Abstract: Provided herein is a transduction cyclic force system and methods of making and using the same.
MECHANICAL TRANSDUCTION CYCLIC FORCE SYSTEM

FIELD OF INVENTION

The present invention generally relates to using a cyclic force system for modulating tissue microenvironment for tissue generation and/or remodeling.

BACKGROUND OF THE INVENTION

Tissue generation, remodeling, and repair continue to be some of the focal points of the medical community. Much of the current technology involves pharmaceutical or medical means that uses drug or man made materials, which can lead to undesirable effects. For example, in sports, athletes often use steroids or other chemicals to stimulate muscle buildup. In cosmetic fields, breast implants are the most common way for breast enlargement. Problems associated with the use of steroids and breast implants are common. Meanwhile, while skeletal or non-skeletal restructuring using metal or non-metal implants are common, tissue integration of the implants continues to be a challenge.

Therefore, there is a need for alternative methods for tissue generation, remodeling, and repair. There is also a need for methods for facilitating tissue integration of a metal or non-metal implant.

The following embodiments address the above identified problems and needs.

SUMMARY OF THE INVENTION

Provided herein is a transduction cyclic force system. The cyclic force system includes a transducer material which, upon exposure to a stimulus such as electricity, generates a cyclic force, thereby providing a cyclic stimulation on a tissue upon which the system is attached.

The cyclic force system provided herein can be used in a variety of applications. An exemplary application of the cyclic force system is bone consolidation for, e.g., implant fixation and/or repair. Other applications of the cyclic force system include, but are not limited to, facilitation of implant tissue integration, implant osteointegration, promotion of repair or remodeling of diseased, damaged and/or traumatized
periodontium by repairing bone matrix around the tooth/teeth, distraction tissue repair, regeneration or remodeling system, e.g., as distraction system for bone formation (for example, orthopedic devices) or tissue repair, regeneration, or remodeling (for example, soft tissue remodeling, e.g., distraction enlargement of a soft tissue).

6 DETAILED DESCRIPTION OF THE INVENTION

Provided herein is a transduction cyclic force system. The cyclic force system includes a transducer material which, upon exposure to a stimulus such as electricity, generates a cyclic force, thereby providing a cyclic stimulation on a tissue upon which the system is attached.

The cyclic force system provided herein can be used in a variety of applications.

An exemplary application of the cyclic force system is for stimulating tissue growth. In some embodiments, the cyclic force system can be used for bone consolidation for, e.g., implant fixation and/or repair. Other applications of the cyclic force system include, but are not limited to, facilitation of implant osteointegration, promotion of repair or remodeling of diseased, damaged and/or traumatized periodontium by repairing bone matrix around the tooth/teeth, distraction tissue repair, regeneration or remodeling system, e.g., as distraction system for bone formation (for example, orthopedic devices) or tissue repair, regeneration, or remodeling (for example, soft tissue remodeling, e.g., distraction enlargement of a soft tissue).

In some embodiments, the cyclic force system described herein can be used to stimulate tissue movement. Tissue movement as used herein refers to moving a substantial part of a tissue from one position to another position, with or without tissue growth.

Stress-strain related bone regeneration

As described in Meyer, U. et al. Biomechanical and clinical implications of distraction osteogenesis in craniofacial surgery. J Craniomaxillofac Surg 32, 140-9 (2004), bone has an adaptive behavior toward a changing mechanical environment, which is regarded as phenotype plasticity. Specific strain-dependent signals are thought to control this adaptive mode of bony tissue modeling. The adaptive mechanisms include basic multicellular units (BMUs) of bone remodeling. Effector cells within BMUs have been shown to function in an interdependent manner. While hormones may bring about
as much as 10% of the postnatal changes in bone strength and mass, 40% are determined by mechanical effects. This has been shown by the loss of extremity bone mass in patients with paraplegia (more than 40%). Modeling occurs by separate formation and resorption drifts to reshape, thicken, and strengthen a bone or trabecula by moving its surfaces around in tissue space. Remodeling also involves both resorption and formation of bone. BMUs turn bone over in small packets through a process in which an activating event causes some bone resorption and bone formation is following

**Mechanotransduction of osteoblasts**

It is generally suggested that forces leading to cellular deformation are signaled to the cellular genome through mechanotransduction (Meyer, U. *et al. J Craniomaxillofac Surg* 32, 140-9 (2004)). Mechanotransduction, or the conversion of a biophysical force into a cellular response, is an essential mechanism in bone biology. It allows bone cells to respond to a changing mechanical environment. Mechanotransduction can be categorized in an idealized manner into (1) mechanocoupling, which means the transduction of mechanical force applied to the tissue into a local mechanical signal perceived by a bone cell; (2) biochemical coupling, the transduction of a local mechanical signal into biochemical signal cascades altering gene expression or protein activation; (3) transmission of signals from the sensor cells to effector cells, which actually form or remove bone; and ultimately (4) the effector cell response.

When loads are applied to bone, the tissue begins to deform causing local strains (typically reported in units of microstrain; 10,000 microstrain=1% change in length). It is well known that osteoblasts and osteocytes act as the sensors of local bone strains and that they are appropriately located in the bone for this function.

