IMI1 Final Project Report Public Summary

Project Acronym: EBISC

Project Title: European Bank for induced pluripotent Stem Cells

Grant Agreement: 115582
Project Duration: 01/01/2014 - 31/12/2017

1. Executive summary

1.1. Project rationale and overall objectives of the project

The European Bank for induced pluripotent Stem cells (EBiSC) Consortium has established a facility for distributing qualified human, disease representative stem cell lines for research. The EBiSC cell line repository will make future drug development as well as basic research more effective and provide resources for future EU-funded iPSC projects.

Key objectives of EBiSC were to establish a European iPSC repository with the unique identifying features of a catalogue created by user demand. It will: i) provide sustainable supply of quality-assured, research-grade lines on a not-for-profit basis; ii) develop procedures for engaging a wide scientific and clinical community in a network of cell line derivation centres; iii) apply scientific excellence for standardisation of optimised methodologies for deriving iPSC, their cryopreservation, recovery and differentiation; and iv) demonstrate standards in QC for the routine banking, characterisation and distribution of cell lines. The cell line distribution model is supported by a harmonised ethics and legal governance framework and information management system developed to accommodate user-generated content. It will continue to establish mechanisms to facilitate ongoing stakeholder enhancement of the biobanking process in support of a strategic business strategy based on a phased execution to ensure self-sustainability.

1.2. Overall deliverables of the project

Demonstrating effective project management, to include both strong financial and strategic leadership, developing the banking business rationale tuned to user needs and linking this to an EBiSC brand were key deliverables from overall project development. A key consequence of developing a better understanding of user needs led to the recruitment of additional EFPIA companies as integrated partners.

Procuring existing cell lines and deriving new ones commissioned by partners built a diverse collection. The established effective infrastructure for the centralised processing and storage of these lines including international distribution by harmonised protocols, were core deliverables from the bank operations. Phenotypic assay data from the use of selected cell lines and gene edited derivatives from the collection ensured that the project delivered validation on all elements of the cell line supply chain.

The project provided deliverables that reflect a movement beyond the state of the art in platforms for improved cell processing, QC testing, information management and innovation in human cell line banking governance models. Deliverables related to the development of an EBiSC cell line collection that researchers are using and operations for engagement with paying customers will continue to be key for future self-sustaining business.

1.3. Summary of progress versus plan since last period

In late 2016, IMI JU agreed to a request by the EBiSC Consortium to budget neutral extend the project for a fourth and final year. Period 4, M37-48, started on 1 January 2017 and ended 31 December 2017, which was also the end of the Project as a whole. The work undertaken by the Consortium during the Period consisted of five major themes which collectively aligned with the plan set out in the revised DoW and addressed the KPIs:

- Ongoing management of the Consortium to ensure timely completion of the Tasks set out in the DoW;
- Completing the establishment of an operational infrastructure including improved worldwide reach of the repository;
- Preparing for the continued operation of the EBiSC Repository after the end of the Project with the identification and establishment of the EBiSC Banking Entity taking on the operations of EBiSC;
- Extending the catalogue of cell lines available from EBiSC plus continue the integration of iPSC lines established in the IMI JU StemBANCC;
- Increasing awareness across the research community of the availability of iPSC lines from EBiSC.

Management of the Consortium

As of 1st February 2017 (M38), Janssen assumed the role of Project Coordinator. Simultaneously along with the other members of the Executive Office, Janssen successfully coordinated both a budget neutral extension to the project and associated revision to the DoW. Through weekly Executive office calls, monthly Consortium Board calls and an annual meeting of the General Assembly which included WP leader face to face communication, Janssen and the Executive Office were able to manage all aspects of the Consortiums operation in a timely manner. This resulted in completion of 25 deliverables and 17 milestones from M37 to M48.

While focusing primarily on the finalisation of pre-agreed collaborative projects, 3 new collaborative projects were commissioned in Period 4. These focused on the generation and characterisation of disease relevant hiPSC lines, adding further to the variety and number of lines available from the catalogue and the associated data sets. With the completion of Whole Genome Sequencing (WGS) on 70 EBiSC lines, the Consortium also formed the EBiSC Data Access Committee to allow managed access to the datasets and development of an allelic search query built into the EBiSC cell line catalogue.

Establishing a Sustainable Operational Infrastructure

During the Period, RCS continued to operate the EBiSC central facility, overseeing cell line receipt, expansion, banking and/or QC of >400 deposited hiPSC lines which were then transferred to DH-CC for long term storage and distribution and also to Fraunhofer IBMT, the EBiSC Mirror Facility.

To ensure sustainability of EBiSC operations from 2018 onwards, RCS, DH-CC and Fraunhofer IBMT worked on a number of activities to harmonise central and secondary facility processing to ensure cross-site capability for cell line expansion, banking and QC. This has included streamlining and simplification of SOPs by RCS and dissemination of these to DH-CC and Fraunhofer IBMT. Scientists

from DH-CC and Fraunhofer IBMT received training by RCS on cell line deposition, biosample acquisition, data management on the EBiSC IMS, labelling and certification. These activities ensure that staff at all sites are competent in all areas of central facility processing.

In addition, Fraunhofer IBMT successfully validated the EBiSC workflow in a PoC study with the Bavarian Research Network for induced pluripotent stem cells (ForIPS). In this collaboration, six iPSC lines were shipped to Fraunhofer IBMT from ForIPS to study comparability of the EBiSC processes using cell lines and workflows derived from an external national consortium in terms of sample logistics, cryostorage and QC.

The resilience of the EBiSC governance framework was strengthened by UEDIN which completed review of EBiSC governance frameworks and, together with RCS, compiled the EBiSC Policy & Contract Manual for operation of the established EBiSC Bank. This Manual provides a systematic documentation of the EBiSC governance documents.

Also during the Period, UEDIN provided continuing legal support for resolution, on a case by case basis, of issues which arose from depositors wishing to deposit lines with EBiSC. This experience led to changes of the standard EBiSC Material Deposition Agreements which make deposition of iPSC lines into the Bank easier to complete, and addressed a key goal of the Project to implement, disseminate, and use a harmonised contractual framework. UEDIN also supported the establishment of the data access management system for genetic datasets associated with cell lines being deposited from the StemBANCC Project.

More generally, the EBiSC Information Management System (IMS) which collects, stores and presents information about EBiSC cell lines and batches, continued to be developed and improved throughout Period 4. With the core infrastructure, deployment and data flow already established in preceding periods, development in Period 4 focused upon improving the user experience of the EBiSC data portal and providing added value to the cell lines. The information held on EBiSC lines has been enhanced through more detailed metadata descriptions, catalogue display improvements for familial relationships, the specific mutations of gene edited lines, and the provision of WGS data for some lines. All these features provide a more detailed product description and improve the business capabilities for EBiSC.

