Topic: A sustainable European induced pluripotent stem cell platform

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Topic details

Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Since their introduction in 2007 [1] human inducible pluripotent stem cells (human iPSCs) have been rapidly and broadly incorporated into research to understand their potential for disease and are a very powerful tool for translational research. This has substantiated interest to incorporate this resource into drug discovery pipelines, prospective patient stratification, recruitment for clinical trials and post-clinical drug assessment of safety issues following rare event reporting. In addition, human iPSCs can potentially provide unlimited autologous cells for therapy and therefore hold great promise for regenerative medicine [2]. The evolution of these applications depends on facilitated and unfettered access to a standardised and well characterised iPSC resource to help avoid dissemination of unauthenticated or substandard cell lines to the research community.

iPSCs are cells derived from somatic cells of the body and reprogrammed by introducing specific transcription factors in order to re-establish pluripotency [1] [3] iPSCs can be differentiated intothe three germ layers, the mesoderm, endoderm, and ectoderm, which form the organs during embryonic development. The continued optimisation of protocols now allows producing large quantities of differentiated, human cells in a reliable and reproducible manner. Human iPSCs are established from patients with the promise to capture in cell models specific human disease phenotypes which cannot be revealed in animal models, and to allow studying these in a human context. With the advent of gene editing technologies like the -Clustered Regularly Interspaced Short Palindromic Repeats/associated (Crispr/Cas)-system, specific mutations relevant for a certain disease are being introduced into human iPSCs to again model specific phenotypes and compare with the isogenic parental line. While these efforts will foreseeably improve the consistency with which new cell lines will be developed they will not necessarily foster the standardised and scalable distribution of pre-established or new lines to the wider hiPSC research community.

The rising demand by academia and industry has instigated a number of large scale public and privately funded disease and/or population oriented human iPSC banking initiatives in the US, Japan and UK [4]. However, "several issues should be overcome to advance the field quickly. First, it will be critical to network iPSC resources around the world to create an iPSC library of both normal and diseased cells using a common quality standard. Second, a systematic approach to develop an iPSC library in conjunction with a clinical database, tissue bank and genome-wide association study (GWAS) would be most useful. Third, further development of efficient and standardised *in vitro* iPSC differentiation protocols into many more cell types is essential for progress in the field. Forth, continuous effort to recapitulate phenotypes of late-onset diseases *in vitro*, at least partly, would be critical to extend their applications. Lastly, reducing complexity of culture methods will be important to make the system more easily applicable to high throughput screening" (cited from [5]). Several efforts are ongoing worldwide to address these matters, but still in a highly fragmented way.

In Europe, the project **EBiSC** (https://www.ebisc.org/) funded by the Innovative Medicines Initiative Joint Undertaking has demonstrated the feasibility and challenges of coordinating existing organisational capacities across Europe to fast track the establishment of a centralised network and facilities to access a standardised resource of established hiPSC lines and data. EBiSC has established a unique European based iPSC repository and has delivered harmonised and publically accessible Standard Operations Procedures (SOPs) for tissue procurement, bio-sample tracking, iPSC expansion, cryopreservation, qualification and distribution to the research community. These were implemented to create a quality managed foundational collection of lines and associated data made available for distribution [6].

The critical challenge addressed by this topic is to build on these important infrastructure, capabilities and knowledge to create a fully sustainable European hiPSCs distribution platform with worldwide reach.

Need and opportunity for public-private collaborative research

The complexity of setting up the logistics and infrastructure to secure continued housing, support, and distribution of an iPSC collection in general, and to secure availability of iPSC assets established within public private partnerships including EBiSC plus associated information, needs to be addressed by a public-private-partnership involving a variety of stakeholders as it cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Only a collaborative endeavour bringing together academic laboratories and Small- and Medium-sized Enterprise (SMEs) with access to and ownership of necessary hiPSC lines, technologies and logistics and EFPIA partners that closely interact with the hiPSC banking entity, advising and supporting the further expansion of the hiPSC repository will ensure that therapeutically relevant areas will continue to be addressed and that consistency and quality of preparations meet the needs of drug development campaigns. EFPIA will provide critical feedback on quality and differentiation potentials of iPSC lines and precursor cells provided by the bank facility. Information and data obtained from certain iPSC lines will be added to the banking entity's information management to disseminate knowledge on disease understanding and facilitate development of screening models to be used in drug development.

This engagement of EFPIA will uniquely enable to capitalise on existing capabilities and knowledge to reach the ultimate goal of self-sustainability of the hiPSC banking entity.

