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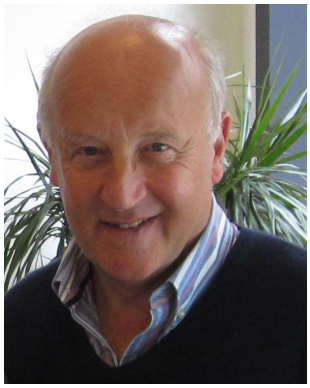
EDITORIAL

STEM CELLS TRANSLATIONAL MEDICINE

An urgent need for standardization of stem cells and stem cell-derived products toward clinical applications



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Stem cells are defined by their abilities to self-renew and differentiate into various cell lineages with the physiological "SMART" feature,[1,2] which makes them attractive cell sources for the treatment of a broad range of diseases requiring tissue regeneration, such as hematopoietic/immune diseases, cancers, and many other degenerative disorders.[3] In addition to hematopoietic stem cell (HSC) transplantation, which has been the classic stem cell therapy used mainly for hematopoietic diseases, other tissue stem cells and embryonic stem cells (ESC) or induced pluripotent stem cell (iPSC)-derived cell products also offer unique or alternative regenerative sources for stem cell therapies.[3,4] However, despite enormous progress in basic stem cell research during the past two decades since the establishment of human ESC lines, and especially the later Nobel-winning iPSC technology, translation of many basic discoveries on stem cells into clinical practice has been disappointingly limited and, problematically, some unproven stem cell therapies still exist.[5] One of the bottleneck factors limiting the pace of translational stem cell medicine is the significant lack of stem cell standardization and guidelines for many stem cell therapies. Back in 2000, the Cellular, Tissue, and Gene Therapies Advisory Committee meeting in Gaithersburg, Maryland, held by the U.S. Food and Drug Administration (FDA), recommended that the regulations for other cellular therapy products could also be applied to stem cell products.[6] In 2009, the FDA revised and established a set of regulations and guidelines to improve the safety of regenerative therapy.[7] Recently, the International Society for Stem Cell Research issued new guidelines for the clinical application of stem cell products.[8] In light of this regulatory guidance, aiming to best serve our patients,[9] specific standard measures for each type of stem cell product are an essential requirement. This issue is even more important and urgent for China, where stem cell science has rapidly risen to the front line and a higher expectation has been set for stem cell products to serve the most populated nation in the world.[10] Therefore, it is necessary and would be valuable to share the views and practical guidelines on this important topic to better meet the need in the field.

This Special Edition of *STEM CELLS Translational Medicine*, inspired by the proceedings of the seventh International Forum on Stem Cells (IFSC) held in Tianjin in November 2020, illustrates the prevailing view that advances in stem cell biology are bringing regenerative medicine a step closer. In particular, this issue contains a number of review articles summarizing the current advances in stem cell translation and the development of reliable standardization for preclinical assessment of stem cell products.

In the first of two Perspectives, Haidan Chen describes how the complexities of translating scientific discovery into clinically efficacious stem cell therapy are managed in the Tianjin model of stem cells translational medicine. The author shows how scientific, technological, social, economic, and political variables are coordinated in the efforts to make cell therapy available in China. Dr Chen goes on to compare the perceived strengths and weaknesses of the Tianjin model with translational programs in Europe and the United States.

In the second Perspective, Shi-Jiang Lu and Qiang Feng assess the impact of new methods for producing chimeric antigen receptor (CAR) T cell "off-the-shelf" therapeutics. Natural killer (NK) cells are specialized immune effector cells that recognize and kill target cells without human leukocyte antigen restriction or prior sensitization,

and do not cause graft vs host disease. NK cells are currently in clinical trials to treat a spectrum of hematological malignancies and solid tumors. Importantly, NK cells can be obtained from pluripotent stem cells (PSCs), which can be manipulated genetically and engineered with CARs to enable the establishment of permanent, stable, and clonal PSC-CAR cell banks. The development of next-generation 3D bioreactor platforms provides for PSC expansion and NK cell production that overcome the major cost and scalability barriers to produce unlimited homogeneous CAR-NK cells. These inexhaustible cell sources can be used for standardized targeted immunotherapy, in "off-the-shelf" mode for patients with cancer, viral infection, and autoimmune disease.

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into an array of cell types, including osteoblasts, chondrocytes, myocytes, and adipocytes. Their immunomodulatory and antimicrobial properties and capacity for self-renewal while maintaining multipotency have generated intense interest in their potential applications in regenerative medicine. The review by Zhongchao Han and colleagues presents an update on the regulatory procedures required for MSC products to achieve investigational new drug status to enable their clinical use in China. It provides useful guidelines for a cohesive approach by scientists, biotech companies, and clinical trial investigators involved in the development of MSCs as therapeutic products.

