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Scientific Life

Hot Start to European Pluripotent Stem Cell Banking

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Achieving consistency in standards of access to and quality of human induced pluripotent stem cells has lagged behind their use. In Europe, a network of academic and industrial partners has been established to overcome this challenge. The experience reveals the devil in the detail of worthy ambitions informing future efforts.

In Europe, over 452 human induced pluripotent stem cell (hiPSC) lines originating from 24 research institutions have been registered in the European hPSC registry (hPSCreg; www.hPSCreg.eu). Despite centralising this knowledge, subsequent access to these lines has been a conflicting experience often characterised by painstaking one-on-one communications with busy scientists and overworked and under-resourced legal and commercial institutional representatives. Cell lines are often exchanged amongst colleagues with lack of informed donor approval to do so, or documentation to support custodianship, cell line identity, or lack of any assurances or warranties of performance or quality. These practices are not new to research, but under the worst of circumstances, these experiences erode researcher and public confidence in science, at significant expense and loss of time. Recognising the need for a harmonised framework of best practices to provide standardised access to hiPSCs in Europe, the Innovative Medicines Initiative Joint Undertaking (IMI JU), a pan-European public–private partnership between the European Commission and European Federation of Pharmaceutical Industries and Associations (EFPIA; www.efpia.eu), funded through cash and in-kind contributions the establishment of the European Bank for induced pluripotent Stem Cells (EBiSC). Its mission is to (i) identify key cohorts of patients useful for research purposes; (ii) create a large single European hiPSC repository through the integration of existing infrastructures; and (iii) generate a centre of scientific excellence for standardisation and optimisation of hiPSC banking-associated practices.

Launched in January 2014, EBiSC has used established European resources and capabilities in the public and private sectors to forge a centralised network and facilities for standardised biosample procurement, cell line creation, quality-controlled banking and distribution of hiPSCs (Figure 1). To become operational rapidly, EBiSC undertook a 'Hot Start' in effect defining and implementing standardised practices in the process of commissioning several centres to provide the bank with established cell lines [1]. This approach yielded a distribution-ready foundational collection of 27 hiPSC lines (https://cells.ebisc.org), and executive, operational, and administrative experience worthy of reflection to inform future efforts.

Devil in the Detail

Facilitating third-party user access to hiPSC lines has been central to the EBiSC mission. At an executive level, it was apparent that competitive interests in research on disease representative hiPSC lines by depositors themselves constituted a first bottleneck to deposition and prospective access by third parties. In the absence of any alterative tactic to support deposition, such as inducement to co-publish, EBiSC subsequently purposed fully commissioned lines for which there was identified demand not already addressed through existing projects under terms that dictated immediate deposition and distribution. The goal was to expedite access to lines, the absence of which would inevitably lead to delay by the years it would take to undertake and publish subsequent research. The EBiSC new line commissioning process facilitates access to EFPIA partners, providing matched funding to the EBiSC project, and as a process has today usurped the Hot Start phase, in addition to lines originating from other projects. Nevertheless, the establishment of standardised templates to govern patient consent, hiPSC deposition and user access arising from the Hot Start has constituted a significant step forward for the EBiSC project, although a requirement remains for flexible terms to accommodate variations in legal and cultural norms. In one instance, such variation affected the principle of centralised distribution of hiPSC lines originating from a European member state for which laws governing distribution are in place. Other legal regulations or cultural norms, such as a protective patient–clinician relationship, data protection laws, consent templates that do not allow for future unforeseen research or requiring absolute donor anonymity, are likely to be encountered in the future to impose further restrictions on efforts to globalise procurement.

