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Progress towards Clinical Use of iPS Cell Derived Therapies

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Abstract

A decade has passed since Shinya Yamanaka published his landmarking publication on how to produce pluripotent stem-cell-like cells and the term induced pluripotent stem cells, iPS cells, was coined. This past decade has been a decade devoted to pluripotent cells, scrutinizing molecular mechanisms in cell identity, and optimizing derivation methods, culture conditions and characterization methods to xenofree and chemically defined clinical-grade pluripotent stem cells. The early promises of autologous cell therapies are now replaced by creation of highly selected donor cell banks matched to provide cells for the majority of a target population. Several of the initial safety concerns with iPS cells have been addressed with the use of non-integrating derivation methods and chemically defined and xenofree culture conditions, but some remain and will not be fully resolved until conclusions from *in vivo* experiments in larger animal models can be made. Published studies on safety and proof of concept performed in nonhuman primates are few but show promising results for spinal cord injury and Parkinson's disease for example. But questions remain; on how to provide functional and long-term integrating grafts and whether these can fulfill the promises of recovery and potential cure?

Keywords

Human pluripotent stem cells, Human induced pluripotent stem cells, Cell therapy, Chemically defined media, Xenofree conditions, Immune rejection, Tumorigenicity, Clinical applications

Abbreviations

iPS cells: Induced Pluripotent Stem Cells; ES cells: Embryonic Stem Cells; GMP: Good Manufacturing Practice; CMC: Chemistry and Manufacturing Control; HLA: Human Leukocyte Antigen; RPE: Retinal Pigmented Epithelial; FISH: Fluorescence *in situ* Hybridization; FACS: Fluorescent Activated Cell Sorter; BMDW: Bone Marrow Donors Worldwide; ISSCR: International Society for Stem Cell Research

Introduction

Millions of humans worldwide have already been cured from life-threatening diseases through stem cell transplantations. This is part of standard treatments for leukemia's, lymphoma´s, inherited immune system disorders and metabolic disorders as well as for bone marrow diseases (see list at https://bethematch.org). The regenerative capacity of bone marrow was explored in the 50 s and 60 s [1,2] and daring experiments with blood transplantations pioneered the cell transplantation field [3]. Bone marrow stem cells are multipotent stem cells and have the capacity to reconstitute the irradiated stem cell niche and give rise to all cell types that make up the blood. The ability to cure and not just alleviate the disease symptoms is amazing and gave hope to other patient groups with serious conditions and life-long suffering, conditions such as diabetes mellitus, neurodegenerative disorders, cardiovascular diseases and trauma injuries.

Pluripotent stem cell have the capacity to form all the cell types that make up the human body and the first derivation of human embryonic stem cells, ES cells, by James A Thomson Lab in 1998 [4] evoke hope for future cell based therapies. ES cells are not easily accessible and the use of preimplantated embryos raises ethical and legal concerns. The hope of new and effective cures came closer to reality as Shinya Yamanaka published a method to derive pluripotent stem-cell-like cells from somatic mouse and human cells. The cells were called induced pluripotent stem cells, iPS cells [5,6]. Yamanaka's method is genial in its simplicity and pluripotent cells are produced simply by ectopic expression of four ES cell-associated transcription factors, Oct4, Sox2, Klf4 and cMyc. iPS cells are easily derived, free from the ethical concerns of ES cells and with the capacity to be autologous to the patient, abolishing the needs for life-long systemic immunosuppressive treatments. Creation of autologous stem cell banks is not feasible on large scale and current strategy is based on collected knowledge from organ transplants, with creation of highly selected donor cells chosen to match the majority of a population. Several clinical trials involving human pluripotent stem cells are registered, moving cell based therapies into a new clinical era.

Here we review current knowledge on the production of clinical-grade iPS cells, their derivation, culture conditions and donor selection. We discuss their potential for cell transplantation, remaining hurdles to overcome and future perspectives.

State of the art, derivation and culturing of clinical-grade iPS cells

Clinically relevant iPS cells and derivatives thereof need to fulfill three main criteria; they need to be i) safe, ii) functional and iii) possible to consistently grow in large quantities, mainly to provide ready-to-use, available and affordable cell for transplantation with minimum risk for recipients concerning immunogenicity and tumorigenicity. Below we will review and discuss these aspects.

