Perspective

For reprint orders, please contact: reprints@futuremedicine.com

Regenerative Medicine

Bridging stem cell research and medicine: a learning health system

Seydina B Touré*[,1], Erika Kleiderman[1] & Bartha M Knoppers[1]

[1]Centre of Genomics & Policy, Department of Human Genetics, McGill University, Montréal, QC H3A 0G1, Canada

*Author for correspondence: seydina.toure@mail.mcgill.ca

Stem cells may not systematically obey traditional Phase I–IV clinical translation models. In response, various actors have suggested that stem cell-based medical innovation models could catalyze translation instead. Accordingly, calls were made to adopt more permissive approaches to stem cell translation. Yet, the Phase I–IV paradigm remains the standard within the scientific community. This article seeks to advance the stalemated discussions by proposing an alternative model for consideration. In it, we argue that a stem cell-based learning health system may be able to reconcile these two models. Centered on the acceleration of evidence and knowledge flow, a stem cell-based learning health system could maximize patient retention and data follow-up, thereby promoting inclusive system learning and improvement.

First draft submitted: 11 September 2017; Accepted for publication: 20 June 2018; Published online: 25 July 2018

Keywords: learning health system • regenerative medicine • stem cells

Amid 'stem cell tourism' safety concerns and the costs of regenerative medicine, the debate around clinical translation of stem cells is simmering. Some advocate traditional Phase I–IV clinical translation models to maximize patient safety. Others contend that permissive medical innovation policies could pave a path forward for stem cell translation. 'Medical innovation' was defined in the *Belmont Report* as a medical care departing significantly from standard practice [1]. Although both approaches have merit – indeed, phase-based translation ordained the primacy of safety while medical innovation has brought about advances such as anesthesia [2] and smallpox inoculation [3] – both suffer drawbacks. Stem cells are biochemically and pharmacokinetically complex and may fit poorly with Phase I–IV models [4,5]; while medical innovation is inherently risky. Yet, ignoring this debate or addressing it in a vacuum will only further alienate the growing number of patients who fly abroad to receive unproven treatments despite cautionary medical advice [6,7]. The obvious question flowing from this deadlock then is how these approaches could be reconciled.

As a matter of discussion, we suggest that a stem cell-based learning health system (hereafter scLHS) could be an interesting model to consider. As defined by the US Institute of Medicine, a learning health system (LHS) is *"designed to generate and apply the best evidence for the collaborative health care choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety and value in health care"* [8]. In short, it seeks to mutualize knowledge flow between bench and bedside by enmeshing clinical research with medical care.

The purpose of this article is to offer an alternative policy perspective to the ongoing debate on stem cell translation. It aims to spark conversation among stakeholders and does not purport to offer a fully developed translational model. To do so, the article unfolds in two parts. In part I, we explore the ways in which an LHS could be useful in the broader stem cell context. Namely, we first highlight the strengths of the scLHS model by contrasting it with conventional and other existing translational models. We then argue that by promoting patient retention and data follow-up, an LHS could mitigate the impact of 'stem cell tourism'. We conclude part I by deriving ethical principles from the history of bone marrow transplantation. In part II, we provide a high-level conceptual roadmap for the potential implementation of an scLHS.

Future Medicine

10.2217/rme-2017-0129

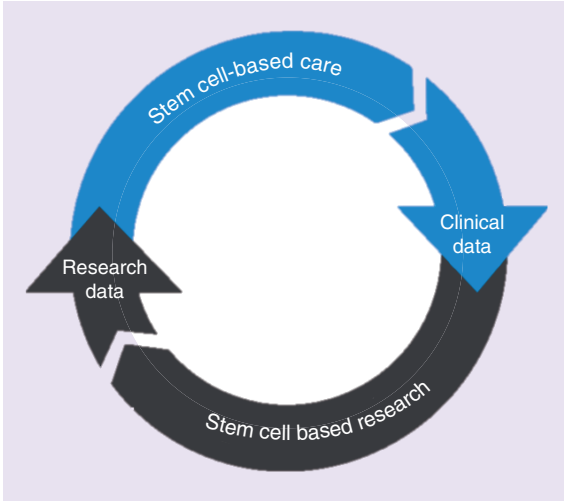

Figure 1. Knowledge flow in a stem cell-based learning health system.

The case for a stem cell-based learning health system

Despite the promise of regenerative medicine, progress has been slower than expected [9]. This is due in no small part to the sheer complexity of the discipline, and challenges associated with the generation of conclusive evidence. That said, the absence of both a unified objective and aggregated pursuits within the stem cell community are also contributing factors that ought to be recognized and addressed. Until this happens, this disaggregation will perpetuate scatteredness in stem cell science – exemplified by not only the divergence or uncertainty in standards (e.g., evidentiary [10], cost–effectiveness [11], taxonomic-nomenclatural [12]) but also by the intensification of the purveyance of unproven therapies. An scLHS would double as a centralized hub to maximize standardization and minimize research dispersion; distinguish legitimate scientific inquiry from illicit exploitation; and optimize resource use.

An essential clarification is that the purpose of an scLHS is not the 'acceleration of access' to stem cell therapies *per se*, but the 'acceleration of knowledge flow' and evidence generation. In that sense, it must be viewed neither as a substitute for stem cell clinics, nor as an 'enabler' of scientifically unsound therapies. Rather, it is intended to bridge the gap between stem cell research and medicine by cyclizing knowledge flow between bench and bedside (Figure 1).

To illustrate the value of an scLHS, we discuss three specific contexts: the contrast with existing translational frameworks; 'stem cell tourism' and patient data drain and the genesis of bone marrow transplantation.

Contrast with existing frameworks

Currently, translation in stem cell science relies largely on the Phase I–IV model. Undoubtedly, this paradigm has been an impressive response to the over-reliance on medical intuition and uncontrolled medical interventions [13]. Indeed, a number of stem cell clinical trials are being successfully carried out. Notably, per a recent report, at least 6% of the registered trials have reached Phase III or IV [14]. However, the overall success rate of drug development is approximately 12% [15]. This discrepancy reveals disproportionately low developmental success rates for stem cells. Although it does not necessarily mean that the phase-model is ill-adapted for stem cells, it may be symptomatic of structural impediments to knowledge flow and evidence generation – a major challenge to the progress of regenerative medicine.

