Stem Cells: Sources, Therapies and the Dental Professional

A Peer-Reviewed Publication
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Educational Objectives
Upon completion of this course, the clinician will be able to do the following:
1. Understand the range of diseases for which stem cell therapies are being investigated
2. Be knowledgeable about the various sources of stem cells and the advantages and disadvantages of each source
3. Understand the fundamental reasons for the effectiveness of stem cells and the meaning of tissue differentiation
4. Understand the basics of cryopreservation and the banking of stem cells

Abstract
Recent exciting discoveries place dentists at the forefront of engaging their patients in potentially life-saving therapies derived from a patient’s own stem cells located in deciduous and permanent teeth. Adult stem cells, including dental stem cells, have the potential, like bone marrow-derived stem cells and adipose-derived stem cells, to cure a number of diseases.

In medicine, stem cell-based treatments are being used and investigated for conditions as diverse as Parkinson’s disease, neural degeneration following brain injury, cardiovascular disease and autoimmune diseases. Stem cells will be used in dentistry for the regeneration of dentin and/or dental pulp, biologically viable scaffolds will be used for the replacement of orofacial bone and cartilage, and defective salivary glands will be partially or completely regenerated.

Dental stem cells can be obtained from the pulp of the primary and permanent teeth, from the periodontal ligament, and from associated healthy tissues. Exfoliating/extracted deciduous teeth and permanent teeth extracted for orthodontic treatment, trauma or dental implant indications are all readily available sources of dental stem cells. The harvest of these dental stem cells results in minimal trauma. Dental professionals have the opportunity to make their patients aware of these new sources of stem cells that can be stored for future use as new therapies are developed for a range of diseases and injuries.

Introduction/Overview
Recent exciting discoveries place dentists at the forefront of engaging their patients in potentially life-saving therapies derived from a patient’s own stem cells located in deciduous and permanent teeth. In 2000, the National Institutes of Health (NIH) released two studies of research on human teeth detailing the discovery of adult stem cells in impacted third molars and even more resilient stem cells in deciduous teeth.

Dentistry and medicine are evolving into new forms, in which care is being delivered with increasing frequency through biologically based approaches. The first wave of this paradigm shift in health care is likely more imminent than anyone is willing to predict at present, and its impact will eventually be felt in every medical and dental office and setting. In medicine, stem cell-based treatments are being used and investigated for conditions as diverse as Parkinson’s disease, diabetes, liver disease, neural degeneration following brain injury, cardiovascular disease and autoimmune diseases. Biomolecules will be used in dentistry for periodontal regeneration, stem cells will be used in the regeneration of dentin and/or dental pulp, biologically viable scaffolds will be used for the replacement of orofacial bone and cartilage, and defective salivary glands will be partially or completely regenerated.

No longer will it be necessary to rely on the chance of finding a cellular match from a donor, and devastating and formerly incurable diseases could potentially be treated. This is no longer science fiction. Some stem cell therapies have already been approved or are being reviewed by the U.S. Food and Drug Administration (FDA), while others are at various stages of development. Starting in the 1970s, it was discovered that cells taken from bone marrow postnatally had the ability to differentiate into bone, cartilage and marrow fat cells when they were transplanted. Stem cell research has increased dramatically in recent years as the potential for use of stem cells has become better understood. Degenerative diseases increase in incidence with age, and as the baby boomer population ages it can be anticipated that the need for viable and improved treatment options for these diseases will increase. Patients are being treated using stem cells for cardiovascular, orthopedic, dental, oncological and other conditions.
New stem cell therapies will become available in the future, and in the next three years it is anticipated that stem cell product therapies for graft-versus-host disease, damaged heart muscle due to cardiac disease and knee cartilage repair will become available.\(^4\) The stem cell market in 2006 represented approximately $36 million, and it has been estimated that it will reach $8 billion by 2015 with the advent of new therapies and increased treatment needs.\(^5\)

**Stem Cell Types and Sources**

Stem cells are immature, undifferentiated cells that can divide and multiply for an extended period of time, differentiating into specific types of cells and tissues. Autogenous stem cells are derived from the patient being treated, while allogeneic stem cells are derived from other individuals. Stem cells available commercially are currently mainly allogeneic (donor-derived). While it is believed that allogeneic stem cells will not produce an immune response, this is not known with certainty.\(^6\) Autogenous stem cells, on the other hand, reduce the risk of rejection and, provided they are handled correctly, remove the risk of cross-infection from allogeneic transplanted tissue. In addition, autologous stem cell transplant recipients will not require immunosuppressive drugs to combat rejection.