**In vitro mechanical stimulation**

The ability of living tissues to remodel in response to cyclic loads suggests that similar adaptive processes may occur in engineered tissues *in vitro*. Since the early work of Glucksmann in 1939 (Glucksmann A. Anatomical Record 73:39-56 (1939)), a vast array of stimulation devices have been constructed to load cells in compression, tension, bending, out-of-plane distension, in-plane distention, shear, and combinations of the above (recently reviewed by Brown). A number of studies have shown that mechanically challenged tissue constructs show hypertrophy and increased orientation of
fibers and cells in comparison to control constructs. Fink et al subjected cells in a collagen gel to cyclic stretch at 1.5Hz and observed significant changes in cell arrangement into parallel arrays, increases in cell length and width, and increases in myochondrial density. Functionally, the tissue had a contractile force 2-4 times that of the control (Fink, C.; et al., Faseb Journal 14(5):669-79 (2000)). Buschmann et al found increased extracellular matrix biosynthesis in collagenous tissues by subjecting chondrocytes in an agarose gel to 3% strain at .01-1.0Hz (Buschmann, MD; et al., Journal of Cell Science, 108 (Pt 4):1497-508 (1995)). Zeichen et al found increased cell proliferation by cyclically stretching the cells 5% strain (50,000 microstrains) at 1Hz for 15-60 minutes (Zeichen, J; et al., American Journal of Sports Medicine 2000 Nov-Dec, 28(6):888-92). Similarly, Desrosiers et al reported significant increase in cell proliferation, collagen synthesis, and proteoglycan synthesis by 10% strain (100,000 microstrains) at 0.1 Hz for 24 hours on an elastomeric substrate and (Desrosiers, E. A., et al., Ann. Chir 49, 768-774 (1995)).

**High frequency effects**

It has long been known that low strain, high frequency stimulation (e.g. 50 µε @ 30 Hz) can induce similar (Qin, Y. X., et al., J. Orthop. Res. 16,482-489 (1998)), if not more (Hsieh Y.F. and Turner C.H., Journal of Bone and Mineral Research 16:918-924 (2001)), stimulatory effects than high strain low frequency (e.g. 1,000 µε @ 1 Hz). Recently, Rubin et al. uncovered evidence that brief applications (e.g. 10 minutes) of barely perceptible vibrations at high frequencies (e.g. 0.25 g @ 90 Hz) stimulated bone growth better than weight-bearing activity for the same duration (Rubin C, et al., FASEB J. 15(12):2225-9). Osteoblast response to low frequency, high loads has been shown (Tanaka, S.M., et al., Journal of Biomechanics, 36(l):73-80 (2003)) to be sensitized by high frequency (50 Hz), low amplitude signals through a phenomenon termed stochastic resonance which has been reported by Collins et al.(Collins JJ., Imhoff T.T. and Grigg P. Noise-enhanced tactile sensation. Nature 1996, 383:770) to enhance the sensitivity of mechanoreceptors.

**Soft tissue remodeling or regeneration**

In some embodiments, the cyclic force system described herein can be used for stimulating soft tissue growth or remodeling. As used herein, the term "hard tissue"
refers to a bone(s), cartilage tissue and hair. As used herein, soft tissue refers to any body tissue which is not hard tissue. Some examples of soft tissue include skin, muscle, or tissues in body parts or organs such as breasts or genital organs.

Mechanical cyclic forces can stimulate cell generation. For example, cyclic loading of human tendon fibroblasts on elastic silicone dishes for 5% stretch (50,000 microstrains) at 1Hz for as little as 15-60 minutes resulted in increased cell proliferation (see, for example, Zeichen, J., M., et al., Am J Sports Med, 28(6):S88-92 (2000)). Similarly, cyclic loading of canine ACL fibroblasts on an elastomeric substrate for 10% strain (100,000 microstrains) at 0.1Hz for 24 hours led to increased in cell proliferation, collagen synthesis, and proteoglycan synthesis (see, for example, Desrosiers, E.A., et al., Ann Chir, 49(8): p. 768-74) (1995). For example, it has been shown that fibroblasts seeded in collagen matrices can reorganize the surrounding matrix and adopt a specific orientation in a contracted collagen lattice as a function of culture conditions and time (see, e.g., Auger, F.A., et al., Br J Plast Surg, 46(2): 136-42 (1993); Auger, F.A., et al., In Vitro Cell Dev Biol Anim, 31(6):432-9 (11995); Bell, CC, Science, 214(45 19):450-53 (1981)). Other studies have shown the effects of mechanical stimuli on ultrastructural and histological properties of connective tissues. Lopez et al., found that the addition of an anchorage to the dermal equivalents resulted in cell and collagen alignment in a direction parallel to the constraints exerted by the anchoring device (Lopez Valle, C.A., et al., 127(4):365-71 (1992)).

Mechanotransduction of mesenchymal cells can involve specialized structures that link cells to the extracellular matrix, such as the focal adhesions complexes (Burridge, K., et al., Annu Rev Cell Biol, 4:487-525 (1988); Izzard, CS., and L.R. Lochner, J Cell Sci, 21(1): 129-59 (1976)). It is established that mechanical stimulation plays a significant role in ligament formation. Exercise has been correlated to ligament properties in that exercise results in ligament hypertrophy, while immobilization results in atrophy. The ligament adaptation to exercise occurs both at the ligament-bone junction as well as in the midsubstance of the ligament. At the ligament-bone junction, attachment strength can be increased with exercise.