Following the generation of raw WGS data on 70 EBiSC lines, EMBL-EBI oversaw making these data available to researchers to download from the European Genome-Phenome Archive. The mapped variant calls (processed data) is currently under production at EMBL-EBI and now expected to be delivered shortly after the end of the project. The delay is due to the late delivery of data to EMBL-EBI from the sequencing centre. The data will be made available through an EBiSC Data Access Committee, which checks that users wishing to access the data are bona-fide researchers and that their research meets any restrictions of the cell line in question.

Generating WGS data for iPSC lines facilitated the development of an allelic query service within the IMS. This advanced search service allows scientists to identify the best line for their research from the EBiSC collection based on the underlying variation data. This is a live search in real time of the genetic variation data, rather than a search of text supplied by depositors of the line. Combined, these presentation and cell line detail improvements, have the overall goal of improving iPSC

discoverability, and enabling researchers to quickly select the most appropriate cell line from the collection for their research, thus advancing therapeutics and scientific innovation.

Preparing for continued Operation after the end of the Project

In order to ensure that the EBiSC repository continues to operate after the end of the EBiSC project in December 2017, DH-CC agreed to become the EBiSC Banking Entity (EBE). The creation or designation of a not-for-profit organisation to act as EBE was a key objective for the Project as a whole. Although financial self-sustainability of a fully operating repository is not possible at this stage, the wider cell storage and distribution operations at DH-CC will minimize the cost of ongoing maintenance costs in the short term and these will be offset by revenue generated from distribution of iPSCs. A formal transfer agreement has been signed and the EBE role has now been assumed to DH-CC. All end users have been notified of this assignment which is a requirement of the End User Access Agreement (EAUA) signed by all end users. DH-CC's role as EBE is further supported by Fraunhofer IBMT committing to continue its role as EBiSC Mirror Bank after the end of the project and providing appropriate capability to back-up the EBE if necessary.

It is expected that further funding for a European iPSC Repository will be made available by IMI through a new call. In the meantime, DH-CC will continue to operate as EBE and promote the EBiSC catalogue to researchers, while Fraunhofer IBMT will continue as Mirror Bank and provide capability for cell line be-banking requests.

Extending and promoting the Catalogue

In the final Period of the Project, substantial effort was devoted to concluding a diverse range of cell line commissioning projects and finalising the deposit of cell lines from the sister IMI project, StemBANCC. As a consequence, additional **638** iPSC lines have been included on new deposit agreements for EBiSC distribution in 2017, including lines deposited by StemBANCC and those generated within commissioning projects.

Twelve different commissioning projects initiated by the EBiSC consortium during the project in response to requests from EFPIA participants were completed in Period 4. These projects contributed **92** of the lines currently available through the catalogue – adding to the lines similarly commissioned which were already been deposited in Period 3.

The deposit of iPSC lines generated within the StemBANCC project added 467 hiPSC lines to the EBiSC catalogue. Four of these lines have been used by EBiSC consortium members to generate isogenic control & disease variant lines which have also been deposited with EBiSC. This use of gene editing technology to create new iPSC lines of very significant scientific value, represents both a major collaboration between EBiSC and StemBANCC and also demonstrated the ability of the EBiSC consortium to allocate resources during the lifetime of the projects to activities which could not have been foreseen at the project inception in 2013 – and using the latest gene editing technology.

In addition, to cell line deposition from StemBANCC, members of both consortia have collaborated to enable data generated by the StemBANCC project, held in the StemDB database, to be transferred into the EBiSC IMS. This collaboration ensured that the maximum data available for public use is available through the EBiSC IMS.

The Central Facility has continued to process other cell lines and a further 16 lines have undergone expansion and banking and 86 have been subjected to QC testing.

In total, DH-CC, which is responsible for the EBiSC long-term storage and distribution activity, received stock for the 795 iPSC lines listed on the EBiSC main IMS. Almost all cell lines are available for purchase through DH-CC's e-commerce facility with dynamic links to the main EBiSC IMS in order to access full data on each cell line. Data updates are received automatically from the IMS to the DH-CC website allowing for full synchronisation of data.

For a small proportion of the resource, final QC checks still need to be made or distribution stock need to be manufactured before they are available. This additional processing will be done on demand. For seven lines deposited by the Spanish Stem Cell Bank which are listed on both DH-CC (ECACC) and EBiSC websites, customers are directed to access them from the Spanish bank due to Spanish Law.

EBiSC is promoted through DH-CC's ECACC regular marketing channels such as website news articles, social media, newsletters, webinars, ResearchGate and scientific conference exhibitions. DH-CC (ECACC) has also produced a specific eight pages brochure highlighting EBiSC with a focus on the resources available to the scientific community in an effort to generate demand for the cell lines. To support iPSC sales, RCS commissioned an external consultancy to review the iPSC bio-banking landscape based on direct interviews and surveys of iPSC researchers. This real world data will feed into the marketing and dissemination activities led by DH-CC.

As a result of this and other public dissemination activities, this year 155 EBiSC lines have been ordered and distributed to six different countries and to 26 different end users. To date all evidence suggests these have been received successfully as no complaints have been received from end users. One third of the lines have been distributed to customers from USA, a significant target market for iPSC lines and where most of EBiSC's competition lies.

To increase global distribution, DH-CC signed, on behalf of EBiSC, a non-exclusive distribution agreement with Merck (Millipore-Sigma) to distribute EBiSC lines. This is expected to dramatically increase the awareness of the EBiSC brand on a global basis. An immediate effect is that the EBiSC catalogue is promoted via the Sigma distribution channels (eg https://www.sigmaaldrich.com/life-science/stem-cell-biology/ebisc-cell-lines.html)

Engaging the Research Community

Despite the cost neutral extension of the project duration, a number of high-impact dissemination activities have been carried out in Period 4, which were not initially planned for in the DoW. Key activities included participation in the ISSCR Annual Meeting 2017 in Boston through participation of several EBiSC representatives and a EBiSC-HipSci booth organised by the EBiSC partner DH-CC, the organisation of a final EBiSC workshop in November 2017 in Berlin, the preparation of a 6-minute EBiSC film, recording of EBiSC sessions and the publication of an EBiSC article as a new "Success Story" on the EC website. These added activities to regular news and tweets (via www.ebisc.eu and the EBiSC twitter account) enabled EBiSC to continue raising awareness for the EBiSC catalogue and to attract new clients and potential end-users, and increase sales worldwide.

An important aim of the Project was to complement increased availability of iPSCs lines with an increased ability of researchers to use iPSCs and derivatives in their research. DH-NIBSC and ARTTIC led a consortium wide effort to create a virtual training resource library for key EBiSC SOPs and a short-form business case for sustainable training activity. DH-NIBSC and ARTTIC also coordinated and delivered a final two-days public EBiSC workshop in Berlin (November 2017). This focused on disseminating the learning from the establishment of EBiSC and addressing perspectives on stem cell applications over the next five years.