While their virtues need no further recounting, the shortcomings of prevailing translation models in the stem cell context must be acknowledged (see Table 1). First, physicians who administer these therapies are presumably under pressure to reach internal validity, which in effect tightens patient selection criteria. This narrowed inclusion band may skew data toward a specific segment of the population. Extrapolating the analysis, a hypothesis could be made that disparity between early- and late-stage demographics (the latter requiring larger – by extension more heterogeneous – populations) may be a factor in the disproportionately high failure rates in late-stage trials. In relation to this, a second criticism is the fact that each trial is typically organized *de novo* [16] which, in combination with the fragmentation of stem cell research and lack of standardization [12], translates into unnecessary duplication and waste. In light of the time-, resource- and data-sensitive nature of stem cell science, this waste is particularly

Table 1. Contrast between existing translational frameworks and a stem cell-based learning health system

	Shortcomings of existing frameworks	How an scLHS addresses them
Adaptability	Limited adaptability of trial design (leading to resource waste upon failure)	Uses adaptive trial design
	New 'adaptive pathways' models, premised on acceleration of 'access to therapies', suffer from transparency issues	Avoids regulatory transparency issues by prioritizing acceleration of 'knowledge diffusion' (e.g., results)
Use of resources	Issues of standardization and harmonization leading to duplication and waste	Promotes harmonization and interoperability by bringing both stem cell research and care under a single, large-scale community undertaking
	Waste of resources stemming from the *de novo* requirement of clinical trial design	Avoids unnecessary duplication by accelerating knowledge flow (e.g., publication and adverse events)
	Limited inclusivity due to pursuit of internal validity	Adaptive, and pragmatic trial design models to increase inclusivity and absorb risk of late-stage failure early
Communication of results	No mandatory requirement for communicating results	– Built-in peer expectation (or requirement) to communicate results – Enables tracking of results, but also volume, gravity and predictability of adverse events – Reduction of stigma around negative results through universal requirement
'Compassionate use'	– Premised on access to therapies – Limited inclusivity, which undermines the objective of access to therapies – No robust ethical framework for patient contribution to access to knowledge	– Premised on access to knowledge – Features ethical framework for patient contribution to diffusion of knowledge
Influence of 'rogue' stem cell clinics	Vulnerable to 'sham' clinical trial registrations intended to lure unsuspecting patients	Distinguishes licit and illicit stem cell study. As a network, participation within an scLHS would be contingent upon satisfaction of minimum ethical standards. an scLHS could also double as a certification system
	Reputational damage to stem cell science and regenerative medicine	

scLHS: Stem cell-based learning health system.

problematic. Flowing from this, a third criticism is that current translation models have no mandatory requirement to communicate results. As we elaborate in the next subsection, only 45% of the completed stem cell trials have published results [14]. As a solution, the authors of this finding have advocated for journal-enforced standards. In contrast, an scLHS, being essentially a network of peers and colleagues, would have a built-in expectation (or requirement) to report (or publish) results. This would allow tracking of not only results, but also the volume, gravity and predictability of adverse events. Fourth, as elaborated below, the clinical trial model is prone to capture by stem cell clinics that may register clinical trials solely for financial gain [14]. These 'trials' are sometimes harmful to patients [17], 'sullying' the field along the way [13].

Emerging alternative translation models may also be insufficient. These models have emerged in response to the criticism that conventional phase-based models are too rigid to respond adequately to emerging knowledge [18]. High-profile responses include the European Medicine Agency's 'Adaptive Pathways' to translation, as well as the US *21st Century Cures Act.* Both of these frameworks emphasize 'adaptive' trial designs, which would allow changes and revisions of prior assumptions in ongoing clinical trials when new data emerge. Interestingly, in its concluding report, the EMA has indicated that the 'adaptive' trial model can *"support medicine development in [areas] where evidence generation is challenging, such as [degenerative diseases]"*. This is an interesting proposition for regenerative medicine, especially in light of the potential for long-term adverse events. However, the flaw in these legislative and regulatory responses lie in the fact that their primary objective is acceleration of access to therapies and not the acceleration of knowledge and evidence flow. While laudable, this objective may carry risk related to lack of regulatory transparency and governance [19].

'Compassionate use' models do not address the challenges raised by traditional translation models either. The reason is that these 'one-off' pathways are not only of limited use (by definition), but also are premised, like 'Adaptive Pathways', on access to therapies. In its 2016 guidelines, the International Society for Stem Cell Research attempted to reorient the premise of this pathway by recommending that the administering physician immediately move on to clinical trials [20]. While this effectively pulls 'compassionate use' toward the pursuit of generalizable knowledge, it merely tethers it to the clinical trial system and does not solve the shortcomings of the latter (discussed above). In addition to this, the lack of inclusiveness in patient selection discussed above is problematic. Put differently, the pursuit of positive results may cause the physician to be more selective which, ironically, undermines the very objective of increasing access. Finally, 'compassionate uses' lack the ethical framework to encourage patient

participation in the pursuit of knowledge [21]. This places this pathway in comparative disadvantage to LHSs, which, as some authors argue, ought to impose soft obligations for patient contribution [22].

'Stem cell tourism' & patient data drain

The solution to the stem cell translation debate cannot be reached in isolation, and must be informed by the issue of 'stem cell tourism' and data drain. To be clear, our usage of the phrase 'stem cell tourism' refers exclusively to the pursuit and commercial act of administering unproven and scientifically unsound stem cell-based treatments. In that regard, this article acknowledges the ethical and moral grey areas in the stem cell tourism conversation [23,24]. That said, our position is that an scLHS could mitigate the associated data drain by directly involving the patient.

