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Stem Cells in Teeth:

Supporting Information for Dental Pulp Stem Cells

A healthy future is in your hands

Parent's guide to dental stem cell banking

Stem Cells from Dental Tissue

The presence of stem cells in dental tissue was first reported in the year 2000 by Songtao Shi during his time as a researcher at the National Institute of Health. Since that time there have been thousands of peer reviewed publications by top quality researchers around the world that have studied these cells. These thousands of papers all overwhelmingly support the usefulness of these cells as a human therapeutic approach for the treatment of disease. These cells are found in high abundance, are not controversial, are safe and have tremendous potential for regenerative medicine.

The FDA has not approved stem cells from teeth for therapy yet but those treatments are on the horizon. Here are just a few of the many review articles that represent of hundreds of other peer reviewed papers all of which support the usefulness of stem cells from teeth for the treatment of disease in regenerative medicine.

Dental stem cells-characteristics and potential.

Bojic S, Volarevic V, Ljujic B, Stojkovic M.
Histol Histopathol. 2014 Jun;29(6):699-706. Epub 2014 Jan 21. Review.

http://www.ncbi.nlm.nih.gov/pubmed/24446280

Imperative role of dental pulp stem cells in regenerative therapies: a systematic review.

Kabir R, Gupta M, Aggarwal A, Sharma D, Sarin A, Kola MZ.
Niger J Surg. 2014 Jan;20(1):1-8. doi: 10.4103/1117-6806.127092. Review.

http://www.ncbi.nlm.nih.gov/pubmed/24665194

Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine.

Huang GT, Gronthos S, Shi S. J Dent Res.
2009 Sep;88(9):792-806. doi: 10.1177/0022034509340867. Review.

http://www.ncbi.nlm.nih.gov/pubmed/19767575

Can SHED or DPSCs be used to repair/regenerate non-dental tissues? A systematic review of in vivo studies.

Daltoé FP, Mendonça PP, Mantesso A, Deboni MC. Braz Oral Res. 2014 Jan-Feb;28(1).
pii: S1806-83242014000100401. Epub 2014 Aug 21. Review.

http://www.ncbi.nlm.nih.gov/pubmed/25166769

Stem Cells from Dental Tissue

Stem cells of the dental pulp.

Ranganathan K, Lakshminarayanan V. Indian J Dent Res. 2012 Jul-Aug;23(4):558 doi: 10.4103/0970-9290.104977. Review.

http://www.ncbi.nlm.nih.gov/pubmed/23257502

A novel method for banking dental pulp stem cells.

Gioventù S, Andriolo G, Bonino F, Frasca S, Lazzari L, Montelatici E, Santoro F, Rebulla P. Transfus Apher Sci. 2012 Oct;47(2):199-206. doi: 10.1016/j.transci.2012.06.005. Epub 2012 Jul 11. Review.

http://www.ncbi.nlm.nih.gov/pubmed/22795998

Osteoblastic/cementoblastic and neural differentiation of dental stem cells and their applications to tissue engineering and regenerative medicine.

Kim BC, Bae H, Kwon IK, Lee EJ, Park JH, Khademhosseini A, Hwang YS. Tissue Eng Part B Rev. 2012 Jun;18(3):235-44. doi: 10.1089/ten.TEB.2011.0642. Epub 2012 Mar 6. Review.

http://www.ncbi.nlm.nih.gov/pubmed/22224548

Biological approaches toward dental pulp regeneration by tissue engineering.

Sun HH, Jin T, Yu Q, Chen FM. J Tissue Eng Regen Med. 2011 Apr;5(4):e1-16. doi: 10.1002/term.369. Epub 2010 Dec 30. Review

ttp://www.ncbi.nlm.nih.gov/pubmed/21413154

Neural crest stem cells: discovery, properties and potential for therapy.

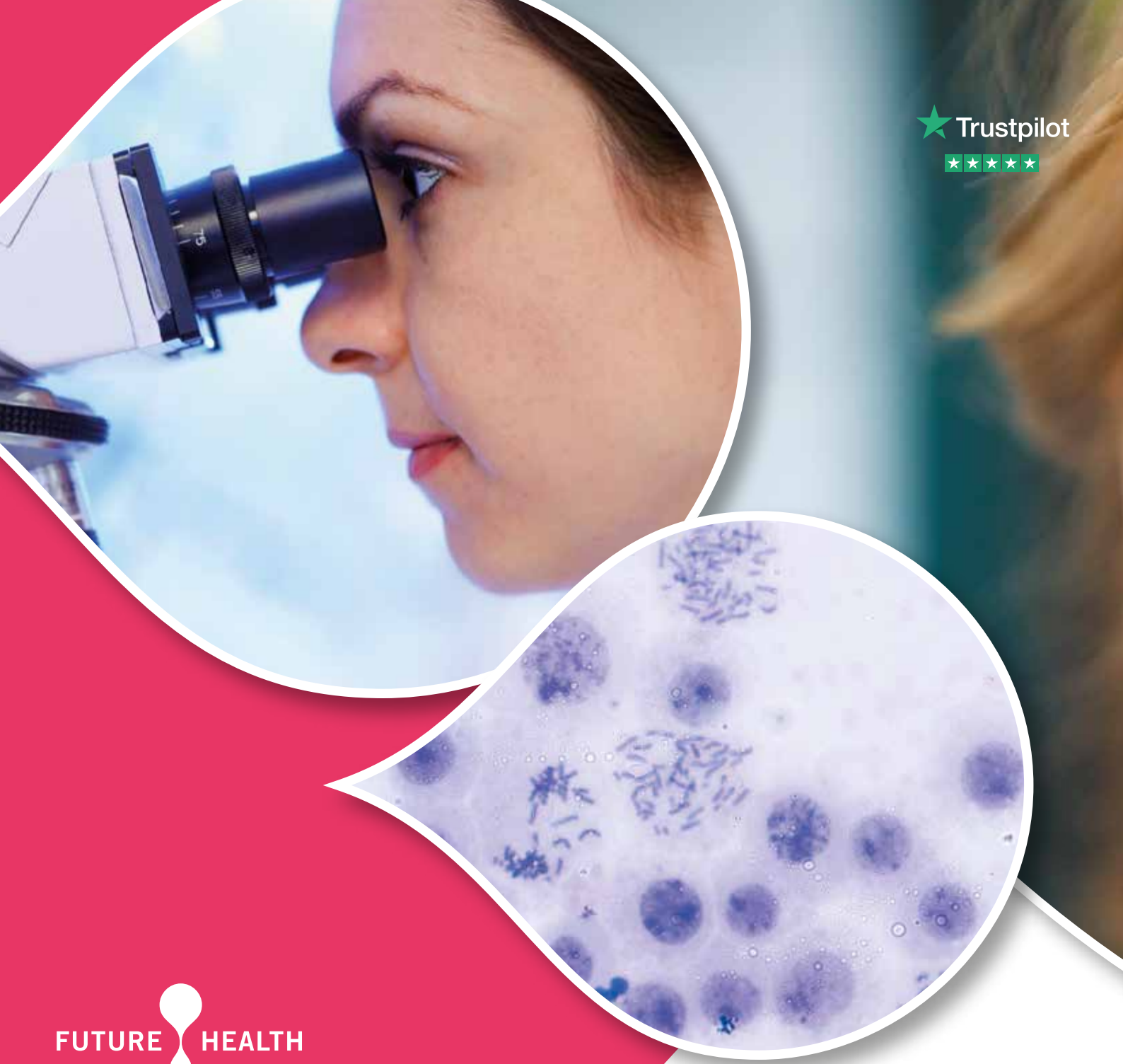
Achilleos A, Trainor PA. Cell Res. 2012 Feb;22(2):288-304. doi: 10.1038/cr.2012.11. Epub 2012 Jan 10. Review.

http://www.ncbi.nlm.nih.gov/pubmed/22231630

Stem cells in dental pulp of deciduous teeth.

Kerkis I, Caplan AI. Tissue Eng Part B Rev. 2012 Apr;18(2):129-38. doi: 10.1089/ten.TEB.2011.0327. Epub 2011 Dec 28. Review.

http://www.ncbi.nlm.nih.gov/pubmed/22032258



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Stem Cells in Teeth:

Supporting Information for Dental Pulp Stem Cells

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Selected Publications on Therapy Using Stem Cells

This of peer-reviewed publications shows the use of mesenchymal stem cells (MSC) in Humans (in vivo) these highlighted in BOLD. This list peer-reviewed publications illustrates research using Dental Pulp Stem Cells (DPSC) in Animals/ Humans (in vivo) and in a dish (in vitro). In vivo studies are those in which the DPSC are evaluated in living organism using animal models or humans in a clinical trial. In vitro studies are those in which DPSC are evaluated with cells in a laboratory. This document is intended to illustrate the current work (since 2001) being completed for each disease/disorder, it is NOT comprehensive. There are hundreds of clinical trials being conducted with MSC for various conditions or diseases, and many news stories of individual applications that have never been published in a medical journal. There are also thousands of publication papers available regarding stem cells from teeth.

Cartilage Repair

Stem cells have been shown to differentiate into chondrocytes. Stem cells have been used to repair knee cartilage damaged by ageing, trauma, or degenerative diseases.

Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study.

Vangsness CT Jr, Farr J 2nd, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. "Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study." J Bone Joint Surg Am. (2014). PMID: 24430407

http://www.ncbi.nlm.nih.gov/pubmed/24430407

** Randomized, double-blind, controlled study, the safety of the intra-articular injection of human mesenchymal stem cells into the knee. There was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human mesenchymal stem cells.

Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months.

Wakitani S, Okabe T, Horibe S, Mitsuoka T, Saito M, Koyama T, Nawata M, Tensho K, Kato H, Uemat su K, Kuroda R, Yoshiya S, Hattori K, Ohgushi H. "Safety of autologous bone marrowderived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months." J Tissue Eng Regen Med. (2011). PMID: 20603892

http://www.ncbi.nlm.nih.gov/pubmed/20603892

**Autologous BMSCs are thought to be safe due to absence of immunological reactions and disease transmission. The potential for tumor formation over long-term follow up was evaluated in this study. No tumors nor infections were observed between 5 and 137 months of follow up. Autologous BMSC transplantation is a safe procedure and will be widely used around the world.

Cartilage Repair - cont.

Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells.

Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. "Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells." Pain Physician. (2008). PMID: 18523506

http://www.ncbi.nlm.nih.gov/pubmed/18523506

**Case study showing bone marrow mesenchymal stem cells used for knee transplantation. After 24 weeks significant cartilage and meniscus growth was observed as well as increased range of motion. BMMSC can be used in the future for treatment of osteoarthritis and meniscal

Dental Injury/Disease

Stem cells can provide a novel approach to treat diseases like periodontitis, dental caries, and many more. Clinical applications including regeneration of teeth, periodontal ligament regeneration, and salivary gland regeneration will continue to emerge in the near future.

Osteogenic potential of mesenchymal cells embedded in the provisional matrix after a 6-week healing period in augmented and non-augmented extraction sockets: an immunohistochemical prospective pilot study in humans.

Heberer S, Wustlich A, Lage H, Nelson JJ, Nelson K. "Osteogenic potential of mesenchymal cells embedded in the provisional matrix after a 6-week healing period in augmented and non-augmented extraction sockets: an immunohistochemical prospective pilot study in humans." Clin Oral Implants Res (2012) Jan; 23; PMID:21435013

http://www.ncbi.nlm.nih.gov/pubmed/21435013

**The osteogenic potential of mesenchymal cells embedded in a matrix of Bio-Oss was evaluated in human extraction sockets after 6-weeks of healing time. No evidence of acute or chronic inflammation was observed. The matrix demonstrated a high proportion of cells displaying a mature osteoprogenitor cells to osteoblasts.

Dental Injury/Disease - cont.

A novel approach to periodontal tissue regeneration with mesenchymal stem cells and platelet-rich plasma using tissue engineering technology: A clinical case report.

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) Aug; 26; PMID:16939018

http://www.ncbi.nlm.nih.gov/pubmed/16939018

**MSC were isolated from a bone marrow aspirates, platelet-rich plasma (PRP) was isolated from peripheral blood. Treatment results showed a disappearance of bleeding and tooth mobility. There was also evidence of interdental papillae regeneration. The use of MSC in PRP gel might be useful for periodontal tissue regeneration.

