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Review Article

From Banking to International Governance: Fostering Innovation in Stem Cell Research

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Stem cell banks are increasingly recognized as an essential resource of biological materials for both basic and translational stem cell research. By providing transnational access to quality controlled and ethically sourced stem cell lines, stem cell banks seek to foster international collaboration and innovation. However, given that national stem cell banks operate under different policy, regulatory and commercial frameworks, the transnational sharing of stem cell materials and data can be complicating. This paper will provide an overview of the most pressing challenges regarding the governance of stem cell banks, and the difficulties in designing regulatory and commercial frameworks that foster stem cell research. Moreover, the paper will shed light on the numerous international initiatives that have arisen to help harmonize and standardize stem cell banking and research processes to overcome such challenges.

1. Introduction

Since the pioneering isolation and culture of human embryonic stem cells (hESCs) over a decade ago, a new era of clinical promise in regenerative medicine has emerged. Stem cell research promises to improve our ability to prevent and cure disease by providing cells for organ transplantation and cell therapies. It will also be used to create a successful model system for drug discovery, including the development of new testing methods for drug efficacy, toxicity, and safety, as well as providing a deeper understanding of the processes of human cell differentiation for the treatment of several diseases including cancer [1].

Stem cell research is steadily entering the clinical translation field with the launching of the first clinical trial (Phase I) testing a hESC-derived cell therapy by Geron [2], and two other trials recently approved by the FDA by Advanced Cell Technology Inc's [3]. With the discovery of induced pluripotent stem (iPS) cells [4], the opportunities of stem cell research have grown exponentially [5]. For example, the use of disease-in-a-dish models is accelerating the building of platforms for drug screening [6]. Disease-specific iPS cell lines are also offering new platforms to increase the understanding of the pathophysiology of complex diseases. iPS research also offers great promise for the field of personalized medicine as it will enable the generation of autologous therapies [6]. Indeed, pluripotent stem cell is now recognized as a valuable starting material for the development of cell products and therapies, as exemplified by the increase of the pharmaceutical industry's involvement (and investment) in fields beyond the traditional area of stem cells for drug discovery [7].

Given the scientific potential of the stem cell field, stem cell banks are an essential resource of biological materials for both basic and translational research [8]. According to the Organisation for Economic Co-operation and Development (OECD), advances in regenerative medicine and stem cells are leading to the development of a bioeconomy: "a world where biotechnology contributes to a significant share of economic output" [9]. Consequently, stem cell banks are destined to constitute a pillar of the bioeconomy in many countries. Indeed, in 2009, Time magazine recognized "biobanks" generally as one of the "top 10 ideas changing the world" [10].

Stem cell banks and registries support transnational access to quality-controlled and ethically sourced stem cell

lines from different origins and of varying grades (e.g., research versus clinical). They are also the "*de facto*" depositories of "biological standards" [11].

The emergence of national stem cell banks [12] has been accompanied by international initiatives seeking to harmonize and standardize processes [13] for stem cell research and banking [14]. These initiatives share the vision of stem cell research as a global enterprise. Illustrative of this trend are the projects launched by the ISCF's International Stem Cell Banking Initiative (ISCBI), UMASS International Stem Cell Registry (ISCR), and the European hESC Registry. Likewise, regulatory bodies are increasingly developing policy frameworks for safe and effective cell-based therapies [15–17]. Until recently, these efforts adopted an "embryocentric" approach, leaving behind other timely and promising sources, such as iPs cells, and stem cells derived from placentas, amongst others. Today, the size and diversity of the collections are growing, as witnessed by the increasing number of registries of disease samples [18] and iPs cell lines [18–21].

Given the growing interest in stem cell banking, it is timely and important to examine key issues of governance, regulatory and commercial frameworks, and the possibilities and desirability of international governance in this field. It is beyond the scope of this paper to provide a comprehensive analysis of the wide range of approaches and challenges to these issues and their implications. Nonetheless, we seek to provide an overview of the most pressing challenges facing the governance of stem cells banks and the challenges of designing regulatory and commercial frameworks to foster stem cell research.

