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Cores laboratories: Organization for stem cell technology advancement

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As new technologies develop in biomedical sciences, pockets of technical expertise arise in individual scientific Institutions and these in turn evolve into centers of excellence for a given technology. These centers of excellence tend to be referred to as 'shared' or 'core' facilities and they play a key role in establishing best practice, setting quality standards, providing skilled services, advancing technologies and through economies of scale, delivering value for money (Meder et al., 2016; Chang and Grieder, 2016; Hockberger et al., 2018). With the generation of human embryonic stem cell (hESC) lines in 1998 (Thomson et al., 1998; Ludwig et al., 2018) and their promise as tools for development, disease modelling and therapeutic application, a new portfolio of cell culture techniques began to be developed and along with this, associated technologies. This field required expertise and training in a number of areas and soon centers providing training in hESC work were established.

The WiCell Stem Cell Bank was the first center to be set up in 1999. They not only distribute hESC lines but also provide characterization services and initially offered training for the culture of hPSCs. Subsequent to this, a number of similar centers were launched globally. In 2007 the generation of human induced pluripotent stem cells (hiPSC) (Yu et al., 2007; Takahashi et al., 2007) provided yet another branch of research and development in this scientific area. As the field grew so did the number of core facilities, providing training, services and materials to both research and translational scientists. Quality standards were established (International Stem Cell Banking Initiative, 2009) and common practices were shared between expert centers. A need to establish networks of core facilities was identified by groups of pluripotent stem cell facility directors and this resulted in the formation of the COREdinates and the Pluricore groups.

1. The COREdinates

At the June 2009 International Society of Stem Cell Research (ISSCR) meeting, Sunita D'Souza at Mount Sinai School of Medicine in New York City organized the first meeting for seven to eight Stem Cell Core heads, who were mostly from the east coast of the USA, to explore the benefits of working together, sharing expertise and being connected. In a subsequent meeting in 2010 at the NIH, Mark Tomishima, then at Memorial Sloan Kettering Cancer Center, coined the term "COREdinates" for this group (https://www.coredinates.org/). The following years, as the field of human pluripotent stem cell blossomed, the number of core facilities covering this field increased rapidly and the COREdinates group became more structured to accommodate a larger number of members. In 2019, the COREdinates group includes 47 core facilities, mostly from the USA (33 facilities) and Europe (9 facilities). Every other year, presidency of the association is rotated amongst the members of COREdinates.

The common mission of these core facilities is to facilitate and support all aspects of human pluripotent stem cell research. Most of the facilities have a fee-for-service based model in combination with grant and/or institution support. The distribution between grant funded projects and fee for service varies greatly between the facilities. Some facilities focus on supporting the researchers from their University only, others provide their services to other Academic Institutions as well as for profit organizations. Together, these core facilities offer a variety of services including iPSC derivation and characterization, banking and distribution, gene editing, differentiation and training. Some facilities provide space and offer reagents preparation and testing. Other areas of expertise include cGMP cell manufacturing, bioengineering, chemical screening and laboratory automation.

One of the goals of the COREdinates is to share common practices between the different core facilities. In 2011, an email server list was established to facilitate the communication between the COREdinate members. This email server list is commonly used to share protocols. Since 2016, an annual meeting has taken place in the USA where members openly discuss topics related to pluripotent stem cells. In 2018, the focus was on gene editing since many core facilities were starting to

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offer it as a service. The topics covered reagents, standard operating procedures, automation and workflows, as well as quality control of the targeted clones. These meetings and the email server have been extremely valuable for the COREdinate members since each core facility has a set of expertise that can be quickly transmitted to the rest of the group.