Stem cells from dental pulp may one day be used to engineer whole, implantable teeth to replace teeth that are lost due to injury or disease. Pulp regeneration, periodontitis, and root canal formation are some of the active areas of research with dental pulp stem cells.

In vivo

Mobilized dental pulp stem cells for pulp regeneration: initiation of clinical trial. Nakashima M, Iohara K. "Mobilized dental pulp stem cells for pulp regeneration: initiation of clinical trial." J Endod (2014) Apr; 40; PMID:24698690

http://www.ncbi.nlm.nih.gov/pubmed/24698690

**The efficacy and safety of pulp stem cell transplantation was evaluated before initiation of a clinical trial. Quality of dental pulp stem cells was assured by lack of abnormalities/ aberrations in karyotype and lack of tumour formation after transplantation in mice. This study helped establish preclinical safety, feasibility, and efficacy of pulp regeneration by mobilized dental pulp stem cells in an animal model.

Allogeneic Stem Cells From Deciduous Teeth Mediated Treatment for Periodontitis in Miniature Swine.

Fu X, Jin L, Ma P, Fan Z, Wang S. "Allogeneic Stem Cells From Deciduous Teeth Mediated Treatment for Periodontitis in Miniature Swine." J Periodontol (2014) Jun 85; PMID:24001042

http://www.ncbi.nlm.nih.gov/pubmed/24001042

**Regeneration of lost periodontium in periodontitis is a challenge because bone, cementum and periodontal ligament need to be regenerated. Significant restoration in a periodontitis miniature swine model was observed after treatment with stem cells isolated from mini pig deciduous teeth or periodontal ligament. Periodontal ligament connective tissue regeneration was observed with both stem cells groups as compared to controls.

Dental Injury/Disease - cont.

Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells.

Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. "Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells." Pain Physician. (2008). PMID: 18523506

http://www.ncbi.nlm.nih.gov/pubmed/18523506

**Case study showing bone marrow mesenchymal stem cells used for knee transplantation. After 24 weeks significant cartilage and meniscus growth was observed as well as increased range of motion. BMMSC can be used in the future for treatment of osteoarthritis and meniscal

Immunohistochemical and histochemical analysis of newly formed tissues in root canal space transplanted with dental pulp stem cells plus platelet rich plasma.

Zhu X, Wang Y, Liu Y. Huang GT, Zhang C. "Immunohistochemical and histochemical analysis of newly formed tissues in root canal space transplanted with dental pulp stem cells plus platelet rich plasma." J Endod (2014) Oct; 40; PMID:25260728

http://www.ncbi.nlm.nih.gov/pubmed/25260728

**Tissue regeneration in root canals after pulpectomy can be achieved by transplantation of autologous dental pulp stem cells and/or platelet-rich plasma. Molars were extracted in dogs and then dental pulp stem cells alone or mixed with autologous platelet-rich plasma was implanted into each root canal. The tissue formed in the dog mature root canals after regenerative endodontic procedures are not pulp tissues but rather periodontal tissues.

Dental pulp tissue engineering in full-length human root canals.

Rosa V, Zhang Z, Grande RH, Nor JE. "Dental pulp tissue engineering in full-length human root canals." J Dent Res. (2013). Nov;92(11):970-5. PMID:24056227

http://www.ncbi.nlm.nih.gov/pubmed/24056227

**This study investigated whether stem cells from exfoliated deciduous teeth can generate a functional dental pulp when injected into full length root canals. Roots of human premolars were injected with scaffolds containing SHED and implanted into immunedeficient mice. It was found that scaffold containing SHED had similar cellularity and vascularization as compared to control human dental pulps

Dental Injury/Disease - cont.

Preliminary study on dental pulp stem cell-mediated pulp regeneration in canine immature permanent teeth.

Wang Y, Zhao Y, Jia W, Yang J, Ge L. "Preliminary study on dental pulp stem cell-mediated pulp regeneration in canine immature permanent teeth." J Endod. (2013) Feb;39(2):195- 201. PMID:23321230

http://www.ncbi.nlm.nih.gov/pubmed/23321230

**The potential of using autologous dental pulp stem cells for pulp regeneration in a canine pulpless animal model was investigated. Dental pulp stem cells were found to generate pulp-like tissues containing blood vessels and dentin-like tissues. The study illustrates the possibility of using stem cell mediated tissue engineering for pulp regeneration in immature teeth.

Autologous Dental Pulp Stem Cells in Regeneration of Defect Created in Canine Periodontal Tissue.

Mohamadreza BE, Khorsand A, Arabsolghar M, Paknejad M, Ghaedi B, Rohn AR, Moslemi N, Nazarian H, Jahangir S. "Autologous Dental Pulp Stem Cells in Regeneration of Defect Created in Canine Periodontal Tissue." J Oral Implantol (2012) Aug 1; PMID:22852766

http://www.ncbi.nlm.nih.gov/pubmed/22852766

**This study investigated the effects of dental pulp stem cells on regeneration of the defect experimentally created in periodontium of canine model. It was observed that a combination of dental pulp stem cells and Bio-Oss scaffold led to regeneration of bone, cementum and periodontal ligament. The use of a scaffold with dental pulp stem cells can be a promising tool in regeneration of periodontal tissues.

Dental Stem Cell Therapy with Calcium Hydroxide in Dental Pulp Capping.

Ji YM, Jeon SH, Park JY, Chung JH, Choung YH, Choung PH. "Dental Stem Cell Therapy with Calcium Hydroxide in Dental Pulp Capping." Tissue Eng Part A. (2010) Feb 17. PMID: 20055661

http://www.ncbi.nlm.nih.gov/pubmed/20055661

**Calcium hydroxide is used for direct pulp capping and is known to induce hard tissue repair. The relationship between calcium hydroxide and recruitment, proliferation, and mineralization of postnatal dental stem cells obtained from immature dental tissue of beagle dogs was examined. It was found that calcium hydroxide increases recruitment, migration, proliferation, and mineralization of the DPSCs and periodontal ligament stem cells.

Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth.

Cordeiro MM, Dong Z, Kaneko T, Zhang Z, Miyazawa M, Shi S, Smith AJ, Nör JE. "Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth." J Endod. (2008) Aug;34(8):962-9. PMID: 18634928

http://www.ncbi.nlm.nih.gov/pubmed/18634928

**The morphologic characteristics of tissue formed when SHED seeded in biodegradable scaffold within human tooth slices were transplanted into immune-deficient mice in this study. It was found that the new tissue had similar cellularity and architecture as physiological dental pulp.

Diabetes Mellitus (Type I/II)

In type I diabetes mellitus insulin producing cells are destroyed leaving the body incapable of regulating blood glucose. Type II diabetes mellitus is characterized by hyperglycemia or high blood sugar with insulin resistance and relative lack of insulin. A significant number of clinical trials have been reported using stem cells to treat diabetes in humans. The following examples are used to illustrate the type of work being conducted.

Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells.

Carlsson PO, Schwarcz E, Korsgren O, Le Blanc K "Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells." Diabetes (2015) Feb:64(2); PMID:25204974

http://www.ncbi.nlm.nih.gov/pubmed/25204974

**This clinical study describes patients with recently-onset type 1 diabetes being treated with mesenchymal stromal cells. It was observed that patients treated with MSC had preserved response to C-peptide or increased as compared to the non-treated. In addition no side effects of MSC treatment were observed. Autologous MSC treatment in newonset type 1 diabetes constitutes a safe and promising strategy to intervene in disease progression and preserve β-cell function.

Efficacy and safety of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus: a randomized placebo-controlled study.

Bhansali A, Asokumar P, Walia R, Bhansali S, Gupta V, Jain A, Sachdeva N, Sharma RR, Marwaha N, Khandelwal N. "Efficacy and safety of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus: a randomized placebocontrolled study." Cell Transplant (2014); PMID:23561959

http://www.ncbi.nlm.nih.gov/pubmed/23561959

**Autologous bone marrow derived stem cell transplantation resulted in significant decrease in the insulin dose requirement along with an improvement in C-peptide levels.

Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis.

D'Addio F, Valderrama VA, Ben Nasr M, Franek E, Zhu D, Li L, Ning G, Snarski E, Fiorina P. "Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis." Diabetes (2014); PMID:24947362

http://www.ncbi.nlm.nih.gov/pubmed/24947362

**A total of 59% of individuals with type 1 diabetes obtained insulin independence within 6 months after receiving immunosuppressive therapy and a single infusion of autologous HSC. All treated patients observed a decrease in HbA1c and an increase in C-peptide levels.

Diabetes Mellitus (Type I/II) - cont.

Umbilical cord mesenchymal stem cells transfusion ameliorated hyperglycemia in patients with type 2 diabetes mellitus.

Kong D, Zhuang X, Wang D, Qu H, Jiang Y, Li X, Wu W, Xiao J, Liu X, Liu J, Li A, Wang J, Dou A, Wang Y, Sun J, Lv H, Zhang G, Zhang X, Chen S, Ni Y, Zheng C. "Umbilical cord mesenchymal stem cells transfusion ameliorated hyperglycemia in patients with type 2 diabetes mellitus." Clin Lab (2014); PMID:25651730

http://www.ncbi.nlm.nih.gov/pubmed/25651730

**Umbilical cord MSC transfusion is safe and well-tolerated. It effectively alleviates blood glucose, and increases C-peptide levels.

Long term effects of the implantation of Wharton's jellyderived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus.

Hu J, Yu X, Wang Z, Wang F, Wang L, Gao H, Chen Y, Zhao W, Jia Z, Yan S, Wang S. "Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus." Endocr J (2013); PMID:23154532

http://www.ncbi.nlm.nih.gov/pubmed/23154532

7 **This study accessed the long-term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells (WJ-MSC) from the umbilical cord for newly-onset type 1 DM. Newly-onset type 1 DM according to the American diabetes association and diabetic duration of no more than 6 months. There were no reported acute or chronic side effects with patients treated with WJ-MSC. HbA1c and C peptide were significantly better than the non-treatment. Implantation of WJ-MSC for treatment of newly onset type 1 DM is safe and effective. This therapy can restore the function of islet B cells in a longer time, although precise mechanism are unknown.

Long term effects of the implantation of autologous bone marrow mononuclear cells for type 2 diabetes mellitus.

Hu J, Li C, Wang L, Zhang X, Zhang M, Gao H, Yu X, Wang F, Zhao W, Yan S, Wang Y. "Long term effects of the implantation of autologous bone marrow mononuclear cells for type 2 diabetes mellitus." Endocr J (2012); PMID:22814142

http://www.ncbi.nlm.nih.gov/pubmed/22814142

**Long term effects of using autologous bone marrow in the treatment of type 2 diabetes mellitus was evaluated. BM cells were injected into patients' pancreas via catheter. No reported acute or chronic side effects were observed. HbA1c and C-peptide was significantly better with the patients receiving bone marrow mononuclear cells. Mean value of HbA1c showed gradual decrease and reached lowest level at the end of the first year.

Diabetes Mellitus (Type I/II)

Autologous hematopoietic stem cell transplantation modulates immunocompetent cells and improves β-cells function in Chinese patients with new onset of type 1 diabetes.

Li L, Shen S, Ouyang J, Hu Y, Hu L, Cui W, Zhang N, Zhuge YZ, Chen B, Xu J, Zhu D. "Autologous hematopoietic stem cell transplantation modulates immunocompetent cells and improves β-cells function in Chinese patients with new onset of type 1 diabetes." J Clin Endocrinol Metab (2012) May:97(5); PMID:22419704

http://www.ncbi.nlm.nih.gov/pubmed/22419704

**Patients with newly onset type 1 diabetes (within 12 months) were treated with autologous hematopoietic stem cells with cryopreserved CD34+ progenitor cells. (11/13) patients required significantly reduced doses of insulin for glycemic control accompanied by reduced levels of glycosylated hemoglobin and increased C-peptide concentrations. (3/13) experienced exogenous insulin independence for 7-54 months.

