbreaking innovations in cell reprogramming

Among a broad spectrum of disrupting innovations impacting the cell reprogramming space, Fortuna Fix is

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pioneering stem cells reprogramming through the utilization of autologous neural precursor cells produced by direct reprogramming (drNPC™). Such advances may significantly accelerate the development of efficient and definitive clinical therapeutics to treat many neurological diseases. Its lead therapy is based on an autologous A9 dopaminergic Neuronal Precursor Cells (drNPC-A9) for Parkinson's disease and oligodendroglia-biased drNPCs for spinal cord injury. Fortuna Fix' technology platform uses chromatin remodeling techniques to maintain master and secondary genes expression stable, while locking into the particular neural pluripotent epigenetic state. Under this methodology, the DNA wrapped within nucleosomes becomes reachable to transcription factors and the replication machinery. Whereas some reprogramming factors releases the chromatin, the DNA of the cell is exposed so that other reprogramming factors capable of leading the reprogramming of the somatic cell to the neural multipotent cell. This process is directly carried out by triggering the expression of a master gene regulator, which can express secondary genes according to the structural and functional properties of the desired neural multipotent cell. The chromatin remodels and locks into the new neural multipotent epigenetic state. The reprogramming event is held *in vitro*. Then, new cells are incubated and maintained within reagents and media components specifically enriched to meet neural cells requirements. Remarkably, the resulting directly reprogrammed Neural Precursor Cells (drNPCs) have the ability to continue proliferating for many passages and differentiate along their specific neural, astrocyte and/or oligodendrocyte cell lineage, ultimately resulting in mature functional neurons, astrocytes and/or oligodendrocytes. Moreover, one of the effects of the direct cell reprogramming is the lengthening and stabilization of the telomeres, with consequent rejuvenation of the reprogrammed cells. Fortuna Fix' patented technology portfolio also includes regenerative implants Regeneration Matrix™ (RMx™) and fully automated manufacturing of the drNPC™ for scaling-up and production acceleration of their proprietary drNPC™.

Other companies are mostly focused on the use of Sendai and episomal reprogramming methods to overcome viral clearing challenges. Another promising tool is mRNA reprogramming. Indeed, cell reprogramming via mRNA transfection, which utilizes mRNA rather than DNA to release reprogramming factors into somatic cells, constitutes one of the most promising methods to generate iPSCs [2]. Although more complex than episomal and Sendai virus vectors, mRNA transfection technology is clearly safer and more efficient. One company committed to obtain iPSCs from human fibroblasts using a proprietary mRNA transfection methodology is Cellular Reprogramming. Cellular Reprogramming's platform technology enables the speedy, cost-effective, footprint-free, xeno-free generation of human induced Pluripotent Stem Cells (iPSCs) directly obtained from human fibroblasts by using a proprietary mRNA transfection methodology.

Alternatively, gamida cell developed and patented a nicotinamide (NAM) technology for the potential treatment of several types of blood cancer and solid tumors, through the use of natural killer (NK) cells. Their lead clinical candidate, NiCord®, is undergoing Phase 2/3 clinical trial as an allogeneic hematopoietic stem cell transplant solution for high-risk blood cancers and bone marrow failure disorders. NiCord® comprises umbilical cord blood expanded via NAM technology to preserve the cell capability to grow and keep stem cell behavior, and immune cells to provide immune value. NiCord® is the first bone marrow transplant product to receive Breakthrough Therapy Designation from the US Food and Drug Administration (FDA) and has also received Orphan Drug Designation in the US and EU. NAM technology has also been expanded to the field of immunotherapy, becoming an important factor in the potential treatment of several types of blood cancer and solid tumors, through the use of Natural Killer (NK) cells. NAM-NK is undergoing phase 1 clinical study used in combination with antibodies to treat relapsed or refractory multiple myeloma or non-Hodgkin lymphoma.

FORTHCOMING INNOVATIONS ACCELERATING THE PACE OF CELL REPROGRAMMING

Most cell reprogramming technologies are based on collaborative environments that promote the development of innovative therapeutics by leveraging vanguard genome editing innovations. Best suited approaches are directed to enlighten both the initial processes and final outcomes of cell reprogramming. This perspective attempts to provide a framework applicable to diverse temporal processes in stem cells biology [3].

Empowering gene editing, a wide range of bioinformatics tools are facilitating the analysis of epigenetics-related datasets, even those provided by DNA methylation and hydroxymethylation analysis, as well as, ChIP-seq and RNA-seq analysis. Such tools merge mathematical modeling techniques with epigenomics [4]. The increasing trend to standardize and integrate processes for personalized stem cell-based drug prediction using reprogrammed stem cells is also encompassed by these novel approaches, along with the development of core imaging technology platforms introducing differentiation protocols to increase the chances of success during the generation of viable, functional and mature cells from either patient material or existing iPSC lines [5]. In terms of biomanufacturing, iPS master cell banks meeting GMP conditions are gaining attention to guarantee the development of production platforms for the on-demand generation of specific stem cell therapeutics. Because the mass production of clinical-grade iPSCs is still a critical issue, an increasing number of programs and initiatives are being launched to make stem cell reprogramming therapies available to a larger population at

affordable costs. Encompassing this trend, advanced quality control strategies are also being updated to promote the clinical translation of reprogrammed cells.

FINAL REMARKS

As one of the most promising approaches in healthcare transformation, therapies based on stem cell reprogramming urgently claim the commitment of large pharmaceutical companies to work in expanding their cellular therapy portfolio. Major focus on stem cells reprogramming is expected to reveal a solid evidence of the role of cell reprogramming in the treatment of a broad spectrum of life-threatening diseases.

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REFERENCES

1. Foveau B, Correia AS, Hebert SS, Rainone S, Potvin O, et al. (2019) Stem cell-derived neurons as cellular models of sporadic Alzheimer's disease. J Alzheimers Dis 67: 893-910.
2. Van Cauwenberghe C (2019a) Technological advances enabling stem cells reprogramming - Technologies opening up new avenues to drive breakthrough research toward the discovery of next-generation therapeutics (TechVision). Frost & Sullivan Research Service D89C-01. Available at: https://www.frost.com/d89c
3. Schiebinger G, Shu J, Tabaka M, Cleary B, Subramanian V (2019) Optimal-transport analysis of single-cell gene expression identifies developmental trajectories in reprogramming. Cell 176: 928-943.
4. Van Cauwenberghe C (2019b) Technologies transforming the biomanufacturing landscape - integrating technology innovation and business development (TechVision). Frost & Sullivan Research Service D8BA-01. Available at: https://www.frost.com/d8ba
5. Spyrou J, Gardner DK, Harvey AJ (2019). Metabolism is a key regulator of induced pluripotent Stem cell reprogramming. Stem Cells Int.