As well as training in standard procedures, the Consortium continued to take a lead in key areas of the technology, particularly QC. DH-NIBSC and RCS led the preparation of two reports on the extended characterisation methods of the EBiSC lines. This included work on miRNA data of lines, comparative karyology using three different methods, impact of gene-editing on pluripotency assays, directed differentiation of iPSC lines from Bioneer to neural stem cells. In addition, DH-NIBSC and others continued horizon scanning to identify new and emerging technologies affecting cell characterisation.

Similarly, a central aim of the Project has been to undertake “Pathfinder studies” to demonstrate that iPSC lines banked in the EBiSC repository can be used at EFPIA sites as valuable model tools in early drug development. Overall 15 members of the consortium, including both public and EFPIA partners, worked with a selected panel of lines representing potential tools for drug development in the areas of neurodegenerative diseases, diabetes, liver diseases and pain disorders. Each specific study covered a variety of central elements for lines to develop into the relevant cell type (e.g. sub-specific neurons), identifying potential relevant read-out panels and verification of disease-relevant phenotypes. Data from these studies both validated the utility of the iPSC lines available from EBiSC and also demonstrated the value of iPSC resources for drug discovery. The outcome of these studies has been and will continue to be published in peer-reviewed journals.

Deviations from Plan

There were no major deviations from Plan during the Period and the Consortium was able to conclude all major goals set out in the DoW, and thus, address the overall objectives of the Project.

1.4. Significant achievements since last report

Management of the Consortium

Following the approval to extend the Project by 1 year, the Executive Office successfully managed the final modifications to the DoW and related budget realignment between consortium partners which allowed the Project to be concluded by December 2017 through a budget neutral extension. Subsequently all Tasks set out in the DoW have been completed on a timely basis.

The 2017 General Assembly was held in Amsterdam in April 2017, enabling discussion not only of scientific data generated within the project, but also how EBiSC would be sustained long-term after the funded period of the project. Arrangements put in place after the GA led to DH-CC assuming the role of EBE.

Management of the Project included ensuring the completion of 12 collaborative projects focused on generation of disease relevant hiPSCs, 4 pathfinder projects which displayed proof of principle for the use of hiPSCs using differentiation and phenotyping assays, and also successful collaboration with other iPSC networks, such as ForIPS, ADAPTED, and StemBANCC.

An EBiSC Data Access Committee was also established to enable managed access to WGS data for 70 iPSC lines which were sequenced as part of one of the projects. This data is now available through the EBiSC Data Access Committee with an allelic search functionality available through the catalogue.

Establishing a Sustainable Operational Infrastructure

During the Period, a number of process improvements were identified and implemented by RCS and DH-NIBSC to streamline cell line processing and QC. This included introducing a directed differentiation assay which was more robust than using a spontaneous differentiation method to determine pluripotent potential of each cell line. In addition, a new method for high sensitivity of Mycoplasma detection using a Taqman based detection kit was introduced into core processing, reducing both the cost of the assay and the time taken to perform it.

RCS, DH-CC and Fraunhofer IBMT continued operating in line with the EBiSC Quality Manual and established cross training for staff to harmonise and strengthen capabilities. DH-CC staff are now fully trained in banking and QC procedures to enable stock replenishment as required.

Fraunhofer IBMT in its capacity as the EBiSC Mirror Facility also validated EBiSC workflows concerning sample logistics, cryostorage and QC in a proof of principle study of synchronising hiPSC data and workflows from different stem cell initiatives for integration into the EBiSC Bank. Specifically, a proof of concept study in collaboration with ForIPS was completed. In this collaboration, six iPSC lines were shipped to Fraunhofer IBMT to study comparability of the different workflows to validate the EBiSC workflow using cell lines and workflows derived from an external national consortium in terms of sample logistics, cryostorage and QC. 423 cell lines shared to the Mirror Facility for secure storage within Period 4.

The governance and administration of the Bank was strengthened by UEDIN which reviewed and updated the harmonised governance frameworks that constitute the Bank. This resulted in a model of good governance that will serve the operations of EBiSC indefinitely and provide a standard by which other initiatives may design similar arrangements to facilitate access to biomaterials for the promotion of research.

Development of the IMS during Period 4 focused on improving the customer experience when interacting with data related to EBiSC cell lines and increasing the biological detail of information accompanying each EBiSC cell line. The Human Induced Pluripotent Stem Cell Registry (hPSCreg) has continued to develop the recording of information from EBiSC depositors and raise the information standard for recording metadata on EBiSC iPSC lines.

The most significant improvements surround recording of specific modifications for gene edited lines. These lines are increasing in prevalence and are amongst the most ordered cell lines in the EBiSC collection. The clear and accurate display of the specific mutations and familial relationships within the EBiSC catalogue are essential for researchers to select appropriate lines from the collection for their research. The Allelic query service, takes this knowledge led iPSC line selection process a step

further, by allowing the researcher to query the cell lines for specific mutations in real time based on the underlying genetic variation data. An example of a query is "Locate lines homozygous for the E2 allele for the ApoE gene". Importantly, the technology being developed will allow queries to be made to data held in the European Genome-Phenome Archive (EGA) on a managed access basis, with queries automatically extended to data held in the EGA based on the user's Data Access Committee credentials. Developers are currently finalising the web interface for the allelic query service, in collaboration with a small group of testers drawn from the EBiSC community. Due to the delays in sequencing of EBiSC iPSC lines, this service will be deployed for production early in 2018, once the appropriate data has been processed and archived in the required data stores.

Preparing for continued operation after the end of the Project

As planned, DH-CC assumed the role of EBiSC Banking Entity (EBE), ensuring capacity for cell line deposition, small-scale expansion, banking & QC after the funded period of the project. Fraunhofer IBMT has undertaken to continue its Mirror Bank facility operation until funding for a new repository is available near the end of 2018, to provide capacity for large-scale expansion and agreed to secure availability of iPSC lines deposited in EBiSC throughout 2018.

Extending and promoting the Catalogue

EBiSC now has 795 cell lines available to order through the catalogue, covering 33 disease areas from donors aged 3-4 to 85-89. Building the catalogue to this scale and diversity, while ensuring that only high-quality iPSCs are deposited is a major achievement for the Project and will maximise the impact on the research community.

Inclusion of the StemBANCC generated lines and successful transfer of donor & cell line data into the EBiSC IMS is a major achievement. Additionally, collaborative projects commissioned by the Consortium during the Project which focused on the generation of cell lines of immediate interest to EFPIA consortium members, has greatly contributed to the calibre of the Catalogue.

Collaboration with the IMI-JU's ADAPTED project has also successfully generated 4 cohorts of isogenic ApoE variants from affected and unaffected donors, a collection which is unique and has shown great popularity across both internal and external customers within Period 4. This work also allowed the ADAPTED project to accelerate its own research programme.

