

Dental Application Potential of Mesenchymal Stromal Cells and Embryonic Stem Cells

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In the past decade, research on the potential applications of stem cells in dentistry has made great progress. There are at least five different types of multipotent mesenchymal stromal cells (MSCs) originating from exfoliated primary teeth, including dental pulp, apica papilla, periodontal ligament, and dental follicle. It has been reported that dental tissue-derived MSCs are able to generate dentine–pulp-like complexes as well as differentiate into periodontal and craniofacial progenitor cells. Similar to these dental tissue-derived MSCs, bone marrow-derived MSCs are also capable of developing into ameloblasts, odontoblasts and periodontal ligament progenitor cells, as well as regenerating cementum, alveolar bone, craniofacial bone and articular condyles. Besides adult stem cells, embryonic stem cells are an alternative cell source for dental tissue regeneration, but the current data are preliminary and are based predominantly on in vitro data. In addition to these commonly reported stem cells, other progenitor cells with MSC properties are also found in salivary glands, tongue muscle, taste buds and oral mucosa, and these may play a role in recovering the function of the residing tissues. Other than these regenerative applications, many reports have demonstrated the utility of these stem cells in cytotoxicity testing, biocompatibility testing and developmental research. The present article summarises the above findings regarding the regenerative and other potential applications of both MSCs and embryonic stem cells.

Key words: dental application, embryonic stem cells, mesenchymal stromal cells, regeneration

Stem cells represent a particular cell population that is at an unspecialised stage capable of self-renewal and differentiation into more committed lineages¹. According to their origins and differentiation abilities, stem cells are broadly classified into two categories: embryonic stem cells (ESCs) and adult stem cells. The former is theoretically immortal and pluripotent, capable of producing all cell types of three germ layers and body². However, the latter has a limited life span^{3,4} and is capable of generating committed cell lineages

of the resident tissues/organs^{5,6}. Among various adult stem cells, mesenchymal stem cells have the widest distribution in the human body and have been isolated from diverse tissues/organs⁷. Unlike ESCs, there is no scientific consensus about the immunophenotype of the bona fide mesenchymal stem cells. The currently isolated ‘mesenchymal stem cells’ always present high levels of heterogeneity, which is suggestive of a mixture of stromal progenitor cells at various developmental stages⁸⁻¹⁰ that can be maintained by a minor population of bona fide stem cells^{9,11}. Therefore, the International Society for Cellular Therapy would like to name these cells *multipotent mesenchymal stromal cells* (MSCs) rather than *mesenchymal stem cells*¹². Based on the above knowledge, a more practical definition for MSCs is the stromal-derived cells that can be propagated long-term *in vitro* and have multiple differentiation capacities.

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So far, it has been proposed that both MSCs and ESCs have great potential in the therapy of many diseases^{7,9,13,14}. In the past decade, progress has been made in exploring the clinical potential of MSCs and ESCs in dentistry. However, most attempts focused on the regeneration of tooth and periodontal tissues by oral tissue-derived MSCs¹⁵⁻¹⁷, which have been intensively reviewed. Additionally, other clinical and non-clinical application potentials of MSCs and ESCs will be examined in the present review.

Tissue/organ regeneration

Oral tissue defects and loss are major dental problems, greatly reducing patients' quality of life. The causes are various, including congenital malformation, aging, periodontitis, post-cancer ablative surgery, trauma, osteoporotic fractures and progressive skeletal disease. Currently in clinical dentistry, dental sealants, osseointegrated implants, dentures, bone grafting and osteoconductive biomaterials are common remedies to recover the anatomical structure of the damaged oral tissues. However, the ideal therapy for those lost or damaged tissues/organs is not only the recovery of their morphology but also the recovery of their physiological functions. Stem cell-based replacement therapy provides a promise to achieve this goal.

Tooth reconstruction

Among various MSCs originating from different tissues, bone marrow-derived MSCs are most extensively investigated for regenerating most tissue types all over the body. Evidence to support tooth reconstruction by these MSCs can be seen in a report by Ohazama et al¹⁸. Upon transplantation of a recombination of MSCs and embryonic oral epithelium, tooth crowns associated with bone and soft tissues formed in the renal capsule. A similar tooth structure was formed when this recombination was transferred into the jaw. These results were supported by Hu and coworkers, who mixed MSCs with embryonic dental epithelial cells followed by re-association with dental mesenchyme *in vitro*¹⁹. Results showed that c-kit positive MSCs could be differentiated into ameloblast- and odontoblast-like cells in contact with the epithelial-mesenchymal junction. In the same assay system, c-kit negative MSCs could also be induced to odontoblast-like cells. Both groups showed the independence of the amelo-differentiation of MSCs without cell fusion.

Despite feasible evidence that bone marrow-derived MSCs can reconstruct teeth, abundant data suggest dental tissue-derived MSCs to be an alternative cell

source suitable for whole tooth regeneration²⁰. These MSCs are separated from exfoliated primary teeth (SHED, stem cells from human exfoliated deciduous teeth)²¹, dental pulp (DPSC)²², apical papilla (SCAP)²³, periodontal ligament (PDLSC)²⁴, and dental follicle (DFSC)²⁵. It is reported that both bone marrow-derived MSCs and dental tissue-derived MSCs reside in the perivascular area in their respective tissues, and express some common surface molecules, such as stro-1 and CD146²⁶. By proteomic characterisation, the regulation of selected proteins, involving Hsp27, Annexin A4 and CRMP4, was conserved between different MSCs of different origins from different species²⁷. Both bone marrow- and dental tissue-derived MSCs can differentiate into at least three committed lineages^{16,28,29}: osteo/odontogenic, neurogenic and adipogenic lineages. Interestingly, similar to bone marrow MSCs, SHED, DPSC, SCAP and PDLSC display low immunogenicity and immunosuppressive activity³⁰⁻³⁴. Also, the mechanisms under this immunosuppressive activity are independent of apoptosis and are mediated by soluble molecules. These properties imply that these cells are suitable for allogeneic transplantation. However, dental tissue-derived MSCs are more committed to odontogenic cells^{16,35,36}, while bone marrow-derived MSCs are more osteogenesis-oriented under non-inductive conditions¹⁶. In comparison with bone marrow-derived MSCs, DPSC, SHED, SCAP and PDLSC have higher proliferation rates and more population doublings^{16,26}, except for DFSC²⁵. With the colony-forming unit-fibroblast (CFU-F) assay, DPSC, SHED and PDLSC displayed higher incidence of the number of colonies after 10 to 12 days in the same culture conditions at the same plating cell numbers²⁶.

