CELL & GENE THERAPY INSIGHTS

INDUCED PLURIPOTENT STEM CELLS (iPSCS)

SPOTLIGHT

COMMENTARY

Unlocking the full potential of human induced pluripotent stem cells from haplo-selected cord blood samples—the how and the why

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There is a critical need worldwide for tissue for transplantation in patients with organ failure and with degenerative diseases with no treatments available. Cell therapy can represent an alternative to organ transplantation and for the treatment of degenerative diseases (such as heart failure, macular degeneration, type 1 diabetes, or Parkinson's disease, among others). The generation of human induced pluripotent stem cells offers a unique opportunity to obtain an unlimited supply of specialized cells. The use of patient's cells for the generation of human induced pluripotent stem cells and their derivatives for treatment ensures immunological compatibility and minimizes the risk of rejection. However, the time and cost necessary to produce customized human induced pluripotent stem cell lines and their derivatives in GMP conditions are excessively high.

An alternative to the use of patient-specific human induced pluripotent stem cells would be an human induced pluripotent stem cell collection from allogeneic healthy donors that could be expanded and differentiated to treat different patients. This collection should comprise lines with enough diverse and compatible homozygous human leukocyte antigen to reduce the risk of immune rejection in a high percentage of the population. Homozygous human leukocyte antigen-matched iPSC lines suitable for a wide variety of homozygous human leukocyte antigen genotypes would be valuable for significant numbers of patients and will allow delivery of off-the-shelf cells for the manufacturing of cell therapy products for multiple diseases by reducing time and costs.

HAPLO-iPS aims to create a collaborative network to provide a framework for human induced pluripotent stem cell generation of human induced pluripotent stem cells homozygous for frequent homozygous human leukocyte antigen haplotypes, compatible with a

significant percentage of the population to be used for cell therapy clinical trials, and to collect a data collection system for such lines and all the associated data.

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INTRODUCTION

There is a critical need worldwide for cell and tissue for transplantation in patients with organ failure and an increasing impact of degenerative age-related human diseases for which there are very limited or no treatments available [1]. Cell therapy can constitute a future alternative to organ transplantation and for the treatment of degenerative diseases (such as macular degeneration, Parkinson's disease, heart failure, type I diabetes, or spinal cord injuries, to name a few) [2,3]. The generation of human induced pluripotent stem cells (hiPSC) from somatic cells offers a unique opportunity to obtain a virtually unlimited supply of a broad spectrum of specialized cells [4,5]. iPSC-derived differentiated cells have great potential for cell replacement therapy even though the clinical relevance of such treatments is still to be clinically realized in the form of licensed cell-based medicines. The reason for this is that the time and costs required for the production of customized hiPSC lines and their derivatives that would be suitable for use in humans is prohibitively high. For a large-scale therapeutic landscape, immune- homozygous human leukocyte antigen (HLA) matched iPSC lines suitable for a wide variety of HLA genotypes would be valuable for significant numbers of patients. An alternative to the use of patient-specific hiPSC would be a hiPSC collection from allogeneic healthy donors that could be expanded and differentiated to treat different patients. To reduce the risk of immune rejection, this allogeneic hiPSC collection should comprise lines with sufficiently diverse and compatible homozygous HLA haplotypes to ensure maximum possible population coverage. Manufacturing of scalable unique cell standardized final products from haplo-selected hiPSCs suitable for various types of diseases and multiple clinical indications, should in addition reduce the cost of the final products and patient immune-suppression. Moreover, cell derivatives from HLA-matched hiPSC banks will allow delivery of off-the-shelf cell therapy products, easily accessible for critical acute or subacute diseases and for new emerging diseases such as the current pandemic SARS-Cov-2-induced inflammatory disorders and cancer. To achieve this goal a new initiative, the HAPLO-iPS project, led by the Bellvitge Biomedical Research Institute in Barcelona, and supported by the European Research Infrastructure for Translational Medicine, the European Research Infrastructure for Translational Medicine, has created a first of its kind collaborative network through a recently funded European Cooperation in Science and Technology (COST) action across 30 EU countries and beyond [6]. The aim of this multistakeholder network is to provide for the first time a framework for hiPSC generation of hiPSC homozygous for frequent HLA haplotypes, compatible with a significant percentage of the population to be used for cell therapy clinical trials and to create a data collection system (REGISTRY) for such lines. This network will pioneer new approaches that will foster the progress of a haplo-selected hiPSC generation of therapeutics by the development, implementation, and exploitation of a registry with all the information required for the benefit of patients.