2. From Registries to Biorepositories: Stem Cell Banking in a Comparative Perspective

2.1. Banks and Registries: National and International Initiatives. Stem cell banks represent a collection of biological materials (e.g., embryos, somatic tissues, etc.) and the associated data stored within an organized system [22]. The term "stem cell bank" can refer to a number of different banks and types of operations, as well as institutions [23]. It can refer to a centralized institute that provides cell lines for research (e.g., Singapore SCB), a national supply centre, or a repository of stem cell lines for a broad range of researchers (e.g., Indian National Centre for SC Science). Similarly, stem cell banks range from public banks, such as the UKSCB and the Spanish National SCB, to institutional banks (e.g., Stem Cell Research Centre, Kyoto University) and commercial banks (e.g., BioTime, etc.). Finally, the term "stem cell bank" is often also used to refer to stem cell registries; these are databases systematically cataloguing the scientific and ethical provenance of stem cell lines, including the European hESC Registry and the UMass ISCR. It is important to highlight that both stem cell banks and registries have distinct yet complementary scientific value. However, given their nature (biorepository versus database), they encounter different challenges pertaining to issues of governance, regulation, and commercialization. Here, we use the term "stem cell bank" to encompass all these typologies of banks.

Stem cell banks aim to ensure the quality, availability, and ethical provenance of tissues, cells, or embryos used for research and eventual therapies. Like other biorepositories, stem cell banks have as a core objective to avoid redundancy in research projects and to eliminate the need for the collection and derivation of additional human materials. Moreover, stem cell banks are encountering issues similar to those found in international biobanking more generally [24], including institutional governance, informed consent and privacy, secondary uses of samples, commercialization, withdrawal, and access (open versus controlled). Both face similar challenges of ensuring safety through traceability, while protecting the autonomy and privacy of donors [25, 26].

Stem cell banks are challenged by a myriad of policy frameworks relating to the permissibility of conducting research [27]. The latter is of particular relevance to cell lines of embryonic origin given the accompanying political and moral controversies. Due to the heterogeneous nature of current policy approaches and their lack of interoperability, uncertainties remain concerning the legality of certain practices, for instance, material derivation and distribution [8]. Similar to biorepositories, these uncertainties relate to the ethics of both national and cross-jurisdictional material and data use.

Policy frameworks significantly impact research environments, underscoring the importance of developing effective, adaptive, and prospective policies to manage the socioethical and legal issues associated with the translational cycle [28]. Nevertheless, such an endeavor is challenging. For instance, for both contemporary and emerging sources of stem cells and their prospective or retrospective use, the need to resolve important issues that remain controversial has intensified. For instance, even when dealing with core ethical principles [29] such as autonomy (e.g., informed consent, right to withdraw), respect for privacy and confidentiality (e.g., protection of donor identity given the need for traceability of stem cell lines), and the noncommercialization of human reproductive materials (e.g., translated into restrictions on monetary compensation for gamete and other tissue donation), the ethical and policy landscape remains largely uncharted [30].

2.2. Stem Cell Banking: Governance. Governance has been defined as the exercise of authority within a given sphere. It has been employed as a synonym for the efficient management of a broad range of organizations and activities [31]. Current stem cell banking initiatives foresee, like the immortal cells they curate, a long-term existence. In fact, most platforms have been created for prospective banking, research, and clinical applications. Although the scope and governance structure of national stem cell banks and registries vary, they all accord importance to the centralization of quality controlled and ethically sourced stem cell lines. Likewise, they are committed to governance mechanisms that promote transparency, stewardship, and accountability to generate public support and trust.

Good governance should be understood at all levels, from the initial institutionaldesign to the institution's

performance. The process chosen to create, govern, and evaluate the scientific and ethical integrity of the initiative must also ensure the legitimacy of its raison d'être [32]. Governance mechanisms act at two levels: at the internal level through mechanisms governing the day to day activities of the bank, and at the external level, by independently assessing the overall bank performance and by making the bank accountable to all its stakeholders.