To date, SHED, DPSC and SCAP have been reported to be able to differentiate into odontoblast-like cells^{21,33,37}. *In vivo*, both DPSC and SCAP can regenerate dentine-pulp-like complexes^{26,32,33,38,39}, while SHED can only form a dentine-like structure^{21,26}. For dentine formation, DPSC predominantly produce reparative dentine, while SCAP is involved in the production of root dentine^{32,33,39}. Besides these three dental MSCs, there are no data on the reconstruction of enamel, dentine and pulp by PDLSC and DFSC. Interestingly, outside bone marrow and dental tissues, dermal-derived MSCs are also able to be induced into odontogenic lineage cells by exposure to a conditioned medium of embryonic and neonatal tooth germ cells in culture⁴⁰.

Because of the finite *in vitro* expansion ability of MSCs^{16,26}, there is a requirement to identify other cell sources as possible replacements for large-scale clinical usage. ESCs are such immortal cells, which theoretic-

cally can be infinitely propagated *ex vivo* and are inducible to develop into all adult cell types of three germ layers. Unlike the gene-transformed immortal cell lines, they have a normal karyotype and strong expression of telomerase to maintain the gene stability⁴¹. This telomerase activity is normally absent in MSCs^{42,43}. Recently, trials to induce ESCs to oral cell types were performed. It was found that ESCs could attach to the extracted tooth root slice surface and proliferate after 2 days of direct seeding. Upon co-culture with periodontal ligament cells in osteogenic inductive medium, ESCs could synthesise osteogenic markers, such as osteopontin and osteocalcin⁴⁴. However, after the embryoid body formation, ESCs are easier to induce to odontogenic epithelial cells, which produce ameloblast-specific proteins, such as cytokeratin 14, ameloblastin and amelogenin⁴⁵.

Periodontal reconstruction

Periodontal tissues are composed of gingiva, periodontal ligament, cementum and alveolar bone. They serve as a proprioceptor to detect the force on teeth, and a glue to keep the teeth attached to alveolar bone. Periodontal diseases are highly prevalent worldwide and result in bone tissue destruction and subsequent tooth loss. It has been found that a mixture of autologous bone marrow-derived MSCs and atelocollagen could repair experimental class III periodontal defects by the regeneration of periodontal ligament and alveolar bone⁴⁶⁻⁴⁸. It has been hypothesised that cytokines and signalling molecules could accelerate the periodontal differentiation of MSCs^{49,50}. In the presence of platelet-rich plasma, bone marrow-derived MSCs displayed prominent periodontal tissue regeneration⁵¹. When these MSCs were transfected with basic fibroblast growth factor (bFGF), the regeneration of periodontal bone tissue was accelerated⁵². In addition, bone marrow-derived MSCs were also able to produce cementum when they were cultured on root slices pre-treated with enamel matrix proteins⁵³ or implanted with dl-lactide-co-glycolide scaffold⁵⁴. The regeneration of cementum, periodontal ligament, and alveolar bone was enhanced by the transfection of the sonic hedgehog gene⁵⁵.

Among dental tissue-derived MSCs, stro-1-positive PDLSC and DFSC displayed the regenerative abilities of cementum^{24,56-58} and periodontal ligament⁵⁸⁻⁶⁰. Moreover, *in vivo*, PDLSC could form cementum-periodontal ligament-like structure and alveolar bone with/without being loaded onto scaffolds^{24,26,61,62}. The differentiation to periodontal cells could be programmed by enamel matrix derivatives, bone morphogenetic protein 2 (BMP-2) and BMP-7^{56,63}. So far, there is no

evidence about the periodontal tissue regenerative ability of DPSC, SHED and SCAP. However, there have been two trials to induce ESCs to periodontal lineages by co-culturing with periodontal ligament fibroblasts and directly contacting with tooth root slices^{44,64}. Only a minority of cells in colonies showed the characteristics of periodontal ligament progenitor cells.

Craniofacial skeleton and temporomandibular joint/condyle reconstruction

Bone regeneration is one of the prominent characteristics of MSCs suitable for clinical application^{65,66}. Abundant studies have reported that bone marrow-derived MSCs are able to heal critical-sized segmental bone defects⁶⁷, cranial defects^{11,68,69}, alveolar bone destruction^{11,68}, and mandibular defects⁷⁰, as well as reconstruct mandibular condyle⁷¹⁻⁷³. The formation of lamellar bone in maxillary sinus augmentation by bone marrow-derived MSCs provides a reliable base for dental implants⁷⁴. Most of this progress was made in combination with the utility of MSCs, biomaterials and/or growth factors²⁶. In the repair of the critical-sized mandibular bone defects, bone marrow-derived MSCs were loaded onto poly-dl-lactide-co-glycolic acid scaffolds⁷⁰. In the reconstruction of articular condyles, bone marrow-derived MSCs were firstly differentiated into osteo- and chondro-genic cells followed by the encapsulation in poly(ethylene glycol)-based hydrogel layers⁷¹; the transfection of telomerase reverse transcriptase could enhance the osteogenesis of MSCs^{42,43}.

Among dental tissue-derived MSCs, SHED and PDLSC are well tested for osteogenesis. Currently, studies have shown that they could be directly inducible into osteogenic lineages^{21,75-79}. PDLSC are sensitive to the induction of retinoic acid⁷⁵, pharmacological stimulation⁷⁷ and pulsating fluid shear stress⁷⁸. In comparison with PDLSC, SHED are less sensitive to retinoic acid stimulation⁷⁵. Besides the direct osteogenic differentiation, SHED can recruit host osteogenic cells to repair bone defects⁷⁶, but the bone formed by SHED lacks hematopoietic marrow elements, which are always observed in the bone formed by bone marrow-derived MSCs⁷⁶. Besides SHED and PDLSC, there are a few trials to induce DPSC and DFSC to osteogenic progenitor cells^{77,80,81,82}. Although the osteogenic markers could be detected on these cells after the osteoinduction, it needs *in vivo* data to consolidate these findings.

