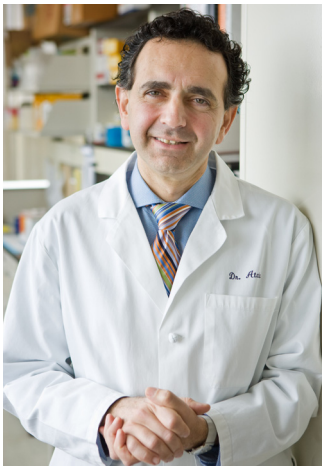
Received: 13 January 2021 | Accepted: 13 January 2021

DOI: 10.1002/sctm.21-0016

EDITORIAL

STEM CELLS TRANSLATIONAL MEDICINE

STEM CELLS Translational Medicine: A Decade of Evolution to a Vibrant Stem Cell and Regenerative Medicine Global Community



Anthony Atala
Editor-in-Chief, *STEM CELLS Translational Medicine*

Wasn't it just yesterday that we published the first review editorial covering the best and most cited papers of the first year of *STEM CELLS Translational Medicine*? Here we are, entering our 10th year—thousands of articles have been submitted and many printed, highlighting the groundbreaking research being conducted around the world and resulting in an impressive body of research.

Our sister journal, *STEM CELLS*—the brainchild of our visionary publishers from AlphaMed Press, Drs. Ann and Martin Murphy—was first published in 1983 and was the first journal in the history of the entire field. *STEM CELLS Translational Medicine* was created 3 decades later at an ideal time when the stem cell field, long an area of inquiry and basic research, was maturing to the point where therapies were entering the realm of clinical translation. We are grateful to CIRM and to Quintiles (now IQVIA) for their founding grants that helped launch *STEM CELLS Translational Medicine*. Stem cell therapies and regenerative medicine have the potential of eventually repairing or replacing tissues with damage from disease. Clinical translation requires many areas of expertise, including preclinical research, technology transfer, process development, regulatory adherence, manufacturing, quality assurance, quality control, clinical trial design, and human trials. By helping to disseminate knowledge based on the emerging discoveries from the laboratory into clinical trials and bedside applications, *STEM CELLS Translational Medicine* ultimately aims to improve patient outcomes.

Over the years, the journal has been able to attract the best work in the field. In honor of our 10th anniversary, we highlight a selection of the Most Cited Articles of the first decade of our journal. The most cited articles are mainly representative of the evolving progress we have seen develop through research worldwide and cover 3 major areas: stem cell research; stem cells byproducts, such as extracellular vesicles; and research that has advanced to human clinical trials.

Four of the most cited papers of the decade represent the natural evolution we have seen with different specific stem cell topics: human pluripotent stem cells, adipose tissue-derived multipotent stromal cells, perivascular stem cells, and amniotic fluid-derived stem cells. At the time of publication of "Rapid and Efficient Directed Differentiation of Human Pluripotent Stem Cells into Retinal Pigmented Epithelium," by Clegg and colleagues[1], retinal pigmented epithelium cells derived from human embryonic stem cells were in clinical trials for the treatment of age-related macular degeneration. The protocols to generate retinal pigmented epithelium from human pluripotent stem cells were time-consuming and relatively inefficient. The 2013 study by Clegg and colleagues[1] found that the addition of defined factors at specific times leads to conversion of approximately 80% of the cells to a retinal pigmented epithelium phenotype in only 14 days. The authors' work showed that their protocol would be useful for rapidly generating retinal pigmented epithelium for transplantation as well as for studying disease development in vitro. In the article "Adipose Tissue-Derived Multipotent Stromal Cells Have a Higher Immunomodulatory Capacity Than Their Bone Marrow-Derived Counterparts," Roelofs and colleagues[2] systematically compared the immunomodulatory capacities of bone marrow-derived multipotent stromal cells and adipose tissue-derived multipotent stromal cells derived from age-matched donors. They found that while the immunomodulatory capacities for bone marrow-derived multipotent stromal cells and adipose tissue-derived multipotent stromal cells are similar, the differences in cytokine secretion cause the former to have more potent

