COST ACTION CA21151 — HAPLO-iPS

D.1.2: Report on the coordination of information seeking tracing, collection and data curation of the selected samples

Proceedings of the workshop “iPSC to the Clinic: where are we? A Donor Perspective” including a survey of cord blood banks on the transfer of clinical-grade samples for iPSC haplobank development.

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Working Group 1: Sample selection

Prepared by: Sergio Querol, David Turner and Leonardo Martin on behalf HAPLO-iPS WG1 (Sample selection)

Contact: sergi.querol@fcarreras.es and haploips@idibell.cat

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Executive Summary:

D1.2. Deliverable on Coordinated Information Seeking, Traceability, Collection and Data Curation for iPSC Haplobanking

This report (Deliverable D1.2 of COST Action CA21151 – HAPLO-iPS) presents a coordinated European framework to enable the identification, traceability, collection, and data curation of selected biological samples—primarily cord blood units (CBUs)—for the generation of clinical-grade induced pluripotent stem cell (iPSC) haplobanks.

This deliverable builds on a multidisciplinary effort led by Working Group 1 (Sample Selection), combining scientific, regulatory, ethical, and operational perspectives collected through the workshop *"iPSC to the clinic: where are we? A donor perspective"*.

Purpose and Scope

The deliverable establishes a structured approach to coordinating the end-to-end pathway from donor/sample identification to the creation of curated datasets supporting iPSC haplobank development. This includes:

- Systematic **information seeking** across registries and cord blood banks to identify candidate donors with desirable HLA profiles
- Robust **traceability frameworks** ensuring full linkage between donor, biological material, derived iPSC lines, and downstream applications
- Proposed **collection strategies** aligned with regulatory and GMP requirements
- Standardized **data curation processes** enabling interoperability, quality control, and future reuse

These elements are essential to ensure that selected samples are suitable, ethically sourced, and clinically translatable.

Key Outputs

- Workshop synthesis
- Survey findings
- Operational recommendations
- Proposed roadmap for future harmonization

Key Findings

- **Fragmentation of current practices:** Cord blood banks show heterogeneous levels of readiness in ethical approval, traceability systems, and data governance for iPSC use. While technical capabilities are largely established, implementation is constrained by regulatory and consent limitations.
- **Traceability and data governance gaps:** Although traceability is often partially ensured through existing transplantation frameworks, there is no harmonized approach for:

    - Long-term donor follow-up and “look-back” procedures
    - Monitoring of genetic findings
    - Secure and standardized transfer of donor-linked data
    - This limits scalability and cross-border collaboration.
- **Need for standardized information flows**: The absence of shared templates (e.g., material transfer agreements, consent forms) and data models hampers efficient exchange of samples and associated metadata between institutions and projects.
- **Strategic importance of coordinated selection:** HLA-based prioritization and population coverage modelling underline the necessity of coordinated, pan-European sample selection to:
    - Avoid redundancy
    - Maximize population coverage
    - Ensure equitable representation of diverse populations across Europe.
- **Demonstrated feasibility:** National initiatives (e.g., IPSPANIA, German, Norwegian and French programmes) confirm that coordinated pipelines—from donor selection to GMP-grade iPSC line generation—are feasible when supported by structured data curation, re-consent procedures, and regulatory alignment.

Recommendations emerging from discussion

Based on the workshop discussions, survey outcomes, and examples from existing national initiatives, the following recommendations are proposed to support coordinated and scalable development of clinical-grade iPSC haplobanks in Europe:

- **Establish harmonized ethical and consent frameworks:** Develop adaptable consent models, including provisions for future clinical applications, genomic analyses, donor re-contact, and dynamic consent mechanisms where appropriate.
- **Strengthen traceability and donor governance systems:** Implement interoperable traceability infrastructures enabling end-to-end tracking from donor and biological sample to derived iPSC lines and downstream therapeutic applications, including standardized look-back procedures and management of actionable genetic findings.
- **Standardize data exchange and operational documentation:** Promote common templates and standards for material transfer agreements (MTAs), donor documentation, metadata collection, and secure transfer of donor-linked information to facilitate cross-border collaboration.
- **Coordinate HLA-based sample selection at the European level:** Support federated approaches for donor prioritization and haplotype selection to maximize population coverage, reduce duplication of effort, and improve representation of genetically diverse populations.

- **Support regulatory alignment and translational readiness:** Encourage early interaction with regulatory authorities and alignment of sample collection, reprogramming, quality control, and manufacturing workflows with current SoHO, GMP, and ATMP frameworks.
- **Promote sustainability and interoperability of future haplobanks:** Develop mechanisms for long-term governance, data maintenance, benefit sharing, and integration with emerging registries and international iPSC initiatives.
- **Build on existing national initiatives as implementation models:** Leverage lessons learned from ongoing European programs to establish reproducible operational pipelines that can be adapted and expanded across different healthcare and regulatory environments.

Proposed Coordinated Framework

The deliverable proposes an integrated operational model comprising:

- **Information seeking layer:**
    - Use of registries and cord blood inventories to identify HLA-homozygous or high-value donors
    - Integration of demographic, genetic, and quality datasets for prioritization
- **Traceability infrastructure:**
    - End-to-end digital tracking from donor to iPSC line
    - Alignment with SoHO regulation and international standards
    - Mechanisms for reporting actionable findings
- **Collection and processing pathway:**
    - Standardized criteria for sample eligibility (quality, HLA, consent status)
    - GMP-compatible workflows for material transfer and reprogramming
- **Data curation and integration;**
    - Harmonized datasets including donor characteristics, processing history, and quality attributes
    - Interoperability with emerging registries (e.g., hPSCreg-based systems)
    - Continuous updating and validation of data

To operationalize this framework, the report highlights priority actions:

- Develop **harmonized ethical and dynamic consent models** for current and future use of samples
- Implement **standardized traceability and data governance systems**, including look-back procedures
- Establish **common MTAs and data-sharing agreements** across institutions

- Create **centralized or federated data platforms** to support coordinated selection and monitoring
- Align practices with **European regulatory frameworks (SoHO, GMP, ATMP pathways)**
- Foster **international coordination** to build interoperable haplobanks with global relevance

Conclusion

This deliverable demonstrates that the success of iPSC haplobanking depends not only on scientific and manufacturing capabilities, but critically on the **coordination of information flows, traceability systems, and high-quality curated datasets** across institutions and countries.

By establishing a harmonized framework for information seeking, tracing, collection, and data curation, HAPLO-iPS provides a scalable foundation for the development of clinically relevant iPSC haplobanks capable of supporting next-generation cell therapies in Europe and beyond.

Introduction

The workshop *"iPSC to the clinic: where are we? A donor perspective"* was conceived as a joint initiative of HAPLOiPS COST Action CA21151—*Generation of Human Induced Pluripotent Stem Cells from Haplo-selected Cord Blood Samples*—and the Global Alliance for iPS Therapy GAiT, bringing together experts involved in the translational development of induced pluripotent stem cell (iPSC)-based therapies. Organized within the framework of Working Group 1 (WG1) of HAPLOiPS, the meeting focused on donor selection strategies for cord blood–derived HLA haplolines and on defining practical approaches to ensure the availability of suitable starting materials for cell processing facilities.

Held as a one-day meeting on 1 December 2025 at the Royal College of Pathologists in London, the workshop aimed to provide an up-to-date overview of key scientific, technical, regulatory, and organizational challenges associated with the clinical translation of iPSC-based therapies, examined specifically from a donor and starting-material perspective. The programme was structured into six thematic sessions covering: (i) the current status of iPSC-derived advanced therapies in immunotherapy and regenerative medicine; (ii) the role of HLA in the development of universal or broadly compatible cellular products; (iii) comparison of potential cell sources for haplobanking; (iv) presentation of ongoing national haplobank initiatives in Europe; (v) regulatory and translational considerations from both EU and UK viewpoints, including potential business models; and (vi) the perspective of public cord blood banks, addressing the repurposing of existing cryopreserved cord blood units originally donated for hematopoietic cell transplantation.

By fostering multidisciplinary discussion and exchange of experience, the workshop sought to identify areas of consensus and to outline practical pathways for integrating donor-centred considerations into the development of clinically applicable iPSC haplobanks. The present proceedings capture the key contributions and discussions from the meeting, reflecting the collective effort to advance iPSC translation to the clinic within a coordinated European and international framework.