Compared with DPSC and DFSC, more solid evidence about the osteogenic differentiation potential of ESCs is available. ESCs can be inducible to osteogenic cells by the co-culture with periodontal ligament fibro-

blasts *in vitro*^{83,84}, as well as the inducement of a chemical complex with^{85,86} or without⁸⁷ embryonic body formation. They are also able to form bone structure by transplanting with hydroxyapatite/tricalcium phosphate particles into tooth sockets, without the occurrence of teratoma⁸⁸. Besides the osteogenesis, ESCs are also inducible to chondrogenic cells^{89,90}, which may facilitate the reconstruction of temporomandibular joints. These *in vitro* expandable ESC-derived chondrogenic cells repair critical-sized osteochondral defects without evidence of tumorigenicity⁹¹.

Gland restoration

Gland damage will cause a deficiency of saliva and various oral problems, such as mastication and swallowing problems, dental caries, burning sensations, periodontitis, denture problems, and dysgeusia. However, there is a lack of effective treatment to recover gland function. In recent years, stem cells have been proposed as a good remedy^{92,93}. Putative salivary epithelial stem cells⁹⁴⁻⁹⁹ and intercalated duct stem cells^{100,101} were identified from oral glands. These salivary stem cells share the same surface molecule profile as well as proliferation and tri-lineage differentiation abilities as pancreatic acini-derived stem cells and bone marrow-derived MSCs⁹⁷. Also, c-kit is their common molecule expressed on the cell surface^{95-98,101}. Upon isoprenaline stimulation, the intercalated duct cells in parotid glands may develop to acinar cells¹⁰⁰. *In vitro*, these salivary stem cells were inducible to amylase-producing acinar cells, while after transplantation, they could restore the morphology and function of salivary glands^{98,102}. To further explore the properties and future applications of the salivary stem cells, an immortalised cell line was established by the transfection of integrin $\alpha 6\beta 1$ ¹⁰³. These cells were able to achieve both acinar- and duct-like structures.

Other dental tissue regeneration

To date, there is one study suggesting that bone marrow-derived MSCs can be recruited into the cheek and differentiate into buccal epithelial cells without host-recipient cell fusion¹⁰⁴. However, the identity of the particular cells for differentiation is unclear. There are stem cells detected in other oral tissues, such as tongue muscle¹⁰⁵, taste buds¹⁰⁶ and oral mucosa¹⁰⁷. However, their effects in differentiating into dental cells *in vitro* and regenerating oral tissues *in vivo* are unknown. Notably, there are mucosa lamina propria-derived stem cells exhibiting multiple differentiation properties to mesodermal,

endodermal and neural lineages¹⁰⁷. They have the same immunophenotype as bone marrow-derived MSCs and neural stem cells, and have a low level of expression of ESC markers. After transplantation, they can form a tumour consisting of mesodermal and ectodermal tissues.

Non-regenerative application

Cytotoxicity testing for non-biological materials

With reference to the International Standard (ISO 10993 part 5, 1999), immortal cell lines, such as L-929, Balb/3T3 and WI-38 etc., are recommended for cytotoxicity testing. These cell lines have homogeneous morphologies and infinite proliferation, which provide good reproducibility for *in vitro* cytotoxicity screening. However, these cells are normally derived from tumours or are gene-modified, as well as being of animal origin. The lack of genetic integrity and the xeno-origin make their representative identities for normal human cells questionable. As human stem cells are able to self-renew, expand *in vitro*, have normal karyotype, and are usable for cell replacement therapy, they may represent alternative suitable cell sources for cytotoxicity testing¹⁰⁸⁻¹¹¹.

By using bone marrow-derived MSCs, it was found that 2-vinyl-8-hydroxyquinoline derivatives could efficiently decrease oxidative stress-induced cell death¹¹¹. By testing various resin-based sealers on DPSC, CMF bond adhesive showed a better supportive effect on cell viability and proliferation than Prime&Bond NT, Clearfil S(3) and XP Bond¹¹⁰. Being evaluated on the same stem cells, laser phototherapy displayed a positive effect on improving DPSC growth in a nutritionally deficient condition¹¹². Ameloblast stem cells are sensitive to the anti-microtubule agent vinblastine. The cytotoxicity of vinblastine on ameloblast stem cells displayed a dose-dependent effect¹¹³. Recently, human ESC-derived fibroblasts were established and were reported to be more sensitive to the cytotoxicity of mitomycin C than L929¹⁰⁹, suggesting another stable cell source available for *in vitro* cytotoxicity testing. Theoretically, ESCs are immortal, and hence can potentially be an infinite source of fibroblasts.

Biocompatibility testing

Biocompatibility is a broad concept about the behaviour of biomaterials in various contexts. In regenerative medicine, the biomaterials are fabricated as a scaffold or matrix to repair a structural defect or to support physi-

ological activities of *in vitro* expanded cells in the host, without eliciting any undesirable effects on both cells and host. Good biocompatibility is a prerequisite for the clinical application of new biomaterials and their tissue-engineering products, including implants and scaffolds. The current compatibility testing follows the guidelines of ISO 10993 prior to clinical study. As suggested, various stem cells will be promising cell sources for future dental and medical application. Recently, some preliminary data about the biocompatibility of dental biomaterials were obtained based on cytotoxicity, genotoxicity and embryotoxicity tests on bone marrow-derived MSCs¹¹⁴⁻¹²⁰ and ESCs^{121,122}.