The first iPS cells were derived using oncogenic reprogramming factors, cMyc and Klf4, expressed by randomly integrating retroviral vectors, in undefined culture conditions with mouse feeder cells as substrate and bovine serum containing medium.

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Method development of iPS cell derivation and culturing has moved forward with a pace that excels all expectations. Source cells for iPS cell derivation, sets of reprogramming factors, number of reprogramming factors, their delivery routes and novel elements enhancing reprogramming efficiency have been explored. The method development has been summarized in several review articles [7,8]. Improved iPS cell derivation and culturing protocols that can be applied already today are for example (1) non-integrating reprogramming methods, (2) xenofree and chemically defined culture conditions, (3) production standards, ensuring traceability and reproducibility, (4) high-resolution characterization methods. Another promising technological advancement, not covered in this review, is the possibility to culture pluripotent cells in large quantities with minimum risk for contaminations using bioreactors and automated systems.

iPS cell derivation methods

The ultimate derivation method is free from any exogenous genetic material, reproducible and efficient. Scientific discoveries moving iPS cells closer to clinical applications are; the first derivation of human iPS cells with non-integrating methods [9], reprogramming without the use of oncogenes, using only OCT4 and SOX2 [10] and eventually only OCT4 in combination with a cocktail of defined chemicals [11], iPS cells derived through direct delivery of reprogramming proteins [12], and for mouse cells only so far, by defined chemicals only [13].

Xenofree and chemically defined culture conditions

The derivation of human pluripotent stem cells, most frequent ES cells and iPS cells differ, but the same culture conditions can be applied for their propagation. Years of experience from human ES cell culturing enabled the first derivation of human iPS cells and moved iPS cell quickly into clinically relevant cells. Culturing on feeder layers, mouse or human feeder cells, was for a long time the only way to culture human pluripotent stem cells. This is suboptimal and undefined, resulting in batch-to-batch variations and risk for transfer of pathogens and immunogenicity in the pluripotent stem cells [14]. The first chemically defined and xenofree culturing substrate for human pluripotent cells was human recombinant vitronectin, an extracellular matrix (ECM) glycoprotein [15]. Other xenofree and chemically defined culturing substrates used today are human recombinant ECM proteins for example laminin-521 [16] and synthetic substrates like human recombinant synthetic polymers [17] and thermo responsive synthetic hydrogels [18].

The requirement of feeder-free culture conditions was made possible through studies of molecular mechanisms of pluripotency and self-renewal in human ES cells. Basic FGF is crucial for self-renewal of human pluripotent stem cells and was previously provided by the feeder cells. Increased levels of basic FGF to culture medium enabled feeder-free culturing of human pluripotent cells [19,20]. The first xenofree and chemically defined culture medium capable of long-term propagation of human pluripotent cells was TeSR [21]. Today several defined and xenofree culturing media are commercially available. The first publications of human iPS cells derived and cultured under chemically defined and xenofree conditions came in 2014 [22,23].

Setting Standards and Characterization Criteria's for Clinical-Grade iPS Cells

All steps and products in the derivation, propagation, characterization and banking of the iPS cells and any derivatives thereof for clinical applications have to be produced in a standardized and controlled manner. Applying good manufacturing practices (GMPs) and chemistry and manufacturing controls (CMCs), enables traceability and reproducibility of all steps and reagents in the production line, this in combination with vast technical assay improvements having made high-resolution characterization of cells possible and affordable. Genomics, proteomics and metabolomics can be studied in high resolution on population and single cell level, allowing in-depth knowledge on the cells before approving for clinical applications. Great effort on harmonizing the standards has been made over the last years, by the International society for stem cell research (ISSCR) and the International Society for Cell Therapy (ISCT) [24]. However, there is no global regulatory organization responsible for setting the standards of cell transplantation therapies today [25].