Table 1 summarizes the programme of the workshop held on 1 December 2025 at the Royal College of Pathologists (London, UK), jointly organized by HAPLO-iPS COST Action CA21151 and GAiT. The agenda was structured into six thematic sessions covering clinical translation, HLA strategies, starting cell sources, national haplobank initiatives, regulatory frameworks, and an open discussion with cord blood bankers to identify priorities and challenges for clinical-grade iPSC haplobank development.

Table 1. Agenda and scientific programme of the workshop "iPSC to the Clinic: Where Are We? A Donor Perspective"

Time	Activity	Responsible
08:00–08:15	Welcome	Moderators: Anna Veiga (HAPLO-iPS) and Mark Turner (GAiT)
08:15–09:30	**Session 1. Clinical Science**	Moderator: Sergi Querol (REDMO–Josep Carreras Leukemia Foundation, Barcelona, Spain)
	iPSC-derived immunotherapies (25 min)	Belen Alvarez-Palomo (Blood and Tissue Bank, Barcelona, Spain)
	Regenerative medicine (25 min)	Anna Falk (Lund University, Lund, Sweden)
	Discussion (25 min)	
09:30–10:45	**Session 2. Role of HLA**	Moderator: David Turner (Scottish National Blood Centre, Edinburgh, UK)
	Which is the best ranking of HLA-haplotypes to cover Europe? (25 min)	Martin Maiers (NMDP, Minneapolis, USA)
	Role of gene editing in allogeneic regenerative cell therapies (25 min)	Kourosh Saeb-Parsy (Cambridge University, Cambridge, UK)
	Discussion (25 min)	
10:45–11:00	Coffee Break	
11:00–12:15	**Session 3. Cell Sources**	Moderator: Begoña Aran (IDIBELL, Barcelona, Spain)
	Pro-cord blood as starting material (25 min)	Angel Raya (IDIBELL, Barcelona, Spain)
	Pro-adult sources as starting material (25 min)	Joel Glover (University of Oslo, Oslo, Norway)
	Discussion (25 min)	
12:15–13:15	Lunch	Free
13:15–14:30	**Session 4. Haplobank Initiatives**	Moderator: Anna Veiga (IDIBELL, Barcelona, Spain)
	IPSPANIA: The Spanish iPSC clinical-grade haplobank (15 min)	Sergi Querol
	German Haplobank experience (15 min)	Gesine Koegler
	Analysis of a future Greek haplobank (15 min)	Helen Latsoudi
	CiTHERA: The French cGMP-iPSC haplobank program (15 min)	Annelisse Bennaceur
	Discussion (15 min)	
14:30–15:45	**Session 5. Regulatory Science**	Moderator: Dolores Hernandez (ONT, Madrid, Spain)

	iPSC regulatory status Europe (20 min)	Andreas Kurtz
	iPSC regulatory status UK (20 min)	Rehma Chandaria and Jacqueline Barry
	Business models (20 min)	Glyn Stacey
	Discussion (15 min)	
15:45–16:00	Coffee Break	
16:00–17:00	**Session 6. Open Discussion with Cord Blood Bankers (Q&A)**	Moderators: David Turner and Sergi Querol
16:45–17:00	Adjourn	Anna Veiga (HAPLO-iPS) and Mark Turner (GAiT)

Session 1: Clinical science

This session was dedicated to practical European examples of iPSC clinical translation, with a particular focus on immunotherapy and regenerative medicine. The objective was to illustrate that several iPSC-based projects are now approaching clinical application and to demonstrate that the logistical, ethical, and legal challenges associated with the generation of clinical-grade iPSC lines can be effectively addressed. Moderated by Sergi Querol, the session brought together complementary perspectives spanning advanced immunotherapies and regenerative medicine pipelines. Belen Alvarez presented current developments in iPSC-derived immunotherapies, including CAR-NK products and hematopoietic applications, while Anna Falk shared her experience in the development and translation of iPSC-based regenerative medicine products. Together, these contributions provided a concrete and realistic view of the current readiness of iPSC technologies for clinical implementation in Europe.

1.1. iPSC-derived immunotherapies (Belen Alvarez-Palomo)

Cell immunotherapies have revolutionized the treatment of cancer in the last two decades: Tumour Infiltrating Lymphocytes (TILs) and Chimeric Antigen Receptor (CAR) modified T-cells have given hope to survive to patients unresponsive to any other treatments. Currently, several cellular immunotherapies are already approved and routinely used, saving the life of hundreds of patients. The applications of CAR-T cells are quickly expanding beyond the cancer field to autoimmune diseases, fibrosis and beyond. Mesenchymal Stem Cells (MSC) are also showing promising results as immunomodulatory cells for the treatment of Graft versus Host Disease and other immune related conditions.

Despite the impressive results in the clinics, TILs and CAR-T cells present some challenges derived from the fact of being autologous treatments e.g. limitation of the availability of fit T-cells, the long manufacturing time and the high production cost. Some of these issues could be overcome by using allogeneic approaches. In the case of CAR therapies, alternative allogeneic approaches include donor-derived NK, macrophages or other candidates. Potential sources of donor cells for immunotherapies are peripheral blood or umbilical cord blood or tissue, although they are subject to donor availability and variability.

Induced pluripotent stem cells emerged as a new source of cells for immunotherapy presenting several advantages: limitless access to the starting cell (donor consistency), the possibility to choose the genetic background (for example an HLA homozygous donor for an HLA-match with a patient) and amenability for gene editing and clonal expansion, allowing the introduction of CAR molecules and other enhancing genetic features without the use of costly, inconsistent and risky viral vectors, and producing homogeneous population with controlled gene expression.

The landscape of current iPSC-immunotherapies is reflected in the clinical trials registered so far with iPSC-derived cell products: iNK cells dominate the field, particularly CAR-NK for the treatment of cancer, followed by iMSC for GvHD, and iCAR-T cells for cancer.

iNK and iT immunotherapies have been pioneered by one USA company, FATE Therapeutics, which has introduced a number of promising genetic enhancements and

strategies. The use of feeder cells for the up-scaled production of NK cells is still an undesirable feature, but one which the field seems to be evolving to overcome.
iT-cells had been harder to produce from iPSC, but new advances have made it possible to catch up with CAR-immunotherapies and three clinical trials are registered so far.
MSC, iNKT, macrophages and dendritic cells are also emerging as new candidates to iPSC-derived immunotherapies.
Finally, in terms of possible allo-rejection of iPSC-derived immunotherapies, avoiding the attack of host immune cells might improve the effectiveness of the process. Different approaches are being tested such as enabling an HLA match with a panel of HLA homozygous donors, HLA knock-out or overexpression of molecules to attack or downregulate allo-reactive host immune cells.

1.2. Regenerative therapies: Harmonized Quality Control and Neural Differentiation Strategies (Anna Falk)

Anna Falk's research focuses on understanding human neural development and disease through the use of patient-specific iPSCs. Her group develops advanced neural differentiation platforms, including neuroepithelial stem cells and three-dimensional brain organoids, to investigate the mechanisms governing neural stem cell fate decisions, neuronal maturation, and the pathogenesis of neurodevelopmental and neuropsychiatric disorders. In parallel, the laboratory drives translational efforts aimed at developing regenerative therapies based on iPSC-derived neural cells, including the establishment of GMP-compliant iPSC lines for future clinical applications. A complementary line of research addresses the quality and standardization challenges that underpin successful iPSC differentiation and clinical translation. Through international Quality Assessment Rounds involving laboratories worldwide, the group has contributed to the development of harmonized quality control approaches for pluripotent stem cells, demonstrating the reproducibility of genomic integrity testing and identifying OCT3/4, TRA-1-60, and SSEA5 as robust markers for assessing the undifferentiated state. The work further highlighted the importance of standardized workflows for accurately tracking transitions from pluripotency to differentiation and provides a framework for interoperable iPSC banking, regulatory alignment, and scalable manufacturing of regenerative medicine products. Together, these studies bridge fundamental neurodevelopmental biology, iPSC differentiation, and the translation of stem cell technologies into clinically applicable therapies.

