# STEM CELL BANKS
## investing in the promise of cancer stem cell science

The national and international demand for stem cell lines of varying origins (eg human embryonic, induced pluripotent, somatic) and grades (eg research, clinical) is growing. This is in response to the expectation that stem cell science will radically improve our ability to understand and treat disease, to develop model systems of drug development, and to generate novel clinical therapies. A sustainable supply of stem cell lines that are scientifically and ethically sourced is both a practical and legal prerequisite for the continued progression of stem cell research towards clinical therapies. To this end, stem cell banks have become an invaluable resource, providing access to ethically sourced stem cell lines that meet high quality and safety standards.

**By Madeline Page and Rosario Isasi**

The international nature of stem cell research is challenging national stem cell banks to navigate through complex and often divergent national regulations pertaining to the permissibility of stem cell research. Differences across banks and jurisdictions in technical practices, standard operating procedures and ethical and legal requirements can pose significant barriers to international collaboration, and if left unaddressed, can potentially limit the possibilities of stem cell research to deliver on its many promises. This article provides an overview of how stem cell banks are contributing to the advancement of stem cell research and clinical therapies, while highlighting the principal challenges and opportunities of the heterogeneous policy landscape.

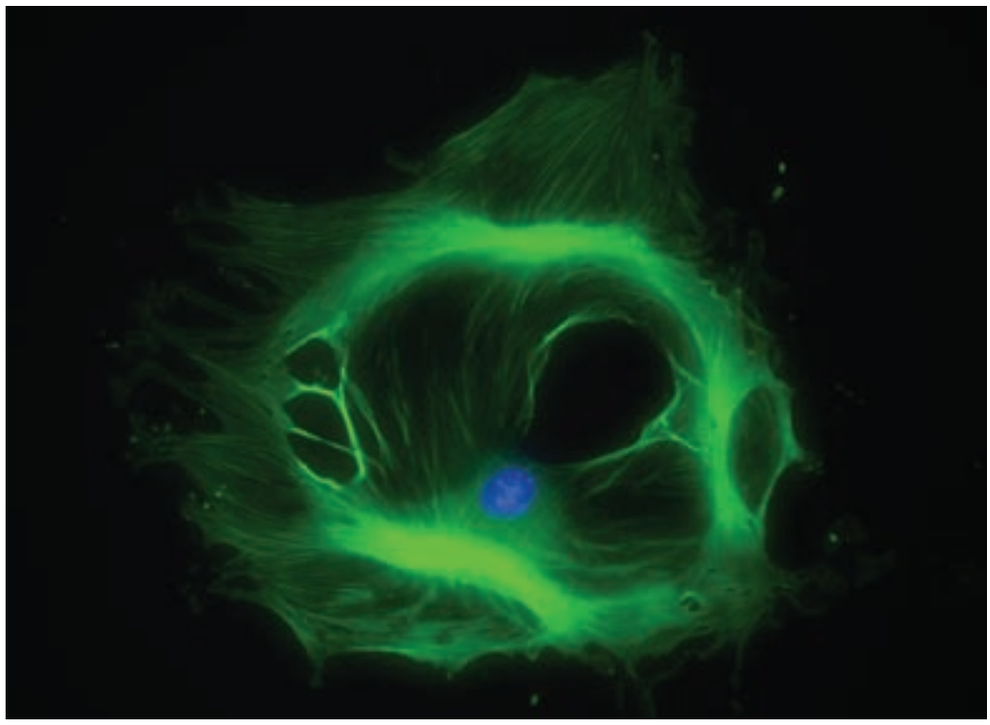
### The growing necessity of stem cell banks

The pioneering isolation and culture of human embryonic stem cells (hESC) in 1998[1], combined with the rapid developments of induced pluripotent cells (iPSC) since 2006, have led to the proliferation of stem cell research projects worldwide. Disease-specific iPS cell line research is leading to a better understanding of the patho-physiology of complex diseases[2], while the contribution of iPS research to personalised medicine is promising to generate autologous therapies[3].

One area of stem cell research that has generated particular attention is the field of cancer research. The identification of cancer stem cells (CSC) within a tumour has led some researchers to believe that CSC may be responsible for the development and perpetuation of several forms of human cancer[4]. Sharing similar properties to adult stem cells, CSC can self renew and differentiate, having the capacity to expand both the CSC pool, and the heterogeneous non-tumourgenic cells that constitute the majority of cells within a tumour[5]. Research suggests that by specifically targeting and eradicating the CSC rather than all the cells within a tumour, the cancer can be eliminated and traditional cancer therapy side-effects of toxicity and drug resistance be avoided[6].