Around 70 iPSC lines were also successfully identified as being generated from primary tissue which was donated under consent templates permissive for genetic analysis. With the permission of depositors, 70 of these iPSC lines were selected and underwent DNA extraction and WGS analysis, with data then shared and deposited with in the European Genome Archive. These data will assist selection of cell lines and any future research.

Additionally, since last report, all EFPIA supported gene editing projects are completed. The resulting EBiSC lines will serve as valuable tools in future disease mechanistic evaluation and early drug discovery.

With the growing catalogue, DH-CC has been able to both promote a greater diversity of lines and offer them through its e-commerce platform. EBiSC was extensively promoted by DH-CC throughout 2017 via various media. This promotion was greatly enhanced near the end of 2017 with the inclusion

of the EBiSC cell lines in the distribution agreement agreed and signed between DH-CC and with Millipore-Sigma (Merck) to facilitate global marketing and distribution.

In all, 795 EBiSC cell lines have been promoted during 2017 and available for order through ECACC's e-commerce platform. Of these, 155 cell lines were ordered and supplied to 26 non-project members in 6 different countries.

The marketing efforts were complemented by a comprehensive review of the global iPSC market, including detailed information on end user requirements from an iPSC bank and an assessment of competitor offerings has been completed and disseminated across the consortium. Real world data generated through this market assessment has informed marketing and dissemination campaigns which have resulted in significant increases in website traffic and subsequent orders.

Engaging the Research Community

The highlights among the dissemination and communication activities carried out in Period 4 were notably the participation for the third time in the Annual Meeting of the International Society for Stem Cell Research (ISSCR) in June 2017 in Boston, the preparation of the EBiSC film presenting the EBiSC project and promoting the iPSC catalogue to potential end-users and the very successful public EBiSC Final Workshop on 2-3 November 2017 in Berlin with more than 70 participants (and 93 registrations) from across Europe.

Figure 1: The EBiSC film prepared in November/December 2017 and published on www.ebisc.eu and YouTube on 18 January 2018

The workshop focused on the learning from the establishment of EBiSC and addressed perspectives on stem cell applications over the next five years. Ten of the talks given during the workshop have been made available in short videos on www.ebisc.eu. An "EBiSC success story" had furthermore be prepared and published on the EC and IMI JU websites and a specific EBiSC brochure was prepared by ECACC who also regularly disseminated news from EBiSC in their monthly newsletters. Furthermore, 2 articles describing the establishment of EBiSC and lessons learned were published

(Hot Start to European Pluripotent Stem Cell Banking & Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC) - the Hot Start experience). At the end of period 4, a number of EBiSC related publications are under preparation at several partner organisations.

Figure 2: EBiSC Final Workshop on 2-3 November 2017 in Berlin

The two-days public workshop on 2-3 November 2017 in Berlin represented a significant achievement for the Project. The workshop was able to attract world renowned speakers to deliver talks on cutting edge stem cell topics. Over 75 people attended and feedback from the delegates was very positive. The EBiSC talks were recorded and have been made available on the EBiSC website (https://ebisc.org/documentation/videos.php). This type of workshop enhanced both the reputation and visibility of the EBiSC bank, which will help to increase sales of the cell lines.

In addition, the EBiSC virtual training library was made available on the EBiSC website in April 2017 (https://ebisc.org/trainings/). The library offers users the opportunity to watch videos explaining key processes in iPS cell culture, which is support and training that other banks do not offer.

Four disease modelling Pathfinder studies within neurology were completed in the last period (2017). In several cases, these have resulted in further development internally at both EFPIA, SMEs and academia. This is an important output from this work package as actual implementation of such models has been the overall aim – in that way demonstrating the user potential of EBiSC lines.

In parallel, Period 4 saw the successful completion of the directed differentiation of the Bioneer iPSC lines to neural stem cells. This shows the robustness and reproducibility of both the iPSC lines and

the protocols generated by the EBiSC consortium. The data generated from this work adds value to the iPSC lines, which acts as a unique selling point for the EBiSC lines.

1.5. Scientific and technical results/foregrounds of the project

Over its four years, the EBiSC project has created very substantial foreground intellectual assets. While mainly concerned with the smooth operation of a large not-for-profit biological repository, specific advances in the technology of producing and using iPSCs were made and specific research results arose from the Pathfinder studies.

Operational Governance and Quality System

The following templates to support governance of an international hiPSC biobank have been generated within EBiSC:

- EBiSC Material Transfer Record
- EBiSC Material Deposit Agreement
- EBiSC Access & Use Agreement
- EBiSC Participant Access & Use Agreement
- EBiSC Consent Participant Information sheet
- EBiSC Informed Consent Form
- EBiSC Cell Line Information Pack

In addition, a rigorous and robust Quality Management System has been developed to ensure cell line deposit and biobanking is performed in line with ethical guidelines and to a consistently high standard. Key features of this system are:

- SOPs for feeder-free thawing, passaging, maintenance and cryopreservation of iPSC lines.
- SOPs detailing biosample acquisition (including ethical review of consent provenance and finalisation of Material Deposition Agreements), cell line and data management, cell line shipping and receipt.
- a Certificate of Analysis with standardised data outputs generated for every cell line processed, and
- a standardised human and computer readable cryo-label for each cryovial of cells produced – each with a unique and unambiguous ID which is linked to the EBiSC IMS.
- Guidelines for robust QC screening methods suitable for processing iPSC lines from variable provenance and ensuring a standardised end product.

Operational Infrastructure

The scale of iPSC processing involved in the project led to the development and scale up of several important operational capabilities, including:

- RCS and Fraunhofer IBMT extended their expertise in scheduling, processing and screening high numbers of pluripotent stem cell lines in a standardised manner,
- RCS and DH-NIBSC developed and implemented a robust panel of cell line characterisation assays suitable for a large iPSC banking initiative,

- Fraunhofer IBMT developed and implemented protocols for automated large-scale expansion technologies using suspension-bioreactors for both hiPSC line expansion, neural differentiation and cardiac differentiation,
- Fraunhofer IBMT also implemented expansion, cryopreservation and banking procedures under DIN EN ISO9001:2015 at the Mirror Facility,
- Fraunhofer IBMT has successfully validated the established EBiSC workflows for sample logistics, cryostorage and QC using external hiPSC lines from an external consortium (ForIPS),
- Fraunhofer IBMT further reserved suitable capacity to back-up the Main Facility if necessary.

The development of a bespoke IMS by EMBL-EBI, DC and DH-CC built around the iPSC work flow represents a major output from the Project. In particular, the IMS has been developed further to accommodate WGS data on iPSC lines. The raw and analysed results will be made available through the European Genome Phenome Archive with user access managed by the EBiSC Data Access Committee. This represents a sustainable sharing mechanism using existing infrastructure (EGA). Combined with the extensive genetic characterisation of the HipSci lines that now form part of the EBiSC collection, researchers have access to extensive characterisation data to enhance and accelerate their research. This capability has been extended by DH-CC which has modified its own website and e-commerce facility to accommodate EBiSC cell lines and provide a dynamic link to the IMS.