UNDERSTANDING THE CHALLENGES

Currently, some registries of available hPSCs do exist. The most prominent is hPSCreg,

which was created as a registry of European human embryonic stem cells (hESC) lines, but that now involves hESC and hiPSC lines from over the world [7]. Although individual approaches for using hiPSCs for therapeutic applications already exist [3] and also for setting up the first haplo-banks throughout Europe, these initiatives are not yet working as a coordinated community and only have the capacity to provide cell lines for a limited number of common HLA haplotypes. To date, these approaches, which are still at the proof-of-principle stage, will at best cover only a limited percentage of the population in need. With their limited resources, they result in a social-economic imbalance and even exclusion of certain population groups from future medical possibilities. Furthermore, there are key scientific and regulatory discussions yet to be resolved to achieve a European consensus on essential issues that must be tackled to progress such haplo-registry/bank resources to a clinical reality. The use of patient's cells for the generation of hiPSC and subsequent differentiation to the desired cell type for treatment ensures immunological compatibility and minimizes the risk of rejection. However, the time and cost necessary for the production of customized hiPSC lines and their derivatives that would be suitable for use in humans is prohibitively high. For a large-scale therapeutic landscape, immune-HLA matched iPSC lines suitable for a wide variety of HLA genotypes would be valuable for significant numbers of patients. An alternative to the use of patient-specific hiPSC would be a hiPSC collection from allogeneic healthy donors that could be expanded and differentiated to treat different patients. To reduce the risk of immune rejection, this allogeneic hiPSC collection should comprise lines with sufficiently diverse and compatible homozygous HLA haplotypes to ensure maximum possible population coverage. Manufacturing of scalable unique cell standardized final products from haplo-selected hiPSCs suitable for various types of diseases and multiple clinical indications can reduce the cost of the final products and patient immune-suppression. This idea was already proposed by Bradley *et al*. and Taylor *et al*. for hESC. hiPSC technology facilitates the prospective selection of interesting donors based on their particular HLA haplotypes [8].

The selection of homozygous donors for common HLA haplotypes for the generation of hiPSC can facilitate compatibility with potential recipients. Nakatsuji *et al*. calculated that 30 carefully selected hiPSC lines would provide coverage to 82.2% of the Japanese population coinciding in the three loci (HLAA, HLA-B and HLA-DR), and 90.7% of the population would be covered with 50 hiPSC lines [8]. However, identifying these 50 potential donors would necessitate studying the HLA system of 24,000 individuals. Okita *et al*. calculated that 140 homozygous donors for HLA haplotypes would cover 90% of the Japanese population, requiring the screening of 160,000 potential donors [9]. Similarly, Gourraud *et al*. calculated that 26,000 donors of European-American ancestry and 110,000 donors of African American ancestry would need to be screened to obtain hiPSC representing the 20 most frequent HLA haplotypes, and that these lines would provide coverage to 50% and 22% of these populations, respectively [10]. All of this confirms that relatively few donors, if very carefully selected, would allow the generation of hiPSC lines with a strong potential for clinical utility. Similar calculations have been established for Korean population in comparison with China, Japan, and the West [11]. Alvarez-Palomo *et al* calculated that ten cord blood units from homozygous donors stored in the Spanish cord blood banks can provide matching for 28.23% of the Spanish population [12]. Abberton *et al* and Clancy *et al* have calculated similar estimations with Australia and Finnish populations respectively [13,14]. The estimated number of hiPSC lines needed to coverage several populations is shown in Table 1.

The collaboration of multiple centers worldwide is therefore necessary to perform

TABLE 1

Estimated number of hiPSC lines needed to coverage several populations

Author	Number hiPSC lines	Coverage (%)	Population	Potential donors
Nakajutsi *et al*., 2008	30	82.2	Japanese	24.000
	50	90.7	Japanese	
Okita *et al*, 2011	140	90	Japanese	160.000
Gourraud *et al*, 2012	20	50	European-American	26.000
	20	22	African-American	110.000
Lee *et al*, 2018	10	41.1	Korean	4.200
Alvarez-Palomo *et al*, 2021	10	28.2	Spanish	30.000
Abberton *et al*, 2022	33	50	Australian	13.679
Clancy *et al*, 2022	41	69.3	Finnish	20.737

hiPSC: human induced pluripotent stem cells.

the screening and identifying individuals among the large number of potential donors [15].

