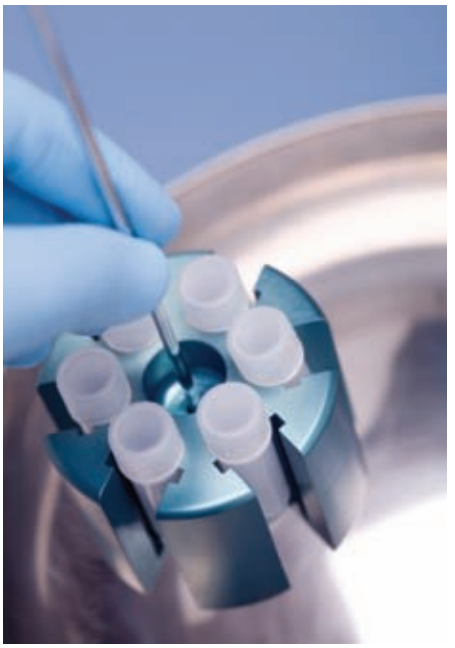


Stem Cells: Emerging Medical and Dental Therapies for the Dental Professional

by Jay B. Reznick, DMD, MD
Private Practice
Tarzana, CA

Dentaltown is pleased to offer you continuing education. You can read the following CE article in the magazine and go online to www.dentaltown.com to take the post-test and claim your CE credits, free-of-charge, or you can mail in your post-test for a nominal fee. See instructions on page 52.

Educational objectives

Upon completion of this course, participants should be able to achieve the following:

- Understand the basic science regarding the different types of stem cells;
- Understand the various available sources of recovery for adult stem cells from within, and outside of, the oral cavity, as well as the advantages and disadvantages of each source;
- Understand the benefits of recovering and cryopreserving dental stem cells;
- Understand the clinical relevance in recovering dental stem cells;
- Understand the potential uses of dental stem cells and their role in regenerative therapies.

Introduction

Recent exciting new discoveries place dentists at the forefront of helping their patients benefit from potentially life-saving therapies derived from a patient's own stem cells obtained from deciduous teeth and permanent teeth. We now stand at the threshold of a potential revolution in medical treatment for diseases and disorders in which organs stop working properly. At present, some such conditions, such as heart, kidney and liver disease, can be treated by transplantation of a replacement organ from another person. But demand for donor organs is far outstripping supply and the failure rate of such surgery is quite high, mainly because of the problem of rejection. Many other disorders, such as stroke, diabetes and Alzheimer's disease, cannot presently be treated by transplantation. The great hope is that suitable stem cells, produced in large quantities through cell culture methods and injected into failing tissues and organs, will produce fresh, replacement cells to take

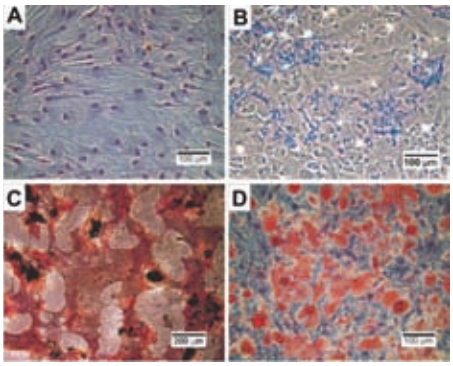
Academy of General Dentistry
PACE Program Approval for Continuing Education

Approved PACE Program Provider
FAGD/MAGD Credit
Approval does not imply acceptance by a state or provincial board of dentistry or AGD endorsement.
12/01/04 to 12/01/08
AGD PACE Approval Number: 304396

Dentaltown.com, Inc. is an AGD PACE Recognized Provider.
This course offers two AGD PACE Continuing Education Credits free-of-charge.

continued on page 44

continued from page 42



Stem Cell differentiation
A. Stem cells *B. Cartlidge cells*
C. Bone cells *D. Adipose cells*

over from lost or damaged ones. It is now known that adult stem cells taken from one area of the body can be transplanted into another area and grown into a completely different type of tissue. This ability to grow and regenerate tissues is the focus of the emerging field of personalized medicine which uses a patient's own stem cells for biologically compatible therapies and individually tailored treatments. The dental professional will play an important role in both the recovery and the use of these stem cells in both Dental and Medical regenerative therapies.[1,2,3]

What is a Stem Cell?

