REVIEW / SYNTHÈSE

Stem cells and regenerative medicine — future perspectives

Keith R. Brunt, Richard D. Weisel, and Ren-Ke Li

Abstract: Stem cell research has expanded at an exponential rate, but its therapeutic applications have progressed much more slowly. Currently, the research focuses on understanding embryonic, adult, and inducible pluripotent stem cells. Translation of adult stem cell research has established a definitive benefit that is greater than that of the current standard of care in the field of cardiovascular medicine. The future of stem cell research and therapy will continue to provide novel avenues of diagnostics, therapeutics, and tissue regeneration. Here we discuss a brief history of stem cell research as it transitioned from the 20th to the 21st century. We address lessons learned in the first decade of the new millennium that could help guide others to translate research into therapy across disciplines. Finally, we highlight future goals and challenges that must be overcome and offer some perspective on the bright future of stem cell research and therapy.

Key words: stem cells, regenerative medicine, history, future, clinical.

Résumé : La recherche sur les cellules souches avance d'une façon exponentielle, mais ses applications thérapeutiques ont progressé beaucoup plus lentement. Actuellement, la recherche se concentre sur la compréhension des cellules souches tant embryonnaires qu'adultes et pluripotentes inductibles. La recherche translationnelle sur les cellules souches adultes a montré un bénéfice définitif qui est supérieur à celui des standards de soins actuels dans le domaine de la médecine cardiovasculaire. L'avenir de la recherche et de la thérapie avec les cellules souches continuera d'ouvrir de nouvelles avenues dans le diagnostic, la thérapeutique et la régénération tissulaire. Nous présentons ici un bref historique de la recherche sur les cellules souches et discutons de sa transition du 20^{ième} au 21^{ième} siècle. Nous traitons des leçons apprises au cours de la première décennie du nouveau millénaire qui pourraient aider à guider les autres à transférer leur recherche vers la thérapie, à travers les disciplines. Finalement, nous mettons l'accent sur les objectifs et les défis futurs qui devront être surmontés, et nous offrons une certaine perspective du brillant avenir de la recherche et de la thérapie avec les cellules souches.

Mots-clés : cellules souches, médecine régénératrice, histoire, avenir, clinique.

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Stem cells — a history brief

The goal of this review is to discuss the origins of stem cell research and recent studies and to provide a future perspective, particularly for young scientists whose imaginations will drive research examining stem cells and regenerative medicine into the unknown over the next 10 years. Based on previous experience, scientists attempt to predict the future and discover new knowledge and apply new understanding. Scientists rely on their vision to plot a course and sustain public interest, with foreknowledge that the course will be dynamic, possibly disappointing, or maybe even in direct opposition to their predictions. The process of discovery relies heavily on both healthy scepticism and considerable reflection on past and present knowledge. We must also prepare ourselves to undertake the work necessary to achieve our lofty goals when the hype ebbs. What will stem cell research look like in 2020? Carl Sagan wrote, "You have to know the past to understand the present."

Stem cell terminology began at the turn of the 20th century as German scientist and Darwinist Ernst Haeckel merged concepts of phylogeny and ontogeny to describe the *stammzelle* (stem cell), an evolutionary concept for a primordial cell that evolves into all cells and multicellular organisms. Haeckel's argument was generally given as self-evident from his observations of embryo development and the distinction between fertilized and nonfertilized eggs. Stem cells, as a term, officially entered the scientific vernacular when used

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by other histoembryologists, such as Theodor Boveri and Valentin Haecker, who described the hereditary characteristics of germ cells (spermatogonia and oocytes), developed the term pluripotency (the ability to become all adult cells), and established the definitive characteristics of a stem cell as self-renewal and differentiation into somatic (adult) cells (as reviewed by Maehle 2011). Hematologist Artur Pappenheim also presented the notion of stem cells in describing a postulate for a common cell origin that could produce both red and white blood cells (Pappenheim 1917). Premodern scientists like Conheim and Pappenheim also conceptualized the idea of stem cells in the formation of tumours and leukemia (Cohnheim 1877; Pappenheim 1907). From these first observations, 3 decades followed before the first evidence for single-cell self-renewal was demonstrated by the ability of leukemia cancer cells to transmit cancer from a single cell (Furth and Makhn 1937).