In order to both the development of the Bank to become a self-financing not-for-profit operation and also to maximise the scientific value of the catalogue, the Project performed a detailed assessment of the iPSC bio-banking landscape which generated extensive datasets on global use of iPSCs and user requirements and the overall market of international iPSC banks.

The Catalogue

As well as accepting deposits from major iPSC programmes, the Project also commissioned generation of 259 iPSC lines and delivered 145 new iPSC cell lines which were requested by the EFPIA participants, with an additional 114 lines to be delivered in early – mid 2018. These cell lines represent cell lines of high value which are or will be used extensively in further research.

WGS data for 70 of these lines was generated and made available to researchers under managed access through the EBiSC data access committee. Importantly, among these lines are parental iPSCs used for gene editing which increases the number of iPSC lines available through EBiSC with WGS data attached.

As of 31 December 2017, 795 EBiSC iPSC lines are listed available for sale through the DH-CC (ECACC) e-commerce platform with access to extensive data via the main EBiSC IMS via the EBiSC website.

Research results

The Pathfinder studies completed during the Project have demonstrated the capabilities and possibilities for pharma companies to use specific EBiSC consortium lines for implementing neural, pancreatic and hepatocyte differentiation protocols and potentially use these differentiated cells in their early drug discovery. These studies have also demonstrated the use of gene editing in EBiSC consortium lines as a route to accessibility to lines with relevant disease specific mutations or relevant reporter systems.

Included in the studies, four gene edited iPSC cell lines with isogenic controls were evaluated for their performance in a partner protocol (Bioneer) for the preparation of neurons with the results compiled as a report.

Throughout the project, trouble-shooting carried out by DH-NIBSC and RCS on the routine application of high-throughput qPCR for mycoplasma contamination and pluripotency assays advanced the efficiency and suitability of these critical QC tests. All assays are now functioning as intended.

A specific focus of the Project was to assess and develop new technologies for the effective processing and biobanking of cells, including the development of automated protocols for parallel iPSC line processing. Different automation/expansion technologies most fit for purpose of scalable expansion of hiPSC lines have been evaluated, e.g. robotic cell culture platforms for completely automated workflows and suspension bioreactor systems. A microcarrier-based cultivation system available at Fraunhofer IBMT has been adapted to hiPSCs culture. Additionally, Fraunhofer IBMT has developed a protocol for passaging hiPSCs on alginate-microcarrier in the suspension bioreactor BiolevitatorTM. With this protocol it was possible to transfer the whole workflow from thawing the iPSC, expanding and re-banking with only one passage in one vessel. No significant differences were found in viability, adhesion rate, or stemness markers after doing the whole workflow in the BiolevitatorTM. Finally, WP3 has recommended an expansion system based on suspension bioreactor design for installation at the central EBiSC facility, and innovative biobanking technologies for a closed cold chain and reliable sample identification at the mirror EBiSC facility.

Publications and engagement with the Research Community and wider public

The Project's first publications, the EBiSC Hot Start Paper, was published in April 2017 and a related article in the Trends in Biotechnology journal in July 2017. Other EBiSC related publications have been published before or are under preparation at partner organisations.

In line with the Project's key objective to demonstrate standards in QC for the routine banking, characterisation and distribution of cell lines, a substantial portion of the Projects results and foreground were focussed on engaging other researchers and promoting best practice. Actions and results include:

- A training platform including online SOP training videos and test questionnaires created by DH-NIBSC, ARTTIC and RCS which is now available at the EBiSC website.
- 16 videos from EBiSC presentations at the ISSCR meeting 2016 and the EBiSC Final Workshop.
- An EBiSC Focus Session and meet-up hub at the ISSCR Annual Meeting 2016 in San Francisco and participation in the ISSCR Meetings in 2015, 2017 and the next meeting and an EBiSC booth was organised at the ESGCT meeting in Florence in October 2016. EBiSC partners will be attending and promoting the catalogue at the ISSCR meeting in Melbourne 2018.
- An EBiSC conference, "Scalability of iPSC Technology" was organised for 93 registered participants (including speakers) on 2-3 November 2017 in Berlin. This covered wide ranging applications of iPSC technology including use in drug development and cell therapies. In addition, key EBiSC learning in a range of issues for the development of large-scale iPSC supply were outlined including quality assurance, banking processes and data management. A report on the meeting is in preparation to be submitted for publication in 2018.

The checklist for derivation and control of CRISPR edited lines developed with EBiSC partners at the UKSCB technical forum in 2015 has now being further developed with the ISSCR Coordinates group and the International Stem Cell Banking Initiative to develop a best practice document for the development and use of gene edited and reporter iPSC lines.

The Project also engaged the wider public through

- Public website (www.ebisc.eu), EBiSC twitter account
- Project video
- EBiSC article (Success Stories) on the EC website

1.6. Potential impact and main dissemination activities and exploitation of results

With its aim of establishing a facility for the distribution of high-quality disease-representative cell lines for research, the EBiSC Project supports IMI's mission to speed up the development of innovative medicines by facilitating collaboration between the key players involved in healthcare research, including academic researchers, the pharmaceutical and other industries, SMEs and patient organisations.

Consisting of 26 partners operating in nine EU member states, the EBiSC consortium has had a significant impact across Europe in many areas of medical research ranging from developing best practice for the operation of a stem cell biorepository, to developing models of specific diseases. Bringing together many leaders in the use of stem cell derivatives for medical research, EBiSC has helped develop Europe as the most attractive place for biopharmaceutical research and development and provides a new and major resource for future medicine development which will improve the health of European citizens. More immediately, by engaging with the wider public, EBiSC has been to articulate the value to society of using cells derived from human tissue which were donated altruistically in commercial research, and provided a framework for this to be done.

The impact of creating a large-scale Europe-wide cell banking operation

The Europe-wide remit of EBiSC means that it operates at scale and across national boundaries, in a manner which distinguishes it from other stem cell banks. This allows EBiSC to be an authoritative voice internationally promoting best practices for the use of stem cells in medical research.

Governance: EBiSC has developed a robust framework for a functional, multi-partner iPSC biobank able to accept iPSC lines from wide-ranging sources. The framework includes consent templates which ensure fully informed consent is provided by tissue donors while providing subsequent freedom to operate for researchers wishing to use derivatives generated from iPSCs. The donor consent forms have already served as templates for other IMI collaborative projects such as IMI PHAGO or IMI ADAPTED, where iPSC lines are being derived from human donors. The framework also facilitates cell line deposit on terms which allow subsequent research. This framework has raised the profile of iPSC research and has highlighted the benefits of depositing cell lines into a publically accessible, not-for-profit repository.

The harmonised governance framework reflects the interests of all members of the large EBiSC consortium, who in turn represent virtually all aspects of work in the iPSC research community.