Cell adhesion to extracellular matrix (ECM) is well-documented phenomenon of cellular response to their environment. Studies have shown that anchorage dependent cells such as fibroblasts and osteoblasts must adhere to the ECM in order to survive. The
biological functions of bone marrow stromal cells are highly sensitive to material surfaces. ECM proteins influence focal adhesion formation, cytoskeleton organization, and gene expression through transmembrane receptors such as integrins, indicating that some of the same cellular proteins, receptors, and other components are common to cell adhesion and mechanotransduction (Juliano, R.L. and S. Haskill, J Cell Biol, 120(3): 577-85 (1993)).

Accordingly, while both mechanotransduction and cell-adhesion can act independently to influence cell function, both processes share common molecular cellular structure and signaling machinery. Besides the cell membrane itself acting as a stress sensor, membrane bound components such as stretch-sensitive cation channels and cell adhesion receptors, such as integrins, can also serve as physical links by which the cells interact with external mechanical loads. Integrins can directly involved in the formation of mechanosomes, which are multiprotein complexes of focal adhesion associated proteins and nucleocytoplasmic shuttling DNA-binding proteins that are believed to mediate external stress into changes in gene transcription (Pavalko, F.M., et al., J Cell Biochem, 88(1): 104-12 (2003)).

Dermis

The skin is the largest organ of the body essential for the survival of an individual. It prevents dehydration, regulates body temperature, and acts as a barrier against chemical, mechanical, and infectious insults. Anatomically, skin is divided into epidermis and dermis. The epidermis is the superficial multi-cellular protective layer. The dermis is composed of two layers: the papillary dermis and the reticular dermis. The papillary dermis, which inter-digits with the epidermis, contains a rich supply of blood vessels and nerve endings. The deeper reticular dermis contains fibroblasts surrounded by a bulk matrix of collagen spaced with elastin, GAG, and proteoglycans. Recent studies uncovered that, in addition to their structure functionality, extracellular matrix (ECM) components harbor a wealth of biological information necessary for normal skin metabolism. These information reside in either the primary protein sequences of these ECM molecules, or in ECM bound growth factors, and establish an dynamic reciprocity between fibroblasts and ECM. The reticular dermis also harbors sweat glands and hair follicles - source of regenerative epidermal cells (Cohen, Diegelmann, Lindblad. Wound Healing: Biochemical and Clinical Aspects. Eds.; Saunders, 1992). Therefore, the dermis
provides not only mechanical support, but also contains functional subunits essential for skin integrity and regeneration in injury repair.

The massive network of collagen fibers in dermis determines the mechanical stability of the skin, its resistance to deformation, and its limited extensibility. Collagens are synthesized by fibroblasts into characteristic fibers. In human tissues at least 13 types of collagens have been identified. Dennis contains primarily types I, III, and V collagens. The primary structure of collagen, i.e., proline hydroxylation, crosslinks between adjacent collagen molecules, as well as fiber diameters form the basis for collagen strength and viscoelasticity to perform its structural role. Collagen fiber diameters and orientations greatly influence the tensile strength and viscoelasticity of the skin. In vivo, dermal collagen fibrils diameter correlates to the amount of tension the skin experiences (e.g. rat tail skin has large diameter collagen fibrils). Transmission electron microscopy recently revealed that dermis can adapt at the microstructural level to repetitive stress by increasing collagen diameter in comparison to contralateral, un-stressed controls, without significant changes in macroscopic features such as dermal layer thickness and cell density (Sanders, J.E., Goldstein, B.S., J. Biomechanics 34(2): 1581-7 (2001)). Dermal adaptation is opposite to the rapid epidermal thickening response to repetitive brushing, and contradictory to stressed ligaments, where small-diameter fibers increased in response to exercise after four weeks (relative to non-exercised controls) (see, e.g., Oakes B.W., et al., Connective Tissue Research, 9:212 (1982); Mackenzie I.C., Journal of Investigative Dermatology, 62:80-85) (1974)). Exercised animals have more small fibrils (diameters 80-100nm), while control animals have more medium fibrils (125-162nm). Immobilization led to a decrease in the number of small diameter fibrils. The biochemical as well as the morphological/structural properties of collagen in the dermis are also influenced by age, anatomical location, previous insult (scars), and soluble factors such as hormones. Aged skins contain higher amount of crosslinked collagen. Collagen fibers in normal skin and normal scar tissue appear relaxed and are arranged in a random array. In contrast, in hypertrophic scars and keloids collagen fibers are thicker, and appeared stretched and aligned in the same plane as the epidermis (Tuan TL and Nichter LS: The molecular basis of keloid and hypertrophic scar formation. MoI Med Today, 4:19-24 (1998)).
GAGs function in regulating collagen diameter, increasing collagen resistance to degradation, increase dermal elasticity and higher energy to fracture, and increasing dermal pore size. For this reason, Integra is made of crosslinked collagen with chondroitin-6-sulfate (up to 25g/100g total dispersed solids). Chondroitin-6-sulfate, although not a native constituent of dermis, was chosen for its availability (see, e.g., Yannas IV, Burke JF, J. Biomed Mater Res., 14(1):65-81 (1980); Yannas, Tissue and Organ Regeneration in Adults, Springer, New York, 2000)). It is clear that the biochemical environment mediates the microstructure adaptation to mechanical stimulation. Engineering viable skin substitutes relies on biologically, structurally, and mechanically predictable dermal construct. Collagen scaffolds with defined biological and mechanical properties are in demand for successful construction of bioengineered skin coverage:

Dynamic reciprocity between fibroblast and its ECM environment—essential considerations in bioengineering deliverable dermal tissues - Fibroblasts are the major cell type in the dermis and are the effector cells in dermal injury repair. A novel feature of cellular mechanics revealed by studies of fibroblast-collagen matrix remodeling is the adaptive response of cells to mechanical loading, i.e., situation in which fibroblasts exert force on collagen in development of tension in the matrix. As mechanical loading increases, fibroblasts change the mechanisms that they use to remodel the matrix. These mechanisms include, but not limited to, growth factor responsiveness, integrin utilization, ion channel and gap junction activation, focal adhesion complex formation, and the intracellular signalings and gene regulations which lead to cell proliferation or differentiation (see, e.g., Cukierman, E., et al., Curr. Opin. Cell Biol. 14:633-639 (2002)).

Fibroblasts within collagen matrices can reorganize the surrounding matrix and adopt a specific orientation in a contracted collagen lattice as a function of culture conditions and time. For example, the addition of an anchorage to the dermal equivalents resulted in cell and collagen alignment in a direction parallel to the constraints exerted by the anchoring device (see, e.g., Lopez et al., Br J Dermatol. 127(4):365-71 (1992)). At the cellular level, fibroblasts switch matrix signaling mechanisms (Rac vs. Rho) and predominant integrins before and after, respectively, isometric tension is reached within collagen gels (see, e.g., Grinnell, Trends in Cell Bio, 13(5):264-9 (2003)). In a recent
review, Grinnell summarizes that mechanically loaded fibroblasts are associated with increases in proliferation, collagen accumulation, growth factor responsiveness, fibrillar fibronectin organization, and focal adhesion and actin stress fiber formation - phenotypes resemble an actively repairing dermis as compared to the un-loaded, floating collagen gels, which resemble resting dermis (Grinnell F., Trends in Cell Bio,13(5):264-9 (2003)). Persistent mechanical loading creates contracture (see, e.g., Tomasek et al., Nature Cell Biology, (2002)), analogous to in vivo pathological scar contracture which is correctable by releasing the accumulated tension in the scar during scar revision.

During skin wound repair, fibroblasts synthesize and/or encounter new arrays of ECM molecules, such as fibrinogen, fibronectin, thrombospondin, tenacin, etc. Using in vitro fibroplasia model, a 3-D fibrin culture system, and 3-D collagen gel system, we demonstrated a differential growth factor TGF-beta modulated ECM-specific induction and activation of two major ECM remodeling proteases and protease inhibitors, i.e., plasminogen activator (PA)/plasminogen activator inhibitor (PAI-I) and the metalloproteinase (MMP)/tissue inhibitor of metalloproteinase (TIMP) (Tuan TL, et al., J Invest Dermatol, 106:1007-1011 (1996); Han et al., J Biol Chem, 77(30):273 19-27327 (2002); Han YP, et al., J Biol Chem, 276(25):22341-22350 (2001); Tuan et al., Am. J. Pathol., 162(5): 1579-1589 (2003)). These proteases/inhibitors, in turn, modify the ECM molecules surrounding fibroblasts. Fibrinogen is the most abundant ECM in the wound. Its pliability and supportive nature in cell migration and growth have made it a highly successful biomaterial in mending tissue defects as well as delivering genetically engineered cells or protein products that favor tissue repair. The precise mechanisms by which mechanical stresses in combination with ECM specificity are transduced into molecular signaling events in fibroblasts are largely unknown, and understanding the interactions between cell and matrix is central to the analysis of normal or pathologic connective physiology and to biomimetic design in the emerging field of tissue engineering.

Nerve regeneration

Stimulations have been proven to stimulate nerve regeneration. Examples of such stimulations can be mechanical stimulation, electric stimulation, magnetic field stimulation, etc., or combinations thereof. For example, long-term electric stimulation has been shown to stimulate peripheral nerve fibers as well as reinnervation of distal

Peripheral nerve regeneration has been documented using percutaneous electrical stimulation. For example, Chen et al, reported that percutaneous electrical stimulation generated from using silicone rubber chambers causes peripheral nerve regeneration, see, Chen, et al., J Biomed Mater Res., 57(4):541-9 (2001).

End-to-side repair has been used to provide functional recovery in the upper spinal cord. Electrical stimulation of an end-to-side attached radial or median/ulnar nerves after repair has been shown to facilitate functional recovery in contraction of muscles in the upper limb (see, e.g., J.Peripher. Nerv. Syst, 10(1):58-68 (2005). Mechanical distal muscle constriction has also shown to have effect on nerve regeneration in injured nerve (see, e.g., J. Neurol. Sci., 68(1):1-14 (1985)).

Transduction cyclic force

The cyclic force system described herein includes transduction cyclic force. Such transduction cyclic force can be generated by exposing a transducer material(s) in the cyclic force system to a stimulus such as light, electricity, heat, electric field, radiation, ultrasound, or magnetic field.