By the mid-20th century, identification of histocompatibility proteins and graft-versus-host disease provided the basis for the hypothesis of immunologic tolerance. When the hematology and immunology fields converged in 1955 through the widespread study of the effects of radiation, it was shown that bone marrow reconstitution ensured successful skin grafts (Main and Prehn 1955). It was through similar reconstitution experiments that the stem cell theory was proven correct in 1961 by Canadian scientists Dr. James Till and Dr. Ernest McCulloch, who provided definitive evidence for the existence of hematopoietic stem cells (HSCs) and confirmed for the first time the unitarian view of hematology. Fifty years of research would follow, much of it led by McCulloch's own protégé, Dr. John Dick, who introduced a modern cancer stem cell theory and recently identified the univariate HSC (Notta et al. 2011). Hundreds of thousands of patients have survived leukemia because of Till and McCulloch's seminal findings. More recent studies have demonstrated that stem cell transplantation is a unique, although not ideal, treatment for autoimmune disease that also shows curative potential for HIV using a genetically HIV-resistant bone-marrow donor. There is currently widespread acceptance in clinical medicine for HSC therapies. However, numerous tissue-specific or resident stem cells have been described in the epidermis, intestine, brain, and to varying degrees in all somatic tissue and organs of the adult body. An outstanding question for all somatic tissue stem cells is, are these stem cells reticent to development, or are itinerant bone marrow populations predisposed to resident tissue differentiation, transdifferentiation, or mimicry?

The existence of stem cell self-renewal was postulated 4 decades before the proof was established in 1961 by studying somatic stem cells of the hematopoietic system. Pioneering work involving pluripotent stem cells gained traction 2 decades later in 1981 with the successful isolation and culture of embryonic stem cells (ESCs) from the inner cell mass of blastocysts (pre-embryos) by British and American scientists (Evans and Kaufman 1981; Martin 1981). A scientific revolution for studying the embryonic to somatic cell transition was made possible for the first time, including the ability to study ESC self-renewal and differentiation outside the developing embryo. Even so, despite the availability of the method, it took Canadian scientists an additional 12 years to achieve the difficult and essential proof of ESC self-renewal and pluripotency (totipotency) by generating living mice entirely from ESCs in 1993 (Nagy et al. 1993). Just 5 years later, in 1998, the ability to isolate human ESCs was described for the first time by American scientist Dr. James Thomson, revealing the possibility of a pluripotent stem cell as a source for new organs (Thomson et al. 1998). However, controversy over human cloning techniques and embryo destruction during ESC sourcing was in part the failure of scientists to adequately engage the general public, which resulted in policies that limited ESC research.

That position, however misguided, was untenable, since a series of fundamental discoveries forever altered the ESC debate and redirected our understanding of the pluripotent and the static somatic cell state. In 2006, an unimagined realization arose from the laboratory of Japanese researcher Dr. Shinya Yamanaka — that somatic cells could revert to a pluripotent-like form through re-expression of key embryonic genes suppressed in the somatic state (Takahashi et al. 2007). A new concept of induced pluripotent stem cells (iPSCs) was established. It followed that a pluripotent cell could also be produced by somatic cell nuclear transplantation into blastocysts (French et al. 2008). Further eroding any semblance of an argument from the anti-stem cell position was the discovery that ESCs could be isolated without destruction of the embryo (Chung et al. 2008). Together, these discoveries provided an opportunity to produce pluripotent stem cells while avoiding ethical objections and immunological rejection by using the recipient's own cells. The pace and excitement for stem cell research continue to grow exponentially. For example, in contrast to the 12 years it took for Canadian scientists to generate mice from ESCs, Chinese and American scientists were able to generate living mice derived from iPSCs just 3 years after the Japanese discovery (Boland et al. 2009; Kang et al. 2009; Zhao et al. 2009). Given the pace of discovery and the imagination it evokes, it is not surprising that huge expectations of superhero proportions have grown around the field of stem cell research. Stem cell research (not therapy) is at near-exponential rates of growth. Although many definitive works have been established, there is still room for young scientists to make significant advances.

Despite 2 decades of discovery that have detailed somatic and ESC states, there are significant gaps in our understanding of stem cells and their environments. Only a few hundred clinical trials of somatic stem cell therapy have entered phase III, and only 3 phase I clinical trials using ESCs have been approved since 2010.