immunomodulatory effects. The authors showed that lower numbers of adipose tissue-derived multipotent stromal cells evoke the same level of immunomodulation, indicating thar they can be considered as a good alternative for immunomodulatory therapy. The article, "Perivascular Stem Cells: A Prospectively Purified Mesenchymal Stem Cell Population for Bone Tissue Engineering," by Soo and colleagues[3], reported the use of fluorescence-activated cell sorting to purify human perivascular stem cells from adipose tissue and compared their bone-forming capacity with that of traditionally derived stromal vascular fraction. The resulting work proposed that adipose-derived human perivascular stem cells were a new cell source for efforts in skeletal regenerative medicine and are a stem cell-based therapeutic that may be readily approvable by the U.S. Food and Drug Administration, with potentially increased safety, purity, identity, potency, and efficacy.The article "Bioprinted Amniotic Fluid-Derived Stem Cells Accelerate Healing of Large Skin Wounds," by Soker and colleagues[4], investigated whether amniotic fluid-derived stem cells could augment wound healing in a mouse model of skin regeneration. The researchers used 3D bioprinting to deliver cells within a polymer gel to a full-thickness skin wound, facilitating quick wound coverage and closure. The research presented in this article demonstrated that bioprinter-mediated deposition of stem cells in hydrogels has the potential to build tissues and organs from the ground up.

Three of the most cited papers in the first 10 years of the journal highlight research related to stem cell by-products. In "Human Umbilical Cord Mesenchymal Stem Cell Exosomes (hucMSC-Ex) Enhance Angiogenesis Through the Wnt4/β-Catenin Pathway," Xu and colleagues[5] isolated and characterized exosomes that promoted the proliferation, migration, and tube formation of endothelial cells in a dose-dependent manner. The authors further demonstrated that hucMSC-Ex promoted wound healing and angiogenesis in vivo by using a rat skin burn model. Their results proposed that these cells and their exosomes could be an important mechanism for cutaneous wound healing. In the article "Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression," Hermann and colleagues[6] looked to define whether extracellular vesicles derived from stem cells improve postischemic neurological impairment and brain remodeling. The authors postulated that if extracellular vesicles mediate their restorative action by equilibrating peripheral immune responses, blood measurements might provide an "elegant strategy" for monitoring the therapeutic responses to mesenchymal stem cell-derived extracellular vesicles. They predicted that with stringent proof-of-concept strategies, it might be possible to translate this therapy from rodents to human patients, providing clinically relevant evidence warranting rapid proof-of-concept studies in stroke patients. In the article "Mesenchymal Stem Cell-Derived Extracellular Vesicles as Mediators of Anti-Inflammatory Effects: Endorsement of Macrophage Polarization," Tasso and colleagues[7] looked at how mesenchymal stem cell paracrine activity favors tissue repair modulating inflammation-associated immune cells and offer an alternative approach to regulate the inflammatory response. The strategy relied on the use of extracellular vesicles derived from human adipose tissue-derived MSCs as mediators of the anti-inflammatory effects, switching macrophages into an alternative activation profile. Despite the remaining challenges, the results of the three papers in this category highlighted the importance of extracellular vesicles as a handy cell-free approach guiding regenerative processes.

In the final group of most cited papers of the decade, we highlight three research efforts that advanced to clinical trials. In "Human Mesenchymal Stem Cell Transfusion Is Safe and Improves Liver Function in Acute-on-Chronic Liver Failure Patients," Wang and colleagues[8] discussed a new and efficient therapeutic strategy for acute-on-chronic liver failure that is urgently needed. In this study, the researchers assessed the safety and initial efficacy of umbilical cord-derived MSC transfusions, which have been shown to reverse fulminant hepatic failure in mice, for liver failure patients associated with hepatitis B virus infection. They found that the transfusions significantly increased the survival rates in the patients and may serve as a novel therapeutic approach. Rabelink and colleagues[9] looked at why the long-term survival of transplanted kidneys has not improved in "Autologous Bone Marrow-Derived Mesenchymal Stromal Cells for the Treatment of Allograft Rejection After Renal Transplantation: Results of a Phase I Study." In this article, mesenchymal stromal cells were identified as an interesting candidate for treatment because of their immunosuppressive and regenerative properties. Of importance, no other clinical studies had investigated the effects in allograft rejection and fibrosis. The authors demonstrated that these first clinical observations support the potential of mesenchymal stromal cells as a novel cell therapy to prevent allograft rejection and interstitial fibrosis/tubular atrophy. The observed systemic immune suppression implies that careful monitoring of opportunistic viral infection is needed. Finally, osteoarthritis is the most widespread musculoskeletal disorder in adults, leading to cartilage damage, inflammation, pain, and disability. The study detailed in "Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial," by Jorgensen and colleagues on behalf of the ADIPOA Consortium[10], was aimed at evaluating the safety of a dose-escalation protocol of intra-articular injected adipose-derived stromal cells in patients with knee osteoarthritis, as well as clinical efficacy as secondary endpoint. In spite of a limited number of patients, the study showed that local injection of autologous adipose-derived stem cells was safe and well tolerated, offering encouraging preliminary evidence of efficacy. Larger and controlled long-term studies are now mandatory, the authors stated, to confirm whether this new strategy of cell therapy can improve pain and induce structural benefit in osteoarthritis.