Developmental research

The initiation signals for tooth development are from the contact of oral epithelium with neural crest-derived mesenchyme¹²³. These signals mainly involve the members of hedgehog, Wnt, FGF and the transforming growth factor-beta superfamilies. However, the particular molecules triggering and regulating this process are still unclear, and most of the evidence is based on studies of mouse embryos. Therefore, to address these questions, human tooth developmental models will be of great importance. In 2004, Ohazama and coworkers found that a complete tooth primordium could be produced from bone marrow-derived MSCs upon interaction with embryonic oral epithelium¹⁸, suggesting that the neural crest-derived mesenchyme is an optional cell source during the development of teeth. Furthermore, an *in vitro* three-dimensional human DPSC-scaffold-dental epithelial cell model was created to investigate the epithelial-mesenchymal interactions during tooth morphogenesis¹²⁴. In this model, DPSC and dental epithelial cells showed a different pace of differentiation and a different spatial expression of dentine sialoprotein in the absence of the differentiation medium. These results confirm the possibility and feasibility of establishing *in vitro* tooth developmental models.

Summary

In summary, the present review has reported the clinical and non-clinical application potential of bone marrow-derived MSCs, dental tissue-derived MSCs and ESCs in dentistry. Although the research progress is promising for regenerative medicine, it is not readily translatable to the clinic. Firstly, differentiation to desired committed lineages by these stem cells is not controllable. This differentiation uncertainty will subsequently lead to low efficiency and efficacy upon transplantation or transfu-

sion. Secondly, the biosafety of these stem cells is a concern. Currently, all cells are expanded *ex vivo* under culture conditions with xeno-components. The possible contamination of unknown xeno-biohazard will put patients in danger. Additionally, in spite of limited life span and restricted differentiation ability, adult stem cells still have a high risk of being tumorigenic¹²⁵. It was reported that long-term *in vitro* culture of stem cells could cross-present exogenous antigens¹²⁶. These exogenous antigens can possibly trigger an immune response after being transplanted, thereby decreasing the viability of stem cell grafts. Thirdly, the topographic structure of tooth and other oral tissues/organs is not reproducible by using pure stem cells. It is necessary to apply scaffolds or other carriers. The biocompatibility of stem cells and scaffolds requires further testing. Fourthly, limitation in the availability of autologous stem cells will hinder its application in tissue/organ regeneration. The application of allogeneic adult stem cells as alternative cell sources is still debatable. Recently, induced pluripotent stem cells were successfully established from oral mucosa fibroblasts via retroviral gene transfer of *oct4*, *sox2*, *c-myc* and *klf4*¹²⁷. This is another solution towards achieving personalised regenerative cells. However, safety and gene integrity are questionable. Last but not least, the cost effectiveness of stem cell-based therapy should be another consideration.

Practically, stem cells are good tools for dental research and cytotoxicity testing *in vitro*. Nevertheless, some time is required to establish a standard operation protocol for evaluating the cytotoxicity of dental/medical chemicals and medicine.

Acknowledgments

The authors wish to thank Dr Boon Chin Heng for critical comment on this manuscript.

This work was partially supported by grants from the Ministry of Education of Singapore (R223000014112 and R223000018112), the National University of Singapore (C221000302001) and the Ministry of Science and Technology of China (2008DPB30090).

References

1. Potten CS, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development* 1990;110:1001-1020.
2. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS et al. Embryonic stem cell lines derived from human blastocysts. *Science* 1998;282:1145-1147.
3. Kern S, Eichler H, Stoeve J, Kluter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 2006;24:1294-1301.