Transducer materials

The transducer material or compound that can be used to provide for the cyclic force system includes any transducer material, either known or will become known in the future. Some exemplary transducer materials or compounds include, but are not limited to, materials in the general categories of piezoelectric crystals, ceramics, polymers, magnetostrictive alloys, and electrostrictive ceramics. Examples of common piezoelectric crystals include quartz, barium titanate, lithium niobate, Rochelle salt, ammonium dihydrogen phosphate, potassium dihydrogen phosphate, tourmaline, zinc blende, lithium tantalate, and bismuth germanium oxide. Common piezoelectric ceramics include barium titanate, lead titanate, lead zirconate, lead metaniobate, and lead zirconate titanate. Piezoelectric polymers are exemplified by polyvinylidene fluoride and their copolymers with trifluoroethylene and tetrafluoroethylene, polyamides, polyureas, and liquid crystal polymers, and amorphous polymers such as
polyacrylonitrile, poly(vinylidene cyanide vinylacetate, polyvinyl chloride, polyvinyl acetate, poly(9,9-di-n-octylfluorenyl-2,7-vinylene) (PFV), poly(benzyl glutamate), poly(methyl glutamate), cellulose triacetate, poly(propylene oxide), poly(1-bicyclobutane carbonitrile) and combinations thereof. Electrostrictive ceramics such as lead magnesium niobate-lead titanate and magnetostriuctive materials such as terbium dysprosium iron (Terfenol-D), and terbium dysprosium can also be used for the said applications.

Some examples of piezoelectric crystals, ceramic materials or compositions include, but are not limited to, LiNbO₃, LiTaO₃, BaTiO₃, PbTiO₃, PbZrO₃, Pb₂Nb₂O₆, and combinations thereof. In some embodiments, the ceramics can be a compound of two or more ceramics, some embodiments of these ceramic compounds include, but are not limited to, Pb(Mg₁₋ₓZrₓ)O₃₋₉-PbTiO₃₋₉-PbZrO₃₋₉, Na₀.₅K₀.₅NbO₃₋₉, Pb₀.₆Ba₀.₄Nb₂O₆, Pb(Zr₀.₅Tio.₄5)O₃, Pb₀.₉₉Ca₀.₀₁(Zro.₅3Tio.₄7)O₃, Pb₀.₉₅Sro.os(Zro.₅3Tio.₄7)O₃, Pb₀.₉₈Sro.i₇(Zro.₅3Tio.₄7)O₃, Pb₀.₈Sro.i₂(Zro.₅3Tio.₄7)O₃, Pb₀.₈Sro.i₂(Zro.₅3Tio.₄7)O₃, and combinations thereof.

In some embodiments, the transducer material can be a transducer composite material. The composite can be a transducer material and a non-transducer material. The non-transducer material can be any biocompatible material, which can be polymer or a non-polymer. In some embodiments, the polymer can be polyolefins such as rubber, polyester, epoxy polymer, rubber, etc., and the non-polymer can be, e.g., glass, carbon fiber, glass fiber, glass spheres, silica, alumina, ceramics, etc. Some exemplary composite materials include, but are not limited to Pb(Zr₅₋₈TiO₃₋₅ (PZT), PZT-epoxy, PZT-rubber, PZT-epoxy with glass spheres, PbTi θ 3-rubber, and combinations thereof.

In some embodiments, the transducer material can exclude any of the above crystals, ceramics, polymers, and/or composites.

**Force frequency**

The frequency of cyclic force of the device described herein can be determined by the transducer material used. Each transducer material or compound has a frequency, which is well documented in the art. Some exemplary frequencies of piezoelectric compounds are found at Yuhuan Xu, Ferroelectric Materials and Their Applications, North Holland, 1991, Amsterdam, London, New York, Tokyo.
The magnitude of cyclic force of the device described herein can be determined by the amount of the transducer compound or material used in the device. The cyclic force can be aligned to any of the x, y, or z direction or any of the planes that can be defined by a set of coordinates (x,y,z). For example, to align the cyclic force to a given direction or plane, the opposite direction or plane of the device can be fixed or locked to a hard tissue such that the cyclic force can act on the given direction or plane. One of ordinary skill in the art would determine, according to a given prescription, to choose an amount of one or more transducer compound/material for forming the device defined herein or to select a formed device containing an amount of one or more transducer compound(s)/material(s).

In some embodiments, the systems provided herein is capable of providing a cyclic force having a frequency above about 0.001 Hz, above about 0.01 Hz, above about 0.1 Hz, above about 1 Hz, above about 2 Hz, above about 10 Hz, above about 20 Hz, above about 40 Hz (for example, 40.1 Hz or above), or above about 100 Hz. Some exemplary ranges of frequency are from about 0.001 Hz to about 100,000 Hz, from about 0.01 Hz to about 100,000 Hz, from about 1 Hz to about 100,000 Hz, from about 5 Hz to about 100,000 Hz, from about 20 Hz to about 100,000 Hz, from about 40 Hz (e.g., 40.1 Hz) to about 100,000 Hz, from about 100 Hz to about 100,000 Hz, from about 0.01 Hz to about 100 Hz, from about 1 Hz to about 100 Hz, from about 2 Hz (e.g., 2.1 Hz) to about 100 Hz, from about 5 Hz to about 100 Hz, from about 20 Hz to about 100 Hz, from about 10 Hz to about 100 Hz, from about 40 Hz (e.g., 40.1 Hz) to about 100 Hz, from about 1 Hz to about 40 Hz, from about 10 Hz to about 40 Hz, from about 20 Hz to about 40 Hz.

In some embodiments, the systems provided herein can specifically exclude any of the above mentioned frequencies or frequency ranges.