One feasible possibility is to prospectively search for potential donors in registries/banks of bone marrow and cord blood (CB), since these donations are already typed for elements of the HLA system. There are several reasons why CB cells are the cell type of choice to generate homozygous HLA haplotype hiPSC collections for clinical translation:

- There is no risk for either the mother or the newborn at collection;
- CB units, preserved in CB banks, are already HLA typed, which facilitates donor screening;
- Cells in the CB are less likely to have accumulated genetic or epigenetic risks compared to adult and differentiated cells; and
- hiPSC generation methodology with CB samples is well established [9,16].

The use of CB-hiPSC as an alternative to the use of patient-specific hiPSC would minimize the time and cost necessary for the production of customized hiPSC and their derivatives. Moreover, although CB samples are designated for clinical application for hematological pathologies, many CB banks keep surplus samples sufficient to generate hiPSC lines and CB samples with an insufficient number of hematological progenitors not suitable for transplantation might also be used. Methodology for GMP-grade $CD34^+$ selection from HLA-homozygous CB units has been reported [17]. Lee *et al.* described the generation of hiPSC lines with the ten most frequent HLA-homozygous haplotypes, which can match 41.07% of the Korean population. Comparative HLA analysis indicates that the lines are relevant to other Asian populations, such as Japan, with some limited utility in ethnically diverse populations, such as the UK. Similarly, Rim *et al.*, report the generation of 13 homozygous GMP-grade hiPSC lines from blood and CB cells with selected homozygous HLA types from the Catholic Hematopoietic Stem Cell Bank of Korea [18].

The World Marrow Donor Association estimates 256,006 CB units preserved in the CB banks in Europe and 798,372 units in the world [19]. Bone marrow registries represent an alternative to CB banks as potential providers of samples for hiPSC generation, but both the availability, lower invasiveness, and the easy access to samples in the latter are obvious advantages to be considered.

There are 37,346,669 bone marrow donors registered in the World Marrow Donor Association registry [19].

Another option to be considered to make hiPSCs compatible with a significant percentage of the population is the use of genetic modification techniques in hiPSC or hESC to knock-out or down-regulate HLA genes to generate 'universal' donor cells. Xu *et al.*, described two genome-editing strategies for making immunocompatible donor hiPSCs [20]. First, they generated HLA pseudo-homozygous hiPSCs with allele-specific editing of HLA heterozygous hiPSCs. Second, they generated HLA-C-retained hiPSCs by disrupting both HLA-A and -B alleles to suppress the natural killer cell response while maintaining antigen presentation. HLA-C-retained hiPSCs could evade T cells and natural killer cells *in vitro* and *in vivo*. The authors estimated that 12 lines of HLA-C-retained hiPSCs combined with HLA-class II knockout are immunologically compatible with over 90% of the world's population, greatly facilitating hiPSC-based regenerative medicine applications. Other publications also report encouraging results using similar or RNA silencing techniques as well as cell-based immunomodulation strategies genetic ablation of HLA molecules from hiPSC combined with gene transduction of several immunoregulatory molecules [21–22]. These 'universal' hypo-immunogenic strategies could be valuable for rare haplotype cells, and in relevant clinical applications such as hematopoietic cell transplantation (where HLA mismatches profoundly affect engraftment) and in autoimmune diseases (where autoantigen presentation would cause side effects). Non-HLA minor histocompatibility antigens from Y chromosome genes and single-nucleotide polymorphism profiling should also be taken in account. However, genome editing could induce a risk of off-target modifications that must be extensively controlled, and such modifications can enhance the complexity of safety evaluation and regulatory delay. Both of these non-exclusive models will be enriched by variant models, and innovative strategies will evolve as a step towards complete immune-matched hiPSC lines with fully personalized therapy.

Advantages and disadvantages of different approaches for hiPSC generation are shown in Table 2.

Few commercialized allogeneic clinical-grade hiPSC lines are currently available

TABLE 2

Advantages and disadvantages of different strategies for hiPSC generation for clinical application.