4. Bonyadi M, Waldman SD, Liu D, Aubin JE, Grynblas MD, Stanford WL. Mesenchymal progenitor self-renewal deficiency leads to age-dependent osteoporosis in *Scn-1/Ly-6A* null mice. *Proc Natl Acad Sci U S A* 2003;100:5840-5845.
5. Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. *Stem Cells* 2001;19:180-192.
6. Can A. A concise review on the classification and nomenclature of stem cells. *Turk J Hematol* 2008;25:57-59.
7. Bobis S, Jarocha D, Majka M. Mesenchymal stem cells: characteristics and clinical applications. *Folia Histochem Cytobiol* 2006;44:215-230.
8. Rhodes NP, Srivastava JK, Smith RF, Longinotti C. Heterogeneity in proliferative potential of ovine mesenchymal stem cell colonies. *J Mater Sci Mater Med* 2004;15:397-402.
9. Phinney DG. Biochemical heterogeneity of mesenchymal stem cell populations: clues to their therapeutic efficacy. *Cell Cycle* 2007;6:2884-2889.
10. Maria OM, Khosravi R, Mezey E, Tran SD. Cells from bone marrow that evolve into oral tissues and their clinical applications. *Oral Dis* 2007;13:11-16.
11. Krebsbach PH, Mankani MH, Satomura K, Kuznetsov SA, Robey PG. Repair of craniotomy defects using bone marrow stromal cells. *Transplantation* 1998;66:1272-1278.
12. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006;8:315-317.
13. Karp JM, Leng Teo GS. Mesenchymal stem cell homing: the devil is in the details. *Cell Stem Cell* 2009;4:206-216.
14. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008;8:726-736.
15. Rimondini L, Mele S. Stem cell technologies for tissue regeneration in dentistry. *Minerva Stomatol* 2009;58:483-500.
16. Huang GT, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. *J Dent Res* 2009;88:792-806.
17. Morszczek C, Schmalz G, Reichert TE, Vollner F, Galler K, Driemel O. Somatic stem cells for regenerative dentistry. *Clin Oral Invest* 2008;12:113-118.
18. Ohazama A, Modino SA, Miletich I, Sharpe PT. Stem-cell-based tissue engineering of murine teeth. *J Dent Res* 2004;83:518-522.
19. Hu B, Unda F, Bopp-Kuchler S, Jimenez L, Wang XJ, Haikel Y et al. Bone marrow cells can give rise to ameloblast-like cells. *J Dent Res* 2006;85:416-421.
20. Petrovic V, Stefanovic V. Dental tissue: new source for stem cells. *ScientificWorldJournal* 2009;9:1167-1177.
21. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG et al. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci U S A* 2003;100:5807-5812.
22. Gronthos S, Mankani M, Brahimi J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci U S A* 2000;97:13625-13630.
23. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod* 2008;34:166-171.
24. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahimi J et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004;364:149-155.
25. Morszczek C, Gotz W, Schierholz J, Zeilhofer F, Kuhn U, Mohl C et al. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol* 2005;24:155-165.
26. Shi S, Bartold PM, Miura M, Seo BM, Robey PG, Gronthos S. The efficacy of mesenchymal stem cells to regenerate and repair dental structures. *Orthod Craniofac Res* 2005;8:191-199.
27. Mrozik KM, Zilm PS, Bagley C, Hack S, Hoffmann P, Gronthos S et al. Proteomic characterization of mesenchymal stem cell-like populations derived from ovine periodontal ligament, dental pulp and bone marrow: analysis of differentially expressed proteins. *Stem Cells Dev* 2010;19:1485-1499.
28. Gay IC, Chen S, MacDougall M. Isolation and characterization of multipotent human periodontal ligament stem cells. *Orthod Craniofac Res* 2007;10:149-160.
29. Wang J, Wang X, Sun Z, Yang H, Shi S, Wang S. Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells. *Stem Cells Dev* 2010;19:1375-1383.
30. Pierdomenico L, Bonsi L, Calvitti M, Rondelli D, Arpinati M, Chirumbolo G et al. Multipotent mesenchymal stem cells with immunosuppressive activity can be easily isolated from dental pulp. *Transplantation* 2005;80:836-842.
31. Wada N, Menicanin D, Shi S, Bartold PM, Gronthos S. Immunomodulatory properties of human periodontal ligament stem cells. *J Cell Physiol* 2009;219:667-676.
32. Ding G, Liu Y, An Y, Zhang C, Shi S, Wang W et al. Suppression of T cell proliferation by root apical papilla stem cells *in vitro*. *Cells Tissues Organs* 2010;191:357-364.
33. Ding G, Wang W, Liu Y, An Y, Zhang C, Shi S et al. Effect of cryopreservation on biological and immunological properties of stem cells from apical papilla. *J Cell Physiol* 2010;223:415-422.
34. Yamaza T, Kentaro A, Chen C, Liu Y, Shi Y, Gronthos S et al. Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. *Stem Cell Res Ther* 2010;1:5.
35. Yu J, Wang Y, Deng Z, Tang L, Li Y, Shi J et al. Odontogenic capability: bone marrow stromal stem cells versus dental pulp stem cells. *Biol Cell* 2007;99:465-474.
36. Ohta S, Yamada S, Matuzaka K, Inoue T. The behavior of stem cells and progenitor cells in the periodontal ligament during wound healing as observed using immunohistochemical methods. *J Periodontol Res* 2008;43:595-603.
37. Huang GT, Shagaramanova K, Chan SW. Formation of odontoblast-like cells from cultured human dental pulp cells on dentin *in vitro*. *J Endod* 2006;32:1066-1073.
38. Yan M, Yu Y, Zhang G, Tang C, Yu J. A journey from dental pulp stem cells to a bio-tooth. *Stem Cell Rev* 2010.
39. Sonoyama W, Liu Y, Fang D, Yamaza T, Seo BM, Zhang C et al. Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS One* 2006;1:e79.
40. Huo N, Tang L, Yang Z, Qian H, Wang Y, Han C et al. Differentiation of dermal multipotent cells into odontogenic lineage induced by embryonic and neonatal tooth germ cell-conditioned medium. *Stem Cells Dev* 2010;19:93-104.
41. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. *Dev Genet* 1996;18:173-179.
42. Gronthos S, Chen S, Wang CY, Robey PG, Shi S. Telomerase accelerates osteogenesis of bone marrow stromal stem cells by upregulation of CBFA1, osterix, and osteocalcin. *J Bone Miner Res* 2003;18:716-722.
43. Shi S, Gronthos S, Chen S, Reddi A, Counter CM, Robey PG et al. Bone formation by human postnatal bone marrow stromal stem cells is enhanced by telomerase expression. *Nat Biotechnol* 2002;20:587-591.
44. Inanc B, Elcin AE, Elcin YM. *In vitro* differentiation and attachment of human embryonic stem cells on periodontal tooth root surfaces. *Tissue Eng Part A* 2009;15:3427-3435.
45. Ning F, Guo Y, Tang J, Zhou J, Zhang H, Lu W et al. Differentiation of mouse embryonic stem cells into dental epithelial-like cells induced by ameloblasts serum-free conditioned medium. *Biochem Biophys Res Commun* 2010;394:342-347.