Stem cells may be totipotent, multipotent or unipotent; i.e., able to differentiate into any tissue, several types of tissue or one type of tissue, respectively. The process by which stem cells are derived from one type of tissue and differentiate into other types of tissue is referred to as plasticity or transdifferentiation. Multipotent stem cells consist of three major types — ectodermal (skin and nerves), mesodermal or mesenchymal (bone, cartilage, muscle and adipose), and endodermal (intestines and other). The two main categories of stem cells are embryonic stem cells and adult stem cells, defined by their source.

**Embryonic stem cells**

Embryonic stem cells (ESCs) are derived from the cells of the inner cell mass of the blastocyst during embryonic development. ESCs have the capacity to differentiate into any cell type and the ability to self-replicate for numerous generations. A potential disadvantage of ESCs is their ability to differentiate into any cell lineage and to proliferate endlessly unless controlled.\(^7\) The clinically observed teratoma is a tumor that is an example of ESCs growing into a “different and undesired tissue.” ESCs can be obtained only from embryos, and therefore are associated with ethical issues.

**Adult stem cells**

Sources of adult stem cells include the umbilical cord, amniotic fluid, bone marrow, adipose tissue, brain and teeth.\(^8,9\) Adult stem cells are not subject to the ethical controversy that is associated with embryonic stem cells; they can also be autologous and isolated from the patient being treated, whereas embryonic stem cells cannot.

**Induced pluripotent stem cells (iPS)**

The newly discovered iPS cells are adult or somatic stem cells that have been coaxed to behave like embryonic stem cells.\(^10,11\) iPS cells have the capacity to generate a large quantity of stem cells as an autologous source that can be used to regenerate patient-specific tissues. However, even the authors of these recent reports have cautioned that any carcinogenic potential of iPS cells should be fully investigated before any commercialization can be realized.

**Amniotic fluid-derived stem cells (AFSCs)**

AFSCs can be isolated from aspirates of amniocentesis during genetic screening. An increasing number of studies have demonstrated that AFSCs have the capacity for remarkable proliferation and differentiation into multiple lineages such as chondrocytes (for cartilage), adipocytes (for fat), osteoblasts (for bone), myocytes (for muscle), endothelial cells, neuron-like cells and live cells.\(^12,13,14,15,16,17\) The potential therapeutic value of AFSCs remains to be discovered.

**Umbilical cord blood stem cells (UCBSCs)**

UCBSCs derive from the blood of the umbilical cord.\(^18\) There is a growing interest in their capacity for self-replication and multilineage differentiation, and UCBSCs have been differentiated into several cell types that resemble cells of the liver, skeletal muscle, neural tissue, pancreatic cells, immune cells and mesenchymal stem cells.\(^19,20,21,22,23,24\) Several studies have shown the differentiation potential of human UCBSCs in treating cardiac\(^25\) and diabetic diseases in mice.\(^26\) The greatest disadvantage of UCBSCs is that there is only one opportunity to harvest them from the umbilical cord at the time of birth. Similarly, amniotic stem cells can be sourced only from amniotic fluid and are therefore subject to time constraints.

**Bone marrow-derived stem cells (BMSCs)**

BMSCs consist of both hematopoietic stem cells that generate all types of blood cells and stromal cells (mesenchymal stem cells) that generate bone, cartilage, other connective tissues...
BMSCs are currently the most common commercially available stem cell. They can be isolated from bone marrow aspiration or from the collection of peripheral blood-derived stem cells following chemical stimulation of the bone marrow, by means of subcutaneous injection, to release stem cells.

