

## Editorial

# Dental-Derived Stem Cells and Their Secretome and Interactions with Bioscaffolds/Biomaterials in Regenerative Medicine: From the In Vitro Research to Translational Applications

**Andrea Ballini,<sup>1</sup> Antonio Boccaccio,<sup>2</sup> Rajiv Saini,<sup>3</sup> Phuc Van Pham,<sup>4</sup> and Marco Tatullo<sup>5</sup>**

<sup>1</sup>*Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, Bari, Italy*

<sup>2</sup>*Department of Mechanics, Mathematics and Management, Politecnico di Bari, Bari, Italy*

<sup>3</sup>*Department of Periodontology and Oral Implantology, Pravara Institute of Medical Sciences, Loni, Maharashtra, India*

<sup>4</sup>*Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam*

<sup>5</sup>*Biomedical Section, Tecnologica Research Institute, Crotona, Italy*

Correspondence should be addressed to Andrea Ballini; [andrea.ballini@uniba.it](mailto:andrea.ballini@uniba.it)

Received 19 November 2017; Accepted 20 November 2017; Published 28 December 2017

Copyright © 2017 Andrea Ballini et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Regenerative dentistry is an innovative field of medicine that is growing involving both dental and maxillofacial sciences [1, 2].

Clinical healing occurs when new regenerated tissue is well integrated into the previously damaged host tissue: in this context, the reparative and regenerative actions of resident and recruited mesenchymal stem cells (MSCs) have been thoroughly performed.

In the most recent literature, the MSC-produced secretome has been widely studied and it has been even more considered as the strategic promoter of the vast majority of the biological effects derived from stem cell transplantation [3–5].

Dental-derived mesenchymal stem cells (D-dMSCs) are today considered as an intriguing milestone of the regenerative medicine as such cells have been reported to have a strong ability to differentiate into osteogenic, adipogenic, and chondrogenic lineages, with a peculiar ability to improve the bone mineralization [6–9].

Complete healing might be achieved by establishing novel strategies, by using scaffolds in combination with oral-derived MSCs in the presence of secretome and growth [3].

The interaction between stem cells and biomaterials is a crucial topic; recent research trends were focused and developed on the interaction both at superficial macroscopic level and at structural microscopic level. About the first ones, involving the researches on scaffold-related macroscopic features, there are evidences that geometrical and mechanical properties of scaffolds are able to influence the cell behavior and their response to differentiating stimulations [10].

Among the manufacturing processes that can be used to fabricate biomimetic scaffolds, the strategy based on the combination of additive manufacturing and computer-aided design (CAD) modelling seems to be one of the most promising [11]. The possibility to design and create any shape for the newly produced scaffolds, and the scientifically confirmed evidence that scaffold geometry plays a crucial role in influencing the MSC response, led researchers towards an increasing attention to scaffold design; more in details, bioengineers designed complex morphologies able to be reproduced on the surfaces of porous biomaterials [12–15].

Other types of research studies were related to microscopic features of scaffolds, demonstrating that many changes

in scaffold microarchitecture modified, for example, the adhesion of stem cells to the scaffold surfaces [16]. The adhesion of stem cells to scaffold is a biologically guided result of complex cellular, physical, and chemical processes, and it is an essential requirement to guarantee a proper and effective tissue engineering aimed to healing and regenerative applications. Differently from the huge number of studies focused on biochemical reactions that trigger stem cell differentiation, very few studies are reported in the scientific literature about how the mechanical environment affects the adhesion of stem cells on biomaterials' surfaces [17, 18].

We believe that extensive studies will be carried out on this topic in the next few years. However, much still needs to be elucidated in order to be able to create efficient and safe bioartificial substitutes for clinical use.

This special issue has reported articles on D-dMSCs used as therapeutic aid in clinical and surgical applications. The human dental pulp stem cells (hDPSCs) seem to be still the most used cell model by the SI authors.

The most reported translational use of D-dMSC therapy is related to tissue regeneration: in fact, authors have investigated about cytotoxicity, genotoxicity, and biocompatibility of endodontic materials for hDPSCs (A. Victoria-Escandell et al.) or compared using this cell line the efficiencies of osteogenic differentiation and *in vivo* bone formation of hydroxyapatite-tricalcium phosphates (HA-TCPs) and demineralized dentin matrix (DDM) (K.-J. Kang et al.).

An interesting general view has been also given on topics related to issues of general interest, as the potential effect of heavy ethanol consumption can inhibit odontogenic differentiation, a factor that needs to be considered in clinical practice during pulp therapy (W. Qin et al.).

Moreover, other authors have focused their researches to consider that nuclear receptor related 1 (NURR1) plays a key role in switching hDPSC differentiation towards osteoblast rather than neuronal or even other cell lines (A. Di Benedetto et al.).

Finally, some authors have also reported interesting aspects about the role of nephronectin (Npnt) to recruit and conducive to mineralization in hDPSCs, offering a promising approach for hard tissue regeneration (J. Tang and T. Saito).

In this special issue, the editors together with the involved authors have well described the D-dMSCs in their different but fundamental roles of promoters, enhancers, and play-makers of the translational regenerative medicine.