Type I diabetes results from destruction of insulin producing cells in the pancreas. Stem cells from teeth have been shown to differentiate into insulin secreting cells. Drugs that suppress the immune response are typically used to prevent the rejection of the stem cells that are transplanted into preclinical models. Immunosuppression drugs can potentially cause an increase in infections and possible cancer. Cells from teeth have been shown to reverse type 1 diabetes in mice without the need for drugs that suppress the immune response.

A feasibility study of an in vitro differentiation potential toward insulin-producing cells by dental tissue-derived mesenchymal stem cells.

Sawangmake C, Nowwarote N, Pavasant P, Chansiripornchai P, Osathanon T. "A feasibility study of an in vitro differentiation potential toward insulin-producing cells by dental tissuederived mesenchymal stem cells." Biochem Biophys Res Commun. (2014) Sep;26(452):581-7. PMID: 25181343

http://www.ncbi.nlm.nih.gov/pubmed/25181343

**In this study it was found that human dental pulp stem cells derived insulin producing cells expressed pro-insulin and release of c-peptide upon glucose stimulation to a better extent than human periodontal ligament stem cells. Overall human DPSC had better differentiation potential towards insulin producing cells as compared to human PDLSC.

In vitro differentiation into insulin-producing β-cells of stem cells isolated from human amniotic fluid and dental pulp.

Carnevale G, Riccio M, Pisciotta A, Beretti F, Maraldi T, Zavatti M, Cavallini GM, La Sala GB, Ferrari A, De Pol A. "In vitro differentiation into insulin-producing β-cells of stem cells isolated from human amniotic fluid and dental pulp." Dig Liver Dis. (2013) Aug;45(8):669-76. PMID: 23643565

http://www.ncbi.nlm.nih.gov/pubmed/23643565

**Human amniotic fluid stem cells and human dental pulp stem cells were induced to differentiate into pancreatic β-cells. By day 21 islet-like structures derived from both human amniotic fluid stem cells and human dental pulp stem cells released insulin in a glucose dependent manner.

Diabetes Mellitus (Type I/II) - cont.

Differentiation of Dental Pulp Stem Cells Into Islet Like Aggregates.

Govindasamy V, Ronald VS, Abdullah AN, Ganesan Nathan KR, Ab Aziz ZA, Abdullah M, Musa S, Abu Kasim NH, Bhonde RR. "Differentiation of Dental Pulp Stem Cells Into Islet Like Aggregates." J Dent Res. (2011) Feb 18. PMID: 21335539

http://www.ncbi.nlm.nih.gov/pubmed/21335539

**DPSC differentiated into pancreatic cell lineage resembling islet-like cell aggregates was investigated. It was confirmed that islet-like cell aggregates were obtained from DPSC via biomarker staining/expression and insulin C-peptide-glucose release. This is the first report demonstrating that DPSC could differentiate into pancreatic cell lineage and offer an unconventional and non-controversial source of human tissue that could be used for autologous stem cell therapy in diabetes.

In vivo Transplantation of Stem Cells Obtained from Murine Dental Pulp Improves Pancreatic Damage, Renal Function and Painful Diabetic Neuropathy in Diabetic Type 1 Mouse Model.

Guimarães, ET, Cruz Gda S, Almeida TF, Souza BS, Kaneto CM, Vasconcelos JF, Santos WL, Santos RR, Villareal CF, Soares MB. "Transplantation of Stem Cells Obtained from Murine Dental Pulp Improves Pancreatic Damage, Renal Function and Painful Diabetic Neuropathy in Diabetic Type 1 Mouse Model." Cell Transplantation (2013). 22(12);2345-54. PMID:23068779

http://www.ncbi.nlm.nih.gov/pubmed/23068779

**A diabetic mouse model was used to investigate dental pulp stem cells treatment. Results indicate that DPSC may contribute to pancreatic B-cell renewal, prevention of renal damage, and production of powerful/long-lasting effect on behavioral neuropathic pain. Stem cell therapy can be option of the control of diabetes complications such as intractable diabetic neuropathic pain.

Transplantation of islet-like cell clusters derived from human dental pulp stem cells restores normoglycemia in diabetic mice.

Kanafi MM, Rajeshwari YB, Gupta S, Dadheech N, Nair PD, Gupta PK, Bhonde RR. "Transplantation of islet-like cell clusters derived from human dental pulp stem cells restores normoglycemia in diabetic mice." Cytotherapy. (2013) Oct;15(10):1228-36. PMID: 23845187

http://www.ncbi.nlm.nih.gov/pubmed/23845187

**It has been shown that stem cells from human exfoliated deciduous teeth were superior to dental pulp stem cells form permanent teeth in terms of treatment of hyperglycemic mice. Diabetic mice that were restored to normoglycemia within 3-4 weeks of treatment persisted for over 60 days. This is the first report in which islet-like cell clusters derived from SHED reversed diabetes in mice without immunosuppression and offer an autologous and non-controversial source of MSC for stem cell therapy in diabetes.

Ischemia/angiogenesis/vasculogenesis

Stem cells can be used to create new blood vessels. They could be used in the treatment of heart damage from heart attack, and to grow blood vessels to give blood a route to regenerated tissue or tissue that has lost its blood supply. Stem cell therapy will have an increased role in the treatment of limb ischemia, which is characterized as the obstruction of arties that reduces blood flow to the extremities like hands, feet, and legs.

A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cells in critical limb ischemia.

Gupta PK, Chullikana A, Parakh R, Desai S, Das A, Gottipamula S, Krishnamurthy S, Anthony N, Pherwani A, Majumdar AS. "A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cells in critical limb ischemia." J Transl Med (2013); PMID:24480430

http://www.ncbi.nlm.nih.gov/pubmed/23758736

**Patients were administered with allogenic bone marrow MSC, improvement was observed in the rest pain scores. Significant increase in ABPI and angle pressure was seen in patients treated with bone marrow MSC. BM-MSC were found to be safe when injected IM.

Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients.

Kirana S, Stratmann B, Prante C, Prohaska W, Koerperich H, Lammers D, Gastens MH, Quast T, Negrean M, Stirban OA, Nandrean SG, Gotting C, Minartz P, Kleesiek K, Tschoepe D. "Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients." Int J Clin Pract (2012); PMID:22284892

http://www.ncbi.nlm.nih.gov/pubmed/22284892

**Bone marrow mononuclear cells were compared to expanded bone marrow cells enriched in CD90+ cells in treatment of diabetic ulcers ability to induce revascularization. The transplantation of of BMC and TRC was proven to be safe and feasible. Improvement of microcirculation and complete would healing was observed in the transplant groups.

Therapeutic angiogenesis in patients with severe limb ischemia by transplantation of a combination stem cells product.

Lasala GP, Silva JA, Minguell JJ. "Therapeutic angiogenesis in patients with severe limb ischemia by transplantation of a combination stem cells product." J Thorac Cardiovasc Surg (2012); PMID:22079876

http://www.ncbi.nlm.nih.gov/pubmed/22079876

**Patients with limb ischemia received an infusion of cell product in the most ischemic leg. Efficacy assessment indicated that after cell infusion there was a significant improvement in walking time an dangle-brachial index.

Ischemia/angiogenesis/vasculogenesis - cont.

A long-term follow-up study of intravenous autologous mesenchymal stem cells transplantation in patients with ischemic stroke.

Lee JS, Hong JM, Moon GL, Lee PH, Ahn YH, Bang OY. "A long-term follow-up study of intravenous autologous mesenchymal stem cells transplantation in patients with ischemic stroke." Stem Cells (2010); PMID:20506226

http://www.ncbi.nlm.nih.gov/pubmed/20506226

**Evaluated MSC transplantation in patients with ischemic stroke. Clinical improvement in the MSC group was associated with serum levels of stromal cell derived factor. IV administration of autologous MSC transplantation was safe for stroke patients during long term follow up.

Dental pulp stem cells can be used to create new blood vessels. They have been used in the treatment of heart damage from heart attack, and to grow blood vessels to give blood a route to regenerated tissue or tissue that has lost its blood supply in animal models. There is proof that transplanted dental pulp cells can increase blood flow by forming high density capillaries in animal models.

Pro-Angiogenic impact of dental stem cells in vitro and in vivo.

Hilkens P, Fanton Y, Martens P, Gervois T, Struys T, Politis C, Lambrichts I, Bronchaers A. "ProAngiogenic impact of dental stem cells in vitro and in vivo." Stem Cell Research. (2014)

http://www.sciencedirect.com/science/article/pii/S187350611400035X

**Dental stem cells had activation of several important components of the angiogenic cascade. This data shows the pro-angiogenic influence of DPSC and SCAPS in vitro/ in vivo in comparison to human fibroblast cells.

Human dental pulp-derived stem cells protect against hypoxic-ischemic brain injury in neonatal mice.

Yamagata M, Yamamoto A, Kako E, Kaneko N, Matsubara K, Sakai K, Sawamoto K, Ueda M. "Human dental pulp-derived stem cells protect against hypoxic-ischemic brain injury in neonatal mice." Stroke (2013) Feb;44(2):551-4. PMID:23238858

ttp://www.ncbi.nlm.nih.gov/pubmed/23238858

**Perinatal hypoxia-ischemia has high rates of neurological deficits and mortality. The therapeutic effects of human exfoliated deciduous teeth (SHED) in neonatal hypoxiaischemia was investigated. It was found that transplanted SHED (not fibroblast) significantly reduced brain tissue loss and improved neurological function. SHED also improved the survival of the mice.

Ischemia/angiogenesis/vasculogenesis - cont.

Stem cells from human exfoliated deciduous tooth-derived conditioned medium enhance recovery of focal cerebral ischemia in rats.

Inoue T, Sugiyama M, Hattori H, Wakita H, Wakabayashi T, Ueda M. "Stem cells from human exfoliated deciduous tooth-derived conditioned medium enhance recovery of focal cerebral ischemia in rats." Tissue Eng Part A, (2013) Jan;19(1-2):24-9. PMID:22839964.

http://www.ncbi.nlm.nih.gov/pubmed/22839964

**In this study they investigated the effect of SHED on permanent middle cerebral artery occlusion (MCAO). Adult rats with MCAO were nasally administered SHED cells. It was found that intranasally administered SHED may help in the recovery of acute stroke. Regenerative therapy using SHED is very safe with no associated problems, it should be considered as a potential candidate for the innovative treatment of cerebral ischemia.

A novel stem cell source for vasculogenesis in ischemia: subfraction of side population cells from dental pulp.

Iohara K, Zheng L, Wake H, Ito M, Nabekura J, Wakita H, Nakamura H, Into T, Matsushita K, Nakashima M. "A novel stem cell source for vasculogenesis in ischemia: subfraction of side population cells from dental pulp." Stem Cells. (2008) Sep;26(9):2408-18. Jun 26. PMID: 18583536

http://www.ncbi.nlm.nih.gov/pubmed/18583536

**A highly vasculogenic subfraction of side population was isolated from dental pulp cells. In a mouse model of hind limb ischemia local transplantation of the subfraction resulted in successful engraftment and an increase in blood flow including high density capillary formation.

Intraventricular injection of human dental pulp stem cells improves Hypoxic-Ischemic brain damage in neonatal rats.

Fang CZ, Yang YJ, Wang QH, Yao Y, Zhang XY, He XH. "Intraventricular injection of human dental pulp stem cells improves Hypoxic-Ischemic brain damage in neonatal rats." PLoS One. (2013) Jun 14;8(6). PMID: 23799131

http://www.ncbi.nlm.nih.gov/pubmed/?term=23799131

**Neonatal rats were injected intraventricularly with human dental pulp stem cells to access hypoxic ischemic brain damage. The hypoxic-ischemic brain damaged group of rats showed improvement as compared to controls on all behavior test. DPSC were found in the injected region and the left cortex. Intraventricular injection of human DPSCs improves hypoxicischemia brain damage in neonatal rats.

Liver Disease

Mesenchymal stem cells have emerged as a promising therapy for various liver conditions/diseases including infection and inflammation (hepatitis), congenital liver disease, and alcoholism. Human clinical trials using MSC for liver pathologies are increasing in number and those that have been published have shown improvements in patient outcome.

Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials.

Ma XR, Tang YL, Xuan M, Chang Z, Wang XY, Liang XH. "Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials." Gastroenterol Res Pract (2015); PMID:25861263

http://www.ncbi.nlm.nih.gov/pubmed/25861263

**Bone marrow MSC therapy significantly improved liver function in patients with end-stage liver cirrhosis. This therapy is safe and effective in improving liver function. Different variables should be controlled to optimize the therapeutic effects.

Short-term evaluation of autologous transplantation of bone marrow-derived mesenchymal stem cells in patients with cirrhosis: Egyptian study.

Amin MA, Sabry D, Rashed LA, Aref WM, el-Ghobary MA, Farhan MS, Fouad HA, Youssef YA. "Short-term evaluation of autologous transplantation of bone marrow-derived mesenchymal stem cells in patients with cirrhosis: Egyptian study." Clin Transplant (2013); PMID:23923970

http://www.ncbi.nlm.nih.gov/pubmed/23923970

**The safety and efficacy of autologous transplantation of bone marrow-derived stromal cells in post HCV liver cirrhosis patients was evaluated. A decrease was detected in the total bilirubin, AST/ALT and an increase in albumin after treatment with BM-SC. This study demonstrates the safety, feasibility, and efficacy of the intrasplenic injection of autologous BM stromal cells in improving liver function in Egyptian patients with cirrhosis.

Pilot study of umbilical cord-derived mesenchymal stem cells transfusion in patients with primary biliary cirrhosis.

Wang L, Li J, Liu H, Li Y, Fu J, Sun Y, Xu R, Lin H, Wang S, Lv S, Chen L Zou Z, Li B, Shi M, Zhang Z, Wang FS. "Pilot study of umbilical cord-derived mesenchymal stem cells transfusion in patients with primary biliary cirrhosis." J Gastroenterol Hepatol (2013); PMID:23855301

http://www.ncbi.nlm.nih.gov/pubmed/23855301

**Symptoms such as fatigue and pruritus were relieved from patients receiving umbilical cord derived MSC. UC-MSC transfusion is feasible and well tolerated in patients.

Dental pulp stem cells have recently been shown to differentiate into functional hepatocyte or liver cells. Stem cells from human exfoliated deciduous teeth (SHED) as well as stem cells from third molar or wisdom teeth have the capacity to differentiate into hepatocytes. They have been used in preclinical animal models to treat acute liver injury or secondary biliary cirrhosis. These cells were found to incorporate into the donor liver and restore liver function.

Liver Disease - cont.

Human dental pulp stem cells derived from cryopreserved dental pulp tissues of vital extracted teeth with disease demonstrate hepatic-like differentiation.

Chen YK, Huang AH, Chan AW, Lin LM "Human dental pulp stem cells derived from cryopreserved dental pulp tissues of vital extracted teeth with disease demonstrate hepaticlike differentiation." J Tissue Eng Regen Med. (2013) Aug;16 PMID: 23950016

http://www.ncbi.nlm.nih.gov/pubmed/23950016

**It is shown that human dental pulp stem cells isolated from liquid nitrogen stored dental pulp tissues or freshly derived dental pulp tissues showed hepatic-like differentiation with morphological change and normal karyotype. Differentiated DPSC expressed hepatic function genes and liver specific genes as well as glycogen storage. It was shown that DPSC can differentiate into hepatic-like cells.

High-purity Hepatic Lineage Differentiated from Dental Pulp Stem Cells in Serum-free Medium.

Ishkitiev N, Yaegaki K, Imai T, Tanaka T, Nakahara T, Ishikawa H, Mitev V, Haapasalo M. "High-purity Hepatic Lineage Differentiated from Dental Pulp Stem Cells in Serum-free Medium." Journal of Endodontics (2012). PMID: 22414832

http://www.ncbi.nlm.nih.gov/pubmed/22414832

**The capacity for and purity of hepatocyte-like differentiated dental pulp stem cells without serum was investigated. It was found that without serum both mesenchymal cells from human deciduous and extracted third molar pulp differentiated into high-purity hepatocyte-like cells.

Novel management of acute or secondary biliary liver conditions using hepatically differentiated human dental pulp cells.

Ishkitiev N, Yaegaki K, Imai T, Tanaka T, Fushimi N, Mitev V, Okada M, Tominaga N, Ono S, Ishikawa H. "Novel management of acute or secondary biliary liver conditions using hepatically differentiated human dental pulp cells." Tissue Eng Part A. (2015) Feb;21.3-4. PMID: 25234861

http://www.ncbi.nlm.nih.gov/pubmed/25234861

**It was examined as to whether SHED could hepatically differentiate and be used to treat acute liver injury or secondary biliary cirrhosis. The test for liver function recovery confirmed presence of human hepatic markers in rat blood serum. It was shown that SHED engraft morphologically and functionally into livers of rats having acute injury or secondary biliary cirrhosis.

Multipotent cells from the human third molar: feasibility of cell-based therapy for liver disease.

Ikeda E, Yagi K, Kojima M, Yagyuu T, Ohshima A, Sobajima S, Tadokoro M, Katsube Y, Isoda K, Kondoh M, Kawase M, Go MJ, Adachi H, Yokota Y, Kirita T, Ohgushi H. "Multipotent cells from the human third molar: feasibility of cell-based therapy for liver disease." Differentiation. (2008) May; 76(5):495-505. PMID: 18093227

http://www.ncbi.nlm.nih.gov/pubmed/18093227

**Novel stem cells called tooth germ progenitor cells (TGPC) obtained from third molar or wisdom teeth as characterized. The TFPC was transplanted into liver injury rat model. It was found that TGPC prevented progression of liver fibrosis in the liver of treated rats and contributed to restoration of liver function. TGPC can be a candidate for cell-based therapy to treat liver diseases and offer opportunities for developing therapies in treating tissue repair and regeneration.

Muscle Disease

Regeneration of muscle tissue has been achieved using mesenchymal stem cells. Muscular diseases or conditions such as tendinitis, muscular dystrophy and myositis are actively being investigated.

Transplantation of human umbilical cord-derived mesenchymal stem cells for the treatment of Becker muscular dystrophy in affected pedigree members.

Li P, Cui K, Zhang B, Wang Z, Shen Y, Wang X, Zhang J, Tong F, Li S. "Transplantation of human umbilical cord-derived mesenchymal stem cells for the treatment of Becker muscular dystrophy in affected pedigree members." Int J Mol Med (2015); PMID:25647308

http://www.ncbi.nlm.nih.gov/pubmed/25647308

**Bone marrow MSC therapy significantly improved liver function in patients with end-stage liver cirrhosis. This therapy is safe and effective in improving liver function. Different variables should be controlled to optimize the therapeutic effects.

A clinical study shows safety and efficacy of autologous bone marrow mononuclear cell therapy to improve quality of life in muscular dystrophy patients.

Sharma A, Sane H, Badhe P, Gokulchandran N, Kulkarni P, Lohiya M, Biju H, Jacob VC. "A clinical study shows safety and efficacy of autologous bone marrow mononuclear cell therapy to improve quality of life in muscular dystrophy patients." Cell Transplant (2013); PMID:24070109

http://www.ncbi.nlm.nih.gov/pubmed/24070109

**This study was carried out with patients diagnosed with Duchenne muscular dystrophy, limb-girdle muscular dystrophy, and Becker muscular dystrophy. Autologous bone marrow derived MSC were used. No adverse events were reported. Neurological improvement and overall 86.67% cases showed symptomatic and functional improvements. These data showed an improvement in quality of life of patients having muscular dystrophy

Dental pulp stem cells have been shown to differentiate into myocytes – muscle cells. These stem cells are now being investigated for treatment of genetic conditions like muscular dystrophy in canine models.

Mesenchymal Progenitor Cells from Different Sources and their Potential to Differentiate In Vitro into Muscle Cells.

Ranjith Kumar Indarapu, Leela Krishna and Subhadra Dravida. "Mesenchymal Progenitor Cells from Different Sources and their Potential to Differentiate In Vitro into Muscle Cells." Cell Dev Biol. (2013) doi:10.4172/2168-9296.1000124

**Dental pulp derived mesenchymal stem cells showed more propensity towards myogenic transdifferentiation as compared to umbilical cord tissue stem cells and adipose tissue stem cells.

Muscle Disease - cont.

In-vivo Early transplantation of human immature dental pulp stem cells from baby teeth to golden retriever muscular dystrophy (GRMD) dogs: Local or systemic?

Kerkis I, Ambrosio CE, Kerkis A, Martins DS, Zucconi E, Fonseca SA, Cabral RM, Maranduba CM, Gaiad TP, Morini AC, Vieira NM, Brolio MP, Sant'Anna OA, Miglino MA, Zatz M. "Early transplantation of human immature dental pulp stem cells from baby teeth to golden retriever muscular dystrophy (GRMD) dogs: Local or systemic?" J Transl Med. (2008) Jul 3;6:35. PMID: 18598348

http://www.ncbi.nlm.nih.gov/pubmed/18598348

**Golden retriever muscular dystrophy (GRMD) dogs represent the best available animal model for therapeutic trials aiming at the future treatment of human Duchenne muscular dystrophy. No signs of immune rejection were observed, and the human immature dental pulp stem cells had significant engraftment in the GRMD dog muscles. Better clinical condition were observed in the dog that received monthly arterial injection of DPSC and was still clinically stable at 25 months of age.

In vivo evaluation of human dental pulp stem cells differentiated towards multiple lineages.

Zhang W, Walboomers XF, Van Kuppevelt TH, Daamen WF, Van Damme PA, Bian Z, Jansen JA. "In vivo evaluation of human dental pulp stem cells differentiated towards multiple lineages." J Tissue Eng Regen Med. (2008) Mar-Apr;2(2-3):117-25. PMID: 18338838

http://www.ncbi.nlm.nih.gov/pubmed/

**DPSC showed the ability to further differentiate along odontogenic, myogenic, and adipogenic pathways in vivo and were able to spontaneously differentiate along odontogenic and adipogenic directions in vivo. Stem cells derived from human dental pulp form a suitable source for tissue engineering and cell-mediated therapy.

Myocardial Infarction (Heart Attack)/ Cardiac Diseases

Myocardial infarction is the leading cause of death in the developing world. Heart attack is defined as permanent damage to the heart muscle due to lack of oxygen rich blood flow. Mesenchymal stem cells have been shown to improve an infarcted heart or heart attack in patients. Stem cell transplantation appears to be safe and effective option for treating patients after a heart attack.

Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cells Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial.

Karantalis V, DiFede DL, Gerstenblith G, Pham S, Symes J, Zambrano JP, FishmanJ, Pattany P, McNiece I, et al. "Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cells Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial." Circ Res (2014); PMID:24565698

http://www.ncbi.nlm.nih.gov/pubmed/24565698

**The impact on cardiac structure and function was evaluated after intramyocardial injection of autologous MSC. After 18 months patients receiving MSC had decrease scar mass and increase LV ejection fraction. Intramyocardial injection of autologous MSC produced a regional functional improvement.

Safety and feasibility of intramyocardial versus intracoronary delivery of autologous cell therapy in advanced heart failure: the REGENERATE-IHD pilot study.

Mozid A, Yeo C, Arnous S, Ako E, Saunders N, Locca D, Brookman P, Archbold RA, Rothman M, Mills P, Agrawal S, Marin J, Mathur A. "Safety and feasibility of intramyocardial versus intracoronary delivery of autologous cell therapy in advanced heart failure: the REGENERATE-IHD pilot study." Regen Med (2014); PMID:24935040

http://www.ncbi.nlm.nih.gov/pubmed/24935040

**The safety and efficacy of three different delivery routes of bone marrow MSC in patients with ischemic heart failure was evaluated. No significant differences were found in terms of safety and feasibility between different delivery routes. There was improved heart failure symptoms in the patients treated with intramyocardial injection of mobilized BMSCs.

Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE trial.