	Autologous therapies	Allogenic therapies	Allogenic haplo-matched hiPSC therapies	Allogenic gene edited hiPSC therapies
Immunosuppression	No or low immunosuppression required	Immunosuppression required	No or low immunosuppression required	No or low immunosuppression required Few lines, high compatibility
Safety	Quality control (genetic stability, genome integrity, and tumorigenicity) required for each line	Quality control performed during characterization	Quality control performed during characterization	Risk of off-target modifications
Time required	Long time (individual generation and characterization)	Short time (the line is already generated and characterized)	Short time (the line is already generated and characterized)	Short time (the line is already generated and characterized)
Costs	Expensive	Less expensive	Less expensive	Gene edition costs to be covered

hiPSC: human induced pluripotent stem cells.

from private companies (e.g. Fuji-CDI, in Wisconsin, USA, from the five most common HLA types matching to 35% of US population), with non-exclusive license fee and restriction rights to develop and commercialize a product. Very few allogeneic hiPSC lines for cell therapy are provided by public research organizations such the NIH through RUCDR Infinite Biologics, Korea HLA-Typed iPSC Banking, and the Center for iPS Cell Research and Application. The Center for iPS Cell Research and Application has generated a total of 27 hiPSC lines made from seven donors (four peripheral blood and three CB) who are homozygous for four of the most frequent HLA types in Japan. These lines cover approximately 40% of the Japanese population [23]. Rim *et al.* published the generation of 13 homozygous GMP-hiPSC lines from blood and CB cells from the Catholic Hematopoetic Stem Cell Bank of Korea [19]. Kim *et al.*, recently reported 22 GMP-compliant homozygous HLA-type iPSC lines, which cover HLA haplo-type matching for 51% of the Korean population [25]. Kuebler *et al.* have generated seven iPSC lines from HLA-homozygous CB samples covering 21.37% of the Spanish population [26]. These lines have been banked in GMP conditions and are ready to be used for cell therapy. Table 3 shows the number of existing hiPSC lines generated in GMP conditions from homozygous HLA types.

The different lines give versatility in HLA typing and differentiation capacity for the treatment of different diseases. Some of these cell lines have already been used in hiPSC cell-based clinical cell therapies. A European hiPSC collection to manufacture cell therapy products needs to be developed within a global organization to face emerging scientific medical and industrial needs.

The feasibility of hiPSC large-scale expansion in existing bioreactor systems under cGMP has been tested for many authors and reviewed by Rivera-Ordaz *et al.* [27]. Relating the quality of hiPSC-based products to critical features and process parameters of existing bioreactors appears the best approach for the future development of hiPSC-tailored culture systems and manufacturing processes. Cell lines for use in human therapy need to be established in GMP conditions in facilities with a relevant product manufacturing license under strict quality assurance. These lines must also be generated with all ethical and legal requirements [28]. Use of hiPSC lines as a starting material for the manufacture of cell

TABLE 3

GMP-hiPSC lines generated from homozygous HLA types

Center	Number of hiPSC lines	Number of haplotypes	Coverage (%)	Population
Fuji-CDI	5	5	35	USA
Center for iPS Cell Research and Application (Yoshida *et al.*, 2023)	27	4	40	Japanese
Pochon CHA University (Lee *et al.*, 2018)	10	10	41.07	Korean
Catholic Hematopoietic Stem Cell Bank of Korea (Rim *et al.*, 2018)	13	13		Korean
Korea National Stem Cell Bank (Kim *et al.*, 2021)	22	22	51	Korean
Banc de Sang i Teixits/IDIBELL (Kuebler *et al.*, 2023)	7	7	21.37	Spanish

hiPSC: human induced pluripotent stem cells; HLA: human leukocyte antigen.

FIGURE 1

Addressing the right challenges with the right stakeholders.

FOCUS AREA	STAKEHOLDERS REQUIRED
Sample selection	CB banks, hiPSC generators
hiPSC production	hiPSC generators, cell therapy products manufacturers
Quality control, biobanking, and regulation of cell lines	hiPSC generators, cell therapy products manufacturers, biobanks, regulatory bodies, hPSCreg
Safety and regulation	Immunologists, regulatory bodies, cell therapy products, manufacturers
Data handling and ethics	CB banks, geneticists, experts in data handling and protection, ethical experts
Training	CB banks, hiPSC generators, immunologists, experts in data handling
Clinical application	Regulatory bodies, cell therapy products manufacturers, clinical researchers, immunologists, hiPSCreg

therapy products requires demonstration of comparability of lines derived from different individuals and in different facilities. This needs agreement on the quality attributes of such lines and the assays that should be used [29–31].