Brain degeneration and damage are difficult to treat because of the limited repair capability of the central nervous system. Human pluripotent stem cell-derived neural cells provide a promising source of cells with the potential for use in the treatment of neurological disease. Baoyang Hu and colleagues review the biological characteristics of neural cells, the status of preclinical studies, and the perceived prerequisites for effective translation of stem cell-derived neural cells into therapy for neurological disorders.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a widely used procedure in which patients with leukemia receive healthy blood-forming stem cells from a donor to replace their own cells that have been destroyed by treatment with radiation or chemotherapy. Ideally, the transplanted HSCs will engraft successfully, reestablish immunity rapidly, and exert a graft vs leukemia effect, without causing severe graft vs host disease in the patient. To date, purified HSCs have not been isolated, and there is no uniform standard for optimizing grafts in allogeneic transplantation. Xiao-jun Huang and Zheng-Li Xu discuss the ongoing efforts to investigate the cellular elements responsible for the effects of allo-HSCT, graft manipulation approaches, and different graft sources, with the overarching aim of defining a uniform standard for optimized grafts.

Xuetao Pei and colleagues review advances and barriers to progress in the production of red blood cells and platelets from human cord blood hematopoietic stem/progenitor cells (CB-HPSCs). To date, information on the clinical translation of stem cell-derived red blood cells and platelets is sparse, both in the literature and at the ClinicalTrials.gov website. The authors propose biological standards for the use of these CB-HPSC derivatives in clinical applications. Further technological advances in blood cell expansion and maturation ex vivo and the establishment of biological standards for stem cell derivatives should facilitate the clinical applications of cultured red blood cells and platelets derived from CB-HSPCs in the short to medium term.

Ischemic vascular disease caused by damaged vasculature reduces blood supply to the tissues and is a major cause of mortality and morbidity worldwide. Many endothelial stem/progenitor cell candidates have been proposed to repair damaged vasculature. Some cell preparations have shown encouraging results in preclinical studies, but the benefits to patients in clinical trials have been inconsistent. Reinhold Medina et al. discuss the current challenges for effective translation of cellular therapies for vascular repair and regeneration and propose potential strategies to overcome the challenges. Among these, the importance of a stricter definition of the molecular marker profile combined with functional assays to define endothelial stem/progenitor cells is emphasized.

Zimin Sun and colleagues discuss the development of umbilical cord blood transplantation (UCBT) and global trends in its clinical usage over the past 30 years. Once considered as medical waste, umbilical cord blood is rich in HSCs, which are naïve and more readily expanded than other stem cells. The authors define the challenges and strategies for the improvement of UCBT, encompassing procedures to increase UCB numbers, cord blood unit selection, conditioning regimen, and graft vs host disease prophylaxis for UCBT, as well as the management of complications associated with UCBT.

Autologous hematopoietic stem cell transplantation (ASCT) is an important post-remission treatment for acute leukemia in China. It is well recognized that cytogenetic and molecular risk stratification and minimal residual disease status are closely related to clinical outcome following ASCT. In addition, multiple factors, such as pretransplant treatment, stem cell mobilization, conditioning regimens, and maintenance treatment after transplantation, affect prognosis after ASCT. Erlie Jiang and colleagues appraise the optimization and quality control measures for ASCT developed at the Institute of Hematology and Blood Diseases Hospital of the Chinese Academy of Medical Sciences aimed at enhancing best practice and improving patient outcome.

Finally, the Meeting Report recounts the topics, speakers, and question and answer sessions that followed each of the 28 presentations at IFSC 2020 and provided the inspiration for this Special Edition of *STEM CELLS Translational Medicine*.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

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REFERENCES

1. Cheng T. Toward 'SMART' stem cells. *Gene Ther*. 2008;15:67-73.
2. Yuan S, Sun G, Zhang Y, Dong F, Cheng H, Cheng T. Understanding the SMART features of hematopoietic stem cells and beyond. *Sci China Life Sci*. 2021 Jul 30:1-15.
3. Blau HM, Daley GQ. Stem cells in the treatment of disease. *N Engl J Med*. 2019;381:890.
4. Desgres M, Menasché P. Clinical translation of pluripotent stem cell therapies: Challenges and considerations. *Cell Stem Cell*. 2019; 25:594-606.
5. Sipp D, Caulfield T, Kaye J, et al. Marketing of unproven stem cell-based interventions: A call to action. *Sci Transl Med*. 2017;9:eaag0426.
6. Moos M Jr. Stem-cell-derived products: An FDA update. *Trends Pharmacol Sci*. 2008;29:591-593.
7. Fink DW Jr. FDA regulation of stem cell-based products. *Science*. 2009;324:1662-1663.
8. Lovell-Badge R, Anthony E, Barker RA, et al. ISSCR guidelines for stem cell research and clinical translation: the 2021 update. *Stem Cell Rep*. 2021;16:1398-1408.
9. Lomax GP, Torres A, Millan MT. Regulated, reliable, and reputable: protect patients with uniform standards for stem cell treatments. *STEM CELLS Translational Medicine*. 2020;9:547-553.
10. Yuan W, Sipp D, Wang ZZ, et al. Stem cell science on the rise in China. *Cell Stem Cell*. 2012;10:12-15.