Stem cells — the cusp of translation

Appropriate clinical trials are usually undertaken after extensive basic science and solid reproducible preclinical evidence. Attempts are made to achieve clinical benefits with the implementation of the best interventions to date, and the results, improved over time, become a new standard of care. Early clinical trials of stem cell therapy ultimately resulted in a series of mixed positive and disappointing negative results. However, from each successive trial, new questions arise that can be explored or from which refined methods can be developed. It is essential that scientists and their supporters bravely take a long view on scientific objectives and their translation to therapy. As a result of past research successes

in pharmacology, diagnostics, and patient management, the proportion of patients surviving acute myocardial infarctions has increased dramatically. However, many of these survivors slowly progress into heart failure because they lack functional recovery. As the leading cause of mortality and morbidity in the developed world, cardiac disease has provided fertile ground for early work in translating stem cell research into clinical therapy. A look back over the past decade should provide insights into how we proceed in the near future.

The ability to culture cells was established 60 years ago (Scherer et al. 1953) and was initially exclusive to cancer cell lines. However, in 1960, Dr. Isaac Harary and Dr. Barbara Farley first cultured mammalian cardiomyocytes from rats in the United States (Harary and Farley 1960, 1963). Yet it was 35 years later that the concept emerged of injecting cardiomyocytes into the heart (Soonpaa et al. 1994; Li et al. 1995) to provide functional benefit following myocardial infarction (Leor et al. 1996; Li et al. 1996). The question that quickly arose was, what will be the source of cardiomyocytes for patients whose hearts are already damaged or diseased? As new research results emerged showing that bone marrow mesenchymal stromal cells had many of the properties of multipotent mesenchymal stem cells, Italian and Japanese scientists demonstrated that mesenchymal stem cells could differentiate into skeletal or cardiac muscle (Ferrari et al. 1998; Makino et al. 1999). The bone marrow offered an attractive cell source owing to its abundance and accessibility for autologous stem cell therapy. In what was to become a seminal translational study, Canadian scientists transplanted bone marrow stem cells into the injured heart of rats and observed improvements in cardiac function (Tomita et al. 1999). With the start of the 21st century, cardiac cell therapy merged with regenerative medicine, as Orlic and colleagues independently confirmed the therapeutic benefit of bone marrow stem cell transplantation following myocardial infarction and detailed the ability of bone marrow cells to regenerate myocardium (Orlic et al. 2001).

However, before optimization in preclinical models (Li et al. 2001), and prior to subsequent refutations against the regenerative mechanisms responsible for the benefits of bone marrow stem cells (Balsam et al. 2004; Murry et al. 2004), the first human patient received bone marrow injections into their myocardium on 30 March 2001, in Germany (Strauer et al. 2001). Within 5 years, autologous stem cell therapy for the myocardium reached its peak of hype and hope (Assmus et al. 2006; Lunde et al. 2006; Schächinger et al. 2006) as clinicians and scientists settled in to deliver on promises. The past 10 years of basic and clinical studies have produced important findings, generated substantial controversy, and raised new questions for the future of cardiac cell therapy, as detailed elsewhere (Strauer and Steinhoff 2011). The general lessons and conclusions that can be drawn from the past decade are important for the next decade of research.

There is little doubt that significant therapeutic gains were achieved through the application of stem cell based therapies compared with the current standard of practice for cardiac interventions (Reffelmann et al. 2009). It is generally acknowledged that unmanipulated bone marrow stem cell populations are unlikely to differentiate to cardiomyocytes to replace those lost from a myocardial infarction. However, the hematopoietic compartment does contain a variety of regenerative cells that can be mobilized from the circulation or directly transplanted into the myocardium to improve cardiac function. In lieu of differentiation, bone marrow stem cells produce humoral factors that increase host cell survival, promote angiogenesis, reactivate cardiomyocyte proliferation, or stimulate resident stem cells (Gnecchi et al. 2005; Chimenti et al. 2010; Loffredo et al. 2011). Alternatively, or additionally, stem cells likely play a reductionist role to buffer oxidative stress and matrix degradation or attenuate the effects of negative cytokines in the local microenvironment (Brunt et al. 2012). Although survival is preferred (Nakamura et al. 2006; Mouquet et al. 2011), even transplanted stem cells that die can provide a boost to the host tissue by passing on additional organelles or substrates and by inflammatory modulation through apoptosomes, microparticles, or cell fusion (Nygren et al. 2004; Thum et al. 2005; Ankersmit et al. 2009; Lichtenauer et al. 2011*a*; Lichtenauer et al. 2011*b*). The hematopoietic compartment remains the safest and most accessible, abundant, and renewable autologous source for stem cell therapy to date, although skeletal myoblasts, adipose-derived stem cells, and, more recently, resident cardiac progenitors are also meritorious.