In some embodiments, the system described herein is capable of providing a cyclic force having a magnitude in the range between about 0.001 Newton to about 20 Newton, e.g., about 0.001 Newton, about 0.005 Newton, about 0.01 Newton, about 0.02 Newton, about 0.03 Newton, about 0.04 Newton, about 0.05 Newton, about 0.06 Newton, about 0.07 Newton, about 0.08 Newton, about 0.09 Newton, about 0.1 Newton, about 0.2 Newton, about 0.3 Newton, about 0.4 Newton, about 5 Newton, about 0.6 Newton, about 0.7 Newton, about 0.8 Newton, about 0.9 Newton, about 1 Newton, about 2 Newton,
about 3 Newton, about 4 Newton, about 5 Newton, about 6 Newton, about 7 Newton, about 8 Newton, about 9 Newton, about 10 Newton, or about 15 Newton.

In some embodiments, the cyclic force system described herein is capable of generating a load of ranging from about 0.1 microstrain to about 1,000,000 microstrains. For example, the cyclic force system is capable of generating a load of about 0.2, about 0.5, about 1, about 5, about 10, about 50, about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1,000, about 2,000, about 3,000, about 4,000, about 5,000, about 6,000, about 7,000, about 8,000, about 9,000, about 10,000, about 15,000, about 20,000, about 25,000, about 30,000, about 35,000, about 40,000, about 45,000, about 50,000, about 55,000, about 60,000, about 65,000, about 70,000, about 75,000, about 80,000, about 85,000, about 90,000, about 95,000, about 100,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 550,000, about 600,000, about 650,000, about 700,000, about 750,000, about 800,000, about 850,000, about 900,000, or about 950,000 microstrains.

In some embodiments, the systems provided herein can specifically exclude any of the above mentioned loads or force magnitudes.

**Method of Using the Cyclic Force System**

In some embodiments, the present invention provides a method for hard tissue growth, generation, repair, fixation, or remodeling using the cyclic force system described herein. The cyclic force can provide a stimulation that can induce, for example, osteogenesis (e.g., craniofacial bones) of a mammal in need thereof. In some embodiments, the present invention provides a method for soft tissue growth, generation, repair or remodeling using the cyclic force system described herein.

That method comprises the steps of (a) applying a cyclical force to a tissue, and (b) repeating applying the cyclic force a plurality of times until a desired result is obtained. The frequency, magnitude, and load of the cyclic force are described above.

The cyclic force system provided herein can be used in a variety of applications. An exemplary application of the cyclic force system is bone consolidation for, e.g., implant fixation and/or repair. Other applications of the cyclic force system include, but are not limited to, facilitation of implant osteointegration, promotion of repair or remodeling of diseased, damaged and/or traumatized periodontium by repairing bone...
matrix around the tooth/teeth, distraction tissue repair, regeneration or remodeling system, e.g., as distraction system for bone formation (for example, orthopedic devices) or tissue repair, regeneration, or remodeling (for example, soft tissue remodeling, e.g., distraction enlargement).

In some embodiments, the cyclic force system described herein can be used for stimulating blood vessel regeneration, soft organ growth or remodeling. In some embodiments, the cyclic force system can be used for modifying cellular matrix of a tissue.

In some embodiments, the cyclic force system described herein can be used to provide stimulation for nerve repair or reinnervation of distal muscle. For example, the cyclic force system can be used to stimulate spinal cord injury across the side of nerve injury through distal muscle stimulation.

In accordance with one aspect of the present invention, cyclic forces are generated through transducer shells and used to expedite the remodeling of teeth and craniofacial bones in living mammal. Thus, in some embodiments, this invention concerns the remodeling of a mammal's face by osteogenesis of the craniofacial bones. Exemplary mammals are humans, apes, monkeys, rabbits, mice, rats and other laboratory animals as well as companion animals such as cats and dogs, and livestock such as pigs, goats, horses, cattle, sheep and the like.

In some embodiments, the system can be used to treat, prevent, reduce or mitigate pain or soreness in a tissue of a mammal. In such embodiments, the mammal can be a human being, a horse, or a pet.

In some embodiments, the transduction cyclic force can be used to achieve craniofacial osteogenesis, to treat, prevent, reduce or mitigate tissue damage/trauma or disease, to achieve implant fixation, tooth fixation, distraction osteogenesis, or distraction soft tissue generation or enlargement.

In some embodiments, the cyclic force system described herein can be used optionally with a non-cyclic force system aligned in a desired direction. The non-cyclic force can be a force generated by a vacuum or a force aligned in a certain direction. For example, in tissue remodeling (e.g., soft tissue remodeling), the cyclic force can be applied to the tissue with a non-cyclic force aligned in a chosen direction. For tissue enlargement (e.g., breast enlargement), the cyclic force can be applied to the tissue with a
non-cyclic force generated by a vacuum. The vacuum can be any pressure below 1 atmosphere (atm). Some exemplary vacuum can be about 0.99 atm, about 0.98 atm, about 0.97 atm, about 0.96 atm, about 0.95 atm, about 0.94 atm, about 0.93 atm, about 0.92 atm, about 0.91 atm, about 0.90 atm, about 0.85 atm, about 0.83 atm, about 0.8 atm, about 0.75 atm, about 0.70 atm, about 0.65 atm, about 0.6 atm, about 0.55 atm, about 0.5 atm, about 0.45 atm, about 0.4 atm, about 0.35 atm, about 0.30 atm, about 0.25 atm, about 0.20 atm, about 0.15 atm, about 0.10 atm, and about 0.05 atm. The non-cyclic force can be in the direction of the cyclic force or in a direction different from that of the cyclic force.