The sustainability of stem cell banks and registries depends on the implementation of governance mechanisms that ensure their scientific and ethical integrity. In order to achieve this goal, stem cell banks' governance structures, processes, and bodies must be independent, accountable, and transparent [33]. Our previous research has identified governance gaps and areas where a lack of concerted effort impedes transnational and translational stem cell research [8]. In the context of embryonic stem cell banking, our international comparative research has demonstrated how the heterogeneous nature of national socioethical and policy frameworks poses a significant challenge to international cooperation, creating additional burdens for innovators seeking to move across national borders [34].

The transnational sharing of stem cell materials and related data is largely dependent on the ability of institutions and jurisdictions to harmonize practices with regards to normative and ethical principles, oversight, governance mechanisms, quality assurance, and scientific practices. While it is recognized that "stem cell research is a global enterprise that begins at the local level" [35], the majority of current and emerging national stem cell banking initiatives do not adopt a prospective governance strategy. Despite platforms being built with the goal of maximizing reproducibility, comparability, and transparency in the field [36], they often lack comprehensive, prospective, and transparent ethical and governance frameworks. The absence of provisions addressing the cross-jurisdictional sharing of stem cell lines or intellectual property rights could potentially thwart the advancement of research by limiting some transactions, thereby narrowing the availability of cell lines, and consequently, impacting the quality and nature of the research. Accordingly, the adoption of interoperable quality assurance standards and clear consent mechanisms for international access, exchange, and governance is essential.

Stem cell banks across jurisdictions are experiencing policy convergence with the adoption of common ethical principles and research governance requirements. For instance, while informed consent requirements for stem cell derivation, use, and banking have evolved along with the pace of scientific developments, policy variations still exist for both somatic and embryonic sources [37]. Similarly, challenges exist with respect to mechanisms to protect the privacy and confidentiality of donors. For example, the "virtual genetic identity between iPS and donor cells raises particular concerns regarding respect for donors" especially given the potential traceability of stem cell lines [38]. Likewise, the possibility of reprogramming such cells back to their origins [39] reintroduces the "embryonic" issues. Consequently, appropriate mechanisms and ethical and legal approaches to solve challenges related to these socioethical and policy issues are yet to be defined for stem cell banking.

Reflecting the policy frameworks governing the permissibility of conducting stem cell research in their respective jurisdictions, stem cell banks have proposed or adopted different criteria with regard to depositing and accessing stem cell lines [40]. These approaches consist of policies that seek to create absolute ethical and legal equivalency (e.g., Czech Republic) or to establish reciprocal policy agreements in order to grant ethical provenance of the cell lines (e.g., California CIRM, Canada CIHR, and UKSCB). A third, and favored approach is use broad "substantially equivalent" or "acceptably derived" criteria (US NAS and NIH, UKSCB) [40].

Licensing requirements demonstrating provenance of the stem cell line are the procedural mechanism with the greatest impact on research. Nonetheless, very little has been said with respect to the type of ethical review and ongoing oversight that is required for long-term and international infrastructures like stem cell banks. In terms of provenance determination, across the board, stem cell banks require proof of prior local ethical and scientific review and approval, as well as compliance with licensing and regulatory requirements by local entities. Similarly, provisions to assess, review, or verify transnational practices in order to vouch for the ethical, scientific, and legal provenance of a stem cell line of foreign origin are only emerging. Given the international realities of stem cell research, this gap in existing regulatory frameworks has the potential to constitute a serious roadblock for seamless collaboration, and ultimately, for the fulfillment of the goals of a stem cell bank itself [8].