Donor Selection, Creation of Homozygous HLA-Matched iPS Cell Banks

The derivation of autologous iPS cells for clinical purposes is expensive, time-consuming and not the answer for most conditions. It is interesting from a scientific point of view but not feasible in a large clinical perspective. An alternative is to create cell banks with highly selected donor cells, chosen to match the majority of a population [26,27]. The ultimate donors are young, healthy, of blood type O (universal donors) and homozygous for the most frequent major human leukocyte antigens (HLAs) in the population Experiences from organ transplants have shown that matching HLA-A, -B and –DR are most beneficial [28]. The donor-recipient matching criteria's are based on decades of experience from solid organ and bone marrow transplants. However, knowledge about pluripotent stem cell-derived tissue transplants in humans is sparse. The acceptance for partial matching of donor-recipient cells is different for different tissue types generated and the transplantation site [29]. The number of theoretical donor lines vary dependent on level of heterogeneity in a population. For example, 50 unique homozygous HLA donors could match over 90% of the Japanese populations [30], whereas the population of United Kingdom would require a bank of 150 unique homozygous HLA donors to ensure a similar match [26]. Homozygous HLA-donors are rare in populations and utilizing information from already registered volunteering cell donors from Bone Marrow Donors Worldwide (BMDW) registry for example would short cut this process [26]. The creation of population specific iPS cell banks has already started in some countries for example in the United Kingdom, Japan, France and the United States of America [31]. Homozygous HLA cell banks will provide cells for the majority of the population but the cells will only provide partial match and the need for immune modulatory substances will still be needed to prevent immune rejections. The level and type of immune modulation will be dependent on tissue type generated and on the graft site [29].

Safety Concerns of iPS Cells for Cell Therapy

Several of the initial safety concerns with iPS cells have been addressed as non-integrating derivation methods and chemically defined and xenofree culture conditions have been developed. However, some concerns remains and will not be fully resolved until conclusions from *in vivo* experiments in larger animal models and clinical trials can be made. Issues addressed in preclinical settings are; (1) genetic abnormalities either from derivation or culturing method or from the source cells, (2) epigenetic abnormalities due to incomplete reprogramming or from effects of long-term culturing, (3) tumorigenicity of iPS cells due to inadequate differentiation or due to culture-induced malignancies and (4) questions of acquired immunogenicity arising from culture conditions.

Genetic and epigenetic variations in iPS cells

Control of genetic and epigenetic variation in iPS cells is of great concern when moving into clinical applications. Genetic variations can be anything from small, single nucleotide variations, copy number variations to larger variations, such as loss of heterozygosity and aneuploidy. The use of non-integrating methods is therefore of the essence. Another source of genetic variation is from genetic mosaicism present already in the somatic source cells. The clonal nature of iPS cell derivation can result in capturing and expansion of even rare genetic variations [32].

The stochastic nature and low efficiency of the reprogramming process can result in iPS cell lines with epigenetic variations. This can be due to insufficient reprogramming, leaving traces of cell type specific epigenetics, (epigenetic memory), in the generated iPS cells.

Recent publication have addressed this issue and concluded that the epigenetic variations between well-characterized iPS cell lines and ES cell lines shown similar inter-individual variations, when applying non-integrating derivation methods [32].

Tumorigenicity of iPS cells

Long term passaging of pluripotent cells, iPS cells and ES cells, can cause selection for genetic and epigenetic malignancies with growth advantages. This can be anything from *de novo* genetic mutations to altered repressive chromatin modifications in imprinted loci, resulting in loss of allele-specific expression [33].

The success rate in differentiation of iPS cells to target cells for transplantation is dependent on the optimization of the differentiation protocol and on the level of heterogeneity of the pluripotent cells. It is crucial to apply standardized routines with high-resolution characterization assays to investigate genetic variations in each cell line, this accompanied by karyotyping or Fluorescence *in situ* hybridization (FISH) to detect potential balanced translocations. Any remnants of pluripotent cells left amongst the cells for transplantation can result in tumor formations. Purifications of cells for transplantation can be important. This can be accomplished either by for example Fluorescent Activated cell sorter (FACS) mediated extraction of the differentiated cells or by selective removal of the remaining pluripotent cells [34,35].

Acquired immunogenicity of iPS cells and cell derivatives

Cells cultured in undefined culture systems, with feeders or with animal-derived medium components can incorporate xenogeneic silica acid components (Neu5Gc). These can evoke immune responses in humans [14]. This is avoided by applying xenofree culture conditions.

Who Could Benefit from Cell Therapy, Today and Tomorrow?