Adipose-derived stem cells (ASCs)
ASCs are typically isolated from lipectomy or liposuction aspirates. They have been differentiated into adipocytes, chondrocytes, myocytes, and neuronal and osteoblast lineages, and may provide hematopoietic support. ASCs express some, but certainly not all, of the cell markers that bone marrow MSCs express. While ASCs have an advantage in that adipose tissue is plentiful in many individuals, accessible and replenishable, the ability to reconstitute tissues and organs using ASCs versus other adult stem cells has yet to be comprehensively compared and documented.

Dental stem cells (DSCs)
Dental stem cells (DSCs) can be obtained from the pulp of the primary and permanent teeth, from the periodontal ligament, and from other tooth structure. Periodontal ligament-derived stem cells are able to generate periodontal ligament and cementum. Extracted third molars; exfoliating/extracted deciduous teeth; and teeth extracted for orthodontic treatment, trauma or periodontal disease are all sources of dental stem cells from the dental pulp. The dental pulp offers a source of stem cells postnatally that is readily available, with a minimally invasive process that results in minimal trauma.

Exfoliating or extracted deciduous teeth offer extra advantages over other teeth as a source of stem cells. Stem cells from deciduous teeth have been found to grow more rapidly than those from other sources, and it is believed that this is because they may be less mature than other stem cells found in the body. Additional advantages of sourcing stem cells from exfoliating deciduous teeth are that the cells are readily available, provided they are stored until they may be needed later in life; the process does not require a patient to sacrifice a tooth to source the stem cells; and there is little or no trauma.

The structures of interest to the dental profession are the enamel; dentin; dental pulp; cementum; periodontal ligament; craniofacial bones; temporomandibular joint, including bone, fibrocartilage and ligaments; skeletal muscles and tendons; skin and subcutaneous soft tissue; salivary glands; and so forth. Without exception, neural crest-derived and/or mesenchymal cells form all these dental, oral and craniofacial structures during native development. Several populations of adult stem cells have been explored for the regeneration of dental, oral and craniofacial structures, including BMSCs, ASCs and DSCs, which, despite important differences between them, are likely the subfamily of mesenchymal stem cells.

Mesenchymal stem cells
Mesenchymal stem cells (MSCs) in general have several important properties: adherence to cell culture polystyrene, self-replication to multiple passages and differentiation into multiple cell lineages. Mesenchymal cells natively form connective tissue, including bone, cartilage, adipose tissue, tendon and muscle, and participate in the formation of many craniofacial structures. MSCs can differentiate into multiple cell lineages, including but not limited to chondrocytes, osteoblasts, myoblasts and adipocytes. MSCs have been viewed as the yardstick by which to measure the regeneration of musculoskeletal tissues and have been utilized in the regeneration of non-musculoskeletal tissues such as cardiac and neural tissues. MSCs can be isolated from the patient who needs the treatment, and therefore can be used autologously without concern for immunorejection. MSCs have also been used allogeneically and been shown to heal large defects.

Applications/Tissue Engineering With Stem Cells
Stem cells from a tiny amount of tissue, such as the dental pulp, can be multiplied or expanded to potentially sufficient numbers for healing large, clinically relevant defects. Stem cells differentiating into multiple cell lineages offer the possibility that a common (stem) cell source can heal many tissues.

<table>
<thead>
<tr>
<th>Embryonic stem cells</th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td>Adult stem cells</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>iPS</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amniotic fluid-derived</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Umbilical cord-derived</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Bone marrow-derived</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adipose-derived</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dental-derived</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No*</td>
</tr>
</tbody>
</table>

* Exfoliating teeth are non-invasive sources of stem cells. Extracted teeth are minimally-invasive sources of stem cells, involving no additional trauma if the teeth are already being extracted.
in the same patient, as opposed to harvesting healthy autolo-
gous tissue to heal like tissue. Finally, stem cells can be seeded in biocompatible scaffolds in the shape of the anatomical structure that is to be replaced. Scaffolds must provide support and should be resorbed when healing has occurred.