Collaboration within the consortium has resulted in a contractual construct - an ethical and legal constitution - that is informed by scientific and economic as well as ethical/legal perspectives. This has led to a model of responsible governance that is capable of responding to the needs of all actors in the system and applicable in other research programmes. As another example, the EBiSC standard template Material Transfer Agreements have already been taken up by another EU Horizon 2020 project (PHAGO: Targeting TREM2 and CD33 of phagocytes for treatment of Alzheimer's disease).

Cell processing: The Project's scale of operation has allowed and required it to address cell processing for large numbers of iPSCs. Through the Project's efforts to improve cell processing techniques within its central facility, EBiSC has led the way in enhancing the delivery of cells to EU researchers. The Project developed new methodologies to improve the efficiency and speed of QC procedures to assure the quality of cell lines. It also demonstrated that large-scale, automated expansion and differentiation of hiPSCs is possible. Additionally, the Project demonstrated biobanking technologies with a closed cold chain increase sample quality in various research and medical areas.

These achievements consequently increase reproducibility and standardisation of all cell processing workflows and make high-quality stem cells and their derivatives available for future applications at an industrial scale. Automation approaches with corresponding protocols will support biopharmaceutical research in Europe through standardisation of workflows and enabling large-scale screenings of new candidate drugs. In the coming years, this standardisation of cell processing will lead to automated differentiation of hiPSCs using new biomaterials for improved efficiency and cell maturation which will result in more physiological cell and disease models for higher predictive drug development.

Training: The large scale of the EBiSC consortium also brought together many of Europe's Key Opinion Leaders in iPSC technology which has enabled the Consortium to take a prominent role in training and disseminating best practice.

The Project's training program has disseminated best practice in the derivation and use of iPSC lines to promote high-quality research. EBiSC training events have provided "hands-on" training for researchers from several European countries such as Denmark, Germany, Sweden, Spain, Italy and the United Kingdom.

EBiSC has reached many more researchers through the online training. In 2017, the EBiSC consortium created a virtual training library (http://www.ebisc.org/trainings/) giving lab scientists worldwide the opportunity to learn about EBiSC SOPs recommended to be used for the cell lines ordered from the EBiSC bank in order to ensure optimal use of the lines. These short films describing the SOPs and including short lab videos have been watched by many researchers. This training service is not only a complementary support tool for EBiSC cell line users which no other iPSC bank currently offers, but significantly contributes to the harmonisation of international standards for best practices in iPSC processing and banking.

An analysis of the success of all training courses provided by EBiSC in the course of the project's lifetime, including the EBiSC conference on Scalability of iPSC Technology (Berlin, 2-3 November 2017) has led to a short business plan for ongoing training activity associated with the EBiSC collection of iPSC lines.

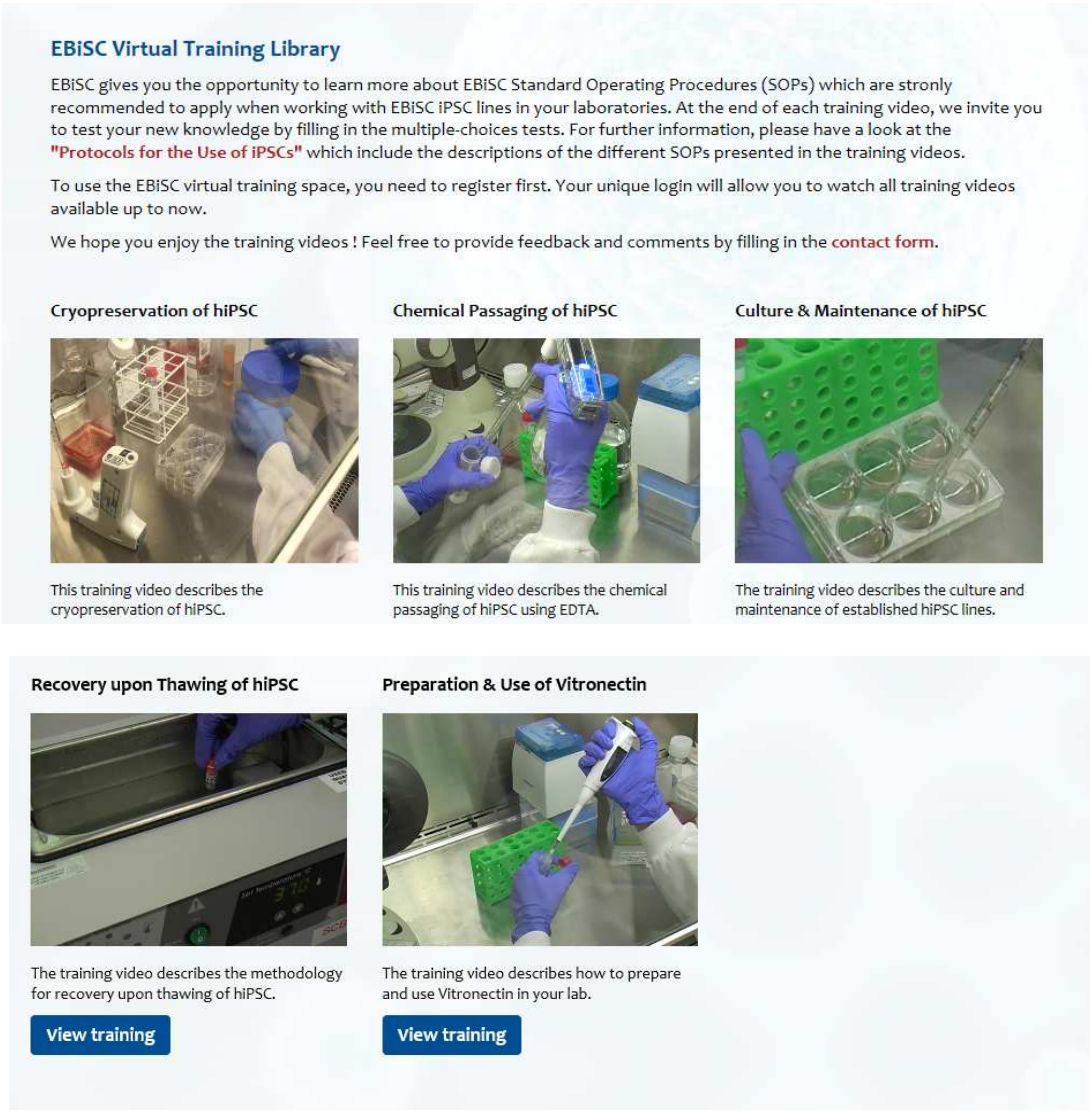

Figure 3: EBiSC Virtual Training Library on www.ebisc.eu/trainings

Best practice has also been disseminated by EBiSC partner presentations at numerous scientific meetings during the Project.