Scope

A European iPSC repository that operates on a non-for-profit basis and allows researchers access to a continuously expanding number of well characterised and fully QC'd iPSC lines with clarified access information is mandatory to fuel basic research and development and drug development campaigns. Although previous activities have prepared the ground for such a banking entity, significant aspects listed below remain to be addressed.

The overall objective of the action generated from this topic is therefore to establish a fully self-sustainable European human iPSC banking facility, that has to be operational within the first three months of the action by seamlessly building on and incorporating existing cell lines, knowledge and infrastructure established within

former European wide initiatives (e.g. EBiSC). The bank has to be able from the start to handle and deliver a minimum of approximately 500 quality-controlled, disease-relevant (in particular for neurodegeneration, Alzheimer's disease and other tauopathies, Parkinson's disease), cardiovascular disease, safety, and diabetes), research-grade iPSC lines, with integrated data and cell services which will be further built on as part of the research and technology work of the action. The ultimate goal is to transform significant pre-existing European banking infrastructures into a sustainable resource for European research and development. The applicant consortium at stage 2 will have to document in the full proposal that this can be achieved efficiently and in the expected timelines as a first go/no go milestone.

Thus the following has to be accomplished:

- Transfer of assets established in previous large standardised European collections with linked data and SOPs to the new bank where appropriate technology is in place to handle cells and guarantee seamless continuation of banking and distribution operations;
- Secure continued housing, expansion and QC of the existing iPSC collection generated in in such previous initiatives;
- Ensure a continued and efficient distribution infrastructure with a European and worldwide reach within the first half year after start of the funding period;
- Provide long-term storage capacity for up to 10,000 iPSC-vials with a minimum of 3 replicates each under liquid nitrogen gas phase and automated handling. Capability for long-term storage of biosamples;
- Banking entity and mirror bank certified to operate according to ISO 9001 standards;
- Secure and further optimise established QC-procedures and SOPs by incorporating newly established and accepted methodologies that become available during this undertaking;
- Ensure a continued Information Management System to monitor the iPSC line status and keep track of iPSC line data, complement available information related to existing lines (e.g. mutation confirmation and exome sequencing), and incorporate relevant information including clinical records to new entries;
- Develop the technology and establish efficient and reproducible protocols for parallelised production of bulk quantities of iPSCs and/or precursor cells in response to drug developers or future costumer demands. Within the project, the cells will be subject to analysis at the participating EFPIA companies in order to establish disease models and screening assays;
- Further expand the repository by incorporating additional iPSC lines (patient-derived and gene-edited) that:
    - will be established by the consortium during the life time of the action. It is expected the consortium to support cell line commissioning projects including gene editing technologies, like the Crispr/Cas-system, that are requested by the consortium (public and industry partners) as well as relevant members of the external research community to fuel the repository with iPSC lines relevant for research of benefit to patients and community. Such requests will be reviewed by the consortium board consisting of the EFPIA-group and the public partners and approved, should the deliverables considered as of relevance for the scientific community and pharmaceutical industry;
    - will become available in other publicly funded consortia with a focus on iPSC technology. It is expected the consortium to actively reach out to other cell line owners or publicly funded consortia in the process of establishing iPSC lines to discuss and secure integration of new lines into the repository. In addition, reaching out to other biobanking entities to complement offering to the scientific community and/or avoid duplication of work is encouraged;
    - are already available in the scientific community.
- Ensure ethical and legal matters are in place for incorporation of iPSC lines into a public accessible bank to allow freedom to operate for research and development purposes;
- Establish clinical networks that allow the access to well described patient biosamples for the establishment of iPSC lines and where the ethical and legal ground is established to allow fast access to samples relevant for academic and industrial research;

- Implement all necessary activities to ensure that by the end of the action the repository is fully self-sustainable.

Expected key deliverables

The key overall deliverable of the action is the establishment of a self-sustainable iPSC banking facility that fully leverages significant pre-existing infrastructures and know-how. Key deliverables and goals are:

- Establish within the first three months of the action of an European standardised and at scale human iPSC banking facility by successful transfer of existing iPSC lines, knowledge and infrastructure established within relevant pre-existing European wide banking (e.g.EBiSC) initiatives to this collaboration;
- Establish and maintain of a cell line housing facility with a capacity matching the need to handle existing lines and to be extendable to incorporate new ones;
- Establish and maintain a mirror cell line bank at capacity;
- Apply and continuously improv SOPs to achieve highest standards in iPSC technology. QC criteria will be defined for characterization of newly established, expanded, and differentiated iPSC lines;
- Establish and maintain a European and worldwide distribution infrastructure;
- Throughout the runtime of the project the consortium is expected to strive for self-sustainability of the iPSC repository. Therefore, applicants need to formulate in their proposals, deliverables, and milestones related to a business plan that details the operations after the funding period. The repository will have to be fully self-sustainable by the end of the action;
- Ensure a continued iPSC line Laboratory Information Management System;
- Establish efficient and reproducible protocols/SOPs to produce bulk quantities of precursor cells that can be differentiated into cells from all three germ layers;
- Further expand the repository by incorporating additional iPSC lines:
    - reach out to governmental funding bodies and the scientific community to discuss and secure integration of new iPSC lines into the repository;
    - to support the cell line commissioning projects requested and partially funded by the EFPIA group or the scientific community;
    - establish clinical networks that will facilitate the establishment of iPSC lines from well described patients of relevance to the EFPIA partners and the scientific community;
    - reach out to and network with other biobanking entities to capitalize on synergisms.
- Support the iPSC banking entity with regard to ethical and legal aspects to secure freedom to operate and unlimited use in research and developmental processes is attached to iPSC lines.

It is expected that applicants address all the above objectives in the Short proposal (within the available duration and budget) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

Expected impact

iPSC research and banking continues to be fragmented across a broad spectrum of institutions in Europe, and lacks sufficient scale to support the current and anticipated demands of academic and industrial research and development. In Europe the IMI JU project EBiSC[1] has prepared the ground for establishment of a self-

[1] https://www.ebisc.org/

sustaining banking entity by creating an QC'ed iPSC repository of currently several hundreds of iPSC lines with ethical and legal standards in place. These lines represent important disease areas among them neurodegenerative diseases (Alzheimer's disease, other tauopathies like frontotemporal dementia, and Parkinson's disease), diabetes, neuropathic pain, and cardiovascular diseases that the participating drug developers are actively researching to provide novel treatments to patients.

Availability of iPSC lines derived from patients, as well as of a broad spectrum of lines from healthy donors of different ages, standardised according to how they were made and their *in vitro* behaviour, and the possibility of linking a gene code to cell line phenotype reflective of the disease, will enable the research community to refine original clinical diagnosis into one based on disease stratification and thereby design more precise experiments to discover novel pathogenic pathways, drug targets and new medicines. This is expected to significantly advance research and development activities across Europe by accelerating the progress to understanding a certain disease aetiology as well as finding potential cures thereby strengthening European competitiveness.

This European iPSC repository will be uniquely positioned to serve as the central European iPSC repository hub to accelerate and facilitate European research and development activities. Therefore, the consortium will have to continuously monitor the sale of cells produced by the banking entity, and its trend in order to develop in the runtime of the project a plan as to how to transform the repository into a self-sustainable business. Ultimately this will secure that the public and private investment will establish a resource that beyond the runtime of the project continues to support and fuel European basic research as well as drug development campaigns in Pharma companies.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

More specifically, the applicants have to demonstrate awareness of the most current iPSC landscape across Europe, to be able to reach out to relevant programs to be incorporated or supported in order to ensure that the new banking initiative fully leverages previous significant public and private investments and infrastructures. In Europe, a unique repository of hiPSCells has been created by the IMI JU **EBiSC** project (https://www.ebisc.org/). Also, the IMI StemBANCC collection of iPSC lines has become part of the repository during the lifetime of the previous IMI EBiSC project. Other examples of IMI research collaborations with a strong iPSC focus are IMI **ADAPTED** (https://www.imi-adapted.eu/), IMI **PHAGO** (http://www.phago.eu/), or IMI **IMPRiND** (https://www.imprind.org/). Additional actions related to or employing iPSC technology will be created in response to the topic launched in the IMI2 12th Call for proposals.

Other European wide or national initiatives are :

- the **Human Induced Pluripotent Stem Cell Initiative** (http://www.hipsci.org/);
- the **Human Pluripotent Stem Cell Registry** (https://hpscreg.eu/);
- national initiatives such as **El Banco de Líneas Celulares de Barcelona** (https://www.cmrb.eu/banco-lineas-celulares/que_es.html);
- the **UK Stem Cell Bank** (http://www.nibsc.org/ukstemcellbank), amongst others.

Furthermore, it will be mandatory for the applicants to monitor collaborative activities across the European R&D landscape to make available the infrastructure to governmentally funded scientific projects in the iPSC area.