The fundamental reasons for the effectiveness of stem cells are as follows:
• Unlike end-lineage cells, stem cells can be expanded ex vivo (outside the body). Thus a small number of stem cells can be sufficient to heal large defects or to treat diseases. In contrast, a large number of end-lineage cells need to be harvested for tissue regeneration, necessitating donor site trauma and defects.
• Stem cells may elaborate and organize tissues in vivo, especially in the presence of vasculature.
• Stem cells may regulate local and systemic immune reactions of the host in ways that favor tissue regeneration.
• Stem cells may provide a renewable supply of tissue-forming cells.

Tissue Differentiation
Experimental data has shown that a single population of mesenchymal stem cells can differentiate into chondrocytes, myoblasts, osteoblasts and adipocytes. Stem cell-derived chondrocytes can be used for the reconstruction of orofacial cartilage structures such as the nasal cartilage and the temporomandibular joint. Stem cell-derived osteoblasts can be used to regenerate oral and craniofacial bones. Stem cell-derived myocytes can be used to treat muscular dystrophy and facial muscle atrophy. Stem cell-derived adipocytes can be used to generate soft tissue grafts for facial soft tissue or breast reconstructions, and may eliminate the need for autologous tissue grafting. Why bother deriving end-lineage cells from stem cells, instead of using end-lineage cells such as chondrocytes or adipocytes?

The short response is that end-lineage cells have a limited life span and cannot self-renew, whereas stem cells, by definition, self-renew and can replenish the supply of end-lineage cells.

Bone and Craniofacial Regeneration
An estimated 1.6 million bone grafts are performed annually in the United States, of which approximately 6 percent are craniofacial grafts.

Bone grafts can be autologous, allogenic or xenogenous in nature. Autologous bone grafting is often considered the clinical gold standard. The use of stem cells is superior to autologous bone grafting. Why? Autologous tissue grafting involves harvesting healthy bone from the patient’s iliac crest, rib bone, femur, chin or retro-molar area. Thus, the key drawback is donor site trauma and morbidity. In contrast, stem cell-based therapeutic approaches could circumvent this drawback. Clinical studies are being conducted using stem cells for alveolar ridge augmentation and long-bone defects. Vascularized bone grafts are also in development using stem cells, and reconstruction of a patient’s resected mandible has been carried out using this technique.

Craniofacial regeneration
As an example of craniofacial regeneration, stem cells have been used in the tissue engineering of a human-shaped temporomandibular joint. MSCs were first isolated from bone marrow and exposed separately to either chondrogenic or osteogenic supplemented culture medium (Figure 2). MSC-derived cells were encapsulated in a poly(ethylene glycol) diacrylate (PEGDA) hydrogel that was molded into an adult human mandibular condyle in stratified yet integrated layers of cartilage and bone. The osteochondral grafts in the shape of human TMJs were implanted in immunodeficient mice for up to 12 weeks.
Upon harvest, the tissue-engineered mandibular joint condyles retained their shape and dimensions. The chondrogenic and osteogenic portions remained in their respective layers, as demonstrated by positive staining using chondrogenic and osteogenic markers (Figure 3). Lastly and most importantly, there was mutual infiltration of the cartilaginous and osseous components into each other’s territory that resembled mandibular condyle.82

Figure 3. Histology of the tissue engineered articular condyle

The cartilage portion and the bone portion remained integrated

Medical Applications

Craniofacial stem cells, including dental stem cells, originate from neural crest cells and mesenchymal cells during development.83,84 Conceptually, tooth-derived stem cells have the potential to differentiate into neural cell lineages. Indeed, deciduous dental stem cells85 and bone marrow-derived stem cells86 both express neural markers.