1.3. Key points of the debate:

- **Advances in IPSC-derived immunotherapies:** Anna Alvarez Palomo and colleagues provided a comprehensive overview of the current landscape, challenges, and innovations in iPSC-derived immunotherapies, focusing on NK and T cell therapies, manufacturing protocols, genetic enhancements, and strategies to address immunogenicity.
    - **Current clinical landscape:** Anna Alvarez Palomo presented data showing a rapid increase in clinical trials for iPSC-derived immunotherapies, particularly NK and T cell therapies, with the US and China leading in trial numbers. She highlighted the dominance of certain

companies, such as Fate Therapeutics, and the expansion of indications beyond cancer to include infectious and fibrotic diseases.

- **Manufacturing and genetic enhancements:** The discussion covered manufacturing protocols for iPSC-derived NK cells, including the use of feeder cells and efforts to eliminate them for regulatory simplicity. Anna described genetic enhancements such as non-cleavable CD16, IL-15 fusion receptors, and CAR expression to improve persistence and efficacy, referencing work by groups like Kaufman and collaborations with Madrid for modular gene editing platforms.
- **Immunogenicity and allorejection:** Anna addressed the challenge of allorejection in iPSC-derived immune cells, discussing strategies such as HLA matching, HLA knockout, and the addition of defence receptors like CD58 and avirulence factors (AVR) to reduce host immune responses. She noted that while NK, macrophage, and mesenchymal cells have limited in vivo persistence, genetic modifications are being pursued to further minimize rejection.
- **Comparative advantages of NK vs T Cells:** Anna and others explained that NK cells offer a safer cytokine profile and are preferable for certain indications where long-term persistence of T cells could be harmful, such as in HER2 or fibrosis targeting. The discussion emphasized that the choice between NK and T cells depends on the clinical context and target antigen.
- **Technical questions and protocol variability:** Participants discussed technical aspects such as the rare expression of KIR in iPSC-derived NK cells, variability in differentiation outcomes, and the influence of culture conditions on cell maturation markers like CD16. Anna noted that even with standardized protocols, small changes in conditions can lead to significant differences in cell phenotype.

- **Standardization and quality control in iPSC manufacturing:** Anna Falk and collaborators presented studies on the impact of culture conditions, transcriptomic profiling, and international quality control initiatives (such as the GAiT study) to improve standardization and reproducibility in iPSC manufacturing, with active discussion on the use of gene panels, flow cytometry markers, and single-cell analytics.
  - **Impact of culture conditions:** Anna Falk described a study comparing iPSC lines grown in defined versus undefined culture conditions, showing that gene expression and differentiation potential are significantly influenced by the culture environment. The study identified calcium signalling as a key factor in maintaining pluripotency, validated through transcriptomic and functional assays.
  - **International quality control initiatives:** The GAiT study, involving over 20 international sites, assessed laboratory consistency in flow cytometry and genomic integrity assays for iPSC quality control. The results highlighted significant variability in marker usage and data interpretation, leading to recommendations for harmonized protocols and the identification of robust markers such as SSEA-5 and TRA-1-60.

- **Gene panels and single-cell analytics:** Participants discussed the potential of using gene panels derived from single-cell transcriptomics to predict product potency and safety, moving beyond traditional flow cytometry markers. Anna and others emphasized the need for innovation in analytics to enable earlier detection of suboptimal cell populations and reduce reliance on animal models.
- **Technical questions and regulatory considerations:** Questions from the audience addressed the relationship between genomic stability and surface marker expression, the challenges of standardizing phenotypic assays, and the regulatory implications of adopting new quality control methods. Anna clarified that while genomic integrity methods showed low variability, flow cytometry remained highly variable across sites.

Session 2: Role of HLA

This session addressed the role of HLA in the development of universal allogeneic therapies, examining complementary and potentially convergent strategies for minimizing immune incompatibility in iPSC-based products. Moderated by David Turner, the discussions contrasted approaches based on maintaining physiological HLA matching with emerging alternatives relying on targeted genetic modification. Martin Maiers reviewed haplobanking as a "physiological" strategy, focusing on the rationale and methods for optimal HLA haplotype ranking to maximize population coverage in Europe. In parallel, Kourosh Saeb-Parsy presented gene-editing approaches aimed at modifying HLA expression to generate immune-evasive cell products. Together, the contributions provided a structured comparison of HLA-based and gene-editing strategies, highlighting their respective scientific, translational, and implementation challenges in the context of universal iPSC-derived therapies.

2.1. Regional HLA diversity in European cord blood units: Implications for collaboration in iPSC haplobanking (Martin Maiers)

iPSC haplobanks based on HLA-homozygous donors have been initiated in several countries, but population-specific HLA diversity limits their utility when developed independently. National efforts risk redundant lines targeting the same common genotypes while leaving gaps in diverse populations. Recent studies have evaluated whether coordinated European haplobanking could improve population coverage while minimizing duplication.

iPSC haplobank coverage has been modelled across 27 European countries using high-resolution HLA genotypes from donor registries and cord blood banks. Coverage was defined as the proportion of patients with no mismatch at HLA-A, -B, and -DRB1 (host-vs-graft). Three scenarios were compared: (1) using European HSCT registry donors + cord blood, (2) using cord blood only, and (3) using cord blood where ≥2 banked examples of a genotype exist (2 copies). Diversity was quantified using the Gini–Simpson index and Good–Turing estimates of unseen genotypes.

A coordinated European haplobank of 270 lines achieved a mean coverage of 82.7% (70% Cyprus–91% Finland). Restricting to cord blood lowered coverage to 77%, and limiting to genotypes with ≥2 copies reduced coverage to 62%. Diversity followed a strong north–south gradient: Gini–Simpson values ranged from 1 in 4,190 (Finland) to 1 in 103,131 (Turkey), and Good–Turing estimates showed higher fractions of previously unobserved genotypes in southern populations.

Europe's heterogeneous HLA landscape underscores the need for interoperable regional rather than national iPSC haplobanks. Coordination reduces redundant investment, improves population coverage, and guides prioritization of genotypes for global sharing. Cord blood can seed such banks, but limited homozygous representation—especially in high-diversity southern populations—requires complementary donor recruitment and shared standards for line generation and exchange. These findings support developing a globally harmonized network of iPSC resources that is efficient, equitable, adaptable to demographic evolution, and representative of diverse patient populations.

2.2. Role of gene edition in allogeneic regenerative cell therapies (Kourosh Saeb-Parsy)

Kourosh Saeb-Parsy's work has highlighted immunogenicity as a major barrier to the clinical translation of regenerative cell therapies and has provided an important rationale for the application of gene-editing technologies. Using human cholangiocyte organoids as a model for biliary tract regeneration, his group demonstrated that inflammatory stimulation induces upregulation of both HLA class I and class II molecules, increasing the potential for immune recognition after transplantation. In vitro and humanized mouse studies showed that allogeneic immune responses were strongly driven by HLA incompatibility and were substantially reduced by donor-recipient HLA matching, whereas fully mismatched grafts exhibited progressive immune rejection. Interestingly, even autologous organoids elicited low-level immune infiltration, potentially related to culture-acquired mutations, cell viability, or extracellular matrix components. These findings provide direct experimental evidence that HLA-mediated allorecognition represents a critical obstacle to scalable organoid therapies and support the development of gene-editing strategies aimed at reducing HLA expression or generating hypoimmunogenic cell products. By defining the mechanisms underlying immune responses to regenerative organoid grafts, Saeb-Parsy's research has established a strong scientific foundation for combining organoid technology with genome engineering to create safer, universally compatible, off-the-shelf regenerative therapies.

2.3. Key points of the debate:

- **HLA haplobanking strategies and population coverage:** Martin Maiers and colleagues presented data-driven strategies for constructing HLA-homozygous iPSC banks to maximize patient coverage across European and global populations, discussing the limitations of current cord blood inventories, the impact of regional diversity, and the potential for federated banking.
    - **Population coverage modelling:** Martin explained the use of large-scale HLA typing data from the World Marrow Donor Association to model optimal haplotype selection for iPSC banks. The analysis showed that a relatively small number of homozygous lines can cover a significant fraction of the population, but coverage varies widely by country and region.
    - **Cord blood inventory limitations:** The presentation highlighted that many optimal HLA genotypes are underrepresented or absent in current cord blood banks, with only a subset of genotypes available in sufficient numbers. Strategies such as using cord blood segments and considering units with lower cell counts were discussed as ways to expand usable inventory.
    - **Regional and global bank coordination:** Martin and others discussed the benefits of federated or regional banks to reduce redundancy and improve efficiency, as well as the challenges posed by population diversity and migration. The need for coordinated international efforts and economic support for cord blood banking was emphasized.