**Examples of Device**

The device containing transducer can be any orthopedic, dental, or other bone fixation/healing device. In some embodiments, the device can be one for stimulating soft tissue growth, integration, generation, moving, or remodeling. Such devices can be removable or fixed.

In some embodiments, the device can be a tooth implant. In some further embodiments, the device can be a non-tooth implant such as skeletal bone implant or other non-tooth implant such as a cardiovascular implant (e.g., a stent). The transducer material included in the device provides stimulations for implant fixation. The implant can be a metallic implant such as a titanium implant or an implant that includes titanium or a titanium alloy. In one embodiment, the implant can have other metal(s) such as platinum, stainless steel, gold and alloys therefrom. In another embodiment, the implant can include biocompatible polymers, which can be nondegradable or degradable, ceramic, bioglass, and/or combinations thereof.

In other embodiments, the device can be a non-tooth and non-skeletal implant such as a soft tissue implant. In one such embodiment, the transducer material included in the device provides stimulations for improved soft tissue tensile strength in tissues such as, but not limited to tendons, ligaments, and skin. In some embodiments, the transducer system can be a device to treat, prevent, or mitigate inflammation or arthritis in a human or an animal such as racing horses or aged pets, for example.

In some embodiments, the cyclic force device provided herein can be used to treat, prevent, or mitigate spinal cord injury or other types of nerve injury. In these
embodiments, the device can be used to provide stimulation across the side of injury or in the distal muscle.

In some embodiments, the cyclic force device described herein can be used to treat, prevent, or mitigate pain. For example, the device can elicit electric stimulation at a frequency that can disrupt or inhibit nerve conducting signal (e.g., by disrupting or otherwise interfering with paracrine signaling) so as to treat, prevent or mitigate pain (e.g., back pain or pain resulted from injury or wound).

In some embodiments, the cyclic force device described herein can be used to stimulate blood vessel growth so as to facilitate wound healing, tissue repair, or tissue growth.

In some embodiments, the device described herein can be used for improving soft tissue viscoelastic properties to enhance tissue expansion and/or prevent capsular contracture such as in breast implants.

In some embodiments, the device described herein can be used to stimulate hair growth. In these embodiments, the device can be made to have a close contact with the scalp or an area in the scalp. The cyclic force provided by the device can exert a massage-life effect on the scalp so as to improve the microenvironment for hair growth and/or preventing or delaying hair loss. Such a device can also be used for treating or mitigating a condition that involves physiological microenvironment in the brain, e.g., migraine headache, etc.

In some embodiments, a device including transducer material(s) described herein can be used for tissue enlargement. For example, the device can be used for the enlargement of breasts, or male genital organ. In these embodiments, the device described herein can be made to have a close contact with the breast or male genital organ. The cyclic force generated by the device can stimulate the breast(s) or male genital organ growth. In some embodiments, the device can be a distraction tissue growth device.

In some embodiments, the device described herein can be used to stimulate muscle buildup. In these embodiments, the device can be made to have a close contact with the part of body where muscle growth is desirable, and the cyclic force generated by the device can stimulate muscle growth.
In some embodiments, the device can be a non-implant external device that stimulates tooth, skeletal, or non-tooth, non-skeletal tissues. In one such embodiment, the transducer material included in the external device provides stimulation for skeletal tissues to accelerate fracture healing. In another such embodiment, the transducer material included in the external device provides stimulation for non-skeletal tissues to accelerate ligament and/or tendon healing. In yet another embodiment, the transducer material included in the external device stimulated improved soft tissue viscoelastic properties to improve the appearance of aged skin. One embodiment of the device can be an antiaging facial mask.

In some embodiments, the device described herein can be used to facilitate/promote repair or remodeling of diseased, damaged and/or traumatized periodontium by repairing bone matrix around the tooth/teeth.

The device described herein can be formed by a process that includes (1) providing a transducer material and (2) forming the device that includes the transducer material according to conventional methods of making the device.

While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.
We Claim:

1. A device capable of generating a cyclic force, the device comprising a transducer material,
   wherein the transducer material is capable of generating a cyclic force upon exposure to a stimulus,
   wherein the cyclic force is effective for stimulating osteogenesis, tissue integration, or tissue growth or generation when applied to a tissue for a period of time, and
   wherein the tissue is a hard or soft tissue.

2. The device of claim 1, wherein the device is capable of providing a cyclic force having a magnitude above about 0.001 Newton.

3. The device of claim 2, wherein the cyclic force has a frequency above about 0.001 Hz.

4. The device of claim 2, wherein the transducer material is selected from the group consisting of piezoelectric crystals, ceramics, polymers, magneostriective alloys, electrostrictive ceramics, and combinations thereof.

5. The device of claim 1, wherein the stimulus is electricity or a magnetic field.

6. The device of claim 1, which is effective for stimulating hair growth.

7. The device of claim 1, which is effective for treating damaged, diseased, or traumatized periodontium by repairing bone matrix around the tooth/teeth.