For context, the paucity of data is a gap in stem cell science. As discussed above, only 45% of the completed trials had published results as of 2017 [14]. Additionally, none of the known stem cell tourism clinics had reported results. More concerning still is the increasingly sophisticated veneer of legitimacy of stem cell tourism clinics from manoeuvres like sham clinical trial registrations to lure unsuspecting patients [25,26]. These observations merely add to the underparticipation in clinical trials and underreporting of adverse events by stem cell clinics, with some said to discard patient data entirely [27]. The combined effects of these trends reflect a large-scale syphoning of otherwise clinically useful data away from domestic structures. Yet, the medical tourism market (of US$54.5–72 billion) is unrelenting, with a yearly growth rate of 15–25% [28]. Against this patient outflow, the issues of patient recruitment into legitimate clinical trials become stark. In the case of Geron's human embryonic stem cell trials, it took 18 months to enroll five patients, over multiple US study sites. In another case, *"[a] Phase I/II study for chronic spinal cord injury with umbilical cord blood mononuclear cells could not be completed in Hong Kong, due to the inability to recruit sufficient patients"* [9]. If we accept the premise that this market creates a zero-sum dynamic over patient data, we must recognize that this patient exodus transfers much of the costs of uncertainty onto domestic research structures. That is, patients who fly abroad take with them the potential of collecting data and advancing stem cell science. Indeed, when they receive unproven treatments, stem cell 'tourists' may become ineligible for clinical trials [29,30]. Against this drain, the human costs and opportunity costs of inaction may no longer justify the status quo.

An scLHS could alleviate this problem by maximizing patient retention and data recirculation. By design, one of the cornerstones of LHSs is to inform the research–care continuum with patient input. In a way, the patient becomes an active participant. Intuitively, when patients are personally invested in their healthcare, they are less likely to rely on foreign institutions. Notably, an scLHS would offer superior value to the modest postoperative care plans, low adverse event responsiveness and poor scientific bases of which 'rogue' stem cell clinics are accused of providing their services [31,32]. Interestingly, in the final report of the EMA's 'Adaptive Pathways' pilot, the first identified area of improvement was patient involvement. This will, per the EMA, *"provide insights on feasibility, ethical aspects, and [support for] enrolment in trials and registries"* [33]. Critically, by providing for centralized patient registries and involving patient communities, an scLHS should reasonably address underparticipation issues associated with low awareness of enrollment opportunities. As we discuss below, an scLHS can accommodate patient-centeredness and elevate the patient to a partner in the medical and research missions. In turn, the new knowledge feeds back into both the research and care realms to ensure continuous system learning and improvement. In terms of expected returns, improved patient selection and recruitment would be among the most noteworthy.

In this endeavor, an scLHS should not be a substitute for stem cell clinics. That is, where a treatment has no scientific rationale, such treatment should not be undertaken within an scLHS. In the stem cell tourism context, the value of an scLHS should instead lie in patient involvement and knowledge dissemination. After all, the anticipated benefit is that the direct involvement of patients will have a knock-on effect that will apprise the wider patient community of the real benefits and challenges of stem cell science and regenerative medicine. To do so, it should seek to mend the fracture between traveling patients and the research process.

The genesis of bone marrow transplantation

An scLHS has the potential to emulate the coming-of-age of bone marrow transplantation (BMT) – to this day one of the most frequently used stem cell-based therapies. Relying on rodent preclinical evidence, Thomas and colleagues began canine and human transplantation in the 1950s. They proceeded empirically and attracted criticism as a consequence [34]. Despite initial setbacks – indeed, mortality rates in their research were relatively high [13] – they continually refined and realigned their methods contemporaneously with medical science. Slowly, their procedure became increasingly efficacious, forging its way into standard medical practice. Although one could

argue that hematopoietic stem cells are different from other known stem cells (e.g., by virtue of the liquid state of blood), it remains undeniable that BMT reduced the morbidity and mortality of many ailments. Assuredly, it was an inflection point in medicine.

More relevant to our analysis is the fact that the methods of Thomas and colleagues had many of the hallmarks of an LHS. In addition to publishing their results and expanding scientific knowledge [35] (communication of results), they were continually readjusting their methods based on prior results and general science ('adaptive' experimental designs). Importantly, they reconciled patient care with the pursuit of generalizable knowledge by deriving research questions from their transplantation procedures and gradually overcoming substantive and procedural learning curves as a result (cyclized bench-bedside knowledge flow). Unsurprisingly, Thomas attributed the growing institutional familiarity in BMT to this latter activity [36]. It was subsequently demonstrated that experience and incremental integration of new knowledge were instrumental both in reducing mortality and economic burden of hematopoietic stem cell transplantation [37], but also in refining patient selection [38] (incremental, but continuous learning). Above all, a major feature of the advent of BMT was the synergistic deployment of resources toward a common objective (aggregation of pursuits). Similarly, this basic cohesion could be a vital strength for an scLHS.

The advent of BMT can also be instructive of a few principles. Thomas' experiments began a few years after the *Nuremberg Code* was published, a decade before the *Declaration of Helsinki*, and three decades before the *Belmont Report* was issued. To our knowledge, the *Nuremberg Code*, although nonbinding [39], was the only guide for human experimentation at the time. Yet, it is widely agreed that it had little impact on medical research practices [40]. What emerges then is the notion that the regulatory environment at the time of Thomas' experiments was more permissive than contemporary systems. This raises the question of whether BMT would have seen the light of day in today's regulatory and ethical climate. While this question is impossible to answer, our position is that an scLHS does not and should not mean deregulation. In the *Nuremberg Code*, which ideally should have guided Thomas' research, articles 3, 6 and 8 respectively provide for prior preclinical evidence; commensurability between the risk of the intervention and the severity of the disease and proper scientific expertise as prerequisites of human experimentation [41]. Regardless of the applicability of the *Nuremberg Code* at the time, these principles were all present in BMT research. Likewise, they should be part of the ethical framework of an scLHS. Within proper bounds, an scLHS could be a powerful catalyst for the pursuit of stem cell knowledge.