Coordinating activities of 28 partners distributed across Europe and representing diverse sectors and interests required significant executive, scientific and administrative leadership and commitment. This coordination was reflected by weekly executive office and monthly consortium board reporting and tracking project resource commitments against the progression of the entire process of cell line procurement, processing and distribution. To ensure the sustainability of the resource and the incorporation of Europe-wide standards, EBiSC aimed to integrate multiple established public resources for data and cell management. The Hot Start provided a working example for piloting the development and integration of these databases for EBiSC. The

hPSCreg project (www.hPSCreg.eu) emerged as an established community for registering human pluripotent stem cell donor and cell line data along with ethical provenance. hPSCreg implemented the use of ontology tools hosted by the European Molecular Biology Laboratory – European Bioinformatics Institute (EMBL-EBI) to annotate cell lines using a controlled vocabulary, which ensures that cell line scientific data are accurately described and more easily discoverable in the Web portal. Seamless and automatic sharing of data across these resources in addition to integration with EBiSC's information management system and that of the European Collection of Authenticated Cell Cultures (ECACC) managed by Public Health England (www.phe-culturecollections.org.uk) ensures consistent data tracking both internally and externally.

Operationally, the interface with hiPSC line depositors encompassed the spectrum of experience to be expected from academic and biotech laboratories, reflective of variations in staffing, resources and operational diligence. The Hot Start Foundational Collection relied on collating depositor-derived hiPSC line data along with data arising from standardised quality control (QC) measures implemented at the EBiSC Central Facility. This effort revealed significant variation between laboratories in the extent to which hiPSC line-associated data could be tracked, and not too surprisingly, this variation occasionally extended to cryostorage records. Other frequent issues included insufficient or ambiguous ethical approval, impeding the ability to make hiPSC lines available for purposes other than ones that were consented to and failure of operators at hiPSC supplying centres to comply with EBiSC standard operating protocols for cell cryopreservation and processing, despite the availability of formalised training.

The importance of measures to safeguard against microbiological contamination and