8. The device of claim 1, which is effective for stimulating tissue integration of an implant.

9. The device of claim 1, wherein is effective for treating or mitigating inflammation or arthritis in a mammal.

10. The device of claim 11, wherein the mammal is a human being, a horse, or a pet.

11. A method of forming a device of claim 1, comprising
    providing a transducer material, and
    forming the device comprising the transducer material, wherein the device is capable of generating a cyclic force upon exposure to a stimulus.

12. The method of claim 11, wherein the device is capable of generating a cyclic force having a frequency above about 0.001 Hz.

13. A method of enhancing bone healing/fixation, comprising applying a cyclic force
generated by the device according to any of claims 1-5 to a mammalian subject.

14. A method of stimulating implant fixation, comprising applying a cyclic force generated by the device according to any of claims 1-5 to a mammalian subject receiving an implant.

15. The method of claim 14, wherein the implant is a tooth implant.

16. The method of claim 14, wherein the implant is a metallic implant, a polymeric implant, a ceramic implant, or a bioglass implant.

17. The method of claim 14, wherein the metallic implant comprises titanium or titanium alloy.

18. A method of promoting hair growth, comprising applying to the scalp or an area in the scalp a cyclic force generated by the device according to any of claims 1-5.

19. A method of promoting muscle growth, comprising applying to an organ or part of the body where muscle growth is desired of a cyclic force generated by the device according to any of claims 1-5.

20. A method of promoting breast enlargement, comprising applying to one or both breasts a cyclic force generated by the device according to any of claims 1-5.

21. A method of treating or mitigating inflammation or arthritis in a mammal, comprising applying to the mammal a cyclic force generated by the device according to any of claims 1-5.

22. The method of claim 21, wherein the mammal is a human being, a racing horse, or a pet.

23. A method of treating, reducing or mitigating pain or soreness in a tissue, comprising applying to the tissue a cyclic force generated by the device according to any of claims 1-5.

24. A method of treating, preventing or mitigating skin aging, comprising applying to an area of skin where treatment is desired of a cyclic force generated by the device according to any of claims 1-5.
25. A device capable of generating a cyclic force, the device comprising a transducer material, wherein the transducer material is capable of generating a cyclic force upon exposure to a stimulus, and wherein the cyclic force is effective for stimulating tissue growth, regeneration, or remodeling when applied to a soft tissue for a period of time.

26. The device of claim 25, wherein the device is capable of providing a cyclic force having a magnitude above about 0.001 Newton.

27. The device of claim 25, wherein the cyclic force has a frequency above about 0.001 Hz.

28. The device of claim 25, wherein the transducer material is selected from the group consisting of piezoelectric crystals, ceramics, polymers, magnetostrictive alloys, electrostrictive ceramics, and combinations thereof.

29. The device of claim 25, wherein the stimulus is electricity or a magnetic field.

30. The device of claim 25, which is effective for muscle growth, or genital organ enlargement.

31. The device of claim 25, which is an antiaging mask.

32. The device of claim 25, which is effective for breast enlargement.

33. The device of claim 25, wherein the mammal is a human being, a horse, or a pet.

34. The device of claim 25, which is effective for nerve regeneration or muscle reinnervation for treating, preventing or mitigating a nerve injury.

35. The device of claim of claim 25, which is effective for nerve regeneration or muscle reinnervation for treating, preventing or mitigating spinal cord injury.

36. The device of claim 25, which is effective for treating, preventing or mitigating pain.

37. The device of claim 36, wherein the pain is back pain.

38. The device of claim 25, which is effective for stimulating blood vessel regeneration.

39. A method of promoting muscle growth, comprising applying to an organ or part of the body where muscle growth is desired of a cyclic force generated by the device according to any of claims 25-30.

40. A method of promoting breast enlargement, comprising
applying to one or both breasts a cyclic force generated by the device according to any of claims 25-30.

41. The method of claim 41, wherein the mammal is a human being, a racing horse, or a pet.

42. A method of treating, reducing or mitigating pain or soreness in a tissue, comprising
applying to the tissue a cyclic force generated by the device according to any of claims 25-30.

43. A method of treating, preventing or mitigating skin aging, comprising
applying to an area of skin where treatment is desired of a cyclic force generated by the device according to any of claims 25-30.

44. A method of breasts enlargement, comprising
applying to one or both of the breasts a cyclic force generated by the device according to any of claims 25-30.

45. A method of providing stimulation for nerve generation or distal muscle reinnervation, comprising
applying to an area across a nerve injury or a distal muscle a cyclic force generated by the device according to any of claims 25-30.

46. The method of claim 45, wherein the nerve injury is a spinal cord injury.

47. A method of providing stimulation for blood vessel generation, comprising
applying to an area across a wound or injury in a tissue a cyclic force generated by the device according to any of claims 25-30.

48. The method of claim 47, which is for treating or mitigating a wound or facilitating healing of the wound.

49. A method for remodeling of a tissue, comprising
applying to a tissue a cyclic force generated by the device according to any of claims 25-30, and
applying to the tissue a non-cyclic force aligned in a desired direction.

50. A method for enlargement of a soft tissue, comprising
applying to the soft tissue a cyclic force generated by the device according to any of claims 25-30, and
applying to the tissue a non-cyclic force aligned in a desired direction.
51. The method of claim 51, wherein the soft tissue is a breast(s).
52. The method of claim 50, wherein the non-cyclic force is generated by a vacuum.