Perin EC, Sanz-Ruiz R, Sanchez PL, Lasso J, Perez-Cano R, Alonso-Farto JC, Perez-David E, Fernandez-Santos ME, Surreys PW, et al. "Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE trial." Am Heart J (2014); PMID:24952864

http://www.ncbi.nlm.nih.gov/pubmed/24952864

**The safety and feasibility of transendocardial injections of adipose derived regenerative cells was evaluated in patients with no options that had ischemic cardiomyopathy. Isolation and transendocardial injection of autologous ADRCs in no-option patients were safe and feasible. Results suggest that ADRCs may preserve ventricular function, myocardial perfusion, and exercise capacity in these patients.

Myocardial Infarction (Heart Attack)/ Cardiac Diseases - cont.

Late TIME: a phase-II, randomized, double-blindied, placebo-controlled, pilot trial evaluating the safety and effect of administration of bone marrow mononuclear cells 2 to 3 weeks after acute myocardial infarction.

Traverse JH, Henry TD, Vaughan DE, Ellis SG, Pepine CJ, Willerson JT, Zhao DX et al. "Late TIME: a phase-II, randomized, double-blindied, placebo-controlled, pilot trial evaluating the safety and effect of administration of bone marrow mononuclear cells 2 to 3 weeks after acute myocardial infarction." Tex Heart Inst J. (2010); PMID:20844613

http://www.ncbi.nlm.nih.gov/pubmed/20844613

**This study evaluated cardiac output after a single infusion of autologous bone marrow mononuclear cells administered 2-3 weeks after acute myocardial infarction. Insight into the clinical feasibility and appropriate timing of autologous cell therapy in high risk patients after myocardial infarction.

Combined delivery approach of bone marrow mononuclear stem cells early and late after myocardial infarction: the MYSTAR prospective, randomized study.

Gyongyosi M, Lang I, Dettke M, Beran G, Graf S, Socher H, Nyolczas N, Charwat S et al. "Combined delivery approach of bone marrow mononuclear stem cells early and late after myocardial infarction: the MYSTAR prospective, randomized study." Nat Clin Pract Cardiovasc Med (2009); PMID:19002124

http://www.ncbi.nlm.nih.gov/pubmed/19002124

**Patients were randomly assigned stem cell delivery via intramyocardial injection and intracoronary infusion after acute myocardial infarction. A high number of cells was required for significant improvements in the primary end points. Combined cardiac stem cell delivery induce a moderate but significant improvement in myocardial infarct size and left ventricular function.

Heart attack often leads to injured/damaged cardiomyoctes or heart cells. Dental pulp stem cells could provide an alternative cell population for repair of damaged cardiac tissue due to heart attack. Preclinical animal models have been treated with human dental pulp stem cells for heart injury caused by a heart attack.

Injured cardiomyocytes promote dental pulp mesenchymal stem cell homing.

Di Scipio F, Sprio AE, Folino A, Carere ME, Salamone P, Yang Z, Berrone M, Prat M, Losano G, Rastaldo R, Berta GN. "Injured cardiomyocytes promote dental pulp mesenchymal stem cell homing." Biochim Biophys Acta. (2014) Jul;1840(7):2152-61. PMID: 24631652

http://www.ncbi.nlm.nih.gov/pubmed/24631652

**A rat dental pulp stem cell line (MUR-1) was used to access stem cell migration in an exvivo model of heart ischemia. It was shown that the cells could reach the injured cells/tissue and make contact with damaged cardiomyocytes. A similarity was reported between what happens during heart organogenesis and early migration of stem cells in ischemic models. Further understanding of the early phase of stem cell migration with a damaged organ will help with future stem cell mediated organ regeneration.

Human dental pulp stem cells improve left ventricular function, induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction.

Gandia C, Armiñan A, García-Verdugo JM, Lledó E, Ruiz A, Miñana MD, Sanchez-Torrijos J, Payá R, Mirabet V, Carbonell-Uberos F, Llop M, Montero JA, Sepúlveda P.
"Human dental pulp stem cells improve left ventricular function,
induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction." Stem Cells. (2008) Mar;26(3):638-45. PMID: 18079433

http://www.ncbi.nlm.nih.gov/pubmed/18079433

**In this study DPSC were used to treat rats that had undergone an induced heart attack. After 4 weeks it was found that cell treated rats had an improvement in cardiac function, anterior wall thickening, and that went along with reduction in infarct size. This data shows that DPSC could provide a novel alternative cell population for cardiac repair.

Neurological Disorders

Stem cell therapies have emerged as a promising option for treating many neurological conditions. Clinical trial data associated with mesenchymal stem cell transplantation is available for neurological conditions such as autism, stroke, cerebral palsy, spinal cord repair, multiple sclerosis, and Parkinson's disease.

Continuous improvement after multiple mesenchymal stem cell transplantation in a patient with complete spinal cord injury.

Jarocha D, Milczarek O, Wedrychowicz A, Kwiatkowski S, Majka M. "Continuous improvement after multiple mesenchymal stem cell transplantation in a patient with complete spinal cord injury." Cell Transplant (2015); PMID:25807231

http://www.ncbi.nlm.nih.gov/pubmed/25807231

**Safety and efficacy of bone marrow nucleated cell and multiple mesenchymal stem cell transplantation in spinal cord injury was evaluated. There were no complications related to the transplantations and no side effects related to the therapy during 2 years of treatment. The patient had improved sensation, bladder control, and improvement in lower muscle control. Repeated intrathecal infusions of MSCs might have the potential to produce clinically meaningful improvements for SCI patients.

Intracerebral implantation of autologous peripheral blood stem cells in stroke patients: a randomized phase II study.

Chen DC, Lin SZ, Fan JR, Lin CH, Lee W, Lin CC, Liu YJ, Tsai CH, Chen JC, Cho DY, Lee CC, Shyu WC. "Intracerebral implantation of autologous peripheral blood stem cells in stroke patients: a randomized phase II study." Cell Transplant (2014); PMID:24480430

http://www.ncbi.nlm.nih.gov/pubmed/24480430

**Peripheral blood stem cells were implanted in stable stroke patients. No serious adverse events were observed and improvements in stroke scales and functional outcomes were greater in the PBSC group than in the control. Implantation of autologous CD34+ PBSC was safe, feasible, and effective in improving functional outcomes.

Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism.

Lv YT, Zhang Y, Liu M, Qiuwaxi JN, Ashwood P, Cho SC, Huan Y, Ge RC, Chen XW, Wang ZJ, Kim BJ, Hu X. "Transplantation of human cord blood mononuclear cells and umbilical cordderived mesenchymal stem cells in autism." J Transl Med (2013); PMID:23978163

http://www.ncbi.nlm.nih.gov/pubmed/23978163

**The safety and efficacy of combined transplantation of human cord blood mononuclear cells and umbilical cord derived mesenchymal stem cells was evaluated in treating children with autism. There were no significant safety issues related to the treatment and no observed severe adverse effects. Differences were shown on childhood autism rating scale, aberrant behaviour checklist, and clinical global impression. Transplantation of CBMNCs showed efficacy compared to the control group.

Neurological Disorders - cont.

Human umbilical cord blood stem cells transplantation for the treatment of chronic spinal cord injury: Electrophysiological changes and long-term efficacy.

Yao L, He C, Zhao Y, Wang J, Tang M, Li J, Wu Y, Ao L, Hu X. "Human umbilical cord blood stem cells transplantation for the treatment of chronic spinal cord injury: Electrophysiological changes and long-term efficacy." Neural Regen Res. (2013); PMC:4146127

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146127/

**Patients with traumatic spinal cord injuries were treated with human umbilical cord blood stem cells. Autonomic nerve functions were restored and latent period of sensory was reduced. No severe adverse effects following stem cell transplantation.

Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study.

Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, Du MQ, Luan SL, Altmann DR, Thompson AJ, Compston A, Scott MA, Miller DH, Chandran S. "Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study." Lancet Neurol (2012); PMID:22236384

http://www.ncbi.nlm.nih.gov/pubmed/22236384

**Patients with secondary progressive multiple sclerosis involving visual pathways received autologous bone-marrow derived mesenchymal stem cells. No severe adverse events were reported. Improvement after treatment in visual acuity and visual evoked response latency was observed.

Treatment of one case of cerebral palsy combined with posterior visual pathway injury using autologous bone marrow mesenchymal stem cells.

Li M, Yu A, Zhang F, Dai G, Cheng, Wang X, An Y. "Treatment of one case of cerebral palsy combined with posterior visual pathway injury using autologous bone marrow mesenchymal stem cells." J Transl Med. (2012); PMID:22607263

http://www.ncbi.nlm.nih.gov/pubmed/22607263

**Autologous bone marrow mesenchymal stem cells were evaluated for treating cerebral palsy. No adverse reactions were observed. Patient was able to walk more smoothly and vision significantly improved 6ml after transplantation.

Neurological Disorders - cont.

Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life.

Sharma A, Gokulchandran N, Chopra G, Kulkarni P, Lohia M, Badhe P, Jacob VC. "Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life." Cell Transplant (2012); PMID:22507683

http://www.ncbi.nlm.nih.gov/pubmed/22507683

**Children suffering from incurable neurological disorders or injury were evaluated with autologous bone marrow derived mononuclear cells. After transplantation there were improvements in neurological muscle power and shift on assessment scales such as Brooke and Vignos. No significant adverse events were noted. The results show that treatment is safe, efficacious, and also improves the quality of life in children with incurable neurological disorders and injury.

A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study.

Kang KS, Kim SW, Oh YH, Yu JW, Kim KY, Park HK, Song CH, Han H. "A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study." Cytotherapy (2005); PMID:16162459

http://www.ncbi.nlm.nih.gov/pubmed/16162459

** Human umbilical cord blood derived stem cells were directly transplanted into the spinal cord site of a 37-year old female patient with a spinal cord injury. HUCBSC improved sensory perception and movement in the SPI patients' hips and thighs. MRI and CT scans revealed regeneration of spinal cord at the injury site.

Dental pulp stem cells have been shown to differentiate into functional neurons in animal models. Dental pulp stem cells have been used to investigate facial nerve defect regeneration, heat stroke, optic nerve injury, and spinal cord injury.

Neurogenic potential of dental pulp stem cells isolated from murine incisors.

Ellis KM, O'Carroll DC, Lewis MD, Rychkov GY, Koblar SA. "Neurogenic potential of dental pulp stem cells isolated from murine incisors." Stem Cell Res Ther. (2014) Fed;27(1). PMID: 24572146

http://www.ncbi.nlm.nih.gov/pubmed/24572146

**Dental pulp stem cells developed a neuronal morphology and high expression of neural markers. In addition intracellular electrophysiological analysis revealed voltage gated channels in the majority of cells with neuronal morphology.

Neurological Disorders - cont.

Midbrain cues dictate differentiation of human dental pulp stem cells towards functional dopaminergic neurons.

Kanafi M, Majumdar D, Bhonde R, Gupta P, Datta I. "Midbrain cues dictate differentiation of human dental pulp stem cells towards functional dopaminergic neurons." J Cell Physiol (2014) Oct; 229(10): 1369-77. PMID: 24477667

http://www.ncbi.nlm.nih.gov/pubmed/24477667

** Dental pulp originating from the neural crest are considered a better source of postnatal stem cell-based therapies in neurodegenerative diseases. Functional studies showed that induced DPSC could secrete dopamine and the induced DPSC showed ATP simulated calcium channel exchange. This study clearly shows for the first time that DPSC in the presence of embryonic midbrain cues show a tendency towards a functional dopaminergic cell type.

Neurogenic differentiation of human dental stem cells.

Lee Joo-Hee, Um S, Song I, Kim H, Seo B. "Neurogenic differentiation of human dental stem cells." J Korean Assoc Oral Maxillofac Surg. (2014) Aug;40(4):173-80. PMID: 25247147

http://www.ncbi.nlm.nih.gov/pubmed/25247147

**Human dental stem cells including human dental pulp stem cells (DPSC), periodontal ligament stem cells (PDLSC), and stem cells from apical papilla (SCAP) may have neurogenic differentiation capability in vitro. Human dental pulp stem cells are a possible alternative source of stem cells for therapeutics use in the treatment of neurological diseases.

Multifaceted neuro-regenerative activities of human dental pulp stem cells for functional recovery after spinal cord injury.