46. Kawaguchi H, Hirachi A, Hasegawa N, Iwata T, Hamaguchi H, Shiba H et al. Enhancement of periodontal tissue regeneration by transplantation of bone marrow mesenchymal stem cells. *J Periodontol* 2004;75:1281-1287.
47. Kawaguchi H, Hayashi H, Mizuno N, Fujita T, Hasegawa N, Shiba H et al. [Cell transplantation for periodontal diseases. A novel periodontal tissue regenerative therapy using bone marrow mesenchymal stem cells]. *Clin Calcium* 2005;15:99-104.
48. Hasegawa N, Kawaguchi H, Hirachi A, Takeda K, Mizuno N, Nishimura M et al. Behavior of transplanted bone marrow-derived mesenchymal stem cells in periodontal defects. *J Periodontol* 2006;77:1003-1007.
49. Zhao Q, Gong P, Tan Z, Yang X. Differentiation control of transplanted mesenchymal stem cells (MSCs): a new possible strategy to promote periodontal regeneration. *Med Hypotheses* 2008;70:944-947.
50. Mizuno N, Ozeki Y, Shiba H, Kajiji M, Nagahara T, Takeda K et al. Humoral factors released from human periodontal ligament cells influence calcification and proliferation in human bone marrow mesenchymal stem cells. *J Periodontol* 2008;79:2361-2370.
51. Yamada Y, Ueda M, Hibi H, Baba S. A novel approach to periodontal tissue regeneration with mesenchymal stem cells and platelet-rich plasma using tissue engineering technology: a clinical case report. *Int J Periodontics Restorative Dent* 2006;26:363-369.
52. Tan Z, Zhao Q, Gong P, Wu Y, Wei N, Yuan Q et al. Research on promoting periodontal regeneration with human basic fibroblast growth factor-modified bone marrow mesenchymal stromal cell gene therapy. *Cytotherapy* 2009;11:317-325.
53. Song AM, Shu R, Xie YF, Song ZC, Li HY, Liu XF et al. A study of enamel matrix proteins on differentiation of porcine bone marrow stromal cells into cementoblasts. *Cell Prolif* 2007;40:381-396.
54. Marei MK, Saad MM, El-Ashwah AM, Ei-Backly RM, Al-Khodary MA. Experimental formation of periodontal structure around titanium implants utilizing bone marrow mesenchymal stem cells: a pilot study. *J Oral Implantol* 2009;35:106-129.
55. Risbud MV, Shapiro IM. Stem cells in craniofacial and dental tissue engineering. *Orthod Craniofac Res* 2005;8:54-59.
56. Kemoun P, Laurencin-Dalicieux S, Rue J, Farges JC, Gennero I, Conte-Auriol F et al. Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) *in vitro*. *Cell Tissue Res* 2007;329:283-294.
57. Handa K, Saito M, Yamauchi M, Kiyono T, Sato S, Teranaka T et al. Cementum matrix formation *in vivo* by cultured dental follicle cells. *Bone* 2002;31:606-611.
58. Yang ZH, Zhang XJ, Dang NN, Ma ZF, Xu L, Wu JJ et al. Apical tooth germ cell-conditioned medium enhances the differentiation of periodontal ligament stem cells into cementum/periodontal ligament-like tissues. *J Periodontol Res* 2009;44:199-210.
59. Liu Y, Zheng Y, Ding G, Fang D, Zhang C, Bartold PM et al. Periodontal ligament stem cell-mediated treatment for periodontitis in miniature swine. *Stem Cells* 2008;26:1065-1073.
60. Yang Z, Jin F, Zhang X, Ma D, Han C, Huo N et al. Tissue engineering of cementum/periodontal-ligament complex using a novel three-dimensional pellet cultivation system for human periodontal ligament stem cells. *Tissue Eng Part C Methods* 2009;15:571-581.
61. Kim SH, Kim KH, Seo BM, Koo KT, Kim TI, Seol YJ et al. Alveolar bone regeneration by transplantation of periodontal ligament stem cells and bone marrow stem cells in a canine peri-implant defect model: a pilot study. *J Periodontol* 2009;80:1815-1823.
62. Silverio KG, Benatti BB, Casati MZ, Sallum EA, Nociti FH, Jr. Stem cells: potential therapeutics for periodontal regeneration. *Stem Cell Rev* 2008;4:13-19.
63. Chen YL, Chen PK, Jeng LB, Huang CS, Yang LC, Chung HY et al. Periodontal regeneration using *ex vivo* autologous stem cells engineered to express the BMP-2 gene: an alternative to alveoloplasty. *Gene Ther* 2008;15:1469-1477.
64. Inanc B, Elcin AE, Unsal E, Balos K, Parlir A, Elcin YM. Differentiation of human embryonic stem cells on periodontal ligament fibroblasts *in vitro*. *Artif Organs* 2008;32:100-109.
65. Yamada Y, Ueda M, Hibi H, Nagasaka T. Translational research for injectable tissue-engineered bone regeneration using mesenchymal stem cells and platelet-rich plasma: from basic research to clinical case study. *Cell Transplant* 2004;13:343-355.
66. Yamada Y, Ueda M, Naiki T, Takahashi M, Hata K, Nagasaka T. Autogenous injectable bone for regeneration with mesenchymal stem cells and platelet-rich plasma: tissue-engineered bone regeneration. *Tissue Eng* 2004;10:955-964.
67. Qi M, Hu J, Zou S, Zhou H, Han L. Mandibular distraction osteogenesis enhanced by bone marrow mesenchymal stem cells in rats. *J Craniomaxillofac Surg* 2006;34:283-289.
68. Schantz JT, Huttmacher DW, Lam CX, Brinkmann M, Wong KM, Lim TC et al. Repair of calvarial defects with customised tissue-engineered bone grafts II. Evaluation of cellular efficiency and efficacy *in vivo*. *Tissue Eng* 2003;9(Suppl 1):S127-139.
69. Dumas A, Moreau MF, Gherardi RK, Basle MF, Chappard D. Bone grafts cultured with bone marrow stromal cells for the repair of critical bone defects: an experimental study in mice. *J Biomed Mater Res A* 2009;90:1218-1229.
70. Abukawa H, Shin M, Williams WB, Vacanti JP, Kaban LB, Troulis MJ. Reconstruction of mandibular defects with autologous tissue-engineered bone. *J Oral Maxillofac Surg* 2004;62:601-606.
71. Alhadlaq A, Elisseeff JH, Hong L, Williams CG, Caplan AI, Sharma B et al. Adult stem cell driven genesis of human-shaped articular condyle. *Ann Biomed Eng* 2004;32:911-923.
72. Abukawa H, Terai H, Hannouche D, Vacanti JP, Kaban LB, Troulis MJ. Formation of a mandibular condyle *in vitro* by tissue engineering. *J Oral Maxillofac Surg* 2003;61:94-100.
73. Alhadlaq A, Mao JJ. Tissue-engineered neogenesis of human-shaped mandibular condyle from rat mesenchymal stem cells. *J Dent Res* 2003;82:951-956.
74. Sauerbier S, Stricker A, Kuschnierz J, Buhler F, Oshima T, Xavier SP et al. *In vivo* comparison of hard tissue regeneration with human mesenchymal stem cells processed with either the FICOLL method or the BMAC method. *Tissue Eng Part C Methods* 2010;16:215-223.
75. Chadipiralla K, Yochim JM, Bahuleyan B, Huang CY, Garcia-Godoy F, Murray PE et al. Osteogenic differentiation of stem cells derived from human periodontal ligaments and pulp of human exfoliated deciduous teeth. *Cell Tissue Res* 2010;340:323-333.
76. Seo BM, Sonoyama W, Yamaza T, Coppe C, Kikui T, Akiyama K et al. SHED repair critical-size calvarial defects in mice. *Oral Dis* 2008;14:428-434.
77. Kadar K, Kiraly M, Porcsalmy B, Molnar B, Racz GZ, Blazsek J et al. Differentiation potential of stem cells from human dental origin: promise for tissue engineering. *J Physiol Pharmacol* 2009;60(Suppl 7):167-175.
78. Kraft DC, Bindslev DA, Melsen B, Abdallah BM, Kassem M, Klein-Nulend J. Mechanosensitivity of dental pulp stem cells is related to their osteogenic maturity. *Eur J Oral Sci* 2010;118:29-38.
79. Zheng Y, Liu Y, Zhang CM, Zhang HY, Li WH, Shi S et al. Stem cells from deciduous tooth repair mandibular defect in swine. *J Dent Res* 2009;88:249-254.
80. Yalvac ME, Ramazanoglu M, Rizvanov AA, Sahin F, Bayrak OF, Salli U et al. Isolation and characterization of stem cells derived from human third molar tooth germs of young adults: implications in neovascularization, osteo-, adipo- and neurogenesis. *Pharmacogenomics J* 2010;10:105-113.
81. Koyama N, Okubo Y, Nakao K, Bessho K. Evaluation of pluripotency in human dental pulp cells. *J Oral Maxillofac Surg* 2009;67:501-506.