Stem cell banking initiatives aim to interconnect national efforts in order to facilitate collaboration. However, access to research needs to be streamlined and simplified [8]. Stem cell banks exist to promote scientific advances and thereby to respect the wishes of donors. The existence of multiple and sometimes even contradictory ethics review, undermines the possibility of creating transparent and accountable governance mechanisms by creating REB "mission creep" and "reduces the likelihood that studies are in keeping with relevant ethical standards" [41]. Thus, international governance models, including collaborative ethics review models such as those proposed by the 2010 Canadian TCPS [42] or by the UK Academy of Medical Sciences [43]—provide illustrative examples of the possibility of creating a proportionate, consistent, efficient, and coordinated approach to ethics review, governance, and regulation. Promoting ethical stem cell research is a delicate balancing act between minimizing overregulation while still assuring adequate protection of research subjects.

These issues have been highlighted by the recommendations recently adopted by the Hinxton Group [44]. According to the Hinxton Group, both issues of governance (i.e., licensing, ethics review, etc.) and access (to data and samples) could be resolved with the establishment of a centralized and comprehensive hub providing information about provenance, governance, and intellectual property, amongst other features. It is indeed the overall aim of ongoing major international stem cell initiatives such as

the International Stem Cell Banking Initiative (ISCBI) and the UMASS International Stem Cell Registry [45] to promote coordinated and harmonized efforts of domestic and international governance. Moreover, these initiatives have been established with the objective of systematically collecting, organizing, and disseminating cell-line specific information. Most importantly, these initiatives all aim to promote international collaboration with the establishment of a global and interoperable network of stem cell banks [46]. To this end, the Hinxton Group's call to "encourage, support and coordinate human stem cell banks and tissue/cells repositories" should be interpreted as a call to support the sustainability of efforts such as ISCBI and UMASS.

2.3. SC Banking: Regulatory Issues and Challenges. The regulatory framework for stem cell research is currently a complex patchwork [47, 48], becoming increasingly complicated as translational research brings new modes of governance into play [49]. Researchers developing therapeutic applications for use in humans are subject to additional regulatory requirements designed to ensure the safety, efficacy, and quality of such products. Regulatory uncertainty has been identified as a significant barrier to the commercialization and utilization of regenerative medicine products [50–52]. With a wide range of stem cell clinical trials continuously moving forward [53], the need for clarity and harmonization of national and international regulatory requirements is gaining moment [54].

Effective regulation is also made more difficult by the fact that stem cell-based products are diverse. Some clinical applications using stem cells, for example in oncology, are well established, whereas more novel interventions derived from hESCs or induced pluripotent stem (iPS) cells carry distinct risks, some of which are unpredictable [55–57]. Still, both iPSCs and hESCs may face similar regulatory and technical challenges in terms of their clinical translation [58]. Indeed, across jurisdictions, regulatory requirements, including criteria for donor eligibility and screening, together with levels of oversight and governance, should be proportional to the degree of risk, type of research (e.g., in vivo animal versus human; in vitro animal versus human hCT/transplant) and degree of donor/sample identifiability.

Regulatory agencies have the difficult task of balancing competing demands: avoiding overly intrusive regulation that will impede innovation or restrict access to urgently needed innovative therapies, while at the same time ensuring that safety, efficacy, and quality are maintained to protect the public. Recent reports of serious adverse events have renewed concerns about potential long-term safety issues [59]. Concerns about "stem cell tourism" [60–62] highlight the tension between demands for access to novel therapies and the need for rigorous oversight of safety, efficacy, and quality. Overall, regulatory agencies have adopted a "risk-based" approach to cell therapies and products, focusing primarily on safety issues rather than on efficacy matters [54]. This risk-based approach deals with intrinsic (e.g., cell origin) and extrinsic factors such as donor selection and sample procurement (e.g., limiting risk of transmission of communicable diseases) to manufacturing and handling practices (e.g., adverse events), amongst others [63].