Stem cells are the master cells of the body. There are two major types of stem cells, Embryonic and Adult stem cells. One Embryonic stem cell has the potential to differentiate into all 220 types of specialized cells that make up the human body. Adult stem cells are responsible for the regeneration and replacement of tissue damaged by disease or injury. There are two properties of stem cells that make it different from any other specialized cells in the body. These properties are self renewal – the ability to go through numerous cycles of cell division while maintaining their undifferentiated state and the ability to differentiate into a specialized cell type. Another unique property of stem cells is their ability to grow in vitro – outside of the body in a laboratory.

Embryonic Stem Cells

Embryonic stem cells are the result of the fertilization of an egg by a sperm. Cells produced by the first few divisions of the fertilized egg are **totipotent.** At about the fifth day this ball of cells becomes a blastocyst, an early stage embryo that is made up of 50-150 cells. **Pluripotent** stem cells are those embryonic stem cells that are harvested after the fifth day from the inner mass of this blastocyst. These pluripotent stem cells go on to differentiate into any of the tree types of cells that derive the germ layers: ectoderm, endodem and mesoderm. These stem cells are then called **multipotent** or adult stem cells and form around day 14.

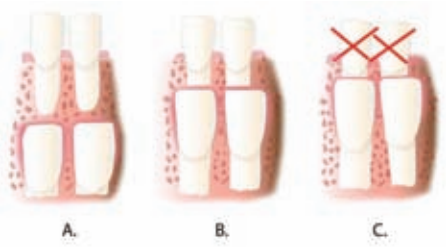
After 20 years of research, there are no approved treatments or human trials using embryonic stem cells. Their tendency to produce teratomas and malignant carcinomas, cause transplant rejection, and form the wrong kinds of cells are just a few of the hurdles that embryonic stem cell researchers still face. Comparing the different stem cell types, adult stem cells, which have the least amount of ethical concerns, are presently being used in medical therapies and are readily accessible.

Adult Stem Cells

Adult stem cells are usually designated according to their source and their potential. Adult stem cells are multipotent because their potential is normally limited to one or more lineages of specialized cells. However, a special multipotent stem cell that can be found in bone marrow and dental pulp is called the *mesenchymal* stem cell and can produce different cell types: bone, cartilage, fat, muscle, and connective tissues. However, a number of recent studies show that stem cells from one area may be manipulated to grow into cells types of a completely different tissue. This ability is called *transdifferentiation* or *plasticity*, and different types of adult stem cells have varying degrees of plasticity. Adult stem cells look like any other cell and are found diffusely spread throughout the body buried deep in tissue and organs of the body. Stem cell markers are surface glyoprotiens called receptors that have the capability of selectively binding or adhering to other "signaling" molecules. Use of these stem cell markers allow researchers the ability to identify and separate the stem cells from surrounding cells.

continued on page 46

continued from page 44



Deciduous teeth must contain healthy pulp.

Developing third molars with follicle.

When discussing transplantation of tissues, two terms are always mentioned and they are both of significant importance. These terms are autogenous and allogenic. Autogenous is the harvest of tissue from an individual and reimplanting this tissue back into the same individual. The other term is allogenic. Allogenic is the harvest of tissue from one individual and transplanted into another individual. This term is used for organ transplantations. No matter how close the cellular match of the donor is with the recipient there is always the potential for an immune reaction and host rejection of the transplanted tissue. In most instances the recipient requires immune-suppression drugs to prevent rejection and the recipient is always susceptible to host vs. graft disease. In principle, some of the patient's own stem cells could be harvested (most likely from bone marrow or dental pulp), multiplied in culture and injected into a diseased or damaged region to produce new cells. Stem cells derived from the patient's own body would have the great advantage that they would not be rejected.[10, 27]

The adult stem cells can be recovered from the following:

Bone marrow derived mesenchymal stem cells. Bone marrow transplants were the first successful stem cell therapies. A bone marrow transplant involved a donor and recipient with a close cellular match. Presently peripheral blood stem cell collection is being used in place of bone marrow aspiration.[8]

Adipose derived adult stem cells have also been isolated from human fat, usually by method of liposuction.[9]

Umbilical cord stem cells derived from the blood of the umbilical cord.[6,7]

Amniotic fluid-derived stem cells can be isolated from aspirates of amniocentesis during genetic screening or collection at the time of delivery.[5]

Induced pluripotent stem cells derived from epithelial cells. These are not adult stem cells, but rather reprogrammed epithelial cells with pluripotent capabilities.[4]

Dental stem cells are the most accessible stem cells. They are isolated from the dental pulp of healthy teeth both primary and permanent teeth, periodontal ligament including the apical region of developing teeth and other tooth structures. Craniofacial stem cells, including dental stem cells, originate from neural crest cells and mesenchymal cells during development.[11]