Industry consortium

The industry consortium will contribute the following expertise and assets:

- Facilitation of transfer of capabilities and knowledge from EBiSC to reach the ultimate goal of self-sustainability of the iPSC banking entity;
- Test of the consistency and quality of iPSC lines as well as preparations of bulk quantities of precursor cell preparations;
- Interaction to ensure banking of iPSC lines which will aid in disease understanding and development of screening models to be used in R&D;
- Establishment of robust and reliable iPSC disease models and screening assays demonstrating proof of concept for the use of iPSCs for disease and pharmaceutical research;
- Support for research activities focusing on:
    - differentiating and analysing iPSC derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration.
    - producing iPSC derived cardiomyocytes and analysing effects of e.g. pro-arrhythmogenic mutations or pharmacological treatments on the electrophysiological characteristics of cells.
    - producing and analysing iPSC derived pancreatic cells to study the underlying mechanisms of diabetes and beta cell dysfunction.
    - They will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Indicative duration of the action

The indicative duration of the action is 36 months.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium, which should include SMEs with relevant expertise and experience in iPSC line derivation and QC, is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. **Significant experience, knowledge and know-how in logistics and infrastructure to operate a European-wide cell line repository including a mirror iPSC bank according to ISO 9001 standards are prerequisites.** In addition, this may require mobilising, as appropriate, the following expertise on:

- Storage and distribution of cells;
- The procurement of biosamples for iPSC generation;
- Long term storage of biosamples to build aclinically relevant source of primary material and allow re-derivation of iPSC lines;
- Reprogramming of human derived cells using state-to-the-art technologies;
- Gene-editing approaches to generate isogenic pairs of iPSC cells;
- Comprehensive QC of established iPSC lines;
- Knowledge in long term storage of biosamples;
- Knowledge in reprogramming of somatic cells to generate pluripotent stem cells;

- State of the art gene editing technology (Crispr/Cas);
- Handling, expansion and QC of iPSC lines;
- Technology and know-how to handle large-scale iPSC cultures as well as the ability to produce bulk quantities of precursor cells or cells with a mature phenotype for distribution;
- Database management to monitor status of cell bank and maintain and amend information available to each cell line;
- Knowledge in establishing and maintaining online portal for purchasing iPSC lines;
- Experience in ethical and legal affairs related to the derivation and use of iPSC;
- Business or economics experience to transform the iPSC repository into a self-sustainable business;
- Scientific / industrial expertise to guide the expansion of the iPSC repository in therapeutically relevant disease areas;
- General project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

It may also require mobilising, as appropriate, the following resources:

- A pre-existing European-wide quality controlled foundational collection of iPS cell lines representing specific disease backgrounds with a focus on neurodegeneration (Alzheimer's disease and related tauopathies, Parkinson's disease), diabetes and cardiovascular diseases and healthy controls including associated data made available for distribution;
- IT capabilities to maintain and support the laboratory infrastructure management system that hosts iPSC related information and to make accessible the catalogue and the associated data via the internet;
- Capacities to allow online ordering and payment of iPSC lines;
- Support on legal and ethical matters;
- Commercial / industrial application of iPSC derived assets generated within such a consortium including large-scale production of iPSCs or cell derivatives for medium-/high- throughput screenings;
- Access to logistics and infrastructure to operate a cell line repository including a mirror iPSC bank;
- A fully automated storage system allowing handling of cell lines in the gas phase of liquid nitrogen for long term storage purposes;
- An established distribution pipeline to deliver cell lines to customers and being operational at the outset of the action.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall

facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

In summary, the work plan should enable activities aiming at:

- managing the existing iPSC collection including storage, QC, banking, expansion, and distribution of cell lines;
- further expanding the iPSC collection by providing technology to derive and establish iPSC lines, reaching out to the European scientific community and consortia being operational or in the process of becoming operational to make use of synergisms and support logistics necessary to secure continued access to iPSC related assets generated within these consortia;
- continuous refinement and optimisation of protocols, QC criteria, and SOPs supporting the operation of the banking activities;
- provide gene editing capabilities to generate iPSC with specific relevant mutations and creation of reporter cell lines;
- develop the technology and establish efficient and reproducible protocols to produce bulk quantities of iPSC, precursor cells or cells with a mature phenotype to fuel industrial screening campaigns. Definition of QC criteria to deliver consistent quality of expanded or differentiated iPSC.