In many countries [64], the legal framework and regulatory processes are being adapted to meet the challenge of characterizing and regulating novel types of products [52, 65, 66]. Around the world, countries from Germany [67] to China [46, 68] are enacting legislation to regulate cell and tissue therapies. Moreover, major regulatory reforms have taken place in Europe [69–71], Australia, Canada [72], and United States [73]. Furthermore, the International Stem Cell Banking Initiative is undertaking a major endeavour to standardize regulatory requirements with the adoption of a "Points to Consider" for stem cell banks of clinical grade hESC Lines. This "Points to Consider"—expected to be released in late 2011—will cover a wide range of processes involved in stem cell banking (e.g., procurement, banking procedures and documentation, quality assurance, and access processes). It will also establish technical requirements (release criteria, cell line characterization, traceability, microbiological testing, and shipment). Moreover, it will also address governance, provenance, informed consent, oversight, and licensing.

While regulatory frameworks for stem cell translation are being refined [74, 75], current regulatory uncertainty creates barriers to the commercialization and clinical development of cell therapies [76], thereby stressing the need for clear and harmonized definitions of key concepts and terms [77]. Even in the presence of flexible legal frameworks designed to facilitate innovation—such as those adopting a permissive approach towards research and clinical applications—regulatory systems can still be inhibitors, especially when their onerous nature makes the transaction costs of engaging with them disproportionate (i.e., burdensome and unclear, lack of financial incentives, etc.) or when the international sharing has not been adequately addressed [78].

Finally, existing regulatory frameworks ensure proper methods for donation, procurement, processing, and preservation of cells and tissues but are often based on standard pharmaceutical paradigms. Given the unique characteristics of stem cells to proliferate and differentiate, stem cell lines present certain regulatory challenges for safety and effectiveness that differ from other pharmaceutical products [79]. Regulatory agencies are entrusted with ensuring that only safe, effective, and quality therapies and products reach the market. They are faced with competing goals: to establish a delicate balance between promoting innovation and enabling access to scientific advances, while also protecting the safety and welfare of the public [80]. Regulators are challenged by advocacy groups critical of what they perceive as overly intrusive regulation that may delay or prevent access to potentially beneficial therapies [81]. At the same time, regulators are tested by safety concerns, highlighted by recent reports of serious adverse events following application of certain stem cell interventions [82, 83]. These challenges are also present in the context of stem cell banking as stem cell banks can only be effective if the lines they curate have undergone rigorous screening, derivation, and manufacturing processes [71].

2.4. Stem Cell Banking: Commercialization. Stem cell banking raises numerous challenges with respect to downstream commercialization, reflected by complex access agreements and restrictions to future intellectual property rights (e.g., due to MTAs, informed consent, etc.). Similarly, commercialization introduces challenges with regards to the interests and rights of donors. Indeed, the discovery of novel methods for stem cell line derivation (e.g., iPS cells) brought a new approach to the commercialization and patenting landscape [84]. Today, the patent thicket is looming with iPS patents granted in Japan, the United Kingdom, and the United States [85]. Likewise, broad patent applications to the technology are pending in other countries such as Canada [86]. The accompanying socioethical and political controversies and expected legal challenges associated with the granting and the scope of such patents [87] will inevitably have repercussions for the stem cell banking field, especially as iPS banks continue to proliferate (e.g., WiCell, Japan Riken BioResource Center, and Ontario Pluripotent iPS Facility). What remains to be seen is whether the surge of iPS cells will have negative consequences for the banking field, as researchers may consider the "new reality of pluripotency as a cheap and plentiful commodity" not worth the costs involved in the banking process [88]. Interestingly, patent pools are slowly emerging in the context of iPS cell research as illustrated by the granting of exclusive rights to iPS-related technology between Kyoto University and iPierian Inc. [89].

The current instability of financial markets, the considerable time, and investments needed to both develop and commercialize stem cell products, together with the high degree of uncertainty about expected return on investments, have all contributed to private investors early reluctance to embrace the field [90, 91]. However, as with the patenting landscape, private involvement and investment in the stem cell field is also increasingly growing. This is particularly prevalent in iPSCs research, as shown by the surge of companies developing a wide range of products "from and for iPS cells" [92].