These combined efforts have ensured the on-going dissemination of best practice and skills which will enhance the scientific and ethical quality of EU research. Training events also engaged researchers beyond the EU which will facilitate further international collaboration with EBiSC partners.

The impact of assembling a large catalogue of cell lines available for research

Central to the impact of EBiSC has been the scale and diversity of the collection of iPSC lines which it can provide to academic and commercial researchers.

Scale: Covering 35 diseases with the inclusion of gene-edited isogenic variants, this resource will support biopharmaceutical research in Europe through the availability of hiPSC lines in a not-for-

profit manner. In addition, protocols detailing key cell culture techniques are publicly available to support use of iPSC lines in a standardised manner.

Freedom of use: As EBiSC aims to collect hiPSC lines for which there is freedom to operate for both academic and commercial collaborators, significant expertise has also been generated in managing depositions to minimise any downstream restrictions for use. This includes interpretation of older consent forms in which critical aspects such iPSC derivation, genetic analysis and sharing of cell lines were not included. This is a critical output to ensure that iPSC lines generated through publicly funded projects can be made widely available for future research use including commercial entities.

Quality: By implementing a robust panel of cell line characterisation tests suitable for an international iPSC repository, EBiSC has both set the standard for iPSC banking in Europe and created a collection of well-characterised hiPSC lines available with freedom to operate, addressing challenges experienced by EFPIA partners in obtaining disease relevant hiPSC lines for biopharmaceutical research.

Ease of access: DH-CC distribution capabilities have provided easy and simple access for both academic and commercial organisations to a whole range of iPSC lines at a reasonable cost. The availability to download a standard access and use agreement has been well received and has greatly contributed to end users accessing the resource. With the inclusion of 467 StemBANCC iPSC lines it has quickly become the largest and most accessible iPSC cell line resource in Europe.

User awareness: Publication of the iPSC lines available from EBiSC is essential not just to maximise sales revenue, but also to ensure that research funding is not wasted creating new disease relevant cell lines for which equivalent lines already exist in the EBiSC catalogue. With the launch of the EBiSC cell line catalogue on 23 March 2016, i.e. two years after the launch of the public private partnership project, the outputs of EBiSC could be immediately and broadly spread to the scientific and industrial community by directly distributing already existing as well as newly generated iPSC lines to scientists worldwide for research use.

By that time, several communication activities had taken place such as the first EBiSC Meet-up Hub at the Annual Meeting 2015 of the International Society for Stem Cell Research (ISSCR) in Stockholm which aimed at creating awareness within the international stem cell community for EBiSC and its vision. The second participation of EBiSC in the ISSCR Annual Meetings 2016 in San Francisco including a specific 3 hour EBiSC focus session and a Meet-up Hub as well as the EBiSC-HipSci booth organised by ECACC at the ISSCR Annual Meeting 2017 in Boston, proved that the EBiSC visual identity started to be well recognised among academic and industrial researchers in Europe and the US.

Figure 4: EBiSC participation in the ISSCR Annual Meeting 2016 in San Francisco / USA (22-25 June 2016)

The resource has also been promoted at relevant scientific conferences either as a dedicated EBiSC exhibit or as prominent part of the DH-CC offering and included in its marketing activities e.g. newsletters, brochures and digital marketing e.g. through Twitter and ResearchGate.

These regular dissemination activities, have generated increasing interest in EBiSC cell lines and associated data which has led to a progressively increasing number of cell line orders through the EBiSC catalogue as well as a constantly increasing number of inquiries for specific iPSC lines received through the contact form on the EBiSC public website.

Access to Data: A central element of the Project has been to develop an IMS which provides users with the data they need to evaluate the available iPSC lines to the fullest extent possible. Having access to the data associated with the large collection of iPSC lines being deposited in the bank, provided the data needed to develop and test a fully functional IMS. The result is an IMS which provides an accurate and clear display of the specific disease-causing characteristics of the diverse range of iPSC lines including the increasing number of genetically modified lines in the collection.

The availability of WGS data for 70 cell lines led to the development of the allelic query service within the IMS. This advanced search allows users to identify cell lines of interest based on their underlying genomic variation and will significantly improve the ability of researchers to quickly identify the most appropriate iPSC lines for use in their research. Through strict metadata requirements in hPSCreg,

EBiSC ensures that Europe has an internationally relevant collection of well described, standardised and easily identifiable cell lines.

The information management tooling reduces the research cost and time involved in obtaining a cell line with the appropriate genetic background and donor characteristics for scientific and industrial research questions. This will accelerate biopharmaceutical research and development through rapid provision of research-grade lines with required disease characteristics.

The impact of disease modelling research undertaken in the Project

An essential part of the EBiSC Project has been to demonstrate the value of iPSCs for medical research. In the course of the Project, 10 "Pathfinder" studies within neurology, diabetes and liver diseases have been carried out which used cell lines from the EBiSC Catalogue for disease modelling research. These studies allowed industry partners to evaluate the capabilities and possibilities for the use of disease-specific iPSC lines from the EBiSC catalogue as an early drug discovery tool. At the same time, the studies allowed academic partners to demonstrate that EBiSC iPSC lines are valuable in exploring and understanding disease mechanisms on a cellular level.

By involving partners from both industry and academia in a large number of studies, this comprehensive work confirmed that as a human cell technology, iPSC lines afford sufficient quality of data to support future discovery of novel targets and mechanisms for new medicines discovery and development.

If, as many researchers believe, disease-specific *in vitro* models become the preferred *in vitro* model systems in the pharmaceutical and biotech research, the data and workflows established within the Project by the EFPIA, SME and academic partners will be a driver for further implementation of such models. Prospectively, this will increase the competitiveness of these EU companies making them attractive, both from a professional point of view and from an up-to-date working environment attracting the most talented employees for early drug discovery.

A Permanent Resource for Europe

With DH-CC assuming the role of the EBiSC Banking Entity within their not-for-profit bio-banking activities, the consortium started to address the longevity of the bank and continued function of the repository in depositing and distributing iPSC lines.

The accessibility of this resource for any academic or commercial entity supports research through ensuring availability of high-quality iPSC lines, all of which have clear freedom to operate and traceable provenance back to starting material.

By supplying quality controlled and ethically assured research materials, EBiSC will support and accelerate EU research. Research will not be hampered by the consequences of contaminated or unauthentic cell lines in terms of wasted research resources and the impact of irreproducible scientific data.

As use of iPSC derivatives for routine drug screening and development of therapeutics expands, EBiSC will provide researchers with key resources to support biopharmaceutical research. Furthermore, making the data available through the extensive IMS and EBiSC data access committee will enhance

the value of this resource through making genomic and other data sets of EBiSC lines readily available to researchers. EBiSC will thus support the reputation as an organisationto engage with and to assure delivery of high quality and ethically sound research.

The next step and ultimate goal will be to reach a long-term sustainability of the EBiSC bank so as to ensure in future the competitiveness of Europe in the delivery of iPSC banking services and to furthermore strengthen the high profile and reach that EBiSC has managed to establish even beyond Europe.