The expression of neural markers in dental stem cells elicits imagination of their potential use in neural regeneration, as in the treatment of Parkinson’s disease, for which there is currently no cure. Adult dental stem cells have been and are being investigated to treat Parkinson’s disease, which currently affects an estimated 1 million people in the United States, as well as to treat related neurological diseases and spinal cord injuries. In addition, they appear to replace dead neural cells and support degenerating neural cells.87

Stem cells are also being investigated for the development of myocardial cells to repair damaged heart muscle following cardiac infarct. Heart failure affects more than 5 million people in the United States alone. Mesenchymal stem cells have been found to be able to differentiate into myocardial cells and vascular epithelium,88 as well as to release molecules that are protective for cardiac cells.89 Patients have already been treated with MSCs following cardiac infarcts to regenerate heart muscle and improve function.90,91 It has also been possible to engineer functioning bladders using autologous adult stem cells.92

Stem cells are believed to modulate the immune system and are currently being investigated for use in the treatment of graft-versus-host disease, Crohn’s disease and lupus.93,94 DSCs isolated from dental pulp have been found to exhibit immunoregulatory and immunosuppressive properties.95 Other potential uses include stem cell-derived insulin-producing cells to treat diabetes and MSCs for tissue regeneration following radiation-induced damage.96 Clinical manipulation of stem cells’ DNA is also leading to the development of gene therapies.

Dental Applications

Patients come to the dentist because of infections, trauma, congenital anomalies or diseases such as orofacial cancer and salivary gland disorders. Whereas native tissue is missing in congenital anomalies, conditions such as caries or tumor resection result in tissue defects. For centuries, dentistry has been devoted to the healing of defects with durable materials or the patient’s own (autologous) tissue. However, amalgam, composites and even titanium dental implants can fail, and all have limited service time.97

Why are stem cells better than durable implants such as titanium dental implants? A short response to this question is that stem cell therapy could potentially lead to the regeneration of tooth roots, with periodontal ligaments that can remodel with host bone, which would be functionally superior to titanium dental implants.

Table 5. Medical stem cell applications under investigation

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Stem Cell Applications</th>
</tr>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Crohn’s disease</td>
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<tr>
<td>Other neurological diseases</td>
<td>Lupus</td>
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<tr>
<td>Spinal cord injuries</td>
<td>Diabetes</td>
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<tr>
<td>Bone grafting</td>
<td>Genetic disorders (gene therapy)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Radiation-induced damage</td>
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<tr>
<td>Urological</td>
<td></td>
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<tr>
<td>Immune system modulation</td>
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</table>

The expression of certain end-cell lineage markers by stem cells represents only the first of many steps toward the treatment of a disease. The potential of dental stem cells in both dental and non-dental regeneration should be further explored.

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Table 6. Dental applications under investigation

<table>
<thead>
<tr>
<th>Dental Application</th>
<th>Stem Cell Applications</th>
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<tbody>
<tr>
<td>Craniofacial regeneration</td>
<td>Periodontal ligament regeneration</td>
</tr>
<tr>
<td>Cleft lip and palate</td>
<td>Enamel and dentin production</td>
</tr>
<tr>
<td>Tooth regeneration</td>
<td></td>
</tr>
<tr>
<td>Pulp regeneration</td>
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</table>

Tooth root and supporting periodontal ligaments have been regenerated from dental stem cells in research.98 Cells
from tooth buds can also differentiate into a small tooth structure when used with a carrier and transplanted in vivo.99 Pulpal and dentin repair using dental stem cells is also under investigation, and the mesenchymal stem cells from the pulp are under investigation for their ability to produce dentin.100 The follicle associated with third molars is under investigation for its ability to produce enamel.101

**Stem Cell Handling and Cryopreservation**

Stem cells are released from small amounts of tissue, in the case of dental stem cells from dental pulp. The tissue is placed in an enzyme solution that releases the stem cells, which are then cultured to multiply. This can be accomplished using serum-free medium, removing the need for use of animal serum. Differentiation then occurs and the cells are transplanted – either alone or with a scaffold or other biomaterials, depending on the application.

**Cryopreservation**

Stem cells must be derived from living tissue and must be preserved. This is achieved by cryopreservation. The cells are rapidly cooled to subzero temperatures as low as −196°C Celsius, stopping any cellular or biochemical activity. Rapid freezing is necessary to prevent ice from forming around or inside the cells and to prevent dehydration, as these would cause cell damage and death.