Based on the seminal papers published to date in the journal, further advances are being pursued by a large number of researchers worldwide, indicating that the next decade promises to be just as exciting in terms of breadth of research and the promise of new therapies for the health betterment of so many patients. *STEM CELLS Translational Medicine* is truly living up to its mission to document and help foster the transition from bench research to clinical studies that have the potential to improve patient outcomes.

Over the first 10 years, *STEM CELLS Translational Medicine* has created significant partnerships and serves as the official journal of the Regenerative Medicine Foundation, the Cord Blood Association, and the Regenerative Medicine Manufacturing Society. We are thankful for these partnerships that help to advance the field. The journal is also

proud to disseminate relevant information through its daily outreach venues with the Stem Cells Portal (https://www.stemcellsportal.com), Clinical Trial Index, the Stem Cell News feature, the regularly distributed *STEM CELLS Translational Medicine* newsletter, and through timely scheduled seminars and sponsored conferences. The major accomplishment of the first decade of the journal, in addition to its monthly publications, is the regenerative medicine community that has been established through all the various information dissemination strategies currently in place, facilitating a global and vibrant network of academic, government, and industry members working together to advance the field.

We would like to thank the authors, Editorial Board members, and the members of the AlphaMed Press *STEM CELLS Translational Medicine* team, Ann Murphy, Martin Murphy, Tina Belle, Suzanne Watters, Sharon Lee, Chelsea Kekahuna, Duane Beaudot, and Matt Kenney, for building and maintaining this significant stem cells and regenerative medicine network, all designed to keep our community up to date on the latest advances and news. We are also grateful to our readers; we could not do this without our subscribers' feedback and support. We wish the journal a Happy 10th Year Anniversary and are looking forward with excitement to see what the future brings for the next decade.

CONFLICT OF INTEREST

The author indicated no potential conflicts of interest.

Anthony Atala, MD

Wake Forest Institute for Regenerative Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27101.

Email: aatala@wakehealth.edu

REFERENCES

1. Buchholz DE, Pennington BO, Croze RH, Hinman CR, Coffey PJ, Clegg DO. Rapid and efficient directed differentiation of human pluripotent stem cells into retinal pigmented epithelium. *STEM CELLS Translational Medicine*. 2013;2:384-393.
2. Melief SM, Zwaginga JJ, Fibbe WE, Roelofs H. Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. *STEM CELLS Translational Medicine*. 2013;2:455-463.
3. James AW, Zara JN, Zhang X, et al. Perivascular stem cells: A prospectively purified mesenchymal stem cell population for bone tissue engineering. *STEM CELLS Translational Medicine*. 2012;1:510-519.
4. Skardal A, Mack D, Kapetanovic E, et al. Bioprinted amniotic fluid-derived stem cells accelerate healing of large skin wounds. *STEM CELLS Translational Medicine*. 2012;1:792-802.
5. Zhang B, Wu X, Zhang X, et al. Human umbilical cord mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/β-catenin pathway. *STEM CELLS Translational Medicine*. 2015;4:513-522.
6. Doeppner TR, Herz J, Görgens A, et al. Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. *STEM CELLS Translational Medicine*. 2015;4:1131-1143.
7. Lo Sicco C, Reverberi D, Balbi C, et al. Mesenchymal stem cell-derived extracellular vesicles as mediators of anti-inflammatory effects: Endorsement of macrophage polarization. *STEM CELLS Translational Medicine*. 2017;6:1018-1028.
8. Shi M, Zhang Z, Xu R, et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *STEM CELLS Translational Medicine*. 2012;1:725-731.
9. Reinders MEJ, de Fijter JW, Roelofs H, et al. Autologous bone marrow-derived mesenchymal stromal cells for the treatment of allograft rejection after renal transplantation: Results of a phase I study. *STEM CELLS Translational Medicine*. 2013;2:107-111.
10. Pers YM, Rackwitz L, Ferreira R, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: A phase I dose-escalation trial. *STEM CELLS Translational Medicine*. 2016;5:847-856.