The Cancer Stem Cell Consortium (CSCC) and the International Cancer Genome Consortium (ICGC) are two initiatives that are co-ordinating international cancer research projects with the aim of broadening the understanding of both the causes

Mammary epithelial stem cell progeny by Craig Aarts



of and cures for cancer. These international consortia foster strategic partnerships between cancer researchers worldwide to increase the amount and quality of research findings and to accelerate their translations into clinical applications. In particular, the CSCC has prioritised the need to identify CSC biomarkers and anti-CSC therapeutic agents, two goals that are dependent on researchers having access to sizeable repositories of high quality CSC[7].

The investigation of CSC presents tremendous opportunities for pharmaceutics and will have significant implications for cancer research and drug development[8]. However, much like other areas of stem cell research, cancer stem cell research is in its initial stages, requiring a better understanding of both CSC and SC biology[9]. The need for large-scale biobanks with large, well annotated cohorts of human biological materials is essential to ensure the reliability of data being generated, and to gain a more comprehensive knowledge of these complex and heterogeneous diseases[10]. Indeed, the National Cancer Institute (NCI) cites "the lack of standardised, high quality bio-specimens as one of the most significant road blocks to the progress of cancer research[11]". It is within this context that stem cell banks have emerged as an integral resource for the cancer stem cell research community, providing access to quality controlled and ethically sourced stem cell lines.

## Stem cell banks: repositories and registries

Stem cell banks (SCB) refer to a number of different kinds of institutions and operations[12]. SCB can include stem cell repositories that store biological specimens[13], such as the UK Stem Cell Bank (UKSCB) or the US Wisconsin International Stem Cell Bank (WISC). Alternatively, SCB can refer to stem cell registries that collect, organise and distribute cell line specific information[14], for example the European Human Embryonic Stem Cell Registry and the UMass International Stem Cell Registry. SCB can also be public (USKCB), institutional (Stem Cell Research Centre of Kyoto) or commercial (WISC). For our purposes, we use the term 'stem cell bank' broadly to encompass all of the above mentioned kinds of stem cell repositories and registries.

Stem cell repositories and registries hold distinct yet complementary value. Repositories accept, validate, store and distribute SC lines across jurisdictions[15], while registries catalogue the cell lines' scientific and ethical provenance, distributing this information to a wide range of stakeholders (eg researchers, funding institutions, oversight agencies, etc)[16]. By providing access to ethically sourced and high quality biological materials and data, SCB seek to minimise the need for derivation of additional cell lines, reduce redundancies in research projects and foster international research

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collaboration to accelerate the delivery of SC clinical applications.

SCB regulate the scientific and ethical quality of stored SC lines by subjecting all deposited biological materials to a rigorous set of technical and ethical standards. In terms of quality control, SCB aim to avoid cell line misidentification and cross contamination by meticulously screening all cells to verify their authenticity and their biological purity[17]. Simultaneously, SCB abide by strict standard operating procedures and implement comprehensive quality assurance programmes to regulate SC lines' preservation and storage within the bank. By enforcing these high quality and safety standards, SCB improve the quality of the entire production process and increase the likelihood that research results will be both reproducible and transferable into clinical applications.

In parallel, SCB only admit biological materials that have been derived according to national laws and high ethical standards. While the unique socio-ethical and legal frameworks regulating stem cell research vary considerably across jurisdictions, many SCB have embraced the fundamental ethical principles of research ethics such as respect for donor autonomy (informed consent, right to withdraw), respect for privacy and confidentiality (protection of donor identity), and the non-commercialisation of human biological materials (prohibition of monetary payments for donation). By requiring that researchers depositing or accessing SC lines abide by these principals, SCB can attest to the ethical provenance of the materials they distribute. At the same time, SCB secure public trust by adhering to good governance practices; for example, by having accountable, transparent and independent structures and advisory boards.