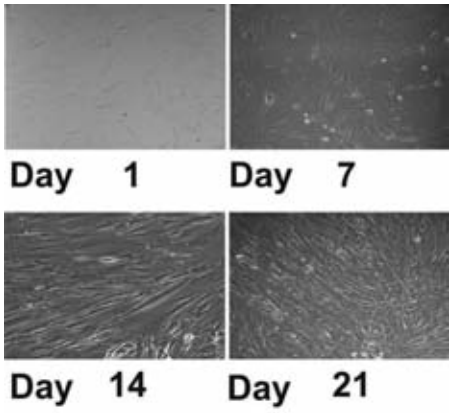
In a child, the most accessible stem cells are from the oral cavity. For deciduous teeth, the best candidates are canine and incisors with the presence of healthy pulp that are starting to loosen. In children, other sources for easily accessible stem cells are supranumerary teeth, mesodens, over retained deciduous teeth associated with congenitally missing permanent teeth and prophylactic removal of deciduous molars for orthodontic indications. When a deciduous tooth becomes extremely mobile it is likely that the pulp has been separated from its blood supply. The tooth might still maintain its gingival attachment and be retained for weeks in the mouth with a necrotic pulp. A tooth "hanging on by a thread" or one that just fell out on its own is not a candidate for stem cell collection.[26]

Adolescents have two excellent opportunities for banking their stem cells from extracted teeth: following extraction of bicuspid teeth for orthodontic treatment and when their wisdom teeth are extracted. The bicuspid teeth are not fully formed until between the ages of 12 to 14 years. Typically, these teeth are extracted for orthodontic reasons before the roots are fully formed, which ensures a better chance for success of harvesting viable stem cells. The same scenario is true with wisdom teeth (third molars). The roots of the wisdom teeth are not fully formed until after the age of 18; extracting these teeth during the teenage years helps to ensure the greatest abundance of proliferative stem cells. The follicular sac of an unerupted tooth may also prove to be a valuable source for stem cells.

continued on page 48

continued from page 46

Liquid nitrogen tanks are constantly monitored and alarmed.



Stem cell proliferation.

The remarkable characteristic of the periodontal ligament is its ability to regenerate and repair virtually every other tissue type that comprises the periodontium. Undifferentiated mesenchymal cells of the periodontal ligament can differentiate into osteoblasts, chondrocytes and adipocytes.

Pulpectomies on vital pulps is another accessible means to collect viable stem cells. Other sources of stem cells accessible from the oral cavity during oral surgical procedures: alveolar bone, periosteum, buccal mucosa, gingiva and muscle.[14]

Banking Stem Cells From Teeth

Tooth-derived stem cells are readily accessible, and provide an easy and minimally invasive way to obtain and store stem cells for future use. Banking teeth and tooth-derived stem cells is a reasonable and simple alternative to harvesting stem cells from other tissues requiring invasive surgical procedures, and does not pose the ethical problems associated with embryonic stem cell harvesting.

Cryopreservation is a process where cells or whole tissues are preserved by cooling to low sub-zero temperatures, such as (typically) -196 °C (the boiling point of liquid nitrogen). At these low temperatures, any biological activity, including the biochemical reactions that would lead to cell death, is effectively stopped.[33]

Potential Uses for Stem Cells

Researchers are approaching this emerging field of stem cells from many different angles. Presently all of the current therapies involve adult stem cells and these are cell-based therapies. Transplanting or "grafting" tissue to combat shortages of donated organs seems to be high on the list of priorities. Currently the longest therapy using multipotent stem cells has been bone marrow stem cell transplants. But other uses for stem cell will prove to have an even more powerful role near term. Stem cells are valuable for testing new drugs. Drugs are being applied directly to human cells and this will provide more relevant data than drug testing on animals.

Stem Cells in Dentistry

Stem cells and stem cell therapies will emerge to become an important aspect in the everyday practice of dental professionals. It is important for all dentists, dental specialists, hygienists and their auxiliary staff to educate themselves on the basics of stem cell science. Adult stem cells may be used to regenerate bone and correct oral and craniofacial defects. Both in vitro studies and in vivo research in animal models has shown that tooth-derived adult stem cells can be used to regrow tooth roots in the presence of proper growth factors and a biologically compatible "scaffold." Regenerative therapy is less invasive than surgical implantation, and early animal studies suggest comparable results in strength and function of the biological implant as compared to a traditional dental implant. Stem cells extracted from the dental pulp of a third molar could be harvested, then directly implanted into the pulp chamber of a severely injured tooth. The goal is to regenerate the pulp inside the damaged tooth, preventing the need for endodontic treatment. Stem cells derived from the periodontal ligament may offer promise for regenerating the periodontal ligament and other supporting structures of the periodontium that have been destroyed by gingival disease, with an alternative approach to traditional clinical therapies. Tissue-engineered bone grafts will be useful for practitioners in all of the dental specialties. Future tissues may also include engineered TMJ joints and cranial sutures, which would be especially helpful to craniofacial and oral maxillofacial surgeons.[12, 13, 17, 19, 20, 28, 32]