CREATING THE RIGHT FRAMEWORK FOR hiPSC GENERATION TO BE USED FOR CELL THERAPY

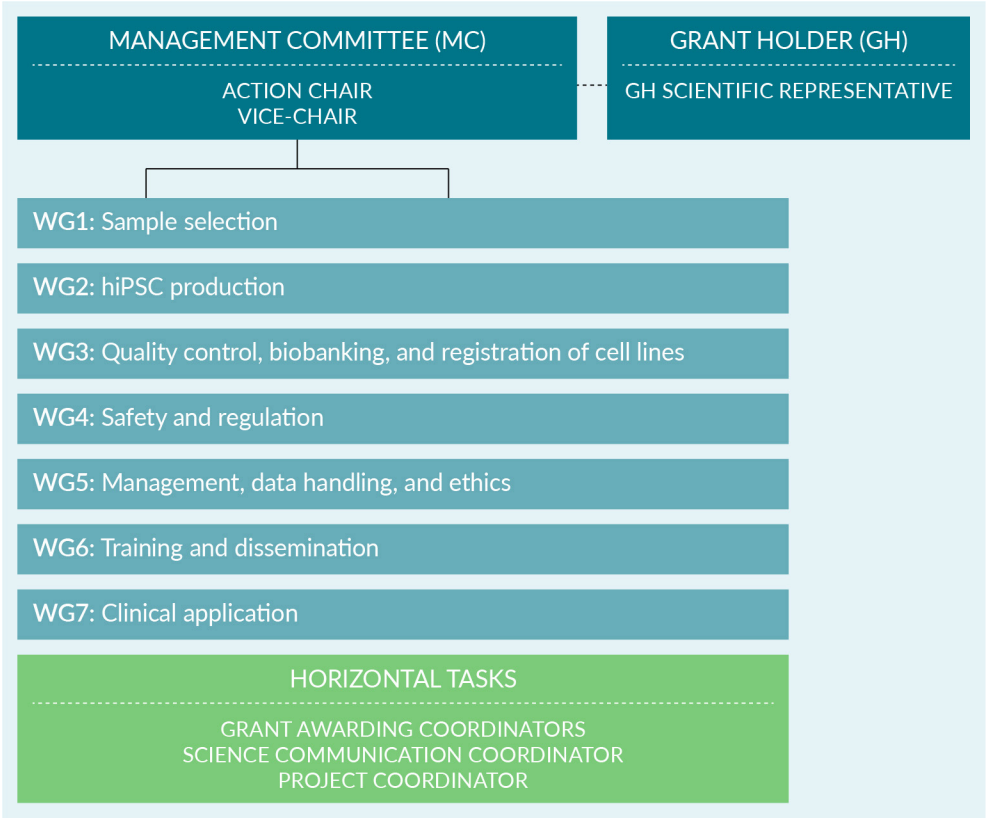
The size of this challenge becomes clear with some numbers. It is estimated that 405 theoretical HLA homozygous combinations are sufficient to cover 100% of the UK Caucasian population—based on a sample of 10.000 real persons to be matched. The hurdle to be overcome is that of these 405, only 236 existed in a pool of 17 million registered donors. Therefore, far more than 17 million need to be screened to find all required combinations. Currently, approximately 22 million HLA-mapped donors are registered worldwide.

One aspect of the HAPLO-iPS network is therefore to elucidate strategies to identify the best possible approach to access donor pools. HAPLO-iPS is now striving to develop a strategic framework using CB sample donations as a source as these provide the most accessible source for hiPSC generation. The framework can be expanded to other HLA typed sources such as bone marrow registries and HLA modified cells, as described above. This network includes all the relevant stakeholders (Figure 1) including: hiPSC generation and banking centers, CB banks that will supply CB units, manufacturing centers complying with GMPs and CMCs to produce stem cell derivatives for cell therapy (advanced therapy medicinal product experts), clinicians, and clinical centers involved or aiming to get involved in cell therapy using hiPSC derivatives, and regulators such as national agencies that supervise compliance with the regulations in the different countries. Ethics experts for the correct handling of samples and adequate data confidentiality and sharing sample procedures are also critical to this network. Immunology experts are also key to ensure an optimal selection of the CB samples.

HAPLO-iPS is managed by the management committee led by a chair and a vice chair. The management committee is the decision-making body. It is responsible for the coordination, implementation and management of the Action activities. The grant holder provides administrative support to the management committee. Seven working groups with working group leaders and co-leaders are in charge of developing the scientific activities. Other key positions

FIGURE 2

Project structure.



are the Grant Awarding Coordinators, the Science Communication Coordinator and the Project Coordinator (Figure 2).