Conceptual roadmap: practical considerations for the potential implementation of a stem cell-based learning health system

If stem cell science is to fit within an LHS framework, the first consideration is to define its scope. This inherent restrictiveness flows from the fact that no single LHS can realistically accomplish all the goals set out in the Institute of Medicine's seminal paper. Indeed, of all the existing LHSs, none purports to fulfill every objective flowing from the Institute of Medicine's vision [42]. For example, the learn from every patient (LFEP) initiative, while undeniably effective, was limited in scope [43]. It was designed *"to systematically drive both clinical quality improvement and reduced healthcare costs"* for managing cerebral palsy in children within a single institution. Likewise, implementing an effective scLHS will require a targeted scope. Generally, the scope of an LHS can be broken down into its focus, objective, methodology and scale.

From this premise, we attempt to propose a conceptual roadmap for the potential implementation of an scLHS (depicted in Figure 2).

Focus

The focus of an scLHS is to be identified early in the decision-making process. Indeed, spanning the plurality of stem cell types, sources, to diseases and treatments [44], the field is currently too vast for a single scLHS.

For the purposes of identifying the primary focus of an LHS, stem cell type appears to be the most appropriate basis. We make this assertion on the grounds that stem cell type – as opposed to source, disease or treatment – is the greatest acceptable common denominator in stem cell literature. For example, a cursory search of a type of stem cell will yield results associated with not only relevant basic or preclinical research, but also clinical applications across the spectrum, as well as satellite research (e.g., economics/political economy, social science, etc.). In contrast, searches based on treatment types may yield an overly narrow range, while those based on disease type would displace stem cells out of focus, effectively defeating the purpose of an scLHS. As such, basing the focus of an scLHS on stem cell type may capture the widest range of relevant activity. One direct benefit would be that a greater number of stem cell experts would invest in the project and lend their expertise independently of the

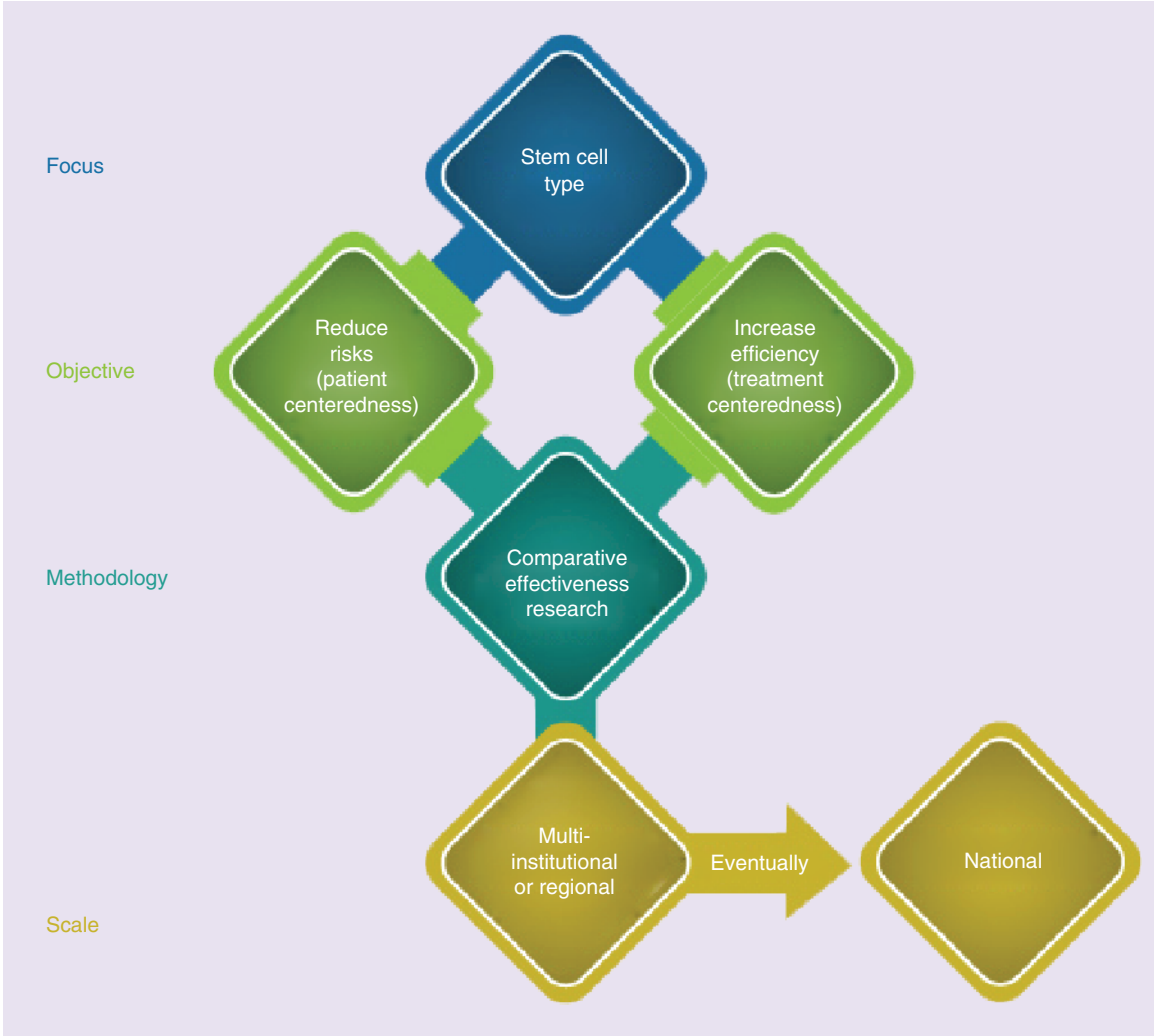

Figure 2. Conceptual framework for the potential implementation of a stem cell-based learning health system.

intended application within the LHS. Another benefit would be the acceleration of multidisciplinary exchange and knowledge flow both within a given stem cell specialty and with the patient community. Of course, determining that the primary point of focus should be the type of stem cell does not answer which stem cell type should be the focus of the LHS. Nevertheless, we consider this reflection to be beyond our expertise and view the scientific community as best placed for such an appraisal.