Starting from the contents of our issue, the scientific community will be stimulated to experiment new ideas, to improve the knowledge of D-dMSCs, and to speed up their clinical application, so to improve regenerative medicine approaches.

Andrea Ballini  
Antonio Boccaccio  
Rajiv Saini  
Phuc Van Pham  
Marco Tatullo

## References

- [1] S. Bardelli and M. Moccetti, "Remodeling the human adult stem cell niche for regenerative medicine applications," *Stem Cells International*, vol. 2017, Article ID 6406025, 10 pages, 2017.
- [2] T. Squillaro, G. Peluso, and U. Galderisi, "Clinical trials with mesenchymal stem cells: an update," *Cell Transplantation*, vol. 25, no. 5, pp. 829–848, 2016.
- [3] B. Parekkadan and J. M. Milwid, "Mesenchymal stem cells as therapeutics," *Annual Review of Biomedical Engineering*, vol. 12, no. 1, pp. 87–117, 2010.
- [4] C. Lechanteur, A. Briquet, O. Giet, O. Delloye, E. Baudoux, and Y. Beguin, "Clinical-scale expansion of mesenchymal stromal cells: a large banking experience," *Journal of Translational Medicine*, vol. 14, no. 1, p. 145, 2016.
- [5] R. Fazzina, P. Iudicone, D. Fioravanti et al., "Potency testing of mesenchymal stromal cell growth expanded in human platelet lysate from different human tissues," *Stem Cell Research & Therapy*, vol. 7, no. 1, p. 122, 2016.
- [6] J. Galipeau, M. Krampera, J. Barrett et al., "International Society for Cellular Therapy perspective on immune functional assays for mesenchymal stromal cells as potency release criterion for advanced phase clinical trials," *Cytotherapy*, vol. 18, no. 2, pp. 151–159, 2016.
- [7] M. Marrelli, F. Paduano, and M. Tatullo, "Human periapical cyst-mesenchymal stem cells differentiate into neuronal cells," *Journal of Dental Research*, vol. 94, no. 6, pp. 843–852, 2015.
- [8] M. Tatullo, G. Falisi, M. Amantea, C. Rastelli, F. Paduano, and M. Marrelli, "Dental pulp stem cells and human periapical cyst mesenchymal stem cells in bone tissue regeneration: comparison of basal and osteogenic differentiated gene expression of a newly discovered mesenchymal stem cell lineage," *Journal of Biological Regulators & Homeostatic Agents*, vol. 29, no. 3, pp. 713–718, 2015.
- [9] A. Ballini, F. Mastrangelo, G. Gastaldi et al., "Osteogenic differentiation and gene expression of dental pulp stem cells under low-level laser irradiation: a good promise for tissue engineering," *Journal of Biological Regulators and Homeostatic Agents*, vol. 29, no. 4, pp. 813–822, 2015.
- [10] A. A. Zadpoor, "Bone tissue regeneration: the role of scaffold geometry," *Biomaterials Science*, vol. 3, no. 2, pp. 231–245, 2015.
- [11] A. Macchetta, I. G. Turner, and C. R. Bowen, "Fabrication of HA/TCP scaffolds with a graded and porous structure using a camphene-based freeze-casting method," *Acta Biomaterialia*, vol. 5, no. 4, pp. 1319–1327, 2009.
- [12] A. Boccaccio, A. E. Uva, M. Fiorentino, L. Lamberti, and G. Monno, "A mechanobiology-based algorithm to optimize the microstructure geometry of bone tissue scaffolds," *International Journal of Biological Sciences*, vol. 12, no. 1, pp. 1–17, 2016.
- [13] A. Boccaccio, A. E. Uva, M. Fiorentino, G. Mori, and G. Monno, "Geometry design optimization of functionally graded scaffolds for bone tissue engineering: a mechanobiological approach," *PLoS One*, vol. 11, no. 1, article e0146935, 2016.
- [14] S. Giannitelli, D. Accoto, M. Trombetta, and A. Rainer, "Current trends in the design of scaffolds for computer-aided tissue engineering," *Acta Biomaterialia*, vol. 10, no. 2, pp. 580–594, 2014.

- [15] A. Boccaccio, M. Fiorentino, A. E. Uva, L. N. Laghetti, and G. Monno, "Rhombicuboctahedron unit cell based scaffolds for bone regeneration: geometry optimization with a mechanobiology - driven algorithm," *Materials Science and Engineering: C*, vol. 83, pp. 51–66, 2018.
- [16] S. Bose, M. Roy, and A. Bandyopadhyay, "Recent advances in bone tissue engineering scaffolds," *Trends in Biotechnology*, vol. 30, no. 10, pp. 546–554, 2012.
- [17] P. P. Provenzano and P. J. Keely, "Mechanical signaling through the cytoskeleton regulates cell proliferation by coordinated focal adhesion and Rho GTPase signaling," *Journal of Cell Science*, vol. 124, no. 8, pp. 1195–1205, 2011.
- [18] A. Buxboim and D. E. Discher, "Stem cells feel the difference," *Nature Methods*, vol. 7, no. 9, p. 695, 2010.