## But which standards to choose?

Stem cell research is becoming increasingly global with research teams stretching across national borders and biological materials being distributed internationally. Initiatives such as the Cancer Stem Cell Consortium are aiming to build cross-jurisdictional partnerships in cancer research, in one case between a variety of Canadian actors (researchers, government, funding agencies, NGOs and the pharmaceutics and biotechnology industry) and the California Institute of Regenerative Medicine. Similarly, the International Cancer Genome Consortium is further fuelling worldwide research collaboration, having gained funding for projects in 13 jurisdictions to study more than 17,000 cancer genomes in 50 different tumour types[18]. The presence of such large-scale multi-jurisdictional research is both beneficial and essential for the advancement of stem cell research, but also sheds light on the legal, ethical and policy challenges that SCB face when trying to work between different national policy frameworks.

To date, national policies governing stem cell research at all its stages (derivation, use, storage and distribution) differ substantially both within and between jurisdictions. Regulations pertaining to cell lines of embryonic origin are particularly contentious, given their political and moral controversies. Indeed, the international stem cell policy landscape has been characterised as a 'patchwork of patchworks', emphasising the complex and sometimes discordant regimes that dictate the scientific and ethical regulations of stem cell research[19]. The heterogeneous nature of current policy approaches and their lack of interoperability challenge stem cell banks to fulfill their mandate of promoting international collaboration and facilitating the seamless sharing of biological materials and data[20]. In response, a variety of initiatives have been launched to standardise scientific and laboratory practices and to harmonise ethical requirements across jurisdictions.

### Managing differences: between harmonisation and standardisation

#### 1. Scientific standardisation

In the context of international research, the standardisation of laboratory practices will be essential for SCB to create parallel technical conditions that will allow for predictable, stable and reproducible results. Particularly when working with SC lines that are genetically fragile and prone to differentiate, it is crucial to develop standard operating procedures for handling, storing and distributing SC lines. Simultaneously, SCB must agree upon common measures, protocols, classification systems and technical benchmarks that will enable researchers operating out of different laboratories and jurisdictions to easily communicate and compare results[21].

The standardisation scientific and technical requirements of stem cell banking have become the subject of numerous international initiatives. For example, in 2007 the International Stem Cell Initiative (ISCI) was established to compare and biologically characterise the majority of hES cell lines available across the globe. Such an initiative was deemed essential to enable research results from different labs in different countries to be compared in a meaningful manner[22]. In a similar vein, the International Stem Cell Banking Initiative (ISCBI) was created in 2007 to develop international minimum standards for banking, characterisation and

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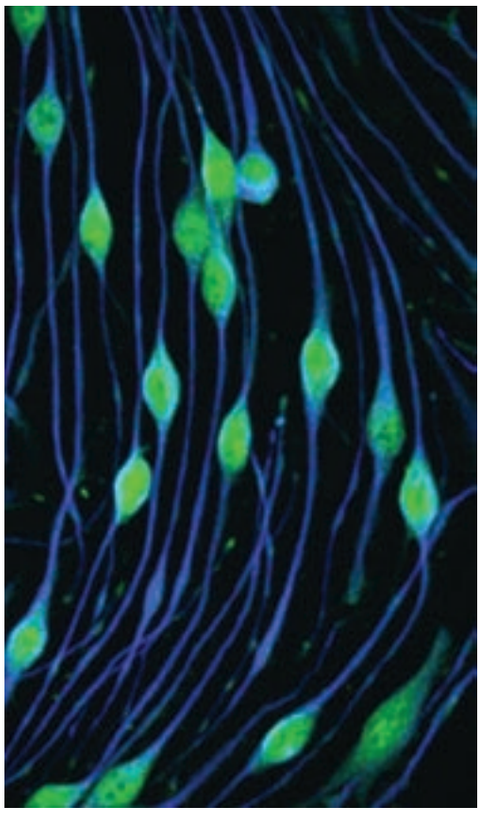

Skin-derived precursors differentiated into Schwann cells by Shaalee Dworski

testing of stem cell lines[23]. The goal of ICGC to create a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 tumour types and subtypes is also being driven by the objective of overcoming historical setbacks of discrepancies in scientific practices and quality measures across projects in different jurisdictions. The efforts of ISCI, ISCBI and ICGC have aimed to standardise laboratory practices as a way to ensure that data generated from different laboratories can be merged, and that subsequent results will be predictable, stable and reproducible[24].