Objective

In the spirit of a targeted and more efficient approach, an scLHS must be guided by a specific objective. This has been a staple of all existing LHSs. The LFEP LHS, cited above, is one such example [43]. Another LHS, in Nova Scotia, seeks to *"develop a framework for incorporating patient engagement into administrative health database research"* [45]. Although we cannot prove the causal relationship between the effectiveness of an LHS and the specificity of its objectives, this relationship can reasonably be presumed. As a result, without any indication to the contrary, an scLHS should obey the same principle. At the highest level of generality, the objectives of an scLHS would fall under two overlapping, but distinct categories: to increase efficiency; or to reduce risks. As we illustrate below, at the heart of this question lies the tension between treatment-centeredness and patient-centeredness.

To increase efficiency (treatment-centeredness)

If the primary objective of the LHS is to increase efficiency, it follows that the analytical framework should be treatment-centered. Plainly, efficiency unfolds into two major components: treatment efficacy and costs.

The more an LHS emphasizes efficacy, the more it exposes patients to potential risk. This was clearly the case when Thomas and colleagues continued improving bone marrow transplantation in the face of high mortality rates [13]. While recognizing its merits, we do not recommend this approach. Instead, a more tempered, perhaps less risky approach would be more adequate. One such approach would be to test whether a technical change to a proven stem cell therapy would improve its efficacy in a given or new disease (e.g., aggressiveness of pretransplantation chemotherapy). Another approach would be to compare invasive (e.g., surgery) against noninvasive (e.g., drugs) interventions. Moreover, the risk toward the patient could be reduced by adopting rigorous patient selection criteria. Ultimately, the end- goal of such an scLHS would be to facilitate technical exploration of existing or novel stem cell therapies and fill evidence gaps. Admittedly, considering the multiplicity of scientific, ethical and economic challenges it would impose, an scLHS based on efficacy would be its most ambitious version. Still, we do not view it as an impossible undertaking and invite concerted action from the scientific, ethical and economic communities in both the public and private sectors.

In terms of costs, an scLHS appears well suited for medium- and long-term cost analysis and reduction. Stem cell therapies are inherently expensive and resource-intensive. And indeed, on this basis alone, some still question whether these therapies, even if efficacious, would be justified [46]. Should an scLHS be designed for cost-reduction, it could emulate existing, real-life models. The LFEP LHS, as discussed above, is one such model [43]. Even to the extent that the LFEP and the scLHS differ on specific grounds (e.g., LFEP focuses on reducing costs of standardized care and does not involve novel therapies), they would remain sufficiently analogous on the overarching objective of reducing the costs of otherwise expensive medical care. As such, we do not see an overriding reason to rule out a cost-oriented scLHS.

To reduce risks (patient-centeredness)

Alternatively, if the primary objective of the LHS is to reduce risks, then patient-centeredness principles should animate the scLHS. Stem cell therapies are procedurally risky. In addition, stem cells are pharmacokinetically unpredictable and long-lived. This makes them prone to medical misevaluation. Within an scLHS, there exist structural elements that could reduce risk. Among those, the capacity for centralized patient registries would be a valuable asset. Within such a system, patient feedback would be quickly integrated into the knowledge cycle. This feedback could in turn inform downstream issues such as treatment selection. Patient feedback could also inform decision-making on aspects related to patient selection such as cohort discovery, recruitment range and procedure. Encouragingly, these are only a few examples of possible objectives that could be pursued under a risk-oriented scLHS.

A related, but no less relevant, aspect of patient-centeredness considerations are concerns of misalignment between physician and patient outcome measurements. These mainly flow from the pressures on physicians to focus on functional endpoints (e.g., restoration of organ function) at the exclusion of alternative endpoints. This deficit is pronounced for patients who undergo stem cell-based treatments, and for whom functional outcome measurements may be less meaningful than alternative outcome measurements such as quality of life improvement. For example, while a stem cell physician treating multiple sclerosis may focus on restoration of neurological function, a patient may be more interested in whether they are able to go to work. Unsurprisingly, the relative weights of patient and physician outcome measurements would depend on the specific objective of the scLHS in question. However, as the adequacy of alternative end points remains largely a scientific question, it falls beyond the scope of this article. Nevertheless, choice of endpoint is a question that decision-makers will have to deliberate at the drawing board.

Methodology

Generally, we consider an adaptive comparative effectiveness research (CER) methodology to be best suited for an scLHS. The pith and substance of CER is captured by the phrase 'what works best' [47]. In that sense, it fits the mold of an LHS. Within the stem cell context, CER is adapted for either of the above-mentioned objectives; namely, improving efficiency or reducing risks.

In the case of improving efficiency, CER is adapted for addressing questions comparing stem cells against drugs; stem cells against stem cells (e.g., aggressive vs mild conditioning regimens); or more broadly, surgical against nonsurgical care. Within an scLHS, these inquiries are proper. Indeed, many correctly wonder whether stem cell

therapies, even if medically efficacious, would be justified on cost–effectiveness grounds. This irresolution leads to uncertainty in treatment selection. A CER methodology would be conducive to evidence-based conclusions about the general cost–effectiveness of stem cell-based therapies, thereby enriching the literature, whether scientific, economic or social. In turn, this evidence could be fed back into patient care for maximizing outcomes.

In the case of reducing risks, CER is also well suited for a patient-centered scLHS. Namely, the Patient-Centered Outcomes Research Institute has issued a methodology report for bridging CER and patient-centeredness [48]. More specifically still, the Washington-based CERTAIN initiative has shown that CER could be useful in LHSs for addressing not only uncertainty *"in treatment selection [but also] differences in desired outcomes between patients and clinicians"* [49]. Yet, as we noted in the previous section, the long-lasting and risky nature of stem cell therapies may lead to the splintering of physician and patient outcome measurements (functional vs quality of life, respectively). In response, CER within an scLHS could be designed for gathering evidence on procedural risks, as well as best practices on patient selection and retention. To that end, CER could address risk by embedding patient-reported adverse events within the scLHS's very data analytics apparatus for active accretion of evidence [50]. The scLHS may then leverage its information technology infrastructure to refine patient selection, recruitment and cohort discovery [51]. Incidentally, this latter activity has been identified as an area of improvement in hematopoietic stem cell transplantation in multiple sclerosis [52].