    - **Considerations for heterozygotes and additional loci:** The group considered the potential to include heterozygous lines and additional HLA loci (such as C, DQ, and DP) in future models, as well as the implications for NK cell alloreactivity and antibody-mediated rejection. The complexity of balancing broad coverage with practical inventory constraints was acknowledged.
- **Gene editing and immunogenicity in cellular therapies:** Kourosh Saeb-Parsy and collaborators presented research on gene editing strategies to reduce immunogenicity in cholangiocyte organoid therapies, including CRISPR-mediated HLA knockout, functional validation, and in vivo immune response studies, with extensive discussion on the implications for clinical translation and safety.
    - **Development of low-immunogenic organoids:** Kourosh described the derivation of cholangiocyte organoids from primary adult cells, their expansion, and functional characterization. The team demonstrated that these cells can be gene-edited to knock out HLA class I and II, resulting in reduced immunogenicity while retaining functional properties.
    - **In vivo immune response studies:** The group conducted in vivo experiments in humanized mouse models, showing that both allogeneic and even autologous organoids can elicit immune responses, with regulatory T cell infiltration observed in full mismatch settings. The impact of cell injury and culture conditions on immunogenicity was also investigated.
    - **Off-target effects and genomic integrity:** Whole genome and single-cell sequencing were used to assess off-target mutations in edited organoids. The results indicated that most mutations arise from cell passaging rather than gene editing, but highlighted the need for comprehensive quality control before clinical application.
    - **NK Cell-mediated killing and clinical strategies:** The team found that HLA class I knockout increases susceptibility to NK cell killing, though even wild-type cells are variably affected. Strategies to balance reduced immunogenicity with NK cell evasion, and the use of standard immunosuppression regimens, were discussed as part of the clinical translation plan.

Session 3: Cell Sources

This session focused on the critical importance of selecting the most appropriate starting cell type for the generation of iPSC lines intended for haplobanking. Recognizing that the choice of cell source has significant implications for scalability, quality, regulatory compliance, and population coverage, the discussion aimed to assess which options are best suited to meet the needs of the widest range of patients. Moderated by Begoña Aran, the session brought together complementary perspectives from Angel Raya and Joel Glover, who examined different candidate cell sources and their respective advantages and limitations. Their contributions set the stage for an informed and constructive discussion on defining the most recommended cell sources for iPSC haplobank initiatives.

3.1. Cord blood as starting material (Angel Raya)

The choice of starting material is critical for generating clinical-grade induced pluripotent stem cells (iPSCs). In this presentation, Prof. Raya introduced their pioneering work using cord blood cells for reprogramming to pluripotency, a strategy conferring key advantages over traditional sources like skin biopsies. Cord blood cells are young, harbour fewer somatic mutations, and reprogram with superior efficiency. Crucially, public banks already hold vast, clinically validated inventories of cryopreserved units with high-resolution HLA types. The Regenerative Medicine Program of IDIBELL experience, in collaboration with BST, in building on this to create haplobanks of iPSC lines from donors homozygous for common haplotypes was shared. These master cell lines form the basis of allogeneic therapies, where a single banked line can treat thousands of immunologically matched patients. By detailing the route from cord blood selection to the generation of GMP-grade, HLA-homozygous iPSC banks, this presentation outlined a viable and highly scalable framework for manufacturing the universal cell therapies of the future.

3.2. Adult sources as starting material (Joel Glover)

This presentation began with an introduction of the Norwegian iPSC Biobank for Clinical Applications (NIBCA), as an example of an initiative using adult sources of somatic cells as starting material for generating HLA-haplotyped iPSCs. Glover noted that several initial conditions extant at the start of the NIBCA project led to the choice of adult somatic cells rather than cord blood as the most practical alternative: 1) Norway does not have any national or regional cord blood banking initiatives, 2) Norway has a well-developed national registry of already HLA-haplotyped adult bone marrow donors, 3) Norway has a GMP clinical cell production facility at Oslo University Hospital with prior experience in production of mesenchymal stem cells (MSCs) as ATMPs, and 4) Norway has a national core facility for human pluripotent stem cells (www.ous-research.no/ncs) with extensive expertise in generating iPSCs from skin fibroblasts, which could be transitioned easily into GMP-compliant procurement and production protocols already established for MSCs.

An additional consideration involved the choice of reprogramming strategy. At the time NIBCA was started, skin fibroblasts could easily be reprogrammed using any of the most commonly used strategies, including Sendai virus, episomal vectors, RNA replicons and mRNA, whereas reprogramming of blood cells utilized primarily Sendai virus with mRNA-based reprogramming considered unworkable. Use of Sendai virus requires clearing of the virus through multiple passages, which increases the risk of iPSCs acquiring genomic/genetic aberrations. Use of mRNA on the other hand involves zero risk of genomic integration and clearance can occur simply through degradation without passaging. Although mRNA-based reprogramming of blood cells has since been achieved, it was not seen as a viable option at the start of the NIBCA project. Thus, in terms of facilitating regulatory approval from the Norwegian Medical Products Agency, skin fibroblasts were seen on several points as the most convenient and feasible starting material.

Glover went on to discuss advantages of using adult somatic cells rather than cord blood cells as starting material related to ethics and GDPR. He noted that the donor consent field is moving towards dynamic consent as the norm, and that it is relatively straightforward to obtain dynamic consent from adult donors (indeed, NIBCA has established a working dynamic consent platform implemented through the Norwegian Bone Marrow Donor Registry). The situation is more complicated legally for infant donors of cord blood, because there is a need to foresee rights that can be exercised once the donors become legal adults. This entails challenges for cord blood banks that were initiated long before the dynamic consent concept emerged, with re-contact and consent transfer from parent to child as central issues. This is exemplified by a policy brief from the Global Alliance for Genomics and Health which underscores "…the ethical right of a child to an "open future", which aims to preserve a child's ability to make meaningful decisions later in life when the child is not yet in a position to do so." Thus, with respect to feasibility of dynamic consent (and, in the future, "dynamic governance", an ethical regulatory development that aims to allow donors to actively govern the use of their cells), adult somatic cells provide the easiest alternative.

3.3. Key points of the debate:

- **Selection of Starting Material for Clinical-Grade IPSC Lines:** A session led by Dr. Angel Raya and Dr. Joel Glover compared the use of cord blood versus adult fibroblasts as starting material for clinical-grade IPSC lines, discussing practical, regulatory, ethical, and biological considerations, with contributions from Anna Alvarez-Palomo and other participants.
    - **Cord Blood as Starting Material:** Dr. Raya outlined the advantages of cord blood, including high reprogramming efficiency, availability of HLA-typed units, youth of the cells, and lower viral load. The process for generating iPSCs from cord blood was described, emphasizing the speed and efficiency compared to other sources.
    - **Adult Fibroblasts and National Context:** Dr. Joel Glover explained the rationale for using adult fibroblasts in Norway, citing the absence of a national cord blood bank, existing donor registries, and regulatory familiarity with fibroblast protocols. The Norwegian initiative (NIBCA)

