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NOVEL APPLICATIONS OF UMBILICAL CORD BLOOD

Can cord blood banks transform into induced pluripotent stem cell banks?

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Abstract

The discovery of induced pluripotent stem cells (iPSCs) and the rapid evolution of clinically compliant protocols to generate such lines from a variety of tissue sources has raised the possibility that personalized medicine may be achievable in the near future. Several strategies to deliver iPSCs for iPSC-derived cell-based therapy have been proposed: one such model has been the cell-banking model, using processes developed by the cord blood industry. The cord blood industry has evolved primarily as a banking model in which units of cord blood harvested from discarded placenta are stored either in a public or a private cord blood bank for future use. The consideration of a cord blood–like banking model has been further spurred by the realization that this population of cells is an ideal starting sample to generate pluripotent cells. Spurred by these technological advances, major efforts are underway to develop a current Good Manufacturing Practice–compliant protocol to generate iPSCs from cord blood and to develop a haplobanking strategy. In this article, we discuss the issues that may affect such an effort.

Key Words: *cGMP, consent, cord blood, embryonic stem cells, induced pluripotent stem cells, manufacturing, markers*

Potential uses of induced pluripotent stem cells and models to provide therapy

Human induced pluripotent stem cells (iPSCs) are generated from human somatic cell types, such as skin biopsy and blood, by re-programming technology [1]. Pluripotent stem cells (PSCs) are cells that have the capability of differentiating into all somatic cell derivatives and can also contribute to the germ line. This ability, combined with the property of indefinite self-renewal, provides a unique opportunity for autologous cell-based therapy, and indeed multiple ways of using iPSCs are being developed (Figure 1). One important use of iPSCs is to generate differentiated cells that are unavailable from adult sources that can integrate into the recipient and replace the damaged or missing cells. Examples of such therapies include retinal pigment epithelium replacement in macular degeneration, making liver cells to treat cirrhosis of the liver, the generation of dopaminergic neurons to treat Parkinson disease, or deriving cardiac myocytes or pancreatic islets to treat cardiac disease or diabetes. Using PSCs offers the advantage of a common starting cell that is virtually immortal to generate all of these derivatives. Recent advances in differentiation protocols have extended the repertoire of potential cell replacement therapies, and several groups have initiated clinical trials; in September 2014, the first patient treated with iPSC-derived cells was reported [2].

Another extension of the use of iPSCs was based on the observation that modern gene editing techniques such as TALENS, CRISPR and ZFN, pioneered by various companies work well in iPSCs, even in their primed state [3,4] and could be even more effectively in their naive state [5], thus added another dimension to the use of iPSCs in treating disease. One could imagine engineering into an iPSC line the missing or corrected gene and then differentiating the engineered iPSCs into an appropriate phenotype or, vice versa, knocking out a harmful