Yamamoto A, Kiyoshi Sakai, Kohki Matsubara, Fumiya Kano, Minoru Ueda. "Multifaceted neuro-regenerative activities of human dental pulp stem cells for functional recovery after spinal cord injury." Neuroscience research. (2013) Jan;78:16-20. PMID:24252618.

http://www.ncbi.nlm.nih.gov/pubmed/24252618

**Primary characteristics of human pulp stem cells and their therapeutic benefits for treating spinal cord injury are summarized. Experimental data from multiple preclinical studies suggest that pulp stem cells may promote functional recovery after stem cells injury through multifaceted neuro-regenerative activities.

Neurological Disorders - cont.

Electrophysiologic and functional evaluations of regenerated facial nerve defectswith a tube containing dental pulp cells in rats.

Sasaki R, Matsumine H, Watanabe Y, Takeuchi Y, Yamato M, Okano T, Miyata M, Ando T. "Electrophysiologic and functional evaluations of regenerated facial nerve defects with a tube containing dental pulp cells in rats." Plast Reconstr Surg. (2014) Nov;134(5):970-8. PMID: 25347632

http://www.ncbi.nlm.nih.gov/pubmed/25347632

**Nerve tubes with dental pulp cells (DPC) promoted facial nerve regeneration in rats. Dental pulp cells tubulation could recover facial nerve defects functionally and elecrophysiologically, the recovery was found to be comparable to that of nerve autografting in Lewis rats. Dental pulp may be a source of easily obtainable cells for potential use in facial nerve regeneration. Further studies are necessary to investigate if nerve guide with DPC can bridge nerve gaps or how many DPC are required for regeneration of facial nerve gaps.

Transplantation of human dental pulp-derived stem cells protects against heat stroke in mice.

Tseng LS, Chen SH, Lin MT, Lin YC. "Transplantation of human dental pulp-derived stem cells protects against heat stroke in mice." Cell Transplant (2014) Mar 7. PMID:24612725

http://www.ncbi.nlm.nih.gov/pubmed/24612725

**The therapeutic effects of SHED for the treatment of multiple organs including brain or hypothalamus injury in heat stroke mice was investigated. Intravenous administration of SHED immediately after whole body heat (WBH) exposure to mice offered the following therapeutic benefits for recovery after heat stroke. 1) Inhibition of WBH induced neurologic and thermoregulatory deficits, 2) reduction of WBH induced ischemia, hypoxia, and oxidative damage to brain, among others. Treatment with SHED post WBH reduced induction of pro-inflammation, enhanced plasma induction, and improved lethality in mice.

Intravitreally transplanted dental pulp stem cells promote neuroprotection and axon regeneration of retinal ganglion cells after optic nerve injury.

Mead B, Logan A, Berry M, Leadbeater W, Scheven BA. "Intravitreally transplanted dental pulp stem cells promote neuroprotection and axon regeneration of retinal ganglion cells after optic nerve injury." Invest Ophthalmol Vis Sci (2013). PMID: 24150755

http://www.ncbi.nlm.nih.gov/pubmed/24150755

**Sprague Dawley rats with optic nerve damage were treated with dental pulp stem cells injected into the vitreous of the eye. It was found that dental pulp stem cells and to a lesser extent bone marrow stem cells had higher survival and neuritogenesis/ axogenesis. Intravitreal transplant of DPSC promoted retinal ganglion cells survival and axon regeneration after optic nerve injury.

Neurological Disorders - cont.

Human Adult Dental Pulp Stem Cells Enhance Poststroke Functional Recovery Through Non-Neural Replacement Mechanisms

Leong, Wai Khay, et al. "Human Adult Dental Pulp Stem Cells Enhance Poststroke Functional Recovery Through Non-Neural Replacement Mechanisms." Stem Cells Translational Medicine 1.3 (2012): 177-187.

http://stemcellstm.alphamedpress.org/content/1/3/177.short

**Human adult dental pulp stem cells have the capacity to differentiate into neurons in vitro. Intracerebral transplantation of human DPSC in a rodent model resulted in improvement of forelimb function 4 weeks after treatment. Neural replacement is the likely mechanism in which DPSC enhance recovery. This study provides preclinical evidence for the use of human DPSC to improve outcome for stroke patients.

Human dental pulp-derived stem cells promote locomotor recovery after complete transection of the rat spinal cord by multiple neuro-regenerative mechanisms.

Sakai, Kiyoshi, A. Yamamoto, K. Matsubara, S. Nakamura, M. Naruse, M. Yamagata et al. "Human dental pulp-derived stem cells promote locomotor recovery after complete transection of the rat spinal cord by multiple neuro-regenerative mechanisms." The Journal of Clinical Investigation 122.1, (2012): 80. PMID: 22133879

http://www.ncbi.nlm.nih.gov/pubmed/22133879

**Transplantation of human dental pulp stem cells into completely transected adult rat spinal cord resulted in recovery of hind limb locomotor function. It was also found that transplantation of human bone marrow stromal cells or skin derived fibroblast had less recovery of locomotor function. Tooth derived stem cells can provide therapeutic benefits for treating spinal cord injury.

Human dental pulp cells: a new source of cell therapy in a mouse model of compressive spinal cord injury.

De Almeida FM, Marques SA, Ramalho Bdos S, Rodrigues RF, Cadilhe DV, Furtado D. et al. "Human dental pulp cells: a new source of cell therapy in a mouse model of compressive spinal cord injury." J Neurotrauma. May 25 (2011) PMID: 21609310

http://www.ncbi.nlm.nih.gov/pubmed/21609310

**In this study human dental pulp cells were transplanted into the epicenter of a mouse spinal cord lesion. It was shown that this strategy promoted better tissue organization, larger areas of white matter preservation, and a better functional outcome. Human dental pulp cells may be used for therapeutic intervention after spinal cord injury and in central nervous system disorders in humans.

Neurological Disorders - cont.

Integration of neuronally predifferentiated human dental pulp stem cells into rat brain in vivo.

Király M, Kádár K, Horváthy DB, Nardai P, Rácz GZ, Lacza Z, Varga G, Gerber G. "Integration of neuronally predifferentiated human dental pulp stem cells into rat brain in vivo." Neurochem Int. (2011) Jan 8. PMID: 21219952

http://www.ncbi.nlm.nih.gov/pubmed/21219952

**Engrafted DPSC derived cells integrate into the host brain and have been shown to have neuronal properties including biomarker expression and functionally with voltage dependent sodium/potassium channels. Predifferentiated human dental pulp stem cells can be used as a source of neuronal replacement in vivo.

Implanted Adult Human Dental Pulp Stem Cells Induce Endogenous Axon Guidance.

Arthur A, Shi S, Zannettino AC, Fujii N, Gronthos S, Koblar SA. "Implanted Adult Human Dental Pulp Stem Cells Induce Endogenous Axon Guidance." Stem Cells. (2009) Sep;27(9):2229-37. PMID: 19544412

http://www.ncbi.nlm.nih.gov/pubmed/19544412

**An avian embryonic model system was used to investigate axon guidance in vivo after transplantation of adult human dental pulp stem cells. This is the first direct evidence that dental pulp stem cells may induce neuroplasticity within a receptive host nervous system.

Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues.

Arthur A, Rychkov G, Shi S, Koblar SA, Gronthos S. "Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues." Stem Cells. (2008) Jul;26(7):1787-95. PMID: 18499892

http://www.ncbi.nlm.nih.gov/pubmed/18499892

**In this study it is shown that human adult dental pulp stem cells respond to neuronal induction conditions both in vitro and in vivo. DPSC expressed neuronal markers and acquired a neuronal morphology following transplantation into the mesencephalon of embryonic chicken embryos.

Putative Dental Pulp Derived Stem/Stromal Cells Promote Proliferation and Differentiation of Endogenous Neural Cells in the Hippocampus of Mice.

Huang AH, Snyder BR, Cheng PH, Chan AW. "Putative Dental Pulp Derived Stem/ Stromal Cells Promote Proliferation and Differentiation of Endogenous Neural Cells in the Hippocampus of Mice." Stem Cells. (2008) Aug 7. PMID: 18687995

http://www.ncbi.nlm.nih.gov/pubmed/18687995

**In this study undifferentiated untreated dental pulp stem cells were grafted into the hippocampus of immune suppressed mice. It was shown that grafting of DPSC promotes proliferation, cell recruitment, and maturation of endogenous stem/progenitor cells by changing local microenvironment. DPSC have a unique therapeutic potential because of the simulating/modulating effects expressed on the local repair response in the central nervous system.

Parkinson's Disease

Stem cell therapy will emerge as an option for Parkinson's disease patients in the near future. Current clinical trials using mesenchymal stem cell transplantation show encouraging results.

Intraarterial autologous implantation of adult stem cells for patients with Parkinson disease.

Brazzini A, Cantella R, De la Cruz A, Yupanqui J, Leon C, Jorquiera T, Brazzani M, Ortega M, Saenz LN. "Intraarterial autologous implantation of adult stem cells for patients with Parkinson disease." J Vasc Interv Radiol. (2010); PMID:20346882

http://www.ncbi.nlm.nih.gov/pubmed/20346882

**Parkinson's disease patients were evaluated with autologous implantation of stem cells. Patients showed mean improvements in disability, activities of daily living, and depression. No complications were observed.

Open-labeled study of unilateral autologous bone marrow-derived mesenchymal stem cell transplantation in Parkinson's disease.

Venkataramana NK, Kumar SK, Balaraju S, Radhakrishnan RC, Bansal A, Dixit A, Rao DK, Das M, Jan M, Gupta PK, Totey SM. "Open-labeled study of unilateral autologous bone-marrowderived mesenchymal stem cell transplantation in Parkinson's disease." Transl Res. (2010); PMID:20129486

http://www.ncbi.nlm.nih.gov/pubmed/20129486

**Single dose, unilateral transplantation of autologous bone-marrow-derived mesenchymal stem cells were evaluated in Parkinson's disease patients. 3/7 patients had improvement in unified Parkinson's disease rating scale. Subjective improvement was found in symptoms like facial expression, gait, and freezing episodes. Number of patients and uncontrolled nature of the trial did not allow for the demonstration of effectiveness of the treatment involved.

Dental pulp stem cells can differentiate into functional neurons and have been used in animals to reduce the symptoms of Parkinson's Disease, a disease of the central nervous system.

Human dental pulp stem cells protect mouse dopaminergic neurons against MPP+ or rotenone. Nesti C, Pardini C, Barachini S, D'Alessandro D, Siciliano G, Murri L, Petrini M, Vaglini F. "Human dental pulp stem cells protect mouse dopaminergic neurons against MPP(+) or rotenone." Brain Res. (2011) Jan 7;1367:94-102. Epub 2010 Sep 18. PMID: 20854799

http://www.ncbi.nlm.nih.gov/pubmed/20854799

**Co-culture with DPSCs significantly attenuated MPP+ or rotenone-induced toxicity in primary cultures of neurons. DPSC can be viewed as possible candidates for studies on cellbased therapy in neurodegenerative disorders.

Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells.

Wang J, Wang X, Sun Z, Wang X, Yang H, Shi S, Wang S. "Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells." Stem Cells Dev (2010) Sep; 19; PMID:20131979

http://www.ncbi.nlm.nih.gov/pubmed/20131979

**This study investigated the therapeutic efficacy of human exfoliated deciduous teeth (SHED) in alleviating Parkinson's disease in a rat model. Transplantation of SHED spheres into parkinsonian rats partially improved the behavioral disorders as compared to controls. SHED may be an optimal source of postnatal stem cells for Parkinson's disease treatment.

Ocular Disease/Injury

Stem cells can act as a new source of cells to replace damaged cells in the eye. This is promising for the development of human cornea reconstruction therapies to treat damage due to limbal stem cell deficiencies, chemical injury of the eye, dry eye, and ageing. A number of clinical trial study are attempting to develop new therapies to treat and prevent loss of vision.

Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings.