leverages dynamic consent and GMP-compliant processes for adult donors.
    - **Regulatory and Ethical Considerations:** The session addressed the complexities of regulatory classification (ATMP vs. starting material), licensing issues with reprogramming technologies, and the challenges of dynamic consent for infant donors. The need for context-specific, case-by-case assessment was emphasized.
    - **Genomic Integrity and Mutation Burden:** Participants discussed recent findings on mutation rates in iPSCs derived from blood versus skin, the prevalence of cancer driver mutations after in vitro expansion, and the importance of comprehensive quality control. The lower viral burden in cord blood was highlighted as an additional regulatory advantage.
- **Donor Consent and Ethical Considerations in Cell Therapy:** Participants discussed the complexities of donor consent, commercialization, and ethical issues in cell therapy, focusing on the challenges of informed consent, donor rights, and the implications of future commercialization for both adult and pediatric donors across different jurisdictions.
    - **Commercialization and Consent Waivers:** It was explained that for the NIBCA project, donors are required to waive future commercial interest due to the unpredictability of future commercial developments, highlighting challenges when the donor is a minor, as in the case of cord blood, where legal guardians must provide consent and future rights of the donor as an adult remain uncertain.
    - **International Regulatory Differences:** Participants discussed how informed consent requirements vary internationally, noting that while some countries like South Korea and Japan do not require re-consent when a donor reaches adulthood, the US does, and in Europe, consent is typically obtained from parents or legal guardians, with the donor able to opt out upon reaching legal age.
    - **Dynamic Consent Models:** The group reviewed the concept of dynamic consent, where ongoing contact with donors led to higher retention rates and allowed donors to specify preferences for future uses of their cells, providing flexibility as regulations and ethical standards evolve.
    - **Definitions for Research and Commercial Use:** There was consensus on the need for clear definitions distinguishing research use from commercial application, especially as clinical trials may blur these lines, and participants noted regulatory constraints that limit the use of cord blood for purposes other than hematopoietic transplantation unless laws are updated.
- **Follow-up tasks:**
    - Cord Blood Unit Utilization for IPS: Evaluate and adapt methodologies for using cord blood segments with low cell counts for IPS generation, considering recent advances in progenitor expansion and regulatory requirements. (Martin, Anna, the team)
    - Dynamic Consent for Infant Donors: Develop and finalize a dynamic consent framework and associated documentation specifically

addressing the legal rights and future autonomy of infant cord blood donors for IPS banking. (Joel Glover, Working Group 5)

- Quality Control Standards for IPS Lines: Establish consensus recommendations for quality control and mutation screening thresholds for IPS lines intended for clinical application, considering recent findings on mutation burdens from different cell sources. (Working Group 4)
- Standardization of Flow Cytometry Markers: Harmonize and validate a standardized set of flow cytometry markers for pluripotent stem cell quality control across participating laboratories, based on recent multi-site data.
- Regulatory Guidance on Starting Material Classification: Clarify and disseminate regulatory guidance regarding the classification of starting materials (e.g., fibroblasts, cord blood) versus ATMPs for IPS banking, ensuring alignment with EMA recommendations.
- NK Cell Response Assessment in Edited Cells: Investigate and report on strategies to mitigate NK cell-mediated killing in HLA class I/II knockout cell therapies, balancing immunogenicity reduction and safety concerns.

Session 4: Haplobank initiatives

This session was devoted to the presentation of ongoing national haplobank initiatives that aim to establish iPSC-derived cell resources to support the development of advanced therapies. Recognizing the strategic importance of coordinated and sustainable haplobanking frameworks, the session provided a comparative overview of selected European experiences. Moderated by Anna Veiga, representatives from Spain (Sergi Querol), Germany (Gesine Koegler), Greece (Helen Latsoudi), and France (Annelise Bennaceur) presented the status of their respective national projects. The discussion highlighted both shared challenges and country-specific approaches, offering valuable insights into similarities, differences, and opportunities for alignment across European haplobank initiatives.

4.1. IPSPANIA: The Spanish IPSC-clinical grade haplobank (Sergio Querol)

Cord blood (CB) is a substance of human origin with unique cellular and immunological properties that has been widely used in hematopoietic stem cell transplantation. Although its clinical use has declined in recent years due to comparable outcomes achieved with alternative HLA-mismatched grafts, public cord blood banks hold large inventories of high-quality, clinical-grade units that are increasingly underutilized. This context has prompted a strategic shift toward “cord blood banking 2.0,” aimed at diversifying applications beyond transplantation. Stored CB units represent an attractive starting material for the generation of iPSCs, enabling the development of new cellular medicines and HLA-homozygous iPSC haplobanks.

iPSC technology offers several advantages for universal cell therapy, including ethical acceptability, robust and mature reprogramming methods, scalability through batch manufacturing, and clinically validated feasibility. Leveraging the extensive Spanish CB inventory, the IPSPANIA project was established to generate GMP-grade iPSC haplolines from previously donated, HLA-homozygous cord blood units stored in the national registry. Following regulatory authorization and re-consenting of donors, seven CB units meeting strict quality and biological criteria were selected. $CD34^+$ cells were purified, reprogrammed using non-integrating Sendai vectors, and expanded under GMP conditions to generate master and working cell banks.

The resulting IPSPANIA iPSC lines are early intermediate substances intended for the development of advanced therapy medicinal products and are supported by comprehensive quality dossiers and ongoing stability programs. IPSPANIA represents a publicly owned, GMP-compliant, two-tier iPSC banking model that enables access for both biomedical research and clinical innovation, illustrating how existing cord blood inventories can be repurposed to support next-generation cell therapies in a sustainable and ethically robust framework.

4.2. Generation of GMP-grade HLA-homozygous iPSC-lines and cardiomyocyte aggregate manufacturing technologies for allogenic cell therapy to the heart (EU-consortium HEAL (Gesine Koegler)

Since early reports of pluripotency in cord blood–derived cells, their clinical potential has progressively evolved toward therapeutic application. In 2016, the Düsseldorf Cord

Blood Bank initiated the establishment of a GMP-compliant induced pluripotent stem cell (iPSC) bank derived from HLA-homozygous umbilical cord blood units, supported by German federal funding. Following re-consenting and regulatory authorization, $CD34^+$ hematopoietic stem cells from selected cord blood units were isolated, expanded, and reprogrammed using a plasmid-based, non-integrating approach under GMP conditions. Seventeen HLA-homozygous units representing frequent haplotypes in the German population were processed in collaboration with certified manufacturing partners.
Resulting iPSC lines underwent comprehensive quality control, including assessment of pluripotency, genomic integrity, vector clearance, identity, sterility, and potency. Stable HLA-homozygous iPSC lines covering seven of the most frequent Caucasian haplotypes were successfully generated and banked, including validation batches corresponding to top-ranked haplotypes in Germany.
These iPSC lines are now being leveraged within the EU-funded HEAL project, which aims to develop scalable, GMP-compliant iPSC-derived cardiomyocyte aggregates for cardiac repair. An optimized 3D differentiation protocol targeting WNT, TGF-β/SMAD, and FGF signalling pathways yielded highly pure cardiomyocyte aggregates, followed by development of an optimized cryopreservation strategy ensuring high post-thaw viability and functional marker retention. Preclinical safety studies addressing tumorigenicity and arrhythmogenic risk are ongoing in rodent and large-animal models.
Together, this work demonstrates the feasibility of generating high-quality, HLA-defined iPSC banks from cord blood and their translational potential for advanced cell-based therapies.

4.3. The Regional HLA Heterogeneity: A Determining Factor for a Future Haplobank in Greece (Helen Latsoudi)

The high geographic diversity of HLA haplotypes remains a major limitation for optimal donor matching in allogeneic hematopoietic stem cell transplantation. Induced pluripotent stem cells (iPSCs) derived from donors homozygous for frequent HLA haplotypes represent a promising alternative, enabling the development of haplobanks with broad population coverage and reduced rejection risk. However, population-specific HLA diversity challenges the effectiveness of independent national haplobanking strategies and supports the need for coordinated, regionally informed approaches.
Using a large cohort combining 78,611 and 98,998 cord blood units (CBUs) and bone marrow donors (BMDs) from Greece and Cyprus, we estimated the number of HLA-homozygous haplolines required to maximize zero-mismatch coverage at HLA-A, -B and -DRB1 in the Greek population. We further assessed the impact of incorporating phylogenetically related European populations using a cohort of 110,000 donors from 11 DKMS minority populations and evaluated whether balanced regional donor representation could improve coverage while limiting sampling bias.
Approximately 50 haplolines were sufficient to cover ~54% of the Greek population. While similar estimates were obtained for CBUs and BMDs, the limited availability of homozygous CBUs in highly heterogeneous populations resulted in markedly reduced coverage compared with adult donors. Inclusion of HLA-related South-Eastern Mediterranean and Balkan populations increased cumulative coverage to 79%, significantly outperforming haplotypes derived from more distant North-Western

European populations. Our analysis also identified uneven regional representation within the national registry, underscoring the risk of systematic bias.
These findings demonstrate that haplobank efficiency depends on coordinated donor recruitment strategies, regional haplotype sharing, and real-time population coverage mapping. Collaborative, ancestry-informed European haplobanking initiatives are essential to optimize resource allocation and enable scalable iPSC-based therapies for regenerative medicine and immunotherapy.