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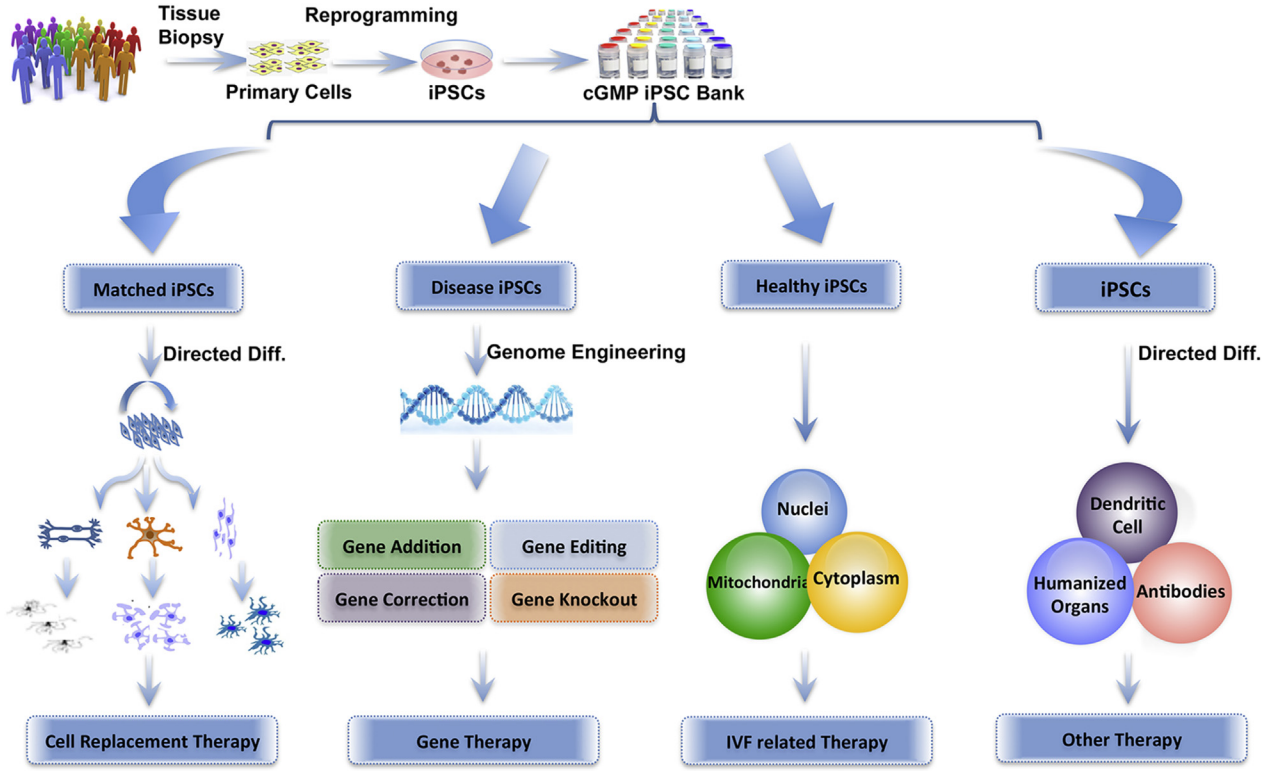

Figure 1. Therapeutic applications of human iPSCs. A variety of specialized cells differentiated from donor- or patient-specific iPSCs can be used for cell replacement therapies. Genetic error from affected patients can be fixed by gene-targeting approaches such as ZFN, TALEN and CRISPR before or after re-programing. Nuclei, cytoplasm and mitochondria can also be derived from iPSCs for *in vitro* fertilization (IVF)-related therapies. iPSC technology can potentially be applied to derive cells of immune system for immunotherapy, to prime the body to produce antibodies for cancer treatment and to generate mixed chimera to harvest humanized organs.

gene in disease with a gain of function mutation. Such therapy can be standardized when targeting is performed at a safe-harbor site or targeting a specific gene in multiple individuals. The efficiencies with editing also permit one to consider precise gene repair customized for each individual by designing the appropriate construct to repairing the exact gene defect in a particular individual. Many examples of such repair are available and have been used successfully in animal models, and several research groups are moving such therapy forward [6,7].

Other, more fanciful uses of iPSC-derived cells have included their use in immunotherapy by generating naive dendritic cells [8], *in utero* transplant to bypass rejection, as a source of nuclei to enhance efficiency of somatic cell nuclear transfer, as a source of cytoplasm for ooplasm transfer to enhance *in vitro* fertilization and provide mitochondrial gene repair [9], as an immunizing source to prime the body to develop antibodies to cancer antigens [10] and, in some more unusual models, to create mixed chimeras to harvest humanized organs [11]. For many of these applications, iPSCs may be the only source or the preferred source, particularly when adult stem cells are not available in sufficient numbers or when gene editing is required. iPSCs may even be preferable to embryonic stem cells because there are fewer ethical concerns and clearer patents rights, as well as the relative ease with which the cells can be generated.

As multiple uses of PSCs are being envisioned, the question has arisen as to how to generate the number of iPSC lines required. Three models have been proposed (Figure 2). The allogeneic (one to many model) approach with the assumption that cell transplants can work without immune suppression or with only limited suppression in certain regions of the body. In this case, the model would be that two or three lines would be identified and carefully selected from individuals who were healthy and with no hereditary disease and who did not carry alleles for increased susceptibility to any common disease. The iPSC clones would be selected for their ability to grow and differentiate into multiple phenotypes.

A second model (many to many model) for iPSC-based therapy is to consider human leukocyte antigen (HLA) matching and make an immune-compatible cell. The model here is to prospectively identify donors whose HLA profile is such that they can donate to many individuals. Thus, a much more limited but