Scale

In terms of scale, the different levels include: single-institution; multi-institution or regional; national; or international. Currently, however, an international scLHS is impracticable. Any potential benefit would be far outweighed by the logistical and legal costs that it would incur. Only the first three options therefore appear viable.

In determining scale, the guiding concern is the cost of standardizing and transmitting information. In other words, the larger the scale of the LHS, the faster data can be acquired, warehoused, processed and integrated; but at the same time, the higher the costs for standardization, coordination and collaboration. Inversely, while a small-scale LHS would be less expensive, costs would presumably translate into longer data aggregation and integration cycles. Yet, against the backdrop of rising healthcare costs and stem cell tourism, stem cell science is sensitive to the timely maximization of data and evidence. Further, due to its high technicality and costs (i.e., manufacturing and cell processing), stem cell therapy is relatively rare and patient populations sparse [53]. On these bases, a single-institution scLHS would be impractical. Therefore, an scLHS must at a minimum be multi-institutional. Presently, this is the scale that we would prescribe for a pilot. Eventually, once the foundations are in place, a scale-up of this scLHS may be considered, as was done in the US when the ImproveCareNow LHS was scaled up nationwide into PEDSnet [54].

Interestingly, the question of infrastructure, though related only tangentially to that of scale, is also relevant to the calculus of an scLHS. Information technology (IT) infrastructure, in particular, is critical for electronic health record support, centralized patient registries, data sharing and processing as well as encryption and decryption for academic or medical inquiry. The PEDSnet and CancerLinQ LHSs, with patient populations of approximately 1.4 and 1 million respectively, have demonstrated the feasibility of large-scale sharing of electronic health information [54–56]. More relevant to stem cells still is the fact that the PEDSnet IT infrastructure, as referenced above, is said to facilitate patient selection as well as cohort discovery [51]. Undoubtedly, an scLHS would benefit greatly from similar computational capabilities. Therefore, investing in robust IT infrastructure for an scLHS is recommended.

Concluding thoughts

In this article, we put forward the notion of an scLHS as an alternative approach to current models of clinical translation regarding stem cells and regenerative medicine. We discussed the value of an scLHS and proposed a framework for its potential implementation. By placing research and care on a continuum instead of watertight silos, an scLHS enables the cohesion necessary to emulate the coming-of-age of hematopoietic stem cell transplantation. The knowledge generated from medical encounters could then be fed back into the system to streamline downstream research such as cost–effectiveness and patient selection. In addition, by directly engaging the patient, an LHS dampens the deleterious effects associated with patient outflow, namely data drain and human costs. The convergence of these benefits leads to continuous, systemic, professional and patient learning. To realize its promise, an scLHS must be targeted in scope, and designed with a clear focus, objective, methodology and scale.

Ultimately, whether an scLHS approach should completely replace, complement or simply permeate the clinical trial model is not currently clear. After all, some stem cell-based clinical trials are well-adapted to the phase model.

The precise delineation of an scLHS must be determined from a cost–benefit assessment – something that will require input and further discussion among stakeholders.

To conclude, it is accepted, and generally welcomed, that prevailing research ethics paradigms be animated by the primacy of subject safety. Yet, as a matter of perspective, analysis is often centered on the drug or treatment being tested, rather than the participant. To be clear, our intent is not to cast definitive judgement on the soundness of this approach. But as regenerative medicine develops, we think it appropriate to ask whether the finality of current paradigms will remain in sync with the changing nature of medicine. As Francis Moore cautioned, with mismatched ethical standards, *"one might be surprised to find that while he is protecting the individual patient, he is exposing society to the hazard of a static rather than a dynamic medicine"* [57].

Future perspective

Some issues remain before an LHS can be a reality in regenerative medicine. The ethical dimensions of the research–care distinction come first to mind. Another issue is the question of reimbursement. More specifically, there remains a general sense of dissatisfaction over the perceived unpreparedness of regulators vis-à-vis the high costs of next-generation therapies such as cell and gene therapies. For instance, in Japan, the fact that patients are expected to cover up to 30% of the costs of unproven stem cell treatments – the government bearing the rest – is unlikely to garner praise from commentators [25]. Similarly, in Canada, the cost of Prochymal, the first approved stem cell-based therapy [58], was slated to reach US$200,000 with no clear reimbursement policy in place [59]. In sum, research on reimbursement policies should be, or remain, a priority.

The continued disagreement over evidentiary standards also remains a challenge for learning health systems and stem cell translation. The EU, USA, Japan and even Canada have begun shifting evidentiary requirements for stem cell therapies toward 'adaptive pathways' [19,25,60,61]. These pathways rely on alternative clinical benchmarks such as surrogate end points and 'real-world' observational evidence when randomized controlled trials are deemed unfeasible. The backlash was swift. While some denounced the fact that patients would be unduly exposed to increased risk [19], others questioned instead the probity and validity of observational evidence in LHSs [62].

Executive summary

- Despite its promise, the development of stem cells and regenerative medicine has been slower than expected. This phase shift between promise and reality led to an ethical debate regarding the efficiency translational model for stem cells.
- This article suggests that a stem cell-based learning health system (scLHS) could offer a viable policy alternative to existing models.

The case for a stem cell-based learning health system

In the stem cell context, an scLHS will be useful in at least two ways:

- An scLHS could address various inefficiencies present in traditional clinical translation pathways, as well as emerging, alternative translational pathways.
- Stem cell tourism and loss of data
  - Through centralized patient registries, promotes streamlined patient selection and recruitment through increased awareness of clinical trial enrolment opportunities.
  - By promoting patient participation, patient retention and data recirculation, it will provide a counterweight to the paucity of stem cell data.
  - By exposing patient communities to the real limits of stem cell science, will have a dissuasive effect against the pursuit of unproven therapies.
- An scLHS has the potential to emulate the coming-of-age of hematopoietic stem cell therapy.