From long-term follow-up and retrospective meta-analysis, it has clearly been demonstrated that stem cell therapy provides significant benefit to patients — just not to all patients. Some patients did not benefit, some benefited marginally, and some demonstrated significant benefits, but these nonuniform outcomes are currently unpredictable. Discord in clinical protocols can partly explain the early failure to deliver the functional improvements observed in young healthy animals. The age and the effect of disease on the stem cell source and (or) the host organ are likely the most significant detractions on measured outcomes. Clinical studies were engaged before long-term follow-up and age- and disease-appropriate preclinical studies could be performed. This is an active deficiency in most clinical trials. Further, even with optimal cell availability, scarred, failing, old, diseased hearts do not respond well to stem cell therapy. Very likely, stem cell therapy alone will be insufficient and will require adjuvants such as gene therapy, cell-based gene therapy, or tissue engineering techniques to stimulate and complement the intervention. The mechanisms responsible for stem cell homing, retention, survival, integration, and function in normal, aged, and diseased systems are still not understood. Most investigators agree that the best cells or the best combination of cells and other therapies has not been identified. Tissue engineering likewise struggles to find its place in cardiac regeneration owing to the limited knowledge of heart remodelling. Until these limitations are better understood, the ability to translate stem cell therapy universally to our patients is stymied. However, we must not lose sight of the success gained.

There is a growing focus toward building on the best knowledge to date and establishing standardized, quality-controlled, good manufacturing processes and protocols for the isolation and reintroduction of cells. This is a critical, but labour-intensive, process that requires numerous patients and long-term follow-up. Since it does not generate hype, it necessitates commitment (funding) from all involved parties for team-based public and private or philanthropic sector partnerships across multiple centres (and multiple countries).

There is growing uncertainty as to whether there are enough translational scientists with sufficient background in both the basic and clinical sciences to accomplish these tasks over the next decade. Alarmingly, there is a depreciating trend to invest in junior personnel across all disciplines in both academia and industry. For future research goals to be reached, significant investment and long-term planning are needed in the intellectual economy at the university, institutional, hospital, and industrial levels to recruit, retain, and encourage young scientists.

Stem cells — back to the future

Given the possibilities of stem cell therapy, expectations have been raised to superhero proportions (Burns 2009). Is it realistic to expect stem cell therapies to be successful in regenerating damaged organs and treating chronic, degenerative conditions for which we can offer few other options? Perhaps. But first we must recognize the challenges ahead and commit to overcoming them (Table 1).

Unlike traditional off-the-shelf therapeutic agents, stem cell therapy is currently limited by the availability of biological substrate from the patient. This presents a unique problem, in that the afflicted patient population could be depleted of stem cells in the organ most in need of therapy, or in the systemic stem cell reservoir (bone marrow) as a consequence of chronic disease or age. In addition, with diseases such as restenosis (Wang et al. 2006) or cancer (Scarlett et al. 2011; Xiao et al. 2011), a contributing factor or causative pathology implicates stem cells directly. It is necessary to examine either combinations of adjuvants and autologous stem cell therapy or to pursue allogeneic stem cell sources. Adjuvant therapy can combine stem cells with new pharmacology, bioengineering, or gene therapy to enhance the therapeutic utility of stem cells for expansion or function. A system of standardized protocols for producing or combining stem cells and adjuvant therapy for clinical intervention could also be considered based on the specific needs of the individual patient. Exploring these combinatorial approaches and moving them toward clinical therapy is an important future direction. Also, an attractive future option is the use of iPSC sources. However, establishing the safety and efficiency of inducing pluripotency in cells from aged and diseased patients under clinical timelines will require extensive research. An alternative to pluripotency could be direct cell reprogramming, such as turning fibroblasts directly into cardiomyocytes while avoiding a pluripotent stage (Ieda et al. 2010). Alternatively, we could access and store stem cells in advance from healthy young donors.