Extracted permanent and deciduous (including exfoliating) teeth can be preserved for future use with cryopreservation. Research has demonstrated that stem cells derived from the dental pulp of extracted third molars retain the ability to differentiate into multiple cell types following thawing after cryopreservation using liquid nitrogen.102 Stem cells derived from the periodontal ligament are viable following cryopreservation.103 After two years of cryopreservation, stem cells have been able to differentiate and to proliferate, and it has been concluded that DSCs can undergo long-term cryopreservation.104 Companies are currently engaged in the collection and cryopreservation of deciduous teeth for patients’ potential use in later life (StemSave, BioEden, Baby Teeth Cell Bank).

![Figure 4. Banking Teeth](image)

**Summary**

Physicians and scientists have recommended that umbilical cord stem cells and amniotic fluid stem cells be banked for potential applications in the treatment of trauma and pathological disorders. Similarly, it is now possible to cryopreserve healthy teeth as sources of autogenous stem cells, either as they are exfoliated or by extraction, should these be needed in future years to treat diseases and/or conditions that the patient develops. With all we have learned about stem cells and tissue engineering of dental, oral and craniofacial structures, we are in a position to bring the awareness to patients regarding proper storage of their extracted teeth in conditions that will preserve craniofacial stem cells, including dental stem cells.

Banking teeth and dental stem cells offers patients a viable alternative to using more invasive or ethically problematic sources of stem cells, and harvesting can be done during routine procedures in adults and from the deciduous teeth of children. Now, dental professionals have the opportunity to make their patients aware of these new sources of stem cells that can be conveniently recovered and remotely stored for future use as new therapies are developed for a range of diseases and injuries.

Our understanding of mesenchymal stem cells in the tissue engineering of systemic, dental, oral and craniofacial structures has advanced tremendously.105,106,107,108,109,110 The conservative treatment of life-threatening and disfiguring de-
fects and diseases and the ability to treat currently incurable diseases are becoming a reality. The impact of this paradigm shift in health care will eventually be seen in every medical and dental office and setting.

References
5. Ibid.
Author Profile

Jeremy J. Mao, DDS, PhD

Dr. Mao is currently Professor and Director of the Tissue Engineering and Regenerative Medicine Laboratory at Columbia University. Dr. Mao has published over 100 scientific papers and book chapters in the area of tissue engineering, stem cells and regenerative medicine. He currently serves on the editorial board of several scientific journals including Tissue Engineering, Journal of Biomedical Material Research, International Journal of Oral and Maxillofacial Surgery, and Journal of Dental Research, and has served as an Associate Editor of Stem Cells and Development, as well as on the editorial board of Medical Engineering and Physics and Frontiers of Bioscience. Dr. Mao is the editor of a new book entitled “Translational Approaches in Tissue Engineering and Regenerative Medicine.” Dr. Mao is also the editor of an upcoming textbook entitled “Principles of Craniofacial Growth and Development.” Dr. Mao is currently a standing member of the Musculoskeletal Tissue Engineering Study Section of the NIH and serves on a number of review panels for NIH, NSF, US Army as well as many other grant review panels in over 18 different countries. Dr. Mao has been invited to give lectures at over 130 national and international conferences including NIH-sponsored Stem Cells and Tissue Engineering Conference. Dr. Mao’s laboratory is currently funded by several research grants from the National Institutes of Health and also from industry. Dr. Mao is a consultant to Tissue Engineering and Regenerative Medicine Centers in the United States and overseas.

Acknowledgements

Dr. Jeremy Mao is responsible for sections on the scientific basis of stem cells and dental, oral and craniofacial regeneration. The following research grants from the National Institutes of Health, especially the National Institute of Dental and Craniofacial Research (NIDCR), are gratefully acknowledged: DE13964.

Disclaimer

Dr. Jeremy Mao is a consultant with the sponsors and the providers of the unrestricted educational grant for this course.