Conceptual roadmap: practical considerations for the implementation of a stem cell-based learning health system

As with all known LHSs, the initial scope of an scLHS should be limited in scale with a clear focus, objective and methodology:

- Focus
  - The focus of an scLHS should be based on stem cell type rather than source, disease or treatment type.
- Objectives
  - Improving treatment efficiency (treatment-centeredness): cost–effectiveness research or efficacy research.
  - Reducing risks (patient-centeredness): treatment selection, patient selection, patient-reported outcomes, among others.
- Methodology: comparative effectiveness research.
- Scale: multi-institutional or regional (with plans for eventual nationwide scale-up).

Although some stem cell therapies are more amenable to traditional standards (e.g., in knee-related treatments, randomization and blinding are possible by treating one knee with a placebo), the determination of evidentiary standards remains a question that must be addressed by the regenerative medicine community.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure

This work was funded by the Quebec Network for Cell, Tissue and Gene Therapy – ThéCell (a thematic network supported by the Fonds de recherche du Québec–Santé). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. National Commission for the Protection of Human Subjects of Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research – the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.* US Government Printing Office, DC, USA (1978).
2. Robinson DH, Toledo AH. Historical development of modern anesthesia. *J. Invest. Surg.* 25(3), 141–149 (2012).
3. Riedel S. Edward Jenner and the history of smallpox and vaccination. *Proc. (Bayl. Univ. Med. Cent.)* 18(1), 21–25 (2005).
4. Martell K, Trounson A, Baum E. Stem cell therapies in clinical trials: workshop on best practices and the need for harmonization. *Cell stem cell* 7(4), 451–454 (2010).
5. Hyun I. Allowing innovative stem cell-based therapies outside of clinical trials: ethical and policy challenges. *J. Law. Med. Ethics* 38(2), 277–285 (2010).
6. Ryan KA, Sanders AN, Wang DD, Levine AD. Tracking the rise of stem cell tourism. *Regen. Med.* 5(1), 27–33 (2010).
7. Levine AD, Wolf LE. The roles and responsibilities of physicians in patients' decisions about unproven stem cell therapies. *J. Law. Med. Ethics* 40(1), 122–134 (2012).
8. Institute of Medicine (US). Round table on evidence-based medicine. In: *The Learning Healthcare System: Workshop Summary.* The National Academies Press, DC, USA, 357 (2007). https://doi.org/10.17226/11903

•• **The Institute of Medicine's seminal paper on learning health systems.**

9. Rosemann A. Why regenerative stem cell medicine progresses slower than expected. *J. Cell. Biochem.* 115(12), 2073–2076 (2014).
10. Maschke KJ, Gusmano MK. Evidence and access to biomedical interventions: the case of stem cell treatments. *J. Health Polit. Policy Law* 41(5), 917–937 (2016).
11. Bubela T, Mccabe C, Archibald P *et al.* Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. *Regen. Med.* 10(7), 897–911 (2015).
12. Shen H. Stricter standards sought to curb stem cell confusion. *Nature* 499(7459), 389 (2013).
13. Daley GQ. The promise and perils of stem cell therapeutics. *Cell Stem Cell* 10(6), 740–749 (2012).
14. Fung M, Yuan Y, Atkins H, Shi Q, Bubela T. Responsible translation of stem cell research: an assessment of clinical trial registration and publications. *Stem Cell Reports* 8(5), 1190–1201 (2017).

• **A statistical account of the current stem cell clinical trial landscape accompanied by recommendations.**

15. Thomas DW, Burns J, Audette J, Carroll A, Dow-Hygelund C, Hay M. Clinical development success rates 2006–2015. Biomedtracker, BIO/Bend: Amplion, DC, USA (2016).
16. President's Council of Advisors on Science and Technology. *Report to the President on propelling innovation in drug discovery, development and evaluation.* Executive Office of the President, DC, USA (2012).
17. Forster K. Three women 'left blinded after botched stem cell trial'. *Independent* (2017). www.independent.co.uk/life-style/health-and-families/health-news/stem-cell-clinical-trial-women-blinded-patients-new-england-journal-medicine-thomas-albini-a7632051.html