Park SS, Bauer G, Abedi M, Pontow S, Panorgias A, Jonnal R, Zawadski RJ, Werner JS, Nolta J. "Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings." Invest Ophthalmol Vis Sci (2014); PMID:25491299

http://www.ncbi.nlm.nih.gov/pubmed/25491299

**Bone marrow CD34+ stem cells were used to access intravitreal therapy for patients with irreversible vision loss from retinal vascular occlusion, hereditary or nonexudative age-related macular degeneration, or retinitis pigmentosa. Transplantation was well tolerated with no inflammation or hyperproliferation.

Stem cells can act as a new source of cells to replace damaged cells in the eye. Dental pulp stem cells have been used for corneal reconstructions and retina regeneration in animal models. In addition more investigations are now focusing on how dental pulp stem cells can overcome on age-related eye diseases and conditions.

Dental pulp stem cells, a paracrine mediated therapy for the retina.

Mead B, Logan A, Berry M, Leadbeater W, Scheven B. "Dental pulp stem cells, a paracrine mediated therapy for the retina." Neural Regen Res. (2014) Mar 15;9(6). PMID:4146241

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146241/

** A review summarizing the alternative of using dental pulp stem cells for neural protection and regeneration in the eye. DPSC have a neural crest origin and this makes them more suitable as compared to other MSC in the treatment of CNS injuries.

Dental pulp stem cells: a new cellular resource for corneal stromal regeneration.

Syed-P, Du Y, Lathrop KL, Mann MM, Funderburgh ML, Funderburgh JL. "Dental pulp stem cells: a new cellular resource for corneal stromal regeneration." Stem Cells Transl Med. (2015). PMID:25713466.

http://www.ncbi.nlm.nih.gov/pubmed/25713466

** DPSC can differentiate into keratocytes which are cells from the corneal stroma. After implantation into mice the DPSC produced corneal stromal matrix and did not affect corneal transparency or induce any immune reactions. DPSC have the potential for clinical use for corneal stromal blindness.

Ocular Disease/Injury - cont.

Corneal reconstruction with tissue-engineered cell sheets composed of human immature dental pulp stem cells.

Gomes JA, Geraldes Monteiro B, Melo GB, Smith RL, Cavenaghi Pereira da Silva M, Lizier NF, Kerkis A, Cerruti H, Kerkis I. "Corneal reconstruction with tissue-engineered cell sheets composed of human immature dental pulp stem cells." Invest Ophthalmol Vis Sci. (2010) Mar;51(3):1408-14. Epub 2009 Nov 5. PMID: 19892864

http://www.ncbi.nlm.nih.gov/pubmed/19892864

** A tissue engineered cell sheet composed of human dental pulp stem cells was used for ocular surface reconstruction in a rabbit animal model. It was shown that the transplantation of the DPSC sheet was successful for the reconstruction of corneal epithelium in the animal model.

Skeletal Disease/injury

Stem cells found in cord blood, bone marrow, and peripheral blood have shown osteogenic differentiation capability when implanted in patients. Several early stage clinical trials have shown improvements in bone formation in human patients.

Pre- and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfect: a two-center experience.

Gotherstrom C, Westgren M, Shaw SW, Astrom E, Biswas A, Byers PH, Mattar CN, Graham GE, Taslimi J, Ewald U, Fisk NM, Yeoh AE, et al. "Pre- and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfect: a two-center experience." Stem Cells Transl Med (2014). PMID: 24342908

http://www.ncbi.nlm.nih.gov/pubmed/24342908

**Two patients with osteogenesis imperfect received prenatal human fetal mesenchymal stem cells transplantation. Normal growth trajectory was observed. No adverse effect was observed with MSC. Prenatal transplantation of allogenic MSC appears safe and likely to offer a clinical benefit.

Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerated a compact rather than a spongy bone: biological and clinical implications.

Giuliani A, Manescu A, Langer M, Rustichelli F, Desiderio V, Paino F, De Rosa A, Laino L, d'Aquino R, Tirino V, Papaccio G. "Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerate a compact rather than a spongy bone: biological and clinical implications." Stem Cells Transl Med (2013). PMID: 23502599

http://www.ncbi.nlm.nih.gov/pubmed/23502599

**Regenerated tissue composed of seeded DPSC's from the graft sites was composed of a fully compact bone with a higher matrix density than control human alveolar spongy bone from the same patient. It creates steadier mandibles, may well increase implant stability, and, additionally, may improve resistance to mechanical, physical, chemical, and pharmacological agents.

Skeletal Disease/injury - cont

Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial.

Kaigler D, Pagni G, Park CH, Braun TM, Holman LA, Yi E, Tarle SA, Bartel RL, Giannobile WV. "Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial." Cell Transplant (2013). PMID: 22776413

http://www.ncbi.nlm.nih.gov/pubmed/22776413

**In this study tissue repair cells (isolated from bone marrow) were investigated to reconstruct localized craniofacial bone defects. No study related serious adverse events were reported. It was shown that tissue repair cells accelerated bone regeneration in jawbone defects compared to guided bone regeneration. Tissue repair cell transplantation appears safe and accelerated bone regeneration.

Injectable bone tissue engineering using expanded mesenchymal stem cells.

Yamada Y, Nakamura S, Ito K, Umemura E, Hara K, Nagasaka T, Abe A, Baba S, Furuichi Y, Izumi Y, Klein OD, Wakabayashi T. "Injectable bone tissue engineering using expanded mesenchymal stem cells." Stem Cells (2013). PMID: 23225744

http://www.ncbi.nlm.nih.gov/pubmed/23225744

**This investigation focused on whether injectable tissue-engineered bone made up of mesenchymal stem cells and platelet-rich plasma was able to regenerate functional bone in alveolar deficiencies. All patients had improved bone volume with no side effects. Newly formed bone areas had significant increase over preoperation baseline.

Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes.

d'Aquino R, De Rosa A, Lanza V, Tirino V, Laino L, Graziano A, Desiderio V, Laino G, Papaccio G. "Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes." Eur Cell Mater. (2009) Nov 12;18:75-83. PMID: 19908196

http://www.ncbi.nlm.nih.gov/pubmed/19908196

** This clinical study demonstrates that a DPC/collagen sponge biocomplex can completely restore human mandible bone defects and indicates that this cell population could be used for the repair and/or regeneration of tissues and organs.

Injectable tissue-engineered bone using autogenous bone marrow-derived stromal cells for maxillary sinus augmentation: clinical application report from a 2-6-year follow up.

Yamada Y, Nakamura S, Ito K, Kohgo T, Hibi H, Nagasaka T, Ueda M. "Injectable tissueengineered bone using autogenous bone marrow-derived stromal cells for maxillary sinus augmentation: clinical application report from a 2-6-year follow up." Tissue Eng Part A. (2008). PMID: 18823276

http://www.ncbi.nlm.nih.gov/pubmed/18823276

**Bone marrow derived stromal cells and platelet-rich plasma were used to augment by placement of bone graft and dental implants in 12 patients. No adverse effects were reported and bone absorption were seen in the 2-6 year follow up time.

Skeletal Disease/injury - cont.

Repair of large bone defects with the use of autologous bone marrow stromal cells.

Quarto E, Mastrogiacomo M, Cancedda R, Kutepov SM, Mukhachev V, Lavroukov A, Kon E, Marcacci M. "Repair of large bone defects with the use of autologous bone marrow stromal cells." N Engl J Med (2001). PMID: 11195802

http://www.ncbi.nlm.nih.gov/pubmed/11195802

**Progenitor cells were isolated from bone marrow and expanded. Three patients with large bone defects were treated with these cells implanted in a scaffold. Results reveal abundant callus formation in implants and good integration with host bones.

Stem cells from dental pulp have been shown to have the ability to differentiate into osteoblasts. Studies have shown that dental pulp stem cells are a promising tool for bone generation. Stem cells from teeth have been expanded, differentiated, and implanted into animal models and have repaired bone defects. Stem cells from dental pulp may one day be used to treat human bone disorders, like osteoporosis, bone injury, and bone deformation.

Transplantation of stem cells from human exfoliated deciduous teeth for bone regeneration in the dog mandibular defect.

Behnia A, Haghighat A, Talebi A, NourbakhshN, Heidari F. "Transplantation of stem cells from human exfoliated deciduous teeth for bone regeneration in the dog mandibular defect." World J Stem cells (2014). PMID:25258673

http://www.ncbi.nlm.nih.gov/pubmed/25258673

**Human exfoliated deciduous teeth which had been isolated and characterized 5 years before were capable of proliferation and osteogenesis and no immune response was observed after 3 months of implantation.

Transplantation of SHED prevents bone loss in the early phase of ovariectomy-induced osteoporosis.

Liu Y, Wang L, Liu S, Liu D, Chen C, Xu X, Chen X, Shi S.

"Transplantation of SHED prevents bone loss in the early phase of ovariectomy-induced osteoporosis." J Dent Res (2014). PMID:25252877

http://www.ncbi.nlm.nih.gov/pubmed/25252877

**Systemic infusion of SHED improves the osteoporotic phenotype in ovariectomized mice by rescuing the bone marrow mesenchymal stem cell deficiency and inhibiting osteoclastogenesis. The immunomodulating properties of SHED are able to overcome osteopenia and are described in detail.

Skeletal Disease/injury - cont.

Micro-CT and PET analysis of bone regeneration induced by biodegradable scaffolds as carriers for dental pulp stem cells in a rat model of calvarial "critical size" defect: Preliminary data.

Annibali S., Bellavia D, Ottolengi L, Cicconetti A, Cristalli MP, Quaranta R, Pilloni A. "MicroCT and PET analysis of bone regeneration induced by biodegradable scaffolds as carriers for dental pulp stem cells in a rat model of calvarial "critical size" defect: Preliminary data." J Biomed Mater Res Part B (2013). PMID: 24142538

http://www.ncbi.nlm.nih.gov/pubmed/24142538

**Addition of dental pulp stem cells to scaffolds has the potential to improve bone regeneration process in rats although the optimal conditions require further investigation.

Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerated a compact rather than a spongy bone: biological and clinical implications.

Giuliani A, Manescu A, Langer M, Rustichelli F, Desiderio V, Paino F, De Rosa A, Laino L, d'Aquino R, Tirino V, Papaccio G. "Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerate a compact rather than a spongy bone: biological and clinical implications." Stem Cells Transl Med (2013). PMID: 23502599

http://www.ncbi.nlm.nih.gov/pubmed/23502599

**Regenerated tissue composed of seeded DPSC's from the graft sites was composed of a fully compact bone with a higher matrix density than control human alveolar spongy bone from the same patient. It creates steadier mandibles, may well increase implant stability, and, additionally, may improve resistance to mechanical, physical, chemical, and pharmacological agents.

Transplantation of human dental pulp stem cells: enhance bone consolidation in mandibular distraction osteogenesis.

Alkaisi A. Ismail AR, Mutum SS, Rifin Ahmad ZA, Masudi S, Razak NH. "Transplantation of human dental pulp stem cells: enhance bone consolidation in mandibular distraction osteogenesis." J Oral Maxillofac Surg (2013). PMID: 24040948

http://www.ncbi.nlm.nih.gov/pubmed/24040948

**SHED can serve as an additional cell resource for distraction osteogenesis enhancement in rabbits and might be a promising model for the reconstruction of large mandibular defects in human oral maxillofacial surgery.

Skeletal Disease/injury - cont.

Fibroin Scaffold Repairs Critical-Size Bone Defects In Vivo Supported by Human Amniotic Fluid and Dental Pulp Stem Cells.

Riccio, Massimo, et al. "Fibroin Scaffold Repairs Critical-Size Bone Defects In Vivo Supported by Human Amniotic Fluid and Dental Pulp Stem Cells." Tissue Engineering Part A 18.9-10 (2012): 1006-1013.

http://online.liebertpub.com/doi/abs/10.1089/ten.tea.2011.0542

**Strong potential of stem cells/fibroin bioengineered constructs for correcting large cranial defects in animal model and is likely a promising approach for the reconstruction of human large skeletal defects in craniofacial surgery

Osteogenic potential of effective bone engineering using dental pulp stem cells, bone marrow stem cells, and periosteal cells for osseointegration of dental implants.