82. Pan K, Sun Q, Zhang J, Ge S, Li S, Zhao Y et al. Multilineage differentiation of dental follicle cells and the roles of Runx2 over-expression in enhancing osteoblast/cementoblast-related gene expression in dental follicle cells. *Cell Prolif* 2010;43:219-228.
83. Inanc B, Elcin AE, Elcin YM. Effect of osteogenic induction on the *in vitro* differentiation of human embryonic stem cells cocultured with periodontal ligament fibroblasts. *Artif Organs* 2007;31:792-800.
84. Elcin YM, Inanc B, Elcin AE. Human embryonic stem cell differentiation on periodontal ligament fibroblasts. *Methods Mol Biol* 2010;584:269-281.
85. Cao T, Heng BC, Ye CP, Liu H, Toh WS, Robson P et al. Osteogenic differentiation within intact human embryoid bodies result in a marked increase in osteocalcin secretion after 12 days of *in vitro* culture, and formation of morphologically distinct nodule-like structures. *Tissue Cell* 2005;37:325-334.
86. Tian XF, Heng BC, Ge Z, Lu K, Rufaihah AJ, Fan VT et al. Comparison of osteogenesis of human embryonic stem cells within 2D and 3D culture systems. *Scand J Clin Lab Invest* 2008;68:58-67.
87. Heng BC, Toh WS, Pereira BP, Tan BL, Fu X, Liu H et al. An autologous cell lysate extract from human embryonic stem cell (hESC) derived osteoblasts can enhance osteogenesis of hESC. *Tissue Cell* 2008;40:219-228.
88. Kang HK, Roh S, Lee G, Hong SD, Kang H, Min BM. Osteogenic potential of embryonic stem cells in tooth sockets. *Int J Mol Med* 2008;21:539-544.
89. Toh WS, Yang Z, Liu H, Heng BC, Lee EH, Cao T. Effects of culture conditions and bone morphogenetic protein 2 on extent of chondrogenesis from human embryonic stem cells. *Stem Cells* 2007;25:950-960.
90. Toh WS, Guo XM, Choo AB, Lu K, Lee EH, Cao T. Differentiation and enrichment of expandable chondrogenic cells from human embryonic stem cells *in vitro*. *J Cell Mol Med* 2009;13:3570-3590.
91. Toh WS, Lee EH, Guo XM, Chan JK, Yeow CH, Choo AB et al. Cartilage repair using hyaluronan hydrogel-encapsulated human embryonic stem cell-derived chondrogenic cells. *Biomaterials* 2010;31:6968-6980.
92. Feng J, Coppes RP. Can we rescue salivary gland function after irradiation? *ScientificWorldJournal* 2008;8:959-962.
93. Kagami H, Wang S, Hai B. Restoring the function of salivary glands. *Oral Dis* 2008;14:15-24.
94. Feng J, van der Zwaag M, Stokman MA, van Os R, Coppes RP. Isolation and characterization of human salivary gland cells for stem cell transplantation to reduce radiation-induced hyposalivation. *Radiation Oncol* 2009;92:466-471.
95. Sato A, Okumura K, Matsumoto S, Hattori K, Hattori S, Shinohara M et al. Isolation, tissue localization, and cellular characterization of progenitors derived from adult human salivary glands. *Cloning Stem Cells* 2007;9:191-205.
96. Lombaert IM, Hoffman MP. Epithelial stem/progenitor cells in the embryonic mouse submandibular gland. *Front Oral Biol* 2010;14:90-106.
97. Gorjup E, Danner S, Rotter N, Habermann J, Brassat U, Brummendorf TH et al. Glandular tissue from human pancreas and salivary gland yields similar stem cell populations. *Eur J Cell Biol* 2009;88:409-421.
98. Lombaert IM, Brunsting JF, Wierenga PK, Faber H, Stokman MA, Kok T et al. Rescue of salivary gland function after stem cell transplantation in irradiated glands. *PLoS One* 2008;3:e2063.
99. Kishi T, Takao T, Fujita K, Taniguchi H. Clonal proliferation of multipotent stem/progenitor cells in the neonatal and adult salivary glands. *Biochem Biophys Res Commun* 2006;340:544-552.
100. Katsumata O, Sato Y, Sakai Y, Yamashina S. Intercalated duct cells in the rat parotid gland may behave as tissue stem cells. *Anat Sci Int* 2009;84:148-154.
101. Matsumoto S, Okumura K, Ogata A, Hisatomi Y, Sato A, Hattori K et al. Isolation of tissue progenitor cells from duct-ligated salivary glands of swine. *Cloning Stem Cells* 2007;9:176-190.
102. Sugito T, Kagami H, Hata K, Nishiguchi H, Ueda M. Transplantation of cultured salivary gland cells into an atrophic salivary gland. *Cell Transplant* 2004;13:691-699.
103. Yaniv A, Neumann Y, David R, Stiubea-Cohen R, Orbach Y, Lang S et al. Establishment of immortal multipotent rat salivary progenitor cell line toward salivary gland regeneration. *Tissue Eng Part C Methods* 2010 Sept 21 [Epub ahead of print].
104. Tran SD, Pillemer SR, Dutra A, Barrett AJ, Brownstein MJ, Key S et al. Differentiation of human bone marrow-derived cells into buccal epithelial cells *in vivo*: a molecular analytical study. *Lancet* 2003;361:1084-1088.
105. Shibuya M, Miura T, Fukagawa Y, Akashi S, Oda T, Kawamura S et al. Tongue muscle-derived stem cells express connexin 43 and improve cardiac remodeling and survival after myocardial infarction in mice. *Circ J* 2010;74:1219-1226.
106. Sullivan JM, Borecki AA, Oleskevich S. Stem and progenitor cell compartments within adult mouse taste buds. *Eur J Neurosci* 2010;31:1549-1560.
107. Marynka-Kalmani K, Treves S, Yafee M, Rachima H, Gafni Y, Cohen MA et al. The lamina propria of adult human oral mucosa harbors a novel stem cell population. *Stem Cells* 2010;28:984-995.
108. Lee HJ, Cha KE, Hwang SG, Kim JK, Kim GJ. *In vitro* screening system for hepatotoxicity: comparison of bone marrow-derived mesenchymal stem cells and placenta-derived stem cells. *J Cell Biochem* 2010 Jun 3 [Epub ahead of print].
109. Cao T, Lu K, Fu X, Heng BC. Differentiated fibroblastic progenies of human embryonic stem cells for toxicology screening. *Cloning Stem Cells* 2008;10:1-10.
110. Trubiani O, Caputi S, Di Iorio D, D'Amario M, Paludi M, Giancola R et al. The cytotoxic effects of resin-based sealers on dental pulp stem cells. *Int Endod J* 2010;43:646-653.
111. Wang TT, Zeng GC, Li XC, Zeng HP. *In vitro* studies on the antioxidant and protective effect of 2-substituted -8-hydroxyquinoline derivatives against H₂O₂-induced oxidative stress in BMSCs. *Chem Biol Drug Des* 2010;75:214-222.
112. Eduardo Fde P, Bueno DF, de Freitas PM, Marques MM, Passos-Bueno MR, Eduardo Cde P et al. Stem cell proliferation under low intensity laser irradiation: a preliminary study. *Lasers Surg Med* 2008;40:433-438.
113. Winther Nielsen H. Light microscopy and morphometry of vinblastine *in vivo* cytotoxicity in the different developmental stages of rat incisor ameloblast epithelium. *APMIS Suppl* 1990;11:1-56.
114. Wang ML, Tuli R, Manner PA, Sharkey PF, Hall DJ, Tuan RS. Direct and indirect induction of apoptosis in human mesenchymal stem cells in response to titanium particles. *J Orthop Res* 2003;21:697-707.
115. Paganelli C, Fontana P, Porta F, Majorana A, Pazzaglia UE, Sapelli PL. Indications on suitable scaffold as carrier of stem cells in the alveoloplasty of cleft palate. *J Oral Rehabil* 2006;33:625-629.
116. Chen F, Lam WM, Lin CJ, Qiu GX, Wu ZH, Luk KD et al. Biocompatibility of electrophoretic deposition of nanostructured hydroxyapatite coating on roughen titanium surface: *in vitro* evaluation using mesenchymal stem cells. *J Biomed Mater Res B Appl Biomater* 2007;82:183-191.
117. Meng B, Chen J, Guo D, Ye Q, Liang X. The effect of titanium particles on rat bone marrow stem cells *in vitro*. *Toxicol Mech Methods* 2009;19:552-558.
118. Douglas T, Liu Q, Humpe A, Wiltfang J, Sivananthan S, Warnke PH. Novel ceramic bone replacement material CeraBall seeded with human mesenchymal stem cells. *Clin Oral Implants Res* 2010;21:262-267.