Stem Cells Used in Medicine Today

Applications of regenerative medicine technology may offer new therapies for patients with injuries, end-stage organ failure, or other clinical problems. Currently,

continued on page 50

continued from page 48

Systemic Diseases

Systemic diseases that can be treated with dental mesenchymal stem cells:

- Diabetes
- Muscular dystrophy
- Parkinson's
- Cardiac infarcts
- Arthritis
- Soft tissue reconstruction
- Liver Disease
- and More

Author's Bio

Dr. Jay B. Reznick is a Diplomate of the American Board of Oral and Maxillofacial Surgery. He received his Dental degree from Tufts University, and his M.D. degree from the University of Southern California, and trained in Oral and Maxillofacial Surgery at L.A. County-USC Medical Center. He is the Director of the Southern California Center for Oral and Facial Surgery in Tarzana, California. His special clinical interests are in the areas of facial trauma, jaw and oral pathology, dental implantology, sleep disorders medicine, laser surgery, and jaw deformities. He can be reached at jreznick@sccofs.com.

Disclosure: Dr. Reznick declares having received an honorarium from StemSave for this course.

This CE activity is supported by an unrestricted grant from StemSave.

patients with injuries, end-stage organ failure, or other clinical problems. Currently, patients suffering from diseased and injured organs can be treated with transplanted organs. However, there is a shortage of donor organs that is worsening yearly as the population ages and new cases of organ failure increase. Scientists in the field of regenerative medicine and tissue engineering are now applying the principles of cell transplantation, material science, and bioengineering to construct biological substitutes that will restore and maintain normal function in diseased and injured tissues. The stem cell field is a rapidly advancing aspect of regenerative medicine as well, and new discoveries here create new options for this type of therapy.[18]

Stem cell-based therapies are being investigated for the treatment of many conditions, including neurodegenerative conditions such as Parkinson's disease and multiple sclerosis, liver disease, diabetes, cardiovascular disease, autoimmune diseases, musculoskeletal disorders, and for nerve regeneration following brain or spinal cord injury. The mesenchymal stem cells found in teeth may be beneficial for the treatment of neurodegenerative diseases and the repair of motor nerves following stroke or injury. This exciting research will lead to future treatment options that allow muscles to repair themselves following injury, such as the muscle damage that occurs after a heart attack, or the structural damage that occurs following a knee injury. New stem cell therapies are already under review or have been approved by the U.S. Food and Drug Administration (FDA). Many other therapies are in various stages of product development. As the number of people affected by degenerative diseases continues to increase, there will be a greater need for new treatment options for the ever-growing aging population. Harvesting and storing stem cells now will ensure their availability in the future when they will be needed most.[15, 16, 21, 22, 23, 24, 25]

Summary

The current research on dental stem cells is expanding at an unprecedented rate. Stem cell-based therapies are being investigated and are going to clinical trials for the treatment of many conditions, including neurodegenerative conditions, liver disease, diabetes, cardiovascular disease, autoimmune diseases, musculoskeletal disorders, and for nerve regeneration following brain or spinal cord injury. As these clinical studies continue to advance in the years ahead, it is widely expected that to avoid autoimmune rejection from donor tissues and to maximize therapeutic efficacy, stem cells will be used to generate a specific treatment for a specific patient. The emerging field of "personalized medicine" is a popular topic in the media, which generally refers to new medical technologies derived from a patient's own stem cells and the use of genomic diagnostics. Recent findings and scientific research supports the use of these very powerful mesenchymal stem cells found within teeth and other accessible tissue harvested from the oral cavity for use in a multitude of regenerative therapies. A young and healthy patient is a better candidate for mesenchymal stem cell collection and storage. At a younger age most individuals are free from chronic diseases and their stem cells have undergone fewer cell divisions and there is a lower likelihood of somatic mutations of these stem cells. In addition, the mesenchymal stem cells found in exfoliating and developing teeth proliferate at a more vigorous rate when compare to other sources of mesenchymal cells presently used in available clinical therapies. While we can see the promise of human stem cell therapies for the future, dentists know that it is important to act now to harvest and store these mesenchymal stem cells cells from deciduous teeth, extracted permanent teeth and other accessible living tissues from the oral cavity and making these opportunities available to their child, adolescent and adult patients for future regenerative therapies.[29, 30, 31]

References for this article can be found on www.dentaltown.com.

continued on page 52

continued from page 50

Post-test

Answer the Post-test Questions Online – for FREE

You have two options to claim your CE credits: 1) Go online and answer the test for free or 2) answer the test on the Continuing Education Answer Sheet and submit it by mail or fax with a processing fee of $35.