18. European Commission. Relation between pharmaceuticals regulatory framework and timely access of medicines to patients: reflection on difficulties and opportunities (2014). https://ec.europa.eu/health/sites/health/files/files/committee/72meeting/pharm642.pdf
19. Lee T-L, Lysaght T. Adaptive pathways regulations for stem cells: accelerating access to medicine or deregulating access to markets? *SCRIPTed* 14(1), 81–99 (2017).
20. Kimmelman J, Heslop HE, Sugarman J *et al.* New ISSCR guidelines: clinical translation of stem cell research. *Lancet* 387(10032), 1979–1981 (2016).
21. Walker MJ, Rogers WA, Entwistle V. Ethical justifications for access to unapproved medical interventions: an argument for (limited) patient obligations. *Am. J. Bioeth.* 14(11), 3–15 (2014).
22. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning healthcare system: a departure from traditional research ethics and clinical ethics. *Hastings Cent. Rep.* 43(1), S16–S27 (2013).
23. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. *Science* 324(5935), 1664–1665 (2009).
24. Sleeboom-Faulkner ME. The large grey area between 'bona fide' and 'rogue' stem cell interventions: ethical acceptability and the need to include local variability. *Technol. Forecast. Soc. Change* 109, 76–86 (2016).
25. Sipp D. Conditional approval: Japan lowers the bar for regenerative medicine products. *Cell Stem Cell* 16(4), 353–356 (2015).
26. Kuriyan AE, Albini TA, Townsend JH *et al.* Vision Loss after intravitreal injection of autologous 'stem cells' for AMD. *N. Engl. J. Med.* 376(11), 1047–1053 (2017).
27. Cohen CB, Cohen PJ. International stem cell tourism and the need for effective regulation: Part I: Stem cell tourism in Russia and India: clinical research, innovative treatment or unproven hype? *Kennedy Inst. Ethics J.* 20(1), 27–49 (2010).
28. Medical Tourism Statistics & Facts. https://patientsbeyondborders.com/medical-tourism-statistics-facts
29. Nine things to know about stem cell treatments. www.closerlookatstemcells.org/stem-cells-and-medicine/nine-things-to-know-about-stem-cell-treatments
30. Master Z, Caulfield T. Patient booklet: What you need to know about stem cell therapies (2014). www.amc.edu/academic/bioethics/documents/SCPatientBookletFeb_2014.pdf
31. Hiltzik M. Lawsuit against stem cell clinic Stemgenex can move forward: judge rules. *Los Angeles Times* (2017). www.latimes.com/business/hiltzik/la-fi-hiltzik-stemgenex-lawsuit-20170418-story.html
32. Matthews KR, Iltis AS. Unproven stem cell-based interventions and achieving a compromise policy among the multiple stakeholders. *BMC Med. Ethics* 16(1), 75 (2015).
33. European Medicines Agency. *Final Report on the Adaptive Pathways Pilot* (2016). www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf
34. Gale RP. E Donnall Thomas (1920–2012). *Leukemia* 27(2), 259 (2013).
35. Main H, Munsie M, O'connor MD. Managing the potential and pitfalls during clinical translation of emerging stem cell therapies. *Clin. Transl. Med.* 3 10 (2014).
36. Blume KG, Forman SJ, Appelbaum FR. *Thomas' Hematopoietic Cell Transplantation*. Blackwell Publishing Ltd, MA, USA, 457 (2004).
37. Waters TM, Bennett CL, Pajeau TS *et al.* Economic analyses of bone marrow and blood stem cell transplantation for leukemias and lymphoma: what do we know? *Bone Marrow Transplant.* 21(7), 641–650 (1998).
38. Farge D, Passweg J, van Laar JM *et al.* Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Ann. Rheum. Dis.* 63(8), 974–981 (2004).
39. Research Ethics Policy. www.humanrightsatsea.org/wp-content/uploads/2015/09/20150905-HRAS-Research-Ethics-First-Edition-Locked.pdf
40. Bracken-Roche D. Reconsidering 'vulnerability' in research ethics: a critical analysis and proposal for the refinement of this concept (thesis). McGill University Libraries, Quebec, Canada (2016).
41. The nuremberg code. *JAMA* 276(20), 1691 (1996).
42. Lessard L, Michalowski W, Fung-Kee-Fung M, Jones L, Grudniewicz A. Architectural frameworks: defining the structures for implementing learning health systems. *Implement Sci.* 12(1), 78 (2017).

- **A prescriptive, high-level analysis of the architectural frameworks of learning health systems.**

43. Lowes LP, Noritz GH, Newmeyer A *et al.* 'Learn from every patient': implementation and early results of a learning health system. *Dev. Med. Child Neurol.* 59(2), 183–191 (2017).
44. Li MD, Atkins H, Bubela T. The global landscape of stem cell clinical trials. *Regen. Med.* 9(1), 27–39 (2014).

- **A statistical survey of the stem cell clinical trial landscape.**

45. Mcdonald T, Krause J, Anne L *et al.* Patient engagement as a component of a learning healthcare system: a case study using small area rate variation research in Nova Scotia, Canada. *IJPDS* 1(1) (2017).
46. NICE issues final guidance on axitinib (Inlyta) and sipuleucel-T (Provenge). www.firstwordpharma.com/node/1265415?tsid=17

47. What is CER? www.hsph.harvard.edu/comparative-effectiveness-research-initiative/definition/
48. Methodology Committee of the Patient-Centered Outcomes Research I. Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *JAMA* 307(15), 1636–1640 (2012).
49. Devine EB, Alfonso-Cristancho R, Devlin A *et al.* A model for incorporating patient and stakeholder voices in a learning healthcare network: Washington state's comparative effectiveness research translation network. *J. Clin. Epidemiol.* 66(8 Suppl), S122–S129 (2013).
50. Basch E. New frontiers in patient-reported outcomes: adverse event reporting, comparative effectiveness and quality assessment. *Annu. Rev. Med.* 65, 307–317 (2014).
51. Forrest CB, Margolis PA, Bailey LC *et al.* PEDSnet: a national pediatric learning health system. *J. Am. Med. Inform. Assoc.* 21(4), 602–606 (2014).
52. Atkins HL, Bowman M, Allan D *et al.* Immunoablation and autologous haemopoietic stem cell transplantation for aggressive multiple sclerosis: a multicentre single-group Phase 2 trial. *Lancet* 388(10044), 576–585 (2016).
53. Nagamura F. The importance of recruiting a diverse population for stem cell clinical trials. *Curr. Stem Cell Rep.* 2(4), 321–327 (2016).
54. Forrest CB, Margolis P, Seid M, Colletti RB. PEDSnet: how a prototype pediatric learning health system is being expanded into a national network. *Health Aff. (Millwood)* 33(7), 1171–1177 (2014).
55. Bailey LC, Milov DE, Kelleher K *et al.* Multi-institutional sharing of electronic health record data to assess childhood obesity. *PLoS ONE* 8(6), e66192 (2013).
56. CancerLinQ. https://cancerlinq.org/
57. Moore FD. Therapeutic innovation: ethical boundaries in the initial clinical trials of new drugs and surgical procedures. *CA Cancer J. Clin.* 20(4), 212–227 (1970).
58. Cyranoski D. Canada approves stem cell product. *Nat. Biotechnol.* 30(7), 571–571 (2012).
59. The next stem cell controversy: pricing. http://busaconsultingllc.com/scsi/organelles/the_next_stem_cell_controversy.php
60. Avorn J, Kesselheim AS. The 21st century cures act: will It take us back in time? *N. Engl. J. Med.* 372(26), 2473–2475 (2015).
61. Reicin C, Mcmahon E, Chung C. Stem cell therapy regulation in Canada: implications of the prochymal approval. *Westlaw J.* 28, 1–4 (2012).
62. Dahabreh IJ, Kent DM. Can the learning healthcare system be educated with observational data? *JAMA* 312(2), 129–130 (2014).