At the same time, private investors have begun to question the open access ethos that has characterized national stem cell banking initiatives [93]. This is particularly relevant in jurisdictions in which depositing or registering a stem cell line is a *sine qua* non requirement of compliance of funding and/or licensing policies (e.g., United Kingdom, France, Czech Republic, Spain, Japan, European hESC Registry, and India). These requirements seek to ensure tight regulation and appropriate governance, while at the same time ensuring effective pooling of resources among the scientific community [8]. However, it has been argued that such policies, while adopted in the public interest, have nonetheless the potential to discourage private investment as well as the development of commercially viable products and therapies. To create an environment that would be more conducive to private investment, it is important that stem cell banking policies facilitate the sharing and eventual licensing of stem cell lines and accompanying data for research. To that end, agreements (i.e., MTA, MDA, RUL, etc.) need to be carefully designed to encourage future research use and possible commercialization of stem cell research downstream [94].

Fundamental uncertainties about intellectual property ownership and other contractual restrictions in the design of access policies for stem cell banks could prevent private investors from adequately protecting their interests as they could impede future commercialization [95]. To that end, an important decision when developing access policies developed by stem cell banks concerns limitations and ownership of future intellectual property rights. These rights can often be a source of dispute and of long negotiations between private companies, funding bodies, and universities [96].

In Europe, the unresolved conflation of patent requirements with ethics and morality [97] could, if contractually transposed to stem cell banking, create a major disincentive for the private sector. Moreover, if the opinion of the advocate general of the European Court of Justice was to prevail [98], products derived from hESCs in Europe would not be patentable. The negative implications for both commercialization and clinical translation of this position would be enormous and will extend beyond the European context.

While it is important that biobank access policies prevent parasitic patenting practices, imposing significant limitations and conditions on future intellectual property rights could have a negative impact on private uptake of academic research. It will not be sufficient to develop institutional or national stem cell banking policies that promote technology transfer; these policies will also need to be sufficiently harmonized to permit large scale international research projects [99]. Given the current nature of the stem cell industry [100], upstream transfer strategies that are less than optimally designed could slow down the transfer of promising research, or contribute to another breakdown in the private development of stem cell research downstream [101]. Thus, to ensure optimal technology transfer of results, there is a need to investigate the use of open access agreements upstream in the research process as well as the impact of these agreements on the ownership of patents downstream.

To this end, the Hinxton Group's 2011 Statement [44] encompasses ambitious recommendations seeking to improve the transparency and management of both intellectual property and commercial transactions, in order to foster innovation. Their recommendations promote the adoption of formal collaborative networks for stem cell banking, including the collective handling of intellectual property. They are a welcome reminder that the road towards the global governance of stem cell research and banking is yet to be traced.

3. Conclusion

Models of stem cell banking governance are beginning to address the sharing of data and samples across borders from the initial consent process to a system for evaluating and monitoring access requirements, together with intellectual property and commercialization issues [102]. While there is an acceleration in activities across a broad typology of biobanks [95], in practice access to samples and data is often hindered, particularly "when interoperability is sought, specific restrictions concealed in variable policies, procedures and contracts constitute an important hurdle" [103].

The international process of reciprocal recognition put in place following the adoption of the 1995 European Directive may be a way to foster accountability, transparency, and innovation in international stem cell banking governance [33]. The recognition of laws, policies, and consent from other countries as equivalent or at a minimum as substantially equivalent underlies the safe harbor approach [33]. Another avenue is the adoption of reciprocal agreements beyond the bilateral to the multilateral; however this too can become a burdensome contractual tool. Evidently, prospective harmonization and policy convergence is the ideal. In this regard, good faith efforts should begin now. Such harmonization serves not only to make stem cell banking efficient but also to respect the wishes of donors that their biological materials actually serve research in real time.

More importantly, efforts should be devoted to the challenges posed by social (i.e., distributive) justice issues related to equitable beneficence in terms of access to research and eventual therapies. Reciprocity for participating individuals and populations is an ethical imperative. A central step towards achieving these goals is to ensure diversity in order to accurately complete our modern societal mosaic. Diversity—through the entire research cycle—should be understood beyond proportionate ethnic representation, to encompass a wide representation of health disorders and conditions.

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