**2. Bioethical harmonisation: SC banking governance**

In terms of the ethical requirements governing the permissibility of stem cell research, and the kinds of governance structures regulating SCB, policy convergence between jurisdictions is only beginning to emerge. While SCB have adopted common research ethics principles, differences in their detailed provisions and applications contributes to the continued 'patchwork' of policies across the international stem cell research landscape[25]. For example, while informed consent requirements for SC derivation, use and banking have steadily evolved alongside the innovations in stem cell research, policies still vary widely for embryonic and somatic sources[26]. Moreover, controversy persists as to whether broad consent to unspecified future research qualifies as an 'informed' decision, given that the participant's sample may be used for purposes that had not been anticipated at the time of initial consent. Finally, the majority of consent requirements do not address the international sharing of samples, casting uncertainty on the legality and ethics of cross-jurisdictional material data use and the secondary use of samples.

Similarly, provisions governing donor privacy and confidentiality also differ considerably between jurisdictions. When trying to balance the scientific utility of distributing samples that are linked to donors' biological characteristics such as genotype, phenotype and medical history, with the need to protect donors' privacy[27], SCB have arrived at different arrangements to safeguard donor confidentiality (eg anonymisation of sample vs data encryption). These arrangements are consequential, as anonymised SC lines that have been irreversibly stripped of all identifying information could be of limited value once distributed. While it is widely recognised that being able to trace SC lines to donor information (traceability) enables SCB to ensure the safety and the quality of SC lines throughout the entire research cycle, some jurisdictions have adopted regulations that inhibit traceability (eg mandating the anonymisation of SC lines)[28].

The varying policy frameworks governing the permissibility of conducting SCR have also led SCB to adopt different criteria in regards to depositing and accessing SC lines. For example, some SCB require absolute ethical and legal equivalency, whereas others have adopted more flexible approaches such as creating reciprocal policy agreements, or establishing a broad set of 'substantially equivalent' policies[29]. While all SCB require prior scientific and ethical review and compliance with legal and regulatory boards, the ability to verify the ethical, scientific and legal requirements of transnational practices is still under development.

The lack of interoperability of ethical and policy frameworks poses a significant challenge to international collaboration in stem cell research. That being said, initiatives are working to overcome current setbacks, pushing for greater harmonisation in ethical policies. The National Cancer Institute and ISCBI have both published 'Best Practice' guidelines for banking, addressing key ethical issues

such as custodianship, access, informed consent, privacy protection, data sharing and intellectual property[30]. The ICGC has also made strides to harmonise the ethical landscape by requiring that all members adopt core ethical principles, policies and procedures as a precondition of membership. Meanwhile, stem cell registries as catalogues of cell line information such as derivation, culture methods, protein expression and pluripotency are facilitating further harmonisation of ethical requirements and standardisation of technical practices.

## Conclusion: moving forwards

Establishing good governance of stem cell banks as a way to ensure their scientific and ethical integrity is crucial to promote public trust in both stem cell banks and in stem cell research. While the scope and governance structures of SCB may vary, national policies are converging on the need to promote transparency, stewardship and accountability. The establishment of independent and transparent public authorities to oversee the conduct of the banks, to grant licences, and to ensure that SCB receive ethical and scientific review[31] from independent committees[32] are crucial measures for the continued sustainability of SCB.

For stem cell and cancer stem cell research to move forwards with dynamism and to deliver their promising clinical applications, national SCB will be pressured to adopt prospective governance strategies that reflect the current global realities of stem cell research. By anticipating the international sharing of data and materials, and by keeping transparent internal governance and standard operating procedures, SCB will continue to move towards greater scientific standardisation and bioethical harmonisation.

Ethically sourced and high quality stem cell lines are the fundamental building blocks of future stem cell clinical applications and drug development. SCB are the necessary infrastructures to connect researchers and clinicians to these stem cell lines, permitting the sustainable evolution of stem cell science. The globalisation of stem cell research and the accompanying ethical, legal and policy challenges require that we approach the global governance of stem cell banks with the same creativity and flexibility that characterises innovation in stem cell science.

As initiatives to support technical standardisation and ethical harmonisation continue to facilitate the translation of stem cell research into clinical applications, SCB will be challenged to address new issues relating to commercialisation and access to research and therapies. SCB will be faced with difficult trade-offs between constructing policies that protect and promote the interests of society, open access and the transfer of technologies, with the need to provide sufficient incentives to attract private investment. Learning from the current challenges facing stem cell banks, it may be beneficial to address these questions concerning intellectual property within a collaborative network that is committed to advancing stem cell science.

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