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1. Dental and medical care is being increasingly provided through ________.
   a. chemical approaches
   b. biological approaches
   c. electrical approaches
   d. none of the above

2. Some stem cell therapies have already been approved or are being reviewed by the FDA.
   a. True
   b. False

3. Conditions for which patients are currently being treated with stem cell therapy include ________.
   a. cardiovascular disease
   b. oncological diseases
   c. orthopedic conditions
   d. all of the above

4. It has been estimated that the stem cell market will reach ________ by 2015.
   a. $2 billion
   b. $5 billion
   c. $8 billion
   d. $12 billion

5. Stem cells ________.
   a. are immature cells
   b. are undifferentiated cells
   c. can divide and multiply for an extended period of time
   d. all of the above

6. ________ stem cells are derived from the patient being treated, while ________ stem cells are derived from other individuals.
   a. Xenogous; allogenous
   b. Allogenous; xenogenous
   c. Autogenous; allogenous
   d. none of the above

7. It is not known with certainty that allogenous stem cells will not produce an immune response.
   a. True
   b. False

8. Autogenous stem cells ________.
   a. reduce the risk of rejection
   b. remove the risk of cross-infection, provided they are handled correctly
   c. are less useful than xenogenous tissues
   d. a and b

9. Multipotent stem cells are ________.
   a. able to differentiate into several types of tissue
   b. able to differentiate into only one type of tissue
   c. able to differentiate into any and all types of tissue
   d. none of the above

10. The two main categories of stem cells are ________.
    a. embryonic and ectopic stem cells
    b. embryonic and adult stem cells
    c. primary and secondary stem cells
    d. exogenous and migratory stem cells

11. Embryonic stem cells can be obtained only from embryos, and therefore are associated with ethical issues.
    a. True
    b. False

12. Sources of adult stem cells include the umbilical cord, amniotic fluid, bone marrow, adipose tissue, the brain and teeth.
    a. True
    b. False

13. Umbilical cord blood stem cells ________.
    a. are derived from the blood of the umbilical cord
    b. have been differentiated into several cell types
    c. have the disadvantage that they can only be harvested at birth
    d. all of the above

14. Bone marrow-derived stem cells ________.
    a. can be isolated from bone marrow aspiration
    b. can be isolated from the collection of peripheral blood-derived stem cells
    c. can be isolated from saliva
    d. a and b

15. Adipose-derived stem cells are typically isolated from lipoectomy or liposuction aspirates.
    a. True
    b. False

16. Dental stem cells can be obtained from ________.
    a. the pulp of primary and permanent teeth
    b. periodontal ligament tissue
    c. other tooth structure
    d. all of the above

17. Periodontal ligament-derived stem cells are able to generate implants.
    a. True
    b. False

18. Exfoliating or extracted deciduous teeth offer extra advantages over other teeth as a source of stem cells because ________.
    a. these teeth are old
    b. the stem cells from them grow more rapidly than those from other sources
    c. the patient does not need to sacrifice a tooth
    d. a and c

19. Mesenchymal stem cells can ________.
    a. adhere to cell culture polystyrene
    b. self-replicate to multiple passages
    c. differentiate into multiple cell lineages
    d. all of the above

20. Stem cell-derived chondrocytes and osteoblasts can be used for the reconstruction of the temporomandibular joint.
    a. True
    b. False

21. Stem cell-derived myocytes can be used to treat ________.
    a. muscular dystrophy
    b. shingles
    c. facial muscle atrophy
    d. a and c

22. The use of stem cells is superior to autologous bone grafting because it does not require harvesting of bone from the patient.
    a. True
    b. False

23. Reconstruction of a patient’s resected mandible has been carried out using vascularized bone grafts.
    a. True
    b. False

24. Conceptually, dental stem cells have the potential to differentiate into neural cell lineages.
    a. True
    b. False

25. Patients have already been treated with mesenchymal stem cells to ________.
    a. regenerate heart muscle
    b. improve cardiac function
    c. engineer functioning bladders
    d. all of the above

26. Potential future uses of dental stem cells include ________.
    a. dental tissue regeneration
    b. treatment of neurological diseases such as Parkinson’s disease
    c. immunoregulation
    d. all of the above

27. Tooth root and supporting periodontal ligaments have been regenerated from dental stem cells in research.
    a. True
    b. False

28. Stem cells must be preserved through ________.
    a. cryodessication
    b. cryopreservation
    c. cyanopreservation
    d. none of the above

29. Stem cells derived from the periodontal ligament are viable following cryopreservation.
    a. True
    b. False

30. The collection and cryopreservation of deciduous teeth for the patient’s potential use in later life is already being carried out.
    a. True
    b. False
### Educational Objectives

1. Understand the range of diseases for which stem cell therapies are being investigated.
2. Be knowledgeable about the various sources of stem cells and the advantages and disadvantages of each source.
3. Understand the fundamental reasons for the effectiveness of stem cells and the meaning of tissue differentiation.
4. Understand the basics of cryopreservation and the banking of stem cells.