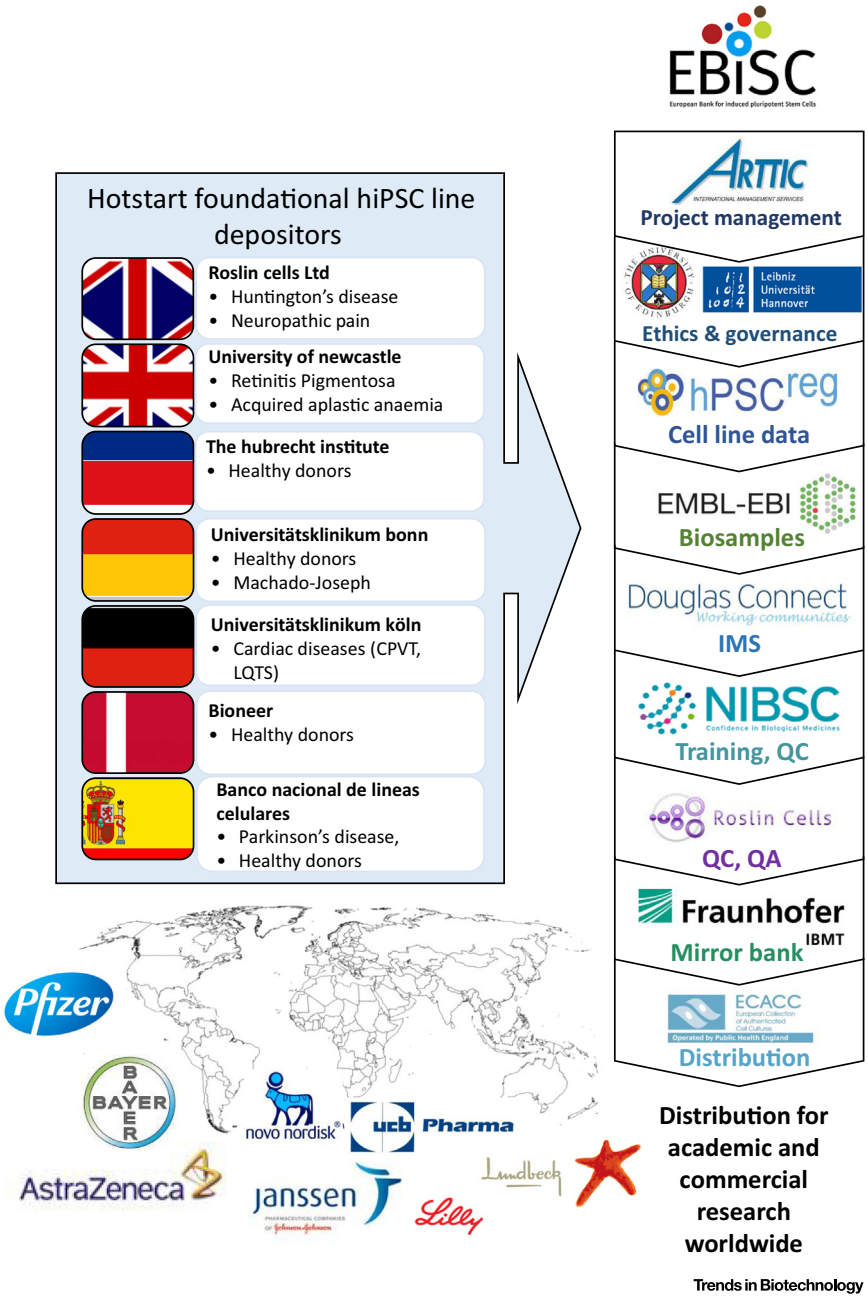

Figure 1. Hot Starting the European Bank for Induced Pluripotent Stem Cells (EBiSC) Network and Establishment of a Foundational Resource of Established Human Induced Pluripotent Stem Cell (hiPSC) Lines. The membership of the consortium defined demand and supply for established hiPSC lines representative of diseased and normal donors from seven iPSC depositor centres across Europe (listed to the left of the figure). These included lines from donors genetically screened and/or affected by Huntington's, Machado–Joseph and Parkinson's disease, neuropathic pain, retinitis pigmentosa, acquired aplastic anaemia, cardiac diseases [catecholaminergic polymorphic ventricular tachycardia (CPVT); long QT syndrome (LQTS)] or healthy donors with no known disease. HiPSC line banking, quality control (QC), data management and distribution were achieved through co-ordination of established European capabilities, with activities overseen by ARTTIC. Each centre was tasked to identify and deposit eight to ten cell lines apiece into EBiSC (key partners listed to the right of the figure) obtained with suitable informed consent and free of third-party obligations (reviewed with guidance from the University of Edinburgh and Leibniz University of Hanover). For each line, 30–50 vial batches cryopreserved at 1×10^6 cells/vial were produced. HiPSC line data were collated in hPSC registry

(See figure legend on the bottom of the next page.)

mislabelling of cell lines is broadly understood and avoidable through the implementation of high-quality standards of operation [2]. Our experience underscores the danger of procuring lines from sources other than banks that routinely implement these measures as a batch release criterion. Cell line identity mismatch was the most frequent cause of QC failure, the consequence being cell bank disposal. The second most-frequent challenge to banking was detection of microbial contaminations including yeast, fungi and bacteria, although mycoplasmas were not detected in any deposited hiPSC line. The most disastrous consequence of QC failure was cell bank disposal. However, the project revealed the robustness of implementing standardised feeder-free culture conditions using current commonly utilised commercially sourced reagents [3,4], irrespective of feeder-dependent and independent methods, which depositors had used originally to derive lines.