Allogeneic stem cell sources can be obtained either from healthy adult donors or from pluripotent sources such as ESCs. An allogeneic source is an attractive option for overcoming quantity, age, and disease limitations, since stem cells can be harvested in sufficient quantity in advance and made available for widespread storage and distribution. A cell bank of allogeneic stem cells representing the permutation of all human histocompatibility is attractive and not entirely inconceivable. The issue of tissue compatibility remains one of the greatest unaddressed challenges. Although undifferentiated stem cells from embryonic (Swijnenburg et al. 2008*a*) and adult (Huang et al. 2010) sources have immune privilege, this is lost upon differentiation. As such, more work is needed to define whether a therapeutic benefit is achievable before cell differentiation and rejection occur. In consideration of the therapeutic paracrine effects from stem cells, it may not be necessary for stem cells to differentiate to be beneficial. It may be necessary, however, to either prolong the immune privilege (adjuvant cloaking device) or perfectly match histocompatibility profiles between the host and allogeneic donor. Since a pluripotent source is capable of nearly unlimited expansion, these cells could address both quantity and compatibility issues. However, a prerequisite is that they be safely produced and free of pluripotent cells before transplantation to avoid teratomas. Depletion of cell populations using pluripotent markers has been used in this regard (Blin et al. 2010). Interestingly, autologous sources should, theoretically, provide a rejection-free source of iPSCs, yet this concept was recently challenged (Zhao et al. 2011), suggesting that reactivation of the embryonic gene program may result in undesirable genetic "choices" in histocompatibility during reprogramming. This raises important ethical questions about reintroducing a patient's own highly manipulated cells (of any type), since the reintroduction could produce unforeseen reactions. It is therefore important for all fields of stem cell therapy that clinical trials follow substantive preclinical evidence.

A balanced approach in the basic and preclinical sciences is needed to determine the most effective stem cell source and protocol for intervention to redress pathologies we still do not fully understand. Therefore, it is important to acknowledge that the only sure way to know whether a protocol for stem cell selection and method of delivery is effective is to conduct a clinical trial. For future successes in stem cell therapy, it will be important to build broader collaborations to achieve genuine clinical translation. In the past, attempts at commercialization of stem cell therapy were unsuccessful. Leveraging private and public resources to produce off-the-shelf stem cell sources for clinical protocols is more likely to succeed and should be embraced more in the future. In addition, future work will be required to determine the most effective methods to track stem cell efficacy in real time. An extensive interaction will be required between disciplines, such as the engineering and biological sciences, to develop novel techniques for functional monitoring of stem cells and the recipient organs. Additionally, biological and epidemiological collaborations could provide a means to predict whether additional positive outcomes are likely using a patient's stem cell health as a guide.

The future of stem cell research and therapy is bright for young scientists. Over the next decade, it is likely that at least one or more stem cell therapy protocols will become the standard of care for cardiac patients. However, there will be a need over the next 10 years for scientific due diligence to maximize the efficacy of stem cell therapy and the number of patients receiving benefit. It is unlikely that pluripotent stem cell sources will enter standard practice in the cardiac field in the immediate future. There will be a high burden of proof to show that a pluripotent source is safe, necessary, or superior to then current guidelines of autologous cell therapy. Despite this, work should continue, as autologous therapy is only effective when there is sufficient cardiac mass remaining to be recovered. Also, there are several conditions that re-

Table 1. Comparison of the advantages and disadvantages of stem cells.