To take the test online: After reading the preceding article, type the following link into your browser and click the button TAKE EXAM: http://www.towniecentral.com/Dentaltown/OnlineCE.aspx?action=PRINT&cid=81

You can also view the course online in a Webcast format by clicking the above link and then the button REVIEW COURSE. If you choose that latter option, you can take the test by scrolling down and clicking "I wish to claim my CE credits."

Please note: If you are not already registered on www.dentaltown.com, you will be prompted to do so. Registration is fast, easy and of course, free.

1. What makes stem cells different from other specialized cells?
   a. They are able to self renew
   b. They are able to turn into other cell types
   c. They are able to grow outside of the body
   d. All of the above

2. Embryonic stem cells are pluripotential and can differentiate into the following cell types:
   a. Endoderm
   b. Mesoderm
   c. Ectoderm
   d. All of the above

3. Mesenchymal stem cells are
   a. Multipotent
   b. Pluripotential
   c. Totipotential
   d. None of the above

4. Plasticity is a stem cells ability to
   a. Transdifferentiate
   b. Differentiate
   c. Grow in tissue culture
   d. Turn into different shapes

5. Allogenic cells
   a. Have a lower incidence of rejection when transplanted
   b. Are preferred over autologous cells
   c. Require immunosuppressive drugs when transplanted
   d. Are harvested from one individual and transplanted into another

6. Adults stem cells can be recovered from
   a. Cord blood
   b. Bone marrow
   c. Dental pulp
   d. All of the above

7. Stem cells can be found in the healthy pulp of
   a. Deciduous teeth
   b. Third molars
   c. Permanent teeth
   d. All of the above

8. Dental stem cells have the potential to treat the following disease:
   a. Liver disease
   b. Cardiac disease
   c. Muscular dystrophy
   d. All of the above

9. Stem cell markers are not used to
   a. Identify stem cells
   b. Separate stem cells
   c. Match individuals for transplantations
   d. Both a and b

10. Stem cells can be used for the following:
    a. Cell based therapies
    b. Testing new drugs
    c. Understanding particular genetic diseases
    d. All of the above

Continuing Education Answer Sheet

Fill out this sheet ONLY if you wish to submit your test by mail or fax. A $35 processing fee applies.

Instructions: To receive credit, complete the answer sheet and mail it, along with a check or credit card payment to: Dentaltown.com, Inc., 10850 S. 48th Street, Phoenix, AZ 85044. You may also fax this form to 480-598-3450. You will need a minimum score of 70% to receive your credits.

Please print clearly. Deadline for submission of answers is 24 months after the publication date.

Stem Cells: Emerging Medical and Dental Therapies for the Dental Professional by Jay B. Reznick, D.M.D., M.D.

License Number ____ ____ ____ ____ ____ ____ ____ ____ ____ ____

AGD# _____

Name _____

Address _____

City _____ State _____ ZIP _____

Daytime phone _____

❑ Check (payable to Dentaltown.com, Inc.)

❑ Credit Card (please complete the information below and sign)

Card Number ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Expiration Date – Month / Year ____ ____ / ____ ____ ____ ____

Signature _____ Date _____

CE Post-test

Please circle your answers.

1.	a	b	c	d
2.	a	b	c	d
3.	a	b	c	d
4.	a	b	c	d
5.	a	b	c	d
6.	a	b	c	d
7.	a	b	c	d
8.	a	b	c	d
9.	a	b	c	d
10.	a	b	c	d

Program Evaluation

Please evaluate this program by circling the corresponding numbers: (3 = Excellent to 1 = Poor)

1. Course objectives were consistent with the course as advertised	3	2	1
2. Course material was up-to-date, well-organized and presented in sufficient depth	3	2	1
3. Instructor demonstrated a comprehensive knowledge of the subject	3	2	1
4. Overall, I would rate this course	3	2	1
5. Overall, I would rate this instructor	3	2	1

For any questions, please contact Rita Zakher, DMD, MBA, director of continuing education at rita@dentaltown.com