1.7. Lessons learned and further opportunities for research

The benefits of Public-Private-Partnerships (PPP)

It would not have been possible to deliver the EBiSC project if the consortium had not been a public private partnership (PPP). With 26 partners in total, including eight EFPIA members, five SMEs and thirteen university and research institutions, the EBiSC consortium was a large PPP which brought together a significant segment of the leading producers and users of iPSCs in Europe. This arrangement was essential for the Project to achieve its core aim to establish a cell line repository which will make future drug development more effective and provide resources for future EU-funded iPSC projects. As an example, the EBiSC iPSC repository and capabilities were of utmost importance for the IMI ADAPTED project to start its activities.

The advantages of the PPP can be summarised under four headings:

Sharing of ideas and best practice: EFPIA members, SMEs and academic partners within the consortium all identified the opportunity to engage with leaders in the field as a major benefit from participating in the PPP.

EFPIA partners identified that EBiSC provided a platform for extensive networking and exchanging stem cell-related expertise across industry and public partners. It also opened up further possibilities for future collaboration with former consortium partners, both from industry and academia. Several projects are currently entertained between former EBiSC partners that help the EFPIA partners to progress their internal research and development pipelines. In addition, engagement in EBiSC fostered and significantly accelerated internal research on iPSCs and supported assay development for drug discovery campaigns.

SMEs identified that the PPP opened the door to collaborations and wider resources which are important factors to boost SMEs businesses and associated fields. It also allows the SME to improve competitiveness from the transfer of skills between entities. On a more technical level, it allows the SME to identify and focus on relevant end-point analysis in disease models that create value in the early drug discovery phase.

Public research institutions also benefit from close contacts and interactions with the pharmaceutical industry and other relevant technology partners which allow new developments underway at the research institution to be brought into direct discussion with industrial partners, resulting in the necessary reflection of the impact, risks and future applications. More generally, engagement with the other members of the consortium allowed individual Research Intuitions to standardise experimental

procedures in alignment with the quality state-of-the-art criteria that were define by the whole consortium.

All partners recognised that discussions with participants of the PPP resulted in clearer views and insights into the necessary processes and possibilities of hiPSC.

Training: All types of consortium member recognised that the capacity of EBiSC to provide training for their staff was a major benefit of participating in the PPP. Developed and led by an SME, RCS, and a research institution, DH-NIBSC, while drawing on expertise from across the consortium, the EBiSC training would not have been as successful without the PPP to combine expertise from both public and private partners. These courses supported the dissemination of harmonised procedures for iPSC processing across the consortium.

Better understanding of Pharma needs: As providers or iPSC lines and developers of new disease models, the SME and Research Institutions benefited greatly from EBiSC by developing a better understanding of the needs of the EFPIA partners. In particular:

- Implementing workflows that fulfil requirements from industrial players
- Developing QC systems that lift the scientific results into an implementation mode
- Being able to identify and focus on relevant end-point analysis in disease models that create value in the early drug discovery phase
- Freedom to operate in using iPSC lines and associated data for drug development purposes

Engagement with the EFPIA companies also informed the development of the IMS and ensured that development of the EBiSC IMS was closely aligned with the business requirements of the pharmaceutical companies (as well as the public partners). By assessing the business and knowledge management needs of EBiSC customers, in particular the EBiSC pharmaceutical partners, the IMS was designed to fit user needs better, for example the capturing and display of detailed information on genetically modified iPSC lines.

Access to iPSC lines: for the EFPIA partners, the large diverse scale of the EBiSC PPP provided much better access to cell lines than would have been the case otherwise. For EFPIA partners wishing to set-up in vitro models in disease-affected cells for evaluation of *in vitro* pharmacology on disease biology, the capacity of EBiSC to provide or generate the relevant iPSC lines (patient and gene-edited) was a key benefit of the PPP. This was particularly the case where the cell line could be commissioned during the project.

Challenges encountered with PPP and the project generally

The large scale of the PPP and the nature of the work being undertaken in the project brought challenges which could be mitigated in future PPPs.

Short duration of the project: For exploratory projects involving significant experimental work, a project duration of only 3 years is too short. This was also the case for EBiSC. The challenge was mitigated by the addition of a one-year extension, but the scope of specific research projects was limited by delays in cell line generation.

Multiple dependencies: In some areas of the work undertaken by the EBiSC consortium, activities were delayed or limited by being dependent on factors outside the responsible party's control. A recurring issue was the deposit into EBiSC of iPSC lines for which the original donor consent was not sufficiently clear or flexible for use in subsequent research. While EBiSC's own documentation can address this issue for lines being created from newly donated tissue, depending on tissue from existing bio-repositories is more challenging. More generally, the use of several different participants within the PPP to process data associated with deposited iPSCs required data to be transferred between different information systems, which created additional workload.

Harmonised legal system: EBiSC set out to acquire iPSC lines from many EU Member States. In most cases the transfer of iPSCs between countries is not problematic. But EBiSC encountered difficulty for lines created in Spain as the national legal system restricted access to iPSC lines to third party researchers.

Opportunities for further research

Gene Editing: Interest in using iPSCs for drug discovery in coming years will be greatly enhanced by the creation of isogenic control lines and reporter lines to complement the original cell line created from donated tissue. The rapid development of CRISPR Cas9 gene editing techniques means that researchers are increasingly requiring additional lines to use in parallel to the original line.

Mature Differentiation: New research needs to focus on protocols to derive defined differentiated (mature) cell types that are highly standardised and, ideally, can be up-scaled for bulk production.

Expanding catalogue: The addition of other disease relevant iPSC lines to the bank such as metabolic diseases, like Diabetes and MODY, and rare diseases would maximise the EBiSC bank potential and all the infrastructures already put in place.

Data: Advances in management, discovery and distribution of large data sets are required to accelerate scientific development in iPSC research. With iPSC collections growing rapidly it is becoming more challenging for scientists to identify the most appropriate lines for use in their research. Accompanying each iPSC line in a catalogue should be extensive, searchable and shareable experimental characterisation data, particularly as sequencing costs continue to drop. There also needs to be significant improvement in the capture, linkage, and access to phenotypic and clinical datasets from iPSC donors. The above research improvements would form the next level of iPSC collection that accelerates therapeutics through a single, intuitive and comprehensive iPSC data portal. This would offer rapid and accurate identification of the most appropriate iPSC lines for a given research question, have freely available (through a Data Access Committee) extensive experimental characterisation data including a complete genome sequence, permissive consent for therapy and IP development and ready access to relevant patient clinical and phenotypic information.

Ethics: There also needs to be continued debate and discussion, about the appropriate balance of consent and ethics for reuse, characterisation and genetic modification of iPSC lines. This allows acceleration of therapeutic development through open and permissive use, but maintains protection for the individual donor.