Another goal of the COREdinate is to disseminate knowledge. Since 2010, the COREdinates group has organized, once a year, a Focus session at the International Society for Stem Cell research (ISSCR) meeting. This Focus session provides an opportunity for some of the COREdinates members to present their work and/or the services offered by their core facility. The presentations cover a wide range of human pluripotent stem cell related work, representing the diversity of the COREdinates group. Another part of the Focus session is dedicated to a unique topic each year. In Los Angeles in 2019, our session focused on Parkinson's disease since the first clinical trial using iPS derived dopaminergic neurons to treat patients with Parkinson's disease had just started in Japan. These focus sessions have been well attended (around 400 attendees in Melbourne in 2018) and have received positive feedback. ISCBI (https://www.iscbi.org) has also held joint meetings with the COREdinates and these joint meetings have enabled a valuable exchange of knowledge and skillsets between these two groups. A few years ago, the COREdinates group teamed up with Stembook to publish a collection of protocols covering many aspects of pluripotent stem cell research and development. Stembook was then inactive for several years but was revitalized in 2018 by IOS Press. The COREdinates group is working again with Stembook to publish validated protocols. In addition, three of the four editors of the Lab Resource section of Stem Cell Research Journal belong to the COREdinates group. The lab resource section aims to catalogue different types of resources, including induced pluripotent stem cells and gene edited lines. Authors are required to adhere to stem cell nomenclature rules (Luong et al., 2011; Kurtz et al., 2018) as well as strict quality control standards in order to have their resource published in Stem Cell Research Journal.

Many core facilities provide workshops to train the next generation of scientists joining the stem cell field. For instance, the UK Stem Cell Bank and the HSCI iPS core facility have organized joint reprogramming workshop for the past 7 years. These practical trainings should improve standardization and good practice in the scientific community.

Lastly, work that was initiated in the Stem Cell Core at Memorial Sloan Kettering Cancer Center headed by Mark Tomishima evolved and facilitated the 250 million dollar investment and the creation of Blue Rock Company, whose goal is to deliver therapeutic stem cell products to the community in the near future. We foresee more and more Cores evolving and assisting with the production of various types of stem cell based therapeutic products in the future.

2. PluriCore

As mentioned previously, achieving a high level of standardization is important for the derivation, propagation, differentiation as well as for the gene editing of human pluripotent stem cells (PSC). Moreover, standardization of materials, processes and the assessment of quality is essential for manufacturing human PSCs for clinical application. Creating such knowledge infrastructure requires a community effort by a network of experts.

This need has motivated scientists in Germany and Europe to create the PluriCore network (http://gscn.org/en/RESOURCES/GermanStemCellCores.aspx), where techniques and protocols are shared and disseminated in the scientific community to ensure the highest standards of research using PSCs. The initiative was launched by Micha Drukker (Helmholtz Center Munich), Harald Stachelscheid (BIH Stem Cell Core, Charite – Universitätsmedizin Berlin) and Sebastian Diecke (BIH Stem Cell Core, Max-Delbrück-Centrum for Molekular Medicin) and is supported by the Berlin Institute of Health (BIH) and the German Stem Cell Network (GSCN).

Currently the network comprises 21 partners from Germany and Europe and is expanding on the European level, which will increase the impact of the technical harmonization and reproducibility. The associated partners meet annually to discuss specific topics and techniques including reprogramming, differentiation, genome engineering, cell characterization and process automation. Furthermore, invited speakers from academia and industry inform the stem cell community about relevant topics including new technological inventions and equipment, optimized quality control measurements and laboratory data management solutions (LIMS and Electronic notebooks). Over the past 5 years, special emphasis has been placed on how to standardize characterization and quality control measurements, in particular the methods for testing and ensuring the genomic integrity of reprogrammed and engineered cells as well as analysis of the differentiation potencies of individual PSC lines. Another important topic addressed by the group was ethics, with a focus on the production of a generalized patient consent form and precise documentation with an emphasis on biobanking initiatives. Working groups within the network were formed to address specific topics and to formulate recommendations for the stem cell community. As a result, the network produced a generic patient consent form that can be used as a general template, as well as a standardized material transfer agreement form to facilitate the exchange of cell lines. Future goals of the network include the establishment of an induced PSC line repository with well characterized lines (including information such as differentiation capacity, omics data and donor information) derived from healthy donors of different age groups which can serve as reference material within the network and beyond. This repository will help research groups of different institutes to increase the reproducibility of experiments and scientific results. In addition, the network plans to establish recommendations to standardize the karyotype stability analysis of PSCs in order to generate a framework for quality measurements. Internationally, the initiative is well connected to the Stem Cell COREdinates network in the US, actively exchanging protocols and discussing technical developments. Together, the networks are planning to initiate a collaboration with journals allowing the publication of negative results from experimental datasets where this experimental data has been generated based on best practice study design. This will promote reproducibility of experiments, reduce repetition and as a result of this, decrease the wastage of funding resources.

Overall, these national and international consortia have a common goal to deliver reproducible, robust and reliable scientific results through standardization and collaboration, in order to assure the value experimental datasets generated for basic biology and clinical translation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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