The overall aims of the HAPLO-iPS network also benefits significantly from broader international interactions that are facilitated through established international stem cell networks. Even so, it must be considered that producing hiPSC that are suitable for manufacture of therapeutic products involves more than quality standards and key cell line characteristics must also be addressed for their impact on safety and efficacy of the final products.

The use of hiPSC derivatives for cell therapy requires special attention not only to quality control processes but also with respect to assessment of the differentiation properties, tumorigenicity, and genome integrity, as well as guidelines for ethics and regulatory advice/contacts (such as license landscape), registration and 'look up' systems (available manufacturing capacities), and strategic roadmap including other possible source materials. In addition, the utility of haplo-banks and registries of hiPSC lines to make a single product type will require special attention to establish appropriate comparability studies to assure that multiple cell lines can generate an equivalent product.

THE FUTURE AIMS OF THE HAPLO-iPS NETWORK

The future aim of HAPLO-iPS is to set the basis for an inclusive approach, making stem cell therapies accessible and affordable for the broadest possible EU population in need. This will be achieved by considering the broad range of haplotypes needed to serve that community. The challenges now being addressed by this collaborative network

require an international approach rather than a national or local one, given the magnitude and complexity of the proposed goals, the rarity of individuals with homozygous HLA haplotypes and the diversity of skills and resources required. Central to this is to consider the pluralistic nature across Europe on the ethical, legal, and socioeconomic levels and the different stages of preclinical and clinical advances. The problem to be solved does not only affect a local or national community, not even a European one, instead it is a global concern for those working in the field. Therefore, the time is ripe to combine the current efforts in one place, to set up a fully coordinated and state-of-the-art European haplo-registry from which to do the groundwork for future patient matched cell-based medicines. Necessary technologies are already described and the first hiPSC-based clinical trial in Europe is progressing (Cynata, UK) and others are moving forward worldwide [2]. Putting in place a first of its kind EU haplo-registry will ensure strict data and procedural standards and harmonization of the procedures used in the different centers involved throughout Europe, together with the definition of the required rigorous standards and regulatory acceptability regarding cell quality and safety. Comparability of the efficiency and safety of different hiPSC lines for therapeutic applications will also be essential. Legal and ethical issues will have to be aligned throughout the different European countries and decentralized GMP manufacturing centers and biobanking hubs will also have to be established with a smoothly working logistic network. Furthermore, to reach the highest quality standards, traceability, and automation solutions, all with effective standardization measures in place must be proactively developed. This is crucial at all stages of cell production, characterization and biobanking. However, hiPSC biobanking procedures are currently being developed largely within individual projects for GMP manufacture of cell-based products and the nature of the haplo-banking challenge means there are huge benefits to be realized from greater co-ordination between device developers, current users, future product developers and regulators at national, European, and international levels. A sophisticated combination of decentralized and centralized facilities for cell production, quality control and distribution are likely to be needed to serve the broad range of hiPSC cell-based medicines under development. This will involve an extended quality control and auditing process to assure the same baseline for quality and safety in all participating resource centers throughout Europe. The HAPLO-iPS network already has a wide geographical distribution among many EU countries in order to achieve this. Currently, there are 42 members in the management committee from 25 countries, and 133 working group members from 32 countries. Moreover, it can increase because COST Actions are open during all the lifespan of the Action. HAPLO-iPS is now well placed to coordinate with broader international haplo-banking activity in Asia and the USA to further increase impact in this regard.

HAPLO-iPS will add value to existing efforts at both the European and International level because it has all the prerequisites to provide a sustainable solution to avoid faulted workflow design and fragmented implementation of hiPSC derived products for cell therapy. HAPLO-iPS brings together an unprecedented pool of experts from CB banks, reprogramming centres, companies, clinicians, regulators, and ethics experts in the relevant science domains. Furthermore, this network aims to update and educate the researchers in the concepts and technologies necessary to further advance this field to deliver a cohort of consistently trained scientists and clinicians fit to engage in effective translational research and the development of future cell-based medicines.

The ultimate goal of the HAPLO-iPS network is to utilize the power of innovative stem cell technology to provide every European citizen with a safety-assured, perfectly characterized, and immunologically

matched stem cell line. This will allow much wider access for European patients to treatment with future cell therapies and regenerative medicine without a long-lasting or even unsuccessful search for compatible cell donors and the need for significant immunosuppression of recipient patients. Creating the right network of stakeholders is only the first step, creating a sustainable ecosystem and the resources to do so in the EU to support the clinical application of hiPSCs, will be the challenge for the next years to come.

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