4.4. Generation and characterization of French clinical grade IPSC lines and off-the-shelf master cell banks by automation process (Annelisse Bennaceur)

CiTHERA (https://cithera-ipsc.com) is transferring disruptive allogeneic IPS cell-based therapies from translational research to foster early-stage clinical programs particularly in oncology. Our state-of-the-art cGMP facility is dedicated to produce clinically-compliant iPSC lines from healthy haplotyped donors as a platform to genetically modify iPS clones and to generate off-the-shelf therapeutic iPS-derived cells such as iNK, iMac/Mono, iDC, iMSC for the design of breakthrough immunotherapies.
Studies have set-up a therapeutic iPSC workflow to produce Haplo-iPSC from healthy donors. Our cGMP compatible reprogramming protocol was validated and 7 pharmaceutical grade-iPSC line (Cith-01-07) were generated from haplotyped CBU-CD34+ cells, as well as from adult leukapheresis and CD3+lymphocytes from peripheral blood. cGMP-compliant Haplo-iPSC are currently manufactured from Triple Homozygous HLA donors: 7 available Cord Blood Units from the French Cord Blood Registry (Biomedicine Registry and the French Blood Establishment) and 8 Cord Blood Units from Ankara University in collaboration with the European Haplo-IPS Cost Action Network. The pluripotency and genomic integrity of selected iPSC clones have been confirmed by release assays (WGS and Optical Genome mapping) as required by international guidelines (GAIT and iSSCR). We use the closed-culture process CliniMACS Prodigy ®, to produce 109 final iPSC batch as Master Cell Banks. This safe and standardized manufacturing platform is reducing minimal process variability and hand-on time.
These studies are now moving on to generate gene-edited universal iPS clones and manufacture CAR-iNK and iMonocytes/iMacrophages for Oncology indications.

4.5. Key points of the debate

- **Technical and regulatory challenges in IPSC banking and therapy:** Speakers such as Sergi Querol, Gesine Koegler, Helen Latsoudi, and others presented national and international initiatives on iPSC banking, highlighting technical, regulatory, and logistical challenges in donor selection, cell line generation, quality control, and harmonization across Europe and beyond.
    - **Spanish IPSC banking initiative:** Sergi Querol described the Spanish national project for IPSC banking (IPSPANIA), which involved all Spanish cord blood banks and regulatory authorities, focusing on immunogenetic selection, informed consent, and the creation of master and working cell banks under GMP conditions, with protocols for donor recontact and privacy.

  - **German GMP-grade IPSC generation:** Gesine Koegler outlined the German experience in generating GMP-grade HLA-homozygous IPSC lines from cord blood, detailing the selection of common haplotypes, reprogramming protocols, quality control measures, and the use of these lines in cardiac therapy research, including preclinical studies in animal models.
  - **Greek population genetics and bank design:** Helen Latsoudi presented an analysis of Greek and Cypriot donor populations, demonstrating high genetic heterogeneity and recommending the use of regional European banks and digital tools to optimize donor selection and coverage, rather than establishing a purely national bank.
  - **French clinical-grade IPSC production:** A summary of the French initiative led by Annelise Bennaceur described the creation of clinical-grade IPSC lines using both cord blood and peripheral blood, with a focus on immunotherapy and oncology applications, and collaboration with public banks and universities for line development and quality control.
- **Donor protection, genetic findings, and dynamic consent:** A panel discussion addressed the ongoing responsibilities of biobanks and registries regarding donor protection, the management of incidental genetic findings, and the implementation of dynamic consent to accommodate evolving knowledge and donor preferences, with input from multiple participants.
  - **Reporting genetic findings to donors:** Participants debated the ethical and regulatory obligations to inform donors or their guardians about genetic findings discovered during screening or after cell expansion, noting the complexity of determining which findings are actionable and the need for expert panels to guide disclosure.
  - **Reclassification and follow-up of genetic variants:** The group discussed the importance of periodically re-examining genetic data as variants of unknown significance may later be classified as pathogenic, with some countries implementing follow-up programs and others relying on expert committees to update actionable findings.
  - **Dynamic consent and legal frameworks:** Dynamic consent was highlighted as a tool to respect donors' changing preferences over time, with reference to the Council of Europe's Oviedo Convention, which mandates the right to know or not know about health-relevant findings, and the need for continuous adaptation of consent forms.

Session 5: Regulatory Aspects

This session addressed the regulatory and commercialization challenges that shape the development of iPSC haplobanks and their downstream medicinal products. Moderated by Dolores Hernandez, the presentations offered complementary personal perspectives on regulatory frameworks, donor-related considerations, manufacturing requirements, and emerging business models relevant to iPSC translation. Andreas Kurtz provided an overview of key issues within the European legislative landscape, while Jacqueline Barry examined the UK regulatory context. The session concluded with a contribution from Glyn Stacey, who discussed pathways toward commercialization following haplobank establishment. Together, these presentations highlighted major jurisdiction-specific hurdles and underscored the importance of coherent regulatory strategies and sustainable business models to enable the clinical and commercial success of iPSC-based therapies.

5.1. IPSC regulatory status in Europe (Andreas Kurtz):

Prof. Andreas Kurtz provided an overview of the evolving European regulatory landscape governing iPSC-based products and their clinical translation. He emphasized that iPSC-derived therapies are generally regulated as Advanced Therapy Medicinal Products (ATMPs), requiring stringent standards for manufacturing, quality control, traceability, and clinical evaluation. Particular attention was given to the interaction between ATMP legislation and the new European Regulation on Substances of Human Origin (SoHO), which aims to harmonize quality and safety requirements for human-derived starting materials while facilitating cross-border exchange within Europe. The presentation highlighted the need for clear regulatory classification of iPSC lines and their derivatives, robust donor consent and traceability systems, comprehensive genomic integrity and quality assessment programs, and early engagement with competent authorities throughout product development. Prof. Kurtz also discussed the role of European initiatives such as hPSCreg and EBiSC in supporting standardization, transparency, and regulatory confidence in pluripotent stem cell resources. Overall, the session underscored that harmonized regulatory frameworks, coordinated governance, and internationally accepted quality standards will be essential to enable the safe, efficient, and equitable implementation of iPSC-based therapies across Europe.

5.2. IPSC regulatory status UK (Jacqueline Barry)

Dr. Jacqueline Barry provided an overview of the United Kingdom's regulatory framework for iPSC-based therapies, highlighting both its continued alignment with European standards and areas where UK-specific pathways are evolving. The presentation described the central roles of the Medicines and Healthcare products Regulatory Agency (MHRA) and the Human Tissue Authority (HTA) in overseeing the procurement of starting materials, manufacturing processes, quality systems, and clinical application of cell-based medicinal products. Particular emphasis was placed on the regulation of iPSC-derived products as Advanced Therapy Medicinal Products (ATMPs), requiring robust GMP-compliant manufacturing, donor traceability, and

comprehensive quality control throughout product development. Dr. Barry also highlighted the importance of early and continuous engagement with regulatory authorities to facilitate clinical translation and discussed the UK's efforts to maintain internationally recognized standards while supporting innovation in regenerative medicine. The presentation underscored the need for harmonization of regulatory expectations, clear governance of iPSC biobanks, and adoption of best-practice frameworks to ensure that emerging iPSC-based therapies can progress efficiently and safely from research to clinical implementation.

5.3. Business models and Sustainability of IPSC Biobanking (Glyn Stacey)

Prof. Glyn Stacey discussed the scientific, regulatory, and economic challenges associated with establishing sustainable iPSC biobanking infrastructures capable of supporting large-scale regenerative medicine. Drawing on the experience of HLA-homozygous haplobank initiatives, he highlighted how well-characterized iPSC resources can reduce development costs, improve product safety, and enable broader patient access to allogeneic cell therapies through HLA matching. However, he emphasized that the long-term viability of iPSC biobanks depends not only on scientific excellence but also on robust governance, internationally harmonized quality standards, regulatory acceptance, and sustainable funding models. Particular attention was given to the substantial investment required for donor qualification, informed consent, traceability systems, GMP-compliant manufacturing, quality control testing, and long-term data management. Prof. Stacey further noted that each iPSC line may present unique biological characteristics, creating challenges for comparability studies and regulatory approval when multiple cell lines are intended for use within the same therapeutic product. International coordination through initiatives such as the International Stem Cell Banking Initiative (ISCBI), hPSCreg, and global iPSC banking networks was presented as essential to establishing common standards, avoiding duplication of effort, and increasing the value of shared resources. Overall, the presentation highlighted that sustainable iPSC biobanking will require a careful balance between public investment, regulatory compliance, industrial partnerships, and the delivery of clinically useful cell products that can justify long-term operational costs.