Worthy Ambitions

The European experience of the Hot Start for the EBiSC project has constituted a positive reflection of what can be achieved when there is a union (consortium) founded on a common will to collaborate across national boundaries for collective benefit. Over 3 years since its launch, it has significantly progressed its aims to create a standardised, quality-controlled, data-managed and globally e-commerce accessible hiPSC collection of utility to academic and industrial research. At the time of writing, this approaches 350 lines providing gender-balanced representation of 20 disease conditions and disease-unaffected controls. Whether EBiSC will continue to demonstrate for Europe that successful science transcends international politics remains to be determined. At the present time, EBiSC's operational costs vastly exceed revenues earned from cell line distribution and its continued existence remains dependent on public funding matched by financial cost sharing with EFPIA partners. Establishment of self-sustainability constituted a long-term aim originally projected to take at least 6 years, the business model for which remains a work in progress. Central to the drive behind the establishment of EBiSC is the ethos to benefit the discovery and development of new medicines through facilitated procurement and standards of donor-specific disease-representative hiPSC lines. The diseases for which new knowledge and medicines are desperately needed are not constrained by national boundaries. It is hoped that the benefits generated by EBiSC and other large-scale, multinational research projects will continue to flourish despite a period of forecasted uncertainty in funding in Europe and the USA as a result of a rising tide in nationalism and antiglobalisation.

Concluding Remarks

In Europe, resources and capabilities in the public and private sectors have been uniquely forged to create EBiSC, a centralised international network of facilities for standardised biosample procurement, cell line creation, quality-controlled banking and distribution of hiPSC. Its Hot Start has defined both immediate rewards and the prospective future challenges to globally benefit the basic and translational use and impact of this resource in discovery and drug development.

Authors' Contributions

T.A. co-led securing funding and is the programme co-ordinator. P.D.S. led the work packages establishing 'Hot Start' hiPSC collection and the operational Central Facility. R.S. contributed operationally, notably to cell line receipt, processing and testing, and supported in manuscript drafting. B.K. supported consortium building, recruitment of hiPSC centres, funding application, daily project management, design and provisions of communication and collaboration infrastructure and materials, and manuscript drafting.

Acknowledgments

EBiSC is supported as a multinational public-private project of the Innovative Medicines Initiative (www.imi.europa.eu) funded by the European Commission and in-kind contributions from the EFPIA partners Pfizer Ltd, H. Lundbeck A/S, Janssen Pharmaceutica NV, Novo Nordisk A/S, AstraZeneca A/B, UCB Pharma SA, as well as Bayer AG and Eli Lilly and Company Ltd (joining after the 'Hot Start'). The views expressed herein reflect only the authors' view and the Innovative Medicines Initiative Joint Undertaking is not responsible for any use that may be made of the information it contains. The authors thank EBiSC consortium members for supportive commentary and proofing of the final article.

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[i]As of December 1, 2015, Roslin Cells Ltd's role in EBiSC was assumed by Roslin Cells Sciences Ltd, which is now a wholly own subsidiary of Censo Biotechnologies Ltd (whose Head Office is Wallace Building, Roslin Biocentre, Roslin EH25 9PP, UK).

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http://dx.doi.org/10.1016/j.tibtech.2017.04.006

(hPSCreg) by individual depositor centres. To ensure traceability, donors, cell lines and batches were registered in the European Molecular Biological Laboratory – European Bioinformatics Institute (EMBL-EBI), which integrated with the EBiSC Information Management System (IMS) produced with Douglas Connect. The UK National Institute for Biological Standards (NIBSC) provided a standardised training regime to promote best operational practice in hiPSC line cultivation and advised on appropriate QC. Upon completion of cell bank production and data deposit, standardised QC and quality assurance (QA) assessment, and collation and review of consent, donor and cell line-associated data were performed at the Central Facility operated by Roslin Cells Ltd, prior to subsequent distribution to the Mirror Facility (Fraunhofer IBMT) for back up and an e-commerce-capable distribution centre (Public Health England, European Collection of Authorised Cultures –ECACC). The specification of hiPSC standards and subsequent utilisation in the first instance was defined by partners of the European Federation of Pharmaceutical Industries and Associations (EFPIA) in the Innovative Medicines Initiative Joint Undertaking (listed on the bottom of the figure).

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Science & Society

What's the Regulatory Value of a Target Product Profile?