### Course Evaluation

Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>1. Was the overall administration of the course effective?</td>
<td>5</td>
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<tr>
<td>5. How do you rate the author's grasp of the topic?</td>
<td>5</td>
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<td>Yes</td>
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<td>9. Would you participate in a similar program on a different topic?</td>
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<td>No</td>
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<tr>
<td>10. If any of the continuing education questions were unclear or ambiguous, please list them.</td>
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### Certificates

Certificates will be mailed within two weeks after taking an examination.

All participants scoring at least 70% (answering 21 or more questions correctly) on the examination will receive a certificate verifying 4 CE credits.

The examination will cover the following:

1. Were the individual course objectives met?  
   - Objective #1: Yes No  
   - Objective #2: Yes No
2. To what extent were the course objectives accomplished overall?  
   - 5 4 3 2 1 0
3. Please rate your personal mastery of the course objectives.  
   - 5 4 3 2 1 0
4. How would you rate the objectives and educational methods?  
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### Additional Questions

11. Was there any subject matter you found confusing? Please describe.  
12. What additional continuing dental education topics would you like to see?

### Mail completed answer sheet to

**Academy of Dental Therapeutics and Stomatology**  
P.O. Box 116, Chesterland, OH 44026  
or fax to: (440) 845-3447

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1. 16. 2. 17. 3. 18. 4. 19. 5. 20. 6. 21. 7. 22. 8. 23. 9. 24. 10. 25. 11. 26. 12. 27. 13. 28. 14. 29. 15. 30.

**AGD Code 149**

### Record Keeping

- Any participant who is not 100% satisfied with this course can request a full refund by contacting the Academy of Dental Therapeutics and Stomatology in writing.
- The ADTS maintains records of all courses completed each year. Please contact your state dental board for continuing education requirements. This report, which will list all credits earned to date, will be generated and mailed to you within five business days of receipt.

### Please photocopy answer sheet for additional participants.

### AUTHORIZED SIGNATURE

- Dr. Jeremy Mao is a consultant with the sponsors and the providers of the unrestricted educational grant for this course.

### SPONSOR/PROVIDER

Dr. Jeremy Mao is a consultant with the sponsors and the providers of the unrestricted educational grant for this course. The opinions of efficacy or perceived value of any products or companies mentioned in this course and expressed herein are those of the author(s) of the course and do not necessarily reflect those of the ADTS. The opinions of efficacy or perceived value of any products or companies mentioned in this course and expressed herein are those of the author(s) of the course and do not necessarily reflect those of the ADTS.
Did you know?

You can easily collect potentially lifesaving stem cells for your patients.

With the recent discovery of stem cells inside teeth, this is now a reality. Imagine being able to offer your patients the promise of stem cell science in the event of a disease or injury. With StemSave®, you can give your patients a convenient and affordable option to preserve the lifesaving benefits of stem cells until they are needed most. To learn more about our stem cell preservation program and to register to become a StemSave Dentist, call 1.877.StemSave or visit www.StemSave.com.
Stem Cells: Sources, Therapies and the Dental Professional

Educational Objectives

1. Understand the range of diseases for which stem cell therapies are being investigated
2. Be knowledgeable about the various sources of stem cells and the advantages and disadvantages of each source
3. Understand the fundamental reasons for the effectiveness of stem cells and the meaning of tissue differentiation
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Course Evaluation

Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

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PLEASE PHOTOCOPY ANSWER SHEET FOR ADDITIONAL PARTICIPANTS.

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RECORD KEEPING

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AGD Code 149
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