5.4. Key points of the debate

- **European and UK regulatory frameworks for cell therapy:** Andreas Kurtz, Jacqueline Barry, and others provided detailed overviews of the evolving European SOHO regulation, UK post-Brexit alignment, and the ISSCR best practices, emphasizing the need for harmonization, clear classification of products, and early engagement with regulators for successful clinical translation.
    - **SOHO regulation in Europe:** Andreas Kurtz explained the new SOHO regulation, which unifies the regulatory framework for substances of human origin across Europe, introduces new requirements for registration, quality management, and authorization, and aims to facilitate cross-border exchange while allowing for stricter national measures.

    - **UK regulatory alignment and divergence:** Jacqueline Barry described the UK's current strong alignment with EU regulations for cell and tissue products, the ongoing role of the Human Tissue Authority, and the potential for future divergence, particularly in the context of Northern Ireland and evolving clinical trial approval processes.
    - **Best practices and regulatory navigation:** The ISSCR best practices document was introduced as a comprehensive, navigable resource for developers, providing guidance on regulatory requirements, timelines, and engagement strategies across multiple jurisdictions, with emphasis on early and repeated consultation with regulatory authorities.
- **Business models and sustainability of iPSC biobanking:** Glyn Stacey and colleagues discussed the financial, technical, and organizational challenges of sustaining iPSC biobanks, including issues of comparability, GMP compliance, public-private partnerships, exclusivity, and the need for clear policies and added-value services to ensure long-term viability.
    - **Technical and regulatory hurdles:** The discussion covered the need for robust characterization and comparability assays for multiple iPSC lines, the challenges of defining GMP status for undifferentiated cells, and the complexities of translating research-grade materials to clinical-grade products.
    - **Commercialization pathways:** Three main commercialization models were identified: direct investment by experienced manufacturers, delayed investment until manufacturing is established, and transfer from non-commercial developers to industry after early clinical trials, with most iPSC projects following the latter route.
    - **Exclusivity and altruistic donation:** The tension between commercial exclusivity and the principle of altruistic donation was highlighted, with suggestions for dual lineage banking and shared risk models, drawing parallels to established practices in vaccine and biotherapeutic manufacturing.
    - **Sustainability and added value:** Suggestions for ensuring sustainability included offering specialized services such as regulatory review, gene editing, training, and secure storage, as well as developing clear agreements for technology transfer, benefit sharing, and public-private collaboration.
- **Geographic representation and donor diversity in registries:** Participants from Spain, Greece, and other countries discussed strategies for ensuring equal geographic and genetic representation in donor registries and biobanks, including the use of digital tools, regional quotas, and continuous demographic monitoring.
    - **Digital tools for donor monitoring:** Helen Latsoudi described the development of digital tools in Greece to register donors with demographic and genetic details, enabling ongoing assessment of geographic representation and identification of underrepresented regions.
    - **Regional quotas and data management:** Spanish representatives explained that each of the 17 regions has its own donor centre with assigned collection targets, ensuring proportional representation, while acknowledging challenges in tracking the actual residence of donors.

- **Follow-up tasks:**
  - **Donor consent and future use:** Review and update donor consent forms to address future commercialization rights and dynamic consent, ensuring compliance with evolving regulations and donor protection requirements.
  - **Geographic representation in donor registries:** Implement or enhance digital tools to monitor and ensure equal geographic representation of donors in national registries and banks, including regular updates of demographic and genetic data.
  - **Harmonization of regulatory standards:** Analyse and map existing GMP-compliant iPSC lines across Europe to identify haplotype coverage and overlaps, and address harmonization challenges with US and other international regulatory requirements.
  - **Material transfer agreements and access policies:** Develop clear material transfer agreements and access policies for the release and supply of iPSC lines from haplobanks to commercial and research entities, including roles, responsibilities, and benefit-sharing mechanisms.
  - **Reporting and management of actionable genetic findings:** Establish a process for regular review and reclassification of genetic findings in donor cells, including guidelines for notifying donors of actionable mutations and updating consent procedures as knowledge evolves.
  - **Sustainability and funding models for haplobanks:** Explore and propose sustainable funding models for European haplobanks, including public-private partnerships, technology transfer compensation, and added-value services to ensure long-term viability.

General discussion including cord blood banking survey

During this session, the results of a survey conducted through WMDA among affiliated cord blood banks were presented. Responses were received from 12 banks: three from Spain, two from Greece, and one each from Australia, the United States, Colombia, the United Kingdom, Germany, the Netherlands, and Sweden. Although the number of respondents is limited and may not be fully representative, the results should be interpreted as exploratory and hypothesis-generating; nevertheless, the findings provide a useful snapshot of the current landscape and perspectives regarding cord blood bank participation in iPSC-related initiatives.

Questions formulated were divided in the following aspects:

- Ethical, Legal:
    - Do you already have ethical and legal approval in place for the transfer of cord blood units for iPSC generation?
    - Is re-consent of donors required for this type of use (e.g., iPSC derivation, genomic analysis, or broader research/clinical applications)?
- Operational:
    - How is traceability ensured, and is there a defined policy for look-back in case of abnormal or clinically relevant genetic findings?
    - What selection criteria are proposed for cord blood units intended for iPSC generation (e.g., HLA characteristics, cell quality, donor characteristics)?
    - Is a Material Transfer Agreement (MTA) template already in place for transferring samples to external partners?
    - How is confidential donor and sample-related data transferred, and how is its appropriate use monitored and controlled?
- Strategic and Economic Considerations
    - Do you consider that cord blood banks should receive an economic return when their units are used for iPSC generation or downstream applications?
    - Have you considered developing a clinical-grade iPSC cell line bank within your institution or network?
    - In your opinion, should cord blood banks actively participate in iPSC-based projects and initiatives?
    - Would your cord blood bank be interested in participating in a haplobank initiative, and do you consider this feasible within your current framework?

Questions included in the survey were grouped into three thematic domains: **(i) ethical and legal considerations**, focusing on consent and regulatory authorization; **(ii) operational aspects**, addressing traceability, sample selection, and data governance; and **(iii) strategic and economic considerations**, exploring sustainability, institutional engagement, and future participation in iPSC haplobank initiatives. Responses were collected from participating cord blood banks and are summarized in **Table 2.**

Table 2. Summary of survey responses from participating cord blood banks regarding ethical, operational, and strategic readiness for participation in iPSC generation and haplobank initiatives (n = 12). Results should be interpreted as exploratory and hypothesis-generating and provide a qualitative snapshot of current practices and perspectives.

Survey Question (n = 12)	Yes	No	Representative Comments
Already have ethical and legal approval in place for transfer of cord blood units for iPSC generation?	3	9	Ethical approval may exist, but in several cases it does not explicitly cover transfer of cryopreserved cord blood units for iPSC generation.
Is donor re-consent required for this type of use?	4	8	Some banks intentionally selected recently banked CBUs to reduce the likelihood of re-consent challenges.
Is traceability ensured, including look-back procedures for abnormal or clinically relevant genetic findings?	5	7	Traceability is often managed through MTAs defining permitted uses; however, post-manipulation genetic abnormalities are not always considered attributable to the original donor.
What selection criteria are proposed for cord blood units intended for iPSC generation?	9	3	Selection generally follows existing criteria used for human application and transplantation, including immunogenetic considerations and established standards (e.g., NetCord/FACT).
Is a Material Transfer Agreement (MTA) template already in place for transferring samples to external partners?	6	6	Several institutions reported active discussions with competent authorities regarding MTA models and mechanisms to recognize public investment.
How is transfer of confidential donor and sample-related data monitored and controlled?	9	3	Data are generally pseudonymized and governed through MTAs, annual reporting, and restrictions on downstream use such as WGS or iPSC generation.
Should cord blood banks receive economic return when units are used for iPSC generation or downstream applications?	9	3	Although resulting products are typically owned by developers, respondents suggested public banks should receive partial benefit-sharing or compensation mechanisms, particularly in non-profit settings.
Has your institution considered developing a clinical-grade iPSC cell line bank?	7	5	Ethical and legal barriers remain substantial, although several institutions reported ongoing research activities in this area.
Should cord blood banks actively participate in iPSC-based projects and initiatives?	8	4	Participants suggested developing registries of clinically compliant iPSC lines covering a broad range of HLA haplotypes (e.g., through WMDA).
Would your institution be interested and likely to participate in a haplobank initiative?	7	5	General interest was high, although obtaining ethical approval remains a major anticipated barrier.