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Target product profiles (TPPs) are used as a regulatory tool for dialog on clinical development or manufacturing plans. Drugs and biologics approved by the FDA that mention TPPs are associated with more efficient regulatory review times, perhaps as a result of increased planning or because the TPP promotes well-organized regulatory dialog.

Multiple Faces of the TPP

Since the rise of product development and branding, industry has sought to communicate the value proposition of its innovations. The TPP was developed as a strategic document to communicate differentiating features of the new product. TPPs were initially used internally in industry (e.g., between R&D and upper management) with technical products such as chemicals and electronics in the 1950s and 1960s (Figure 1, bottom right) [1]. The popularity of this type of TPP grew in the 1980s and 1990s with the rise of project management practices. In the late 1990s, the pharmaceutical industry and regulatory authorities of the US FDA developed a pilot program and then guidance for industry on how to use TPPs to collaborate on the development of the clinical development plan to support proposed labeling claims in the package insert [2]. This activity is represented in the top-left arm of the regulatory TPPs in Figure 1. We refer to this as a labeling-type TPP (LTPP) [3], consistent with the targeted objectives of the document. Early pilot efforts to incorporate LTPPs in the development process were described for anti-infective and antiosteoporosis drugs.

At about the same time, guidance was provided from the International Conference on Harmonization (ICH) on how to communicate between industry and regulatory authorities on strategy and manufacturing elements critical to formulation [4]. A core element of this guidance is the concept of quality by design (QbD), a 'systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management'. The quality TPP (QTPP) is the document in QbD that describes the objectives, or attributes, of the formulation essential to the patient. An example attribute might be 'fast dissolving' for a sublingual wafer. This document is represented in the top-right arm of the regulatory TPPs in Figure 1. A third major TPP form has been well described for interactions between the public health sector and industry to communicate desired attributes of medications. This form has had a particularly strong focus in the infectious disease arena and is represented in the bottom left of Figure 1 [5,6].

A Question of Value

Intuitively, both industry and their regulatory counterparts might want to embrace advice and discussion on the roadmap for

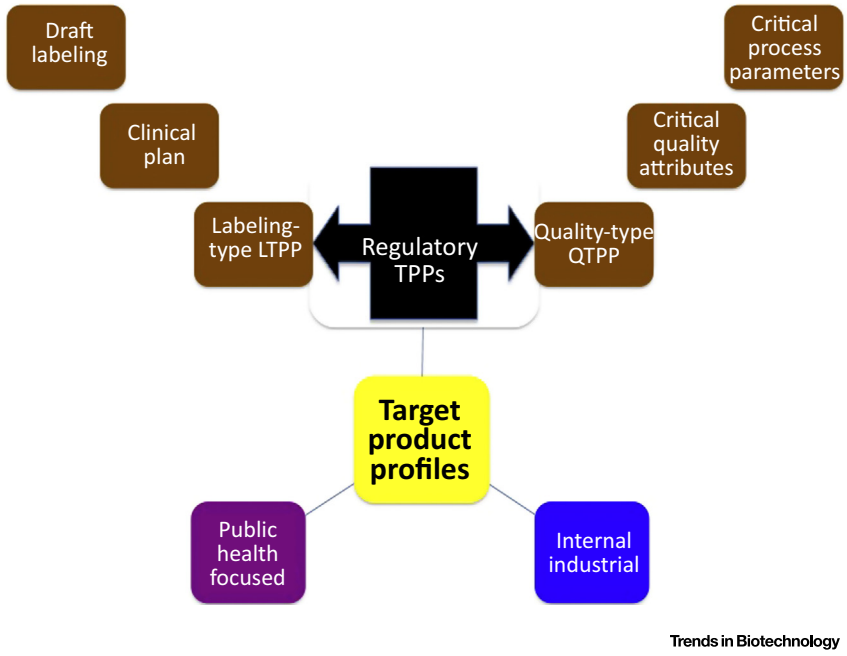

Figure 1. Schematic Diagram of the Different Types of Target Product Profile, with Emphasis on How They Are Used in Regulatory Communication.