The call topic specifically aims to achieve sustainability as well as a further development and maturation of a European based iPSC repository that includes assets that have been developed by previous private public iPSC collaborations. One of the key outcomes of this action will be to build on existing assets, and in the runtime of this project outline a business plan that will allow the future European iPSC Banking Entity to continue operations beyond the runtime of the project to support the European research & development activities. The scientific challenges that will be addressed in the action to be generated by this topic will further add technology, differentiation protocols, and iPSC lines including data attached to individual lines to increase the value of the repository

The bank has to be self-sustainable by end of the action.

Work package 1 – Project management:

- Grant administration;
- Communication (within the consortium and with relevant external collaborators);
- Dissemination of scientific results and research data;
- Sustainability plan facilitating continuation beyond the duration of the action;

Industry contribution:

co-leadership.

Expected Applicant consortium contribution:

All of the above. Preparation of business plan to run iPSC banking operations in a self-sustainable fashion after funding period to achieve sustainability and continue to serve the European research community with access to iPSC technology.

Work package 2:

- Continuation, expansion, and further optimization of banking operations. This includes European and worldwide reach of sales to reach self-sustainability;

- Incorporation of iSPC assets developed in previous public private partnerships;
- Refinement of existing SOPs for QC of cell lines;
- Facilitate integration of appropriate new iPSC lines generated in other scientific projects (IMI2 JU as well as non-IMI2 JU projects);
- Establishing connection to clinical network, biobanks, and other iPSC banking entities, allowing timely access to patient/donor fibroblast attached to full donor consent, free distribution for research and development, and freedom to operate;

Industry contribution:

supporting above activities. Supporting iPSC line establishment by advising which cell lines are of interest;

Expected Applicant consortium contribution:

banking operations as outlined above.

Work package 3:

- Establishment for bulk production capabilities / SOPs for generating iPSC or precursor cells to fuel screening campaigns;
- Definition QC criteria for expanded and differentiated iPSC;

Industry contribution:

Advice and identification of cell lines to be subjected to bulk production;

Expected Applicant consortium contribution:

- Development of protocols for bulk production of iPSC lines and precursor cell lines for all three germ layers;
- Adaptation of differentiation and maintenance protocols.

Work package 4:

- Proof of concept experiments across industry consortium partners using cell lines produced in work packages 2 and 3 and focusing on following areas
    - Neurosciences:
        - Explore accelerated maturation and/or aging in iPSC derived neurons with electrophysiological relevant read outs (multi electrode assays or patch clamp analysis).
        - Co-cultivation with astrocytes and / or microglia to explore effect of clinical relevant mutations (Alzheimer's disease, Parkinson's disease) on neuronal function.
        - Establish brain organoid cultures suitable for high content imaging analysis.
        - Establish *in vitro* or xenograft models for pathology seeding relating to Alzheimer's disease or Parkinson's disease.
    - Diabetes
        - Explore technologies to support the adaptation of established protocols for large-scale production.
        - Molecular and functional analysis of pancreatic progenitors as well as mature pancreatic cells.
    - Cardiovascular Diseases

- Establish standardised differentiation and maturation protocols for derivation of cardiovascular, iPSC-derived cells (including cardiomyocytes, endothelial cells, smooth muscle cells etc.).
- Establish functional assays and readouts to analyse compound/drug efficacy in iPSC-derived cardiovascular cells; harmonise readouts with FDA-approved activities (e.g. in CiPA).
- Assess ability of iPSC-derived cardiovascular cells for patient stratification (drug efficacy depending on common genetic variation).
- Analyse proteomics/metabolomics in iPSC-derived CV cells.

- Gene editing using e.g. Crispr/Cas system to establish disease relevant iPSC lines;
- Reprogramming of patient derived somatic cells using state of the art technologies (non-integrating technologies)

Industry contribution:

- Support in differentiating and analysing iPSC derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration;
- Support in producing iPSC derived cardiovascular cells and analysing effects of e.g. arrhythmogenic mutations or pharmacological treatments on the (electrophysiological) characteristics of cells;
- Support in differentiating and analysing iPSC derived pancreatic cells to study the underlying mechanisms of diabetes. This includes molecular as well as functional assays. Focus will be on establishing large-scale cell culture capabilities as well as competences in gene editing in collaboration with the relevant partners;
- The industry group will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Expected Applicant consortium contribution:

Already established and QC'ed hiPSCell lines for all the above disease areas; support of industry consortium activities by producing iPS-cells and / or precursor cells at quantity to allow screening and other R&D activities. Knowledge and capabilities in gene-editing and reprogramming of somatic cells to derive iPSC.

Reference

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