Ito K, Yamada Y, Nakamura S, Ueda M. "Osteogenic potential of effective bone engineering using dental pulp stem cells, bone marrow stem cells, and periosteal cells for osseointegration of dental implants." Int J Oral Maxillofac Implants (2011). PMID: 22010075

http://www.ncbi.nlm.nih.gov/pubmed/22010075

**Aim of this study is to investigate cell-based effective bone engineering and osseointegration of dental implants and tissue-engineering bone using DPSC, BMSC, and periosteal cells. DPSC showed the highest osteogenic potential and may be a useful cell source for tissue-engineered bone around dental implants.

Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow.

Yamada Y, Ito K, Nakamura S, Ueda M, Nagasaka T. "Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow" Cell Transplant (2011). PMID: 21054950

http://www.ncbi.nlm.nih.gov/pubmed/21054950

** These results demonstrate that stem cells from deciduous teeth, dental pulp, and bone marrow with PRP have the ability to form bone, and bone formation with DPSCs might have the potential to generate a graft between a child and parent.

Skeletal Disease/injury - cont.

A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow derived mesenchymal stem cells for clinical study using tissue engineering technology.

Yamada Y, Nakamura S, Ito K, Sugito T, Yoshimi R, Nagasaka T, Ueda M. "A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow derived mesenchymal stem cells for clinical study using tissue engineering technology." Tissue Eng Part A (2010). PMID: 20067397

http://www.ncbi.nlm.nih.gov/pubmed/20067397

** Demonstrated that dental pulp stem cells (DPSCs) and deciduous tooth stem cells (DTSCs) with platelet-rich plasma have the ability to form bone and vascularization, and this bone formation activity might be useful for osseointegrated hydroxyapatite-coated dental implants with good levels of bone-implant contact.

Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes.

d'Aquino R, De Rosa A, Lanza V, Tirino V, Laino L, Graziano A, Desiderio V, Laino G, Papaccio G. "Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes." Eur Cell Mater. (2009) Nov 12;18:75-83. PMID: 19908196

http://www.ncbi.nlm.nih.gov/pubmed/19908196

** This clinical study demonstrates that a DPC/collagen sponge biocomplex can completely restore human mandible bone defects and indicates that this cell population could be used for the repair and/or regeneration of tissues and organs.

Stem cells from deciduous tooth repair mandibular defect in swine.

Zheng Y, Liu Y, Zhang CM, Zhang HY, Li WH, Shi S, Le AD, Wang SL. "Stem cells from deciduous tooth repair mandibular defect in swine." J Dent Res. (2009) Mar;88(3):249-54. PMID: 19329459

http://www.ncbi.nlm.nih.gov/pubmed/19329459

** Stem cells from miniature pig deciduous teeth, an autologous and easily accessible stem cell source, were able to engraft and regenerate bone to repair critical-size mandibular defects at 6 months post-surgical reconstruction.

Dental pulp stem cells: a promising tool for bone regeneration.

d'Aquino R, Papaccio G, Laino G, Graziano A."Dental pulp stem cells: a promising tool for bone regeneration." Stem Cell Rev. (2008) Spring;4(1):21-6. PMID: 18300003

http://www.ncbi.nlm.nih.gov/pubmed/18300003

**Overview of DPSCs and why they are a promising tool for bone regeneration.

Skeletal Disease/injury - cont.

In vivo evaluation of human dental pulp stem cells differentiated towards multiple lineages.

Zhang W, Walboomers XF, Van Kuppevelt TH, Daamen WF, Van Damme PA, Bian Z, Jansen JA. "In vivo evaluation of human dental pulp stem cells differentiated towards multiple lineages." J Tissue Eng Regen Med. (2008) Mar-Apr;2(2-3):117-25. PMID: 18338838

http://www.ncbi.nlm.nih.gov/pubmed/18338838

**DPSC showed the ability to further differentiate along odontogenic, myogenic, and adipogenic pathways in vivo and were able to spontaneously differentiate along odontogenic and adipogenic directions in vivo. Stem cells derived from human dental pulp form a suitable source for tissue engineering and cell-mediated therapy.

Reconstruction of large cranial defects in nonimmunosuppressed experimental design with human dental pulp stem cells.

de Mendonça Costa A, Bueno DF, Martins MT, Kerkis I, Kerkis A, Fanganiello RD, Cerruti H, Alonso N, Passos-Bueno MR. 'Reconstruction of large cranial defects in nonimmunosuppressed experimental design with human dental pulp stem cells." J Craniofac Surg. (2008) Jan;19(1):204-10. PMID: 18216690

http://www.ncbi.nlm.nih.gov/pubmed/18216690

**Bone formation was present in a cranial bone defect rat model after 1 month. The use of hDPSC in nonimmunosuppressed rats did not cause any graft rejection. hDPSC is a cell resource for correcting large cranial defects in rats and constitutes a promising model for reconstruction of human large cranial defects in craniofacial surgery.

Mesenchymal progenitor cells in adult human dental pulp and their ability to form bone when transplanted into immunocompromised mice.

Otaki S, Ueshima S, Shiraishi K, Sugiyama K, Hamada S, Yorimoto M, Matsuo O. "Mesenchymal progenitor cells in adult human dental pulp and their ability to form bone when transplanted into immunocompromised mice." Cell Biol Int. (2007) Oct;31(10):1191-7. Epub 2007 Apr 14. PMID: 17524678

http://www.ncbi.nlm.nih.gov/pubmed/17524678

**It was shown that DPSC produce bone instead of dentin when they are implanted into immunocompromised mice with a powder based carrier. Evidence shows that DPSC are the common progenitors of odontoblast and osteoblasts. Dental pulp stem cells are useful cell source for tissue engineering and contain the potential of new therapeutic approaches for the restoration of damaged or diseased tissue.

Wound Healing

Wound healing requires a complex bimolecular process including cell movement, cell growth, angiogenesis-or new blood vessel formation, and extracellular remodeling. Angiogenesis or new blood vessel formation is one of the most important aspects of early would healing. Dental pulp stem cells are being investigated for their wound healing ability in pre-clinical animal models.

In vivo Human deciduous teeth dental pulp cells with basic fibroblast growth factor enhance wound healing of skin defect.

Nishino Y, Ebisawa K, Yamada Y, Okabe K, Kamei Y, Ueda M. "Human deciduous teeth dental pulp cells with basic fibroblast growth factor enhance wound healing of skin defect." J Craniofac Surg (2011). PMID: 21403563

http://www.ncbi.nlm.nih.gov/pubmed/21403563

**A combination of hDPC and bFBF was used on a skin defect mouse model. It was shown that hDPC accelerated wound healing and that hDPC enhanced would healing more in the presence of bFGF. It is important to note that rodent skin is very different than human skin in terms of wound healing and the results are presented as a first step to evaluate wound healing effects of hDPCs

Stem cells from human exfoliated deciduous teeth (SHED) enhance wound healing and the possibility of novel cell therapy.

Nishino Y, Yamada Y, Ebisawa K, Nakamura S, Okabe K, Umemura E, Ueda M. "Stem cells from human exfoliated deciduous teeth (SHED) enhance wound healing and the possibility of novel cell therapy." Cytotherapy (2011). PMID:21341975.

http://www.ncbi.nlm.nih.gov/pubmed/21341975

**SHED might offer a unique stem cell resource and the possibility of novel cell therapies for wound healing.

Web Publications Using Mesenchymal Stem Cells in Humans

Stem cell treatment for patients disabled by stroke shows promise.

ReNeuron stem cell therapy shows long-term promise for stroke

http://news.yahoo.com/reneuron-stem-cell-therapy-shows-long-term-promise-125033885--finance.html

Stem cells used to treat rare blood condition in the UK.

Stem cell treatment may signal cure for genetic diseases.

http://www.thestarphoenix.com/health/Stem+cell+treatment+signal+cure+genetic+diseases/10994349/story.html

MSC's used to repair cartilage, collagen, tendon, or bone in orthopedics.

Stem-cell therapy shows promise in orthopedic treatment.

http://www.washingtontimes.com/news/2015/apr/20/stem-cell-therapy-shows-promise-in-orthopedic-trea/

MSC from bone marrow are used to relive back pain.

Stem Cell Treatment for Back Pain Shows Success.

http://www.stemcellsportal.com/stem-cell-treatment-back-pain-shows-success

FDA approved start of clinical trial using MSC to treat patients after heart attack.

Capricor Announces FDA Approval to Inititate ALLSTAR Trial of Allogeneic Stem Cell Therapy in Patients Following Heart Attack.

http://www.fiercebiotech.com/press-releases/capricor-announces-fda-approval-initiate-allstar-trial-allogeneicstem-cell

Cord blood stem cell product, Allocord, has received approval by FDA for use in patients with blood disorders.

Stem-Cell Therapy Approved for Blood Disorders.

http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3908

Patients with amyotrophic lateral sclerosis (ALS) has received stem cells and it slowed muscle degeneration.

FDA-approved Stem Cell Trial Dramatically Slows ALS.

http://www.biosciencetechnology.com/articles/2013/05/fda-approved-stem-cell-trial-dramatically-slows-als

Web Publications Using Mesenchymal Stem Cells in Humans - cont.

Stem cells improve life of boy with cerebral palsy

Boy, 2, is the first to have cerebral palsy 'successfully treated' using stem cells, taking him from a vegetative state to walking and talking.

https://www.dailymail.co.uk/health/article-2330338/Boy-cerebral-palsy-successfully-treated-using-stem-cells-taking-vegetative-state-walking-talking.html

Stem cells improve vision in patients with eye degeneration.

Stem cell therapy success in treatment of sight loss from macular degeneration.

http://www.theguardian.com/science/2014/oct/15/stem-cell-success-in-treating-macular-degeneration

Stem cells from teeth grow into cornea like structures.

Stem cells from wisdom teeth could help repair corneas.

https://www.sciencenews.org/blog/science-ticker/stem-cells-wisdom-teeth-could-help-repair-corneas

Stem cells: First therapy approved by EU.

The European Medicines Agency has approved the use of stem cell therapy for Holocar, a rare eye conditions that lead to blindness. It works around 80% of cases.

http://www.bbc.com/news/health-30550113

World's first successful stem cell treatment of autoimmune diseases.

Patient with multiple sclerosis, autoimmune hearing loss, atopic dermatitis and rheumatoid arthritis had symptoms that became manageable after stem cell treatment.

http://www.sclerodermatt.org/articles/news/422-the-worlds-first-successful-stem-cell-treatment-ofautoimmune-diseases

FDA approves stem cell treatment for heart disease.

Mayo clinic to test technique in human trial Stem cells will be used to fix damaged heart tissue, promising results in cardiac outflow were seen in patients tested in Europe.

http://www.medicaldaily.com/fda-approves-stem-cell-treatment-heart-disease-mayo-clinic-test-techniquehuman-trial-267408

Web Publications Using Mesenchymal Stem Cells in Humans - cont.

Stem cell knee injection shown to regenerate meniscus, reduce pain.

Stem cells were used for meniscal regeneration and the control of knee pain. Treatment was with allogeneic human mesenchymal stem cells.

http://www.healio.com/orthopedics/biologics/news/online/%7B0cd61592-5eed-4b52-a868-e7576aab3fdf%7D/stem-cell-knee-injection-shown-to-regenerate-meniscus-reduce-pain

A woman's own MSC's were used to grow a transplant trachea.

1st Trachea Transplant From Stem Cells Doctors Use Patient's Stem Cells to Prepare Donor's Trachea WebMD Health News; By Miranda Hitti

http://www.webmd.com/news/20081119/1st-trachea-transplant-from-stem-cells

MSC's are used to grow replacement cartilage for damaged shoulders in humans.

Adult Stem Cells for Shoulder Injuries

On Target

http://blog.targethealth.com/?p=3802

MSC's are used for difficult wound healing and skin growth in human patients.

New Study Using Combination of Bioengineered Skin and Stem Cells Shows Promise in Treatment of Non-Healing Wounds

By: PR Newswire

http://uk.sys-con.com/node/866081

MSC's are used to treat multiple sclerosis.

FDA Approves MSC-NP Therapy as Investigational New Drug in MS Clinical Trial: A Research Milestone

http://www.tischms.org/news/fda-approves-msc-np-therapy-investigational-new-drug-ms-clinical-trialresearch-milestone