119. Ning C, Ding D, Dai K, Zhai W, Chen L. The effect of Zr content on the microstructure, mechanical properties and cell attachment of Ti-35Nb-xZr alloys. *Biomed Mater* 2010;5:045006.
120. Ding SJ, Shie MY, Hoshiha T, Kawazoe N, Chen G, Chang HC. Osteogenic differentiation and immune response of human bone-marrow-derived mesenchymal stem cells on injectable calcium-silicate-based bone grafts. *Tissue Eng Part A* 2010;16:2343-2354.
121. Schwengberg S, Bohlen H, Kleinsasser N, Kehe K, Seiss M, Walther UI et al. *In vitro* embryotoxicity assessment with dental restorative materials. *J Dent* 2005;33:49-55.
122. Bedi RS, Beving DE, Zanello LP, Yan Y. Biocompatibility of corrosion-resistant zeolite coatings for titanium alloy biomedical implants. *Acta Biomater* 2009;5:3265-3271.
123. Tummers M, Thesleff I. The importance of signal pathway modulation in all aspects of tooth development. *J Exp Zool B Mol Dev Evol* 2009;312B:309-319.
124. Ravindran S, Song Y, George A. Development of three-dimensional biomimetic scaffold to study epithelial-mesenchymal interactions. *Tissue Eng Part A* 2010;16:327-342.
125. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med* 2009;6:e1000029.
126. Francois M, Romieu-Mourez R, Stock-Martineau S, Boivin MN, Bramson JL, Galipeau J. Mesenchymal stromal cells cross-present soluble exogenous antigens as part of their antigen-presenting cell properties. *Blood* 2009;114:2632-2638.
127. Miyoshi K, Tsuji D, Kudoh K, Satomura K, Muto T, Itoh K et al. Generation of human induced pluripotent stem cells from oral mucosa. *J Biosci Bioeng* 2010;110:345-350.