Type	Advantages	Disadvantages	References
Embryonic stem cells	Pluripotent, unlimited quantity, heritable gene defect correction, off-the-shelf product potential, broad biomedical applications	Allogeneic rejection, limited accessibility, complicated differentiation, teratoma risk	Zhang et al. 2002; Rideout et al. 2002; Swijnenburg et al. 2008*a*, 2008*b*; Bel et al. 2010; Lin et al. 2010; Lü et al. 2010; Song et al. 2010; Dai et al. 2011; Deuse et al. 2011; Xiong et al. 2011
Induced pluripotent stem cells	Pluripotent, autologous, pathology-specific cell production, broad biomedical applications	Susceptible to autologous pathology, low induction efficiency, awaiting standardized production, complicated differentiation, teratoma risk, methodological oncogenesis, induced histoincompatability	Maherali and Hochedlinger 2008; Nelson et al. 2009; Miura et al. 2009; Woltjen et al. 2009; Blin et al. 2010; van Laake et al. 2010; Bar-Nur et al. 2011; Mauritz et al. 2011; Pearl et al. 2011; Narsinh et al. 2011
Hematopoietic stem cells	Multipotent, paracrine effects, autologous, standardized isolation, many biomedical applications	Susceptible to autologous pathology, unable to sustain cells ex vivo, limited number, limited accessibility, limited to hematopoietic lineage	Nygren et al. 2004; Fujita et al. 2007; Templin et al. 2008; Ha et al. 2010; Sun et al. 2010; Li et al. 2010
Mesenchymal stem cells	Multipotent, paracrine effects, autologous, standardized isolation, many biomedical applications	Susceptible to autologous pathology, complicated accessibility, low transdifferentiation potential	Miyahara et al. 2006; Hare et al. 2009; Quevedo et al. 2009; Schuleri et al. 2009; Hatzistergos et al. 2010; Huang et al. 2010; Lee et al. 2010; Chong et al. 2011
Endothelial progenitor cells	Unipotent, paracrine effects, autologous, high accessibility, many biomedical applications	Susceptible to autologous pathology, low quantity, undefined or undefinable immunophenotype, awaiting standardized isolation	Werner et al. 2005; Abou-Saleh et al. 2009; Desai et al. 2009; Frederick et al. 2010; Achneck et al. 2011; Hynes et al. 2011; Richardson and Yoder 2011
Organ-specific precursors (e.g., CSCs, NSCs, SkMBs, PSCs)	Unipotent, autologous, organ-specific applications	Susceptible to autologous pathology, low quantity and (or) accessibility, undefined phenotype(s), awaiting standardized isolation	Andersen et al. 2009; Domian et al. 2009; Hansson et al. 2009; Lee et al. 2011; Le Belle et al. 2011; Leri et al. 2011; Smart et al. 2011; Smukler et al. 2011

Note: CSCs, cardiac stem cells; NSCs, neural stem cells; SkMBs, skeletal myoblasts; PSCs, pancreatic stem cells.

quire cardiac reconstruction, which is likely to be achieved only from a pluripotent source. Further, new methods of diagnosis and high-throughput therapeutic screening will emerge with epigenetic or patient-specific pluripotent cell lines established through standardized production. This will open new opportunities for pharmacologic screening and a basic understanding of development, physiology, and pathology.

Beyond the cardiac field, assuming active phase I trials with ESCs for macular dystrophy, macular degeneration, and spinal cord injury are safe (ClinicalTrials.gov identifiers NCT01345006, NCT0134493, and NCT01217008), the number of clinical trials may grow at an unprecedented rate. There will be an ethical obligation to pursue these trials, and they will likely expand the scope of stem cell therapy in traumatic injury, type I diabetes, muscular dystrophy, Parkinson's disease, or even multiple sclerosis and amyotrophic lateral sclerosis. There are many lessons from the cardiac field that will be invaluable. As in the cardiac field, there will be a need to first initiate preclinical and then clinical trials that address and optimize for safety, stem cell procurement, age, disease, current care, route of administration, dosing, and timing. A growing number of highly qualified personnel will be needed in all sectors of government and in basic, clinical, and industrial science to meet this emerging demand.

Stem cell research and therapy have just begun to provide clinical deliverables. It required a decade to move from first-in-man trials to a definitive retrospective conclusion for the application of autologous stem cell therapy in cardiac recovery. The benefits to health care providers will emerge over a similar period of time. Should investment grow over the next decade, we should see translation happen much sooner and more broadly as we learn from the past. It is important to communicate and establish standardized protocols early in preclinical and clinical trials. Age- and disease-appropriate models are essential and should also consider the type of therapy (pharmacology) already provided to the patients. In the electronic information age, conference organizers could be more focused on standardizing terminology, developing standards of practice, and communicating active trials. Investing heavily in young scientists and educating more translational scientists from both a clinical and basic science background is important. The concept of expanding the number of individual clinical scientists could also include clinical and basic scientist partnerships. Academic researchers should carefully review alternative approaches to knowledge translation. More extensive industrial partnership will be necessary to provide new treatments for all patients requiring therapy. Effective stem cell therapy relies heavily on multicentre trials in all phases. It is important to build multicentre and international partnerships and collaborations, perhaps through shared funding opportunities. However, we conclude with the cautionary fact that we still do not fully understand many of the diseases we hope to treat. Stem cell therapy does offer new promise for therapy, but it cannot succeed without a thorough understanding of our expectations, which is achievable only through extensive basic science.

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