Efforts are made in many therapeutic areas but first in line for pluripotent-derived cell therapies are chronic diseases or conditions without cure for example diabetes mellitus, neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, Amyloid lateral sclerosis and Huntington's disease, trauma injuries such as myocardial infarction, stroke and spinal cord injury as well as eye related diseases. The later, is pioneering stem cell derived therapies. There are several ongoing clinical trials for macular degeneration, using ES cell-derived retinal pigmented epithelial (RPE) cells in USA, South Korea, United Kingdom and Israel [36]. Eye conditions are in front line for practical reasons, differentiation protocols are well developed, only few cells, in number and in cell type, needs to be replaced, the eye is immune privileged to some degree, the target area is accessible, progress can be monitored and one eye can be treated at a time leaving the other as control. Japan is exploring clinical application of iPS cell-derived RPE cells for macular degradation, with ongoing clinical trial [36] and the first treatment of a patient, a 70-year-old woman with iPS cell-derived RPE at the Riken Center for Developmental degeneration, by Masayo Takahashi in Japan [37], no clinical data is yet available. Clinical trials concerning stem cells, reviewed by Trounson, et al. [36] and lists of registered clinical trials can be found at the NIH clinical trials website (https://clinicaltrials.gov/).

Proof of concept studies show beneficial treatments involving human iPS cell derived cells in animal models. These include curing sickle cell anemia mouse models by autologous iPS cells, genetically corrected and differentiated to hematopoietic progenitors [38]. Treatment of mouse models of diabetes by transplanting insulin-producing cells derived from human iPS cells [39]. Treatment of Parkinson's disease, and spinal cord injury by iPS cell-derived neural progenitors in rat and in mouse [40,41]. Animal models using non-human primates show little or no adverse effects and some beneficial effects for treatment of spinal cord injury [42] and Parkinson's disease [43].

Roadblocks in Cell Therapy

Major roadblocks to overcome are the low prevalence of cell survival and functional integration. This is not helped by the chronically diseased and aged surroundings. Studies on mice with humanized immune systems [44] and larger animal models can give some insights on how to address this. Gene editing approaches has proven efficient in reducing the T cell activity and makes the grafted cells less susceptible to the host's immune system [45] and to enhance survival and proliferation of the grafted cells [46].

Preconditioning the cells *in vitro* with anti apoptotic and prosurvival factors might be another way to make the cells more resistant to the disease environment and enhance the chances of cell survival and integration [47,48].

The transplanted cells faces different challenges dependent on therapeutic application and different strategies for transplantation are in development. Glucose-responding insulin-producing cells can be transplanted in capsules, permeable only for small molecules. This encapsulation will protect the transplanted cells from cell mediated autoimmune rejections in patients with type I diabetes [49]. Myocardial infarctions require large number of cells to replace the lost cells. Systemically injected of myocardial progenitors show low homing, integrating and poor long-term survival. Attempts to culture the cells on biocompatible membranes to create patches are ongoing [50].

What cell type to transplant and the level of maturity of the transplanted progenitors and elimination of remaining pluripotent cells or incorrect cell types needs to be further addressed. Injection of cells for neural degenerative disorders such as Parkinson's disease will most likely require neural cells of progenitor type to allow functional integration into already existing networks whereas, myocardial infarction and cardiac failure will require more mature cells types to allow correct electrophysiological propagation and coordinated contractions. Animal models can give some insights into these matters but clinical trials will eventually be the only way to finally assess this issue.

Conclusions and Future Perspective

The field of pluripotent stem cell based therapeutics is still very young but the progress made over the last decade in derivation and culture conditions makes it more promising than ever. The ability to create clinical-grade HLA-matched donor banks of iPS cells in the same man or as for bone marrow transplants moves iPS cell-derived cell therapies from small and local to scalable, affordable and available for future therapies. One major shortage today is the lack of International agencies setting and enforcing standards and characterisation criteria's for derivation and culturing of clinical-grade iPS cells and derivatives thereof for cell transplantations. ES cell-derived therapies are one step ahead of iPS cell-derived therapies, with several ongoing clinical trials. Insights from these will be valuable for iPS cell-derived therapies. It is crucial that the first trials display no or little adverse effects and that therapeutic benefit can be proven in coming phases. Lack of improvements or even signs of malignancies will set back the clinical progress with years.

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Ethical Statement

Not applicable.

Competing Interests

The authors declare no conflicts of interest.

Author's Contributions

Not applicable.

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