The survey results indicate heterogeneous levels of readiness among cord blood banks (CBBs) regarding participation in iPSC-related activities, revealing a distinction between institutional interest and current operational readiness. While respondents generally expressed a positive attitude toward iPSC initiatives and recognized their strategic potential, implementation appears to be constrained primarily by regulatory, ethical, and governance considerations rather than by technical capability. These findings suggest that future progress may benefit from coordinated efforts to promote:

- Harmonized ethical and consent frameworks
- Standardized material transfer agreements (MTAs) and traceability policies
- Clear governance models for ownership, access, and benefit sharing
- Integration with existing registries and collaborative infrastructures (e.g., WMDA-related approaches)

General conclusions:

- **European cord blood bank collaboration and haplotype mapping:** Discussion on the objectives and progress of mapping European cord blood bank haplotypes, the feasibility of establishing a European haplobank, and the challenges in clinical application and bank readiness.
    - **Objectives and deliverables:** The team, with contributions from David Turner and Martin Maiers, outlined the main deliverables: mapping European haplotypes and proposing an internal list for the European haplobank, with the goal of covering at least 50% of the population using 33 main lines.
    - **Bank readiness and feasibility:** A survey of 12 banks revealed that most do not have ethical and legal approval to transfer cord blood units for this type of project, with only two banks ready and others facing restrictions such as research-only use or lack of clinical transfer consent.
    - **Ethical and legal challenges:** Discussion highlighted the complexity of consent, especially regarding whether original donor consent covers new uses, the rights of donors upon reaching adulthood, and the need for updated or dynamic consent models to facilitate participation in new projects.
    - **Material transfer and data handling:** Most banks lack material transfer agreements for these purposes, and there is no standardized mechanism for transferring or tracking donor data, with some banks only able to reidentify donors and others requiring annual reports without specific tracking.
    - **Bank participation and future steps:** While a majority of surveyed banks expressed interest in participating in a European haplobank, significant barriers remain, including ethical approval and operational readiness; the group plans to continue discussions and develop a consensus document.
- **Technical considerations in haplotype extension and matching:** Martin Maiers, David Turner and other participants discussed the technical feasibility of extending haplotype calculations to include additional classical and non-classical HLA genes, the implications for matching, and the challenges posed by incomplete typing and population heterogeneity.
    - **Extending haplotype calculations:** Participants considered the possibility of building extended haplobanks that include a broader range of HLA genes, such as DP and DQ and non-classical genes, noting that while this could improve matching, it is limited by the availability and resolution of existing typing data.
    - **Statistical and practical limitations:** Martin explained that many samples are typed at low resolution, requiring statistical computation and assumptions about population genetics to estimate coverage, and acknowledged that perfect matches are rare, especially for minor antigens.
    - **Relevance to rare diseases:** Sergi and others highlighted the importance of considering additional genetic factors, such as associations with rare skin disorders, and the need to avoid reintroducing certain HLA types to minimize susceptibility in specific populations.
- **Consent models and ethical frameworks for cord blood use:** Participants discussed the challenges of obtaining appropriate consent for new uses of cord

blood units, the need for dynamic or updated consent models, and ongoing efforts to develop standardized consent templates for both adult and infant donors.

- **Current consent practices:** The group reviewed existing consent procedures, noting that most banks require the ability to recontact donors (or mothers) in case of findings, but that original consents often do not cover new research or clinical applications.
- **Dynamic consent and international approaches:** Sergi raised the concept of dynamic consent and the value of learning from international approaches, suggesting that pooled resources and shared models could help banks adapt to evolving ethical requirements.
- **Development of standardized consent templates:** Work was described to create a model consent form for cord blood donors, similar to existing templates for adult donors, but it was noted that legal issues regarding infant donors remain unresolved and are a current stumbling block.

Acknowledgements

- About HAPLOIPS initiative:

HAPLO-iPS (COST Action CA21151) is a European collaborative network funded through **COST (European Cooperation in Science and Technology)**, a funding organization supporting research and innovation networks across Europe. Running from 2022 to 2026, HAPLO-iPS brings together academic institutions, cord blood banks, manufacturing centers, regulatory experts, clinicians, and industry stakeholders to accelerate the development and translation of induced pluripotent stem cell (iPSC)-based therapies. These hiPSC lines will be compatible with a significant percentage of the population, allowing their use in cell therapy clinical trials. Additionally, the network aims to develop a data collection system based on the hPSCreg registry for human pluripotent stem cell lines. HAPLO-iPS will create an excellence network based in Europe, focusing on hiPSC-derived cell-based medicines. This network not only aims to advance the state-of-the-art in this research field but also contributes to Europe's global leadership in medical, scientific, economic, and social development.
By strengthening Europe's competitiveness capacities, the network involves key stakeholders such as hiPSC generation/banking centers, cord blood banks, manufacturing centers compliant with Good Manufacturing Practices (GMP), immunology experts, chemistry and manufacturing controls professionals, regulatory bodies, national agencies, and ethics experts. The approach to this challenge involves networking among stakeholders, sharing knowledge, standardizing methodologies, and developing an educational training program for researchers.
HAPLO-iPS also promotes the participation of researchers from less research-intensive countries, as a significant percentage of the members come from these countries. Participants from these countries will have access to research facilities, training courses, and mentoring programs for young researchers, contributing to spreading excellence and widening participation. Furthermore, key leadership positions in the Action Management are reserved for COST ITC members.
Overall, this project pioneers new approaches that will drive the progress of haplo-selected hiPS generation for therapeutics. It achieves this through the development, implementation, and exploitation of a registry that consolidates all relevant information for the benefit of patients.

- About GAIT:

The Global Alliance for iPSC Therapies (GAiT) is an international, non-profit organization established in 2013 to accelerate the development of clinical-grade induced pluripotent stem cell (iPSC) therapies. It fosters global collaboration to harmonize standards, create haplobanks, and facilitate regulatory approvals for regenerative medicines.
Key Aspects of GAiT are:

- Mission: to enable global access to new-generation cell therapies by supporting the creation and standardization of clinical-grade and haplotyped iPSCs.
- Structure and membership: Based in Edinburgh, Scotland, with Professor Marc Turner as chairperson, the network includes over 500 members across 17

countries, spanning research institutions, cell therapy centers, and industry partners.
- Strategic focus: HLA-Typed Banks: Investigating the construction of a global, homozygous library of iPSCs, particularly using HLA-A, -B, and -DRB1 homozygous donors to maximize immune-matched patient coverage.
- Regulatory and quality standards: Setting harmonized guidelines for the manufacturing and characterization of iPSC-derived therapies.
- International collaboration: Working with key partners including the New York Stem Cell Foundation, Cell and Gene Therapy Catapult (UK), and the French Institute of Health and Medical Research (INSERM).
- Impact on therapy development: GAiT ensures that manufacturing processes are consistent with regulations set by agencies such as the FDA and EMA. It aids in bridging the gap between basic stem cell research and clinical trials, helping to transition iPSC technologies into standard therapeutic products.

- Venue:

The organizers would like to express their sincere appreciation to the **Royal College of Pathologists (RCPath), London, United Kingdom**, for hosting the workshop *"iPSC to the clinic: where are we? A donor perspective"* and for providing the facilities and supportive environment that enabled scientific exchange and multidisciplinary discussion among participants. We also thank all speakers, moderators, organizers, and attendees for their contributions to the success of the meeting.